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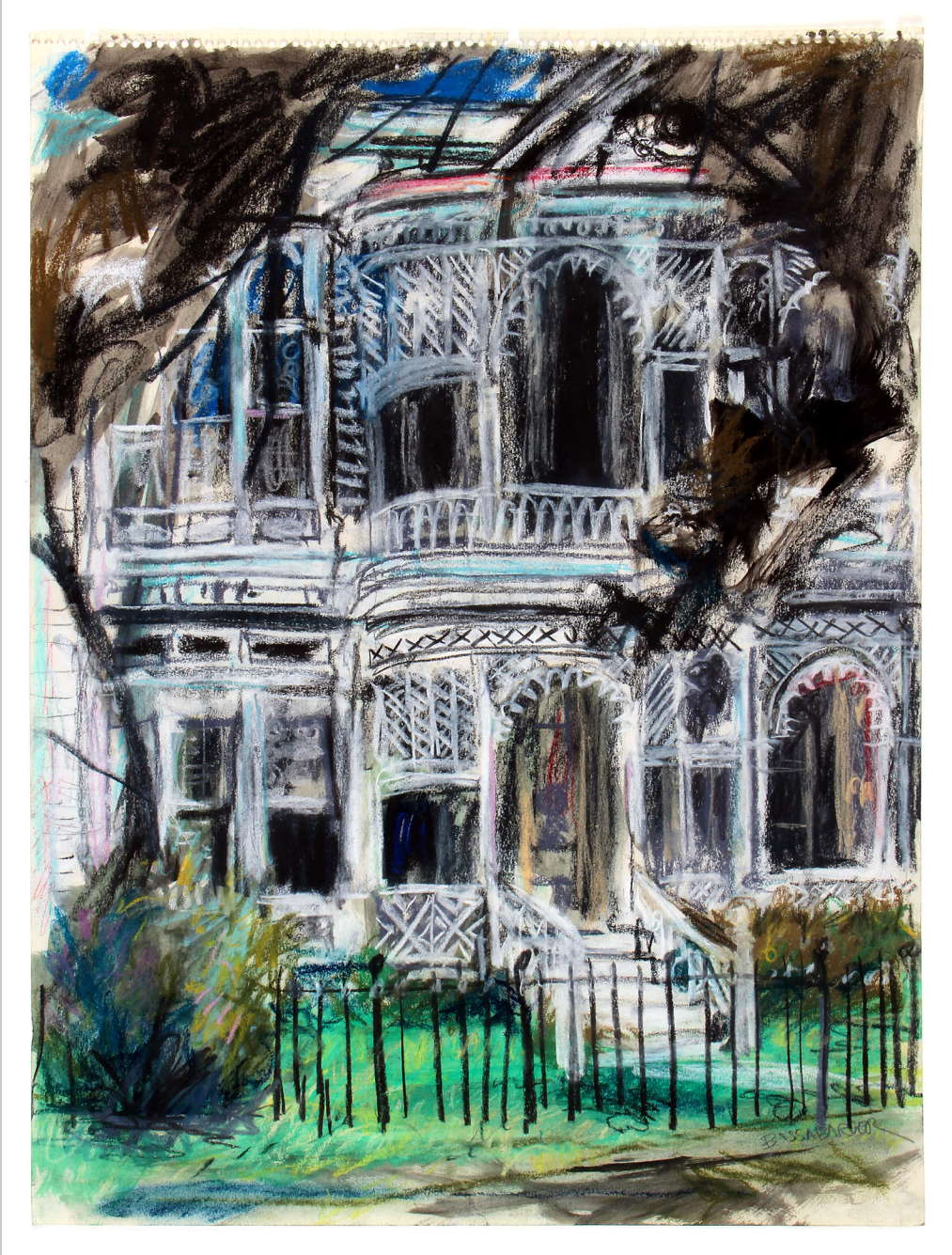

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Cover image: *Galveston House* by Robert Bussabarger, pastels on paper, ca. 1970-80. For more information, see "About the Cover," page 104.

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Letter from the Founding Editor for Volume 7, Issue 2

Richard J. Barohn, MD

Volume 7, Issue 2 is here, and this is a big issue. The September issue is always large because it contains all of the abstracts and proceedings of the annual Neuromuscular Study Group (NMSG) meeting. This year, the NMSG will be in beautiful San Antonio, Texas, where I spent over two decades, first in the US Air Force and then at the University of Texas medical schools in San Antonio and Dallas. I have long wanted to hold the annual NMSG event in San Antonio and in my favorite old-school hotel, the Menger, which is immediately adjacent to the Alamo. A picture-perfect setting for a medical meeting. We publish the abstracts a couple of weeks before the meeting. This year, the meeting will be from September 24 to September 27.

In this issue, we once again have insightful editorials by Dr. Josh Freeman about health care in America that he originally put on his blog site. Dr. Freeman graciously allows us to publish them in this journal. In one editorial, Dr. Freeman focuses on how to improve the situation of primary care physicians by increasing their reimbursement for doing procedures. Dr. Freeman says this is an idea supported by the current Secretary of HHS, Robert F. Kennedy. So, Dr. Freeman says he can now agree with Secretary Kennedy on a topic! In the second editorial, Dr. Freeman discusses the dangers of large corporations like CVS creating vertical integration systems that increase their profits, but at the detriment of patients.

Also in the editorial section is a piece by Suzann Beaupark. Suzann has myasthenia gravis (MG), and she wrote a nice piece on MG in a previous issue. In this article, Suzann reminds health care providers not to dismiss non-motor symptoms of patients simply because they at first do not seem to fit the classical picture of MG. This is an important article because it is written from the patient's perspective.

In the new research section, Dr. Furukawa provides a detailed analysis of surface electromyography (EMG) during sustained muscle contraction. Drs. Shabani, Hussain, and Alexis Taylor conducted a fascinating analysis of online physician ratings in an outpatient neuromuscular practice and came to some interesting conclusions. A large group of doctors from the National Center of Neurology and Psychiatry in Tokyo, Japan, led by Dr. Huki Kondo, conducted a study correlating muscle strength in 18 inclusion body myositis (IBM) patients with various functional abilities.

In the case report section, Dr. Schneider and colleagues from the Medical College of Wisconsin describe a case of unilateral hypoglossal nerve palsy following intubation. Mary O'Rourke and Dr. Erica Seidel at the University of Minnesota Medical School and the Minneapolis VA Medical Center describe a case of complex regional pain syndrome following needle electromyography. A group of clinicians at St. Luke's Medical Center in Kansas City (A. Kuenzel and Drs. Nathan McGraw and Stephanie Kolakowsky-Hayner) describe a sensory ganglionopathy paraneoplastic syndrome in the setting of pulmonary carcinoid.

The reviews section contains a number of articles. We once again publish the lecture turned into an article from our neuromuscular review course. This one is titled "The Diagnosis and Management of Immune-Mediated Polyneuropathies" and is first authored by Jon Katz, with myself, Todd Levine, Dave Saperstein, Mamatha Pasnoor, and Mazen Dimachkie as co-authors. I also continue to publish my lectures turned into articles on the history of neurology and neuroscience. There are four such pieces in this issue, and all focus on the epicenters of the developing field of neurology in Europe in the 1800s in England, France, and Germany-Austria.

The first is on Charles Bell and Francois Magendie and the Bell-Magendie law of sensory input and motor output in the spinal cord. Next, there is a review on the famous Queen Square hospital, in which legions of neurologists were trained by the greats in British medicine, such as Gowers, Jackson, Wilson, and many others. I then go across the English Channel to France and the school of neurologists led by Jean Charcot at the Salpêtrière, as well as other notable French neurologists from the 1800s. In the fourth article, I focus on such well-known neurologists in Germany and Austria as Romberg, Wernicke, Alzheimer, Westphal, Oppenheim, Erb, Jolly... and, of course, Freud. But then we end on a sad note with the infamous neurologists and psychiatrists from this era (Emil Kraeplin, Julius Wagner-Jauregg, Hans Berger, Julius Hallervorden, and Hugo Spatz) who were anti-Semitic and Nazis. The cautionary warning is: It can happen here.

The cover art for this issue is once again from the University of Missouri Museum of Art and Archaeology. It is a pastel on paper by Robert F. Bussabarger called *Galveston House*. I looked through the museum's collections for a work of art that is Texas-based in honor of the NMSG meeting in San Antonio. The museum did not have any classic San Antonio or Alamo images. But this painting of an old house in Galveston is very reminiscent of homes built in the late 1800s and early 1900s in other Texas cities, including San Antonio. San Antonio has a historic area from that era called the King William district, where immigrants from Germany and other European countries settled to begin new lives in America. When I lived in San Antonio, I lived in an old home in the King William district, and this painting by Bussabarger reminds me so much of that era and region. Mary Nau Hunter, the interim director of the University of Missouri Museum of Art and Archaeology, has again provided us with more information about the art and the museum.

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Pay primary care more: Kennedy may be getting this one right!

Joshua Freeman, MD

This article previously appeared in Dr. Freeman's blog, medicinesocialjustice.blogspot.com

I have recently written strong criticisms of Secretary of Health and Human Services Robert F. Kennedy, Jr. and his positions on a number of issues, including most importantly vaccines (see RFK, Jr.: The Secretary of Health and Human Services is Dangerous to Your Health!). Not only is he wrong about vaccines being dangerous, he is in fact creating major danger by discouraging their use. The polio vaccine essentially eliminated a disease that was a major scourge in the US as well as the rest of the world, as did the measles vaccine. Many other vaccines protect our children – and adults – from other serious viral diseases like influenza, COVID, mumps, chicken pox, rubella, shingles, and human papillomavirus (HPV) which causes cervical cancer, as well as bacterial diseases including diphtheria, tetanus, pertussis, and *Hemophilus influenza b.* The last is something most people have not heard of, but early in my career was a major cause of morbidity and death in infants and young children from meningitis, pneumonia, and epiglottitis, which caused their throats to swell rapidly and choke off their breathing. Many others have articulately expressed this concern, including the pediatrician Perri Klass in the *New York Times.* While these diseases affected people of all social classes, they were more prevalent among the poor and minority groups such as the people I cared for at Chicago's Cook County Hospital. Indeed, research has demonstrated tremendous benefits from vaccines on the health of children and other populations that go far beyond just the decrease in the specific diseases that they target to decreasing all-cause mortality!

Kennedy is wrong about many other things, if not all of as of such immediate potential danger as urging people to not get vaccinated. These include nonsense like suggesting that people who eat right and exercise won't get disease, that raw (unpasteurized) milk is better for you, and that "natural" is always better (which, even if we could agree on a definition of "natural", it isn't). One recent example is his arguing for Coke to use "natural" cane sugar rather that high-fructose corn syrup, both of which are sugar and have calories and in large amounts are bad for you.

But there turns out to be one area where Kennedy and I seem to agree, which is the need to take concrete action to increase the number of primary care physicians. Lots of people, including politicians, healthcare providers, and health policy experts, express concern about the shortage of primary care, but have done nothing to address the real cause of this problem – that primary care physicians (and the nurse practitioners and physician's assistants working with them) get paid a lot less than do physicians in other specialties. Kennedy appears to be doing something other than wringing his hands. On several occasions I have written about the RUC, the AMA committee that decides how to divide up the pie of Medicare dollars among specialists by deciding how much each thing doctors do is worth relative to other things that they do. (Changes in the RUC: None. How come we let a bunch of self-interested doctors decide what they get paid? July 21, 2013, Doctors' incomes and patient coverage: both need to be more equal July 26, 2014, and most recently, Not enough primary physicians OR Nurse Practitioners: It's the money, stupid!, June 27, 2024).

Not to get too technical, there is a set amount of Medicare dollars and the RUC decides (or recommends to CMS, which almost always accepts those recommendations) how many physical exams, say, are equivalent to one gall bladder surgery, considering (theoretically) both difficulty and time. This makes a tremendous difference in physician income and, I would argue, specialty choice by medical students. And, over the years, the amount of time it takes for doctors to do some things, particularly procedures, changes. Colonoscopies used to be estimated to take an hour and a quarter, but now are routinely done in 30 minutes. Cataract surgeries take a fraction of the time that they once did. This can result in physicians billing for more procedures than the model assesses as possible in a day. In contrast, the time it takes for a physical exam, or to listen to an interpret a person's story, hasn't changed significantly. The composition of the RUC, according to the AMA, represents all specialties, but its membership has a low proportion of primary care doctors – five of the 32 seats. Unsurprisingly, then, specialist-performed procedures are valued more highly than cognitive work. And, very important, these rates (relative value units) do not affect only Medicare payments – virtually all insurers pay based upon Medicare rates, so it is the whole health system! Prior to this new regulation, alternative models for allocating payment have been developed, such as this 2025 publication from the National Academies of Science, Engineering, and Medicine (NASEM).

So, now, maybe, a change. The *NY Times* reports that, buried in an 1800-page HHS regulation, are proposed changes in the RUC methodology that would benefit primary care. This would be real action! In addition to reassessing these relative values, the action would also look at the current practice of reimbursing more for the same procedures done in a hospital than in a doctor's office, a major way that hospitals make money. And, for those who think "of course it costs more to do something in a hospital", this is a technicality; it simply means that the hospital *owns* the practice or clinic. So two, say, skin biopsies performed in similar doctor's offices across the street from each other are now reimbursed at very different rates if one is owned by a hospital. This is absurd and inequitable, and getting rid of it makes terrific sense!

The diffusion of medical services to people and communities is primarily driven not by the health needs of the populations in different areas but by the potential to

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make the most money for health care providers. These are largely, and increasingly, hospitals and health systems, as well as enormous insurance-company and private-equity owned practices rather than individual or small group physician-owned practices. So, we get enormous hospital campuses and medical facilities in major cities and wealthy suburbs and little or nothing in poor neighborhoods and rural areas. This should change. The only reason for decisions about what healthcare services to provide and where to provide them should be the health needs of people, and not on how much profit can be made.

The new HHS regulation will be a big step in this direction if it redirects Medicare (and thus all insurer) funds to primary care, and does not preferentially favor hospital-owned practices. To the extent that he is responsible for it, Kennedy should be congratulated. However, while it is a big step, it is not a solution. The next, necessary, step is a universal health insurance program where every single person is covered and covered by the same system, and where establishment (and closure) of health facilities, and the services that they provide or do not, is entirely based on the health needs of the people. Of course, there will be a lot of resistance – highly paid specialists will resist the proposed HHS reimbursement changes, and the institutionalized powerful insurance companies and other big players who are making lots of money from "healthcare" will oppose more comprehensive changes. Indeed, they already are, with highly funded social media campaigns against universal health care.

We are glad for this first step, but we need to keep fighting to get a comprehensive health program – like those of every other wealthy country!

Vertical Integration saves money. And CVS and its competitors use that to line their pockets, not provide healthcare

Joshua Freeman, MD

This article previously appeared in Dr. Freeman's blog, *Medicine and Social Justice*
https://medicinesocialjustice.blogspot.com/

I have several times referred to the concept of "vertical integration" in the health care/health insurance/pharmaceutical industry, most recently on March 28, 2026, Everything is becoming more unaffordable, but health care may lead this list!. These posts often reference the posts of former insurance executive-turned-whistleblower Wendell Potter on his substack "Health Care Un-Covered", including "With CVS's Vertical Empire Under Threat in Tennessee, the Company Threatens to Leave", which discusses the fact that CVS, most widely known as large pharmacy chain, also owns the Pharmaceutical Benefit Manager (PBM) Caremark. PBMs are add-on middlemen that negotiate better rates for insurance companies with pharmacies. CVS owns pharmacies, a lot of them. This may seem like conflict of interest (COI), but that is apparently a quaintly outdated concept in this era of mega-corporations.

Actually, the PBM-pharmacy COI is only a part of the CVS megalopoly. They also own one of the nation's largest health insurers, Aetna, so they have both ends *and* the middleman! And, to round it out, they own a large primary care provider group (Oak St. Health) and long-term care company (Signify Health) and urgent care provider (Minute Clinic). Just read the AI summary if you Google "Companies CVS owns", but if you want it, the comprehensive list by the SEC is here. This is what vertical integration is; you buy from yourself, and sell to yourself, set the prices (usually in a way that minimizes tax liability), and make a lot of money. The structure is not hard to understand, but it maximizes the conflict of interest. (For a discussion of why this is conflict of interest and not "potential" conflict of interest, see this blog post from August 20 2010, The AAFP, Coca-Cola, and Ethics: Serving the public interest? . In brief, COI exists when a decider has interests in both parties, and a decision one way would help their other interest. The *conflict* exists whatever the decision is actually made. A judge hearing a case in which one party is a company in which they own a great deal of stock has a conflict of interest; it doesn't require waiting to see how they rule.)

To be clear, CVS is far from the only major player in the "healthcare industry" (quotes on purpose, and emphasis on "industry") that is vertically integrated. The largest health insurance company in the US, UnitedHealth, also owns a PBM, (OptumRx), a primary care group (Optum) and a whole host of other companies (SEC listing here). So does CIGNA (their PBM is ExpressScripts). So, there is competition within the "healthcare" sector; it is an *oligopoly* (few companies) not a complete *monopoly.* But oligopolies don't really compete in the way classic capitalist theory would have it; rather, they tend to set prices and divide up the market so they all do well (although they would prefer the other companies to go out of business, the existence of a few tends to forestall any governmental intervention that might occur with a true monopoly).

Is vertical integration bad? A major argument in favor of it is that it can, and often does, increase efficiency. If you own everything, from insurer to care delivery system to pharmacy, and all the other players in between, you can minimize the obstruction from a piece that is owned by someone else. Things can move more smoothly. Costs can be reduced significantly. These are the arguments most commonly put forward, to the public, by vertically integrated corporations that control a huge market sector, oligopolies as well as monopolies.

It is also the argument put forward to stockholders, particularly large stockholders like private equity firms. Especially the "reduced costs" part. This is very attractive to stockholders. It could also be attractive to those ostensibly served by the "healthcare" industry, those people needing – healthcare. After all, they are heavily burdened by the cost of their healthcare, which constantly goes up. This includes the portion that they are responsible for in the form of premiums, deductibles, copayments and "cost sharing" (meaning insurance only pays a part of the bill and you're on the hook for the rest). Another recent Potter piece, The Bill That Never Ends, summarizes the situation and addresses the fact that deductibles reset every year, so people are constantly behind the 8-ball and can never pay it off. It reminds me of the compound interest that keeps former students in debt for decades even though they may have paid off far more than the original loan! It is an example of how our laws are set up to benefit large businesses, not regular people.

Which, of course, brings us to the issue of efficiency, and lower costs. To what use is this efficiency, this lower cost, put? *Cui bono?* There is an argument that such efficiency could decrease the overall cost of health care to the nation, as well as to the individuals who require care, which has actually been promulgated for decades by academics and others. There are fewer of them these days, as it has been demonstrated repeatedly that such an idea is frightfully naïve. Yes, money is saved, but it is all used for greater salaries and bonuses for management and greater profits for shareholders. If it were being used to lower premiums, decrease deductibles, lower the cost of drugs, or increase the availability and affordability of health care, we would have seen it. We have not. Too bad.

A weak, but possibly useful, analogy is to a family. The adults (usually) generate the income, and certainly choose how to spend it. This can be mainly to provide food and housing, education for children, health care (to the extent that it is available) and other benefits for the family. Or it could be spent on relatively transient pleasure for the adults

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– alcohol, tobacco and other drugs, gambling, etc. Most of us feel that the first is better, a "good" thing, and the second is not good, is selfish, and even reprehensible. Apparently, such moral judgement is not applied to corporations, certainly not, in this case, those involved in "healthcare".

I keep putting "healthcare" in quotes when applied to the industry. This is because it is not an industry that is at any significant level dedicated to providing healthcare to our people; when it does, this is a byproduct. It is an industry that is dedicated to extracting the most dollars possible from the rest of the economy and putting them in their own pockets. While this is, of course, the goal of most of our industries, it seems worse that "healthcare", perhaps because of the veneer that come from ostensibly doing something good, seems to be particularly effective at it.

A single payer health insurance system only addresses coverage. A national health service, such as in Britain, is a more comprehensive manifestation of vertical integration. It doesn't always work well, mostly because it is starved of funds as a political act to demonstrate that the public sector does not run efficiently or effectively, thus an argument to privatize it, which has to some degree been done in the UK. And, like almost all efforts to privatize formerly public services, the cost goes way up, the service does not improve or gets worse, and the money that could have been used to benefit the people is lining the pockets of *ganevem*. This does not seem like a good use of benefits of efficiency and decreased cost arising from vertical integration to me.

Maybe we can do something about it! Imagine if the phrase "healthcare" industry didn't have to be in quotes!

For more (or maybe just more terse):

"The health insurance company gets a cut, the pharmacy benefit manager gets a cut, the drug manufacturer gets a cut, and the patient…gets screwed!" Rep Alexandria Ocasio-Cortez, interviewing CVSHealth CEO David Joyner at a congressional hearing.

Also *"Federal rules require the insurer to spend a certain percent on care. But, when you own the care, when the insurer owns the pharmacy, owns the PBM, owns the drug manufacturer, you also own the health care cost."*

The whole clip is not that long and makes the point about vertical integration very clear, including 1000% *markups on some drugs! Thank you, AOC!* If you have time to do nothing else, watch this video!

https://ocasio-cortez.house.gov/media/press-releases/icymi-ocasio-cortez-calls-out-cvs-healths-corporate-strategy-monopolize.

Uncovering Peer-Review Blind Spots and Their Impact on Patient Outcomes:

Non-Motor Symptoms in Myasthenia Gravis—Re-examining Historical Miscommunication That Undermines Patient Care in MG

Suzann Beaupark

Myasthenia Gravis Clinical Eye Research

"Let us not decide what is 'relevant' until the whole picture is before us" [1] *Simpson, J A, 1960*

Myasthenia Gravis is a misunderstood illness, especially when it comes to the non-motor symptoms. I published an article in the *RRNMF in December 2025* titled "Myasthenia Gravis Misunderstood—Identifying the historical misinterpretations, miscommunication, and misconceptions." [2] In this historical literature review I identified errors in the literature that have caused reverberating miscommunication about Myasthenia Gravis. This included misinformation that dismissed the existence of sensory symptoms in MG, resulting in misconceptions that continue to cause delayed diagnosis and undermine patient care.

Recently while reviewing the history of subtle eye signs that can help with earlier diagnosis of MG, I came across a 1966 paper by Dr. John Alexander Simpson. Simpson is a widely respected MG neurologist of the era, whose 1966 observations strikingly parallel one of the central arguments of my historical review.

My commentary discusses how Simpsons reflections, written sixty years ago, offer a historical lens that deepens the contemporary relevance of this issue of dismissing sensory and other non-motor symptoms in MG. His reflection provides a historical vantage that not only contextualises the issue but intensifies its relevance today.

In his 1966 article, "Myasthenia Gravis as an Autoimmune Disease: Clinical Aspects," J A Simpson stated:

> *"It appears that sensory symptoms were widely recognized until they were summarily dismissed in the classical review by Campbell and Bramwell [3] (1900)…since then, the dominance of the concept of a defect in neuromuscular transmission has led to these symptoms being largely ignored, although occasional reports continue to appear in the literature."* [4]

The 'summary' mentioned by Simpson, dismisses sensory symptoms, despite "being widely recognised," [4] is on page two of the Campbell & Bramwell report from 1900, and is titled "Salient Features of the Disease".[3] I also discussed this in my Historical review, where I highlighted the contradictory remark where the authors stated that "there are no sensory symptoms" associated with MG,[3] despite the plethora of sensory symptoms (including other non-motor symptoms), described their reported 60 case studies, mentioned in detail in the very same report.

The symptoms listed in their review included the patients reporting symptoms like the sensation of heaviness, numbness, feeling of 'stiffness' of face, neck pain, back pain, headaches, tenderness, aching limbs and jaw, severe pain in legs, facial pain, vertigo, giddiness, auditory hyperesthesia, a feeling of weakness exists without actual loss of power, high pulse rate (90-120), tongue becomes heavy, the numbness of tongue, feeling of being weighed down and of weakness and heaviness in arms and legs, a feeling of tightness of the face, a feeling of stupor with higher functions affected.[3]

Both Simpson and I wrote about how we found that this 1900 Review by Campbell and Bramwell [3] is the point in history when sensory symptoms became less frequently reported, and subsequently the statement that 'there were no sensory symptoms in MG' was repeatedly added to the literature.

The Illusory Truth Effect and Peer Review Blind Spots

This repeated exposure to incorrect information fits into the phenomena of the Illusory Truth Effect,[5] where over time this statement was believed to be true and non-motor symptoms including sensory symptoms were dismissed, both in the literature and in the clinical assessment of patients.

Simpson had documented sensory symptoms in his MG patients, and in patients of other authors of the day, including symptoms like paraesthesia, deafness or hyperacusis, facial numbness, and loss of taste or smell.[4] He also noted that occasional reports still appeared in the literature of the day, and one such report by Harvey 1948 states "That sensory disturbances may precede or accompany the first manifestations of weakness is not generally realized. Headache, pain in the eye, numbness and tingling in various regions and other sensory manifestations were described often enough to deserve some consideration."[6]

Yet because of the Illusory Truth Effect in the literature from the repeated misinformation, there was a persistent belief that MG was purely a motor disease. Patients were dismissed as 'not having MG' because the prevailing belief was that MG did not involve pain or other sensory symptoms.

Dr. John A. Simpson – MG as an Autoimmune Disease

Dr. John A. Simpson was a prominent physician known for his many contributions to the field, including his pioneering 1960 article where he hypothesized that MG was an autoimmune response.[1] In this paper he discussed how sensory symptoms in MG research were ignored or discarded as they were difficult to "reconcile with the views which have been current since attention was focussed on the phenomena

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of neuromuscular transmission." Simpson spoke of the importance of "incorporating all the clinical phenomena without exception, and of suggestion completely new lines of inquiry." He challenged the audience of his article: "Let us not decide what is 'relevant' until the whole picture is before us." [1]

In his 1977 paper, when talking about his electrophysiological studies in 1955 he wrote, "So I spent a lot of time talking to myasthenic patients – and this turned out to be a more sensitive probe as I describe!" He stated, "I decided to forget all that the textbooks had to say … and listen to the patients…noted every fact I could elicit about the previous history…including every illness whether it seemed relevant or not." He discussed that by doing this he may find that MG is a part of a multisystem disease.[7]

Dismissing non-motor symptoms in MG persists today

Non-motor symptoms in Myasthenia Gravis (MG) continue to be dismissed as "not MG" in much of the literature, despite sensory symptoms, including ocular pain, headache, paraesthesia, and the sensation of heaviness, reported throughout literature for well over one hundred years.[2, 4]

Even though the non-motor symptoms are still not well recognised in the prominent MG literature, there are recent reports in the literature today of these symptoms in myasthenia gravis causing a range of symptoms, including autonomic symptoms and other systemic symptoms. Symptoms can include but are not limited to, hearing,[8] olfactory function, [9] and taste abnormalities,[10] headaches,[11, 12] pain, [10, 11, 13, 14] tongue sensation of swelling, [15, 16] tongue sensation of heaviness,[17] paraesthesia [18], dizziness[18], cognitive impairment,[19] sleep disorders,[20] psychological involvement. [10, 13, 21] Vision blurring,[22, 23] and pupil abnormalities.[13] Urinary [24], digestive, [25] and cardiovascular dysfunction.[10, 13, 26] These often dismissed symptoms can markedly reduce quality of life of the person living with MG and, when severe, particularly in cases of cardiovascular involvement, may be life threatening.[13, 26-28] Fatigue is a non-motor symptom of MG that is more widely recognised, however the factors that contribute to fatigue developing in a person living with MG are not well understood. [21, 29]

Some recent authors are highlighting the importance of clinicians giving nonmotor symptoms the same level of attention as fatigable muscle weakness. [11, 13, 14, 28] However, despite many reports discussing non-motor symptoms in detail, it is common for patients to have these symptoms dismissed as "not MG." This dismissal of the patient's lived experience is the reason why the underlying mechanisms of non-motor symptoms in MG are still unknown, as there have been only a limited number of researchers actively looking for answers. [11, 13, 14] The prevailing MG information in the literature continues to dismiss the non-motor symptoms of MG.

Uncovering Peer Review Blind Spots and Their Impact on Patient Outcomes

In my historical review, [2] I identified six factors or gaps that have shaped today's misunderstandings of Myasthenia Gravis; issues that continue to cause difficulties in diagnosis and poor understanding of MG patient's lived experiences. They include [2]:

1) Incorrect translation of the intended meaning of the word 'gravis' causing a misinterpretation of the intended meaning for 'gravis' as being 'severe' instead of the intended meaning of 'a painful weight in the limbs'
2) Misinterpretation of meaning of 'gravis,' through miscommunication of MG severity. This also led to the incorrect use of the word 'grave' to describe MG
3) Misinterpreting the prominent MG case series paper by Campbell & Bramwell. This led to the incorrect belief that sensory symptoms are not associated with MG
4) Miscommunication of 'old knowledge' like The Mary Walker Effect [30] and of contributions by the 'MG Greats' like J A Simpson [1, 4, 7]
5) Not listening to patient lived experience
6) Failing to integrate relevant interdisciplinary knowledge to improve knowledge of MG

My argument about how continuing to highlight and analyse these types of gaps in the literature is essential for increasing our knowledge of MG and is emphasised by the invaluable insights we can draw from Simpson's work. His three papers that I have discussed in this commentary[1, 4, 7] correspond to the points 3, 4, 5, and 6 in my above-mentioned list,[2] being, misinterpreting the prominent MG case series paper by Campbell & Bramwell lead to the incorrect belief that sensory symptoms are not associated with MG; Miscommunication of 'old knowledge' like Simpson's reviews; not listening to patient lived experience and dismissing non-motor symptoms; failing to integrate interdisciplinary knowledge to improve knowledge of MG in areas like autonomic effect on MG, cardiac muscle, olfactory, taste, auditory and cognitive effects of MG.

Simpson's key message was lost in the Literature

The essential information in Simpson's papers had been lost in the literature, just as his paragraph in his 1966 article [4] where he stated the error in the Campbel Bramwell (1900) review [3] was lost in the literature.

I hope the irony of this won't also be lost in the literature…

An Autoimmune Disease – MG as a multi system disease

Simpson's hypothesis that MG is an autoimmune disease is the only part of his 1966 argument that has endured, while the rest of his insights have disappeared from the literature. His warnings about the danger of dismissing sensory symptoms simply because they did not fit the prevailing model of a disorder of neuromuscular transmission were

set aside, and this broader perspective was effectively lost in subsequent literature.

Simpson's important writings describing the importance of listening to patients and not dismissing their sensory symptoms were not heeded by mainstream researchers and MG became known as a purely motor disease. Mainstream research failed to absorb a crucial lesson: patients' sensory symptoms were real, and clinically meaningful, yet they were repeatedly set aside.

By overlooking these reported symptoms, the field drifted toward an overly narrow framework, and myasthenia gravis was ultimately defined and taught, as a purely motor disease; a characterisation that never fully reflects the patient's experience.

Restoring Lost Insights from Early Myasthenia Gravis Pioneers

Revisiting Simpson's famous papers provides more insight into MG than he has been credited with to date. His writings not only support my historical review from 2025,[2] by identifying the error in the prominent Campbel and Bramwell paper [2-4], they also provide instructions on the methodology to find the answers to the physiology of the full clinical picture of MG. These instructions are: (1) Listen to patients describe their symptoms and (2) Acknowledge the symptoms that don't appear to fit with the defect at the neuromuscular junction and (2) Be open minded to discovering other mechanisms causing the non-motor symptoms, including looking for answers outside of the neuromuscular junction, in other systems.

Much of the foundational wisdom from the early giants of MG research has faded from modern literature, and I write about this in my 2025 historical review.[2] The goal of Medicine today should be to recover and reinstate the valuable insights pioneers like Simpson left behind, ensuring that clinically meaningful observations, once well understood, are not lost to time.[2] The literature needs to be updated to acknowledge that MG is a multi-system autoimmune disease, with both motor and non-motor symptoms, and has these symptoms reported for at least 126 years.

It's time to re-examine peer review methodology

We need to encourage researchers to look to the past for errors like the ones highlighted in my 2025 historical review.[2] This will help improve our understanding of rare diseases, like Myasthenia Gravis. We still don't understand the physiology behind MG non-motor symptoms, and as Simpson teaches us the most important thing is to stop defining MG as purely a disease of the neuromuscular junction, affecting the skeletal muscles only. The undisputable fact is MG is an autoimmune disease, and there are many factors that can cause the non-motor symptoms that need further investigation.

I can't help but ponder the 'sliding door moment' possible, if 60 years ago Simpson's words were noticed and the literature had corrected this oversight. How people living with MG could have received earlier diagnosis and better care, and how this could have increased MG knowledge in every way, including in drug development. Simpson spoke about the need to stay openminded to the broader landscape of MG and the many interconnected systems involved, [1, 4, 7] yet this perspective is largely missing today at the scale and urgency needed to create meaningful change.

I also can only imagine where we would be today in the care of myasthenia gravis patients if the Campbel Branwell report never mentioned the contradictory statement that there were 'no sensory symptoms' in MG in their summary, when they went on to discuss 60 patients describing sensory symptoms and other non-motor symptoms.[2] This is significant historical error has been constantly restated in literature even today, causing difficulties in diagnosing MG, poor understanding by doctors of the patient's lived experience and undermining patient's ongoing clinical care.[2]

Imagine how many patients might have been saved over the past 60 years had Simpson's findings been heeded-or even over the past 126 years if the original case series had not been misrepresented in its summary.

Highlights - What Truly Matters

The key to clinical diagnosis and understanding diseases is to "not decide what is 'relevant' until the whole picture is before us," [1] which is an important quote by Simpson that should be a guide for all researchers and clinical interactions with patients. Physicians need to stop ignoring non-motor symptoms, by dismissing them as "not MG," when they are difficult to "reconcile with the views which have been current since attention was focussed on the phenomena of neuromuscular transmission." [1] Medicine today needs to be reminded of Simpson's original groundbreaking and subsequently correct hypothesis paper where he wrote about "incorporating all the clinical phenomena without exception, and of suggestion completely new lines of inquiry." This is what we need to emphasise today.

Medicine continues to fall short for many people living with myasthenia gravis because nonmotor symptoms are still too often dismissed as "not MG." Even though some research has begun to revisit these long ignored symptoms, the dominant clinical narrative remains narrow, and patients whose experiences extend beyond motor weakness are frequently left without recognition or meaningful support.

Non-motor symptoms need to be acknowledged in MG, as this is the only way for science to uncover the physiology behind 'all' the MG symptoms. This will help with earlier diagnosis and improved patient care. We need more research looking at the 'larger clinical picture' of MG, including all the symptoms, just as Simpson did when he developed his breakthrough hypothesis 60 years ago.

It's essential to reinstate valuable information that has been lost in the literature from the MG Greats. We truly need to do this to effectively 'stand on the shoulders of the giants' like Dr J A Simpson, ensuring that the depth, nuance,

and foundational thinking that shaped the field continue to inform and elevate our MG knowledge today.

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Analysis of sEMG amplitude temporal change during low-intensity sustained muscle contraction

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Abstract

Context: Surface electromyography (sEMG) is widely used to evaluate muscle fatigue; however, conventional amplitude- and frequency-based parameters may be insensitive to early changes during low-intensity sustained contractions.

Aims: This study aimed to characterize temporal changes in motor unit recruitment during low-intensity sustained isometric elbow flexion using conventional and higher-order sEMG analyses, with a focus on identifying how early fatigue-related changes can be detected for clinical assessment.

Settings and Design: An experimental laboratory study was conducted with healthy young adults performing sustained isometric elbow flexion at a submaximal load until task failure.

Methods and Material: Seventeen healthy adults performed sustained isometric elbow flexion at 25% of maximum voluntary isometric contraction until task failure. sEMG signals from the biceps brachii were divided into 11 equal intervals. Average amplitude, median frequency, zero-crossing rate, mean turn amplitude, kurtosis, skewness, and amplitude probability distribution function (APDF) across normalized amplitude bands were calculated.

Statistical analysis used: Temporal changes were assessed using repeated-measures ANOVA followed by Dunnett's post hoc tests ($\alpha = 0.05$).

Results: Mean endurance time was 680.3 ± 180.5 s. Average amplitude increased from the 40% interval, whereas median frequency, zero-crossing rate, and turn amplitude decreased from the 90% interval. APDF showed early reductions in low-amplitude bands (0-5% peak) and progressive increases in higher bands from the 10% interval.

Conclusions: These findings suggest that recruitment-related adjustments begin early during sustained low-intensity contraction. APDF detected such changes earlier than conventional parameters, indicating its utility for identifying early fatigue-related alterations.

Key-words: muscle fatigue, sustained low-intensity contraction, surface electromyography

Key Messages: Detailed analysis of the sEMG waveform revealed an early redistribution of amplitude from low- to higher-amplitude components that was not apparent in conventional amplitude- and frequency-based measures, indicating that conventional EMG fatigue parameters do not adequately capture early fatigue-related changes during sustained contractions.

Introduction

Surface electromyography (sEMG) is a convenient, noninvasive method for detecting muscle action potentials using electrodes placed on the skin surface. These action potentials are visualized as electromyographic waveforms and provide information about motor unit recruitment through various parameters. Typical parameters include mean amplitude, peak amplitude, integrated EMG, and spectral measures such as mean or median frequency. The integrated EMG value has been reported to reflect the number of active motor units, because it depends on the amplitude, duration, and frequency of action potentials.[1-3] Other parameters, such as zero-crossing rate[4] and turn amplitude[5-7], are selected according to the specific aims of the analysis.

In addition to these conventional parameters, several alternative approaches have been proposed to capture more detailed features of the sEMG waveform. One such method, Amplitude probability distribution function (APDF) analysis[8] evaluates muscle activity based on the probability distribution of sEMG amplitude and has been reported to reflect muscular load and function.[9, 10] Furthermore, in recently years, higher-order statistical measures[11], such as kurtosis and skewness, have been used to characterize the shape of the sEMG amplitude distribution and have shown potential in motion and fatigue analysis.[12-14] These newer parameters may provide additional information about motor unit firing characteristics that is not fully captured by simple amplitude or frequency parameters.

Many studies on muscle fatigue have traditionally used frequency in addition to the mean amplitude value. During moderate to high-intensity exertion, fatigue is often accompanied by two well-known electrophysiological phenomena: increase in amplitude reflecting motor unit recruitment and decrease in the median frequency. However, during low-intensity sustained contractions, only a small number of motor units are recruited to generate the required force, and these units can recover between activation intervals. As a result, force production is sustained for a long time, and conventional parameters based on amplitude and frequency reveal only subtle or delayed changes. This makes it difficult to detect temporal changes in motor unit recruitment under such conditions. Given these limitations, it is necessary to re-examine the characteristics of sEMG parameters observed during low-intensity, sustained isometric muscle contractions. Therefore, in this study, not only conventional fatigue-related parameters (mean amplitude, median frequency, zero-crossing rate, turn amplitude) but also higher-order statistical indicators (kurtosis and skewness) and temporal changes in amplitude distribution were calculated from surface electromyography waveforms during low-intensity sustained isometric elbow flexion. This reveals the characteristics of the temporal changes in each parameter, enabling the elucidation of the characteristics of motor unit recruitment regulation occurring during sustained contraction.

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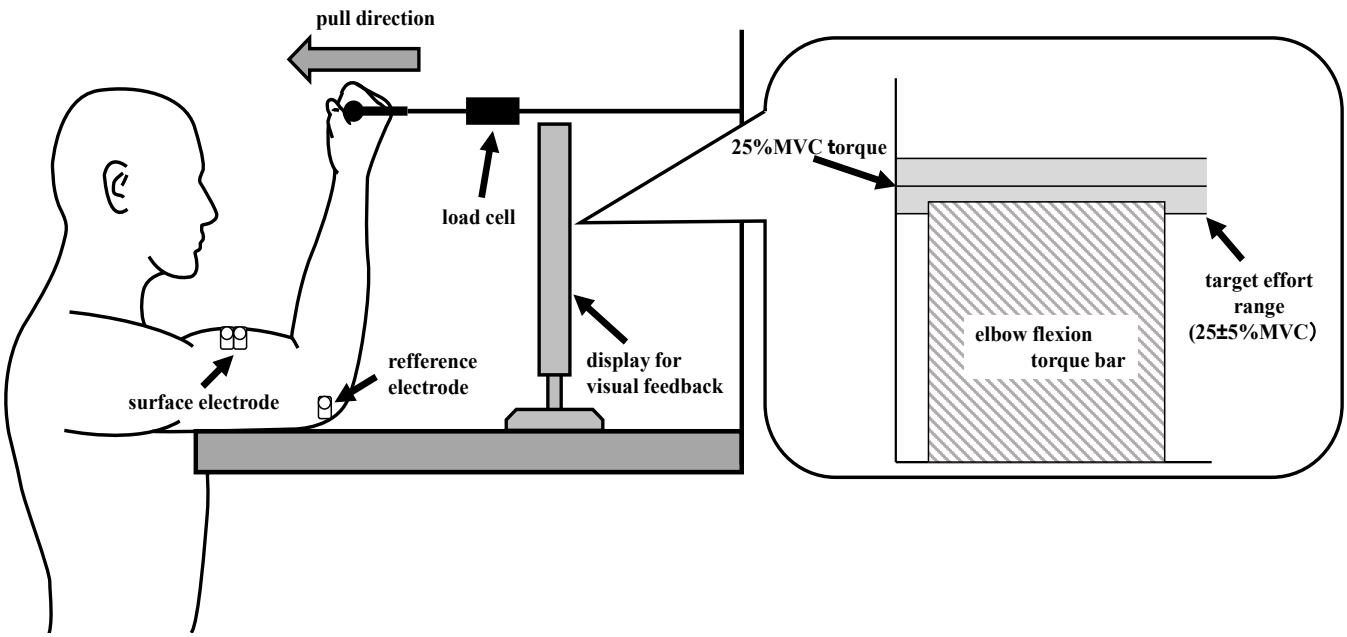
Figure 1: Experimental setting.
The participants sat in a chair, gripped a handle, and performed isometric elbow flexion with visual feedback of their force output.



Given these limitations, there is a need to re-examine motor unit recruitment regulation during low-intensity, sustained contractions using a broader set of sEMG parameters. Therefore, in this study, not only conventional fatigue-related parameters (mean amplitude, median frequency, zero-crossing rate, turn amplitude rate) but also higher-order statistical parameters (kurtosis and skewness) and temporal changes in amplitude distribution derived from sEMG waveforms during low-intensity sustained isometric elbow flexion were analyzed. By performing a detailed, time-resolved analysis of these parameters over the entire duration of the task, the aim of this study was to elucidate changes in motor unit recruitment regulation during sustained low-intensity isometric elbow flexion and to clarify how early such changes can be detected in the sEMG waveform. Such knowledge may serve as a basis for designing strengthening programs that minimize excessive load in individuals with muscle weakness and help reduce the risk of overuse.

Participants and Methods

Participant

This study involved 17 healthy young adults (seven females and ten males). The characteristics of the participants are shown in Table 1. Individuals with functional impairments of the dominant arm due to previous injury or disease were excluded. All participants received oral and written explanations of the study procedures and provided written informed consent before participation.

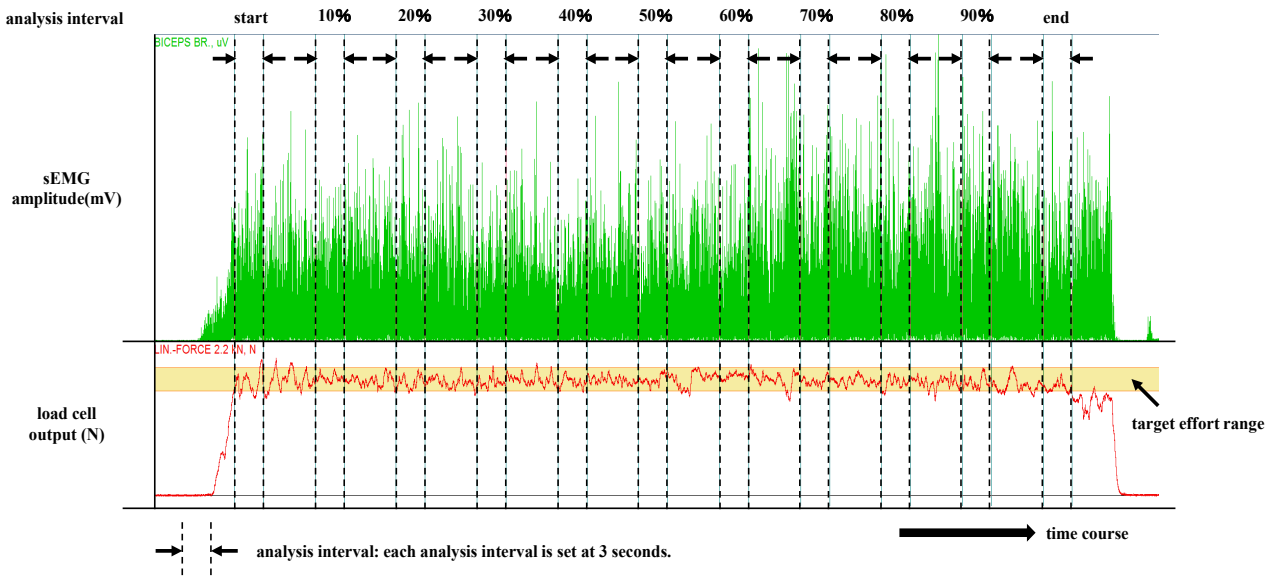
Table 1: Age and anthropometric data of participants

Age (years)	21.6 (0.6)
Height (cm)	163.8 (7.9)
Weight (kg)	55.9 (7.9)

Experimental procedure

Surface electromyography (sEMG) data were recorded from the biceps brachii muscle on the dominant side using a portable EMG system (MyoTrace 400, Noraxon Corp., Arizona, USA) with a sampling rate of 1000 Hz and an analog bandwidth of 10-500 Hz. The skin over the muscle belly was prepared using an abrasive skin preparation gel (Skin Pure, NIHON KOHDEN Corp., Tokyo, Japan). Ag/AgCl surface electrodes (BlueSensor N-00-S, Ambu Corp., Copenhagen, Denmark) were placed over the mid-portion of the muscle belly, parallel to the muscle fiber orientation, with an inter-electrode distance of 2 cm. The reference electrode was placed over the lateral epicondyle of the humerus. This inter-electrode distance and bipolar configuration are commonly used in surface EMG recordings to reduce cross-talk while maintaining an adequate myogenic signal.[15] After electrode placement, inter-electrode impedance was measured; if it exceeded 5 kΩ, as recommended by the International Society of Electrophysiology and Kinesiology (ISEK), skin

Figure 2: Analysis interval setting.
The time period during which the load cell output was maintained within the target effort range was identified, and the eleven 3-s analysis intervals were positioned so that they were evenly distributed within this period.



preparation and electrode placement were repeated until the impedance was below this threshold.

Participants sat on a chair without a backrest and placed their dominant upper limb on a height-adjustable table. The table height was adjusted so that the shoulder joint was flexed to approximately 90°. The elbow joint was flexed to 90°, and the forearm was positioned in 90° supination. A grip handle connected to a wall-mounted force transducer was held in the hand (Figure 1). To determine maximal voluntary isometric contraction (MVIC) force of the biceps brachii, participants were instructed to pull the grip handle with maximal effort for 5 s while maintaining the standardized posture. Three MVIC trials were performed with at least 3 min of rest between trials, and the higher force value was defined as the MVIC force. This value was used to set the target force corresponding to 25% MVIC for the sustained contraction task. A target level of 25% MVIC was based on previous reports that low-intensity contractions in the range of approximately 10-30% MVIC can induce localized muscle fatigue while allowing prolonged performance, and because such contraction levels are representative of many occupational and rehabilitation tasks.[16, 17] After at least 5 min of rest to minimize the influence of prior exertion, participants performed the sustained low-intensity contraction task. They were instructed to pull the grip handle to match and maintain 25% of their MVIC force, which was displayed in real time on a monitor. Fluctuations within ±5% of the target force were permitted during the task. Therefore, each participant maintained 20-30% of their MVIC throughout the task. Data recording was continued while participants maintained the force within this range. Task failure was defined as the inability to maintain the target force within ±5% for at least 5 s, consistent with the definition of muscle fatigue as a failure to sustain the required force. The sustained contraction task was performed once per participant to avoid carry-over effects of fatigue from repeated long-duration contractions; this single-trial design is acknowledged as a limitation with respect to test-retest reproducibility and is addressed in the Discussion.

Data Analysis

For each participant, the total task duration from the onset of the sustained contraction to task failure was divided into ten equal intervals, and eleven equally spaced 3-second analysis intervals were defined at 0% (start), 10%, 20%, …, 90%, and 100% (end) of the total duration. The peak sEMG amplitude obtained during the MVIC task was used as the reference amplitude. For APDF analysis, the amplitude range from 0% to 100% of this peak amplitude was divided into amplitude components with 2.5% intervals, and the APDF value for each component was calculated as the ratio of the number of data points within that component to the total number of data points measured from the start to the end of the task (Figure 2). In addition to APDF, the following conventional sEMG parameters were calculated for each analysis interval: mean amplitude, median frequency, zero-crossing rate, and turn amplitude. Higher-order statistical parameters, kurtosis and skewness of the amplitude distribution, were also computed as exploratory measures of distribution shape. Changes in APDF, mean amplitude, and median frequency were considered primary outcomes, whereas zero-crossing rate, turn amplitude, kurtosis, and skewness were treated as secondary or exploratory outcomes. Temporal changes across the eleven intervals were assessed using one-way repeated-measures analysis of variance (ANOVA) for each parameter.

Table 2: Temporal change of sEMG parameters during 25%MVC sustained muscle contraction

	start	10%	20%	30%	40%	50%
Mean Amplitude					*	**
(mV)	87.9 (36.0)	125.9 (48.4)	145.8 (66.6)	154.9 (56.9)	166.6 (57.4)	186.8 (66.5)
Median Frequency						
(Hz)	59.2 (11.3)	58.2 (9.8)	56.9 (8.2)	55.6 (8.4)	56.2 (8.2)	55.7 (8.8)
Zero-crossing rate						
(times/sec)	72.8 (14.0)	72.5 (10.3)	72.3 (8.0)	71.4 (8.6)	70.1 (9.0)	69.9 (8.5)
Turn Amplitude						
(times/sec)	264.8 (38.0)	264.6 (24.9)	267.9 (21.0)	267.8 (24.8)	262.4 (29.2)	260.7 (28.3)

	60%	70%	80%	90%	end
Mean Amplitude	**	**	**	**	**
(mV)	200.5(56.7)	229.3 (63.0)	267.2 (97.0)	286.5 (97.0)	323.4 (144.7)
Median Frequency				*	**
(Hz)	54.3 (7.4)	54.4 (8.6)	53.2 (9.9)	50.5 (9.8)	47.9 (10.4)
Zero-crossing rate				*	**
(times/sec)	69.1 (7.8)	68.0 (7.9)	64.8 (9.3)	61.4(10.4)	59.2 (10.7)
Turn Amplitude				**	**
(times/sec)	254.0 (30.1)	248.5 (29.1)	244.2 (30.8)	228.1 (30.7)	221.9 (41.9)

mean (standard deviation) *: $p<0.05$, **: $p<0.01$

If a significant main effect of time was detected ($\alpha = 0.05$), Dunnett's post hoc test was applied to compare each analysis interval with the start interval. Because multiple parameters and APDF components were examined, the analyses were considered exploratory, and the increased risk of type I error due to multiple comparisons was acknowledged as a limitation when interpreting statistically significant findings. The procedures for this study were conducted with the approval of the research ethics committee of Seijoh University (2023C0007).

Results

Average time from start to finish of the experimental task The mean duration for which participants were able to maintain 25% MVIC was 680.3 ± 180.5 s.

Mean amplitude, median frequency, zero-crossing rate, and turn amplitude

Mean amplitude showed a significant increase from the 40% analysis interval onward ($p < 0.05$), whereas median frequency, zero-crossing rate, and turn amplitude showed significant decreases from the 90% analysis interval ($p < 0.05$; Table 2).

Kurtosis and skewness

There were no significant temporal changes in either kurtosis or skewness across the analysis intervals (Table 3).

APDF analysis

Table 4 summarizes the statistical significance of APDF values at each analysis interval relative to the start interval. The APDF values of the lowest amplitude components (0-2.5% and 2.5-5.0% of peak amplitude) decreased as the task progressed, whereas the APDF values of components at 5.0% of peak amplitude and above increased. The APDF values of the three components below 7.5% of peak amplitude already showed significant changes at the 10% analysis interval compared with the start interval. Furthermore, the 7.5-10.0% peak amplitude component began to increase significantly from the 30% analysis interval, and other higher-amplitude

Table 3: Temporal change of kurtosis and skewness of sEMG amplitude value during 25%MVC sustained muscle contraction

	start	10%	20%	30%	40%	50%
Kurtosis	0.95(0.76)	0.86(0.69)	1.86(0.66)	0.77(0.49)	0.77(0.49)	0.94(0.82)
Skewness	0.014(0.228)	-0.012(0.178)	0.051(0.198)	0.021(0.198)	0.024(0.234)	0.064(0.220)

	60%	70%	80%	90%	end
Kurtosis	0.90(0.82)	0.73(0.61)	0.90(0.73)	1.12(0.69)	0.88(0.61)
Skewness	-0.060(0.207)	-0.004(0.207)	-0.023(0.178)	-0.122(0.223)	-0.036(0.213)

mean (standard deviation)

Table 4: Statistical significance of each analysis interval relative to the start interval

	10%	20%	30%	40%	50%	60%	70%	80%	90%	end
0-2.5%peak	*	**	**	**	**	**	**	**	**	**
2.5-5.0%peak	**	**	**	*						
5.0-7.5%peak	*	**	**	**	**	**	**	**	**	**
7.5-10.0%peak			**	**	**	**	**	**	**	**
10.0-12.5%peak				*	**	**	**	**	**	**
12.5-15.0%peak					*	**	**	**	**	**
15.0-17.5%peak						*	**	**	**	**
17.5-20.0%peak							**	**	**	**
20.0-22.5%peak								**	**	**
22.5-25.0%peak								**	**	**
25.0-27.5%peak								**	**	**
27.5-30.0%peak								*	**	**
30.0-32.5%peak								*	*	**
32.5-35.0%peak									**	**
35.0-37.5%peak								*	*	**
37.5-40.0%peak									*	**
40.0-42.5%peak									*	**
42.5-45.0%peak										**
45.0-47.5%peak										**
47.5-50.0%peak										**

*: $p<0.05$, **: $p<0.01$

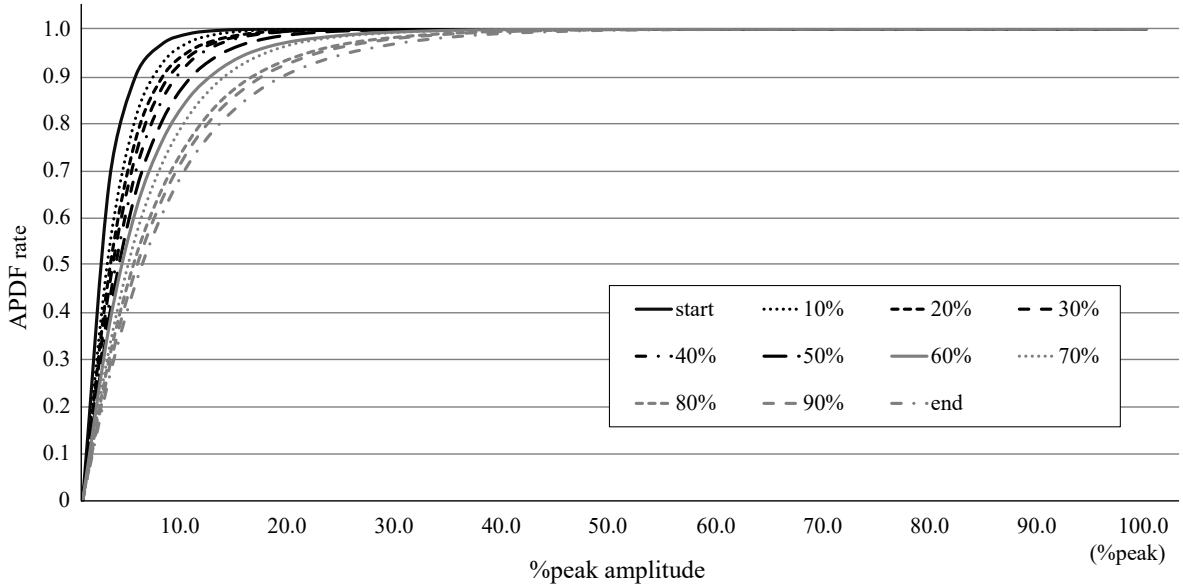
components also showed significant temporal increases in ascending order of their ratio to the peak amplitude. These APDF curves exhibited systematic changes over time without intersecting each other (Figure 3).

Discussion

Muscle fatigue has been defined as a "failure to maintain the required or expected force"[18]. In accordance with this definition, the task in the present study was continued until participants were unable to maintain 25% of their maximum voluntary output. Performing at a low output relative to maximum output results in the recruitment of a relatively small number of motor units. Once a motor unit has been activated, it has sufficient time to recover before being activated again. Consequently, sustained output must be maintained for a relatively long time before task failure occurs. In this study, the mean task duration was approximately 680 s, indicating that the applied load represented a typical low-intensity, long-duration condition rather than a short, high-intensity fatigue task.

To maintain muscle output at a constant level, it is necessary to constantly alter the number of motor units recruited. This regulation consists of a combination of recruitment, firing rate and synchronization, and muscle activity potentials constantly alter during task execution.[19, 20] Despite the progression of muscle fatigue, the maintenance

Figure 3: Temporal change of each amplitude component of APDF
The occurrence frequency of high-amplitude components gradually increased as the task progressed.



of constant muscle output indicates that the demands on the muscles for task performance are increasing. In such cases, the firing rate shifts from low to high, and the motor unit recruitment pattern shifts from asynchronous to synchronous. These mechanisms cause an increase in amplitude values[21] and delays in sEMG waveforms. Chafin[22] reported that sustaining 11% of maximum voluntary contraction force for 1 to 5 minutes slowed the conduction velocity of action potentials along muscle fiber directions and reduced muscle action potential and twitch frequencies. Such muscle fatigue is thought to be related to insufficient blood flow to the muscles, depletion of energy sources, and accumulation of metabolic products (excess hydrogen ions) in muscle tissue.[1] Therefore, when it is necessary to maintain sustained muscle contraction, two electrophysiological phenomena are often observed before the target output can no longer be maintained due to muscle fatigue. One is an increase in amplitude indicating an increase in the number of motor units recruited, and the other is a decrease in the average frequency of the sEMG waveform power spectrum.[21]The present findings partly agree with this classical pattern but also highlight important differences at low intensity. Mean amplitude showed a significant increase from the 40% analysis interval, whereas median frequency showed a significant decrease only from the 90% interval. According to conventional EMG fatigue parameters, this pattern would suggest that fatigue-related changes became clearly apparent only in the late phase of the task. Zero-crossing rate and turn amplitude also showed significant decreases from the 90% interval, similar to median frequency. Because zero-crossing rate and turn amplitude measures reflect the rate of polarity changes in the waveform, they are closely related to the frequency content of the sEMG signal and therefore behaved similarly to median frequency. These results confirm that traditional amplitude- and frequency-based parameters can detect fatigue-related changes even during low-intensity sustained contractions, but primarily when the performance is close to failure.

In contrast, higher-order statistical parameters (kurtosis and skewness) did not exhibit significant temporal changes during the low-intensity sustained contraction. Previous studies have reported that kurtosis tends to approach a Gaussian distribution as contraction intensity increases and that changes in kurtosis may reflect the ability to maintain a constant contraction level.[14, 23] In the present study, however, a constant low isometric tension was maintained, and the variability of the amplitude distribution may have been too small for kurtosis and skewness to detect systematic temporal changes. This suggests that higher-order statistics, at least in their conventional form, may have limited sensitivity for tracking fatigue-related changes under low-intensity, long-duration conditions.

On the other hand, APDF analysis revealed changes that were not apparent in these conventional parameters. The APDF values of the lowest amplitude components (0-2.5% and 2.5-5.0% of peak amplitude) decreased significantly from the 10% analysis interval, while those of the slightly higher components (5.0-7.5% of peak amplitude) increased significantly from the same early stage. Subsequently, significant increases were observed sequentially in components with higher peak amplitude ratios. This pattern indicates a gradual redistribution of the sEMG amplitude toward higher levels over time, even though traditional amplitude and frequency parameters only showed marked changes in the late phase of the task. In other words, detailed analysis of the amplitude distribution suggested that adjustments in motor unit recruitment regulation begin early during

sustained low-intensity contraction, whereas conventional EMG fatigue parameters mainly reflected the later stages of these changes.[24, 25] From a physiological perspective, the early decrease in low-amplitude components and the progressive increase in higher-amplitude components may reflect a gradual increase in the number and/or size of recruited motor units as fatigue develops in initially active units. Under low-intensity conditions, force can be maintained for a long time by rotating the active motor unit pool and by recruiting additional motor units when needed. The present APDF results support the notion that this adjustment process begins long before conventional fatigue parameters indicate a clear change, and that the surface EMG waveform contains subtle information about motor unit recruitment regulation that is not captured by global amplitude or spectral measures alone.[26] Taken together, these findings indicate that during low-intensity sustained elbow flexion at 25% MVIC, neuromuscular adjustments related to motor unit recruitment occur much earlier than suggested by conventional EMG fatigue parameters. Mean amplitude and spectral parameters showed prominent changes only in the late phase, whereas the amplitude distribution began to shift toward higher levels soon after the onset of the task. Such knowledge may serve as a basis for designing strengthening programs that minimize excessive load in individuals with muscle weakness and help reduce the risk of overuse in low-intensity, long-duration tasks.[17, 27]Conclusion

The present study demonstrated that adjustments in motor unit recruitment regulation during sustained low-intensity isometric elbow flexion at 25% MVIC occur from the early phase of the contraction. These early changes were only minimally reflected in conventional EMG fatigue parameters, which showed pronounced alterations mainly in the late phase of the task, but were clearly detected by a detailed analysis of the amplitude probability distribution of the sEMG waveform. The observed early decrease in low-amplitude components and progressive shift of the amplitude distribution toward higher levels indicate that subtle adjustments in motor unit recruitment are already taking place while global amplitude and spectral parameters remain relatively stable.

This finding suggests that reliance on traditional mean-value and spectral parameters alone may obscure early fatigue-related changes during low-intensity, long-duration contractions, and underscores the utility of amplitude-distribution-based analyses for capturing these phenomena. Although the present investigation was conducted in healthy young adults, it is reasonable to assume that in individuals with muscle weakness or reduced endurance capacity, similar neuromuscular adjustments would occur earlier for a given absolute load, leading to an earlier increase in the proportion of higher-amplitude components and a greater local mechanical load, which may contribute to overuse. Such knowledge may serve as a basis for designing strengthening and exercise programs that minimize excessive load in vulnerable populations and help reduce the risk of overuse during low-intensity, long-duration tasks. Future studies should extend this approach to moderate- and high-intensity contractions and to other muscle groups in order to further elucidate the intensity dependence of motor unit recruitment regulation and to refine objective EMG-based parameters for safe load prescription in clinical and occupational settings.

Limitations

This study has several limitations. First, the sample size was small and limited to healthy young adults, so the generalizability of the findings to older or clinical populations and to other muscles is uncertain. Second, only one sustained contraction trial was performed per participant, which prevented assessment of test-retest reliability and the stability of the observed changes. Third, bipolar sEMG recordings were obtained from a single muscle with a bandwidth of 10-500 Hz and a sampling rate of 1000 Hz, which may not capture all low- and high-frequency components and limits inferences about other muscles or recording configurations. Fourth, multiple parameters and APDF components were analyzed within the same repeated-measures ANOVA framework, increasing the risk of type I error and reinforcing the exploratory nature of the statistical analysis. Finally, the task involved only sustained isometric elbow flexion at 25% MVIC; therefore, caution is needed when extrapolating these results to dynamic or task-specific activities in occupational or rehabilitation settings.

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Online Patient Ratings of a Neuromuscular Outpatient Practice: A Retrospective Study

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Abstract

Objectives: Online physician ratings increasingly influence patient choice, yet their trustworthiness and generalizability remain uncertain, particularly in complex specialties such as neuromuscular medicine. Only 5% of patients post reviews, but nearly 40% use online feedback to select physicians.

Methods: We retrospectively analyzed 218 reviews with star ratings posted between May 2016 and June 2025 for a single outpatient neuromuscular practice. Identifiable reviewers were matched to practice records to append referral, diagnostic, and demographic data. Quantitative and thematic analyses were performed.

Results: Among 218 reviews, 182 (83.5%) were positive and 36 (16.5%) negative. Negative themes included feeling dismissed, perceived rudeness, and rushed visits, while positive reviews emphasized thoroughness and effective care. Identifiable negative reviewers were predominantly White female patients (mean age 41) who commonly reported overlapping symptoms including pain, fatigue, motor difficulties, and sensory disturbances. Anxiety or depression was reported in 44.4% of identifiable reviewers.

Conclusions: Online reviews primarily reflect patient experience rather than clinical quality of care or physician competence. Structural pressures—time constraints, diagnostic expectations, and tertiary-care complexity—likely shape negative feedback and should be considered when interpreting online ratings.

Key words: Online physician reviews; patient satisfaction; patient experience; health care quality

Introduction

The growing digital ecosystem has transformed the way patients evaluate and select their physicians. Online platforms have become a primary source of information, and words posted on the internet can have a significant influence across all industries, including health care. Patients are increasingly prioritizing online reviews over referrals and personal recommendations.[1] These reviews are often utilized in medicolegal settings, including legal depositions, to build cases against physicians.[2] Neurology is a branch of medicine that is particularly vulnerable to perception of negligence due to the challenging nature of diagnosing and managing long-term, complex diseases. Physicians in this field are often presented with patients experiencing non-specific, prolonged symptoms that often complicate diagnostic certainty and shape patient expectations. Approximately 22% of neurologists have been sued at least once during their careers.[3] As digital platforms continue to evolve and influence user opinions, especially in healthcare, it is important to study and understand how these changes affect the medical field and how online reviews correlate with physicians' reputations, qualifications, and quality of care, particularly in complex clinical specialties.

Studies show that online physician rating platforms are rapidly growing, with approximately one in six physicians having an online rating.[4] Prior research has demonstrated that patients with positive experiences comprise the "silent majority," while a small number of negative reviews can skew perceptions and influence potential patients.[1] In fact, 40% of patients have switched providers due to negative online reviews, but it is estimated that only 5% of patients take the time to write provider reviews themselves.[1,5] Some medical fields, like neurology, are defined as "high-risk specialties" in regard to garnering negative online reviews, because they manage complex conditions that are less likely to have curative solutions and frequently consult on patients who have not found relief from multiple providers.

Recent research suggests that negative online reviews do not correlate with formal measures of patient satisfaction.[6] Instead, most negative reviews from non-surgical patients focus on non-clinical aspects of care, including communication, office staff, and wait times.[7]

Limited research has examined how gender or other demographic factors influence online physician reviews. Available data indicates that females write 60% more reviews than males, and males are more likely to leave negative reviews.[8] Studies also indicate that female patients are more likely to report disrespect from male physicians—but not from female physicians—and that women more frequently comment on soft skills.[8] However, most gender-based studies rely on qualitative analysis, making it challenging to determine whether reviews accurately reflect real experiences or are influenced by gender-based bias.[8]

Online physician ratings in neurology-related specialties appear to be largely driven by patient perception of physician competence, bedside manner, and office-related factors, with negative comments disproportionately influencing overall scores.[9] Despite this, these platforms are increasingly used by patients when forming impressions of physicians, highlighting their growing influence in clinical decision-making, and in turn, underscoring the importance of understanding factors that shape patient perception. The objective of this retrospective, non-interventional quality improvement project was to evaluate the implications of negative online

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reviews on an outpatient neuromuscular medical practice and to assess the credibility, themes, and potential biases present within these comments.

Materials and Methods

This retrospective, non-interventional study analyzed online patient feedback posted between May 2016 and June 2025 from an outpatient neuromuscular practice. This neuromuscular practice is a tertiary care center, primarily accepting referrals from other neurologists to confirm or assist with complex patient diagnoses. The neuromuscular conditions diagnosed and treated at this practice include, but are not limited to, neuropathies, myopathies, chronic inflammatory demyelinating polyneuropathy (CIDP), myasthenia gravis (MG), and amyotrophic lateral sclerosis (ALS). The practice studied is independent and employs one neuromuscular specialist and ten health care and clinical research professionals.

A total of 221 reviews were collected from seven platforms: Google Reviews, Vitals, Rated, Healthgrades, Birdeye, WebMD, and Yelp. Reviews without star ratings (n=3) were excluded to allow for quantitative and qualitative analysis, leaving 218 reviews for analysis. Reviews were included if they were publicly posted on one of the identified platforms, pertained to the neurologist or the practice, and contained a numerical star rating.

Reviews were classified using the standard 5-star rating system, where negative reviews consisted of 3 stars or fewer, and ratings of 4-5 stars were defined as positive. A total of 36 negative reviews (16.5%) and 182 positive reviews (83.5%) were identified. Among the 36 negative reviews, 18 lacked sufficient identifying information and were excluded from demographic analysis (e.g., age, gender, and symptoms) but were retained for thematic analysis.

The star rating served as the primary quantitative measure, condensing healthcare experiences into a numerical value. Qualitatively, written comments were analyzed for patterns related to soft skill categories (communication, bedside manner), practice-related factors (wait times, office management), and reviewer profiles (gender, age, and presenting symptoms when identifiable).

Quantitative data analysis was collected and organized using Microsoft Excel. Figures were generated using Microsoft Word's chart creation and editing features. Qualitative analysis involved manually reviewing comments for recurring themes to overall patient experience. The primary outcome was characterization of thematic and demographic patterns in online reviews, particularly negative, of a neuromuscular practice. Language editing assistance was used during manuscript preparation; all content, analysis, and interpretation were reviewed and verified by the authors.

This study involved analysis of publicly accessible online information and was conducted in accordance with institutional quality improvement (QI) guidelines. A limited retrospective review of clinical records was performed solely to confirm identity matching and to validate the clinical context of the publicly available reviews. Only de-identifiable and summary-level information was recorded for analysis, and no protected health information was included in the study dataset. No direct patient contact occurred. Since this project was determined to be a quality improvement analysis using publicly available data with limited clinical record validation, formal IRB review was not required under institutional policy.

This project aimed to evaluate demographic and thematic patterns of reported patient experiences in online reviews of a tertiary neuromuscular clinic. Understanding these patterns may help identify areas of miscommunication between patients and providers and highlight the limitations of heavily relying on online reviews when forming impressions of care, especially in specialized neuromuscular clinics.

Results

Of the 218 reviews analyzed, 196 (89.9%) originated from Google Reviews, with the remaining reviews distributed across the six additional platforms. Overall, 182 reviews (83.5%) were positive, and 36 reviews (16.5%) were negative.

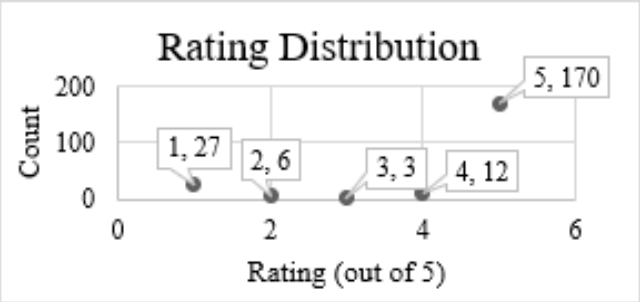


Figure 1. Distribution of online review ratings (N=218). Ratings are heavily skewed toward positive scores, with a clear peak at 5 stars.

From a qualitative perspective, the most common negative themes included perceived lack of empathy, rudeness, and rushed encounters (Figure 2). These findings contrast with positive reviews, which frequently emphasized the physician's thoroughness and effective care (Figure 3). Less frequent complaints involved procedural discomfort, concerns about misdiagnosis, and operational issues such as follow-up or billing. Some negative feedback also reflected frustration with outcomes or system-level factors beyond the physician's control, including parking expenses and travel times.

Figure 2. Negative review tags by frequency (n = 34). Negative reviews were thematically coded, with multiple tags allowed per review. The most frequent themes were perceived lack of empathy or dismissive behavior (21, 61.8%) and poor communication (18, 52.9%). Other reported concerns included inadequate clinical evaluation, diagnostic and treatment concerns, and office or staff professionalism. Less frequently cited issues included billing, privacy, ethical concerns, and access burden.

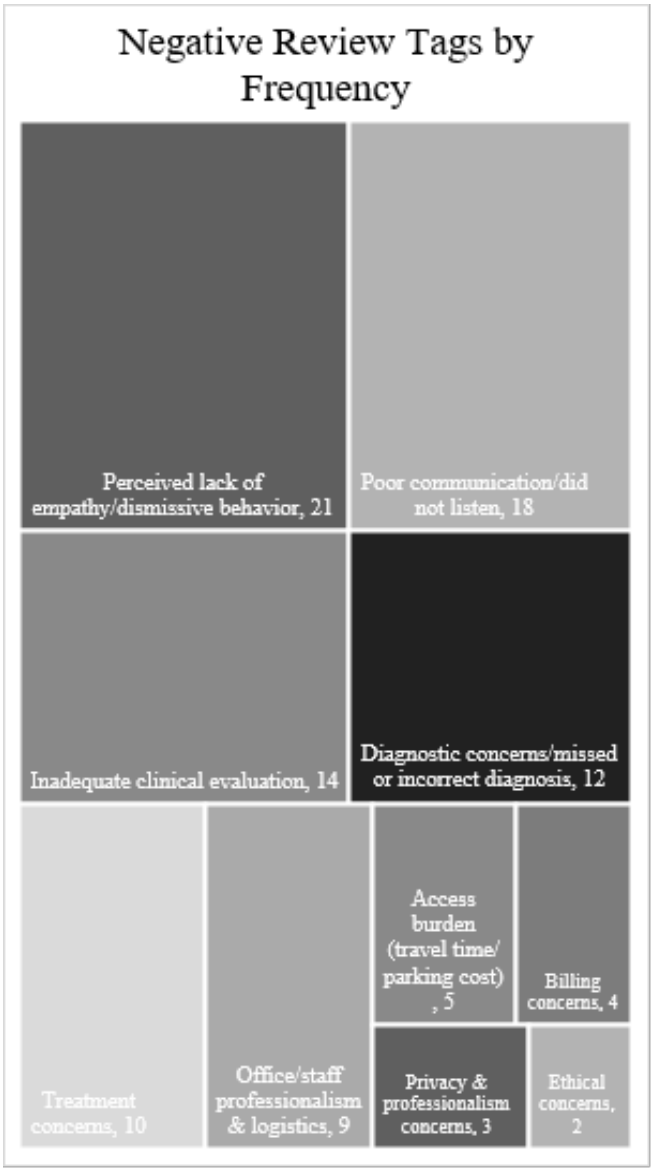
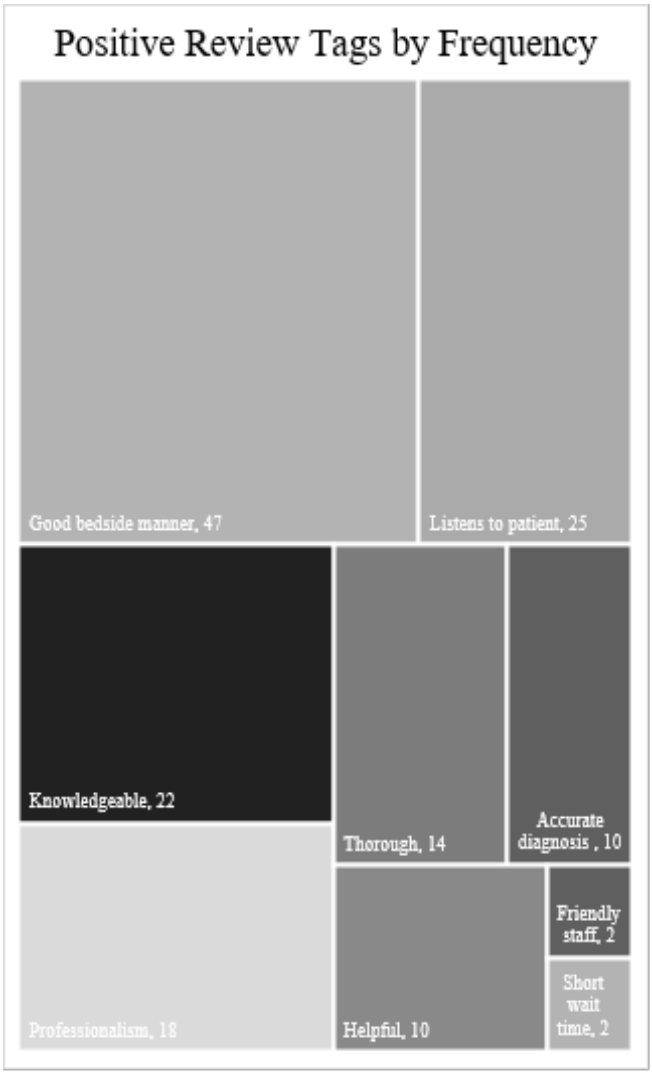


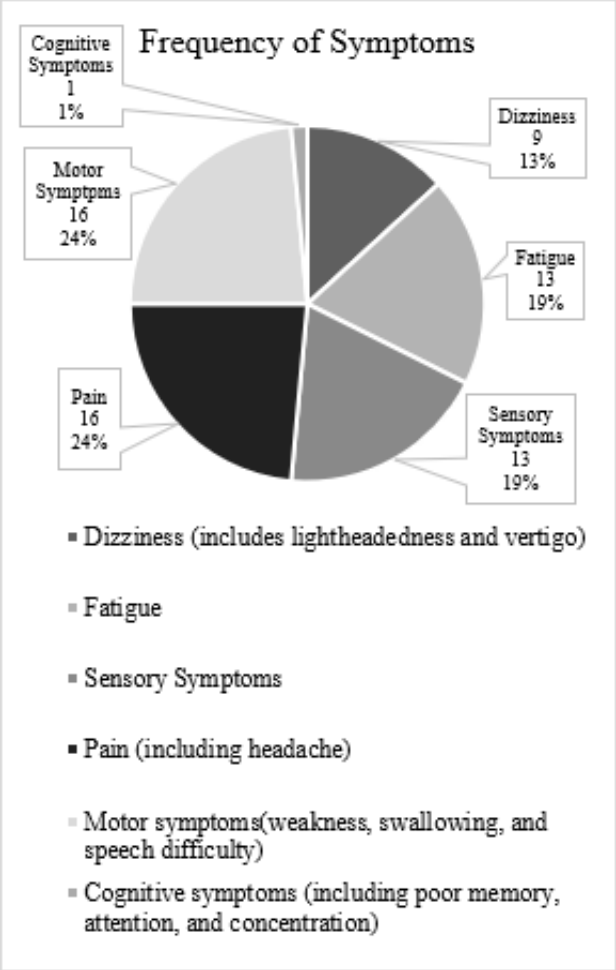
Figure 3. Frequency of positive review themes in online reviews (n = 150). The most frequently cited theme was good bedside manner (n=47), followed by listening to patients, knowledge, and professionalism. Less frequently mentioned themes included friendly staff and short wait time.



While these themes were common within negative reviews, they represented a minority of the overall feedback, which was predominantly positive. Several negative comments appeared inconsistent with the physician's clinical documentation. These discrepancies suggest that a subset of negative reviews may reflect a lack of satisfaction with communication or other non-clinical aspects of care rather than clinical decision-making.

When examining reported symptoms, most individuals mentioned pain, fatigue, motor difficulties, and sensory disturbances—symptoms that are often subjective and multifactorial (Figure 4). These symptoms were collected from a pre-visit patient questionnaire completed prior to physician evaluation. Among the identifiable reviewers, 13 of 18 reported both fatigue and pain, and 12 of 18 reported both motor and sensory symptoms. Some patients also reported co-occurring symptoms of anxiety or depression (44.4%).

Figure 4. Distribution of symptoms among identifiable reviewers (n = 18). Pain and motor symptoms were most frequently reported (16/18, 88.9%), followed by fatigue and sensory symptoms (13/18, 77.2% each). Dizziness was reported by 9/18 (50%), and cognitive concerns were rare and therefore underestimated (1/18, 5.6%).



The demographic data of negative reviews showed a gender skew toward female reviewers (12/18). Among female reviewers, six were under 40 and six were over 40, whereas all identifiable male reviewers (6/18) were over 40 (Figures 5 and 6). The majority of reviews were posted by White patients (74%) (Figure 7).

Figure 5. Gender distribution of identifiable reviewers (n = 18). Most reviewers were female (12/18, 67%), while males comprised 33% (6/18).

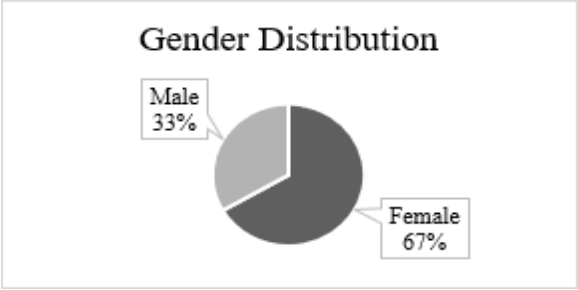


Figure 6. Average age of identifiable reviewers by gender (n = 18). Female reviewers had a mean age of 41 years (6/12 under 40), while male reviewers had a mean age of 66.2 years (6/6 over 40).

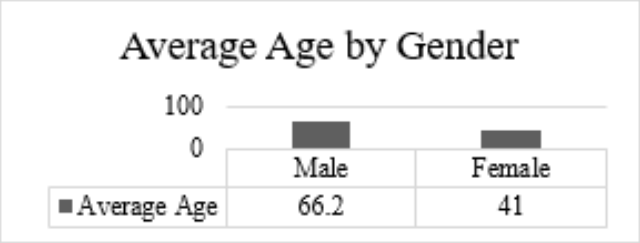
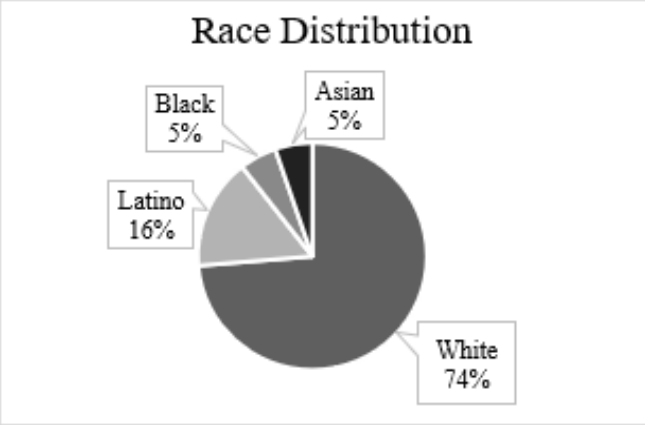


Figure 7. Racial distribution of identifiable reviewers (n = 18). Most reviewers were White (14/18, 74%); remaining reviewers belonged to other racial groups. Racial data were available for 18 of 36 negative reviews.



Among the 36 negative reviews, 18 (50%) lacked sufficient identifiable information to determine age, gender, race, or symptoms. In some cases, negative reviews were followed by contact from alleged IT companies soliciting payment to remove the comments. Among identifiable reviews, White female reviewers (mean age 41) accounted for a significant proportion of negative ratings. Reported symptoms in this group commonly included fatigue, dizziness, and pain.

Discussion

Our observations support prior studies' conclusion that online physician ratings do not accurately reflect a physician's competence or the quality of care provided. The skewed distribution of ratings, the non-representative demographic sample, and the subjective nature of many comments question the reliability of online reviews as an objective indicator of physician performance. Online review systems have proven to be unreliable.[10] Often, comments are biased and not based on real experiences but rather written with the intention of harming or promoting an establishment.[10]

Many negative reviews focused more on office interactions and perceived bedside manners than on clinical decision-making or treatment outcomes. These findings are especially relevant in neuromuscular medicine, where clinicians manage more diagnostically complex cases than many other specialties.[11] Neuromuscular diseases are rare and often difficult to evaluate because of the overlapping and variable symptoms that mimic other diseases.[12] The rarity of most neuromuscular diseases (90%) limits the exposure and familiarity in many primary care settings, leading to prolonged diagnosis.[13] Patients are referred to a tertiary neuromuscular clinic for highly specialized care not typically available in general medical settings, often after seeing multiple providers and experiencing chronic, progressive symptoms and prior unsuccessful diagnoses or treatments.

Patients' elevated expectations from being referred to a tertiary center with specialized expertise may have contributed to their perception that care was "below expected," particularly when patients are seeking diagnostic confirmation or symptom relief after prolonged uncertainty. This is consistent with our findings that many negative reviews reflect dissatisfaction with diagnoses or outcomes, even when appropriate diagnostic procedures and treatment protocols were followed. Patients are often frustrated when informed that no clear neurological explanation can be identified for their symptoms, even though this may be the correct conclusion based on available evidence. Increased access to online health information has contributed to greater self-directed symptom interpretation and self-diagnosis, which may influence patient expectations and contribute to heightened sensitivity.[14] Prior research has shown that complaints from patients with functional neurological disorders often stem from disagreement with the diagnosis, making the concerns difficult to resolve.[15]

In some cases, dissatisfaction arises when patients do not receive confirmation of a long-standing diagnosis that carries implications for disability benefits or ongoing costly therapies, particularly when insurance coverage was limited. For these individuals, their life was centered around a specific diagnosis for years and revising that diagnosis could be inconvenient or uncomfortable.

At a population level, disability benefit data highlight the burden of chronic and complex conditions commonly managed within neurology and related subspecialties. In the United States in 2024, the most common impairment among disabled-worker awards was diseases of the musculoskeletal system and connective tissue (35.3%), followed by mental disorders (13.5%), and diseases of the nervous system and sense organs (9.6%).[16] The categories encompass a range of conditions that are frequently encountered in neurology and neuromuscular practices.

These conditions are associated with an intertwined psychological and financial burden. Patients with neuromuscular diseases experience not only motor and functional impairments but also substantial psychological distress. Recent evidence indicates that anxiety and depressive symptoms are highly prevalent in this population, molded by factors such as onset age, perceived social support, and disease severity, and are associated with reduced quality of life.[17] These conditions may also amplify symptom perception, with depression and anxiety contributing to fatigue, sleep disturbances, and appetite changes, which commonly overlap with chronic neurological disease.[18] Prior research has shown that patients with chronic diseases and higher levels of psychological distress are more likely to report lower satisfaction and poorer evaluations of healthcare services.[19] Notably, just under half of the patients (44.4%) in this study reported anxiety or depression, factors that might increase symptom sensitivity and contribute to reduced satisfaction with diagnostic uncertainty. These conditions were self-reported in the patient intake form rather than assessed using a validated instrument.

Beyond psychological impact, neuromuscular diseases also have significant financial and functional impacts. Recent work has identified four interconnected categories of these burdens: informational challenges, administrative and advocacy demands, employment-related opportunity costs, and reduced independence related to out-of-pocket spending on equipment and home modifications.[20] These factors reveal the considerable pressures experienced by patients and families with neuromuscular diseases, further complicating the clinical context for physicians to provide care and potentially influencing how patient experiences are reflected in online reviews.

This complexity is also reflected in patient-physician communication, where patients may struggle to accurately describe their symptoms, further complicating the diagnostic process. It is common for individuals to use non-specific or

incorrect medical terminology when describing symptoms, for example, reporting "fatigue" when in fact they are experiencing weakness or numbness. These terms have distinct clinical meanings, and such confusion can lead to miscommunication between patients and physicians, potentially affecting patient satisfaction. This is especially relevant in neurology, where symptoms frequently overlap across multiple disorders, complicating diagnostic interpretation.

A further challenge in clinical assessment is that many commonly reported symptoms are subjective in nature. Chronic pain is one of the most common conditions in outpatient medical settings.[18] It cannot be objectively assessed because of its diverse origins and the lack of a single marker for all mechanisms underlying the sensation.[18] As a result, symptom reporting may vary between individuals and may be influenced by contextual factors such as work avoidance, insurance limitations, and other external factors.

The variability and overlap of symptoms were observed in this study, with 13 of 18 patients experiencing both fatigue and pain, and 6 of them also reporting anxiety and/or depression. Research has documented that both pain and fatigue are common and frequently overlapping symptoms.[21] Similarly, 12 of 18 patients reported both motor and sensory symptoms, reinforcing the multifactorial and overlapping nature of symptoms in neuromuscular disease.

Additionally, patients discuss details that physicians may consider less clinically relevant and attempts to redirect the conversation toward a focused history can often be perceived as "rude" or dismissive.

Negative online reviews may reflect these communication barriers and differences in expectations between physicians and (often) patients without formal medical training, particularly in complex neuromuscular evaluations where symptoms overlap, and diagnostic reasoning requires clinically relevant information.

It is important to recognize that physicians aim to deliver objective, evidence-based assessments and guide patients toward effective symptom management and disease treatment. Physicians undergo extensive training over many years, whereas many patients have limited familiarity with the complex reasoning and processes involved in diagnosis and treatment decision-making, especially in neuromuscular medicine, where atypical presentations are common. This difference in perspective can contribute to patient dissatisfaction, particularly when online reviews emphasize perceived delays, miscommunication, or unexpected diagnostic conclusions. This observation reflects an increasing discrepancy between physician and patient perception in complex specialty care. We suggest larger opinion surveys to better understand the generalizability of this problem and the importance of this issue in determining the future role of the physician in an evolving healthcare system.

This pattern suggests that patient ratings may reflect limited understanding of the time constraints and financial models that govern clinical services, where compensation is tied to time spent. As a result, physicians may be evaluated in ways influenced by systemic limitations beyond their control, rather than clinical performance.

This study combines quantitative and qualitative analyses across a dataset of online reviews, allowing for a comprehensive assessment of trends, patient perceptions, and potential discrepancies between reported experiences and documented care in a tertiary medical setting.

Despite these insights, this study has several limitations, including a relatively small sample size, as only 18 of the 36 negative reviews could be linked to identifiable patient records, as reflected in figures 4-7. This study focuses on a single physician in an urban location who treats complex referrals and relies on reviews collected primarily through search engines. Two reviews included only star ratings without written comments, limiting the depth of qualitative analysis. Reviews are inherently subjective, with self-selection bias favoring those with particularly strong feelings. Some demographic data was also missing, limiting interpretation across age and racial groups. Cross-checking reviews against medical documentation helped mitigate some of these limitations, although generalizability remains a concern. Future research should include larger datasets from multiple physicians across both urban and rural settings to better capture the experiences of diverse patient populations and healthcare environments.

Understanding the impact of negative reviews on patient perception, as shown in this study, may help contextualize how online physician ratings are interpreted, particularly in specialized fields like neuromuscular medicine, and may inform future efforts to develop more objective methods of assessing patient experience. More importantly, these findings showcase the challenges physicians face in balancing the time and attention devoted to online feedback with the demands of providing high-quality care.

The implications of online patient reviews of physicians remain a relatively new area of study. This project contributes to the growing body of research examining the content, credibility, and utility of online feedback. In complex neuromuscular care, online physician ratings reflect a mixture of symptom burden, diagnostic uncertainty, communication challenges, and heightened expectations and therefore may not reliably represent clinical competence or quality of care. As digital platforms continue to shape patient perceptions, future research should examine larger, more diverse datasets and explore strategies to improve the accuracy and clinical usefulness of online physician ratings.

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Correlations Between Muscle Group Strengths and Basic Functional Abilities in Inclusion Body Myositis: A Pilot Study

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Abstract

Background: We aimed to examine the correlation between lower-extremity muscle strength and the ability to perform basic functional activities in individuals with inclusion body myositis (IBM).

Methods: We examined how muscle strength correlates with basic functional abilities in 18 participants with IBM. Isometric strength across seven muscle groups was measured using a handheld dynamometer. Functional performance was assessed through gait, standing-up, and stair-negotiation abilities.

Results: Gait ability was associated with strength in hip flexion, hip extension, hip abduction, and knee flexion. Standing-up ability correlated with knee extension strength. No notable correlation existed between muscle strength and stair-climbing ability. All participants relied on upper limb support during stair descent.

Conclusions: Participants possibly employed compensatory strategies, engaging hip and knee flexor muscles for walking support; standing up appeared to depend on knee extension strength. These insights support focused rehabilitation targeting specific muscle groups and improved clinical assessments to preserve function in IBM.

Keywords: gait, muscle strength dynamometer, inclusion body myositis

1. Introduction

Inclusion body myositis (IBM) is a chronic progressive muscle disease typically manifesting in middle-aged and older adults aged >50 years (1-6). Histopathological analysis of skeletal muscle tissue reveals characteristic rimmed vacuoles, accompanied by inflammatory cell infiltration. In addition to these inflammatory features, mitochondrial dysfunction and oxidative stress are increasingly recognized as important contributors to the degenerative component of IBM pathology (7). Muscle weakness is the most distinctive clinical finding in IBM. This weakness, with associated muscle atrophy, primarily involves the quadriceps femoris and finger and wrist flexor muscles, raising clinical suspicion for IBM, although this distribution is not fully specific for diagnosis (1, 3, 4, 6).

With disease progression, muscle strength gradually deteriorates, leading to increasing difficulty in performing activities of daily living. Patients commonly report difficulty with rising from a chair, climbing stairs, entering a car, lifting objects, washing their hair, brushing their teeth, and gripping items (1). IBM is generally refractory to immunosuppressive therapy, in contrast to other inflammatory myopathies, indicating a complex pathogenesis involving inflammatory and degenerative processes (1, 8, 9).

Adequate lower-limb muscle strength, particularly involving the quadriceps, is essential for basic functional activities such as walking, sit-to-stand transitions, and stair climbing; strength thresholds below which performance markedly declines have been identified (10-13), and quadriceps strength correlates strongly with functional mobility measures such as gait speed, chair-rise time, and stair-climbing time (14-18). Largely, patients with IBM maintain their ambulatory ability for extended periods, and complete wheelchair dependency occurs in only 3% of patients (1). However, a wheelchair is reportedly needed by about one-third of patients within 14 years of onset, and by nearly all patients within 20 years — a considerably higher proportion than the overall 3% figure suggests (4). This finding suggests that certain compensatory mechanisms, or the relative preservation of other muscle groups may play important roles in maintaining functional mobility in these patients.

Preservation of walking ability, despite marked quadriceps weakness, presents a clinical paradox that requires further investigation. This study aimed to examine the correlation between lower-extremity muscle strength and the ability to perform three essential basic functional activities—gait, standing up, and stair negotiation—in individuals with IBM. We defined basic functional activities as fundamental motor tasks required for independence in activities of daily living, occupational engagement, and community participation. These activities are characterized by being repetitive, essential for autonomy, and representatively challenging for patients with proximal muscle weakness such as IBM. As a pilot study, the findings of the present study will inform the design of larger studies on the functional implications of muscle weakness in IBM.

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2. Methods

2.1 Ethical approval and informed consent

The study was approved by the Ethics Committee of our institution on April 19, 2022 (approval number: A2022-003). This study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments and followed the STROBE reporting guidelines for observational studies. Written informed consent was obtained from all participants for study participation and publication of their de-identified data.

2.2 Study design

This study was conducted between May 2022 and December 2023 at our institution. Eighteen participants with IBM were included. The inclusion criteria were as follows: (1) adults aged ≥18 years and (2) a history of achieving ambulatory ability during development. Although IBM typically manifests in adults older than 50 years, we set the lower age threshold at 18 years to remain inclusive of the full adult range. The exclusion criteria included: (1) cognitive impairment, defined as a Mini-Mental State Examination score ≤24, and (2) muscle weakness resulting from non-myopathic etiologies.

Participants were hospitalized patients diagnosed with IBM by experienced neurologists in the Department of Neurology at our institution, based on established clinical and histopathological features of IBM. Participants were recruited from the inpatient rehabilitation ward following their receipt of a rehabilitation prescription from rehabilitation physicians. The treating physical therapist approached eligible patients and obtained written informed consent from those willing to participate.

Basic demographic and clinical data were collected, including sex, age, height, weight, body mass index (BMI), age at disease onset, disease duration, and the IBM Functional Rating Scale (IBM-FRS) scores (19, 20).

2.3 Tasks and procedures

2.3.1 Assessor training protocol

All physical therapists conducting muscle strength assessments (n=6, each with ≥5 years clinical experience) underwent standardized training to ensure measurement consistency. Prior to data collection, all assessors completed a joint training protocol in which they performed repeated measurements on the same healthy volunteers until they achieved agreement in dynamometer readings. Although six physical therapists conducted assessments due to clinical scheduling requirements, the bilateral measurements for all muscle groups in each participant were obtained by the same assessor to minimize inter-rater variability for individual participants. This approach ensured consistency within participants while allowing for clinical feasibility.

2.3.2 Assessment procedures and blinding

Functional ability assessments were conducted in a separate location or after an interval, thereby minimizing potential bias. Testers' knowledge of participant functional status was limited to incidental gait observation during transfer between testing areas; standing-up and stair-negotiation abilities were assessed without prior knowledge of participant capabilities.

2.3.3 Muscle strength assessment

Regarding the rationale involving muscle group selection, the focus remained on muscle groups directly involved in the basic functional abilities of individuals with IBM, including gait, sit-to-stand transitions, and stair negotiation. The Manual Muscle Testing 8 (MMT8) clinical tool, recommended by the International Myositis Assessment and Clinical Trials Group as a core outcome measure for idiopathic inflammatory myopathies, evaluates eight muscle groups: the deltoids (shoulder abduction), biceps (elbow flexion), ankle dorsiflexors (ankle dorsiflexion), gluteus maximus (hip extension), gluteus medius (hip abduction), quadriceps (knee extension), wrist extensors (wrist extension), and neck flexors (neck flexion) (21, 22). From these, the upper-limb muscle groups—the deltoids, biceps, and wrist extensors—were excluded. Knee flexors (knee flexion) and ankle plantarflexors (ankle plantarflexion) were included due to their essential role in walking and rising from a seated position (23-27). This modification provided a more comprehensive assessment of lower-extremity function, which is central to understanding the correlation between muscle strength and basic functional abilities in individuals with IBM, a condition characterized by proximal muscle weakness that severely impacts mobility.

Isometric muscle strength was assessed using a hand-held dynamometer (HHD; (microFET®2, Hoggan Scientific, Salt Lake City, Utah, USA) for the following seven muscle-group joint-specific movements: hip flexion, extension, and abduction; knee flexion and extension; and ankle plantarflexion and dorsiflexion. Each muscle-group joint-specific movement was measured twice for 5 s each time. Between measurements, participants were asked about fatigue and given brief rest periods (approximately 30 s) to ensure recovery before the next measurement. If the two measurements differed by >15%, a third trial was conducted to ensure measurement reliability and reduce variability in strength estimates.

HHD was selected for measuring isometric muscle strength based on scientific validity and clinical practicality (Itoh et al., 2025; Stark et al., 2011). Although surface electromyography provides detailed information on muscle activation patterns, it is impractical for comprehensive multi-muscle assessment in a clinical setting. In contrast, HHD offers superior clinical utility as a portable, practical tool for assessing multiple muscle groups, with advantages such as time efficiency, cost-effectiveness, immediate quantifiable results, and suitability for fatigable patients (Bohannon, 2012). These characteristics made HHD ideal for this pilot study examining seven lower-extremity muscle groups in patients with IBM who may experience fatigue during prolonged testing procedures.

Table 1. Demographic and clinical characteristics of study participants. *Data are presented as medians [25–75% interquartile range], unless otherwise specified. IBM-FRS; inclusion body myositis functional rating scale.*

	All Patients	**Gait Ability**		**Standing-up Ability**		**Stair-climbing Ability**	
Total	n=18	Unable n=4	Able n=14	Unable n=13	Able n=5	Unable n=16	Able n=2
Male, % (n)	55.6 (10)	0.0 (0)	71.4 (10)	53.8 (7)	60.0 (3)	56.3 (9)	50.0 (1)
Female, % (n)	44.4 (8)	100.0 (4)	28.6 (4)	46.2 (6)	40.0 (2)	43.8 (7)	50.0 (1)
Age, years	65.5 [60.0–74.0]	74.5 [65.5–76.5]	62.5 [60.0–71.0]	68.0 [62.0–74.0]	63.0 [60.0–71.0]	68.5 [59.5–74.5]	61.5 [60.0–63.0]
Height, cm	163.2 [156.0–171.4]	153.3 [148.8–159.2]	165.8 [156.2–171.6]	162.3 [156.0–166.5]	171.6 [156.2–172.0]	163.2 [156.0–169.3]	164.0 [156.0–172.0]
Weight, kg	54.9 [45.0–59.4]	40.9 [36.0–50.5]	55.6 [46.0–64.7]	54.8 [45.0–64.7]	55.0 [45.7–58.1]	55.4 [45.4–62.0]	49.5 [43.9–55.0]
BMI, kg/m²	19.6 [18.6–21.2]	18.4 [15.2–21.4]	19.6 [18.7–21.2]	20.2 [18.9–23.0]	18.7 [18.6–19.0]	19.8 [18.8–22.1]	18.3 [18.0–18.6]
Age at onset, y	59.0 [51.0–63.0]	59.5 [51.0–61.5]	59.0 [51.0–65.0]	59.0 [50.0–63.0]	59.0 [57.0–66.0]	59.5 [50.5–64.0]	58.0 [57.0–59.0]
Duration, years	8.0 [4.0–14.0]	14.5 [12.5–17.0]	6.5 [4.0–8.0]	11.0 [7.0–15.0]	5.0 [4.0–6.0]	8.0 [4.5–14.5]	3.5 [1.0–6.0]
IBM-FRS	25.0 [21.0–31.0]	15.0 [9.0–21.0]	29.0 [25.0–32.0]	21.0 [15.0–28.0]	31.0 [25.0–32.0]	25.0 [21.0–30.0]	31.5 [31.0–32.0]

Muscle strength measurements followed the standardized positions outlined in the Hoggan Scientific Muscle Testing Positions guide for the microFET (Hoggan Scientific, USA: https://hogganscientific.com/wp-content/uploads/2019/06/HogganScientific-MuscleTestingPositions-11x17-Poster.pdf). To assess hip flexion, the participant was positioned supine with the hip flexed to 90°; the HHD was placed immediately proximal to the femoral condyles. To measure hip extension, the participant was positioned supine, with the knee extended and the distal limb supported on a block; the dynamometer was placed immediately distal to the malleoli over the Achilles tendon. To evaluate hip abduction, the participant was positioned supine, with the hip extended and in a neutral position; the dynamometer was placed proximal to the lateral knee joint line. To measure knee extension, the participant was seated, with the hip and knee flexed to 90°; the dynamometer was positioned proximal to the malleoli. To measure knee flexion, the participant remained seated, with the hip and knee flexed to 90°, and the dynamometer was placed immediately distal to the malleoli over the Achilles tendon. To assess ankle plantarflexion, the participant was positioned supine, with the knee extended and ankle in neutral dorsiflexed position; the dynamometer was placed over the metatarsophalangeal joints. To assess ankle dorsiflexion, the participant remained supine, with knee extended and ankle in neutral dorsiflexion; the dynamometer was positioned proximal to the metatarsophalangeal joints.

2.3.4 Functional ability assessment

Functional ability was assessed through three basic activities: gait, standing up, and stair negotiation. All functional assessments were conducted with the participants wearing their comfortable athletic shoes to simulate real-world conditions.

2.3.4.1 Gait assessment

Regarding gait, participants who walked independently within the hospital without supervision or assistive devices were categorized into the "able" cohort.

2.3.4.2 Standing up assessment

Participants sat on a chair adjusted to achieve 90° knee flexion, with the arms folded across the chest. They were instructed to stand without using momentum, which was defined as avoiding excessive trunk acceleration. Participants

who successfully stood up at least once out of three attempts were categorized into the "able" cohort.

2.3.4.3 Stair negotiation assessment

Participants who continuously ascended 16 steps (each step 18 cm high), placing one foot on each step without using handrails or touching the walls with either upper limb, were categorized into the "able" cohort for stair ascent; those who required upper-limb support during ascent were categorized as "unable." Compensatory movements, such as knee locking during ascent, were permitted. Stair descent was assessed separately using the same 16-step protocol and criteria. Because all participants required upper-limb support to descend, no participant met the "able" criterion for descent; stair descent was therefore excluded from the subsequent able/unable comparisons, and stair-negotiation results reported below refer to ascent performance only.

2.5 Muscle strength normalization

Regarding bilateral measurements, the average left and right limb values were calculated and used in all statistical analyses. The average force value, measured in kilogram-force (kgf), was divided by body weight (kg) to calculate the muscle strength-to-weight ratio (kgf/kg) for standardization.

2.6 Data analyses

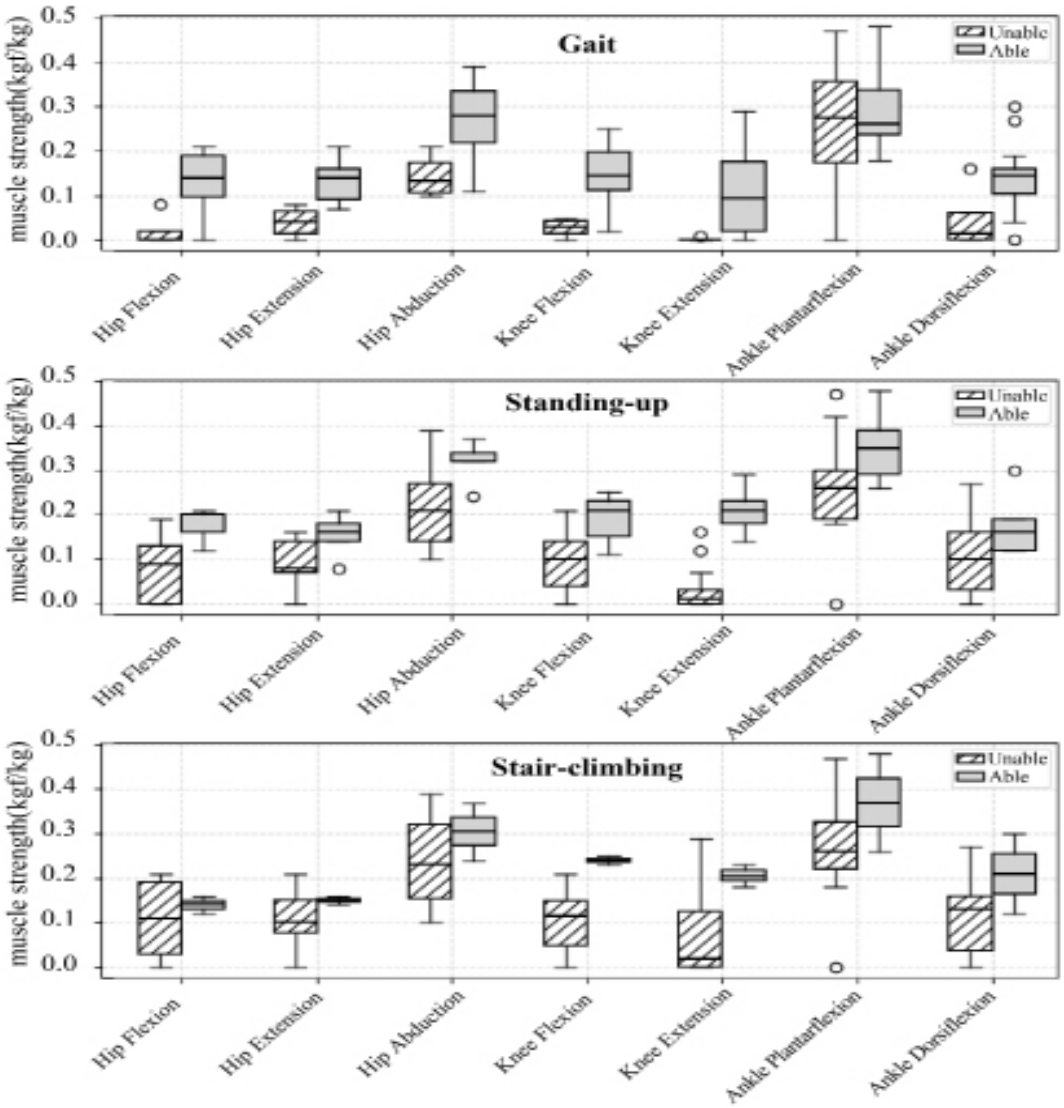
Point-biserial correlation coefficients (r) were calculated to analyze the correlation between muscle strength-to-weight ratios and functional abilities, categorized as able or unable, for each basic activity. This statistical method is appropriate for examining relationships between one continuous variable (muscle strength) and one dichotomous variable (binary functional categorization). To control for multiple comparisons and reduce the risk of Type I errors, the Benjamini–Hochberg correction was applied separately to each functional activity. The 95% confidence intervals (CIs) for r values were calculated using bootstrap resampling (5,000 iterations) because of the small sample size (n = 18). For each iteration, we resampled with replacement from the original data and recalculated the correlation coefficient. The 95% CI was defined by the 2.5–97.5th percentiles of the bootstrap distribution, which does not assume normality of the correlation coefficients. Additionally, non-parametric Mann–Whitney U tests were used to compare muscle strength between participants in the able and unable groups for each functional activity.

Correlations were interpreted using the following categories based on established methodology: values from 0.00 to 0.30 and 0.00 to -0.30 indicated negligible correlation; 0.30 to 0.50 and -0.30 to -0.50 indicated low correlation; 0.50 to 0.70 and -0.50 to -0.70 indicated moderate correlation; 0.70 to 0.90 and -0.70 to -0.90 indicated high correlation; and 0.90 to 1.00 and -0.90 to -1.00 indicated very high correlation (28). This approach enabled standardized interpretation of the strength of correlations between muscle groups and basic functional abilities. All statistical analyses were performed using Python 3.11 (Python Software Foundation, Wilmington, DE, USA). Statistical significance was set at $p < 0.05$.

Table 2. Relationship between muscle strength-to-weight ratio (kgf/kg) and basic functional abilities. *Results are expressed as medians [25–75% interquartile range] for continuous variables.*

	All Patients	**Gait Ability**		**Standing-up Ability**		**Stair-climbing Ability**	
(kgf/kg)	n=18	Unable n=4	Able n=14	Unable n=13	Able n=5	Unable n=16	Able n=2
Hip Flexion	0.13 [0.04–0.19]	0.00 [0.00–0.04]	0.14 [0.09–0.19]	0.09 [0.00–0.13]	0.20 [0.16–0.20]	0.11 [0.02–0.19]	0.14 [0.12–0.16]
Hip Extension	0.13 [0.08–0.16]	0.04 [0.01–0.07]	0.14 [0.08–0.16]	0.08 [0.07–0.14]	0.16 [0.14–0.18]	0.10 [0.08–0.15]	0.15 [0.14–0.16]
Hip Abduction	0.24 [0.16–0.32]	0.14 [0.11–0.18]	0.28 [0.21–0.34]	0.21 [0.14–0.27]	0.32 [0.32–0.34]	0.23 [0.15–0.32]	0.30 [0.24–0.37]
Knee Flexion	0.13 [0.05–0.16]	0.03 [0.01–0.04]	0.15 [0.11–0.21]	0.10 [0.04–0.14]	0.21 [0.15–0.23]	0.11 [0.04–0.15]	0.24 [0.23–0.25]
Knee Extension	0.03 [0.00–0.16]	0.00 [0.00–0.01]	0.10 [0.02–0.18]	0.01 [0.00–0.03]	0.21 [0.18–0.23]	0.02 [0.00–0.13]	0.21 [0.18–0.23]
Ankle Plantarflexion	0.26 [0.23–0.35]	0.28 [0.12–0.40]	0.26 [0.23–0.35]	0.26 [0.19–0.30]	0.35 [0.29–0.39]	0.26 [0.21–0.33]	0.37 [0.26–0.48]
Ankle Dorsiflexion	0.13 [0.04–0.16]	0.01 [0.00–0.10]	0.15 [0.10–0.16]	0.10 [0.03–0.16]	0.16 [0.12–0.19]	0.13 [0.04–0.16]	0.21 [0.12–0.30]

Figure 1. Comparative analysis of muscle strength-to-weight ratios between the able and unable cohorts across various functional activities. *Muscle strength-to-weight ratios (kgf/kg) appear for seven muscle groups in patients with inclusion body myositis (IBM). The image compares those who are able to perform each activity (grey boxes) and those unable (hatched boxes) to do so across three functional activities: gait (top), standing up (middle), and stair climbing (bottom). Box plots show median values with interquartile ranges (25th–75th percentiles), and whiskers indicate the full range excluding outliers.*



3. Results

Between May 2022 and December 2023, eligible participants with IBM were identified from the inpatient rehabilitation ward. All participants who met the inclusion criteria and provided informed consent were enrolled. A total of 18 participants completed the study; no participant was excluded after enrollment.

Participant characteristics are presented in Table 1, including demographic data and the distribution of participants categorized into the able and unable cohorts for each functional activity. Of the 18 participants, 14 were able to walk independently within the hospital, whereas four required assistance and were categorized as unable. Regarding standing-up ability, five participants successfully stood from a seated position without using momentum, whereas 13 were unable to stand. Furthermore, regarding stair-climbing ability, only two participants ascended and descended 16 steps without support, whereas 16 were unable to independently complete the task. Notably, stair descent was assessed separately; none of the participants were able to complete the task without upper limb support, indicating that this activity was universally challenging for all participants with IBM.

The correlations between the participants' muscle strength-to-weight ratios and basic functional abilities are presented in Table 2 and Figure 1. For each muscle-group joint-

specific movement, with the exception of ankle plantarflexion for gait ability, participants in the "able" cohort consistently demonstrated higher median strength values than did those in the "unable" cohort across all three functional activities. Regarding gait ability, five muscle groups showed significant differences: hip flexion (p = 0.01), hip extension (p = 0.007), hip abduction (p = 0.02), knee flexion (p = 0.008), and knee extension (p = 0.02). Regarding standing-up ability, significant differences were found for knee extension (p = 0.002), hip flexion (p = 0.01), knee flexion (p = 0.02), hip abduction (p = 0.04), and hip extension (p = 0.05). Furthermore, regarding stair-climbing ability, only knee flexion showed a significant difference (p = 0.03), limited by the small number of participants that could complete the task (n = 2).

As shown in Table 3, point-biserial r values with 95% bootstrap CIs were calculated to examine the correlations between muscle strength and basic functional abilities. Statistically significant correlations after Benjamini–Hochberg correction were observed for gait ability with hip flexion (r = 0.649 [0.261–0.856]), hip extension (r = 0.704 [0.353–0.881]), hip abduction (r = 0.564 [0.132–0.816]), and knee flexion (r = 0.663 [0.284–0.863]). Regarding standing-up ability, statistically significant correlations were found with hip flexion (r = 0.569 [0.139–0.818]) and knee extension (r = 0.846 [0.627–0.941]). No statistically significant correlations were observed for stair-climbing ability.

4. Discussion

In this study, we examined the correlations between muscle strength and the ability or inability to perform basic functional activities in patients with IBM. Our findings revealed distinct patterns of correlation between specific muscle groups and three fundamental activities: gait, standing up, and stair climbing. Regarding gait, moderate-to-high correlations emerged between muscle strength and functional ability, particularly involving hip flexion, extension, and abduction, as well as knee flexion. Hip extension showed the strongest correlation with gait ability (r = 0.704). Standing-up ability correlated most strongly with knee extension strength (r = 0.846). No notable correlations were observed between muscle strength and stair-climbing ability.

4.1 Hip extension as the primary determinant of gait ability

Moderate-to-high correlations between hip muscle strength and gait ability in participants with IBM suggest the presence of important compensatory mechanisms that

Table 3. Point-biserial correlation coefficients between muscle strength and functional abilities. *Point-biserial correlation coefficients (r) with 95% bootstrap confidence intervals (CIs) [lower limit, upper limit] between muscle strength-to-weight ratios and performance in three functional activities in patients with inclusion body myositis. Raw and Benjamini–Hochberg-corrected p-values are presented. Asterisks (*) denote statistical significance after Benjamini–Hochberg correction (p < 0.05).*

Ability	**Gait**		**Standing-up**		**Stair-climbing**	
	r [95% CI]	**P-value** **p_adj**	**r [95% CI]**	**P-value** **p_adj**	**r [95% CI]**	**P-value** **p_adj**
Hip Flexion	**0.649*** [0.261, 0.856]	0.004 0.02	**0.569*** [0.139, 0.818]	0.01 0.04	0.143 [-0.347, 0.572]	0.57 0.60
Hip Extension	**0.704*** [0.353, 0.881]	0.001 0.01	0.473 [0.007, 0.770]	0.05 0.09	0.244 [-0.252, 0.638]	0.33 0.36
Hip Abduction	**0.564*** [0.132, 0.816]	0.01 0.04	0.517 [0.066, 0.793]	0.03 0.07	0.245 [-0.251, 0.639]	0.33 0.36
Knee Flexion	**0.663*** [0.284, 0.863]	0.003 0.02	0.590 [0.170, 0.829]	0.010 0.06	0.575 [0.148, 0.821]	0.01 0.06
Knee Extension	0.460 [-0.009, 0.763]	0.05 0.09	**0.846*** [0.627, 0.941]	< 0.001 < 0.001	0.463 [-0.005, 0.765]	0.05 0.09
Ankle Plantarflexion	0.130 [-0.359, 0.563]	0.61 0.61	0.397 [-0.085, 0.729]	0.10 0.14	0.277 [-0.218, 0.659]	0.27 0.33
Ankle Dorsiflexion	0.473 [0.008, 0.770]	0.05 0.09	0.417 [-0.062, 0.740]	0.09 0.13	0.373 [-0.114, 0.715]	0.13 0.17

may have developed as the disease progressed. Hip extension strength showed the strongest correlation with gait ability (r = 0.704), likely reflecting an adaptation to compensate for quadriceps weakness, a hallmark of IBM (1, 5-7).

Participants appeared to rely on hip extension to shift the center of mass forward, thereby positioning the ground reaction force vector anterior to the knee joint. This biomechanical adaptation produces an external extension moment at the knee, which may aid in reduced quadriceps strength. The observed correlations of hip flexion, hip abduction, and knee flexion with gait ability provided additional evidence regarding compensatory strategies used by patients with IBM. Notably, the relatively wide CIs observed for these correlations, including hip flexion (0.261–0.856), hip abduction (0.132–0.816), and knee flexion (0.284–0.863), indicated substantial individual variability. This variability suggests that patients may engage different muscle groups or develop coordinated patterns of muscle activation, depending on their unique anatomical characteristics and the course of disease progression.

In contrast to patients with sudden-onset conditions such as stroke, patients with IBM experience a gradual progression of symptoms, allowing them to develop effective compensatory movement strategies. This gradual adaptation may explain why many patients with IBM retain ambulatory function despite marked quadriceps weakness, as previously reported (1).

4.2 Knee extension as the critical determinant of standing-up ability

The exceptionally high correlation between knee extension strength and standing-up ability (r = 0.846) confirmed the crucial role of the quadriceps muscle in this functional ability for participants with IBM. The lower threshold of the CI at 0.627 represents a moderate correlation, further supporting the robustness of this finding.

During the essential transition of the sit-to-stand movement from seated position to buttocks lift-off and through the momentum–transfer phase (29), the quadriceps contract concentrically to produce the knee extension moment necessary to elevate the body against gravity. As IBM progresses, compensatory mechanisms may develop. The biomechanical demands of buttocks lift-off require a threshold level of quadriceps strength. When quadriceps strength falls below this threshold, compensation becomes inadequate. This establishes knee extension strength as the primary determinant of standing-up ability in this population. In clinical practice, patients with advanced quadriceps weakness frequently use various compensatory strategies, including pushing down forcefully on the seat with their upper extremities or twisting their trunk to lock the knee joints. This enables them to stand up in a manner similar to the technique for Gowers' sign in patients with proximal myopathy. In contrast, hip extension and knee flexion, both theoretically implicated in sit-to-stand biomechanics, did not reach statistical significance for standing-up ability in this cohort. This may reflect the biomechanical threshold effect described above, whereby knee extension becomes the dominant, rate-limiting factor once a critical strength level is reached; the limited statistical power afforded by the small sample size may have further reduced the ability to detect smaller, secondary contributions from these muscle groups.

4.3 Stair-climbing: limited correlations and clinical implications

Regarding stair-climbing ability, no notable correlations with muscle strength emerged. Two factors may explain this. First, stair climbing requires coordinated activation of multiple muscle groups and complex neuromuscular control. Second, the sample distribution was substantially imbalanced, with only two participants completing the task and 16 unable to complete the task. In contrast to walking, stair climbing demands greater range of motion of the lower limb joints, increased muscle activation, and enhanced balance and coordination to move the body forward and upward (30). In patients with IBM, compensatory movement strategies may be used to overcome quadriceps weakness, potentially obscuring direct correlations between individual muscle strength measurements and stair-climbing ability. Stair ascent typically relies on concentric quadriceps contraction to generate vertical propulsion (31). Nonetheless, patients with IBM may adopt alternative strategies in the presence of quadriceps weakness. Furthermore, none of the participants were able to descend stairs without using their upper limbs, highlighting the difficulty of stair descent. This ability relies heavily on eccentric quadriceps control, which appears to be more demanding than stair ascent in patients with IBM (32). The lack of notable correlations between muscle strength and stair-climbing ability requires careful interpretation. This finding should not be interpreted as evidence that muscle strength is unrelated to stair climbing in patients with IBM. Rather, the severely imbalanced sample distribution (only two of 18 participants were able to complete the task) resulted in insufficient statistical power to detect meaningful correlations. The ceiling effect—with 16 participants unable to perform the task—prevented analysis of functional variation among those unable to climb stairs. Therefore, no meaningful conclusions can be drawn from the stair-climbing results, and these findings should be considered preliminary and exploratory. Future studies with larger sample sizes and more balanced functional distributions are needed to clarify the relationships between muscle strength and stair-climbing performance in patients with IBM.

4.4 Rehabilitation strategies and clinical screening implications

Our findings suggest that rehabilitation strategies for patients with IBM should prioritize strengthening the compensatory muscle groups identified in this study. In particular, improving hip flexor, hip extensor, hip abductor,

and knee flexor muscle strength may support gait and help preserve functional independence as the disease progresses. Additionally, strengthening the knee extensors appears essential for maintaining the ability to rise from a seated position. Assistive technologies, including robotic exoskeletons, should be designed to provide targeted support to these key muscle groups, potentially sustaining basic functional abilities. However, owing to limited availability and evidence in the IBM population, such technologies should be framed as future research directions rather than present clinical applications. Rigorous intervention studies with adequate sample sizes and appropriate controls are needed to establish the efficacy, safety, and cost-effectiveness of robot-assisted interventions before clinical implementation.

These findings have important implications for home-based rehabilitation, as many patients with IBM lack access to advanced clinical settings or specialized rehabilitation services. The identification of specific muscle groups that correlate with basic functional abilities may inform simplified, accessible rehabilitation strategies suitable for home-based implementation. Simple resistance exercises targeting these muscles could be performed in the home environment, potentially helping patients preserve functional independence despite progressive muscle weakness. The efficacy of resistance exercise is likely to depend on baseline strength: while patients with mild-to-moderate weakness may derive functional benefit, the effectiveness and safety of resistance training in patients with moderate-to-severe quadriceps weakness remain uncertain and require dedicated study before being recommended for this subgroup. Therefore, future research should develop and validate evidence-based, home-based training protocols targeting these muscle groups in patients with IBM with limited access to clinical services.

4.5 Limitations

This study had several limitations. First, our findings revealed notable correlations between specific muscle strengths and basic functional abilities; however, the results did not establish that training of these muscles directly improves functional outcomes. Therefore, caution is required when interpreting these results, as correlation does not imply causation. Further interventional studies are needed to establish such causal relationships and develop evidence-based rehabilitation protocols for this population. Second, the sample size of 18 participants was relatively small, limiting the generalizability of our findings and reducing statistical power (28). Furthermore, this limited sample size prevented us from performing logistic regression analyses, which would have helped us examine the relative contributions of different muscle groups to functional performance, while controlling for potential confounding variables such as age and disease severity (IBM-FRS score). Consequently, the study could not fully elucidate the complex interrelationships among muscle groups and their combined effect on basic functional abilities and did not determine whether the observed correlations remain significant after accounting for overall disease severity and demographic factors. Third, our study focused exclusively on muscle strength measurements and did not assess other potential factors that may affect functional performance, such as joint range of motion limitations or balance impairments. These factors could impact basic functional abilities either independently or in combination with muscle weakness in patients with IBM. Fourth, this study categorized functional abilities as binary variables (able vs. unable), which inevitably loses detail about performance quality, speed, or degree of difficulty. Performance scaling measures, such as gait speed in meter per second, sit-to-stand time in seconds, or stair-climbing time, were not collected due to the pilot nature of this study and variability in participant capabilities. Fifth, regarding stair-climbing ability, the severely imbalanced sample distribution (only two of 18 participants completed the task) substantially limited statistical power and the reliability of findings for this functional activity. The lack of notable correlations for stair-climbing should be interpreted with caution, given the significant limitation in sample size and the ceiling effect for inability. Finally, all participants were recruited from a single hospital in Japan, which may limit the generalizability of findings to other geographical regions and healthcare settings. Disease progression, disease severity distribution, rehabilitation practices, and sociodemographic characteristics of patients with IBM in Japan may differ from those in other populations. Additionally, the results may not be applicable to patients with IBM from different ethnic backgrounds or those with different access to rehabilitation services. Sixth, this study did not include an age-matched healthy control cohort, which limits our ability to define normative functional thresholds and to fully contextualize the observed muscle strength values. Seventh, although all six assessors completed a standardization protocol, formal inter-rater reliabilitywas not calculated, and residual inter-rater variability cannot be excluded. Future studies with larger sample sizes and more comprehensive assessment protocols are necessary to address these limitations and better understand the correlation between muscle impairments and functional limitations in this population.

4.6 Conclusion

The study identified potential muscle–function correlations in study participants with IBM. Particularly, moderate correlations emerged between gait ability and the strengths of hip flexion, extension, and abduction and knee flexion. A strong correlation was observed between knee extension strength and the ability to rise from a seated position. Although the CIs were relatively wide, these findings suggest compensatory mechanisms that may help maintain mobility despite disease progression. These insights lay the groundwork for creating more effective clinical assessments and personalized rehabilitation strategies for individuals with IBM. Future rehabilitation efforts should target strengthening these muscles and consider assistive technologies to support

compensatory strategies. However, intervention studies are needed to establish causality.

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Ethics Approval Statement
The study was approved by the Ethics Committee (EC) of the National Center of Neurology and Psychiatry (NCNP) Hospital on April 19, 2022 (approval number: A2022-003). This study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments and followed the STROBE reporting guidelines for observational studies.

Patient Consent Statement
Written informed consent was obtained from all participants for study participation and publication of their de-identified data.

Conflicts of Interest Disclosure
The authors declare no conflicts of interest relevant to this study.

Data Availability Statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of generative AI in scientific writing
No single sentence or idea within this manuscript was generated with Claude. We utilized Claude to refine the language in the paper and ensure its style aligns with the standards of a scholarly journal.

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Unilateral hypoglossal nerve palsy following intubation

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Introduction

The hypoglossal nerve, cranial nerve XII, functions to control movements of the tongue and infrahyoid muscles.[1] Nerve damage is a known potential consequence following intubation under general anesthesia.[2] The most commonly injured nerves after orotracheal intubation are the recurrent laryngeal, lingual, and hypoglossal nerves.[3] Pressure from the blade of the laryngoscope can cause shearing to the hypoglossal nerve fibers, resulting in damage.[2] This damage can lead to dysarthria, dysphagia, and tongue deviation.[2-6]

This case report details a patient who underwent general anesthesia and endotracheal intubation for an exploratory laparotomy who subsequently experienced unilateral hypoglossal nerve palsy.

Case Presentation

A 22-year-old woman weighing 94.3 kg, ASA III, received general anesthesia for an exploratory laparotomy to biopsy a pelvic mass. She had a past medical history significant for obesity class III, anemia, thrombocytopenia, and ovarian cancer. Prior to the operation, her neurologic exam was completely normal. Her Mallampati score was II with a normal mouth opening. The patient was preoxygenated with an anesthesia mask at 100% FiO2. Subsequently, general anesthesia was induced with propofol. Succinylcholine was used for muscle relaxation to facilitate intubation. After 4 minutes of preoxygenation with a mask, she underwent laryngoscopy and orotracheal intubation. Intubation was performed with a McGrath size 3 laryngoscope blade. The patient was intubated with a 7.5 mm cuffed endotracheal tube, secured at 22 cm at the lips.

Anesthesia was maintained with sevoflurane. The surgery was completed without complications, and the patient was successfully extubated. The total length of anesthesia was 151 minutes.

On evaluation in the post-anesthesia care unit, there was no evidence of damage to the dentition, tongue, mouth, and oropharynx. The following day, the patient complained of right-sided tongue numbness and difficulty swallowing. On evaluation, her tongue was noticeably swollen with a prominent right-sided deviation (Figure 1). The patient reported odd sensations while swallowing but was able to swallow a liquid meal. She was informed that the tongue deviation was likely cranial nerve XII neuropraxia due to intubation, and that her symptoms would likely resolve spontaneously in 1-2 weeks. Eight days later, after the patient had been admitted to our children's hospital oncology unit, pediatric neurology was consulted for further evaluation. She reported minor improvements in tongue swelling and deviation, but continued to struggle with swallowing. An MRI of the brain with and without contrast was obtained to ensure a cranial nerve XII nucleus lesion was not contributing to her presentation. MRI brain with and without contrast demonstrated T2/FLAIR hyperintensity in the right side of the tongue with mild tongue swelling at the posterior aspect of the right half of the tongue, suggesting early denervation changes in the right side of the tongue (Figure 2).

The patient was seen by a speech pathologist who provided recommendations for eating. The patient was discharged home with instructions to continue monitoring for improvement in symptoms.

Discussion

Cranial nerve injuries following airway manipulation under general anesthesia are rare, however, there exist several reports of hypoglossal nerve palsy.[2] The extent of impairment from these types of injuries depends on the extent and duration of the initial insult. These deficits may be transient, involving complete recovery of motor function, or permanent, with partial or no recovery of function.[5] In an analysis of hypoglossal nerve injury conducted by Shah et al., 43.3% of

Figure 1. Tongue deviation to the right on postoperative day 9.

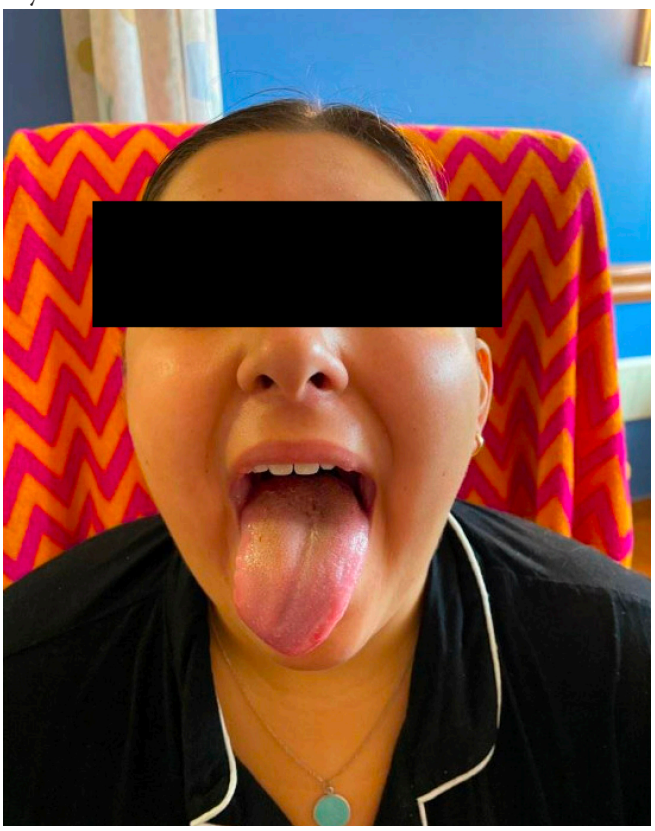

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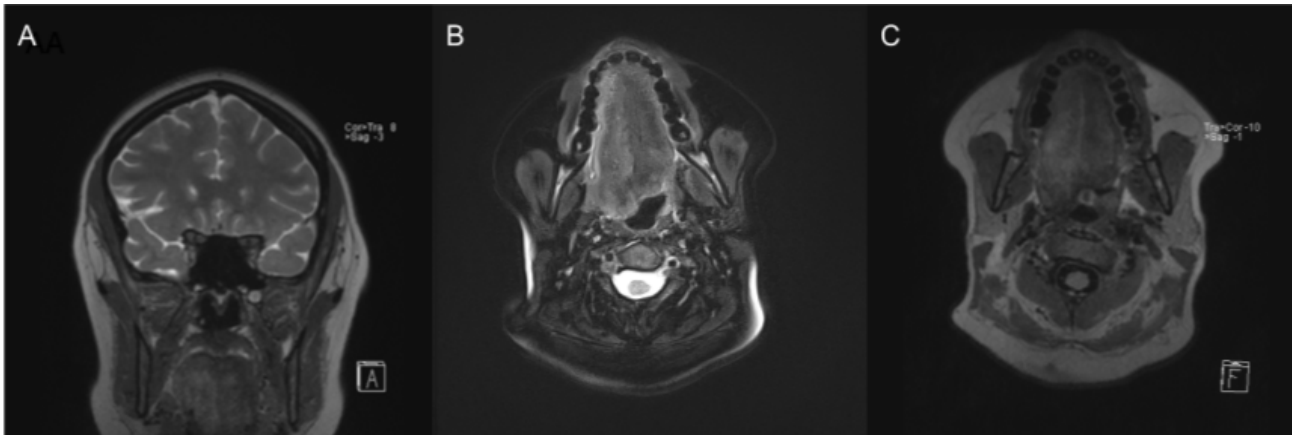
Figure 2. A) MRI Brain Coronal T2 post-contrast. Mild contrast enhancement of patchy T2/FLAIR hyperintensities on right side of tongue. **B)** MRI Brain Axial T2. Mild swelling in the posterior aspect of the right side of the tongue, causing partial effacement of the right oropharyngeal and hypopharyngeal passage. **C)** MRI Brain Axial T2 post-contrast. Mild contrast enhancement of patchy T2/FLAIR hyperintensities on right side of tongue.



patients had complete resolution of symptoms 6 weeks after surgery, 40% had complete resolution of symptoms 6 months after surgery, and an additional 8.3% had persistent symptoms at varying follow-up intervals.[7]Potential mechanisms of hypoglossal nerve injury during intubation include head positioning and excessive inflation of the cuff in the larynx or extubation with an inflated cuff.[4,8,9,10] Other mechanisms of injury specifically involving the anatomy of the hypoglossal nerve have been proposed: nerve compression at the hyoid bone, nerve stretching over the transverse process of the first cervical vertebrae, shearing of the distal nerve fibers from pressure exerted by the laryngoscope blade, and nerve compression via calcification of the stylohyoid ligament.[7] The pathway of the hypoglossal nerve is extensive, exiting the medullary segment of the brainstem, passing through the hypoglossal canal and major vessels of the neck, running near the greater cornu of the hyoid bone, and then terminating along the mylohyoid muscle of the tongue. These fibers are relatively superficial and can be compressed by a laryngoscope blade during intubation.[6]MRI and CT can play important diagnostic and localizing roles in cases of hypoglossal nerve palsy. Depolarization of the resting membrane potential as a result of denervation has been shown to inhibit sodium-potassium pump function, thus increasing intramuscular capillary volume and extracellular fluid.[11] Through this mechanism, denervation edema may be seen on the affected side of the tongue in hypoglossal nerve palsy. On MRI in the acute and subacute settings, this appears as an increase in T2 signal intensity and increased gadolinium enhancement in the affected side. In cases of chronic denervation with associated reduction in ipsilateral muscle bulk and increased fatty infiltration, ipsilateral volume loss and hypoattenuation will be present on CT and T1 shortening on MRI. Imaging may be able to help isolate the site of injury to the carotid or posterior sublingual space if there is atrophy of infrahyoid muscles present.[1] Our patient had a relatively uncomplicated intubation, without note of excessive cuff inflation in anesthesia records. MRI in the subacute setting demonstrated denervation edema, as identified by an increased T2 signal intensity in the posterior aspect of the tongue. There were no imaging findings suggestive of injury and atrophy of the infrahyoid muscles. Four weeks following our patient's initial insult, she had shown very minor improvements in symptoms. Considering this trajectory, we anticipate she will have a relatively slow recovery, if full recovery is possible.

Ethics approval: This study was performed in accordance with appropriate ethical standards.
Consent to participate: Patient consent obtained
Consent for publication: Patient consent obtained
Availability of data and material: Data obtained from chart review, which is protected for participant privacy given the nature of a case report involving a single patient.

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Type 2 complex regional pain syndrome following needle electromyography: A case report

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Abstract: Complex regional pain syndrome describes pain, typically in an extremity, that is more prolonged or severe than expected given the nature of its triggering event. This case report details a 43-year-old female who was initially seen for electrodiagnostic study for right hand weakness with some numbness and tingling. One month later, the patient was evaluated for significant increase in pain and swelling of right upper extremity. At this time, patient met 4/4 on subjective Budapest criteria and at least the sensory and sudomotor objective criteria and was diagnosed with CRPS type 2 (causalgia). To our knowledge, there have been no reports of CRPS or local nerve injury as a direct result of needle EMG. This report highlights the novelty and perhaps underreported nature of iatrogenic nerve injury secondary to needle EMG.
Key Words: Complex Regional Pain Syndromes, Electromyography, Iatrogenic, Nerve Injuries, Case Report

Complex regional pain syndrome (CRPS) is characterized by burning, tingling, and shock-like sensation, that persists longer and is more profound than expected with respect to the inciting event.[1,2] Typical presentation includes sensory abnormalities such as hyperesthesia and allodynia, autonomic dysfunction such as changes in temperature and color of skin, and loss of motor function.[1, 2] There are two types of CRPS: type 1, which shows injury with no nerve involvement, and type 2, or causalgia, which involves nerve injury. Diagnosis of CRPS is clinical and follows the Budapest criteria, which is known to have higher specificity than formerly used International Association for the Study of Pain (IASP) diagnostic criteria.[3] Per Budapest criteria, to be diagnosed with CRPS a patient must exhibit symptoms both subjectively (3/4) and objectively (2+). Subjective criteria include sensory, vasomotor, sudomotor/edema, and motor/tropic categories and is assessed via history taking and patient experience. Objective criteria include the same four categories and are appreciated on physical exam of the affected area.[3] The main goal in treating CRPS is pain management and restoration of function. Treatment modalities include physical therapy, occupational therapy, pain management with oral medications, stellate ganglion blocks, and psychological support.[1,2] Many cases of CRPS naturally resolve, however this condition can become chronic.[2] CRPS is often precipitated by direct trauma, such as injury or surgery, and its pathogenesis is not fully understood but could be linked to inflammatory process, dysfunction of autonomic nervous system, or central pain processing.[1]

Nerve conduction studies and needle electromyography (EMG) are generally thought to be low risk, barring a moment of discomfort at the point of needle insertion. Iatrogenic complications with a needle electrode include bleeding, infection, local trauma, and pneumothorax. Some studies have cited nerve injury as a potential risk, though this outcome has not been reported in the existing literature.[4, 5] A recent quality improvement project aimed to more accurately highlight risk factors for needle EMG identified 3 incidences of complication directly related to needle EMG procedure out of 24,772 cases screened, confirming the low risk of this diagnostic test.[6] There are several areas where nerves travel close to common muscles of diagnostic interest for needle EMG study such as the median nerve's proximity to the pronator teres. To our knowledge, there are no reported cases of nerve injury secondary to needle electromyography.[7] This manuscript adheres to the CARE (Case Report) guidelines for case reports.[8]

Case Presentation

A 43-year-old female patient with a past medical history of depression and hypertension was referred for an electrodiagnostic examination to evaluate for median mononeuropathy. She reported numbness and tingling at the right hand at the palmar aspect including the first digit to the radial half of the fourth digit. Her symptoms started 10 years ago with no recall of an inciting event, however 6 months prior to visit the patient reports increased dull pain in the hand, including the elbow and shoulder. The patient expressed concern over these symptoms impacting her activities of daily living. The patient also endorsed neck pain that is worse on the right side but denied any shooting pain or pain traveling down the arm. At this point, differential diagnosis included radiculopathy vs. carpal tunnel. Additional pathologies considered were entrapment at the level of the brachial plexus or proximal median nerve. Physical exam was unremarkable for atrophy, scarring, or edema. Neurological exam demonstrated normal strength over bilateral upper extremities. Sensation was intact to light touch over bilateral upper extremities except for right arm at the medial aspect of the forearm and at the hand on the palmar side including digits 1 through 3, and the radial half of the 4th digit. Deep tendon reflexes on the left arm were 2+ in the biceps, brachioradialis, and triceps. On the right upper extremity, reflexes were 3+ to brachioradialis and biceps and 2+ for triceps. This patient did not have any underlying

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condition that would explain the hyperreflexia appreciated in the right upper extremity. Spurling maneuver was negative bilaterally. Tinel's sign at both the medial epicondyle and wrist were negative bilaterally. Nerve conduction study results demonstrated prolonged latency of the median motor response with normal amplitude, and a comparison study of the sensory nerve action potentials of the right median and radial nerves showed a latency difference of 0.7 ms in the median nerve indicating evidence of right sensorimotor median nerve mononeuropathy localized to the wrist, as seen in moderate carpal tunnel syndrome. There was no electrodiagnostic evidence of right cervical C5-T1 radiculopathy. NCS/EMG findings seemed to correlate well with patient's symptoms of numbness and paresthesias in digits 1-4, and we hypothesized that other symptoms such as neck pain and forearm sensory disturbances may have been due to non-neuromuscular conditions such as myofascial pain with trigger points or musculoskeletal etiologies. During needle EMG of the bicep, the patient reported intense pain radiating down to the forearm. The needle was removed and re-inserted with improvement of discomfort.

Two weeks after the needle EMG procedure, the patient contacted primary care reporting shooting pain from the upper to lower forearm when reaching to grab something or moving arm, associated with erythema and swelling. Pain began immediately after the procedure and had not improved. Self-care efforts such as heat/cold therapy, NSAIDs, and therapy exercises did not provide any relief. Patient was recommended to visit urgent care to have the area assessed for signs of infection, which was ruled out.

About one week later, the patient returned to clinic for follow-up concerns of ongoing pain and swelling. The patient described burning pain and allodynia affecting the medial forearm as well as slight redness of the area. On exam, mild swelling was appreciated on the upper medial aspect of the forearm extending to the medial epicondyle. In addition, erythema was noted on the medial forearm. There was giveaway weakness with deltoid testing and finger abduction. Sensory testing was notable for allodynia and hyperalgesia in the right medial antebrachial cutaneous (MAC) distribution. Nerve conduction study yielded a normal result in the left MAC, but a non-recordable result in the right MAC, indicating injury through this nerve. At this time, the patient met 4/4 subjective Budapest criteria and at least the sensory and sudomotor objective criteria, leading to diagnosis of type 2 CRPS.

The patient was started on gabapentin and was recommended to start on alpha lipoic acid to promote nerve recovery. Other treatment modalities have included occupational therapy and acupuncture. Four months after the inciting event, the patient received a stellate ganglion block under ultrasound guidance. The procedure was uncomplicated and technically successful due to lack of manifestation of Horner syndrome but did not alleviate pain. The patient has had gradual improvement with pain helped by acupuncture and titration of gabapentin; however, pain level has not returned to baseline. We obtained consent from the patient to write this case as a case report.

Discussion

This case report presents a novel case of iatrogenic nerve injury caused by needle electromyography resulting in CRPS. In this case, needle electromyography was indicated for evaluation for radiculopathy vs. carpal tunnel.

Needle EMG is often used as a diagnostic tool.[5] Significant complications are rare, but have included bleeding, pneumothorax, and compartment syndrome.[7] Iatrogenic nerve injuries have been reported secondary to other medical procedures such as venipuncture, but to our knowledge has not previously been reported from EMG. One study reported 11 patients who developed causalgia after routine venipuncture.[9] Affected nerves reported were the medial antebrachial cutaneous, the lateral antebrachial cutaneous, the superficial radial and the radial and ulnar dorsal sensory branches.[9] These locations follow logically with the proximity of nerves to veins. It is also logical to presume that the branches of the medial antebrachial cutaneous nerve are at greater risk for injury given their course along the medial border of the biceps brachii muscle. This case supports this idea, as the MAC nerve sustained injury after needle insertion into the biceps.

One study suggests that carpel tunnel syndrome (CTS) is one of the most common diagnoses associated with CRPS.[10] This could indicate that this patient's presentation put her at higher risk for development of CRPS; however, this study also concludes that surgery is the most common triggering event of CRPS, and the cases screened in this study were patients who elected for surgical treatment of CTS and then went on to develop CRPS.[10] Another study describes causalgia following major traumatic nerve injury and describes a case of a 60 year old female who developed paresthesia in the right median nerve distribution as well as constant pain and tenderness over the wrist and thenar regions. The case reports mild edema, cool temperature, and pale complexion of the right hand compared to the left. Nerve conduction studies confirmed right carpal tunnel syndrome.[11] It is difficult to discern whether the CTS in the case of our patient put her at higher risk for development of causalgia following needle EMG.

To our knowledge, there have been no reports of CRPS or local nerve injury as a direct result of needle EMG. We speculate that it is possible that iatrogenic nerve injuries secondary to needle EMG are underreported due to difficulty discriminating its clinical presentation from the underlying neuropathic complaints that often prompt the EMG, as well as generally not having any follow up with the electromyographer.

Conclusion

CRPS is complex and can present with a varied clinical picture from patient to patient. Commonly used diagnostic procedures such as needle EMG have not been linked to or identified as a risk factor for manifestation of CRPS. There are no reported cases of CRPS secondary to needle EMG. Further study is indicated to identify the frequency of nerve injury secondary to needle diagnostic procedures.

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Author Contributions: ES conceived of idea for case report. MO reviewed clinical notes and gathered pertinent details. MO drafted the initial manuscript. All authors contributed to its revision. ES is the senior investigator and made final editorial decisions.

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Sensory ganglionopathy as a paraneoplastic manifestation of pulmonary carcinoid tumor

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Introduction

Paraneoplastic neurological syndromes (PNS) represent a diverse group of immune-mediated disorders affecting the nervous system in patients with malignancy, occurring remote from the primary tumor site or its metastases.[1] These syndromes often precede the diagnosis of the underlying malignancy by weeks to months, with neurological symptoms frequently serving as the initial presenting complaint.[1] Among the various paraneoplastic neurological manifestations, sensory ganglionopathy—also termed sensory neuronopathy—is a distinctive syndrome characterized by selective damage to the dorsal root ganglia, resulting in progressive sensory ataxia, areflexia, and profound proprioceptive loss.[2]

Sensory ganglionopathy is most commonly associated with small-cell lung carcinoma, but has also been reported in association with breast, ovarian, prostate, and gastric cancers, lymphomas, and neuroendocrine tumors.[2] The pathophysiology involves an autoimmune attack on dorsal root ganglion neurons, mediated primarily by cytotoxic T lymphocytes and associated with antineuronal antibodies, particularly antineuronal nuclear autoantibody type 1 (anti-Hu), collapsin response mediator protein 5 (anti-CRMP5), and amphiphysin antibodies.[2,3] The presence of these antibodies, while highly specific (99%), demonstrates only moderate sensitivity (82%), indicating that their absence does not exclude an underlying malignancy.[3]

Pulmonary carcinoid tumors, representing well-differentiated neuroendocrine neoplasms of the lung, account for approximately 1-2% of all lung malignancies. While these tumors are generally considered low-grade with favorable prognosis, they can rarely present with paraneoplastic neurological syndromes. The association between carcinoid tumors and classical antineuronal antibody-mediated paraneoplastic syndromes has been infrequently reported in the literature. Tschernatsch et al. documented four patients with carcinoid tumors presenting with various paraneoplastic neurological syndromes, including sensory neuropathy one of whom had detectable anti-Hu antibodies.[4] This finding supports the hypothesis that carcinoid tumors, like small-cell lung carcinoma, can express neuronal antigens capable of triggering an autoimmune response against the nervous system.

The rarity of this clinical presentation poses significant diagnostic challenges. Sensory ganglionopathy may manifest with insidious onset of sensory symptoms, including numbness, paresthesias, and progressive sensory ataxia, which can precede tumor diagnosis by months. The recognition of this association is clinically important, as it may prompt earlier detection of an otherwise occult malignancy and influence treatment decisions.

We present a case of pulmonary carcinoid tumor manifesting as sensory ganglionopathy, contributing to the limited literature on this rare association and highlighting the diagnostic approach, immunological findings, and clinical course of this challenging presentation.

Case Report

A 71-year-old female presented with bilateral axillary burning paresthesias which started abruptly 14 years prior. There was no evidence of dermatologic abnormality including rash or erythema. Symptoms were persistent although would worsen with light touch (such as with clothing) and with sweat production. Topical treatments were attempted, however without any relief in symptoms; she was previously placed on gabapentin for chronic cough which had a modest benefit on her paresthesias. Neuromuscular exam at time of initial presentation revealed diffusely absent pinprick sensation in all extremities and the trunk with preservation of pinprick sensation on the face; strength was largely preserved (except for mild weakness at the bilateral thumb abductors) and reflexes were generally diminished in the lower extremities. Mild ataxia was noted on finger-nose-finger testing.

Initial work up included mildly elevated vitamin B6 (47.9 ng/mL, range 2.1-21.7 ng/mL) and otherwise normal/negative complete blood count, metabolic panel, inflammatory markers, serum electrophoresis, copper, and vitamins B12, folate, B1, and E. An electromyography/nerve conduction study (EMG/NCS) was pursued and showed diffusely absent or very low amplitude sensory studies with normal motor studies and negative needle EMG consistent with sensory ganglionopathy (neuronopathy). Further serologic revealed improved vitamin B6 level (now 10.5 ng/mL) and normal/negative antinuclear antibody, anti-SSa/SSb antibodies, Smith antibodies, anti-DNA antibody, paraneoplastic panel, and HIV antigen/antibody. CT chest revealed a mass in the right middle lobe which was followed with a PET/CT which showed a 13 mm hypermetabolic nodule in the right middle lobe without any evidence of metastatic disease. Biopsy was pursued which revealed a grade 1 carcinoid/neuroendocrine tumor which was subsequently resected.

In follow-up she has reported an improvement in her paresthesias since resection of her carcinoid tumor. She was last seen in neuromuscular clinic about 16-17 months post resection. While her paresthesias had improved she continues to note intermittent symptoms of burning pain in the axilla and continues neuropathic pain medications to mitigate her symptoms. She continues to have mild sensory abnormalities in the extremities to pinprick and vibration, however ataxia was noted to be improved on follow up. Repeat electrodiagnostic testing was not pursued.

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Discussion

As mentioned earlier, this case is unique in its presentation and has very little similarity to other cases presented in the literature.

This case contributes to the limited literature documenting the rare association between pulmonary carcinoid tumors and paraneoplastic sensory ganglionopathy. While sensory ganglionopathy is most commonly associated with small-cell lung carcinoma there this syndrome has been described in patients with well-differentiated neuroendocrine tumors.[4]

This patient presented with paresthesias in a non-length dependent manner which is often the phenotype of sensory ganglionopathy, helping to differentiate it from a length-dependent sensory neuropathy.[2] Neurodiagnostic testing (EMG) was consistent with the diagnosis, with absent/low amplitude sensory nerve responses diffusely and normal motor nerve conduction studies and needle EMG. Vitamin B6 levels were found to be elevated initially, however given the elevation was minimal a vitamin B6 sensory ganglionopathy is thought to be unlikely.

Sensory ganglionopathy typically evolves over days to weeks and can precede a cancer diagnosis by weeks to months. This is somewhat inconsistent with the clinical history in the present case as symptoms had reportedly been present for several years prior to presentation. Records were incomplete, and it is unknown if pulmonary imaging had been completed in the years leading to presentation. Given the well-differentiated nature of her neuroendocrine tumor it is entirely possible that this mass was slow growing for many years as these tumors have a well documented slow growth grate; one study estimated a median volume doubling time of up to 4.1 years for low-grade pulmonary carcinoid tumors with another study suggesting a mean of 40.5 years until these tumors reach their final volume.[5,6]

Another challenge this case presented was the lack of a serologic positive paraneoplastic antibody. As noted above anti-Hu, anti-CRMP5, and anti-amphiphysin antibodies have been described as pathogenic in sensory ganglionopathy. There have been documented cases, however, of paraneoplastic neurologic syndromes related to neuroendocrine tumors without positive paraneoplastic antibodies.[4] The current patient's clinical course suggests an association between her neuroendocrine tumor with sensory ganglionopathy, given the partial clinical improvement seen with removal of the tumor.

Conclusion

This case underscores several important clinical points. First, sensory ganglionopathy should prompt evaluation for underlying malignancy, including neuroendocrine tumors beyond small-cell lung carcinoma. Second, early recognition and aggressive immunotherapy may offer the best chance for neurological stabilization, even if complete recovery is unlikely. Third, treatment of the underlying carcinoid tumor, while essential for oncological outcomes, may not lead to full neurologic recovery. Finally, long-term multidisciplinary follow-up is essential to address both oncological and neurological complications.

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Diagnosis and Management of Immune Mediated Polyneuropathies: A lecture from the Neuromuscular Review Course

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Acute Immune Mediated Polyneuropathies

Acute polyneuropathies are best thought of as a group rather than focusing solely on Guillain-Barré syndrome.

These conditions tend to come on acutely and are monophasic, meaning they begin, reach a plateau, and then resolve (Figure 1). They are often preceded by an infection, though not always. Most cases fall under Guillain-Barré syndrome (GBS) with a characteristic demyelinating pattern, but not all do. GBS is also referred to as acute inflammatory demyelinating polyneuropathy (AIDP). Progression typically occurs over days to a couple of weeks.

GBS classically presents with ascending weakness and large-fiber sensory loss, with motor involvement usually more pronounced than sensory involvement.

It is generally symmetric (Figure 2). Clinical severity varies widely. Some patients may present with relatively mild symptoms, reporting weakness that developed weeks earlier without major progression, while others deteriorate rapidly and require intensive care within 24 hours (Dimachkie & Barohn, 2013).

There are numerous variant presentations that still follow an acute monophasic pattern.

Not all cases are ascending (Figure 3). First symptoms may be ocular, pharyngeal or in the arms and then they descend. These have been labeled the oculopharyngeal and brachiopharyngeal variants. Some patients initially experience radicular pain resembling sciatic or cervical pain for several days before weakness appears. Other presentations include facial weakness or paraparesis that can mimic spinal cord pathology. The classic works by Allan Ropper in the 1980s and 1990s helped define these atypical forms (Ropper 1986; Ropper 1994).

There are also "no-weakness" presentations, most notably Miller Fisher syndrome, first described in the 1950s (Fisher 1956). This syndrome is characterized by acute ophthalmoplegia and ataxia with preserved reflexes. These cases are usually straightforward to recognize and tend to resolve spontaneously within six to eight weeks. Evidence suggests intravenous immunoglobulin (IVIg) does not significantly alter outcomes in this subtype.

Another related condition is Bickerstaff brainstem encephalitis, considered a central nervous system variant in which immune attack targets structures emerging from the brainstem. Patients may develop ophthalmoplegia, ataxia, confusion, and increased reflexes.

Additional variants include acute autonomic neuropathy, sensory ganglionopathy, and pure sensory neuropathy. Axonal forms, such as acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN), are often described as having faster progression. They may be labeled as AMSAN because the most rapidly progressive cases are the ones that come to attention earliest. In other words, it can be confused with typical cases of GBS where nerve conduction studies are done too early and do not show demyelinating changes yet, but this is probably an improper use of the term AMSAN which refers to only cases that have axonal loss in addition to an absence of demyelination.

Diagnostic evaluation typically begins when a neurologist is consulted for acute weakness.

Figure 1

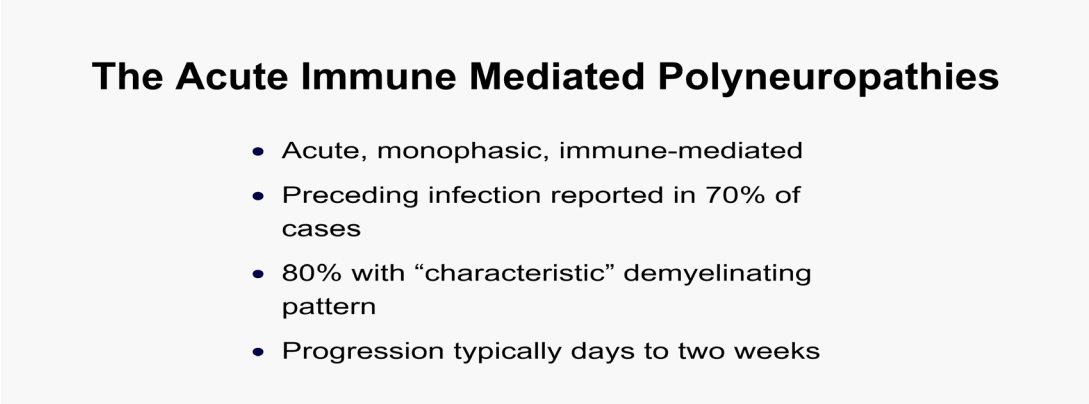

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Figure 2

The Phenotype of Classic AIDP (The Guillain Barre Syndrome)

- Acral paresthesia or dysesthesia
- Objective sensory loss often mild or delayed
- Symmetric ascending weakness
- Severity spectrum from very mild to complete paralysis

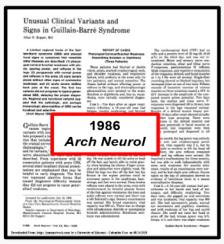
Dimachkie, Barohn. Guillain-Barre Syndrome and Variants. Neurol Clin. 2013 May;31(2):491-510

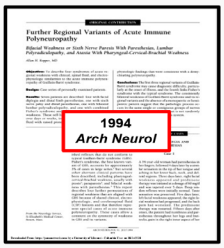
Figure 3

Variant presentations

Atypical patterns of weakness

- Oculopharyngeal, Brachiopharyngeal
- Radicular pain
- Facial weakness
- Paraparesis resembling spinal cord lesion





1986 *Arch Neurol*
Ropper AH. Unusual clinical variants and signs in Guillain-Barré syndrome. *Arch Neurol.* 1986;43(11):1150-1152.

1994 *Arch Neurol*
Ropper AH. Further Regional Variants of Acute Immune Polyneuropathy: *Arch Neurol.* 1994;51(7):671–675.

No weakness (5%):

- Miller-Fisher Syndrome: acute ophthalmoplegia ataxia (AOA)

N Engl J Med. 1956 Jul 12;255(2):57-65. doi: 10.1056/NEJM195607122550201.
An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia)
M FISHER
PMID: 13334797 DOI: 10.1056/NEJM195607122550201

- Bickerstaff's: ophthalmoplegia, confusion, DTR ↑
- Acute autonomic neuropathy, sensory ganglionopathy
- Acute pure sensory neuropathy

Axonal forms:

- AMAN 10%
- AMSAN 5%
- These have "faster progression"

Figure 4

Acute Inflammatory Neuropathy Work Up

- Lumbar puncture
  - WBC count is typically 0 to 5, but can be up to 10-30
    - If WBC count is over 15 consider wider differential: HIV, Lyme, sarcoid, West Nile, leptomingeal carcinomatosis
  - Protein may be normal early on
    - Elevated in 90% after first week
- NCS:
  - Also have relatively poor sensitivity early after presentation (about 22%)
    - Mildly prolonged F-waves or distal latencies may be only finding
  - By 2 to 3 weeks post onset:
    - Temporal dispersion, conduction block, then slowing
    - Sensitivity of NCS is 87% at 5 weeks

Two primary tests support the diagnosis: lumbar puncture and nerve conduction studies (Figure 4). Lumbar puncture is often performed first. The key finding is cytoalbuminologic dissociation, elevated protein with minimal cells. Lymphocytic pleocytosis (up to 50-60 cells per cubic millimeter) can occur and does not exclude the diagnosis but prompts consideration of alternative causes such as HIV, Lyme disease, sarcoidosis, or West Nile virus. CSF protein may be normal or have minimal elevation early on. Normal CSF protein early on does not rule out the diagnosis of GBS.

Similarly, nerve conduction studies may show only minor abnormalities early in the disease course. Slightly prolonged distal latencies or F-waves are usually the earliest electrophysiologic sign of the condition. More definitive demyelinating findings (temporal dispersion, conduction block, slowing) can take up to several weeks to appear.

Treatment

Treatment focuses primarily on IVIg, typically initiated when patients lose independent ambulation. Figure 5 summarizes recommendations from the AAN practice parameters.

Very mild ambulatory cases may not require intervention. Plasmapheresis is an alternative but is usually more logistically complex. Sequential IVIg and plasmapheresis are avoided because plasmapheresis removes therapeutic immunoglobulin. Both IVIg and plasmapheresis are giving the patient a better long-term prognosis. One should not expect rapid improvements after IVIg or plasmapheresis has been administered. In fact, the goal of the treatment is to improve long-term outcome such as decreasing time in the intensive care unit and shortening the time to ambulation. If progression continues after a completed IVIg course, supportive management is usually preferred over repeat treatment (Hughes 2003; Cortese 2011; Walgaard 2021). IVIg has a half-life of about three weeks.

A key transition point is distinguishing AIDP from chronic inflammatory demyelinating polyneuropathy (CIDP) (Figure 6).

Figure 5

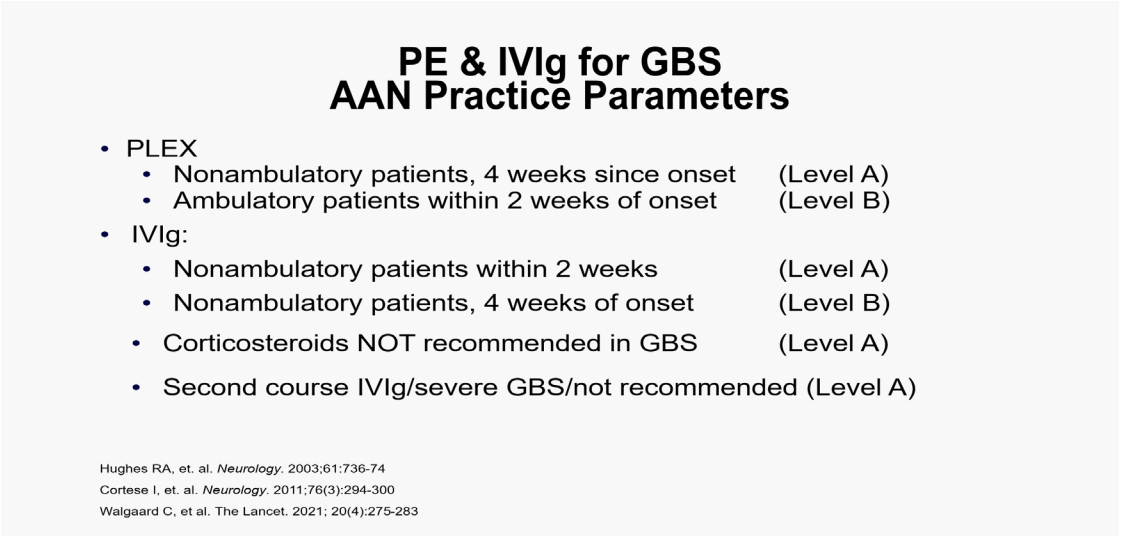


Figure 6

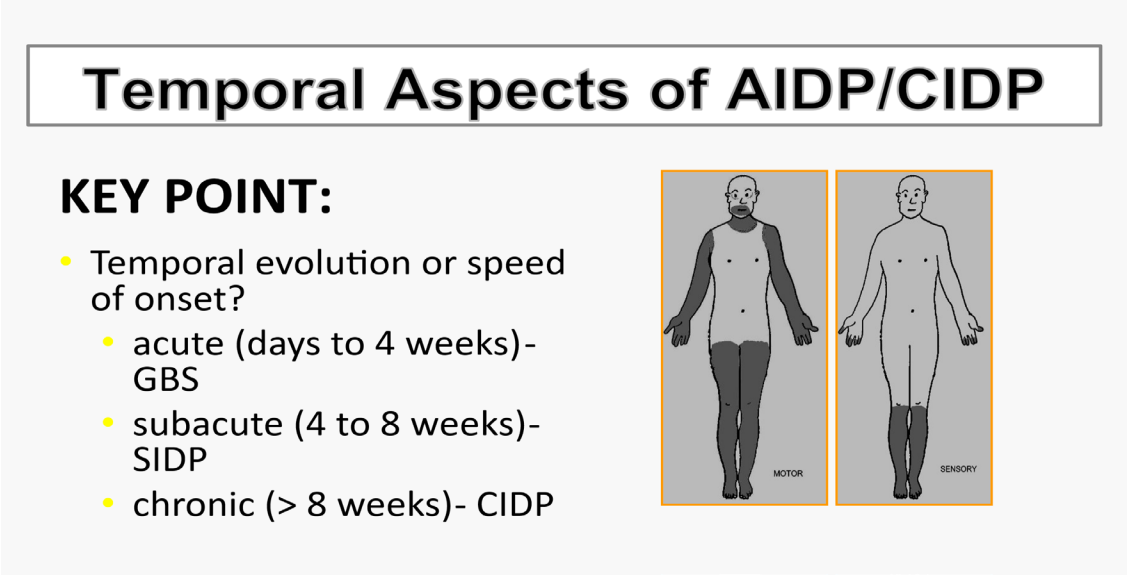


Figure 7

CIDP: Community Bias Slants Towards Over-diagnosis

- Allen and Lewis
  - 50% of CIDP cases referred to tertiary center do not meet disease criteria
  - Based on comparison to disease criteria

Muscle Nerve. 2018 Apr;57(4):542-549

Neurology. 2015 Aug 11;85(6):498-504

- Levine et al.
  - Nearly 70% of immune neuropathies cases where IVIG is approved by insurance do not have CIDP
  - Based on expert review of submitted charts

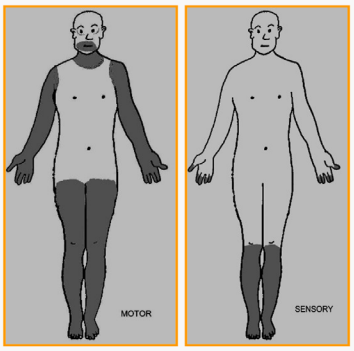
Neurol Clin Pract. 2018 Oct;8(5):429-436

- Diagnoses that may be confused with CIDP/MADSAM/MMN
  - Subacute combined degeneration, POEMS, amyloid, CMT, Diabetic neuropathy, CSPN, primary muscular atrophy, DADS-M, GBS with poor recovery

Figure 8

Early Descriptions of CIDP (Typical CIDP)

- "Tendency towards symmetric proximal and distal weakness"
- Of all FOUR extremities
- Large fiber modalities
  - Large fiber sensory loss
  - Weakness
  - Loss of reflexes



Barohn RJ, Kissel JT, Warmolts JR, Mendell JR. Chronic inflammatory demyelinating polyradiculoneuropathy. Clinical characteristics, Course and recommendations for diagnostic criteria. Arch Neurol 1989;46:878 -884.

Gorson KC, Katz J. Chronic inflammatory demyelinating polyneuropathy. Neurol Clin. 2013 May;31(2):511-32.

The time it takes to present is generally used to differentiate acute (GBS/AIDP), subacute (SIDP), and chronic (CIDP) cases. A patient may present acutely yet continue progressing for months, ultimately meeting criteria for chronic disease. Therefore, this is a fluid diagnosis. Approximately 15% of patients initially diagnosed with Guillain-Barré will continue to progress and later demonstrate CIDP. Conversely, some cases that appear chronic may still be monophasic. Observation over time is essential before making definitive classification.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Typical CIDP presents with symmetric, proximal, and distal weakness, large-fiber sensory loss, and reflex reduction (NP1) (Barohn, Kissel, et al 1989; Barohn, Dimachkie, et al 2024; Barohn, Wolfe, et al 2025; Gorson & Katz 2013; Saperstein, et al 2001).

CIDP carries a high community misdiagnosis rate (Figure 7). Studies by Jeffrey Allen and Richard Lewis (Allen & Lewis 2015; Allen, Ney, Lewis 2018) demonstrated that roughly half of referred CIDP cases referred to an expert clinic failed to meet strict criteria, even when patients seemingly reported objective improvement with therapy.

Figure 9

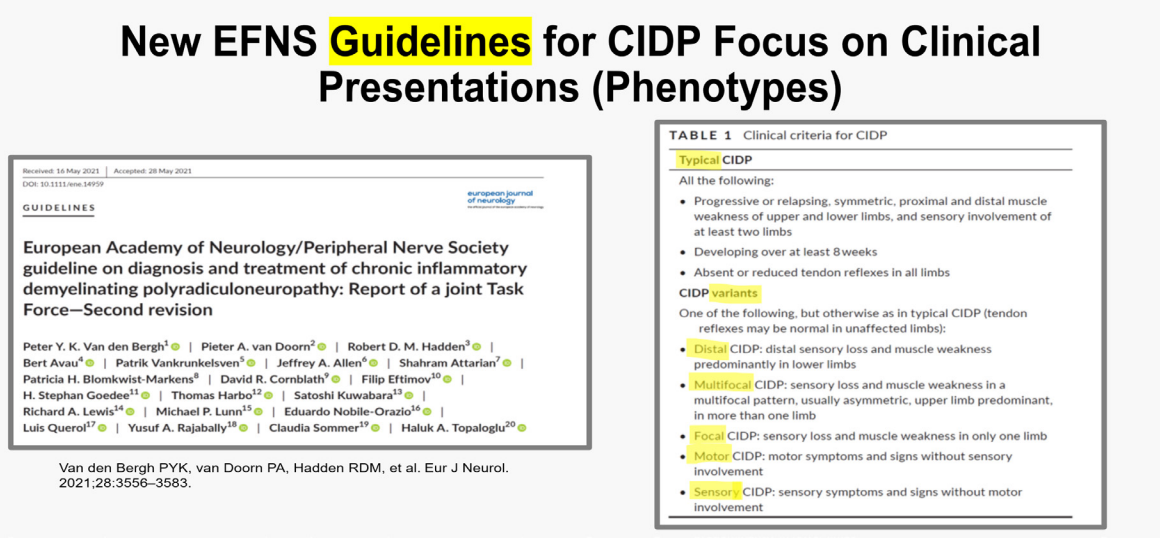
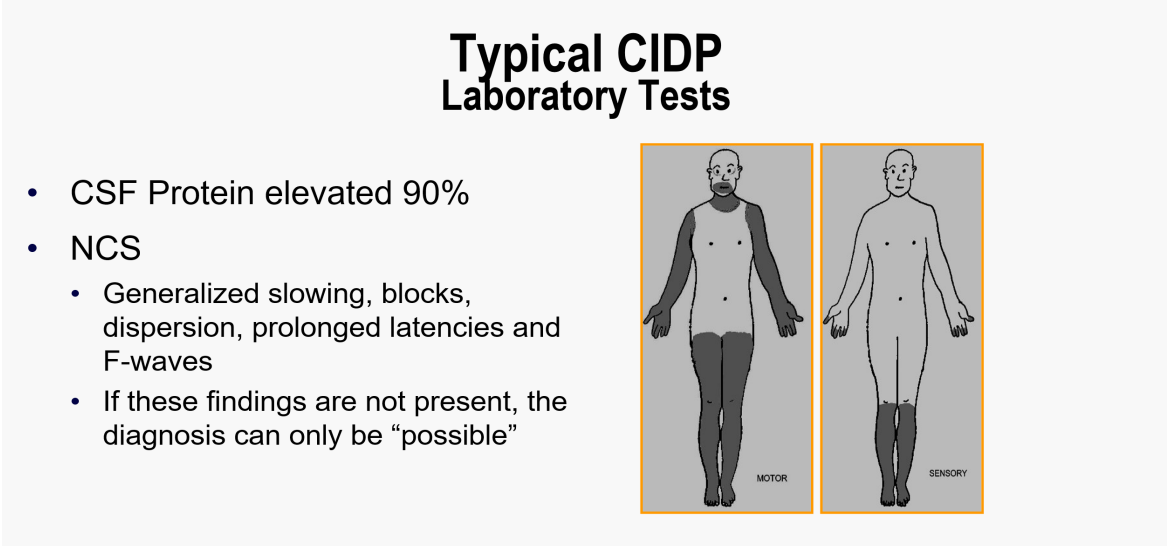


Figure 10



Additional work by Todd Levine found that most insurance-approved IVIG cases lacked convincing diagnostic evidence (Levine, et al 2018).

Early descriptions of CIDP emphasize a tendency towards symmetric proximal and distal weakness of all four extremities (Figure 8). Therefore this is consistent with the neuropathy pattern 1 (NP1) emphasized in the pattern recognition approach to neuropathy (Barohn, Dimachkie, et al 2024; Barohn, Wolfe, et al 2025).

Figure 9 shows the 2021 European Academy of Neurology/Peripheral Nerve Society guidelines which are the most commonly cited criteria (Van den Bergh, et al 2021). The guidelines separate phenotypes and electrodiagnostic findings, considering them each independently. Typical CIDP remains the same condition it was when first described over 50 years ago. In addition, there are five variant forms of the disease. Electrodiagnostic criteria that are "strongly supportive of CIDP" are used to confirm the diagnosis. When electrodiagnostic studies are only weakly supportive, the cases are categorized as possible CIDP. These designations relate to how many different specific nerve conduction abnormalities are found in a study such as conduction block, temporal dispersion, conduction slowing, prolonged distal latencies, and prolonged F-waves. Laboratory testing and response to treatment can be used to upgrade diagnostic certainty when electrodiagnostic testing is only weakly supportive. These guidelines are sensitive and specific for CIDP and were developed to maximize the chance of making a diagnosis. It should be noted that there is no single diagnostic test that can confirm or exclude a diagnosis of CIDP.

Typical CIDP is supported by marked demyelination on nerve conduction studies and elevated CSF protein (Figure 10).

Figure 11

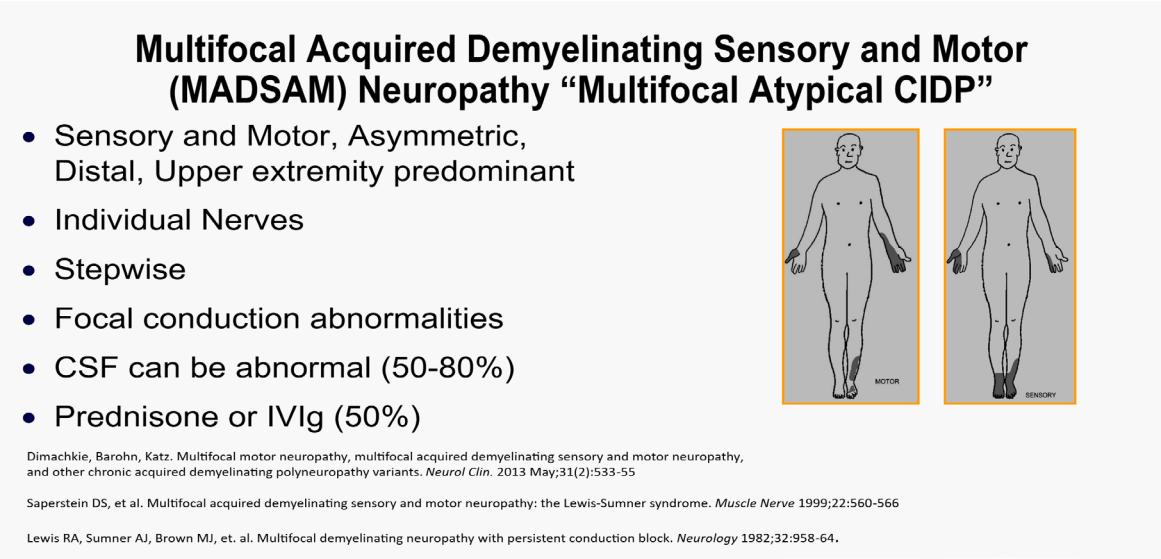
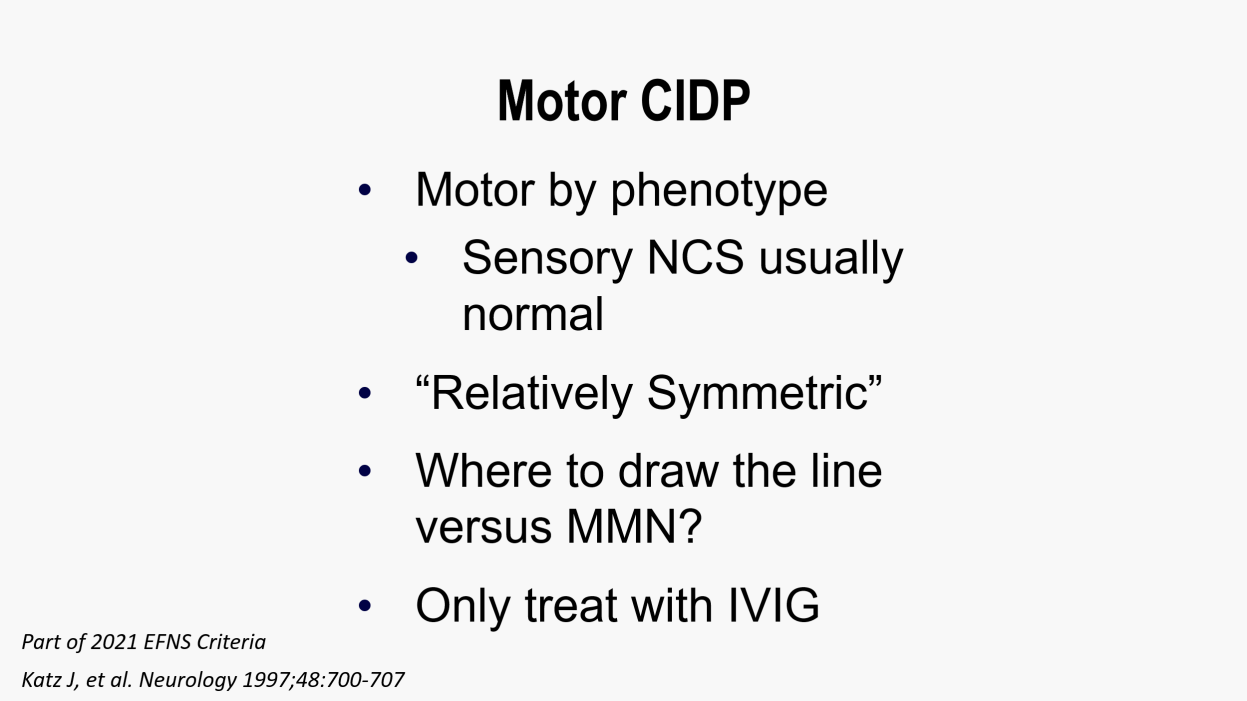


Figure 12



The variant phenotypes include distal, multifocal, focal, pure motor, and sensory presentations, each with different diagnostic challenges.

Asymmetric Phenotypes

Multifocal CIDP, historically called Lewis-Sumner syndrome or multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), involves patchy asymmetric nerve involvement resembling multiple focal lesions (Lewis & Sumner 1982; Saperstein, et al 1999; Saperstein, et al 2001; Dimachkie, Barohn, Katz 2013).

Motor CIDP is rare and presents with symmetric generalized weakness usually involving proximal and distal muscles in the upper and lower extremities (Figure 12).

In contrast to typical CIDP, there is no sensory involvement. These patients may have normal sensory nerve conduction studies, but if sensory nerve conduction studies are abnormal in a case with a motor CIDP phenotype, the condition is called predominantly motor CIDP. Motor CIDP must be differentiated from multifocal motor neuropathy (MMN). The EAN guidelines use the term "relatively symmetric" for motor CIDP while MMN characteristically presents as a clearly asymmetric condition (Figure 13). In our view, the two conditions present on a spectrum (Katz 1997;

Figure 13

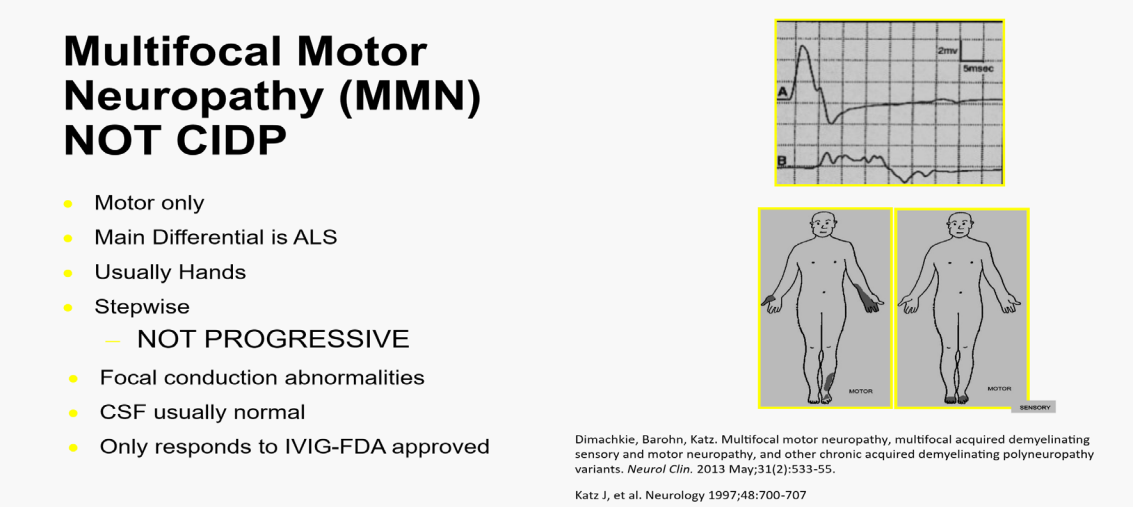
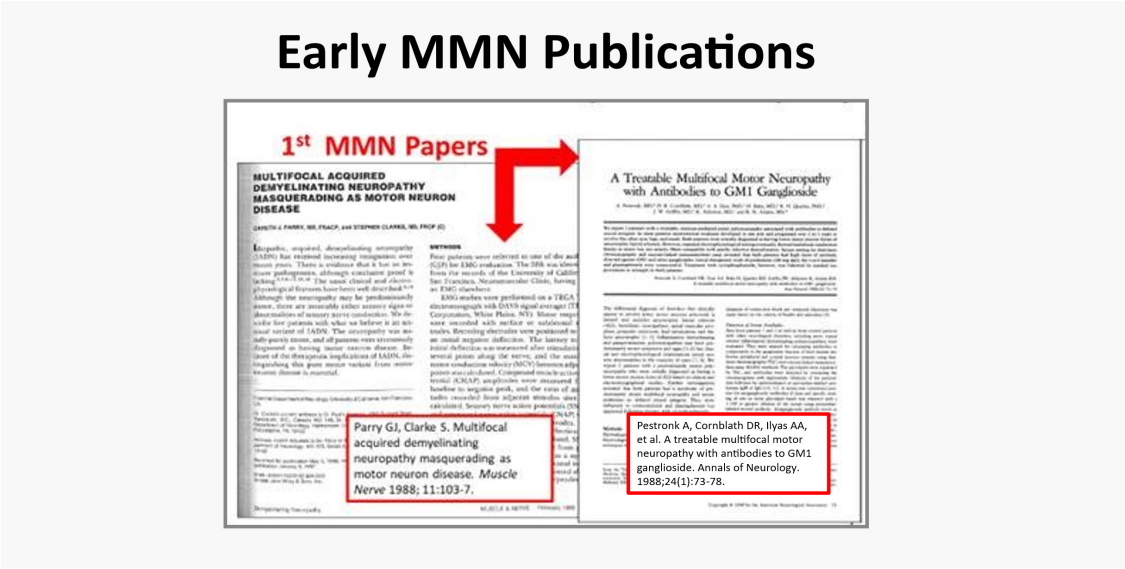


Figure 14



Saperstein, et al 2001). However, the authors of the 2021 EAN guidelines treat MMN as a completely distinct condition from CIDP. Figure 14 shows the two earliest publications on MMN (Figure 14).

Early reports of MMN came from ALS clinics. Before the disease was understood, these patients presented with asymmetric distal motor weakness and were often diagnosed with ALS. As a result, they tended to be patients that sat in ALS clinics for years without progression. It was eventually discovered that many of these patients had conduction block and conduction slowing in motor nerves and later that the patients were responsive to IVIg. The autoimmune nature of this condition also became recognized because of the discovery of autoantibodies against GM1 ganglioside in a percentage of these patients. Unlike other autoimmune peripheral nerve diseases, MMN does not respond to steroids and in fact to date no new treatment has been discovered besides IVIg (Katz 1997; Saperstein, et al 2001; Dimachkie, Barohn, Katz 2013).

Distal presentations of chronic inflammatory demyelinating polyneuropathy (CIDP) are particularly challenging to diagnose. In our prior work, we emphasized the difficulty of recognizing these relatively rare cases among several more common conditions that also present with predominantly distal sensory or both sensory and motor signs.

A paper by Shin Oh in 1992 (Oh 1992) reported on a series of patients who presented with numb feet or numb feet accompanied by weak ankles yet demonstrated profound demyelinating abnormalities on nerve conduction studies indistinguishable from typical CIDP. These patients correspond to the distal CIDP variant in the current EAN criteria and show marked demyelinating abnormalities. They can respond to either IVIG or prednisone, but the response rate is probably much lower than other disease variants. In an early publication, we refer to these cases as distal acquired

Figure 15

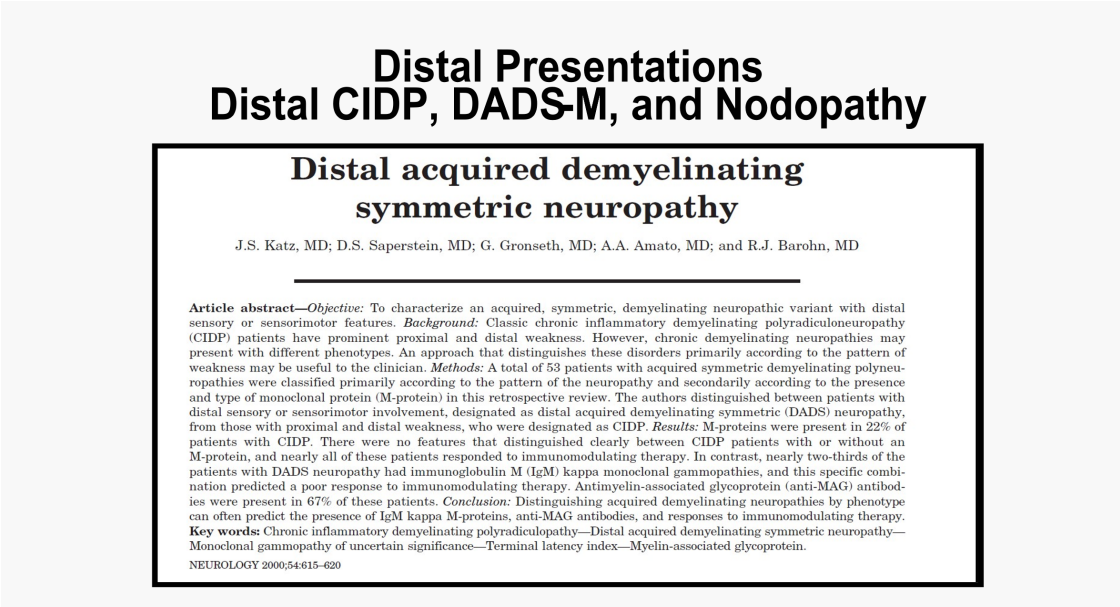
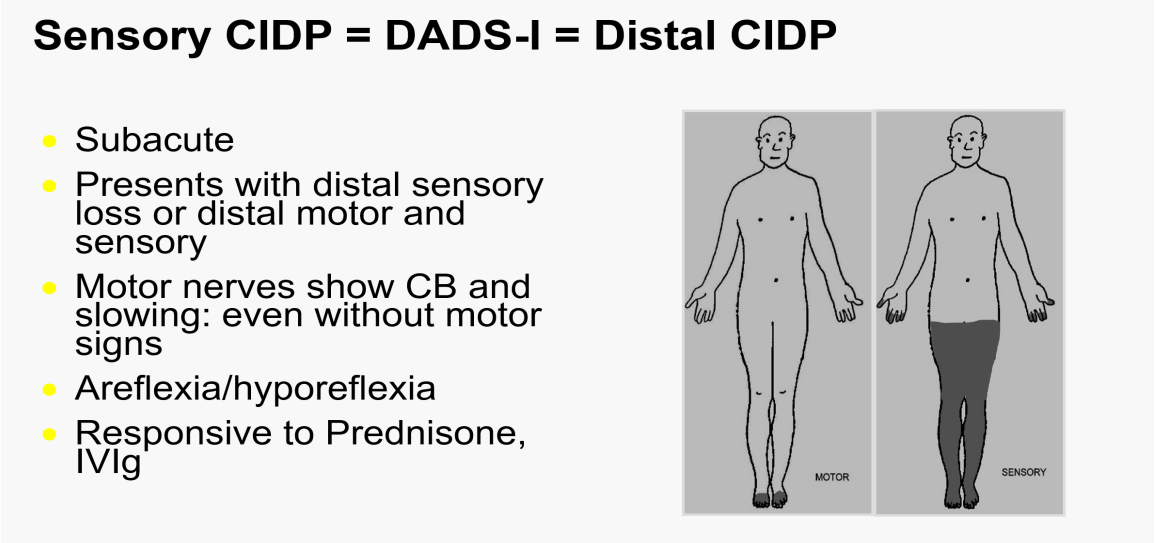


Figure 16



demyelinating symmetric neuropathy without an IgM monoclonal protein or DADS-I (Figures 15 & 16) (Katz, et al 2000). Our goal at the time was to distinguish these cases from DADS-M neuropathy with a monoclonal protein. We also wanted to distinguish it from diabetic neuropathy and CSPN, which sometimes has more than minor degrees of demyelination on nerve conduction studies.

Although nodopathies are not strictly distal and may resemble typical CIDP, they represent a distinct subset of disease and are not considered part of the CIDP spectrum according to the EAN criteria (Querol, et al 2014; Querol, et al 2015; Querol, et al 2017; Doppler, et al 2015; Doppler, et al 2016; Doppler, et al 2017). In these cases, patients have measurable antibodies directed against components of the nodes of Ranvier, which interfere with saltatory conduction. These target proteins include neurofascin and contactin. Clinically, patients are usually younger, present with severe weakness and sometimes tremor. Most importantly, nodopathies are notoriously difficult to treat.

Before we get to DADS-M, it is important to interpret antibody results in the appropriate clinical context. A patient with otherwise typical CIDP who responds well to therapy may have positive anti-nerve antibodies, but in such cases the antibodies may not provide meaningful diagnostic insight. By contrast, a younger patient with a distal-predominant presentation, tremor, and treatment-refractory disease who tests positive for nodal antibodies more closely fits the syndrome of interest.

A recurring issue in the antibody literature is the risk of false-positive results. Many antibody studies originate in laboratory settings, where samples are submitted from a broad range of neuropathy cases. While a small number of samples may represent true disease with positive antibodies, a larger number may reflect unrelated neuropathies in which

Figure 17

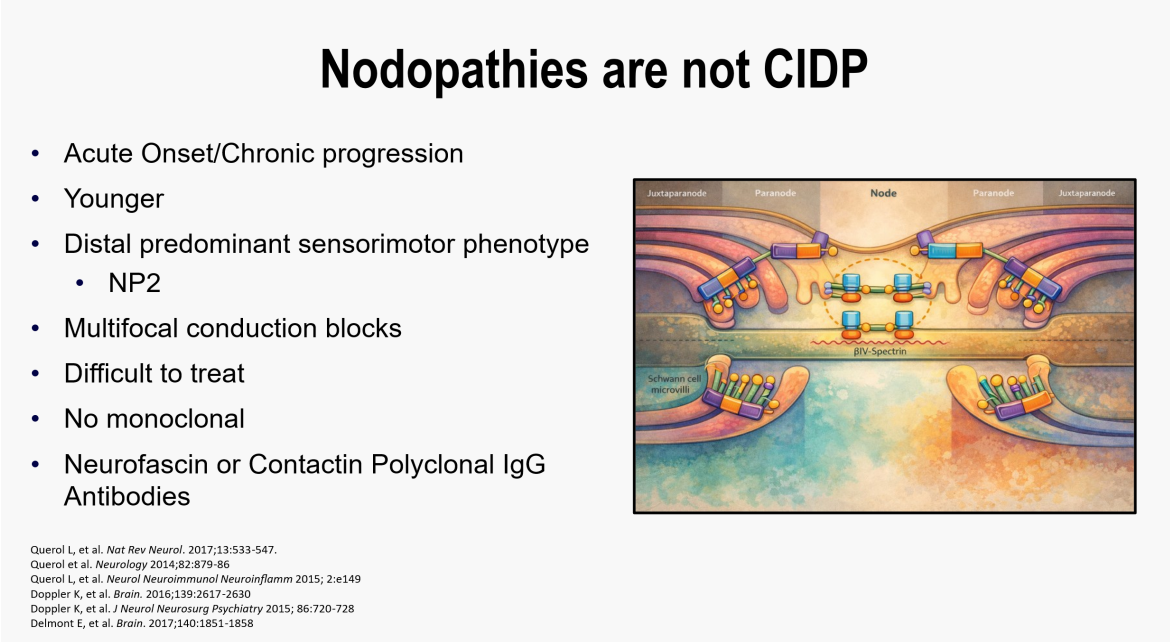
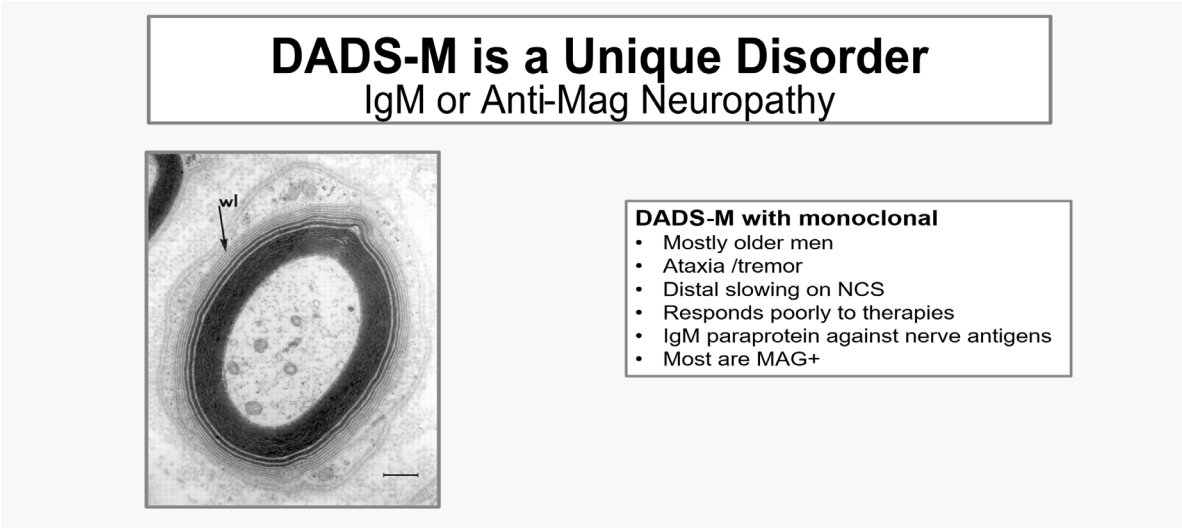


Figure 18



false positives occur. Because true nodopathies represent such a small percentage of cases, false positives within the population of all other neuropathies may outnumber true positives in laboratory datasets. Distinguishing true-positive from false-positive results is essential and we recommend first focusing on the clinical context and making sure that the antibodies are representative of a distinct clinical syndrome. In contrast to conditions such as myasthenia gravis, where antibody positivity closely correlates with clinical disease, antibody interpretation in neuropathy requires considerable caution. This complexity contributes to the diagnostic difficulty of these disorders.

The third distal demyelinating presentation, and the one that is probably the most common in clinical practice, is distal acquired demyelinating symmetric neuropathy with IgM monoclonal gammopathy (DADS-M) (Figure 18).

DADS-M is a distinct disease entity. It affects older men, produces distal slowing on nerve conduction studies, and responds poorly to therapy. Many patients exhibit anti-MAG antibodies. Aggressive treatment has shown minimal long-term benefit and carries risk. Electron microscopy demonstrates a characteristic unraveling of myelin, in which the myelin sheath separates from the axon. As the axon loses trophic support from the myelin, secondary axonal degeneration develops. Over time, the neuropathy may resemble a primary axonopathy despite its demyelinating origin.

DADS-M is characterized by distal sensory symptoms—typically numb feet—in association with an IgM paraprotein (the "M" in DADS-M). DADS-M is not considered part of the CIDP spectrum according to the EAN criteria. These cases have also been labeled "IgM neuropathy" or "anti-MAG neuropathy," but we discourage these terms.

Figure 19

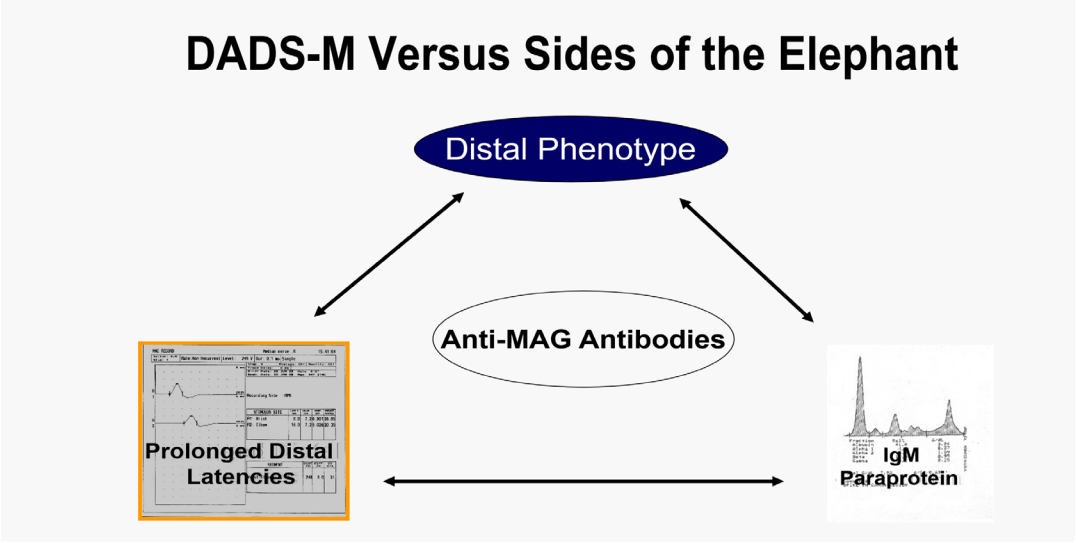
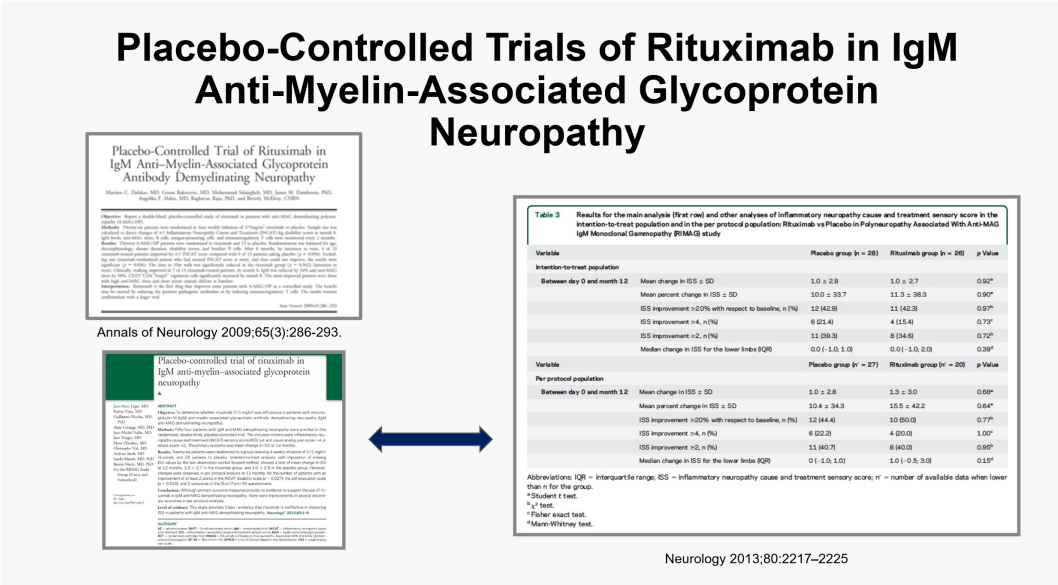


Figure 20



The term "IgM neuropathy" is imprecise. IgM paraproteins may be present in other clinical syndromes. When the typical features of DADS-M are not present, the IgM may represent a monoclonal gammopathy of uncertain significance (MGUS) or be related to another disease process. Similarly, anti–myelin-associated glycoprotein (MAG) antibodies may yield false-positive results, particularly when ordered indiscriminately as part of broad panels. However, when the clinical syndrome is recognized first and anti-MAG antibodies are subsequently identified, the finding supports the diagnosis.

Clinically, DADS-M most commonly affects older men and may be associated with tremor. Nerve conduction studies reveal a distinctive pattern of uniform, distal-predominant slowing, reflected primarily in prolonged distal latencies. Conduction block is typically absent. The condition responds poorly to therapy. Approximately 80% of patients who exhibit the characteristic triad—distal phenotype, prolonged distal latencies, and IgM paraprotein—also have anti-MAG antibodies, although some do not.

Most patients described in the literature as having "IgM neuropathy" or "anti-MAG neuropathy" in fact have DADS-M. Studies, including one from France and another from the National Institutes of Health, demonstrate that these cases are largely refractory to therapy, likely because of substantial secondary axonal involvement. Both studies evaluated rituximab (Rituxan), and outcomes after one year showed no meaningful difference between treatment and control groups, with p-values approximating 0.9 (Figure 20) (Dalakas, et al 2009; Léger, et al 2013).

Shortly after our DADS paper was published, a subsequent report from Italy described 19 patients with IgM

Figure 21

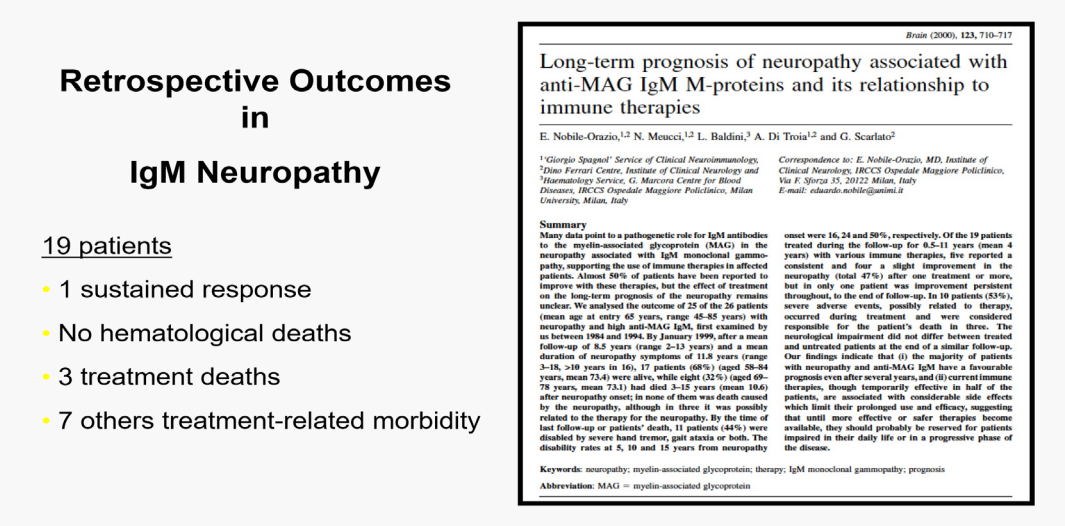
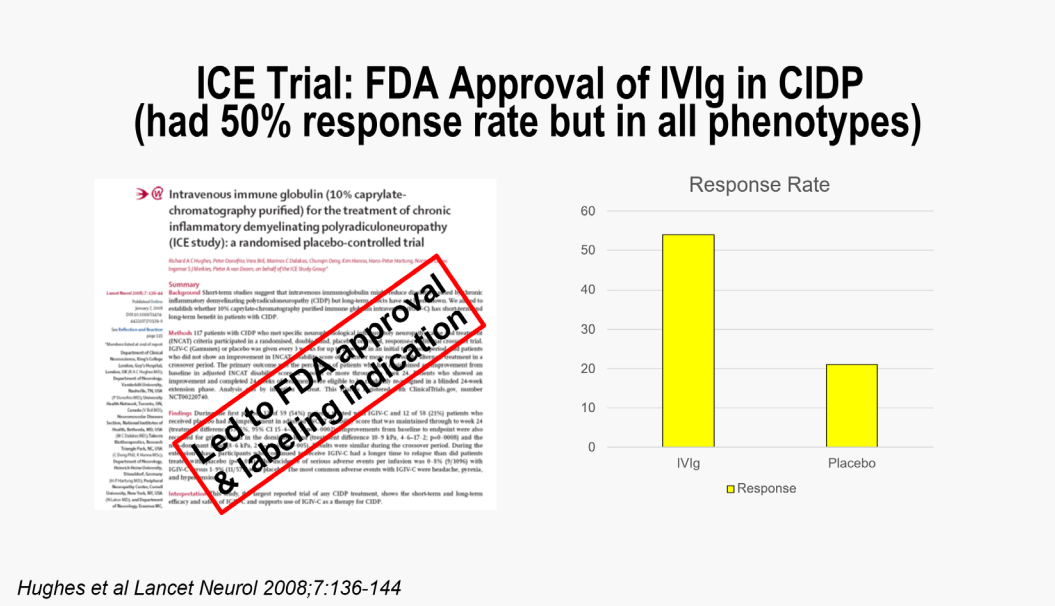


Figure 22



Hughes et al Lancet Neurol 2008;7:136-144

paraproteins who, like our patients with DADS, had been treated aggressively for a presumed diagnosis of CIDP over the years before DADS-M was distinguished as a separate disorder (Figure 21) (Nobile-Orazio, et al 2000).

The paper showed these patients did not have overt malignancy, and the IgM was not indicative of blood cancer. Nonetheless, several patients experienced treatment-related morbidities, and only one achieved a sustained response. In our view, the responder could represent a patient with otherwise typical CIDP who happened to have an incidental IgM paraprotein. Overall, the clinical reality remains that most patients with DADS-M do not experience meaningful improvement with available therapies. Our practice has been to avoid treatment as long as the condition remains low grade and chronic, which it usually does.

In summary, distal neuropathic presentations demand careful clinical assessment. Antibody testing can be informative but must be interpreted within a well-defined clinical syndrome. Without this context, there is substantial risk of misclassification and inappropriate treatment.

Treatment of CIDP and its Variants

Prior to the introduction of IVIg for CIDP, the two primary modes of therapy were prednisone and plasmapheresis. An investigator initiated a clinical trial that demonstrated that IVIg was more effective than placebo in improving the neurologic status of CIDP patients (Mendell, et al 2001). Subsequently, the pharmaceutical industry has been heavily involved in establishing trials in order to get medications FDA approved for CIDP. The first industry-initiated trial that led to FDA drug approval for CIDP was the ICE trial (Figure 22) (Hughes, et al 2008). That study demonstrated that approximately half of patients respond to IVIg. 20% of patients also improved during placebo therapy

Figure 23

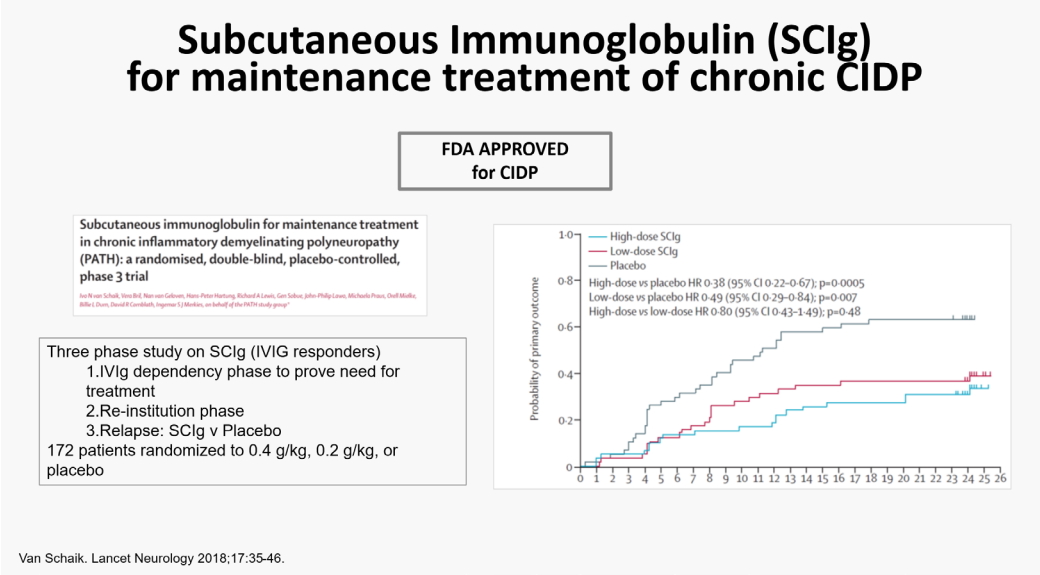
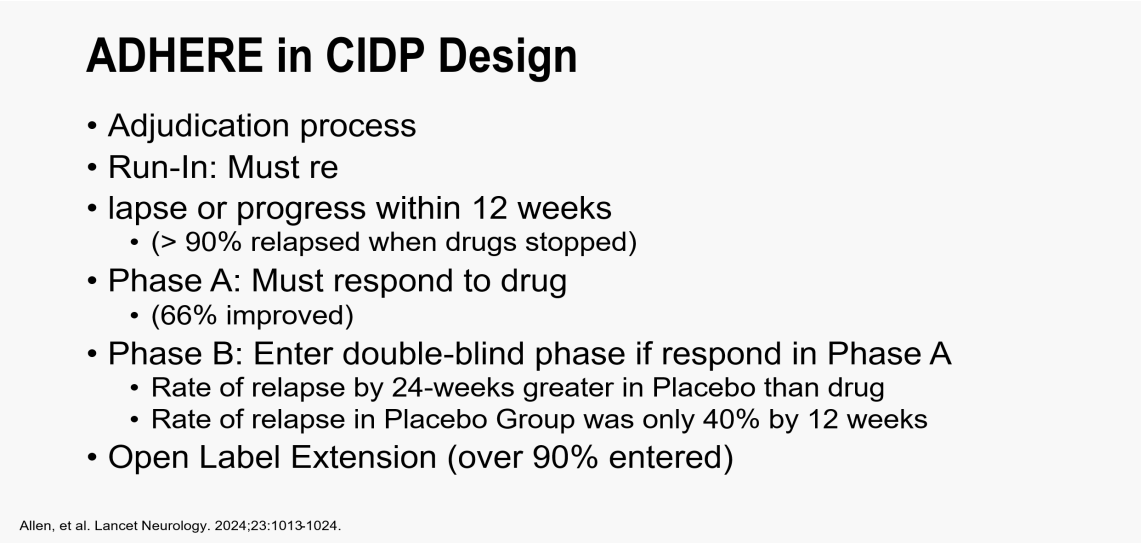


Figure 24



reflecting diagnostic complexity. Most studies use 2 grams per kilogram induction dose followed by 1 gram per kilogram every three weeks.

Subsequently, subcutaneous immunoglobulin was shown to be effective for CIDP in the PATH study (Figure 23) (van Schaik, et al 2018). In this study, patients that were stable on intravenous immunoglobulin were randomized to placebo or to different doses of subcutaneous immunoglobulin and patients randomized to subcutaneous immunoglobulin had a lower relapse rate than patients randomized to placebo. This led to FDA approval of subcutaneous preparation. Keeping up with the theme of diagnostic complexity, not all of the patients randomized to placebo relapsed despite having been stable of IVIg prior to the study. Patients can be converted to subcutaneous immunoglobulin after they have been on a stable dose of IVIg. The usual conversion dose from IVIg is 1:1.

The next new class of drugs approved for CIDP were Fc receptor blockers and thus decreases levels of endogenous immunoglobulin. Figure 24 describes the ADHERE study that led to FDA approval of efgartigimod for CIDP (Allen, et al 2024). The ADHERE trial found that 70% of patients who had been withdrawn from their standard of care treatment and subsequently relapsed, improved when they received open label efgartigimod. The patients who responded to efgartigimod were subsequently placed in a double-blind withdrawal phase where patients treated with efgartigimod relapsed less frequently than those in the placebo arm. The data from this withdrawal phase led to FDA approval.

While the results seem to be encouraging at first glance, the trial data is worth discussing. First, the trial started with an open withdrawal of standard of care therapy. The goal was to determine which patients had treatment-dependent CIDP. Unfortunately, nearly all patients relapsed, suggesting

Figure 25

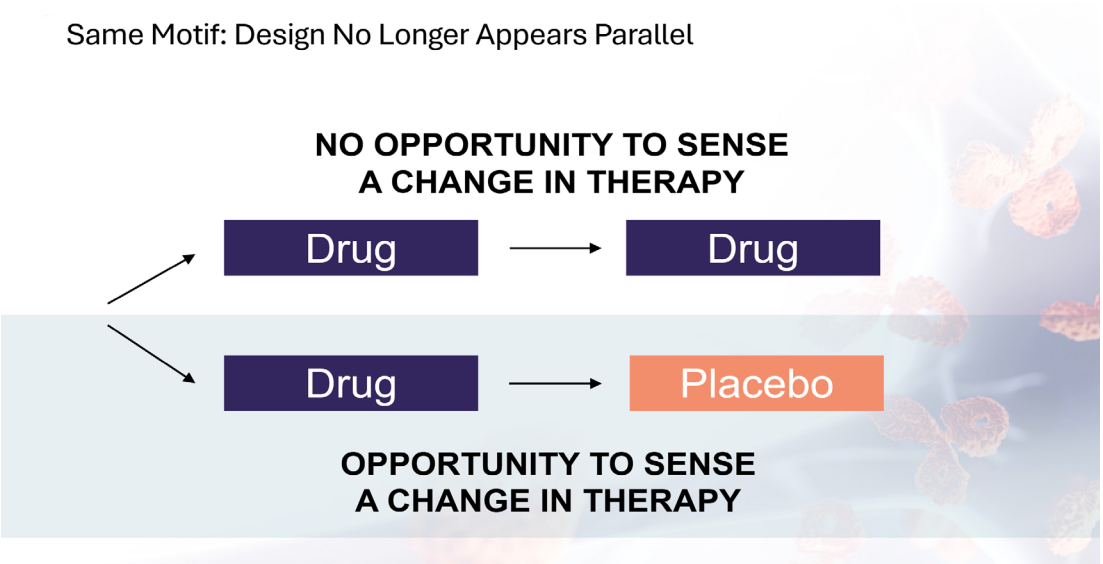
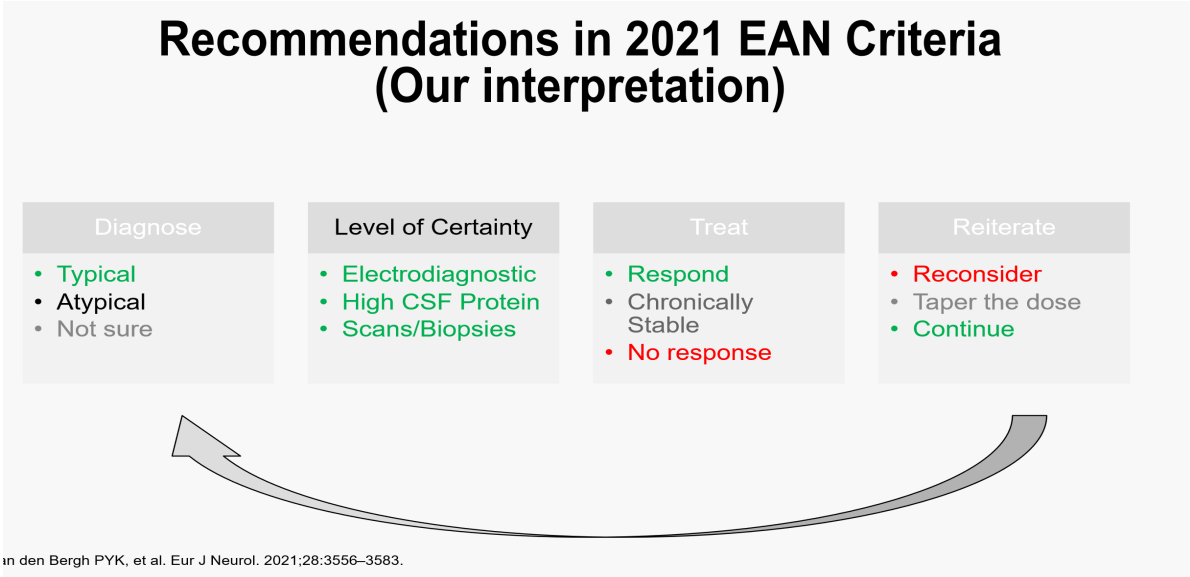


Figure 26



that those who were susceptible to placebo response reacted to the discontinuation of their treatment as well as those who truly withdrew from biologically consistent pathology. The trial used patient reported outcome measures so there was no objective way to control adverse reported outcomes. Similarly, high relapse rates have been seen in previous CIDP trials (Cornblath, et al 2023). The next phase was open label treatment with efgartigimod in patients that were already relapsing from discontinuation of their standard of care therapy. In this phase, approximately 30% of patients left the trial, presumably because they went back on standard of care therapy. We don't know what percentage of the 70% of patients that were rescued by efgartigimod were potentially placebo responders. These responders entered the double-blind withdrawal phase which had two problems. One, as mentioned above, is that the trial may have had a significant number of patients who were prone to placebo responses. The second was that patients had just been exposed to efgartigimod and could have recognized if they were no longer on treatment, particularly if there were any adverse effects that changed. In contrast, the group that remained on treatment had no opportunity to sense any change (Figure 25). In a disease like CIDP where we know that there is a prominent placebo effect, the potential of unblinding could potentially lead to discrepancies in outcomes. After the FDA approved the drug, there were immediate reports of severe worsening in patients that were transitioned from IVIg to Fc inhibitor therapy (Levine & Muley 2025).

Clinically, diagnosis should proceed with structured skepticism. If CIDP is suspected clinically, confirmatory electrodiagnostic findings, CSF abnormalities, and even therapeutic responses are all key diagnostic tools. Lack of improvement should prompt reassessment, taper trials, and reconsideration of the diagnosis. Confidence in the diagnosis

increases when there are reproducible treatment responses and relapse patterns.

Because of the known problem with misdiagnosis and the additional possibility that correctly diagnosed patients may no longer require therapy, the EAN criteria recommend a cautious approach to therapy with detailed diagnostic criteria. In essence, the criteria break down the disease into typical CIDP and variants and encourage the clinician to keep close tabs on outcomes long after the original clinical encounter (Figure 26) (Van den Bergh, et al 2021). The criteria go on to say that when treatments do not lead to clear and objective responses to therapy, the diagnostician should consider stopping therapy, readdressing the diagnosis, and even referring the case to expert centers for confirmation. In other words, they are recommending a Bayesian approach where one should have a probabilistic assumption about the diagnosis before ever starting treatment and to update that probability (either more likely or less likely) after observing the response to treatment. This means that when the diagnosis is highly likely at the start because it is typical and many supporting features are present, a poor response to therapy would suggest that the diagnosis is still likely and other therapies might be considered. On the other hand, if the initial findings are more in line with the variant phenotype, electrodiagnostic findings are weak, or other supporting features are not present, the clinician should be cautious and a negative response to therapy would lead to consideration of other conditions.

Figure 27 summarizes the range of different therapies that CIDP patients reported taking in a 2010 survey (Koski, et al 2011). Most were on IVIg, or prednisone and a number of patients ended up on other less commonly used therapies. We wonder if the new EAN criteria had been developed at that time, how many of the patients on therapy would have been reconsidered as possibly having a different diagnosis. There were probably many patients that did not have active CIDP in that survey.

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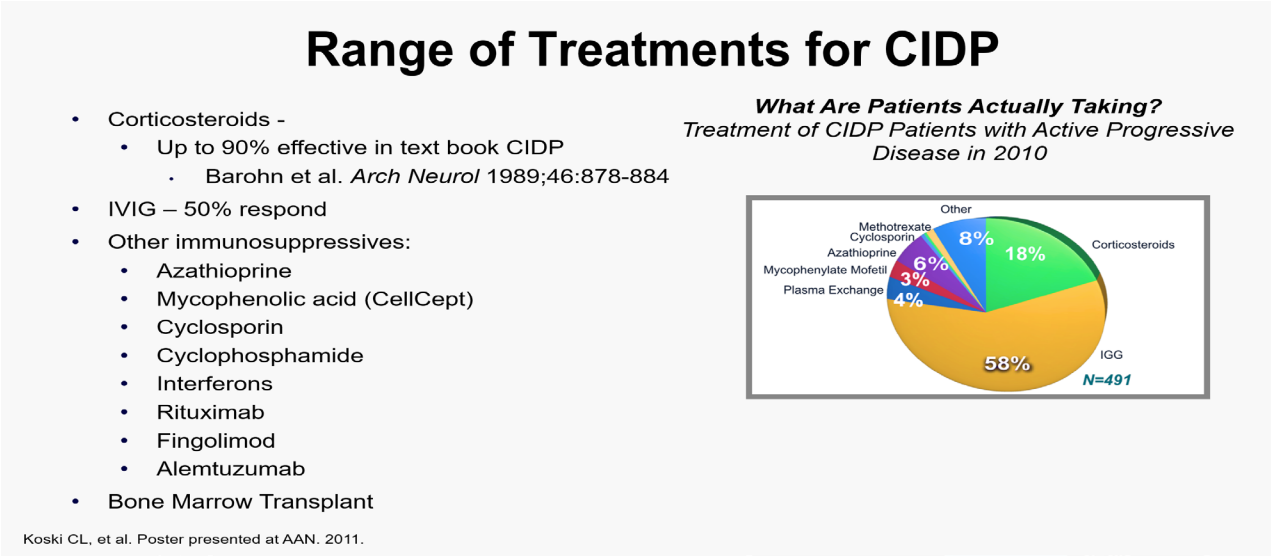
Figure 27



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History of neurology: Charles Bell and François Magendie - British versus French fights in the age of Napoleon and the discovery of the Bell-Magendie Law

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Executive Vice Chancellor for Health Affairs, Hugh E. and Sarah D. Stephenson Dean, University of Missouri School of Medicine

A live recording of this lecture can be viewed here: RRNMF – Charles Bell & Francois Magendie

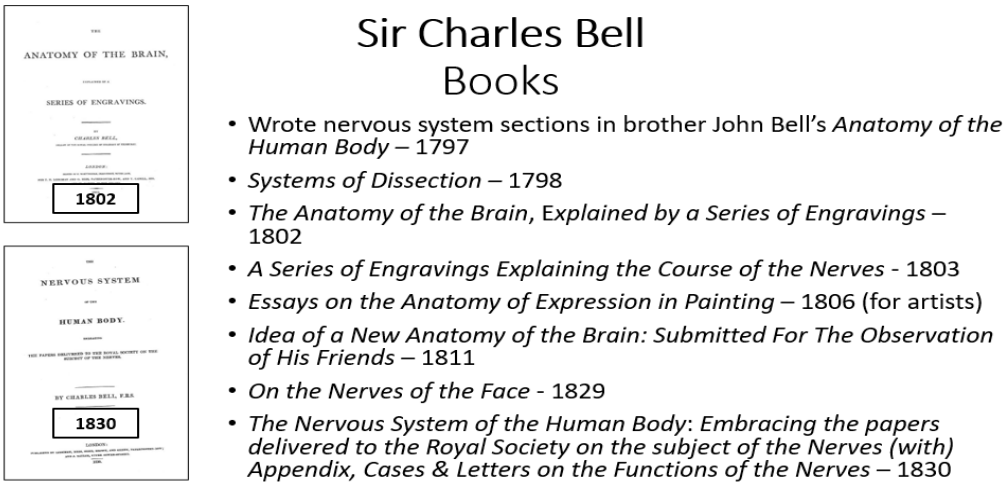
This History of Neurology segment is about Charles Bell and François Magendie. I have subtitled this talk "British versus French Fights in the Age of Napoleon and the Discovery of the Bell-Magendie Law".

Charles Bell, who was eventually knighted as Sir Charles Bell, was born in Edinburgh.[1] He attended medical school in Edinburgh, where one of his mentors was Alexander Monro of the famed Monro dynasty. Bell was also a very talented artist, and many members of his family shared this artistic talent. While he was in medical school, he wrote *Systems of Dissection* to help medical students understand anatomy.[2] He then published this as a book in 1789 and it became very popular.

In 1804, Bell left Edinburgh for London. He was part of a diaspora of highly talented Scottish physicians and anatomists who relocated to London, where his career ultimately developed. Bell served as a physician during the British–French wars, caring for wounded soldiers. He was present at the Battle of Waterloo in 1815 where the Duke of Wellington, the commander of all the Allied forces, finally defeated the Napoleonic forces. Bell served as a battlefield surgeon dealing with many gruesome war injuries. He noted this made him a better surgeon in his civilian practice, as our modern military physicians often report.

Figure 1

Figure 2



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We know Charles Bell through his many publications, especially his books, and many of these have been recently reprinted (Figure 2). He first wrote on nervous anatomy in his brother John Bell's book, *Anatomy of the Human Body,* when he still lived in Scotland.[3] Bell had incredible artistic and drawing skills and he created all of his figures himself. After moving to London, he began publishing important neuroanatomy manuscripts and books. *The Anatomy of the Brain, Explained by a Series of Engravings,* published in 1802, was followed by *A Series of Engravings Explaining the Course of the Nerves*, in 1803.[4,5] The brain anatomy book contains exquisite color engravings of the brain (Figure 3). After he drew the detailed and beautiful images, they would be sent to an engraver, and the engraver would then send them to a publisher. Often the names of the artist (Dr. Bell), the engraver, and the publishing are all listed at the bottom of a figure. One illustration shows a human head with the brain exposed, resting thoughtfully on a hand. These are reminiscent of the naturalistic poses Andreas Vesalius often used in his landmark anatomy book in 1543 (Figure 4).[6]

Bell created his own drawings and then passed these on to an engraver. Vesalius, on the other hand, worked with a workshop of artists led by the famous Venetian artist Titian (Tiziano Vecellio). At the time of Vesalius, the prints of the drawings were made through the woodcut process. In other words, the drawings were given to a woodcut engraver who reproduced the image in a wood block. Ink was placed on the woodcut and paper was applied to transfer the image. At the time of Charles Bell, prints were made by engravings in copper and ink was applied to the copper which was then transferred to paper.

In the 1803 book on *The Course of the Nerves*, in the preface Bell stated his "ambition" was "to dedicate the first years of his profession to the investigation of the strict anatomy of the human body; and to supply the imperfections of the introductory schoolbooks". Also in the preface, he stated the "views are given with simplicity, so as to facilitate an intricate study, and to enable the student to prosecute this department of Anatomy with encreasing interest and to greater minutness". Therefore once again, his goal was to teach

Figure 3

Charles Bell

Anatomy of the Brain - 1802

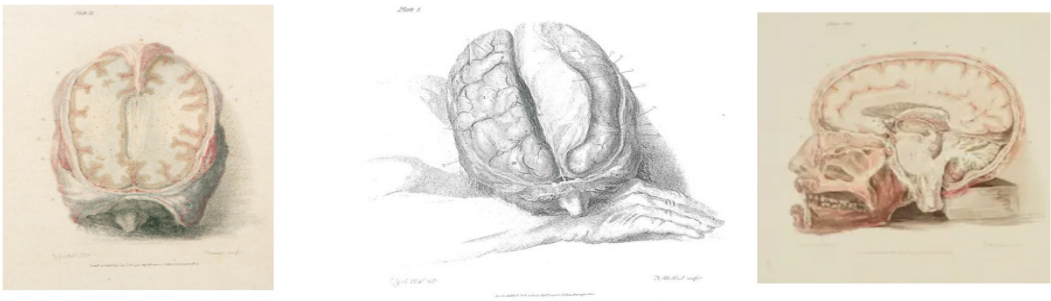


Figure 4

Images from Andreas Vesalius' 1543 Book

De Humani Corporis Fabrica Libri Septem

Figure 5

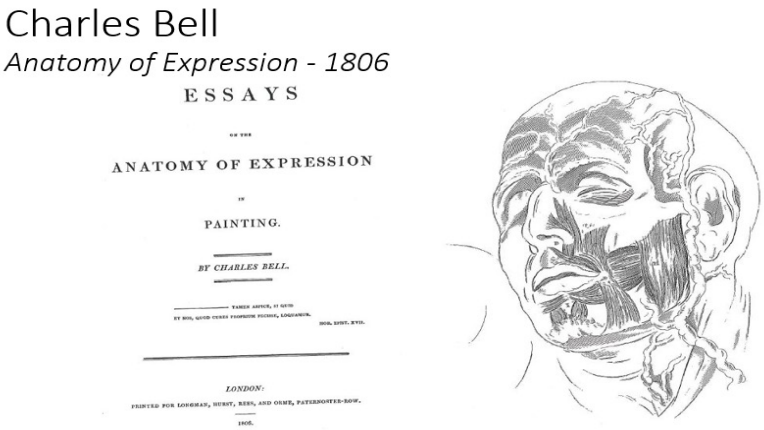


Figure 6

anatomy to medical students. Charles Bell was a teacher, in addition to being a physician and artist.

In 1806, he published *Essays on the Anatomy of Expression in Painting* (Figures 5 & 6).[7] This book was written specifically for artists so they could understand facial expression. This book included not only drawings of human facial expression but also expressions in animals. As a result, his work became well known in the art community, and he gained access to London's social and artistic circles, which he greatly enjoyed. He received a steady income from both the *Systems of Dissection* and *Anatomy of Expression* books that sustained him until his London practice matured.

Bell wrote a small volume called *Idea of a New Anatomy of the Brain* in 1811 (Figure 7).[8] This work was written primarily for his friends, and only about one hundred copies were produced. The early ideas he noted in this brief 36-page book became very important in the later debates with Francois Magendie on who first developed the concept of what would later be called the Bell-Magendie law.

Beginning in 1821, he read a series of papers that were later published in the Philosophical Transactions of the Royal Society of London.[9-12] In the 1821 paper, he described experiments that led him to the conclusion that cranial nerve VII sent nerves to the muscles of the face and cranial nerve V contained nerves that brought sensory information to the brain. This was a new concept that had not been published before this time. It showed that some nerves were predominantly motor and other nerves were predominantly sensory. In 1824, these papers were published in book format.[13] In 1829, he published in the Philosophical Transactions the paper *On the Nerves of the Face,* which he had previously read at the Royal Society.[14] In this publication, he gave detailed descriptions of the course of the seventh cranial nerve. In 1830, he wrote a much larger and more comprehensive book titled *Nervous System of the Human Body* (Figure 8), again featuring many detailed and elegant illustrations which included his now classic figure and description of the nerves of the face.[15] This book was his magnum opus. The title page stated the book was "embracing the papers delivered to the Royal Society on the subject of the nerves" presumably over many years. The 1830 publication contained an "appendix, containing cases and letters of consultation on nervous diseases, submitted to the author since the publication of his papers *On the Functions of the Nerves*, in the transaction of the Royal Society, and illustrative of the facts announced in the preceding pages". In the appendix, he then described case reports of 89 patients on whom he had been consulted. A number of these cases described injuries to the face producing facial paralysis. Other cases in which there were no obvious cause for the facial paralysis were described. We now call

these cases of facial paralysis "Bell's palsy". He also described cases producing paralysis of the lower extremities. These books made Bell famous throughout the world of medicine. At the same time, he maintained a very busy medical practice and he became wealthy.

As seen in Figure 8, Bell produced detailed illustrations of peripheral nerves, including drawings of the brachial plexus and a striking diagram showing all the spinal roots and cranial nerves emerging from the brainstem and spinal cord.

Scientifically, Bell made numerous important contributions (Figure 9). As noted above, he demonstrated that cranial nerve V is primarily sensory to the face. He showed that cranial nerve VII is motor to the muscles of facial expression and described facial palsy due to damage of cranial nerve VII from a variety of causes, including gunshot wounds, syphilis, goring by an ox, and cases in which no cause could be identified. He described the long thoracic nerve which arose from cervical roots 5, 6, and 7 and innervated the serratus anterior muscle. This is now referred to as "the long thoracic nerve of Bell". He also described what is known as Bell's phenomenon or the palpebral-oculogyric reflex, in which the eyeballs rotate upward during voluntary eye closure. Neurologists use this sign routinely in medical practice to determine if a patient is giving full voluntary effort to squeeze their eye shut. When the examiner tries to pry the lids apart, if the pupils are still looking straight ahead, then the patient is not giving full effort.

Figure 7

Charles Bell

Idea of A New Anatomy of the Brain - 1811

- "On laying bare the roots of the fpinal nerves, I found that I could cut acrofs the pofterior fafciculus of nerves, which took its origin from the pofterior portion of the fpinal marrow without convulfing the mufcles of the back ; but that on touching the anterior fafciculus with the point of the knife, the mufcles of die back were immediately convulfed."

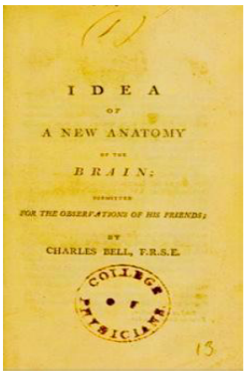


Figure 8

Charles Bell

Nervous System of the Human Body – 1830

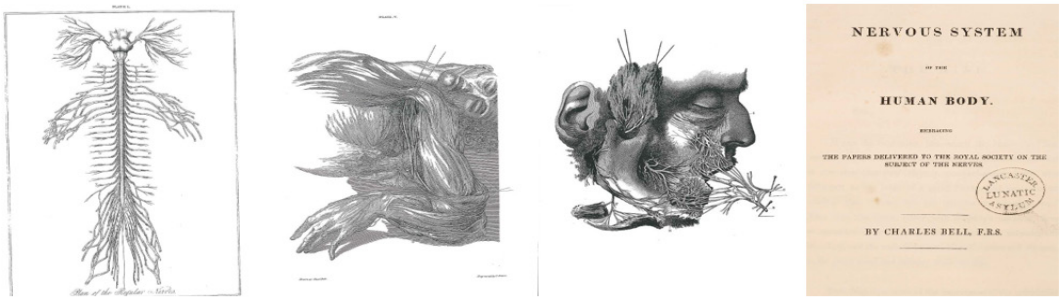


Figure 9

Charles Bell (1774 – 1842)
Scientific Innovations

- Demonstrated CN5 was sensory to the face & motor to mastication
- Demonstrated CN7 was motor to muscles of expression
- Facial palsy was to damage of CN7 due to a variety of causes:
  - Gunshot
  - Syphillis
  - Goring by ox
  - Unknown cause – Bell's Palsy
- Long Thoracic Nerve of Bell
- Bell's Phenomenon: Palpebral – Oculogyric Reflex
- Bell-Magendie Law

Figure 10

François Magendie (1793 – 1855)
Founder of French Experimental Medicine

- B. Bordeaux; family moved to Paris during revolution/political
- Med School 1799: Hotel Diex/Charite
- Mentors: Dupuytrene, Bichat
- Practicing hospital physician whole life
- 1803 – lecturer in anatomy
- 1816 – began experimental physiology in animals
  - Book: *Précis elementary de physiologies*
- 1822 – focused research on nervous system
- 1828 – Prof Physiology & General Pathology; College of France
- Experiments dividing various cerebellar connection & also removing cerebral hemispheres
- Described aperture medialis ventriculi quarti: now called Foramen of Magendie

This brings us to the Bell–Magendie law.

Before discussing the law itself, who was François Magendie (Figure 10)? Magendie is considered the founder of French experimental medicine, predating Claude Bernard. He was born in Bordeaux but moved to Paris because his father was very active in the French Revolution. He attended medical school in Paris, where his mentors included Dupuytren and Bichat.

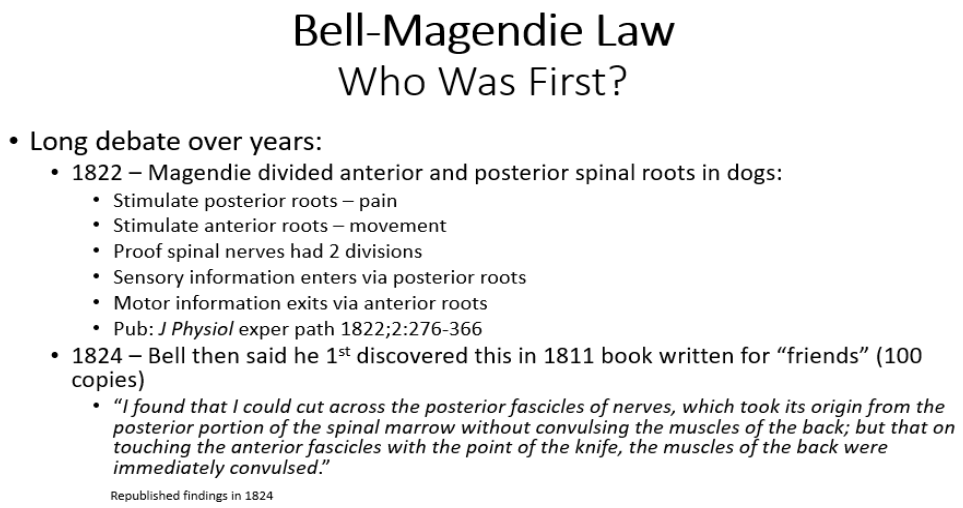
Magendie practiced as a hospital physician throughout his life, but he was also a lecturer in anatomy. He established his own anatomy school and became deeply involved in experimental physiology. In 1816, he published a book describing a wide variety of animal experiments, which became very well-known called *Précis élémentaire de physiologie*.[16] Beginning in 1822, he focused his research on the nervous system and was eventually appointed professor.

Magendie conducted numerous experiments on the central nervous system, including dividing different cerebellar connections and observing the resulting effects in animals. He removed one or both cerebral hemispheres in experimental studies and described the aperture of the median ventricle, now known as the foramen of Magendie.

Regarding the Bell–Magendie law, the key questions are: who was first, and what exactly was discovered? In 1822, Magendie published a paper in a French journal in which he divided the anterior and posterior spinal roots in dogs.[17] These were elegant and precise experiments. When he stimulated the posterior roots, he elicited pain. When he stimulated the anterior roots, he elicited movement. In doing so, he demonstrated that spinal nerves have two divisions: sensory information enters the spinal cord through the posterior roots, and motor information exits through the anterior roots. This became known as the Bell–Magendie law.

After this paper was published, Bell claimed that he had already described this phenomenon in his 1811 book, which had been written for a small circle of about one hundred friends (Figure 11).[8,18] In that book, Bell stated that he could cut across the posterior fascicles of nerves originating from the posterior portion of the spinal marrow without causing muscle convulsions, but that touching the anterior fascicles with the point of a knife immediately caused the muscles to convulse. Bell believed this demonstrated that he had

Figure 11



discovered the principle first, though not in the level of detail provided by Magendie.

As a result, a scientific dispute ensued and lasted for many years. In both his 1824 book and in the preface to the 1830 book *The Nervous System of the Human Body,* Bell relitigated the argument and republished long quotations from his 1811 manuscript. He also tried to explain why he had not published these findings earlier in the transactions of the Royal Society. In addition, in a footnote to the preface, he claimed that some of his students had performed detailed laboratory experiments in 1821 that had been published. He also stated that in July of 1821, he himself read his first paper regarding a quote "new arrangement" of the nerves that contained many of these concepts.[9] Therefore, he was not going to relinquish his claim that he was first. Bell and Magendie also argued over other neuroanatomical issues. While Napoleon was battling Horatio Nelson and the British on the battlefield, Dr. Bell and Dr. Magendie were fighting their own battles in the scientific press. However, he was not always arguing with Magendie. In the 1830 book, he took a more conciliatory approach and frequently mentioned other neuroanatomical contributions of Magendie that he agreed with.

Both Bell and Magendie are now considered giants in the early development of experimental neurophysiology and clinical neurology.

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History of Neurology: Queen Square and Regal Neurology

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A live recording of this lecture can be viewed here: RRNMF - Regal Neurology

This History of Neurology article is about the National Hospital for Neurology at Queen Square in London and is subtitled "Regal Neurology".[1,2]

Figure 1 shows a photograph of the National Hospital for Neurology in Queen Square, London, from the 1800s. The hospital opened in 1860 as the National Hospital for the Paralysed and Epileptic. It later was called at various times the National Hospital for Neurology, the National Hospital Queen Square, and more recently, the National Hospital for Neurology and Neurosurgery. It was and is still located on Queen Square in the historic Bloomsbury district of London. For the remainder of this article, we will simply refer to the institution as "Queen Square."The first two physicians appointed in 1859, one year before the hospital officially opened, were Jabez Ramskill, and Charles-Édouard Brown-Séquard, who was the subject of a History of Neurology article in Volume 7, Issue 1 of this year (See *History of Neurology: Charles-Édouard Brown-Séquard - The Original International Neurologist*, *The Founders of Neurology, p. 181-186* and *Fragments of Neurologic History, p. 221-227*).[2-4] Of course Brown-Séquard became well-known as a young physician by describing the syndrome of cord hemi-section which he produced in animals and described in humans.[5] Brown-Séquard moved back and forth between North America and Europe, and thus I have referred to him as the first international neurologist. He spent three years at Queen Square. While there, he gave a series of lectures and wrote his famous book, *Course of Lectures on the Physiology and Pathology of the Central Nervous System*.[6]

Figure 1

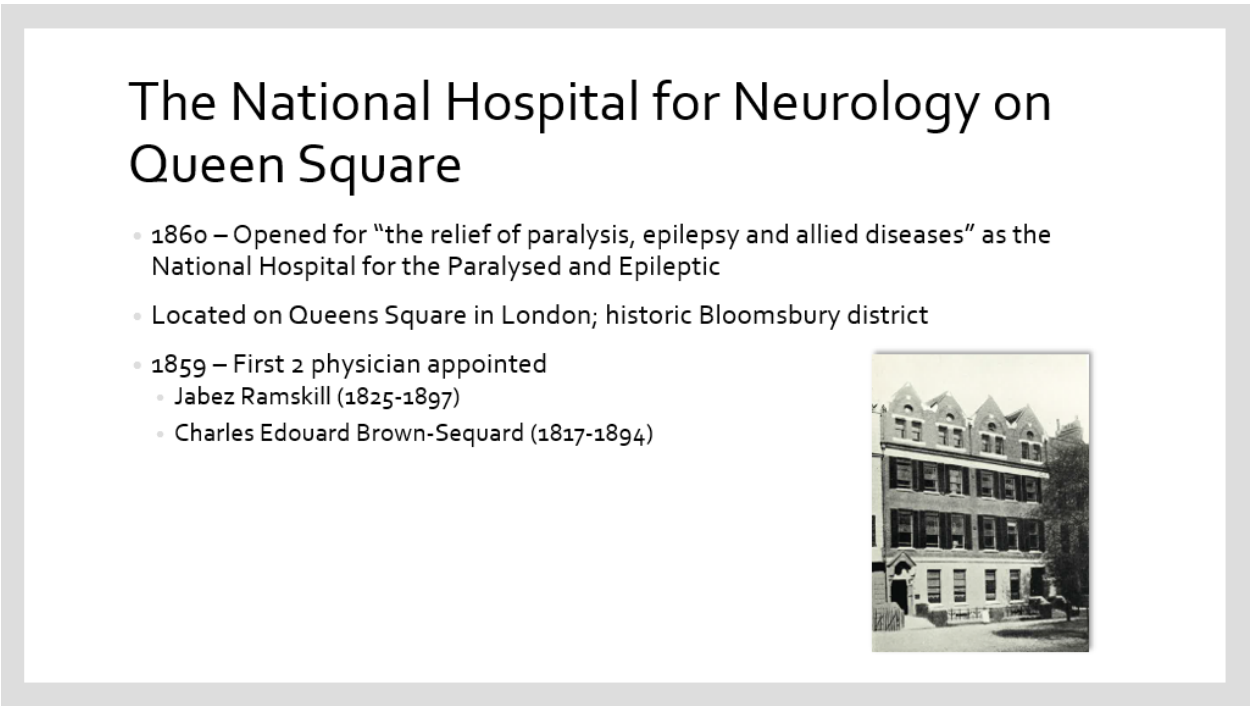

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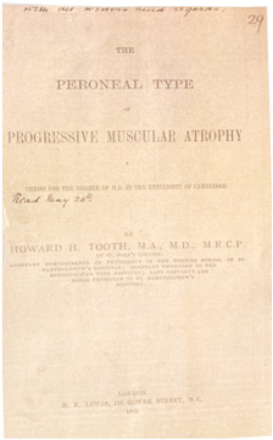
Figure 2

Notable Physicians at The National Hospital for Neurology and Neurosurgery – Queen Square

- 1859 – Appointed 1st 2 physicians:
  - Jabez Ramskill (1825-1897)
  - Charles Eduoard Brown-Sequard (1817-1894)
- 1862 – John Hughlings Jackson
- 1863 – Charles Bland Radcliffe
- 1867 – H. Charlton Bastion
- 1872 – Sir William Gowers
- 1880 – Sir David Ferrier
- 1883 – C.E. Beevor
- 1886 – Sir Victor Horsley (Surgeon)
- 1886 – Marcus Gunn (Ophthalmological Surgeon)
- 1887 – Howard H. Tooth
- 1891 – Sir Charles Ballance (Surgeon)
- 1893 – James Taylor
- 1900 – F. E. Batten
- 1909 – Sir Gordon Holmes
- 1912 – S.A. Kinner Wilson
- 1914 – J.G. Greenfield (Neuropathology)
- 1921 – Sir F.M.R. Walshe
- 1921 – W.J. Adie
- 1924 – G. Riddoch
- 1926 – Sir C.P. Symonds
- 1928 – McDonald Critchley
- 1935- Derek Denny-Brown
- 1944 – C.S. Hallpike

Figure 3

Doctoral thesis of Howard Tooth on The Peroneal Type of Progressive Muscular Atrophy (1886)


THE

PERONEAL TYPE

PROGRESSIVE MUSCULAR ATROPHY

HOWARD H. TOOTH, M.A., M.D., M.R.C.P.

Figure 2 is a list of other well-known neurologists, neurosurgeons, and physicians who were at Queen Square up until the 1940s. As you can see, many of these names are very recognizable to neurologists, neurosurgeons, and neuroscientists. John Hughlings Jackson and William Gowers, whom we will discuss more in this article, are included, as well as Sir Victor Horsley, who created the field of neurosurgery beginning in England (*The Founders of Neurology, p. 562-566* and *Fragments of Neurological History, p. 191-193*).[2, 3] He performed his first brain operation at Queen Square in 1886. The following year, he performed the first spine operation, and in 1889, he performed the first operation of the pituitary gland. He is often considered the father of neurosurgery and influenced many young surgeons. However, Harvey Cushing, was not impressed on his 1900 European tour when he saw Horsley frenetically operate on a Gasserian ganglion on a patient in a British mansion and reported that he had little to learn from British neurosurgery. This anecdote became famously repeated; however, Cushing did acknowledge Horsely's contributions to the field. Horsley also performed electrical experiments in monkeys, stimulating the cerebral

cortex, internal capsule, and spinal cord. He used a string galvanometer to record electrical current. He published his experimental findings in papers and a book.[7,8] Horsley unfortunately died at age 56 while he was serving as a field surgeon for the British Army in Mesopotamia during World War I. He succumbed to heatstroke complicated by intestinal infection while stationed at the British General Hospital in Iraq in Amara near Bagdad.

Other now famous clinicians include: Marcus Gunn, an ophthalmologist, and we still use the term "Marcus Gunn pupil" (*Fragments of Neurological History, p. 245-247*)[3]; William John Adie (*Fragments of Neurological History, p. 249-251*)[3], who described tonic pupils with absent tendon reflexes as a benign disorder[9]; Howard Tooth (*Fragments of Neurological History, p. 324-331*)[3], who made pioneering observations in hereditary neuropathy which he published as his doctoral thesis and whose name is associated with Charcot–Marie–Tooth disease;[10] Kinnier Wilson (*The Founders of Neurology,*

Figure 4

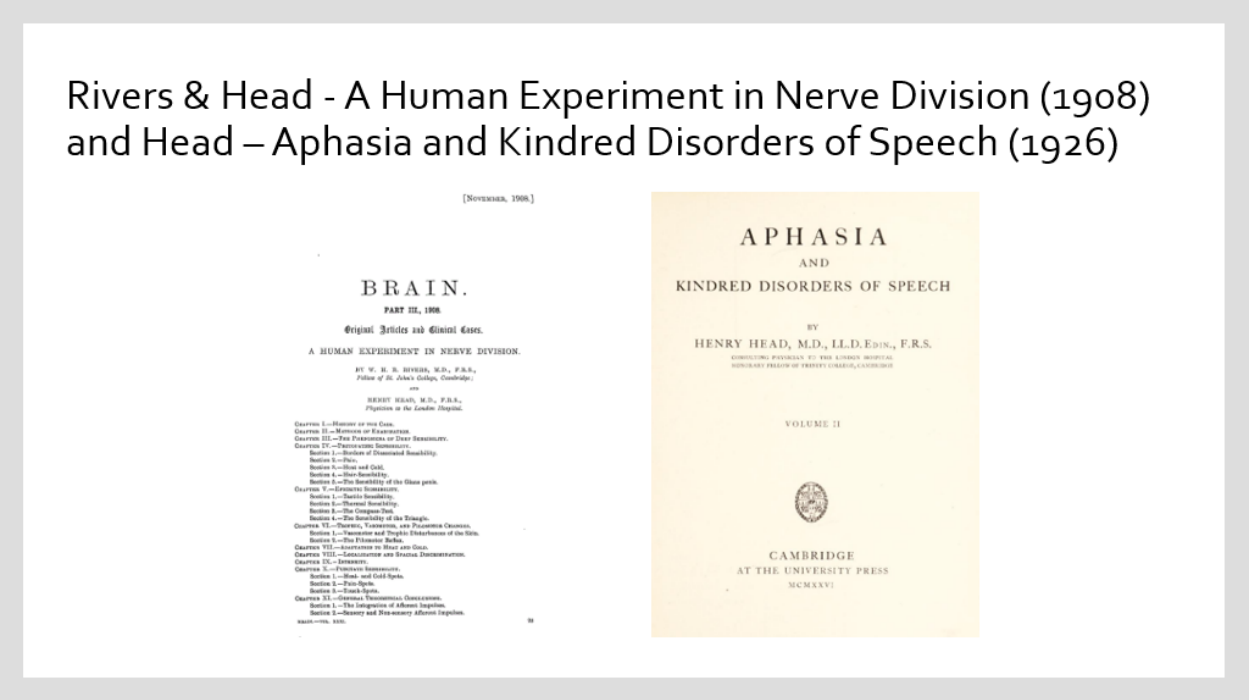


Figure 5

p. 535-539 and *Fragments of Neurological History, p. 404-412*)[2,3], of "Wilson's disease" will be discussed further in this article; Derek Denny-Brown began his career in England and later moved to the United States at Harvard Medical School (*Fragments of Neurological History, p. 573-575*).[3] C. S. Hallpike is known for the Hallpike maneuver in the evaluation of vertigo.

Sir Henry Head was a neurology house staff at Queen Square in the 1890s. While never on the faculty, he became quite famous for his experiments on sensory function and on his concepts concerning aphasia. Head and Rivers published the results of an experiment which Head had done on himself in which he had a surgeon sever his radial sensory nerves in his forearm. He and Rivers then wrote a detailed analysis of both the loss and return of sensory function in his own forearm over time (Figure 4).[12,13]

Figure 5 is a photograph of some of the leaders at Queen Square in the 1880s. It includes many legends of Queen Square including Drs Gowers, Jackson, Gunn, Bastian, Horsley, Beevor, and Ferrier. Gowers, Horsley, and Ferrier were ultimately knighted.

Dr. Ferrier is primarily known for his pioneering work in neurophysiology in which he electrically stimulated the brain of rabbits, dogs, guinea pigs, rats, pigeons, and eventually monkeys (Figure 4) (*The Founders of Neurology, p. 195-198*).[2] He mapped the entire motor cortex. His detailed methodologic experiments were not performed in the National Hospital, but in laboratory space in the West Riding Lunatic Asylum.[11] Ferrier's work extended and elaborated on the work of Hitzig and Fritsch. He published his findings in the now classic book "The Functions of the Brain" (1876)[14] and in his Croonian lectures in 1890.[15] He was the first to apply the experimental principles to observations in man. In some of his publications, he included descriptions of Jackson's patients, connecting the animal experimentation to human disorders. In 1881, at the International Medical Congress in London, Ferrier presented a monkey who had an experimentally produced hemiplegia. Jean Martin Charcot was in the audience and declared: "C'est un malade!" (It's a patient!).

Dr. Hughlings Jackson and Dr. Gowers were among the early physicians at Queen Square. Dr. Kinnier Wilson arrived in the early 1900s. All of them made extraordinary contributions to neurology, and I consider them in some ways the "BIG 3" of Queen Square neurology, which has had a lot of bigs.

Hughlings Jackson was particularly well known for developing foundational concepts of epilepsy, aphasia, hemiplegia (including its development and recovery), and on the doctrine of levels of function of the nervous system (*The Founders of Neurology, p. 456-459*).[2] For the latter, he was influenced by Darwin, whose famous *The Origin of Species* book was recently published in 1859,[16] and Herbert Spencer. Regarding partial epilepsy, he famously observed that a motor seizure could begin in a thumb or toe and then spread in a march-like fashion up the limb and sometimes because generalized.[17] This became known as the Jacksonian march of a seizure.[18] He is considered by many to be the Father of English neurology. Jackson was appointed to be the first assistant physician to the National Hospital in 1862 at age 27. He never wrote a large neurology textbook unlike several other famous Queen Square neurologists. He was one of the founding editors of the journal Brain in 1878 (Figure 6). Several of his papers that he called neurologic fragments were assembled into a book of the same name in 1925 after his death (Figure 8).[19]

Figure 6

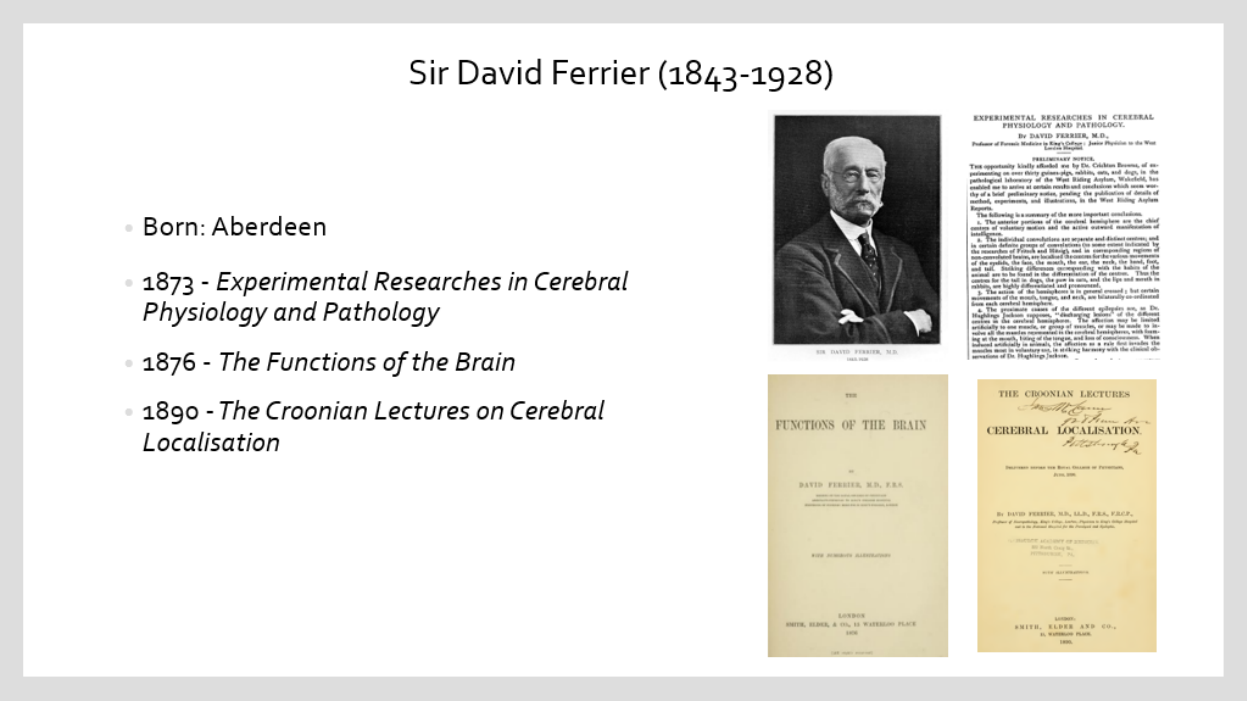


Figure 7

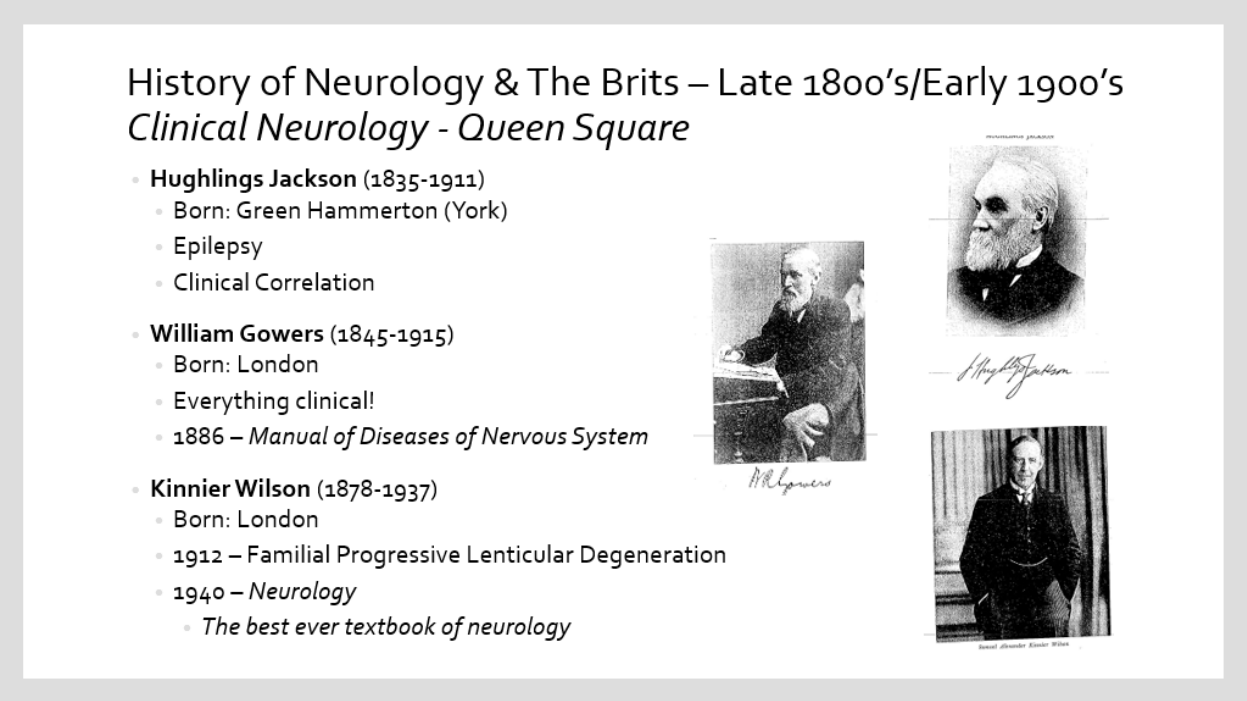
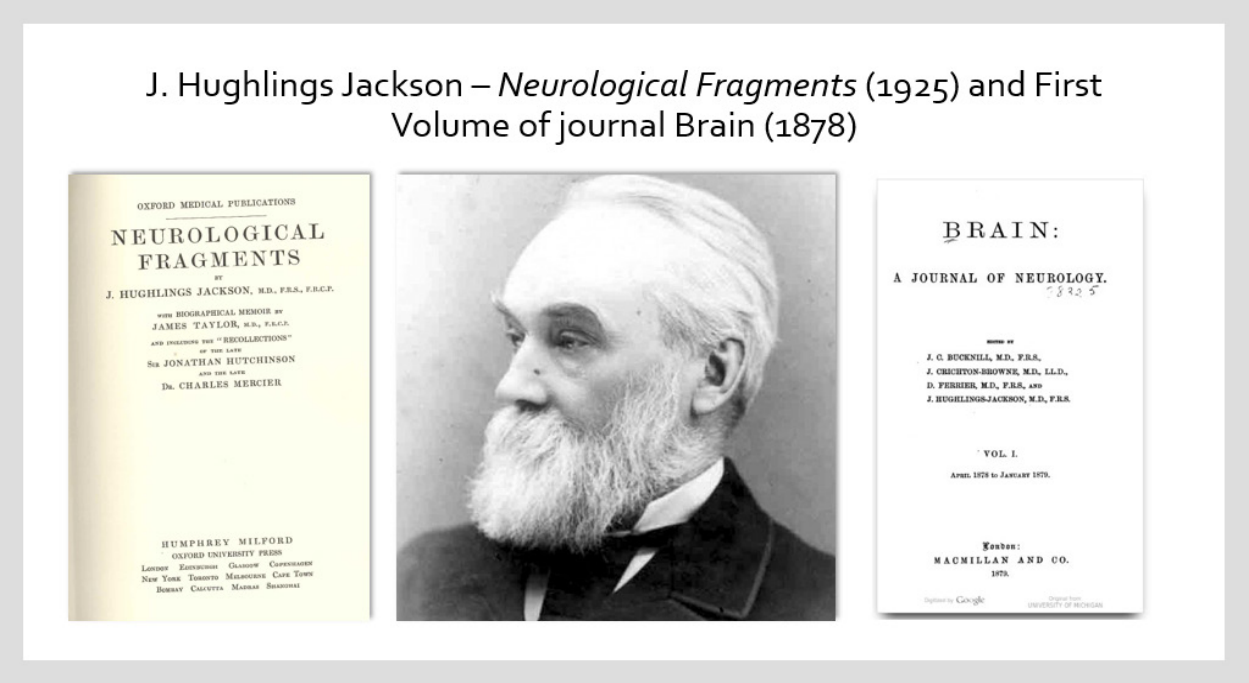


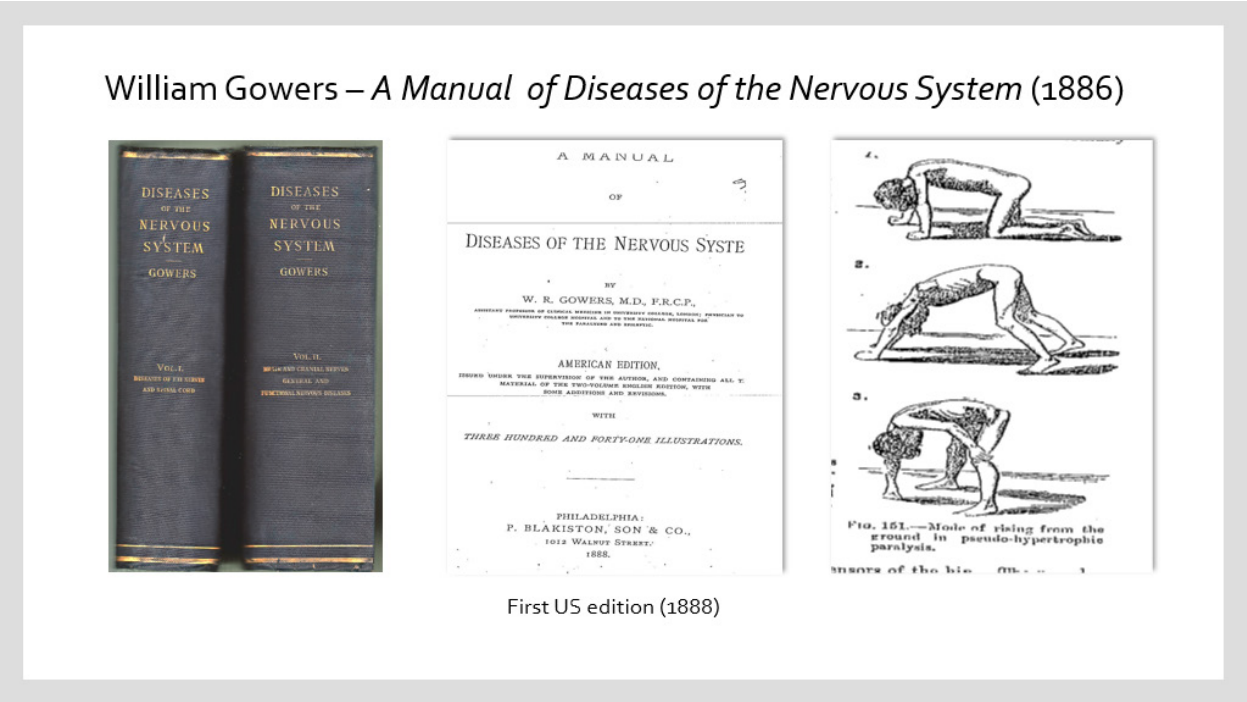
Figure 8



Despite very limited formal education until he was 15 years old, at which time he was apprentice to a physician, he ultimately attended medical school in York, where he practiced medicine before moving to London in 1856. He was considered a genius and profound thinker with colossal ideas, but he was a recluse, eccentric, a poor speaker, and writer. He made few acquaintances but was a kind and gentle man. He thought it was to his advantage not to have been over-educated. His casual reading consisted of westerns from the Victorian era, and his reading habit included tearing a book in two and stuffing each half into the left and right coat pockets-as each was read, he would discard the half, often during his tram or carriage travels. However, Jackson had a "dry sense of humor." Apparently after watching Horsley perform brain surgery on a patient, he was heard to say, "Awful, awful," and when asked by Ferrier why he made that comment, he said, "…he opened a Scotsman's head and failed to put a joke in it."

William Gowers wrote many books and papers, but his most famous work is *A Manual of Diseases of the Nervous System* (Figure 7) (*The Founders of Neurology, p. 441-445*).[2,20]

Figure 9



In 1870, Gowers was made the first medical registrar at Queen Square. Gowers' personality and nature was very different from Jackson's. Like Jackson, he received minimal formal education, and both were largely self-educated prior to entering the medical profession, but Gowers was a brilliant teacher, speaker, and writer, who had an extraordinary command of the English language. This of course continues to be evident in his many articles and textbooks which are still in print today. Gowers was the first of the great outpatient teachers of neurology, and he trained many other neurologists. Both Gowers and Jackson had incredible abilities of close and accurate clinical observation, and they had outstanding methods of recording the clinical findings of their patients.

A Manual of Disease of the Nervous System was published in both two-volume and single-volume formats. In my opinion, this is one of the most impressive neurology textbooks ever written, and it is still useful today. Both during his life and for generations this book was affectionately referred to as the "Bible of Neurology." Figure 7 shows illustrations of what we now call Gowers' sign in a patient with Duchenne muscular dystrophy (*Fragments of Neurological History, p. 378-380*),[3] demonstrating proximal weakness. The image remains remarkably accurate. Gowers, like Charles Bell, was an artist and drew many of the illustrations in his books.

Figure 10 is a patient with progressive muscular atrophy, the lower motor neuron form of ALS, with arms hanging at their sides—what we have referred to as brachial amyotrophic diplegia.[21] Gowers was the first to describe and illustrate this condition. Figure 8 also shows an illustration of a patient with head drop from a neuromuscular disorder that looks very similar to the head drop we described in a paper on isolated neck extensor myopathy.[22] When our group was writing about these neuromuscular presentations over 100 years after Gowers, we were definitely standing on the soldiers of a neurology giant. *A Manual of the Diseases of the Nervous System* is an extraordinary book that covered all areas of neurology and demonstrated that Gowers was truly an expert in everything related to neurology, ultimately becoming the face of neurology in England for decades.[20] Therefore, it is no surprise that he was knighted to become a Regal Neurologist.

Kinnier Wilson was another towering figure at Queen Square. He practiced in the first half of the twentieth century immediately after Gowers and Jackson. He died relatively young at age 58. Near the end of his life, he ultimately wrote a three-volume textbook (Figure 9). This impressive textbook is simply titled *Neurology* (1940).[23] It was published posthumously several years after his death through the efforts of Dr. A Ninian Bruce. Later, *Neurology* went through another edition (UK-1954/US-1955) also edited by Bruce.[24] Arguably, it is the best referenced textbook of the first half of the last century. It summarized the entire neurological literature of the late 1800s and 1900s up to the time of publication, covering every aspect of neurology. I still consult this book when I look up specific neurologic diseases to research who wrote about them prior to 1940. Wilson was a showman, an eccentric, an original, and could "light up in a revealing fashion what had previously been a thing of obscurity."[25] Like Gowers, he was an impressive teacher and it is said, "Wilson's disciples formed a small band of votaries who would meet on Saturday in (a)… sitting room to meditate upon the most puzzling clinical problems in the hospital."[25] He of course remains famous for what we now call "Wilson's disease," progressive lenticular

Figure 10

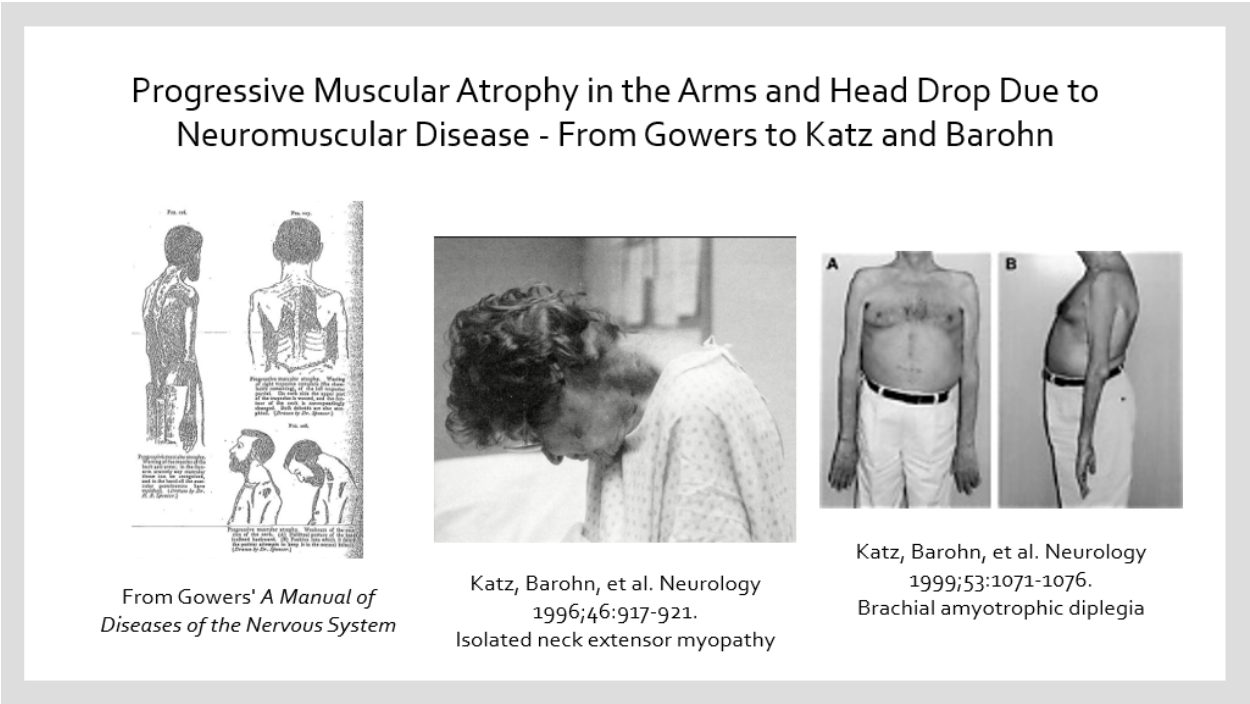


Figure 11

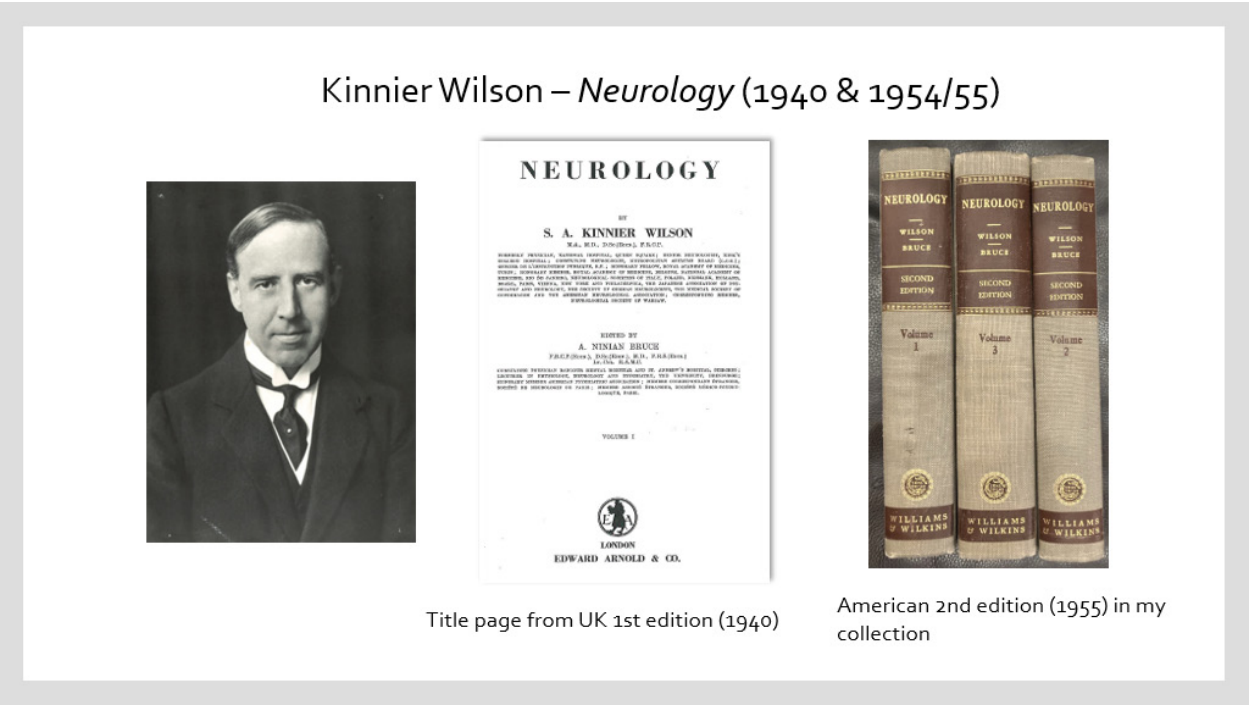


Figure 12

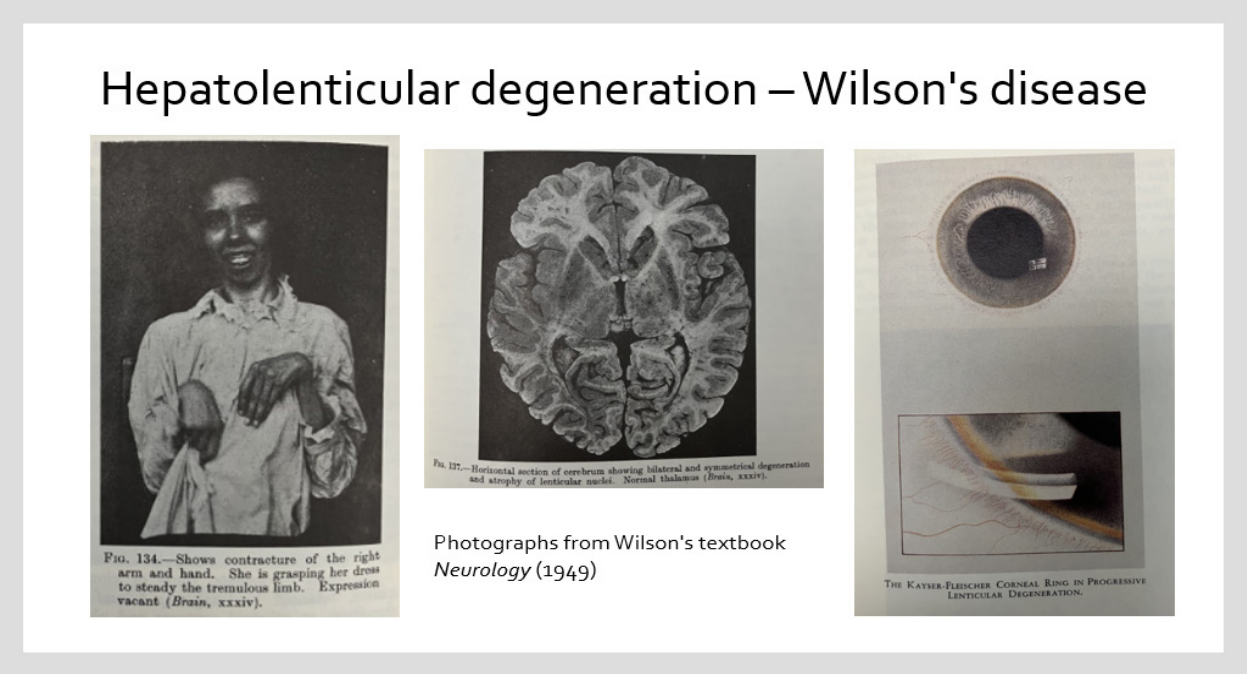
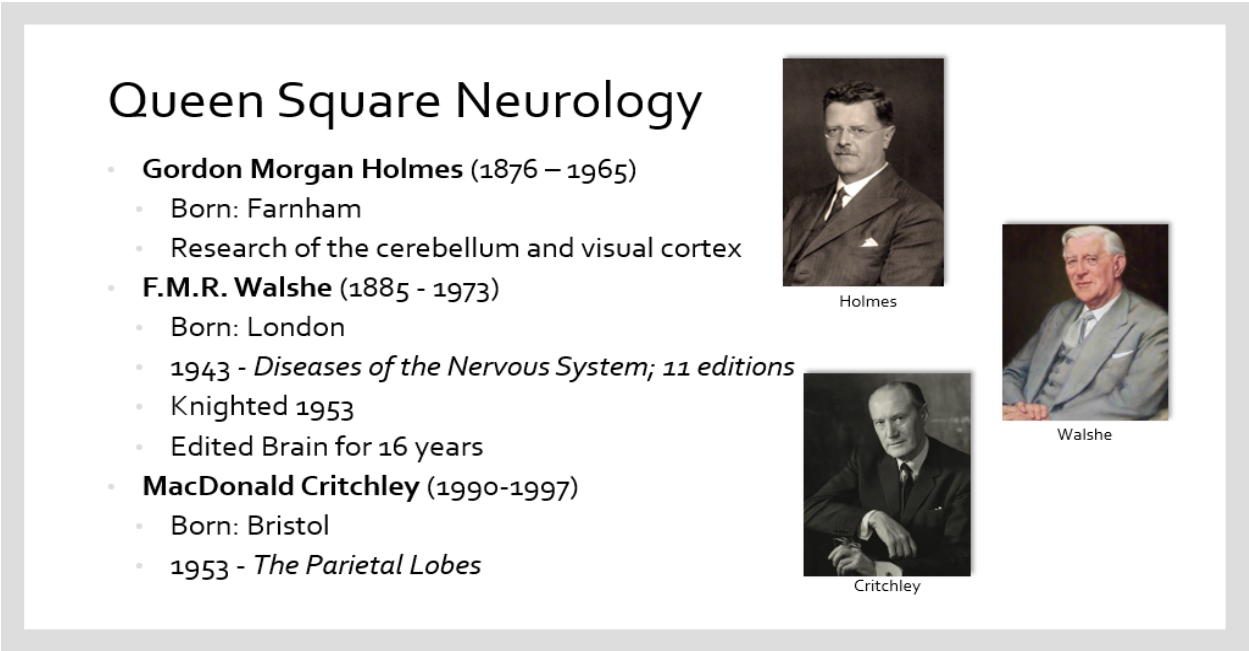


Figure 13



degeneration (also known as hepatolenticular degeneration), and the associated movement and cognitive disorders, liver failure, and ocular changes (Kayser-Fleischer corneal pigmentation) which he described in 1912 when he was still a young physician at Queen Square.[26]

Figure 12 from his textbook shows a patient with hepatolenticular degeneration and the characteristic fixed exaggerated "fixed smile and retracted lips" called risus sardonicus, a cross section of a brain preparation showing a symmetrical degeneration and atrophy of the lenticular nuclei, and the Kayser-Fleischer corneal ring. Wilson also founded a journal called the Journal of Neurology and Psychopathology in 1920 which later became known as the Journal of Neurology, Neurosurgery, and Psychiatry.

Two other well-known neurologists at Queen Square include Gordon Holmes and F. M. R. Walshe. Both were ultimately knighted. Holmes conducted extensive research and clinical reporting on the cerebellum and visual cortex. He wrote the first book on the history of Queen Square in 1954 (Figure 14).[27] Another recent book on the history of Queen Square was published in 2020 by Simon Shorvon and Alistar Compston.[28]

Figure 14

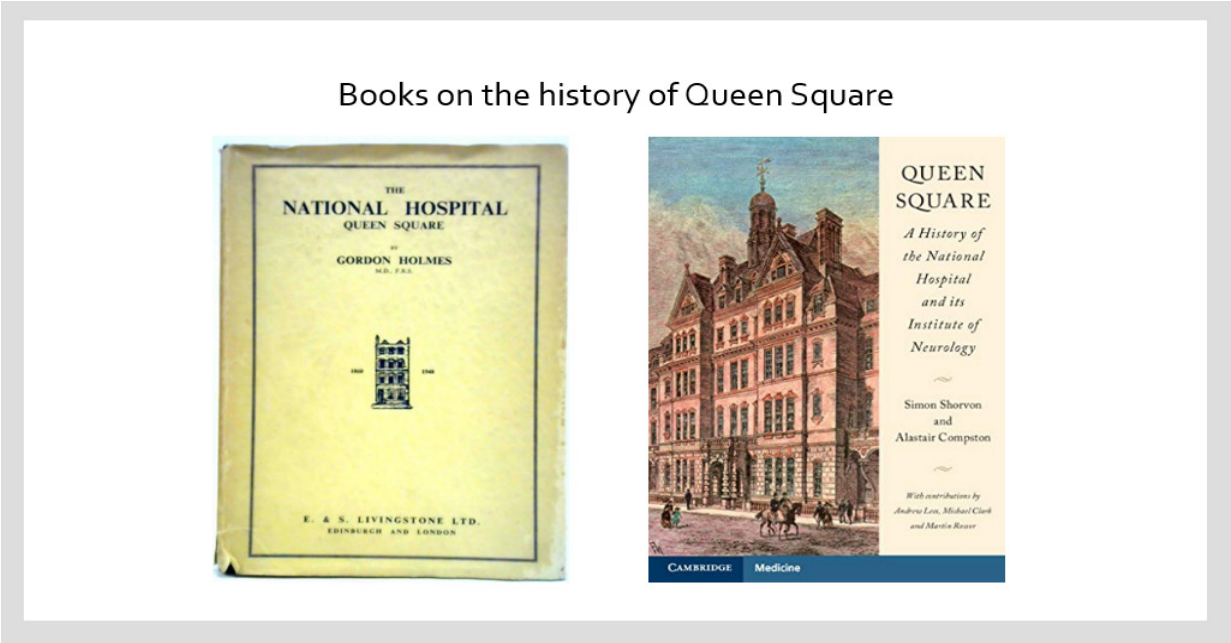
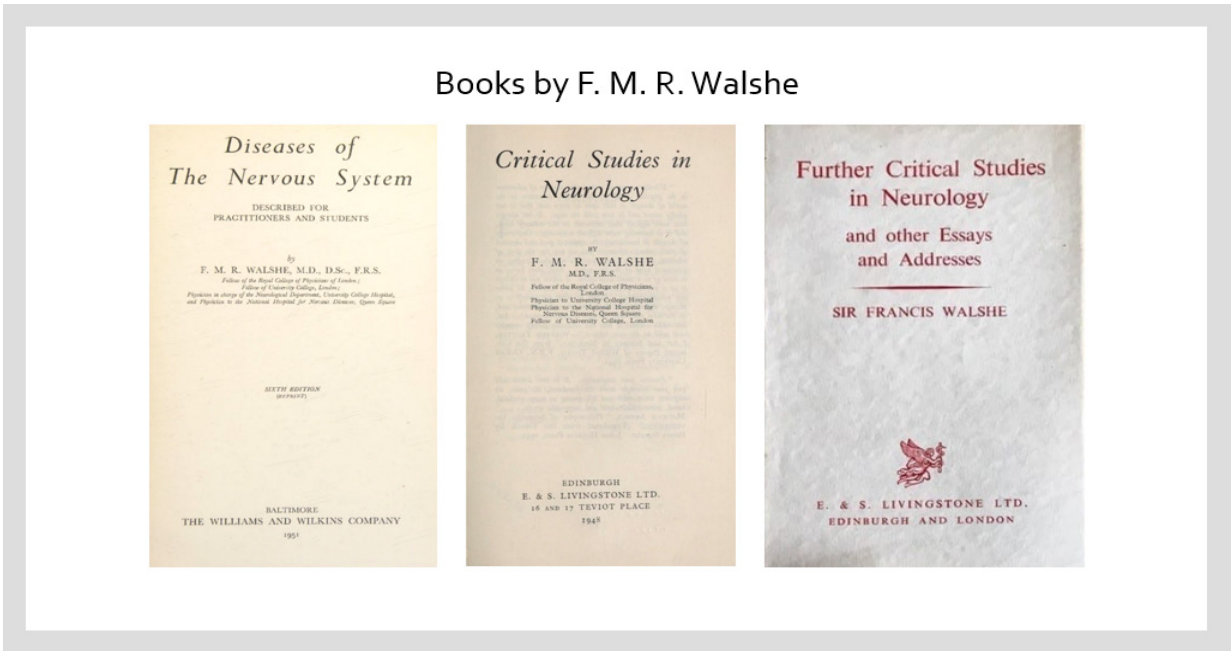


Figure 15



F. M. R. Walshe, wrote *Diseases of the Nervous System*,[29] which became the major neurology textbook after World War II on both sides of the Atlantic and went through 11 editions. He republished many of his articles originally published in the journal Brain in two books: *Critical Studies in Neurology* (1948)[30] and *Further Critical Studies in Neurology and other Essays and Addresses* (1965) (Figure 15).[31]

The 1948 book contains an excellent detailed article about the physiology and significance of the Babinski plantar response.[32] The 1965 book contains a wonderful historical paper about William Harvey and writing in medicine.[33,34]

Macdonald Critchley authored an insightful book on the parietal lobes.[35] Figure 14 shows a color plate from Critchley's book. It is a beautifully written work focused on the clinical aspects of parietal lobe function. Critchley also wrote a biographical article about Hughlings Jackson in the proceedings of the Royal Society of Medicine that ultimately turned into a book titled "John Hughlings Jackson: Father of English Neurology."[36,37] He also published a history titled "The Beginnings of the National Hospital, Queen Square (1859-1960)" in the British Medical Journal.[25]

Figure 16

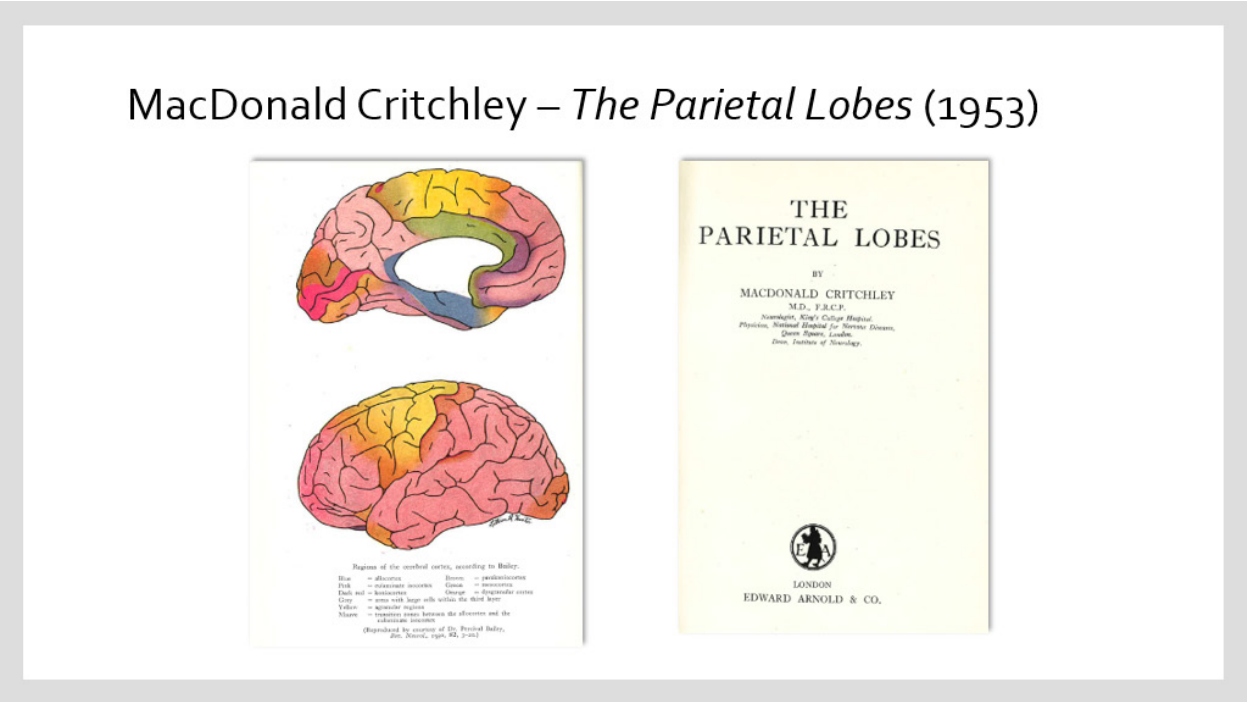
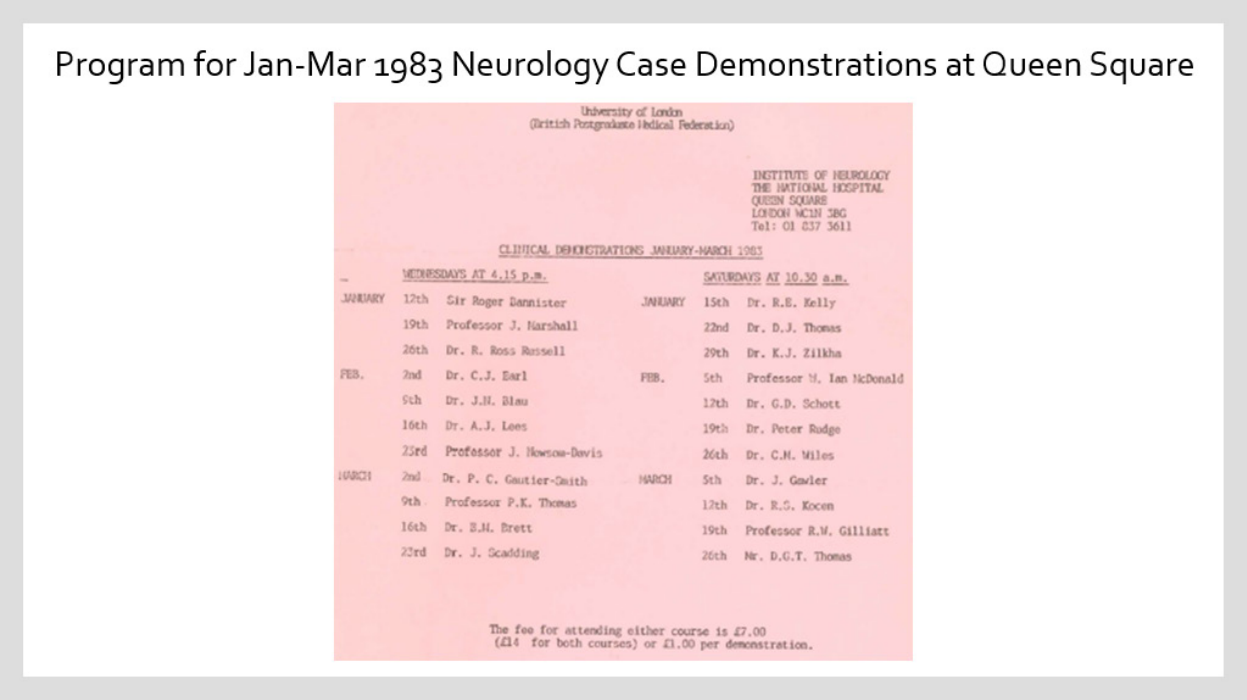


Figure 17



Queen Square, for many generations and continuing to the present day, has been a place not only for patients to be seen by experts in neurology but also as a place of training for generations of neurologists. Many American neurologists made pilgrimages to Queen Square to obtain additional training and to round out their neurology careers. When I was in the US Air Force in the 1980s and stationed outside Cambridge as a general medical officer at RAF Alconbury, I would pilgrimage to Queen Square every Saturday for neurologic demonstrations held in one of the old amphitheaters (Figure 17). Figure 14 is the program I obtained when I was attending the case demonstrations in the winter of 1983.

Figure 18

Institute of Neurology – Queen Square
Dean/Directors Since 1940's

NAME	ROLE	YEAR
Dr. J Purdon Martin	Dean	1943-1948
Dr. MacDonald Critchley	Dean	1948-1953
Dr. Michael Kremer	Dean	1953-1962
Dr. JWD Bull	Dean	1962-1968
Dr. RE Kelly	Dean	1968-1975
Dr. PC Gautier-Smith	Dean	1975-1982
Prof. John Marshall	Dean	1982-1987
Prof. David Landon	Dean	1987-1995
Prof. David Marsden FRS	Dean	1995-1998
Prof. Richard Frackowiack	Dean	1998-2002
Prof. Roger Lemon	Dean	2002-2008
Prof. Alan Thompson	Director	2008-2012
Prof. Michael Hanna	Director	2012-Present

Figure 19

To gain admittance, you would pay a pound (£), put it in a box outside of the classroom, which would allow you to enter a small amphitheater where the trainees sat. One of the Queen Square professors would examine a patient. The patient was unknown to the professor. The professor would open their briefcase that contained their neurology tools, take a history, examine the patient in front of the group, and then pronounce a diagnosis. Of course, they were usually correct. Everyone would clap. This made a huge impression on me in my twenties and was one of the experiences that solidified my desire to become a neurologist. Later I learned more about Kinnier Wilson's Saturday sessions with his trainees 50 years earlier, which have some similarities to my experience-learning at the feet of the great Queen Square professors.

The Institute of Neurology at Queen Square and the National Hospital at Queen Square are related but separate institutions. The National Hospital Medical School was founded in 1898 for post-graduate medical training for physicians to become neurologists. In other words, for registrar training (resident training in the United States). When the National Hospital was transferred to the National Health Service (NHS) in 1948, the medical institute was made into an independent body and called the Institute of Neurology. The Institute of Neurology was incorporated into the University College of London in 1996. It has been led by Deans or Directors and MacDonald Critchley was one of the early Deans.

The current director of the University College of London (UCL) Institute of Neurology at Queen Square is Professor Michael Hanna, a close friend of mine and a muscle disease expert. Shown here is a photograph of Dr. Hanna and me at a Neuromuscular Study Group meeting in Utah, where we were talking about neurology and relaxing during the "evening session." Dr. Hanna and I have co-directed the NMSG since 2015. Dr. Robert C. (Berch) Griggs began the organization as the Muscle Study Group in 1999. The NMSG is an international organization where neuromuscular experts gather annually to discuss advances in clinical neuromuscular research.

Dr. Hanna is the longest serving Dean/Director in the existence of the Institute of Neurology at Queen Square. He will end his long service in this role in December 2026, when he will take on the role of UCL's new Pro-Vice Provost (Clinical) within the office of the Vice Provost (Health).

The National Hospital for Neurology Queen Square and the Institute of Neurology it spawned certainly has had a profound impact on the field of neurology worldwide. Many of the neurologists who practiced, taught, and wrote at Queen Square have become legendary and a few of them have become knights! It deserves to be considered the birthplace and home of Regal Neurology.

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History of Neurology: French Neurology in the 19th Century – Charcot, his Legacy, and Other Notable Physicians

Richard J. Barohn, MD

Professor of Neurology, University of Missouri – Columbia

Formerly Executive Vice Chancellor for Health Affairs, Hugh E. and Sarah D. Stephenson Dean, University of Missouri School of Medicine

Distinguished Professor Emeritus of Neurology, Former Chair Department of Neurology, and Dewey Ziegler Professor of Neurology, University of Kansas

A live recording of this lecture can be viewed here: RRNMF - Charcot and his Legacy

This History of Neurology segment is about the French neurologist Jean-Martin Charcot and his trainees.[1,2]

The great Jean-Martin Charcot is really the founder of modern neurology (Figure 1) (*The Founders of Neurology, p. 420-424* and *Fragments of Neurological History, p. 324-331*).[1-4] He established clinical neurology as a discipline and became the first chair of diseases of the nervous system. He had very humble beginnings. Charcot was the son of a cabinet maker. He actually had difficulty passing his oral exams to become a professor in the French system, but he ultimately did. Shortly after that, he was named superintendent of the Salpêtrière in Paris. He was 37 at the time.

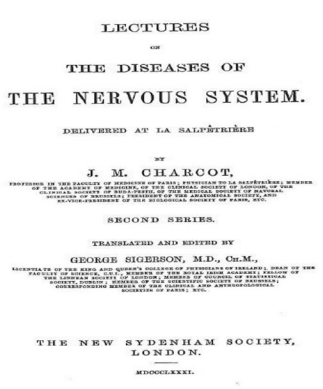
The Salpêtrière was a large welfare medical institution that housed between five and ten thousand poor patients with medical problems, and it was chaotic. Charcot organized the Salpêtrière. He developed a system to diagnose patients and he performed clinical-pathologic correlations. He focused particularly on diseases of the nervous system, although he had other interests as well, particularly disorders of aging (Figure 2). He became an expert brain neuropathologist as well as an expert clinician.

Figure 1

Jean Martin Charcot
(1825-1893)

- "The Founder of Modern Neurology"
- Established clinical neurology as a discipline 1882 – 1st chair of disease of nervous system at the University of Paris
- Son of a cabinet maker
- Difficulty passing oral exams
- Superintendent of Salpêtrière, Paris, France at age 37 (housed 5-10k welfare medical patients)
- ALS, MS, myopathy, neuropathy, tabes dorsalis, Charcot Joints, and diseases of aging
- Clinical pathologic correlations
- Classroom demonstrations – Leçons (Tue & Fri)
- Hysteria/Hypnosis later in career
- Anti-animal research

Figure 2



LECTURES
ON
THE DISEASES OF
THE NERVOUS SYSTEM.
DELIVERED AT LA SALPÊTRIÈRE
BY
J. M. CHARCOT,
PROFESSOR IN THE FACULTY OF MEDICINE OF PARIS; PHYSICIAN TO LA SALPÊTRIÈRE; MEMBER OF THE ACADEMY OF MEDICINE; MEMBER OF THE ROYAL IRISH ACADEMY; FELLOW OF THE CLINICAL SOCIETY OF NEW-YORK, OF THE MEDICAL SOCIETY OF NATURAL SCIENCES OF BRUSSELS; PRESIDENT OF THE ANATOMICAL SOCIETY, AND EX-VICE-PRESIDENT OF THE MEDICAL SOCIETY OF PARIS, ETC.
SECOND SERIES.
TRANSLATED AND EDITED BY
GEORGE SIGERSON, M.D., CH.M.,
SECRETARY OF THE KING AND QUEEN'S COLLEGE OF PHYSICIANS OF IRELAND; DEAN OF THE FACULTY OF SURGERY, U.R.I.; MEMBER OF THE ROYAL IRISH ACADEMY; FELLOW OF THE LINNEAN SOCIETY; MEMBER OF THE ROYAL ACADEMY OF BELGIUM; CORRESPONDING MEMBER OF THE INTERNATIONAL SOCIETY OF BRUSSELS; CORRESPONDING MEMBER OF THE CLINICAL AND ANTHROPOLOGICAL SOCIETIES OF PARIS; ETC.
THE NEW SYDENHAM SOCIETY,
LONDON.
MDCCCLXXXI.

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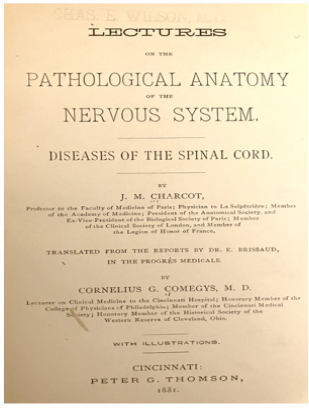
Figure 3

English Translations of Charcot's books in my library



LECTURES

ON THE

PATHOLOGICAL ANATOMY

OF THE

NERVOUS SYSTEM.

DISEASES OF THE SPINAL CORD.

BY

J. M. CHARCOT,

Professor in the Faculty of Medicine of Paris; Physician to La Salpêtrière; Member of the Academy of Medicine; President of the Anatomical Society, and Ex-Vice-President of the Biological Society of Paris; Member of the Clinical Society of London, and Member of the Legion of Honor of France.

TRANSLATED FROM THE REPORTS BY DR. E. BRISSAUD, IN THE PROGRÈS MÉDICALE.

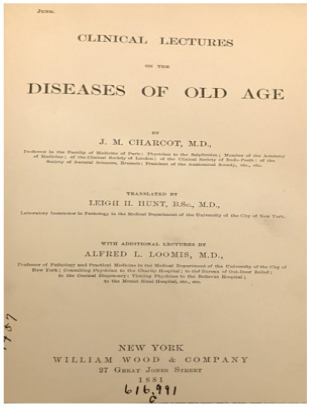
BY

CORNELIUS G. COMEGYS, M. D.

Lecturer on Clinical Medicine to the Cincinnati Hospital; Honorary Member of the College of Physicians of Philadelphia; Member of the Cincinnati Medical Society; Honorary Member of the Historical Society of the Western Reserve of Cleveland, Ohio.

WITH ILLUSTRATIONS.

CINCINNATI:
PETER G. THOMSON,
1881.



CLINICAL LECTURES

ON THE

DISEASES OF OLD AGE

BY

J. M. CHARCOT, M.D.,

Professor in the Faculty of Medicine of Paris; Physician to the Salpêtrière; Member of the Academy of Medicine; President of the Anatomical Society; Member of the Clinical Society of Berlin; Fellow of the Society of Internal Medicine, Brussels; President of the Anatomical Society, &c., &c.

TRANSLATED BY

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WITH ADDITIONAL LECTURES BY

ALFRED L. LOOMIS, M.D.,

Professor of Pathology and Practical Medicine in the Medical Department of the University of the City of New York; Consulting Physician to the Bellevue Hospital; Member of Bureau of Health of New York; Consulting Physician to the Orthopædic Hospital; Visiting Physician to the Bellevue Hospital; to the Mount Sinai Hospital, etc., etc.

NEW YORK
WILLIAM WOOD & COMPANY
27 GREAT JONES STREET
1881

His fame expanded when he started doing Tuesday, and sometimes Friday, lessons that were very well attended by physicians. He is credited to providing early detailed descriptions of motor neuron disease (called Charcot's disease in France),[5] multiple sclerosis, peripheral neuropathy, and various myopathies. In 1869, he described cases of progressive muscular atrophy (originally described by Aran and Duchenne-see below) that also had spasticity and he showed pathologically both anterior horn cell degeneration and degeneration of the lateral cord of the spinal tracks.[6] This is thought to be the first recognition of amyotrophic lateral sclerosis (ALS). In the same year, he described patients with pure upper motor neuron signs that pathologically had predominantly degeneration of the corticospinal tracks and he used the term primary lateral sclerosis (PLS).[7] The following is a translation of Charcot's original description of what he termed amyotrophic lateral sclerosis and primary lateral sclerosis and he also describes labio-gloso-pharyngeal paralysis or what we now call bulbar palsy.[7] This translation was published in the biography of Charcot by George Guillain, MD, translated by Pearce Bailey, PhD, MD, pp. 106-107.[8]

We should note that a similar situation obtained before in relation to progressive locomotor ataxia, (tabes dorsalis), and yet the clinical picture outlined by Duchenne from a small series of cases, almost twenty years ago, has not changed. It still comprises today all its essential elements, without having undergone any significant modifications. Could it be that the description I am about t ogive of amyotrophic lateral sclerosis will have the same good fortune?...A symmetrical sclerosis of the lateral columns of the spinal cord often exists as a primary independent disease. The lesion in these cases in self-contained, so to speak, in the sense that it is not subordinate to any other localized pathological process (tumor, circumscribed focus, etc.), which has developed first somewhere else along the cerebrospinal axis. It is to be placed in a separate category analogous to the primary gray degeneration of the posterior columns (the anatomic substratum of progressive locomotor ataxia, from which amyotrophic lateral sclerosis can be easily distinguished clinically)… This form of symmetrical sclerosis always affects the posterior part of the anterolateral columns throughout the entire length of the spinal cord. The lesion can be traced to the medulla, where it occupies principally the anterior pyramids, and even to the lower level of the cerebral peduncles…The disease begins with a paresis that progressively affects all four extremities and gradually is replaced by more or less pronounced contractures in which the lower extremities are more involved than the upper ones. In very advanced cases, the spasticity increases, rendering the predominant posture of the affected limbs one of forced extension or semiflexion. It is not rare to see, in the course of the disease, symptoms of progressive muscular atrophy, which involve principally the muscles of the upper extremities. The thenar and hypothenar eminences are sometimes remarkably flattened and the hands may present a claw-like deformity. When such a complication is present, one sees at post-mortem, besides bilateral sclerosis, a more or less marked degeneration of the anterior horn cells, particularly at the level of the cervical enlargement of the spinal cord… Symptoms of labioglossolaryngeal paralysis with atrophy of the muscles of the tongue are often associated with primary lateral sclerosis. In several cases of this kind, degeneration of the motor nuclei of the hypoglossal nerve has been clearly established.

There are at least two uses of the term "Charcot's triad". In neurology, it refers to the signs in multiple sclerosis of nystagmus, intention tremor, and scanning speech. Charcot's triad also refers to the three signs of acute cholangitis: fever, right upper quadrant abdominal pain, and jaundice. In his career, he became interested in hysteria, and some believe he used hypnosis in his practice, which was controversial. Interestingly, he was against animal research.

Charcot authored a number of books. Figures 2 and 3 show the title pages of English translations of three of his books that are in my rare medical book library: *Clinical Lectures on the Diseases of Old Age,*[9] *Lectures on the Pathological Anatomy of the Nervous System: Diseases of the Spinal Cord,*[10] and *Lectures on the Diseases of the Nervous System.*[11] *Lectures on the Diseases of the Nervous System* consists of transcripts of the Tuesday lectures that he gave. This book consists of transcriptions of the Tuesday lectures that he gave. Charcot

made extensive notes, and notes were also taken by people in the classroom. His trainees and mentees later put these into book form. Many of his trainees were British, including George Sigerson, who was responsible for getting the English editions of the lectures into print. This is how many in England and the United States, including myself, were able to access Charcot's work.

Figure 4 is a drawing of Charcot examining the brain of a patient who had died. His classic hunched posture has become a famous image. Here is another old neurologist with a hunched posture looking at his cart.

Charcot described the neurologic complications of syphilis to a great degree, including tabes dorsalis. He talked about the joint problems that patients with tabes develop as a result of sensory deprivation. We now call these Charcot joints.

Figure 5 shows Charcot with his wife at their home, again in the classic profile view.[4] He was a great artist in his own right and was able to draw patients with neurologic and other problems.

Figure 6 shows some of his notes of a patient with hemiparesis and extension deformities. There is also a picture from one of the magazines in France depicting Charcot. His drawings in the background are his own and appear to show

Figure 4

Figure 5

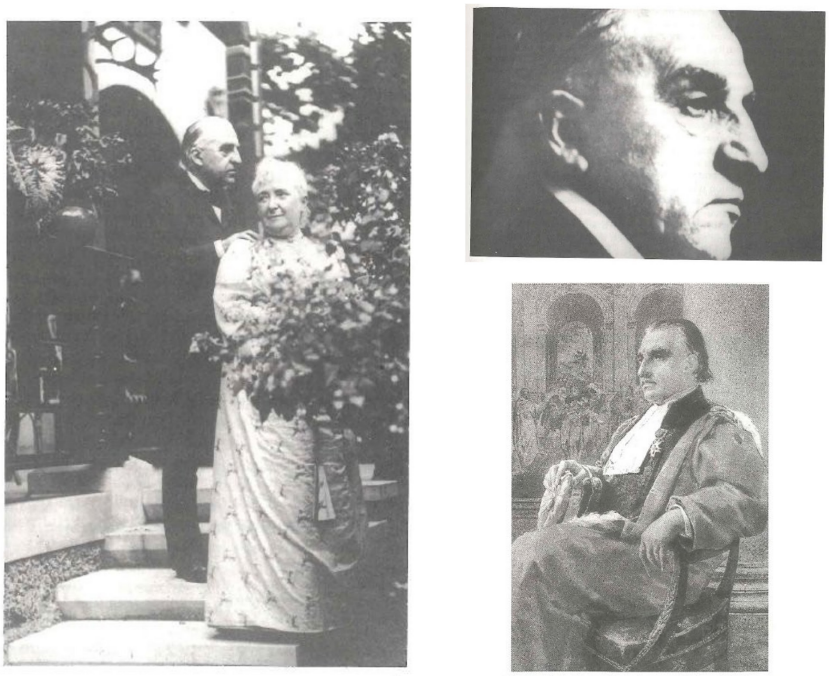


Figure 6

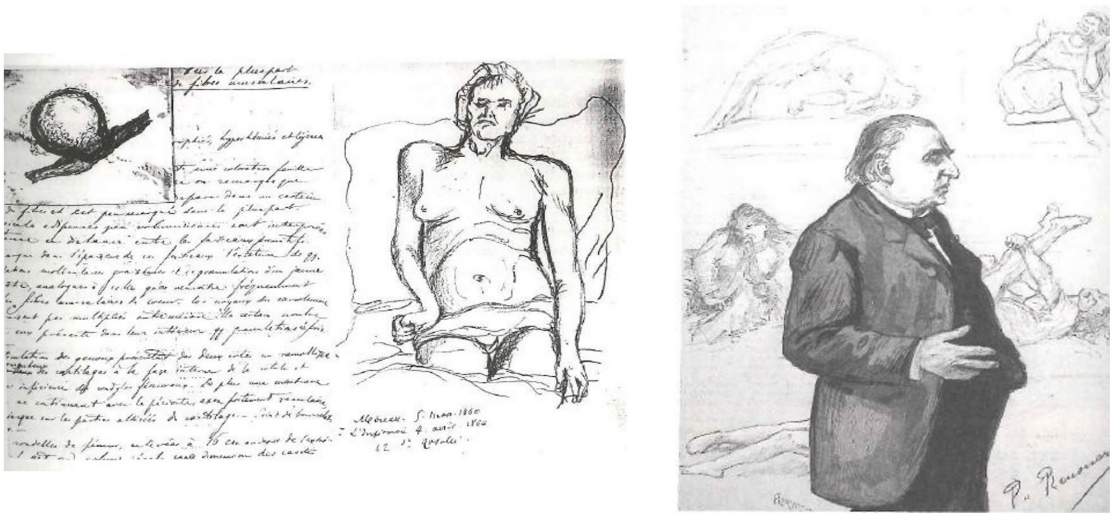
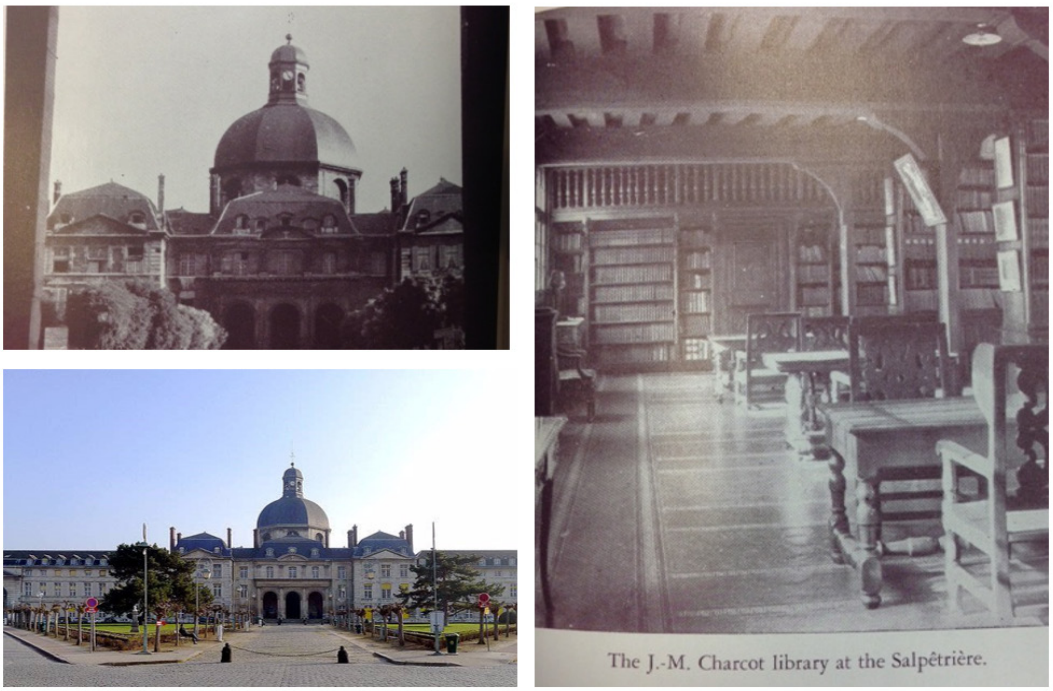


Figure 7



hysterical patients in various contortions.[4]

Figure 7

Figure 7 shows the impressive Charcot library at the Salpêtrière, a photograph of the Salpêtrière in Charcot's time, and a modern image.

Now, let us discuss Charcot's disciples. He trained legions of neurologists and psychiatrists. Figure 8 shows just a handful of the well-known individuals he trained.

Pierre Marie was his right-hand person for a number of years (Figure 9) (*The Founders of Neurology, p. 476-479*).[2] He went on to describe cerebellar ataxia and spinal cord diseases,[12] and of course Charcot-Marie-Tooth disease.[13, 14] He was Charcot's disciple, and in 1886 he wrote the paper describing this condition. Tooth, in England, wrote a similar

Figure 8

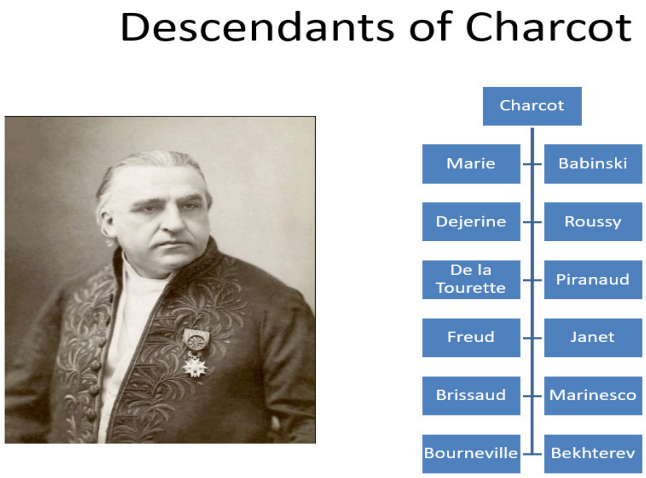


Figure 9

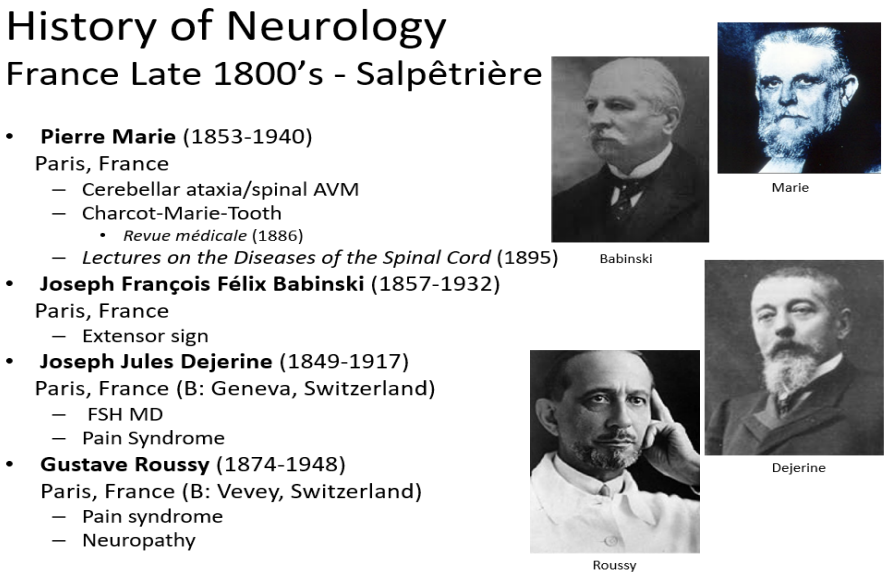
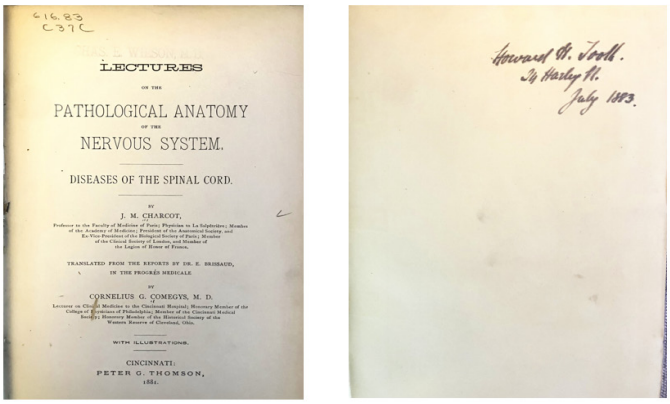


Figure 10

Jean Martin Charcot - *Lectures on the Pathological Anatomy of the Nervous System: Diseases of the Spinal Cord* (1881)



paper, and that is why we now call it Charcot-Marie-Tooth disease. Pierre Marie also wrote the famous book *Lectures on Diseases of the Spinal Cord*.[15]

Figure 10 shows a photograph of another copy of Charcot's book *Lectures on the Pathological Anatomy of the Nervous System: Diseases of the Spinal Cord* (1881) and one of the inside pages signed by a previous owner of the book.[10] Remarkably, the previous owner of this book was Howard H. Tooth of London. This is the very Dr. Tooth whose name we associate with the disease Charcot-Marie-Tooth. I purchased this book from an antiquarian book seller a number of years ago, but I don't think that the book seller realized it was a signed copy of Charcot's book owned by Dr. Tooth. Tooth published his famous monograph on the hereditary disorder he called *The Peroneal Type of Progressive Muscular Atrophy* as his doctoral thesis in 1886, three years after he added his signature in Charcot's 1883 book! Charcot and Marie's paper on hereditary neuropathy was published in the same year as Tooth's dissertation-1886.[14]

Then there is the famous Dr. Babinski, whom we know for the extensor plantar response, or Babinski sign (*The Founders of Neurology, p. 397-399*).[2,16] Dejerine made many contributions, including a description of facioscapulohumeral muscular dystrophy, olivo-ponto-cerebellar degeneration,[17] and the Dejerine–Roussy pain syndrome (*The Founders of Neurology, p. 426-430* and *Fragments of Neurological History, p. 217-220*).[2, 3, 18] Roussy, another disciple of Charcot, also described, with Levy, a hereditary neuropathy with ataxia (*The Founders of Neurology, p. 510-513*).[2, 19]

Figure 11 shows more of Charcot's famous trainees. Gilles de la Tourette described tics, and we now call the condition Tourette syndrome. Henri Parinaud described the dorsal midbrain syndrome with vertical gaze paralysis, often due to pineal tumors.[20] Brissaud first described the locus nigra as a possible site of the lesion in Parkinson's disease, and he later became chair at the Salpêtrière. Pierre Janet became extremely famous and was one of the founders of psychology. Bourneville described tuberous sclerosis, which we now know as Bourneville disease,[21] and he was one of the disciples who edited the lessons in French (*Fragments of Neurological History, p. 391-394*).[3]

These were mostly French disciples from Paris, although some came from outside Paris to train under Charcot. Charcot also trained a number of individuals from foreign countries (See below).

Figure 12 provides more information on Pierre Marie. While working under Charcot, he was chief of the laboratory. At age 60, he left to work at other universities for a few decades, but later returned and succeeded Déjerine in Charcot's chair. Figure 12 shows the title page of his famous *Diseases of the Spinal Cord,* translated into English in 1895.[15]

Figure 13 lists a number of eponyms associated with disorders Dejerine described. These include the Dejerine–Roussy pain syndrome mentioned above; the Dejerine medial medullary syndrome; the onion-peel sensory loss of the face; the Dejerine–Klumpke paralysis, a brachial plexus

Figure 11

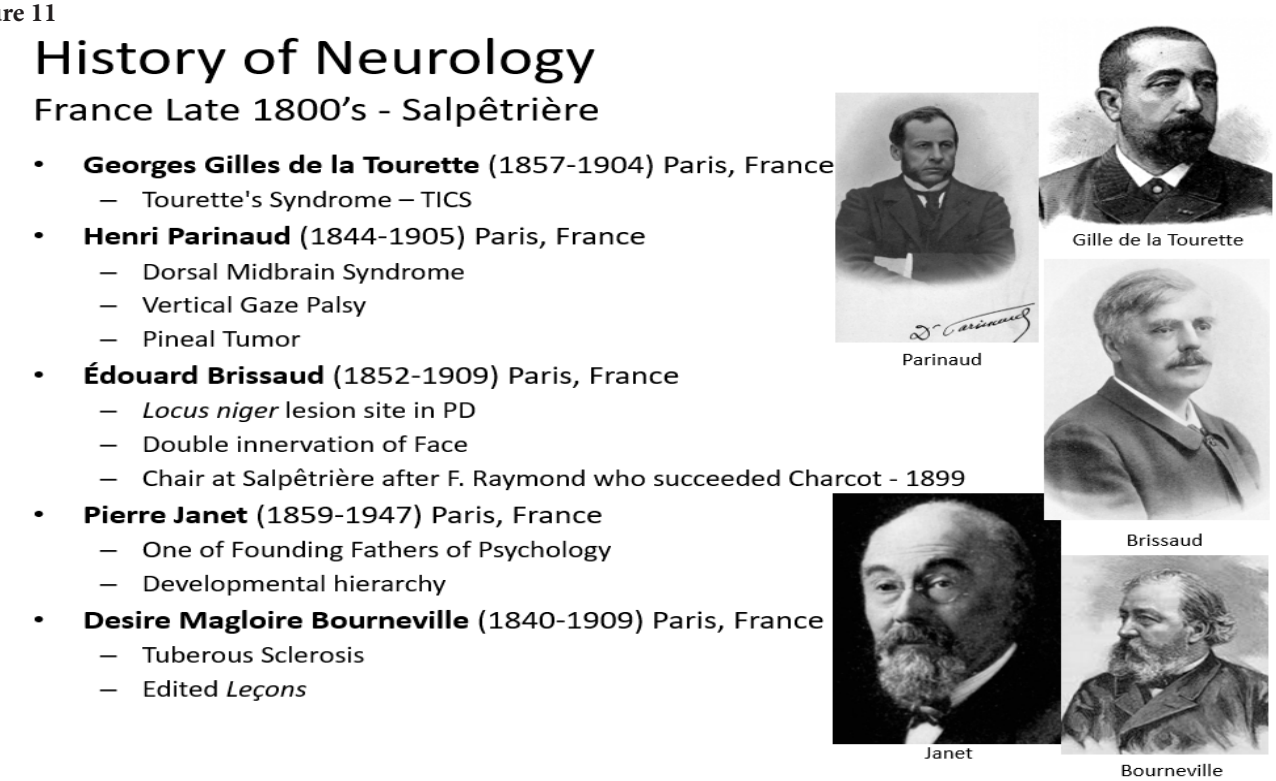
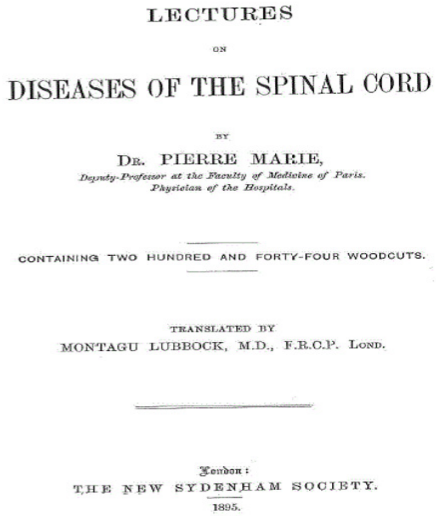


Figure 12

Pierre Marie

Chef de laboratoire under Charcot

At age 60, he succeeded Dejerine in Charcot's chair



LECTURES

ON

DISEASES OF THE SPINAL CORD

BY

DR. PIERRE MARIE,

Deputy-Professor at the Faculty of Medicine of Paris.
Physician of the Hospitals.

CONTAINING TWO HUNDRED AND FORTY-FOUR WOODCUTS.

TRANSLATED BY
MONTAGU LUBBOCK, M.D., F.R.C.P. LOND.

London:
THE NEW SYDENHAM SOCIETY.
1895.

Figure 13

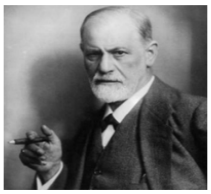
Dejerine Eponyms

- Dejerine's "onion-peel sensory loss"
- Dejerine's cortical sensory syndrome
- Dejerine-Mouzon syndrome
- Dejerine syndrome: medial medullary syndrome
- Dejerine-Klumpke paralysis (Augusta Marie Klumpke was his American wife)
- Dejerine-Roussy syndrome
- Dejerine-Sottas disease
- Dejerine-Thomas olivopontocerebellar atrophy
- Landouzy-Dejerine syndrome

Figure 14

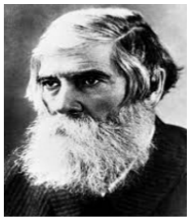
History of Neurology

France Late 1800's – Salpêtrière Visiting Scholars



Freud

Marinesco



Bekhterev

- **Sigmund Freud** (1856-1939)
  - Vienna, Austria
  - Briefly Charcot's visiting "Fellow"
- **Georges Marinesco** (1864-1938)
  - Bucharest, Romania
  - 1897 Chair, Neurology at U. of Bucharest
  - 250 papers
    - Inclusions in substantia nigra
    - Familial amaurotic idiocy
- **Vladimir Bekhterev** (1857-1927)
  - Moscow, Russian
  - Scholarship abroad with Charcot, Meynert, Westphal, Flechig
  - Clinical neurology & experimental psychology in St. Petersburg & Leningrad

palsy that De

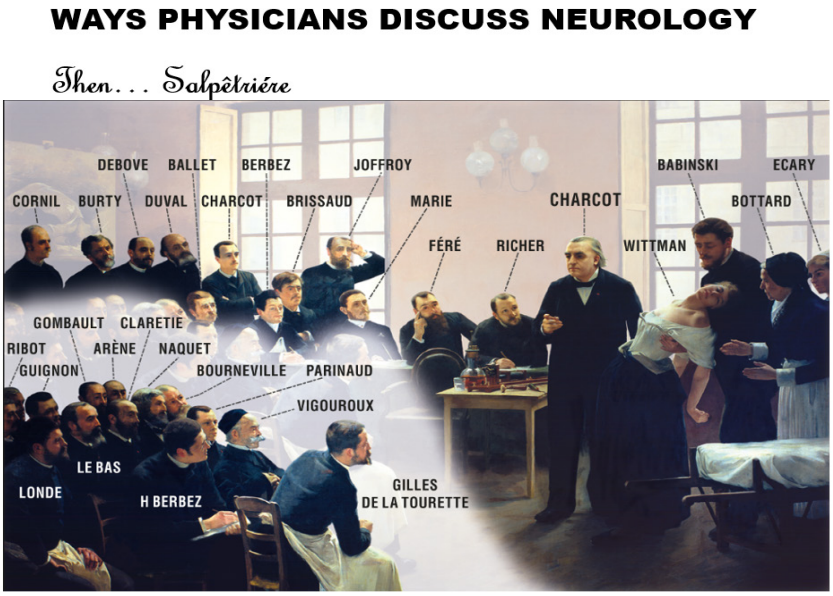
described.[22] She was actually an American physician and one of the early American neurologists to make a major contribution in the field.

Charcot also trained a number of visiting scholars, some of whom became extremely famous in Western civilization (Figure 14). The most well-known is Sigmund Freud, who trained briefly with Charcot. He was only there for a few months in Paris, but it had a profound effect on Freud's development and ultimately on the creation of psychoanalysis. Marinesco from Romania trained with Charcot and later became chair of neurology in Bucharest. He published many papers and described inclusions in the substantia nigra, now known as Marinesco bodies. The famous Russian physician Vladimir Bekhterev also trained with a number of European neurologists, including Charcot, and later led the clinical neurology and experimental psychology department in St. Petersburg and then Leningrad after the Revolution.

Figure 15 shows the well-known painting A Clinical Lesson at the Salpêtrière painted by Andre Brouillet in 1887. The original painting hangs in the corridor of the Descartes University in Paris. This is a modern colorized version, allowing you to see the individuals more clearly. Charcot is demonstrating phenomena in a hysterical patient. Here is Babinski, Gilles de la Tourette, Brissaud, Bourneville. Marie, and a number of other French neurologists and members of the French community.

Charcot's son is pictured in the back row. He was a physician but later became an explorer, which is how he

Figure 15



A Clinical Lesson at the Salpetriere, Andre Brouillet (1887); hangs in corridor of the Descartes University in Paris

Figure 16

Richard Barohn, Mazen Dimachkie, Mamatha Pasnoor, Jeffrey Statland, Jon Katz, Todd Levine, David Saperstein, Katalin Scherer, Aziz Shaibani, Mike Pulley, Tony Amato, Carlayne Jackson, Osvaldo Nascimento, John Kissel, Sara Austin, Tahseen Mozaffar, Anthony Amato, Gil Wolfe, Matt Wicklund, Jaya Trivedi, Omar Jawdat, Laura Herbelin

spent much of his life. This is how neurologists used to be trained in classrooms. Now we are in the modern era, training neurologists through the internet and videos like this one on YouTube.

Figure 16 shows our modernization of the Charcot lecture hall picture, with someone demonstrating, along with many well-known neuromuscular neurologists from across the country who are involved in the RAF5 and the RRNMF (rrnmf.org).

Notable French Physicians Focused on Neurology that were not part of the Charcot Lineage

This brief review of French neurologists and neuroscientists from the 19th century would not be complete without at least mentioning several extraordinary and famous physicians that were contemporary of Charcot, and who influenced Charcot, but were not part of his group.

The first is Amand Duchenne, who is notable for several contributions (*The Founders of Neurology, p. 430-435*).[2] He of course was the first to recognize the hereditary progressive muscle disease restricted to boys with pseudohypertrophy of the calf muscles that we now call Duchenne muscular dystrophy (Figure 18).[23]

He described other neuromuscular disorders as well such as the pure lower motor neuron form of motor neuron disease, progressive muscular atrophy, which is also referred to as the Aran-Duchenne disorder. Duchenne assisted Francois Aran, another French physician, in evaluating patients with this disorder. Aran published the cases in 1850.[24] Duchenne later described progressive muscular atrophy in great detail in his textbook *A Treatise on Localized Electrization*.[25] There appears to have been some dispute on who described the disorder first and Duchenne felt that he should have been given this credit, although it appears from a distance in time that they were collaborators. Debates on who described a medical disorder first have existed for a long time! We also saw this type of

Figure 17

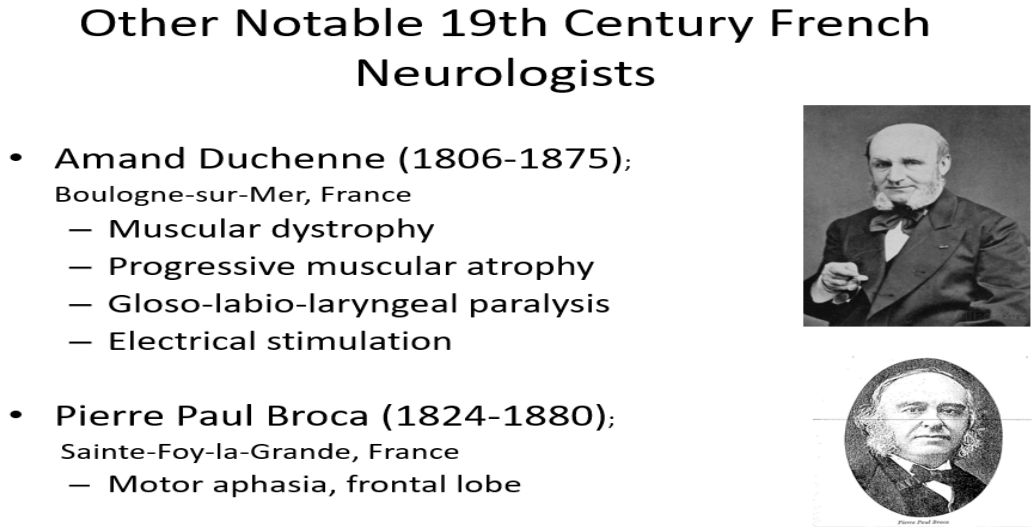


Figure 18

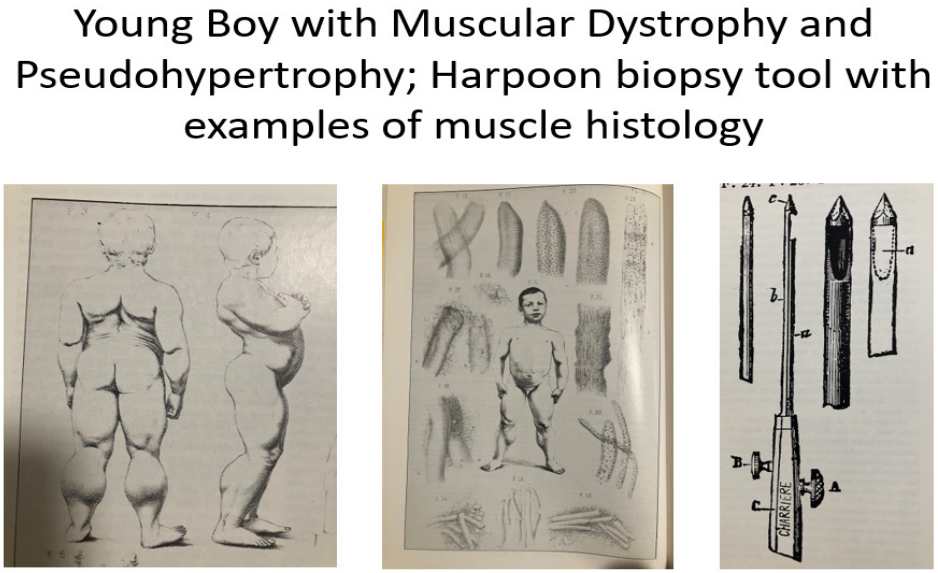
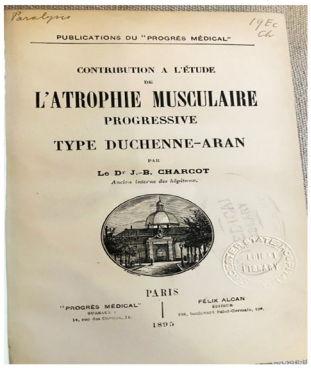


Figure 19

Contribution à l'étude de l'atrophie musculaire progressive, type Duchenne-Aran (1895)



PUBLICATIONS DU "PROGRÈS MÉDICAL"

CONTRIBUTION A L'ÉTUDE DE

L'ATROPHIE MUSCULAIRE PROGRESSIVE

TYPE DUCHENNE-ARAN

PAR

Le Dr J.-B. CHARCOT

Ancien Interne des Hôpitaux.

PARIS

"PROGRÈS MÉDICAL"

FÉLIX ALCAN

1895

Figure 20

Amand Duchenne

Electrophysiology

A TREATISE

ON

LOCALIZED ELECTRIZATION,

AND ITS APPLICATIONS TO PATHOLOGY AND THERAPEUTICS.

By DR. G. B. DUCHENNE.

TRANSLATED FROM THE THIRD EDITION OF THE ORIGINAL,

By HERBERT TIBBITS, M.D.,

LICENTIATE OF THE ROYAL COLLEGE OF PHYSICIANS OF LONDON; MEDICAL SUPERINTENDENT OF THE NATIONAL HOSPITAL FOR THE PARALYSED AND EPILEPTIC.

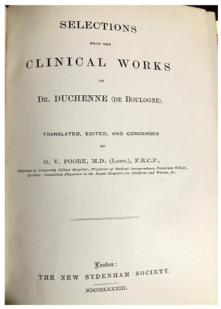
WITH NUMEROUS ILLUSTRATIONS,

AND NOTES AND ADDITIONS BY THE TRANSLATOR.

PHILADELPHIA:
LINDSAY & BLAKISTON.
1871.

Figure 21

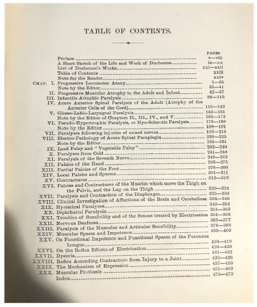
Selections of the Clinical Works of Dr. Duchenne (De Bologne) - Translated by G.V.Poore in 1883



SELECTIONS FROM THE CLINICAL WORKS OF DR. DUCHENNE DE BOULOGNE.

TRANSLATED, EDITED, AND CONDENSED BY G. V. POORE, M.D. (Lond.), F.R.C.P.,

London:
THE NEW SYDENHAM SOCIETY.
MDCCCLXXXIII.



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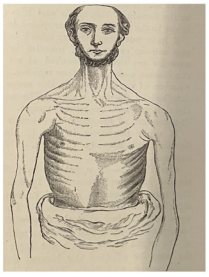


controversy between Charles Bell and Francois Magendie regarding the organization of motor and sensory pathways into and out of the spinal cord as we discussed in another article in this volume (See *History of Neurology: Charles Bell and François Magendie - British versus French Fights in the Age of Napolean and the Discovery of the Bell-Magendie Law*).[26] Two years after Charcot's death in 1895, an extensive monograph on progressive muscular atrophy was published posthumously in which Charcot cites the pioneering work of both Aran and Duchenne (Figure 19).[27]

Duchenne also described progressive bulbar palsy, which he called glosso-labio-laryngeal paralysis, and this entity has at times been referred to as Duchenne's disease.[28] Duchenne was the first to perform muscle biopsies using a "histological harpoon" and examined the tissue under the microscope (Figure 18). Duchenne was one of the early physicians who used the new technique of photography in his medical publications. Finally, he was a pioneer in the field of electrophysiology, and he was one of the early physicians that utilized electrical stimulation of muscles both to observe the action of certain muscles as well as to provide potential electrotherapy.

Duchenne published his findings regarding electrotherapy and the movement of muscles in three textbooks. The first was *A Treatise on Localized Electrization and its Applications to Pathology and Therapeutics* published in French in 1855. Dr. H Tibbets published the first English translation from 1871 (Figure 20).[25]

Tibbits only translated the first half of the book on electrical stimulation. Over the years, in subsequent additions, Duchenne kept adding numerous clinical cases to the second half of the book. In 1883, G. V. Poore published these clinical sections in English, and this is when Duchenne's amazing insights and accurate clinical observations of so many neuromuscular disorders became available to the English-speaking world (Figure 21).

His second book published in 1862 was called *Mécanisme de la physionomie humaine, ou, Analyse électro-physiologique de l'expression des passions*. This book was only recently translated into English (in 1990!) and contains many examples of Duchenne's use of photography in his medical publications (Figure 22).[29]

Duchenne's third important book was called *Physiologie des mouvements démontrée a l'aide de l'expérimentation électrique et de l'observation clinique et applicable a l'étude des paralysies et des deformations* published in 1867 and translated in English as *Physiology of Motion Demonstrated by Means of Electrical Stimulation and Clinical Observation and Applied to the Study of Paralysis and Deformities* (Figure 23).[30]

Charles Darwin reprinted photographs of Duchenne performing electrical stimulation on humans to mimic various facial expressions in his 1872 book called *The Expressions of the Emotions in Man and Animals*.[31]

It is interesting that scientists in the 1800s were fascinated by facial expressions in both humans and animals and it was thought that the understanding of facial expressions provided a window into feelings and brain function. Recall that Charles Bell fifty years earlier wrote a book of observations on facial expression in humans and animals that was valued by artists, scientists, and physicians (see *History of Neurology: Charles Bell and François Magendie - British versus French Fights in the Age of Napolean and the Discovery of the Bell-Magendie Law* this issue).[26, 32]

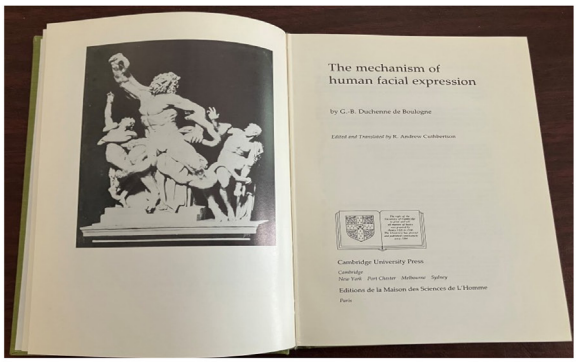
Duchenne practiced in Boulogne, where he was born, but then spent the majority of his adult life practicing in Paris. Duchenne never had any official attachment to any hospital, nor did he receive any recognition by the French academy or institute. However, he was well known to Charcot and others as a pioneering observer and diagnostician. Charcot apparently assisted Duchenne to become familiar with the microscopic examination of tissue. He also allowed Duchenne to serve as a physician on his service at the Salpêtrière in 1862. So while Duchenne was nearly twenty years older than Charcot, Charcot had become a leader in French medicine and assisted Duchenne in integrating into the Parisian medical circle. In return, Duchenne taught Charcot how to use photography in medical practice and publications. When I read Duchenne's clinical descriptions of various neuromuscular diseases, which are now so well known to us, I am amazed about his observational accuracy and prescience. Charcot may be considered by many as the father of modern clinical neurology, but Duchenne can rightly be considered the first true neuromuscular neurologist and electrophysiologist.

Another notable French physician from this era who contributed a great deal to neurology was Pierre Paul Broca (*The Founders of Neurology, p. 12-16* and *Fragments of Neurological History, p. 70-75*).[2, 3] Broca is of course most known for observing that motor aphasia was produced by damage to the left frontal lobe which contains the primary speech area.[33] While Broca was writing about the frontal gyrus as the motor location for speech, Wernicke was simultaneously writing about the superior temporal gyrus as the localization for understanding speech and where lesions produced a sensory aphasia (see *History of Neurology: German and Austrian Neurology (and some Psychiatry) in the 1800s - A Cautionary Tale* this issue).[34, 35] Hughlings Jackson in England (See *History of Neurology: Regal Neurology* this issue)[36] and Broca corresponded and agreed with one another on brain localization and presented papers at joint scientific meetings. Interestingly, Pierre Marie, who at one point was Broca's student, apparently disagreed with his mentor's brain localization ideas.

Another important physician who contributed a great deal to neurology as well as a variety of other areas of medicine was Claude Bernard (*The Founders of Neurology, p. 175-178* and *Fragments of Neurological History, p. 252-255*).[2, 3] Bernard was a pioneer in creating the field of academic experimental medicine by performing research on small animals, observing the effect, and extrapolating the significance to humans.[37] Today we call this translational medicine. He often credited his

Figure 22

The mechanism of human facial expression (1862) – First English translation 1990



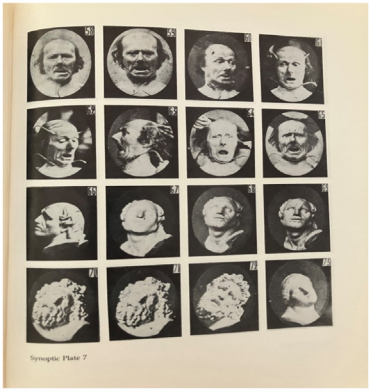
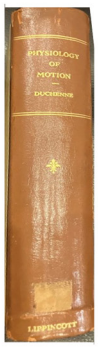


Figure 23

Physiology of Motion Demonstrated by Means of Electrical Stimulation and Clinical Observation and Applied to the Study of Paralysis and Deformities (1949) – Originally published in French in 1867



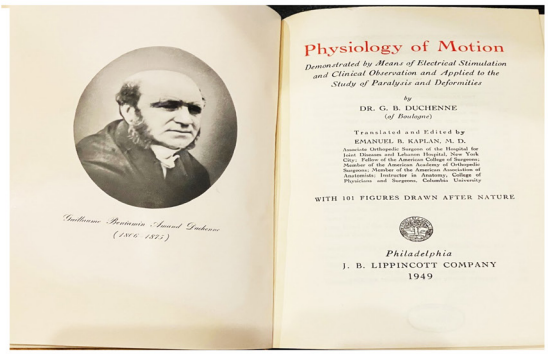
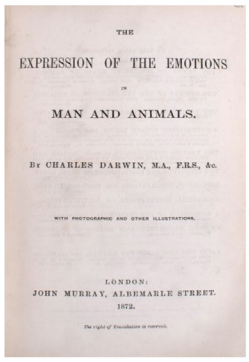


Figure 24

The Expressions of the Emotions in Man and Animals - Charles Darwin (1872)



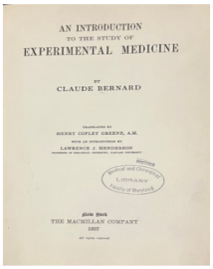
mentor, François Magendie, as his forerunner of experimental physiology in France (see *History of Neurology: Charles Bell and François Magendie - British versus French Fights in the Age of Napolean and the Discovery of the Bell-Magendie Law*).[26] He performed a number of experiments on the sympathetic nervous system. In 1852, he performed an experiment in rabbits in which he cut the cervical sympathetic nerve and showed that it produced constriction of the pupil, flushing, and rise of temperature in the ear. Subsequently, in 1869, a Swiss ophthalmologist Johann Horner described a man with myosis and ptosis and since then the disorder is either called Horner syndrome or Claude Bernard-Horner syndrome.[38] But Bernard is best known for his book called *Introduction à l'étude de la médecine expérimentale* (1865) translated into English by Greene in 1927 as *Introduction to the Study of Experimental Medicine*.[39] It continues to be republished in English and many other languages and is still read avidly by aspiring young medical scientists. This book gives a great deal of wise advice to scientists and physicians about pursuing a career in experimental medicine and is still very readable to this day. Bernard never practiced clinical medicine and devoted his entire career to laboratory research.

The final French physician of note who trained in Paris and spent a great deal of his career in France is of course Charles Edouard Brown-Séquard, who we discussed in a previous history of neurology article (See *History of Neurology: Charles-Édouard Brown-Séquard - The Original International Neurologist* and *Fragments of Neurological History, p. 221-227*).[3, 40] While Brown-Séquard traveled across the globe spending time as a physician in Mauritius, Paris, the Untied States, and London in Queen Square, he both began his career and finished it in France. Brown-Séquard is of course most well-known for his experimental cord hemisections showing

Figure 25

Claude Bernard (1813-1878)

- B: Paris, France
- Student of Francois Magendie
- In 1852, severed cervical sympathetic nerves in rabbits and produced animal model for what later became known as Horner's syndrome (Described in humans by Horner, 1869)
- *Introduction to the Study of Experimental Medicine – 1865*
  - First English translation, 1927


AN INTRODUCTION
TO THE STUDY OF
EXPERIMENTAL MEDICINE
BY
CLAUDE BERNARD
THE MACMILLAN COMPANY

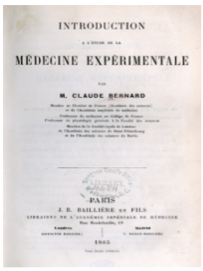
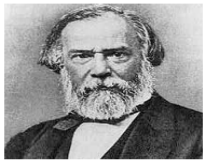
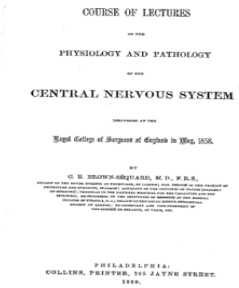

INTRODUCTION
MÉDECINE EXPÉRIMENTALE
M. CLAUDE BERNARD
PARIS
J. B. BAILLIÈRE ET FILS
1865

Figure 26

Édouard Brown-Séquard (1817-1894)

- Born: Port Louis, Mauritius
- Travel: Paris/USA/UK-Queens Square
- First international neurologist
- Cord hemisection/crossed pathways

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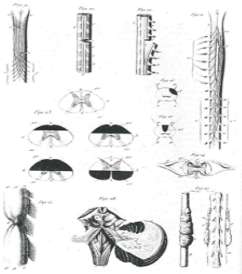
PHYSIOLOGY AND PATHOLOGY
CENTRAL NERVOUS SYSTEM
PHILADELPHIA:
COLLINS, PRINTER, 705 JAYNE STREET.



that motor pathways are ipsilateral whereas some sensory pathways are contralateral in the spinal cord and therefore a lesion of half the spinal cord produces what we now call the Brown-Séquard syndrome.

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German and Austrian Neurology (and some Psychiatry) in the 1800s - A Cautionary Tale

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A live recording of this lecture can be viewed here:
RRNMF - German and Austrian Neurology

This History of Neurology article is about German and Austrian neurology in the 1800s and into the 1900s. I will discuss both famous and infamous neurologists, neuroscientists, and psychiatrists from that period. This history really serves as a cautionary tale, showing that events that happened in Germany can happen anywhere.[1]

Before we focus on neurology (and psychiatry), we should mention Professor Rudolf Virchow, who many consider to be the father of modern medicine due to his pioneering work in the 1800s (Figure 1). Virchow conceived of the concept of the cell and cellular pathology as the basis for medical disease. He was a giant in the field of medicine, and he laid the foundation for medical thought and discoveries in all medical fields. He also became an expert in anthropology and published numerous anthropology articles in the second half of his career. Throughout his medical career, he was a progressive thinker and was an elected official to the Prussian House of Representatives. He authored more than 2000 scientific writings. He founded the journal that ultimately became known as Virchow's Archive, and he also started an ethnology journal through the German Anthropological Association. He was a progressive thinker and advocated for social and political reform.

The father of German neurology—and in many ways Western neurology—is Moritz Romberg (Figure 2) (*The Founders of Neurology, p. 506-509; Fragments of Neurological History, p. 373-374*).[2,3] Romberg was born in Germany and spent his medical school years and his entire career in Berlin. Interestingly, he also did some postgraduate work in Vienna. He is best known for two main contributions.

Figure 1

Rudolf Virchow (1821-1902)

- B: Schivelbein, Pomerania (Prussia) (now Świdwin, Poland)
- Practiced medicine and conducted pathology research at Berlin's Charité Hospital
- Served as Professor of Pathological Anatomy at the University of Berlin and Director of the Charité's Institute of Pathology
- Founder of the cell theory of pathology
- First to describe and name leukemia, chordoma, embolism, thrombosis, neuroglia, agenesis, parenchyma, osteoid, amyloid degeneration, and spina bifida
- Developed the first systematic method of autopsy

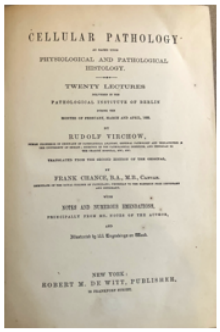
CELLULAR PATHOLOGY
PHYSIOLOGICAL AND PATHOLOGICAL HISTOLOGY.
TWENTY LECTURES
RUDOLF VIRCHOW.
FRANK CHANCE, M.A., M.B., Cantab.
NEW YORK:
ROBERT M. DE WITT, PUBLISHER.

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Figure 2

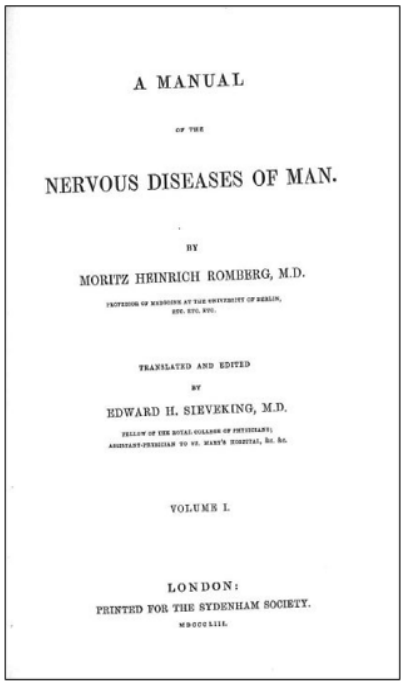
German Neurology
Early 1800's

Moritz Heinrich Romberg (1795-1873)

- Founder of German Neurology
- B: Meiningen, Germany
- Medical School – Berlin
- Post-grad – Vienna
- Career – Berlin
- *Lehrbuch der Nervenkrankheiten des Menschen* (1846)
- *A Manual of the Nervous Diseases of Man*
  - *3 Volumes: 1840 – 1846 in German; 1853 in English*
- 1st Neurology Textbook
  - In book, discussed tabes dorsalis. Described pathognomic sign: Loss of balance when standing patient closes eyes.
  - Now known as "Romberg Sign" due to sensory tract, pathology in spinal cord

Figure 3

Moritz Heinrich Romberg
1st Neurology Textbook



A MANUAL

OF THE

NERVOUS DISEASES OF MAN.

BY

MORITZ HEINRICH ROMBERG, M.D.

PROFESSOR OF MEDICINE AT THE UNIVERSITY OF BERLIN,
ETC. ETC. ETC.

TRANSLATED AND EDITED

BY

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VOLUME I.

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MDCCCLIII.

The first is the writing of what I consider the first true neurology textbook, *A Manual of Nervous Diseases* (Figure 3 & 4). It was published in Germany in three volumes in the 1840s and later published in English in London in 1853.[4] It is a wonderful book and remains readable to this day.

In that book, Romberg also described the second contribution for which he is famous: what we now call the Romberg sign. In his textbook, he described that in patients with tabes dorsalis, one of the signs was loss of balance when standing with the eyes closed.[5] We now understand this as the Romberg sign, indicating sensory tract pathology in the spinal cord or peripheral nerves. Romberg had a huge impact on the field, and all subsequent Western neurologists acknowledge him as the true first neurologist and founder of the field.

There were many other famous German and Austrian neurologists immediately after Romberg. One was Nikolaus Friedreich, who spent his career in Heidelberg, Germany

Figure 4

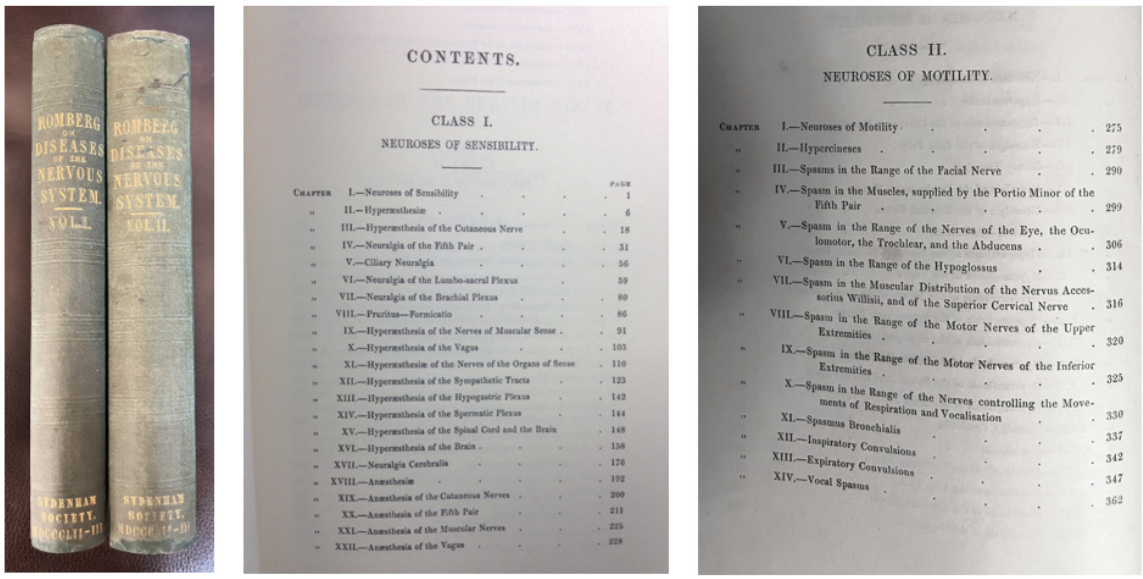
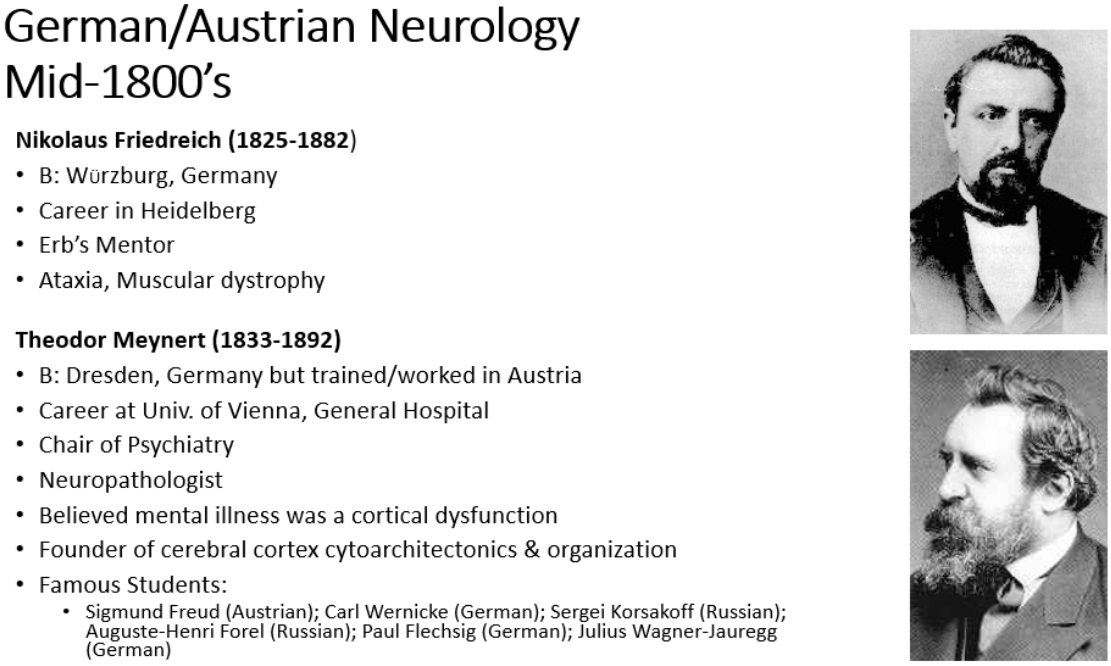


Figure 5



(*The Founders of Neurology, p. 439-441*).[2] He described ataxia and muscular dystrophies, which we now recognize as Friedreich's ataxia.[6,7] Another was Theodor Meynert, who was born in Dresden but spent his entire career in Austria at the University of Vienna (*The Founders of Neurology, p. 57-62*).[2] He was chair of psychiatry and a neuropathologist who believed mental illness had an organic, cortical basis. He founded the field of cerebral cortex cytoarchitectonics and organization.[8]

Meynert had many famous students, including Sigmund Freud, whom we will discuss shortly. Other students included Sergei Korsakoff from Russia, Honoré Parrell, and Julius Wagner-Jauregg, who will be discussed later as one of the more infamous figures.

Other neurologists who made major contributions during this time include Carl Wernicke, who was born in Poland but trained and spent his career in Berlin (*The Founders of Neurology, p. 531-535; Fragments of Neurological History, p. 81-83*).[2,3] He described the sensory form of aphasia resulting from temporal lobe lesions.[9] He also described the alcoholic complications to the central nervous system consisting of nystagmus, ataxia, ophthalmoplegia, and disturbances of consciousness.[10] He described the pathology of this disorder as an acute hemorrhagic superior polioencephalitis and we still refer to the clinical presentation as Wernicke's syndrome. Eduard Hitzig was prominent in the field of cortical localization and was the first to stimulate the motor cortex and demonstrate movement on the opposite side of the body (*The Founders of Neurology, p. 229-233*).[2,11] Alois Alzheimer, born in Munich, devoted his career to the study of dementia and wrote his famous monograph in 1907, describing presenile dementia with plaques and tangles (*The Founders of Neurology, p. 315-319; Fragments of Neurological History, p. 103-107*).[2,3,12]

It is impossible to discuss neurology and psychiatry in Germany and Austria without mentioning Sigmund Freud (*Fragments of Neurological History, p. 615-621*).[3] Freud was born in what is now the Czech Republic, but his family moved to Vienna early in his life, and he was educated there. Early in his career, Freud was very much a neuroscientist. He conducted research on the nervous system of the eel and developed new staining techniques, which he published in the journal Brain.[13] He also spent time studying under Charcot in Paris, an experience that had a lasting influence on him (*History of Neurology: French Neurology in the 19th Century – Charcot, his Legacy, and Other Notable Physicians*).

Freud later founded psychoanalysis and developed the concepts of the unconscious, the ego, and the superego. His most famous book, The Interpretation of Dreams, was published in 1900.[14] However, before this work, he wrote important neurological texts on aphasia and infantile cerebral palsy, underscoring his early identity as a neurologist.[15,16]

Other well-known neurologists from this era include Carl Westphal, who spent his career at the Charité Hospital in Berlin and became the first professor of neurology at Berlin University. He noted absent deep tendon reflexes of the knees in patients with tabes dorsalis.[17] Hermann Oppenheim, a student of Westphal, also spent his career in Berlin (*The Founders of Neurology, p. 492-495; Fragments of Neurological History, p. 359-361*).[2,3] He wrote on traumatic neuroses, tetany, and myotonia congenita, and authored a highly regarded two-volume textbook on nervous diseases in 1911 which is still very readable.[18]

Figure 6

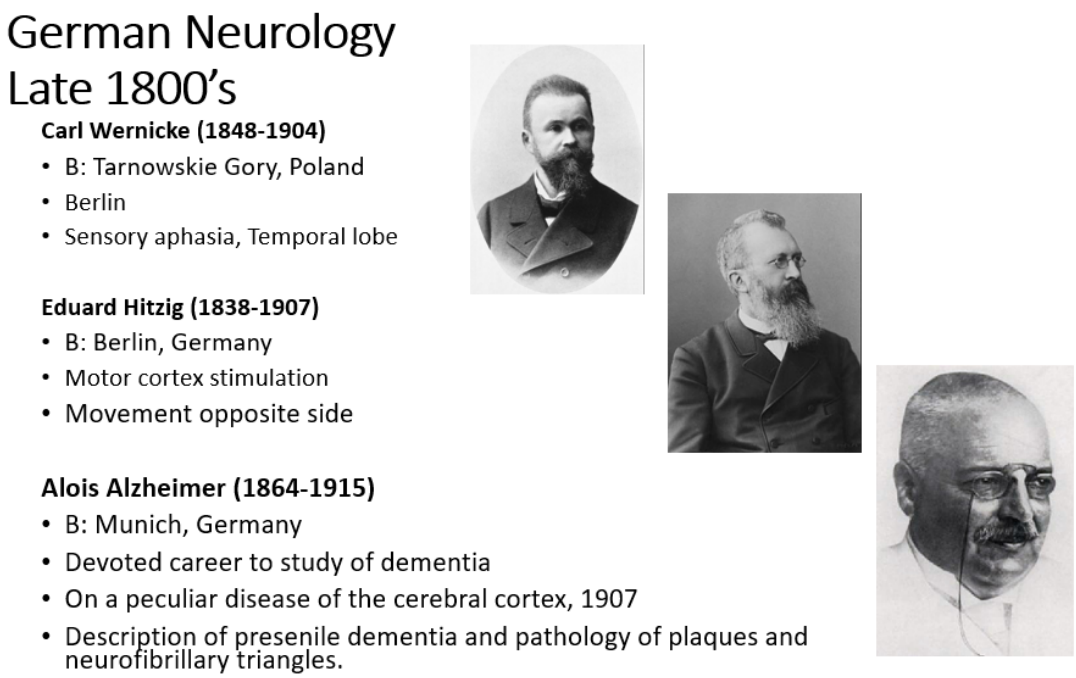
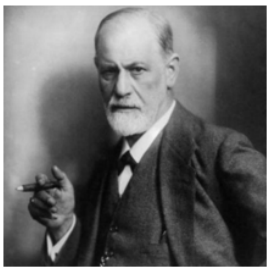


Figure 7

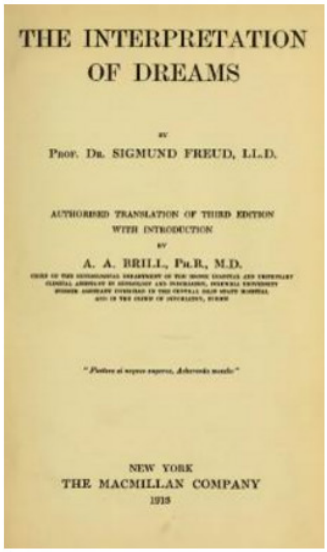
Austrian Neurology
Sigmund Freud (1856-1939)

- B: Pribor, Czech Republic
- Education & career in Vienna
- Early in career did lab research on nervous system of eels (gold chloride staining)
- Briefly with Charcot
- Founder of psychoanalysis
- Unconscious – ego, super-ego, id
- *Interpretation of Dreams* – 1900
  - But he was a Neurologist!
- *On Aphasia*
- *Infantile Cerebral Palsy*



Poster of the youthful and elderly Freud that I purchased at the Freud Museum
(Freud's Vienna home and office in 1982)

Figure 8


THE INTERPRETATION OF DREAMS

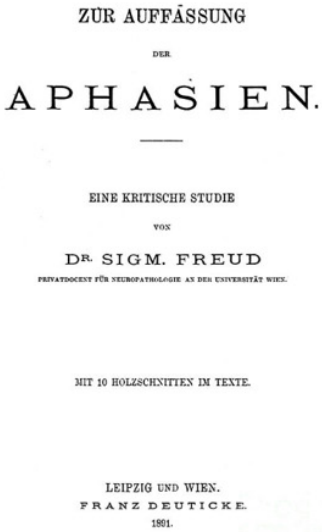
BY

PROF. DR. SIGMUND FREUD, LL.D.

AUTHORIZED TRANSLATION OF THIRD EDITION WITH INTRODUCTION BY

A. A. BRILL, PH.B., M.D.

NEW YORK
THE MACMILLAN COMPANY
1913


ZUR AUFFASSUNG

DER

APHASIEN.

EINE KRITISCHE STUDIE

VON

DR. SIGM. FREUD

PRIVATDOCENT FÜR NEUROPATHOLOGIE AN DER UNIVERSITÄT WIEN.

MIT 10 HOLZSCHNITTEN IM TEXTE.

LEIPZIG UND WIEN.
FRANZ DEUTICKE.
1891.

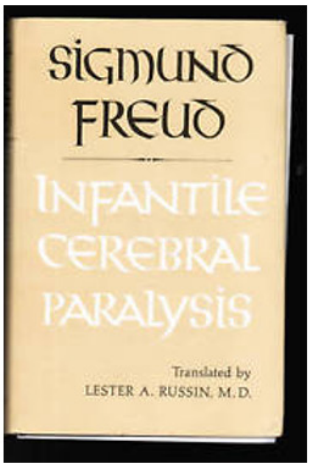
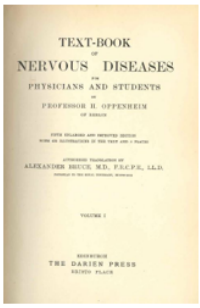


Figure 9

German Neurology
Late 1800's


TEXT-BOOK
OF
NERVOUS DISEASES
FOR
PHYSICIANS AND STUDENTS
OF
PROFESSOR H. OPPENHEIM
OF BERLIN

AUTHORIZED TRANSLATION BY
ALEXANDER BRUCE, M.D., F.R.C.P.E., LL.D.

VOLUME I

EDINBURGH
THE DARIEN PRESS
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Carl Friedrich Otto Westphal (1833-1890)

- B: Berlin, Germany
- Charité Hospital in Berlin
- First Professor of Neurology at a Prussian University
- Absent knee reflexes in tabes

Herman Oppenheim (1858-1919)

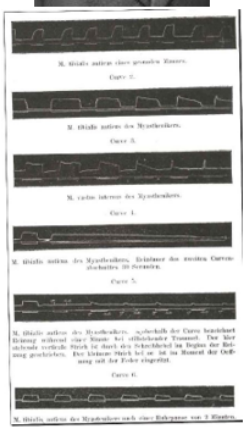
- B: Warburg, Germany
- Charité in Berlin; Student of Westphal
- Traumatic neurosis, dystonia, tabes, amyotonia congenital
- *Textbook of Nervous Diseases for Physicians and Students of Professor H. Oppenheim* – translated into English (1911)

Figure 10

German Neurology
Late 1800's

Wilhelm Heinrich Erb (1840-1921)

- B: Winnweiler, Germany
- Career in Heidelberg
- MG, MD, spastic spinal paralysis, upper brachial plexus palsy



Friedrich Jolly (1844 – 1904)

- B: Heidelberg, Germany
- Berlin - Followed Westphal at Charité as Chair
- "The Myasthenic Reaction" on rep stim
- Jolly Test – i.e. Repetitive Nerve Stimulation in MG (1895)

Wilhelm Erb was another major figure who practiced in Heidelberg throughout his career. He wrote extensively on myasthenia gravis, muscular dystrophy, spastic paralysis from spinal cord lesions, and is perhaps most famous for describing upper brachial plexus palsy (*The Founders of Neurology, p. 435-438; Fragments of Neurological History, p. 44-47*).[2,3,19] Friedrich Jolly, though his name may not sound German, was born in Heidelberg and practiced in Berlin. He succeeded Westphal as head of neurology at the Charité Hospital and wrote widely on myasthenia gravis. Jolly invented repetitive nerve stimulation testing and described the decremental response, a test that some still refer to as the Jolly test (Although it does not feel Jolly to patients on the receiving end of the electrical stimulus).[20]

There were also infamous neurologists whose legacies are more troubling. Emil Kraepelin, born in Germany, spent his career in various German cities and is considered the founder of modern scientific psychiatry.[21,22] He classified psychiatric diseases in ways still used today in the DSM system. However, he was also a proponent of eugenics and racial hygiene, believing it was important for Germany to preserve and enhance the race. His writings included explicitly antisemitic views.

Julius Wagner-Jauregg, who trained under Meynert in Austria, later became professor of psychiatry and nervous diseases in Vienna (*The Founders of Neurology, p. 528-531*).[2] He is known for developing pyrotherapy, using fever as a treatment for neurosyphilis-related dementia by inducing

Figure 11

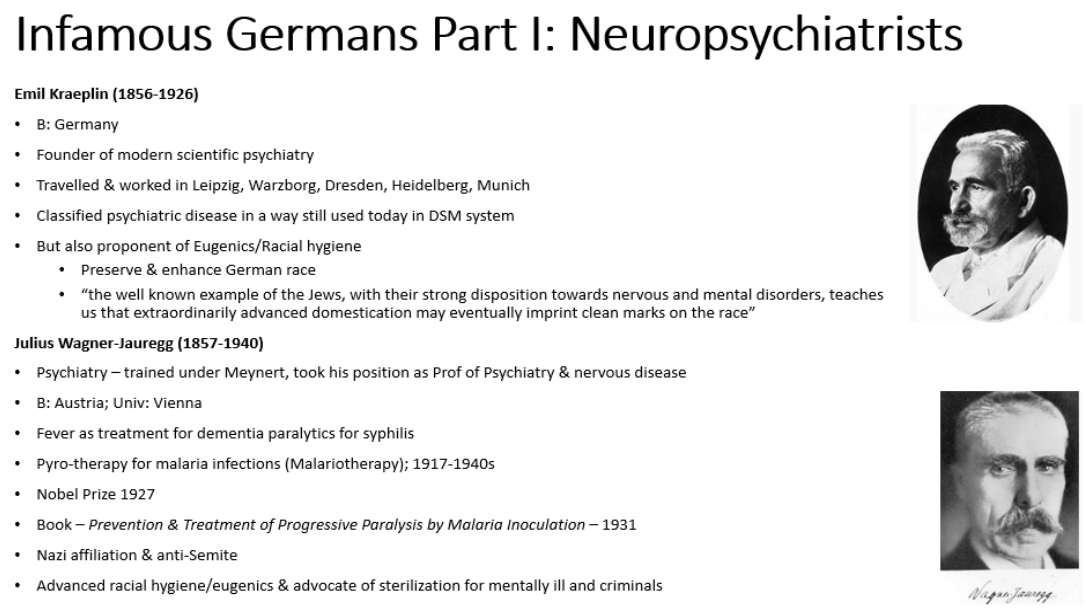


Figure 12

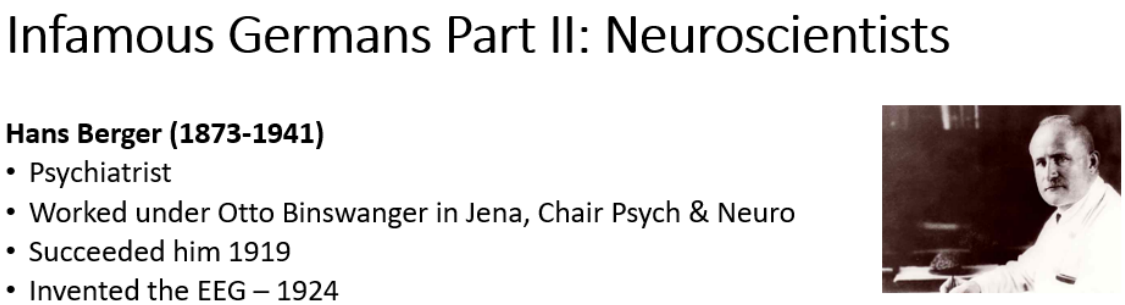
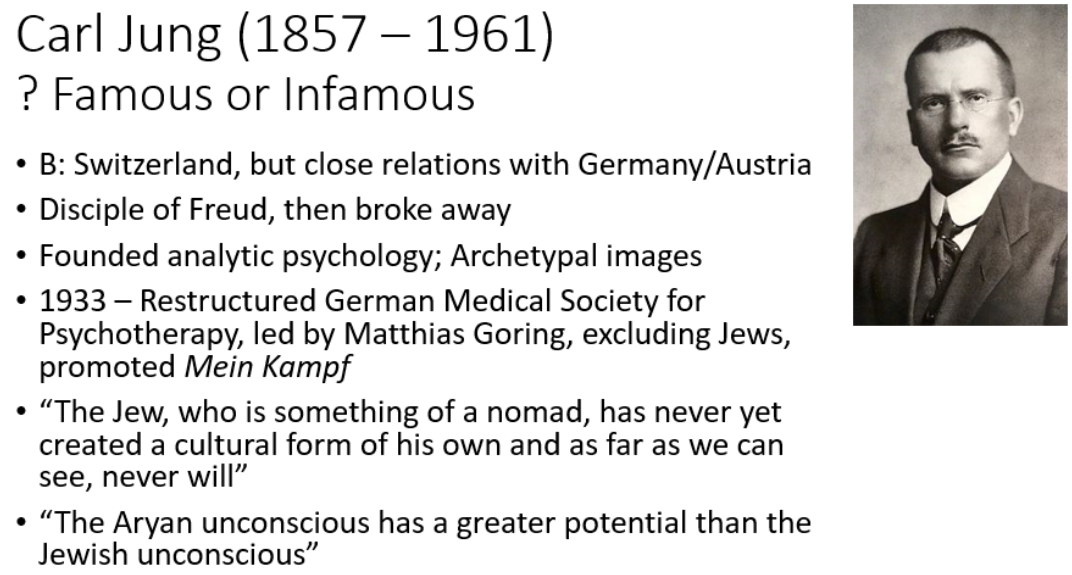


Figure 13



malaria infections. Remarkably, he won the Nobel Prize in 1927 for this work. In 1931, he wrote a book on the prevention and treatment of progressive paralysis.[23] However, he later had strong Nazi affiliations and supported racial hygiene, eugenics, and sterilization of the mentally ill and criminals.

Hans Berger, a German psychiatrist who worked under Otto Binswanger, invented the EEG and was the first to recognize the alpha rhythm of the brain (*The Founders of Neurology, p. 171-175*).[2,24] This was a major scientific breakthrough. However, it was later discovered that Berger was a Nazi and a member of the SS, information that only became widely known in 2005.[25,26]

Similarly, Julius Hallervorden and Hugo Spatz (*The Founders of Neurology, p. 369-375*), who described the disorder once known as Hallervorden–Spatz disease, were later revealed to be Nazi Party members.[2,27] As a result, the condition is now referred to as pantothenate kinase–associated neurodegeneration, and the original eponym has been abandoned.

To conclude, I will mention Carl Jung, who was almost as famous as Freud and perhaps equally controversial.[28] Born in Switzerland, Jung maintained close ties with Germany and Austria throughout his career. Initially a disciple of Freud, he later broke away and founded analytic psychology, introducing concepts such as archetypes. In the 1930s, Jung helped restructure the German Medical Society for Psychotherapy, which excluded Jews and promoted Nazi ideology. His published statements from this period reflect antisemitic views. However, Jung is such a towering figure in the field of psychoanalysis, and he has had many defenders over the decades that attempt to mitigate what to many seemed like an antisemitic mindset and Nazi sympathizer.

As you can see from this brief overview, German and Austrian neurologists, psychiatrists, and neuroscientists made extraordinary contributions to neurology and psychiatry in the 1800s and early 1900s. However, during the 1930s, many of these same figures were influenced by, and in some cases actively supported, Nazism. This history shows that such developments can occur anywhere, even in advanced cultural societies. As I said at the beginning, it can happen here—to paraphrase the title of Sinclair Lewis's famous novel, It Can't Happen Here.[29] A similar theme is discussed in Philip Roth's novel, *The Plot Against America.*[30]

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Museum of Art and Archaeology,
University of Missouri

Cover image: Robert Bussabarger (American, 1922-2013), *Galveston House*, late 1970s-early 1980s, pastels on paper, gift in memory of the artist Robert F. Bussabarger from his family (2014.108)

Attendees of the upcoming NMSG meeting might well encounter scenes similar to the one featured on this journal's cover as they make their way through the state of Texas to San Antonio for the convening. And while the one pictured memorializes a home in Galveston, Tx., situated on the Gulf coast, San Antonio's neighborhoods boast many a Victorian mansion to be admired.

The cover image reproduces a pastel on paper scene by artist Robert Bussabarger, a longtime and well-known resident of Columbia, Missouri. Bussabarger was a faculty member of the University of Missouri's then-termed the Fine Arts Department from 1953 until his retirement in 1991, teaching painting and ceramics to countless undergraduate and graduate students. He died in 2013, after which several of his works were gifted to the Museum of Art and Archaeology, including *Galveston House*.

A 2015 article in the *Columbia Missourian* highlighted how Bussabarger's family distributed much of their patriarch's remaining works of art after his death, and highlighted the artist's long career:

> "Robert Bussabarger was intent on capturing the world around him as soon as he saw it. He could be found drawing intricate doodles on empty Styrofoam cups, beverage napkins or random scraps of paper. During a brief World War II naval tour, Bussabarger carried a sketchbook. He would draw the people and the landscapes he encountered, calling it his visual journey."

Bussabarger's visual journey took him to Texas after he married in 1946 and finished college at Michigan State University. Eventually he landed a job teaching at Stephen F. Austin State University in Nacogdoches, Tex., allowing him to explore the state, including Galveston, a city well known for its Victorian architecture. He would have had his pick while visiting the city.

Museum records describe the composition of *Galveston House* as a "view of part of the front of an ornate two-story house in Galveston, Texas. The house and its ... yard are enclosed within a low iron fence[,] [and] [a] stairway with several steps leads up to the house's porch and front door. The...exterior is decorated [in] ornate teal, white, and pink moldings, pilasters, [and] arched openings...[with] [d]ark brown and black tree branches partially obscur[ing] the house's upper level."

If there's time in between neuromuscular study sessions and reports on related drug trials, the architecture of San Antonio is worth taking in, particularly the neighborhoods where one will see many homes like the one in Galveston drawn by Bussabarger.

In 1979, Bussabarger was interviewed by a student reporter at the *Columbia Missourian* about his philosophy as an artist and teacher. He was quoted in a subsequent article as saying: "Whether my work will be forgotten, or I'll be forgotten in connection with it is less important than what I did and that I got all I could out of it at the time." In featuring *Galveston House* as a cover image, NMSG has helped Bussabarger's work to be remembered and enjoyed. Given the many works in our permanent collection and our very limited gallery space, I'm grateful for your selection as it allows us to highlight a work of art that is in storage.

As I have written in past columns, if you are reading this from a screen in central Missouri, or ever find yourself here, please visit the museum. And while Robert Bussabarger's *Galveston House* is not currently on display, there's much to see and enjoy. As always, works of art are best viewed in person, so if you can't visit the Museum of Art and Archaeology (MA&A), I hope you'll take time to darken the door of an art museum near you.

For those of you contemplating a trip to Columbia, Mo., MA&A is located on the lower east side of Ellis Library, with entrances off Hitt Street, Lowry Mall, and from within Ellis. Regular hours during the week are 10 a.m. to 4 p.m. Tuesday through Friday, and noon to 4 p.m. on Saturdays and Sundays. Admission to the museum is always free. Please ask for me if you visit as it would be my pleasure to tour you through the galleries.

For more information about the MA&A, in general, including a calendar of events and a searchable database of the museum's permanent collection of more than 16,000 objects, including several by Robert Bussabarger, visit maa.missouri.edu.

Author's Note: Years ago as a fine arts major at the University of Missouri, I was lucky enough to take beginning watercolor from Robert Bussabarger. It was the semester before I changed my major to art history and archaeology. I am a better art historian because I learned to paint and draw and design from artists like Bussabarger. I remember his class well and still have some of the paintings I made that semester.

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Welcome to the 27th Annual NMSG Scientific Meeting!

Richard J. Barohn MD
Michael G. Hanna MD

Dear Colleagues,

On behalf of the Neuromuscular Study Group (NMSG), we are delighted to welcome you to San Antonio, Texas, for our 27th Annual Scientific Meeting.

For nearly three decades, the NMSG has united researchers from around the world to collaborate on advancing neuromuscular science. This meeting in particular has become a unique opportunity for our community to come together for a vibrant exchange of ideas that reinforces our commitment to progressing innovation in our field. Whether you are presenting a poster or discussing trials between sessions, we encourage you to engage fully with your colleagues and our industry partners, as your active participation will greatly strengthen the value of our time together.

A few meeting highlights for this year.

- Emerging Investigators: We welcome back this valuable session where emerging talent can connect with and learn from established leaders in the field. Join us at 3:40 pm on Friday.
- Abstract Poster Presentations: We had 138 submissions this year. Please stop by to see their work at 5 pm on Friday in the Minuet and Patio Rooms.
- Industry Partners: We appreciate the immense industry involvement. Please join us for their presentations starting at 2:00 pm on Saturday and visit their tables daily in the Grand Ballroom.
- Shark Tank: In its seventh year, the Shark Tank session will feature four exciting proposals, with the winner receiving a $10,000 grant. New this year: Everyone who attends the session will be able to score the presentations. Join us at 9:00 am on Sunday.

Outside of the scientific program, take time to enjoy the history and charm of the Alamo here in San Antonio. Starting at the historic Alamo, with its cypress-shaded River Walk and tucked-away patios just steps away, San Antonio offers a truly welcoming setting. We hope you will soak in the rich heritage, savor South Texas hospitality and cuisine, and make the most of this charming location during your visit.

We are excited for the continuing opportunity to share breakthroughs, clinical insights, and new ideas that can improve the treatment and care of our patients. Let us continue to embrace the spirit of collaboration as we explore the latest research and inspire one another with our findings.

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2026 NMSG Scientific Meeting Platform Presentations

33 - Multilevel Neurophysiologic Assessment of Cortical and Peripheral Motor System Dysfunction in Amyotrophic Lateral Sclerosis

Arsh Ketabforoush[1, 2], Vaibhav Oberoi[2], Kris Kelly[2], Roisin McMackin[3], Arash Karimi[4], Jaime Basnett[2], Jess Mills[2], Ryan Castoro[2], W. David Arnold[2]
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Introduction:
Amyotrophic lateral sclerosis (ALS) is characterized by progressive upper and lower motor neuron degeneration. While cortical hyperexcitability has been implicated in ALS pathogenesis, most transcranial magnetic stimulation (TMS) studies have focused on upper limb muscles. Relationships between cortical dysfunction, peripheral motor unit remodeling, and muscle impairment within the same lower limb motor system remain incompletely understood.
Objectives:
To characterize cortical excitability abnormalities in ALS using single- and paired-pulse TMS and determine their relationships with peripheral motor unit integrity and muscle performance within the same lower limb muscle, the vastus lateralis (VL).
Methods:
This prospective pilot study included 10 ALS patients and 10 matched controls. Participants underwent strength testing, single- and paired-pulse TMS over the VL motor cortex representation, and peripheral motor unit assessment using motor unit number index (MUNIX), and motor unit size index (MUSIX). TMS measures included resting motor threshold (RMT), cortical silent period (CSP), short-interval intracortical inhibition (SICI), short-interval intracortical facilitation (SICF), intracortical facilitation (ICF), and long-interval intracortical inhibition (LICI).
Results:
ALS demonstrated increased RMT (57.96vs45.08%, $p=0.045$) and markedly reduced CSP duration (67.57vs164.4ms, $p<0.0001$). SICF and ICF were significantly enhanced (both $p<0.0001$), while SICI and LICI were preserved. Reduced CSP correlated with lower muscle torque ($p<0.01$). Greater SICF responses and inhibitory dysfunction correlated with MUSIX ($p<0.05$), linking cortical dysfunction to peripheral motor unit remodeling.
Conclusions:
ALS is associated with impaired corticospinal conduction, reduced sustained cortical inhibition, and enhanced facilitatory intracortical responses. Cortical excitability abnormalities within the VL motor system were strongly associated with muscle weakness and peripheral motor unit remodeling, supporting integrated cortical-peripheral motor system degeneration in ALS.

114 - Clinical Outcomes and Safety of Nucleoside Therapy for Thymidine Kinase 2 Deficiency in a Brazilian Cohort

Cristiane Araujo Martins Moreno[1], Tatiana Ribeiro Fernandes[1], Clara Gontijo Camelo[1], Gabriel Keller[1], Ana Paula Lança[1], Andre Macedo Serafim Silva[1], Michelle Abdo Paiva[1], Edmar Zanoteli[1]
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Introduction: Thymidine Kinase 2 deficiency (TK2d) is a rare mitochondrial DNA (mtDNA) depletion syndrome leading to a severe and progressive myopathic disorder. Nucleoside supplementation (deoxythymidine and deoxycytidine) has been shown to favorably alter the disease's course, particularly in severe infantile-onset cases. However, long-term data on efficacy and safety remain limited.
Objectives: To demonstrate treatment efficacy and safety among patients with TK2d treated with nucleosides.
Methods: This is a retrospective, long-term follow-up study of 14 patients with TK2d (5 children and 9 adults) who were receiving nucleoside supplementation through a compassionate use program. Patients were systematically evaluated over a period ranging from 18 to 36 months, with assessments conducted every 3 months during the first year of treatment and every 6 months thereafter. Comprehensive functional assessments of motor, respiratory, and bulbar function were performed in addition to periodic measurements of liver and pancreatic function.
Results: All 14 TK2d patients showed beneficial effects across motor, respiratory, and bulbar function domains. Milestones were regained/gained in all children and 3 out of 9 adults. Adults reported severe gastrointestinal symptoms. Liver and pancreatic enzyme abnormalities were noticed in most of the adults.
Conclusions: Deoxythymidine and deoxycytidine were found to be safe and beneficial in this long-term cohort of pediatric and adult TK2d patients, though elevations in liver and pancreatic enzymes were observed and require regular monitoring. This study provides valuable evidence supporting this therapy as an effective, safe, long-term, disease-modifying treatment option for both pediatric and adult patients.

43 - Longitudinal assessment of motor function in Duchenne Muscular Dystrophy in a pediatric cohort: development of Italian centile curves for the North Star Ambulatory Assessment, 10-Meter Walk/Run Velocity and Rise from Floor Velocity

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Introduction: Individuals with Duchenne Muscular Dystrophy (DMD) show highly heterogeneous motor function progression, complicating clinical monitoring.
Objective: To develop Italian centile curves for the North Star Ambulatory Assessment (NSAA), 10-meter walk/run velocity (10MWRV), and rise from floor velocity (TRFV), and to compare them with UK centiles.
Methods: Subjects were selected from the Italian DMD Registry; patients enrolled in clinical trials were excluded. NSAA scores and timed test measures were rescaled to the [0,1] interval and analyzed using GAMLSS models with beta inflated distributions, modelling age effects on mean, dispersion, and skewness.
Results: A total of 7201 assessments from 720 participants were analyzed, including 430 individuals who lost function during follow-up. The 10th, 25th, 50th, 75th, and 90th centiles were evaluated. Comparison with UK centiles in individuals aged 5-16 years showed only partial overlap: NSAA curves differed mainly at the extreme centiles, whereas age at loss of function was similar between cohorts. Italian patients were initially slower in TRFV but remained more stable over time, while decline in 10MWRV occurred earlier compared with the UK cohort. Longitudinal centile monitoring showed variability over time: for NSAA, 206/586 patients remained within the same centile, while 380 changed centiles; for rise from floor, 270/578 remained stable and 308 changed centiles; for 10MWRV, 235/575 remained stable and 340 changed centiles.
Conclusions: Italian centiles for NSAA, 10MWRV, and RFFV are useful tools for longitudinal monitoring of motor function in DMD, particularly during advanced stages of disease progression.

5 - Neuromuscular junction failure in sarcopenia is linked to NaV1.4 loss and reversed by ClC-1 inhibition

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Introduction: Sarcopenia is the age-related loss of muscle strength and size that leads to mobility limitations and loss of independence in older adults. The underlying cellular mechanisms remain unclear, and treatments are limited.
Objectives: We examined the reliability of neuromuscular junction (NMJ) synaptic transmission for force production in older humans and rodents as the critical interface between the nervous system and muscle.
Methods: Ten older adults with complaints of physical limitations (85.9±4.4 years; 40% female) and eight control adults (29.5±8.7 years; 38% female) were measured for isokinetic leg extensor strength and single fiber electromyography for their quadriceps muscles. Adult and old C57BL/6N mice and Wistar rats were analyzed using electrophysiological and immunofluorescent methods to evaluate neuromuscular transmission, muscle excitability, NMJ morphology, and protein expression levels.
Results: Older individuals exhibit NMJ transmission failure that correlates with muscle weakness. Pre-clinical experiments showed similar NMJ transmission failure in aged mice and rats that was associated with localized loss of muscle fiber excitability at NMJs. This excitability defect highlights a novel mechanism of sarcopenia. Across species, immunohistochemistry revealed a reduction in the voltage-gated sodium channel specific for skeletal muscle (NaV1.4) at the post-synaptic NMJ membrane. Acute NaV1.4 inhibition with μ-conotoxin GIIIB in adult rats reproduced findings of NMJ transmission failure observed in aged rodents and humans. Finally, ClC-1 chloride channel inhibition enhanced muscle excitability and muscle function in old rodents.
Conclusions: NMJ transmission deficits are a key, reversible driver of sarcopenia and reveal a novel therapeutic target for addressing muscle weakness in aging.

92 - Real-World Givinostat Tolerability and Dose Modification in Nonambulatory Males with Duchenne Muscular Dystrophy

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Introduction:
Givinostat is approved for Duchenne muscular dystrophy (DMD) with weight-based dosing up to a target of 6 mL (53.2 mg) twice daily. In the EPIDYS clinical trial, participants included were fully ambulatory, which differs from real-world populations that include nonambulatory individuals. Data describing givinostat tolerability in this broader population remains limited.
Objectives:
To describe dosing patterns and tolerability of givinostat among nonambulatory males with DMD in a real-world neuromuscular clinic.
Methods:
This retrospective study included nonambulatory males with DMD treated with givinostat at a single center. Data collected included dose modifications and adverse effects. Descriptive analyses were performed.
Results:

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118 - Lysosome Remodeling in CMT1A Neuropathy: Pathogenic Mechanism or Compensatory Response?

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Introduction: Charcot-Marie-Tooth disease type 1A (CMT1A), caused by *PMP22* gene duplication, is the most common inherited peripheral neuropathy and currently lacks disease-modifying therapies. Although PMP22 overexpression is central to disease pathogenesis, the downstream cellular mechanisms that drive myelin dysfunction remain poorly understood. Emerging evidence implicates lysosomal pathways in PMP22-associated neuropathies, primarily from cellular models and studies of protein quality control. However, whether lysosomal abnormalities occur within intact myelin from physiologically relevant models of CMT1A has not been established and their functional significance remains unclear.
Objectives: To determine whether PMP22 overexpression in a genetically relevant mouse model of CMT1A is associated with lysosomal remodeling in peripheral nerve myelin and to explore the potential pathogenic or compensatory nature of these changes.
Methods: Teased peripheral nerve fibers from CMT1A and control mice were analyzed by confocal immunofluorescence. Lysosomal abundance, morphology and degradative potential were assessed using LAMP1 and Cathepsin D. Three-dimensional quantitative imaging was used to measure lysosome number, volume, intensity and spatial distribution within peripheral nerve myelin.
Results: Quantitative analyses revealed accumulation of LAMP1-positive lysosomes within CMT1A myelin, accompanied by altered lysosome abundance and morphology. Studies assessing lysosomal proteolytic capacity through Cathepsin D localization and expression are ongoing.
Conclusions: Lysosomal remodeling is a prominent feature of peripheral nerve pathology in CMT1A. Ongoing studies integrating lysosomal morphology, function, ultrastructure, trafficking dynamics and pharmacologic manipulation will determine whether lysosome accumulation contributes to disease pathogenesis or represents a compensatory response to PMP22 overexpression. Defining the role of lysosomes in CMT1A may reveal new therapeutic opportunities.

117 - Manifesting dystrophinopathy in a girl with Williams-Beuren syndrome: a dual molecular diagnosis supported by skewed X-inactivation

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Introduction: Duchenne muscular dystrophy (DMD) is an X-linked neuromuscular disorder predominantly affecting males. Manifesting dystrophinopathy in females is very rare, typically reflecting mechanisms favoring expression of the pathogenic *DMD* allele, particularly skewed X-chromosome inactivation. Williams-Beuren syndrome (WBS) is a 7q11.23 microdeletion syndrome associated with neurodevelopmental delay, growth restriction, dysmorphic features, and multisystem involvement.
Methods: Case report.
Results: A preschool-aged girl presented with developmental delay, growth restriction, dysmorphic features, motor clumsiness, and a family history of dystrophinopathy in male relatives. On examination, axial hypotonia and a broad-based gait were observed, while laboratory testing showed hyperCKemia with mild transaminase elevation. Chromosomal microarray identified a heterozygous 1.57-Mb deletion at 7q11.23, confirming WBS. Persistent hyperCKemia and family history of dystrophinopathy prompted targeted molecular testing, which identified a heterozygous familial *DMD* nonsense variant (c.1966C>T). Karyotyping excluded structural X-chromosome abnormalities, whereas X-chromosome inactivation analysis demonstrated non-random inactivation (74:26), supporting the diagnosis of manifesting dystrophinopathy. Follow-up revealed persistent motor incoordination, thigh and calf hypertrophy, restricted ankle dorsiflexion, and a toe-walking tendency.
Conclusions: Early recognition of coexisting dystrophinopathy has direct implications for surveillance, rehabilitation, and genetic counseling.

107 - Near infrared spectroscopy during non-ischaemic handgrip exercise reveals distinct muscle oxygenation signatures in mitochondrial disease and sarcopenia

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Introduction:
Mitochondrial dysfunction is a putative contributor to sarcopenia. Genetically confirmed mitochondrial disease offers a definitive model to validate novel functional assessments as biomarkers for conditions where mitochondrial dysfunction plays a key role.
Objectives:
Determine whether Near-InfraRed-Spectroscopy (NIRS) detects impaired oxygen extraction during handgrip exercise in mitochondrial disease, compare oxygenation profiles with sarcopenia, and assess mechanistic biomarker potential.
Methods:
Two cohorts were studied: adults with genetically confirmed mitochondrial disease (n=10) and matched controls (n=19); and MASS Lifecourse participants (n=23), stratified by EWGSOP2 sarcopenia status (7 probable sarcopenia, 16 no sarcopenia). Maximal voluntary contraction (MVC) and 3-minutes intermittent isometric handgrip exercise (40% MVC, 1 Hz) with continuous digital dynamometry and simultaneous NIRS measurement of Tissue Saturation Index (TSI) was performed. MVC peak force, MVC relaxation time, total exercise force, integrated TSI and total haemoglobin (THb) in the last 30 seconds of exercise (compared to pre-exercise baseline) were measured. Statistical significance was assessed using t-tests, Mann-Whitney U, ANOVA, or Kruskal-Wallis tests depending on normality and comparison number.
Results:
Participants with mitochondrial disease showed *attenuated* TSI reduction (-39 for Mito vs -110 for controls, p=0.01). In contrast, participants with sarcopenia, particularly men, showed *exaggerated* TSI reduction (overall -256 for sarcopenic vs -121 for non-sarcopenic, p=0.05; -317 for sarcopenic men vs -36 for non-sarcopenic men, p=0.03). THb responses were comparable across groups. Differences in TSI were not explained by difference in MVC peak force or exercise force.
Conclusion:
Handgrip exercise NIRS identifies distinct muscle oxygenation signatures in mitochondrial disease and sarcopenia.

123 - Retrospective Analysis of MG-ADL Data Outcomes Following Zilucoplan Treatment in Myasthenia Gravis

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Introduction: Myasthenia Gravis (MG) is an autoimmune disease targeting the neuromuscular junction. Since the approval of eculizumab in 2017, several complement inhibitors and Fc receptor (FcRn) blockers have become available, with zilucoplan receiving approval in October 2023. Despite the growing number of targeted therapies, comparative real-world data remain limited.
Objectives: The primary objective of this analysis was to evaluate the real-world effectiveness of zilucoplan based on documented subjective and objective improvement. This poster presents a subset of data from a larger study evaluating and comparing all approved complement inhibitors and FcRn blockers in AChR-positive MG.
Methods: Prospective patients with AChR-positive MG were identified between October 2017 and December 2025. The broader study drugs of interest include all 7 FcRn and terminal complement inhibitors approved since 2017. Exclusion criteria included other causes of weakness. A retrospective chart review was performed, and de-identified patient data were collected.
Results: 174 medication trials were identified across 104 patients. Zilucoplan represented 12.1% of all trials. 57% (n=12) achieved a ≥2-point reduction, and 38% (n=8) achieved a ≥3-point reduction in MG-ADL. Minimal symptom expression was achieved in 1 patient (5%).
Conclusion: A smaller percentage of patients had a meaningful reduction in MG-ADL scores (≥3) when compared to the original clinical trial (38% vs 73%). Notably, a large majority of our patient population had failed multiple oral and targeted therapies before zilucoplan. Zilucoplan is effective and a viable first-line or second-line option after failing other targeted immunotherapies.

122 - Dose-Finding Safety and Tolerability Study of Clenbuterol in Facioscapulohumeral Muscular Dystrophy (FSHD)

Rebecca Clay[1], Michaela Peterson[1], Leann Lewis[2], Brianna Brun[2], Seth Friedman[3], Leo Wang[4], Stephen Tapscott[5], Jeffrey Statland[1]

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Facioscapulohumeral muscular dystrophy (FSHD) is a progressive, DUX4-mediated neuromuscular disorder with no FDA-approved disease-modifying therapies. Clenbuterol, a β2-adrenergic agonist with established anabolic properties, has shown preclinical efficacy in suppressing DUX4 expression and promoting muscle growth, providing strong biologic rationale for therapeutic repurposing. We are conducting a 6-month, open-label, dose-escalation trial evaluating the safety, tolerability, and preliminary efficacy of clenbuterol in adults with genetically confirmed FSHD (NIH Wellstone Center, P50 AR065139). Thirty participants are planned across three sequential cohorts (20, 40, and 60 mcg twice daily) at three U.S. sites. Primary endpoints include adverse events, safety laboratories, vital signs, and electrocardiographic monitoring. Exploratory efficacy outcomes include functional assessments, RNA sequencing, and quantitative MRI. Cohort 1 (20 mcg BID; n=10) enrollment is complete; nine participants have finished 6 months of treatment, with the last anticipated to complete by July 2026. In this interim analysis, clenbuterol has been well tolerated. Adverse events were predominantly mild and consistent with the known pharmacologic profile, including nervous system, musculoskeletal, and cardiac-related effects. No protocol-defined stopping criteria have been met, and no dose interruptions or discontinuations have occurred. Cohort 2 (40 mcg BID) is currently enrolling. These initial findings demonstrate acceptable safety and tolerability at the starting dose, supporting continued dose escalation and further evaluation of clenbuterol as a potential disease-modifying therapy for FSHD.

I. Investigator Abstracts

7 - COS-PREPARED: Clinical Outcome Study in PRe- and Early-symptomatic Patients with Recessive Dysferlinopathy

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Introduction
Early stage diagnoses are increasingly generated through incidental CK results, screening for segregation analysis, or where families have opted for additional screening following the diagnosis of a symptomatic family member, creating the opportunity to expand current knowledge of early natural history and disease onset.
Objectives
1) Define the early natural history of dysferlin-deficient limb girdle muscular dystrophy LGMDR2 by monitoring muscle function, strength, and biomarkers of muscle pathology.
2) Identify early indicators of disease onset to inform recognition, diagnosis, care, clinical trial design and treatment indications.
Methods
Assessments include functional and patient reported outcome measures, quantitative MRI (T2, Dixon), and instrumented gait. Functional outcome measures include North Star Assessment for Limb-girdle type muscular dystrophy, 100 metre timed test, selected items from both 1000 Norms project, and Bruininks-Oseretsky Test of Motor Proficiency (BOT).
Results
Five participants (aged 13-19, 3 male, 2 female) with a confirmed diagnosis of dysferlin-deficient LGMDR2 proven by two pathogenic variants in the DYSF gene who can still stand on tiptoes and hop have completed baseline visits.
Annual and further baseline visits will be completed by September 2026. Fat Fraction and T2 are higher than controls, with changes most visible in the Gastromedialis. Functionally, all participants had speeds below the 10th centile on timed tests. Four subjects demonstrated no impairment on the BOTS 'Balance' dimension. Impairments were seen in all subjects in 'Running speed and agility' and 'Strength' subscales.
Conclusions
The recruitment target is 20. We seek the support of Muscle Study Group members for recruitment.

8 - Online Patient Ratings of a Neuromuscular Outpatient Practice: A Retrospective Study

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Introduction: Patients increasingly rely on online reviews and star ratings of physicians when choosing healthcare providers, but the reliability of these ratings, especially in subspecialty fields such as neuromuscular medicine, remains uncertain.
Objectives: Online physician ratings increasingly influence patient choice, yet their trustworthiness and generalizability remain uncertain, particularly in complex specialties such as neuromuscular medicine. Only 5% of patients post reviews, but nearly 40% use online feedback to select physicians.
Methods: We retrospectively analyzed 218 reviews with star ratings posted between May 2016 and June 2025 for a single outpatient neuromuscular practice. Identifiable reviewers were matched to practice records to append referral, diagnostic, and demographic data. Quantitative and thematic analyses were performed.
Results: Among 218 reviews, 182 (83.5%) were positive and 36 (16.5%) negative. Negative themes included feeling dismissed, perceived rudeness, and rushed visits, while positive reviews emphasized thoroughness and effective care. Identifiable negative reviewers were predominantly White female patients (mean age 41) who commonly reported overlapping symptoms including pain, fatigue, motor difficulties, and sensory disturbances. Anxiety or depression was reported in 44.4% of identifiable reviewers.
Conclusions: Online reviews primarily reflect patient experience rather than clinical quality of care or physician competence. Structural pressures—time constraints, diagnostic expectations, and tertiary-care complexity—likely shape negative feedback and should be considered when interpreting online ratings.

13 - Neurofilament Light Chain as a Biomarker for Chronic Inflammatory Demyelinating Polyradiculoneuropathy

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Introduction: The Guillain-Barré Syndrome (GBS)|Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) Foundation proposed standardized definitions of CIDP disease activity based on patient perception of worsening and changes in disability and impairment. Objective biomarkers are needed to supplement clinical assessments of disease activity and treatment response. Neurofilament light chain (NfL) is a promising candidate biomarker to meet this need, but it was not included as a component of the disease activity definitions due to inconclusive data at the time the definitions were developed.
Objectives: To assess the association between elevated NfL levels and evidence of disease activity (EDA) or no evidence of disease activity (NEDA) according to the consensus-based definitions.
Methods: We reviewed the charts of patients with CIDP who were seen at the University of Pennsylvania between 11/2023 and 3/2026 and had their NfL levels tested. We collected scores for Inflammatory Neuropathy Cause and Treatment (INCAT), Inflammatory Rasch-built Overall Disability Scale (I-RODS), Medical Research Council Sum Score (MRC-SS), grip strength, patient perception of symptoms, and NfL levels. An odds ratio was computed to determine the odds of EDA for patients with elevated NfL compared to patients with normal NfL.
Results: 53 patients were included for analysis, and full data was available for 38 patients. Patients with elevated NfL had higher odds of EDA than patients with normal NfL. The results will be updated at the time of presentation.
Conclusions: Elevated NfL is associated with CIDP EDA based on consensus-based definitions integrating objective disability and impairment scales with subjective patient perceptions of worsening.

15 - Electrodiagnostic assessment reveals myasthenia gravis and cervical dystonia in a case of dropped head syndrome: Linked or coincidental?

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INTRODUCTION:
Botulinum toxin (BTX) is considered contraindicated in patients with myasthenia gravis (MG). However, recent reports suggest it may be used safely in selected cases. We present a patient with dropped head syndrome secondary to longstanding, untreated, seronegative, generalized MG who received BTX therapy for cervical dystonia.
CASE REPORT:
An 82-year-old man presented with head drop, fatigable ptosis, and proximal arm weakness. Antibodies to acetylcholine receptor, LRP4, and MuSK were negative, and chest CT showed no thymoma. He was diagnosed with possible seronegative MG and treated with plasmapheresis with marked improvement but was subsequently lost to follow-up.
8 years later, he presented with head drop and neck pain. Examination showed torticollis with hypertrophy of the splenius capitis, levator scapulae and trapezius. There was moderate neck extensor weakness and mild proximal weakness without fatigability. Abnormal neck postures worsened during gait.
Single-fiber EMG (sfEMG) demonstrated markedly increased jitter and blocking, consistent with a generalized neuromuscular junction disorder. Surface EMG showed lack of relaxation of antagonist muscles and co-contraction of agonist and antagonist muscles during neck movements.
Pyridostigmine was ineffective, but prednisone improved neck and limb weakness. Mycophenolate mofetil was initiated. Given severe neck pain and abnormal posture, low-dose BTX injections were administered, resulting in pain relief while neck strength continued to improve. Repeat sfEMG was essentially unchanged.
CONCLUSIONS:
In this patient with multifactorial dropped head syndrome, electrodiagnostic assessment helped identify contributing factors and guide therapy. Low-dose BTX may be considered for cervical dystonia in carefully selected MG patients after immunotherapy initiation.

17 - Seroreversion and Clinical Recovery Following FcRn Inhibition in Anti-Contactin-1 Autoimmune Nodopathy

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Introduction: Autoimmune nodopathies (AN) are often treatment resistant. Specifically, these types of conditions with IgG4 antibodies specific to proteins within the neuronal axon often do not respond to intravenous immunoglobulin (IVIG). Inhibiting the neonatal Fc receptor (FcRn) can lower the circulating IgG antibodies that are thought to cause these conditions, and this could be an effective treatment for AN.

Methods: Longitudinal clinical, electrophysiologic, and serologic data of a patient with an anti-contactin-1 nodopathy treated with efgartigimod was collected for a case study.

Case Report: A 76-year-old woman developed rapidly progressive weakness, sensory loss, and gait impairment, becoming wheelchair-dependent within 12 weeks. She did not improve with IVIG. Clinical evaluation, lab tests, and an electromyography (EMG) confirmed a demyelinating polyradiculoneuropathy and anti-contactin-1 IgG4 antibodies. Subcutaneous efgartigimod, an FcRn inhibitor, and prednisone were initiated, and this treatment plan showed early stabilization. Over 6 months, with continued efgartigimod and a steroid taper, she improved to reach independent ambulation. Clinically, she showed gains in her Inflammatory Neuropathy Cause And Treatment (INCAT) score, Inflammatory Rasch-built Overall Disability Scale (I-RODS), grip strength, and Medical Research Council Sum-Score (MRC-SS). She also showed improved nerve conduction parameters, normalization of serum neurofilament light chain, and her anti-contactin-1 antibodies disappeared.

Results: In this IgG4 anti-contactin-1 AN, FcRn inhibition was associated with clinical, electrophysiologic, and serologic improvement, including seroreversion.
Conclusion: While this case study showed improvements after treatment with a FcRn inhibitor, more research is required to understand if this will work for future AN patients.

20 - Interrogation of AAV9-induced acute toxicity in large animal models resembling advanced Duchenne muscular dystrophy

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Introduction. Acute lethality is a major safety concern for systemic adeno-associated virus (AAV) gene therapy of neuromuscular diseases. Two nonambulatory Duchenne muscular dystrophy (DMD) patients died within one week of AAV9 dosing.

Objective. To understand high-dose AAV9-induced acute toxicity, we evaluated clinical, molecular, and immunological outcomes in canines that resemble late-stage DMD patients.

Methods. We injected an AAV9 firefly luciferase vector into four affected dogs that were at an advanced disease stage (1.9 to 2.7 years old). One animal dosed with $1x10^{14}$ vg/kg AAV was terminated at 3 days. One animal dosed with $1x10^{14}$ vg/kg AAV and two animals dosed with $2.6x10^{14}$ vg/kg AAV were terminated at 7 days. Studies included clinical observation, chest X-ray, cardiac function, blood biochemistry and hematology, AAV biodistribution and expression, single-nucleus RNAseq and in situ hybridization, serum biomarkers, ELISpot, AAV antibody, and histopathology.

Results. Biodistribution by ddPCR showed robust uptake in the liver and lymphoid tissues, followed by lung, kidney, and skeletal muscle. High levels of AAV transcripts were detected in the liver, skeletal muscle, lymphoid tissues, lung, and kidney. Prominent serum cytokine elevation was detected in two high-dose animals. Importantly, one high-dose animal developed non-infectious pneumonitis resembling acute respiratory distress syndrome seen in the human patient who died following AAV9 delivery. Single-nucleus RNAseq revealed pronounced transgene expression in immune cells in this animal.

Conclusion. Our study modeled acute toxicity seen in nonambulatory DMD patients and revealed potential underlying mechanisms.

30 - Patient-Reported Correlation with Caregiver-Reported Disease Burden in Duchenne Muscular Dystrophy

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Introduction: We previously developed a regulatory-grade, Duchenne muscular dystrophy (DMD)-specific patient-reported outcome measure (the DMD-HI) and caregiver-reported outcome measure (the DMDCR-HI) for use in DMD therapeutic trials. In preparation for future studies, it is important to understand how respondent perspectives influence quantifiable disease burden and be able to calibrate scores based on respondent type.
Objectives: To examine the relationship between patient- and caregiver-reported scores using the DMD-HI and DMDCR-HI and develop methods for calibrating scores across instruments.
Methods: Using matched patient-caregiver dyads, we concurrently evaluated disease burden using the DMD-HI and DMDCR-HI. Associations and agreement between total and subscale scores were evaluated using Pearson correlation and Bland-Altman analyses. We used linear mixed-effects and standard linear models to develop crosswalk formulas between DMD-HI and DMDCR-HI total and subscale scores.
Results: Twenty-one paired patient-caregiver assessments were completed, revealing a strong correlation between DMD-HI and DMDCR-HI total scores ($r = 0.821$, $p < .0001$), with significant correlations in 14/17 subscales. Caregivers consistently reported higher disease burden compared to patients, with an average difference of 13.8 points on the 100-point scale. Bland-Altman analysis indicated all but one observation fell within the limits of agreement. Crosswalk models yielded lower residual error for total scores and specific subscales such as Gastrointestinal Health and Mobility, indicating improved precision.
Conclusions: When comparing the DMD-HI and DMDCR-HI, caregiver-reported disease burden is consistently higher than patient-reported burden, despite strong correlations. Crosswalk models provide a robust approach for calibrating patient- and caregiver-reported scores, facilitating their effective use in longitudinal DMD studies.

35 - The IBM-HI: Correlation between patient-reported disease burden and clinical function in the INSPIRE-IBM study

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Introduction: The Inclusion Body Myositis-Health Index (IBM-HI) is a regulatory-grade patient-reported outcome measure (PRO) developed and validated to measure point-in-time disease burden in 13 symptom areas in IBM patients during therapeutic studies. INSPIRE-IBM is a longitudinal observational study of IBM patients that is using the IBM-HI as a key marker of disease burden.

Objectives: To evaluate the association between IBM-HI scores and clinical function using data from INSPIRE-IBM.

Methods: We compared IBM-HI total and subscale scores to other PROs (EAT-10, Sydney Swallow), functional measures (IBM-FRS, timed up and go), strength measures (manual muscle testing, hand-held dynamometry), and pulmonary function tests (FVC, MIP, MEP). We performed known groups analyses using unpaired t-tests and correlation analyses using Spearman's correlation.

Results: In a cross-sectional analysis of 118 patients from INSPIRE-IBM, the IBM-HI demonstrated known groups validity, detecting higher disease burden in patients who relied on use of a mobility aid. The IBM-HI exhibited variable correlations with other PROs ($r>0.8$, $p<0.0001$), functional assessments ($r>0.6$, $p<0.0001$), and strength and pulmonary tests ($r<0.5$, p variable).

Conclusions: In the context of INSPIRE-IBM, the IBM-HI and its subscales demonstrate moderate to strong correlations with other patient-centric and clinician-reported outcome assessments. The convergent validity of the IBM-HI is promising and supports longitudinal investigation to determine its minimal clinically important difference (MCID) as well as to assess its sensitivity in detecting disease worsening or improvement in current and upcoming observational and therapeutic studies.

36 - Using PMP22 Antisense Therapy to Define Disease Pathogenesis in CMT1A

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Introduction: Charcot-Marie-Tooth disease type 1A (CMT1A), caused by PMP22 duplication, is the most common inherited peripheral neuropathy and is characterized by progressive demyelination, impaired nerve conduction and sensorimotor dysfunction. While molecular disorganization of myelin domains has been reported in CMT1A, the temporal relationship between these abnormalities and functional decline remains poorly understood. Antisense oligonucleotide (ASO)-mediated reduction of PMP22 provides a unique opportunity to investigate disease pathogenesis while simultaneously evaluating therapeutic response.
Objectives: To determine whether ASO-mediated normalization of PMP22 expression restores molecular myelin architecture prior to, concurrent with or following improvements in peripheral nerve function in a CMT1A mouse model.
Methods: CMT1A mice received a single subcutaneous injection of PMP22-targeting ASO (10 mg/kg). PMP22 reduction is being quantified with molecular methods. Longitudinal motor phenotyping, peripheral nerve electrophysiology, teased sciatic nerve immunofluorescence and electron microscopy are being evaluated for functional and molecular improvement. Analyses will focus on nodal/paranodal organization, adherens junction integrity and Schmidt-Lanterman incisure structure.
Results: PMP22 expression reduction following ASO treatment was successfully validated in treated CMT1A mice. Studies are ongoing to define the temporal relationship between restoration of molecular myelin organization and improvements in electrophysiological and behavioral outcomes following PMP22 reduction.
Conclusions: These studies will establish PMP22 ASO therapy as a mechanistic tool to investigate disease pathogenesis in CMT1A in addition to its therapeutic potential. Defining the temporal relationship between molecular myelin disorganization and functional decline may provide new insight into early pathogenic events and identify structural features of myelin that are closely linked to peripheral nerve dysfunction.

37 - Limb-onset weakness is associated with loss of independent ambulation in oculopharyngeal muscular dystrophy (OPMD).

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Introduction: OPMD can present with ptosis, dysphagia, and/or proximal muscle weakness. A subset of patients eventually loses "independent ambulation", defined here as the ability to walk without an assistive device. However, it remains unclear whether eventual loss of independent ambulation is associated with presenting symptomology.
Objectives: To evaluate whether the presence of limb muscle weakness at symptom onset is associated with a higher frequency of loss of independent ambulation in our retrospective OPMD cohort.
Methods: Institutional review board approval was obtained. Age and type of symptom onset (ptosis, dysphagia, and/or limb weakness), follow-up duration, and ambulatory status at the time of the last visit were retrieved from 70 genetically confirmed OPMD patients. Two groups were defined: limb-onset weakness with or without ptosis or dysphagia (n=19) and oculobulbar-onset weakness only at initial presentation (n=51).
Results: Age at both symptom onset and last clinic visit and duration of follow-up did not differ between groups. 13 out of 19 with limb-onset weakness also had ptosis and/or dysphagia at presentation. 34 out of 51 with oculobulbar-onset symptoms eventually developed limb weakness. Ten out of 19 (52%) with limb-onset weakness and only 8 out of 51 (15%) with oculobulbar-onset symptoms had lost "independent ambulation" by the last follow-up visit ($p = 0.002$).

Conclusions: Patients with OPMD who presented with limb muscle weakness (27% of our cohort) more frequently lost independent ambulation during the retrospective follow-up period. In addition to therapies targeting dysphagia, investigational treatments addressing limb weakness are needed for OPMD patients.

39 - Modeling Treatment Response Trajectories in Spinal Muscular Atrophy: Results from the MAP THE SMA study

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Introduction: Spinal muscular atrophy (SMA) has undergone a major therapeutic transformation with the introduction of disease-modifying therapies, although treatment response remains highly variable and incompletely understood.

Objective: This study aimed to develop and validate a predictive framework for forecasting individual treatment trajectories and identifying clinically meaningful response phenotypes.

Methods: We conducted a monocentric observational study including 236 SMA patients (3176 visits). Longitudinal motor outcomes predictions were generated using both full and recursive chain prediction approaches. Multivariate latent class models were applied to identify trajectory-based response groups.

Results: The models showed strong short-term predictive accuracy across functional scales. Latent class analysis identified three main response phenotypes: minimal, mild, and super responders. Age and baseline functional status were the main determinants of class assignment. Super responders showed better motor trajectories, functional independence, and quality of life, whereas minimal responders had persistently poorer outcomes. Patient-reported outcomes confirmed significant differences across classes in daily functioning, perceived health status, and treatment impact. Agreement between predicted and observed classifications ranged from 63% to 84%. Early functional slopes within the first six months showed potential to predict long-term response class.

Conclusions: This integrated framework combining longitudinal modelling and latent class analysis accurately predicts SMA treatment response and identifies clinically relevant response phenotypes. These findings support prediction-driven patient stratification, personalized management, and the use of AI-derived models for dynamic prognostication in SMA care and clinical trial design. This study was funded by the Italian Ministry of Health and the Neuromuscular Study Group.

40 - Beyond Total Scores: A Granular Item Analysis of Functional Changes During 24 Months of DMTs in Type III SMA

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Introduction

While DMTs slowed type III SMA progression, literature largely relies on total HFMSE scores, obscuring granular functional dynamics. This approach fails to distinguish specific motor skills acquired versus those lost. Elucidating long-term trajectories by analyzing item-specific gains and losses is essential to identify which abilities are truly recovered and which remain areas of clinical vulnerability.

Objectives

This study evaluates granular motor activity shifts to map detailed functional trajectories, identifying which HFMSE items are most frequently acquired or lost and determining how these changes impact different age groups and functional levels.

Methods

Using retrospective iSMAc data, we conducted granular shift analyses on individual item changes over 24 months from treatment initiation. We used two approaches: determining functional gain or loss (0 to 1-2 or vice versa) and detecting dynamic changes within the 1-2 range. Patients were stratified by age (<5, 5-9, 10-17, >18 years) and baseline status (walker, sitter, non-sitter).

Results

Evaluating 125 type III SMA patients (93 nusinersen, 32 risdiplam), the cohort showed clear clinical benefit. Per-item analysis revealed 24% showed only gain events, 11.2% only loss, 11.2% stable, and 53.6% mixed results. Items 25-33 proved most resistant to recovery. Age-dependent gains were significant (e.g., item 24 in <5 years, item 21 in >18 years), with distinct functional subgroup patterns.

Conclusions

DMTs at 24 months shift the paradigm from progression-slowing to active functional restoration. Moving beyond total scores to granular, item-specific analysis is essential to reveal therapeutic benefits and support personalized clinical decision-making and tailored rehabilitation plans.

41 - Multivariable prediction of treatment response in type II SMA: beyond single outcome measures

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Introduction: Disease modifying therapies have produced a dramatic change in the progression of disease course in type II spinal muscular atrophy. The changes observed, however, are quite variable, and the interpretation of the response to treatment can be difficult. The aim of this study was to establish whether combining multiple variables might improve prognostic accuracy of 12-month motor outcomes in treated SMA type II, using both HFMSE and the SMA Functional Composite score revised (SMA-FCR).

Methods: Random forest, elastic-net, and linear regression models were compared using baseline predictors including age, motor function, respiratory status, and scoliosis severity. Models stratified patients into tertiles of predicted response.

Results: 200 SMA type II patients from the ITASMAC registry were included in the study. Random forest models achieved optimal performance. Tertile-based stratification revealed gradients in treatment response. For HFMSE, observed 12-month changes were: Q1=0.15 points (95%CI: -0.21;0.51), Q2=0.40 (0.04;0.77), and Q3=3.00 (1.92;4.08). The highest tertile comprised younger patients (median age 2.90 years) with better baseline function, spontaneous breathing, and minimal scoliosis. In the pediatric subgroup (<14 years, N=89), tertile separation was more pronounced. SMA-FCR analysis demonstrated enhanced discrimination, particularly in the pediatric cohort.

Discussion: Our findings demonstrate that the combination of age and motor function with other variables such as respiratory status and scoliosis severity at treatment initiation can help to better predict 12-month motor improvement. SMA-

FCR captured multi-domain improvements better than HFMSE alone, providing clearer separation between response groups.

42 - Oral and Swallowing Abilities Tool- Expanded (OrSAT-E): a new module for assessment of bulbar function in Spinal Muscular Atrophy (SMA)

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Background

The Oral and Swallowing Abilities Tool (OrSAT), originally developed for infants with type I SMA, was limited in scope. This study introduces the OrSAT-Expanded (OrSAT-E), a revised instrument designed for all SMA types and ages, enhancing the assessment of bulbar function across the full spectrum.

Objectives

We aimed to validate the OrSAT-E, comprehensively assessing its applicability, discriminative ability, and sensitivity across the entire SMA patient spectrum compared to a general population control group.

Methods

We analyzed 1,252 OrSAT-E assessments from 251 SMA patients and 217 controls. We evaluated age-related functional trajectories using non-linear modeling and analyzed item-specific impairment frequencies, along with ceiling and floor effects in relation to disease severity and *SMN2* copy number.

Results

Patients showed significantly lower OrSAT-E scores than controls ($p < .001$). In severe phenotypes (type I), impairment was widespread: 71.9% of patients required intervention and 64.1% experienced cough stagnation. Conversely, milder phenotypes exhibited prominent ceiling effects, with 87.6% of type III and 86.4% of pre-symptomatic observations reaching the maximum score of 7. Floor effects were observed exclusively in type I (46.8% of observations). Discrimination was optimal for type I (AUC 0.89) but decreased significantly in milder subtypes, reflecting high functional overlap.

Conclusions

The OrSAT-E demonstrates high sensitivity for severe phenotypes, accurately capturing critical feeding and swallowing difficulties. However, its clinical utility in milder forms is constrained by significant ceiling effects. The tool effectively supports dynamic monitoring of bulbar function, although further refinements are necessary to capture functional variability in less severe populations.

44 - Concordance and discordance between functional outcome measures in Duchenne Muscular Dystrophy: A 12-month longitudinal analysis

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Introduction: In Duchenne Muscular Dystrophy (DMD), the main functional outcome measures are the NSAA, TRF, and 10MWT. Timed items are highly sensitive to functional change, requiring reliable criteria to define improvement, stability, and deterioration. As no standard threshold exists for timed tests, three classification methods were applied: stopwatch range, Minimal Detectable Change (MDC), and MDC velocity.

Objective: To assess concordance and discordance among NSAA, TRF, and 10MWT over 12 months by identifying patients with concordant change across scales. The study also compared methods for defining clinical stability to identify the most appropriate criterion for interpreting functional changes.

Methods: The analysis included 1792 assessments from 567 patients aged 4-7 years enrolled in the Italian DMD Registry and cohorts from the UK and Spain; patients enrolled in clinical trials at the time of assessment were excluded. Longitudinal 12-month data were analyzed using the three stability methods.

Results: In the overall cohort, timed measures worsened over 12 months (+2.12 s TRF; +0.29 s 10MWT), while NSAA remained stable (+0.84 points). At 4 years, all three scales showed concordant improvement. At 5 years, TRF showed the earliest signs of decline, although changes remained within the MDC stability range. At 6 years, both TRF and 10MWT showed decline, while at 7 years all three scales demonstrated concordant deterioration.

Conclusions: Motor progression in DMD is age dependent. Different concordance between scales suggests they assess different motor domains and show variable sensitivity to change over time and should be carefully analyzed in both observational and experimental studies.

48 - Whole-body Electrical Muscle Stimulation Exercise in a Patient with Sporadic Inclusion Body Myositis: A Promising Novel Approach for Disease Management

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1. **Introduction:** Sporadic inclusion body myositis (sIBM) is a degenerative muscle disease whose management focuses on rehabilitation therapies, including exercise, for supportive care in the absence of proven medical treatments. However, current literature shows mixed results of traditional exercise paradigms, demonstrating need for more effective approaches.
2. **Case Report:** A 72-year-old Caucasian male with a 10-year history of sIBM uses a single-point cane for longer-distance walking and grab bars in the bathroom. He reports falling 5-10 times within 6 months prior to enrollment. He is the primary caregiver for his wife and worries about their future as sIBM progresses. He currently engages in no regular exercise and struggles to tolerate moderate-intensity physical activity. He has significant co-morbidities, including type 2 diabetes, coronary artery disease, multiple spinal pathologies, and major polypharmacy.
3. **Methods:** The participant completed an 8-week whole-body electrical muscle stimulation (WB-EMS) exercise intervention utilizing a commercially available system. Each session consisted of 10-12 exercises performed over 20 minutes at mild to moderate intensity, twice weekly. Stimulation parameters were individualized according to tolerance and response. Outcome measures were collected within 1 week prior to and following intervention, testing strength, motor function, power, balance, pain, fatigue, and quality of life.
4. **Results:** Clinically meaningful improvements were seen in power, balance, pain, and fatigue. Functionally, tasks completed at post-test that were impossible at pre-test included descending stairs without handrails and broad jumping. No falls occurred during the 11-week study period.
5. **Conclusions:** WB-EMS Exercise may enhance safety and independence with functional mobility in people with sIBM. Further study is warranted to determine mechanisms and generalizability.

52 - Evaluating the Evidence Behind the Myasthenia Cautionary Drug List

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INTRODUCTION: Certain classes of medications are avoided in Myasthenia Gravis (MG) patients due to the reported risk of MG exacerbation.
OBJECTIVE: To conduct a review of the literature on medications and vaccines that have historically been avoided or used cautiously in patients with MG.
METHODS: Ovid MEDLINE searches were conducted; a study was included if it met the following criteria: peer-reviewed source, published after 1984, and the study described outcomes in MG patients who received a cautionary drug or vaccine. Search categories included cardiac medications, statins, antibiotics, immunosuppressants, minerals, vaccines, and miscellaneous which comprised 17 different drug classes. Studies were screened by two physician reviewers to determine if an MG exacerbation occurred following administration of a cautionary drug. If exacerbation did occur, the Naranjo Adverse Drug Reaction (ADR) Probability Scale was applied to characterize exacerbation as doubtful, possible, probable, or definite. Severity was classified by need for hospitalization or MG crisis.
RESULTS: Seventeen drug classes comprising 7830 patient exposures were included in final analysis. Medications with notable exacerbation rates following exposure included magnesium (33.8%), beta blockers (45.6%), and botulinum toxin (30.8%). Most drug classes had low exacerbation rates (<20%). These included hydroxychloroquine, calcium channel blockers, fluoroquinolones, macrolides, statins, and vaccinations. Across all categories, there were no “definite” exacerbations caused by cautionary drugs by the ADR scoring system.
CONCLUSION: Published evidence to support some MG cautionary drug categories is limited. Certain previously classified cautionary drugs may be safe in MG, expanding therapeutic options for MG patients.

58 - Ten top tips for non-pharmacological management in Facioscapulohumeral muscular dystrophy (FSHD): informed by evidence, clinical practice and lived experience

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Introduction
Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common muscular dystrophies, typically emerging in young adulthood. It has no cure, making conservative non-pharmacological management the mainstay of treatment. FSHD has a variable presentation, and the limited evidence base contributes to clinical guidance gaps and care variability. This paper presents 10 top tips for the conservative management of adults with FSHD.
Objectives
To develop practical guidance for the conservative non-pharmacological management of FSHD by integrating available evidence, best clinical practice and the perspectives of people with FSHD (PwFSHD), carers, and clinicians.
Methods
These tips were derived from key lessons learned across three stages of a mixed-methods study: 1) a systematic review and meta-analysis of non-pharmacological interventions in muscular dystrophies; 2) surveys and ethnographic observations of UK FSHD care; and 3) focus groups with adults with FSHD, carers and clinicians, to define high-quality care.
Results
The 10 tips address: 1) physical activity; 2) safe symptom monitoring and management; 3) exercise modalities including strength and aerobic training, stretching and water-based activities; 4) personalised exercise prescription tailored by type, dosage, intensity and setting; 5) non-pharmacological pain management via massage, heat therapy, hydrotherapy and yoga/Pilates; 6) fatigue management through pacing, rest, relaxation and activity planning; 7) psychological support; 8) patient-clinician communication; 9) information and resource sharing; 10) shoulder surgery: indications and timing.
Conclusions
These 10 tips address a critical gap in clinical guidance for FSHD, offering a readily applicable framework to support equitable, best practice care for adults with FSHD across settings.

59 - Magnetic resonance-compatible handbike platform for clinical investigation of skeletal muscle in ambulatory and disabled patients with neuromuscular disease

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Background & Aim: Magnetic resonance imaging and spectroscopy (MRS) afford comprehensive study of muscle anatomy, biochemistry and physiology in neuromuscular disease (NMD). MR-compatible ergometers, however, typically employ leg exercise, ruling out their use in wheelchair-bound patients. We transformed a leg-cycle ergometer into a handbike accommodating both ambulatory as well as disabled patients. ^{31}P MRS recordings of ATP metabolism in biceps brachii (BB) muscle of disabled patients with spinal muscular atrophy (SMA) are presented to demonstrate feasibility.
Methods: An MR-compatible cycle ergometer was fitted with carbon ski poles (Leki, Italy) equipped with 3D-printed handles and mounted on a mobile platform (Lode, NL). Subjects were positioned head-first supine on the patient support of a clinical 3T MR scanner (Philips, NL) and fitted with a 6 cm ^{31}P surface coil over the BB. The ergometer platform was positioned over the lower body such that subjects held onto the skipoles with a resting elbow angle of 90°. The ensemble was then moved into the scanner such that the BB was in its center. Dynamic ^{31}P MRS data were collected at rest, during arm-cycling and subsequent recovery.
Results: The platform accommodated wheelchair-bound comfortably. The upper-arm remained robustly in position during arm-cycling resulting in high-quality spectra. Unprecedented Pi and pH dynamics were observed providing a window on motor unit recruitment and composition.
Conclusion: Our adapted MR cycle platform affords clinical investigation of skeletal muscles in both ambulatory and disabled patients with NMD and should be readily translatable to commercially available MR cycle ergometers.

61 - Conventional and in-magnet cardiopulmonary exercise testing of patients with neuromuscular disease to investigate peripheral causes of exercise intolerance

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Background & Aim: Exercise intolerance severely affects daily functioning in patients with neuromuscular diseases (NMD), yet the relative contributions of mitochondrial and microvascular dysfunction remain unclear. This study evaluated the feasibility of a non-invasive magnetic resonance (MR) platform to simultaneously assess muscle energy metabolism and microvascular responsiveness during maximal in-magnet cycling.
Methods: Nineteen patients with NMD participated, including nine with Chronic Progressive External Ophthalmoplegia (CPEO; 20-80 years) and ten with Inclusion Body Myositis (IBM; 46-73 years), alongside thirteen healthy older controls (66-84 years). Patients first underwent conventional cardiopulmonary exercise testing (CPET) to assess exercise intolerance. Within two weeks, all participants performed a maximal incremental cycling test on an MR-compatible ergometer (Jeneson this meeting) inside a 3T MRI-scanner. Interleaved quantitative T2*-mapping and phosphorus-31 magnetic resonance spectroscopy (31P-MRS) data were acquired from the vastus lateralis muscle every 4 seconds.
Results: Median predicted maximal oxygen uptake during CPET was 66.9% in CPEO and 70.1% in IBM patients, confirming exercise intolerance. End-exercise phosphocreatine (PCr) depletion and pH reductions were comparable across groups. However, post-exercise PCr recovery time was significantly prolonged in CPEO patients versus controls (214s versus 86s; p=0.003), indicating mitochondrial dysfunction. Conversely, IBM patients exhibited a variable range of PCr recovery times (56-206s), reflecting the clinical and histopathological heterogeneity inherent to the disease. Microvascular outcomes, derived from the T2*-maps demonstrated substantial interindividual variability without significant group differences.
Conclusion: Combined qT2* mapping and 31P-MRS during in-magnet cycling is a feasible, non-invasive approach to investigate peripheral mechanisms underlying exercise intolerance in NMD.

62 - Impact of SMN2-modifying treatments on the proteomic profile of plasma and CSF samples from adult Spinal Muscular Atrophy patients

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Spinal muscular atrophy (SMA) is a genetic neuromuscular disorder caused by deficiency of survival motor neuron (SMN) protein resulting from loss of the *SMN1* gene. SMN2-modifying therapies increase functional SMN protein levels and improve clinical outcomes; however, molecular mechanisms underlying treatment response remain incompletely understood. Recent proteomic studies suggest broader biological effects to these therapies. This study aimed to characterise proteomic changes associated with treatment response in adults with SMA.

Plasma samples were obtained from SMA patients pre-treatment with either Nusinersen or Risdiplam; cerebrospinal fluid (CSF) samples were collected from patients receiving Nusinersen. Follow-up plasma and CSF samples were collected at 6 months post-treatment. Quantitative proteomic profiling was performed using Sequential Window Acquisition of all Theoretical Mass Spectra (SWATH-MS), with significant protein alterations defined as $p<0.05$ and ≥25% fold change. Samples were also analysed using the Alamar NULISA™ CNS panel targeting 131 proteins associated with neuronal injury, synaptic function, neuroinflammation, and neurodegeneration.

Proteomic analyses identified treatment-associated alterations in pathways related to neurodegeneration, synaptic remodelling, inflammation, extracellular matrix organisation, and proteostasis. Nusinersen-treated plasma demonstrated reduced neuroaxonal injury markers and changes linked to synaptic plasticity and extracellular remodelling. Risdiplam treatment was associated with reduced inflammatory and microglial activation markers plus altered protein-folding and stress-response pathways. CSF analyses revealed modulation of synaptic, neurovascular, and inflammatory proteins and cytokine-associated pathways.

These findings indicate that SMN2-modifying therapies induce broad molecular changes extending beyond SMN restoration and motor neuron survival, supporting a multisystem model of SMA involving neuroinflammatory, synaptic, vascular, and extracellular matrix pathways.

63 - Neurofilament light chain in Charcot-Marie-Tooth disease and related disorders

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Introduction
Charcot-Marie-Tooth disease (CMT) comprises a heterogeneous group of inherited peripheral neuropathies characterised by chronic axonal degeneration. Neurofilament light chain (NfL) is a biomarker of neuroaxonal injury measurable in blood using ultrasensitive assays and is elevated in several neurodegenerative and peripheral neuropathic disorders. However, its relevance in slowly progressive inherited neuropathies such as CMT remains unclear.
Objectives
To assess serum NfL levels in patients with CMT and explore associations with clinical characteristics.
Methods
Serum NfL levels were measured in 100 adults with genetically or clinically diagnosed CMT. Levels were expressed as a fraction of the age-adjusted upper limit of normal (fULN; value/ULN), with values >1 considered abnormal. Demographic and clinical data were collected.
Results
The cohort included 65 males and 35 females, with a mean age of 48 years and mean disease duration of 23 years. Patients represented a broad spectrum of inherited neuropathies, including CMT1, CMT2, intermediate CMT, hereditary motor neuropathy, hereditary sensory neuropathy, hereditary neuropathy with liability to pressure palsies (HNPP), and CANVAS. Serum NfL levels ranged from 0.14 to 2.86 fULN. No significant associations were found between NfL levels and disease duration ($p=0.752$) or disease severity measured by the CMT Examination Score (CMTES) ($p=0.778$). Elevated NfL levels were observed in 11 patients (11%), predominantly in CMT1A and CMT2.
Conclusions
Serum NfL levels are normal in most patients with CMT, consistent with the disease's slow progression. Longitudinal studies are needed to determine the utility of NfL as a biomarker of disease activity, progression, and treatment response.

66 - Audit of a Needle Muscle Biopsy Service Using the UCH Modified Bergström Needle at a Tertiary Neuromuscular Centre

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Introduction: Open muscle biopsy (OMB) has traditionally been the reference standard for pathological assessment, but needle muscle biopsy (NMB) using the UCH modified Bergström needle became the preferred technique at our centre in 2023.

Objectives: To evaluate the tolerability and safety of our NMB service and compare the adequacy of NMB with OMB.

Methods: We audited 166 consecutive patients undergoing NMB at the Queen Square Centre for Neuromuscular Diseases between February 2023 and May 2026. Pain scores (0-10 numerical rating scale) were recorded during and immediately after the procedure; post-procedural adverse events were collected where available. We also retrospectively reviewed 127 NMB and 137 OMB to compare specimen characteristics and diagnostic adequacy.

Results: Mean age was 49.4 years (SD 16.7); 88/166 (53%) were male. Among 128 patients with pain data, mean pain score was 5.7 (SD 3.0) during the procedure and 3.4 (SD 3.0) immediately after. Among 124 patients with adverse-event data, swelling occurred in 18 (14.5%), mild bruising in 12 (9.7%), moderate bruising in 3 (2.4%), with no severe bruising or infection. NMB yielded smaller specimens than OMB (largest fragment 81 vs 860 mm^3, $p<0.01$), but adequacy was similar: 121/127 (95%) NMB and 133/137 (97%) OMB were diagnostically adequate.

Conclusions: NMB using the UCH modified Bergström needle is well tolerated, safe, and provides high diagnostic adequacy despite smaller tissue volumes, supporting its use as a standard muscle biopsy method in our centre.

71 - Assessing perceived physical fatigability in Charcot-Marie-Tooth disease: learnings from the SMA EFFORT

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Introduction: Fatigue is common in spinal muscular atrophy (SMA) and Charcot-Marie-Tooth disease (CMT).[1-4] Fatigability, or the objective decline in motor output with sustained activity, is a hallmark of SMA,[5] and may be problematic in people with CMT.[6] Fatigue focused patient-reported outcomes (PROs) evaluate the patient's perspective on the severity and impact of this symptom; however, associations with objective fatigability assessments are limited.[6,7] While in-clinic fatigability measures are valuable, there is a need for valid PROs that can assess this experience with daily activities. The SMA EFFORT, originally developed for SMA, anchors physical activity to intensity and duration to measure perceived physical fatigability (PPF) across phenotypes.[7] Preliminary data show good test-retest reliability and strong associations with measures of performance fatigability and motor function.
Objective: The purpose of this study was to investigate the SMA EFFORT as a measure of PPF in adolescents and adults with CMT.
Methods: CMT experts were surveyed on the relevance of the SMA EFFORT items. Individuals with CMT (≥ 12 years) completed the scale, rating PPF (5-point Likert scale) with pertinent physical activities performed in the past 30 days. Total and subscale PPF% descriptive scores were generated, and associations with clinical characteristics were explored.
Results: Results will be presented at the NMSG Meeting in San Antonio, TX.
Conclusions: Fatigability may impact daily function in individuals with CMT. An evolving clinical trial landscape necessitates sensitive tools that measure meaningful symptoms. This work explores the utility of assessing PPF in CMT, and its potential to monitor response to treatment.

72 - TDP-43 pathology induces CD8 T cell activation through cryptic epitope recognition

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Introduction
Aggregation and nuclear depletion of the RNA-binding protein TDP-43 are crucial pathological features of amyotrophic lateral sclerosis (ALS), inclusion body myositis (IBM) and multisystem proteinopathy (MSP). The loss of TDP-43 nuclear function results in the aberrant inclusion of cryptic exons in mRNA transcripts, leading to the expression of de novo proteins. Clonally expanded and highly differentiated CD8+ T cells have been observed in individuals with TDP-43 proteinopathies. However, the target antigens mediating T cell activation have remained elusive.
Objectives
Here, we investigate whether the de novo proteins induced by aberrant cryptic splicing due to TDP-43 nuclear loss can act as neo-antigens.
Methods
RNA-sequencing, immunohistochemistry and proteomics were used to identify TDP-43 cryptic peptides and immune gene enrichment in patient samples. TetTCR-SeqHD, a high-throughput and multidimensional single T cell profiling approach, was used to characterise the specificity, clonality and activation of T cells.
Results
We detect the HDGFL2 cryptic peptide and multiple other TDP-43 cryptic exons in IBM skeletal muscle, where their presence correlates with enrichment of T cells and MHC-I antigen presentation. Furthermore, we identify epitopes from HDGFL2 and IGLON5 cryptic peptides, which are recognised by clonally expanded and functionally differentiated CD8+ T cells in ALS and IBM patients. Finally, we demonstrate that T cells engineered to express the identified TCRs can activate in response to the cryptic peptides and are able to kill TDP-43-deficient cells.
Conclusions
This work identifies, for the first time, specific T cell antigens in TDP-43 proteinopathies, directly linking adaptive immune response to TDP-43 pathology.

78 - Dissociation Between Perceived Exertion and Heart Rate Response During Cycling in Myotonic Dystrophy Type 1

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1. Introduction: Fatigue is a highly disabling symptom in myotonic dystrophy type 1 (DM1), yet physiological mechanisms remain poorly understood. Cardiac involvement is common in DM1, but impact of cardiac performance on fatigue has not been explored.

2. Objectives: To characterize heart rate and perceived exertional responses during moderate-intensity cycling in individuals with DM1 compared to healthy controls (HC).

3. Methods: Participants with DM1 and sex/age-matched HCs completed 30-minute moderate-intensity cycling protocol with continuous HR monitoring and repeated ratings of perceived exertion (RPE). Target HR was individualized using the Karvonen equation. HR and RPE trajectories were analyzed over the first 20 minutes to reduce bias from unequal exercise duration. Additional analyses included cumulative target HR achievement and HR-RPE relationships.

4. Results: Five people with DM1 and 4 HCs participated. DM1 participants had received recent echo- and electrocardiograms that were relatively unremarkable. HR trajectory showed blunted cardiovascular responses in DM1 while RPE trajectory demonstrated earlier and greater exertional burden. Scatterplot revealed dissociation between HR and RPE: DM1 participants reported higher RPE at comparable HR levels and peak RPE at lower HR levels. They also had delayed/reduced achievement of target HR during exercise. Three terminated cycling early: one demonstrated heart rate response consistent with deconditioning, but two others experienced chronotropic incompetence, never reaching target heart rate.

5. Conclusions: Individuals with DM1 demonstrated greater exertional burden despite submaximal cardiovascular responses during moderate-intensity cycling. Future research should explore whether this occurs more widely in DM1, requiring additional workup to inform exercise recommendations and interventions for combating fatigue.

80 - Clinical Characteristics of Late-Onset Pompe Disease: A 15-Year Single-Center Experience

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Introduction: Late-onset Pompe disease (LOPD) is a rare lysosomal storage disorder characterized by progressive skeletal and respiratory muscle involvement and frequently delayed diagnosis.
Objective: To characterize the clinical presentation, diagnostic pathways, and treatment patterns of patients with LOPD evaluated at a tertiary neuromuscular center.
Methods: Retrospective review of adults with confirmed LOPD evaluated at Penn State Health Hershey Medical Center from January 2010 to May 2025, with descriptive analysis of demographic, clinical, diagnostic, and treatment data.
Results: This ongoing study includes approximately 44 patients evaluated over a 15-year period; preliminary analysis included 24 patients. The cohort was predominantly female (16/24) and White (22/24). Mean age at symptom onset was 38.7 ± 12.4 years and mean age at diagnosis was 44.8 ± 13.1 years, corresponding to a diagnostic delay of 8.6 ± 7.9 years. Twenty-one patients (87.5%) received disease-specific therapy (11 alglucosidase alfa, 8 avalglucosidase alfa, and 2 cipaglucosidase alfa plus miglustat), while 3 (12.5%) remained untreated. Among treated patients, the mean delay from diagnosis to therapy initiation was 1.86 ± 2.46 years. Mean FVC change from baseline was −0.44 in treated patients versus −0.89 in untreated patients; cardiac function remained stable (mean EF change +2.43%). Muscle biopsy was performed in 15 patients and genetic testing in 14 patients. At last follow-up, 21 patients were alive and 3 had died.
Conclusion: This single-center study highlights diagnostic delays in LOPD, describes real-world clinical presentation and treatment patterns, and compares available enzyme replacement therapies and their effects on muscle strength and respiratory function.

83 - Growing Up with Myotonic Dystrophy Type 1: Clinical Changes Across the Transition to Young Adulthood

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Transition to young adulthood is a critical period for DM1 patients, as early disease manifestations may compromise autonomy and socio-educational adaptation. Managing this phase is challenging due to the high variability between individuals.

We aimed to identify the main clinical features of CDM and ChDM patients during the transition phase and to explore patient and caregiver expectations in the era of emerging therapies.

Thirty-two patients aged 10-18 years (17 CDM, 15 ChDM) with at least two motor, respiratory, and neuropsychological assessments were included. A structured questionnaire was administered once to caregivers and cognitively preserved patients to explore expectations across several domains, including autonomy, relationships, and future therapies.

Comparing the two subgroups, CDM patients showed lower intellectual functioning (FSIQ 40.00 [40.00-43.00] vs 83.50 [72.50-100.50], p=0.001) and higher disease burden (CCMDHI total-scores 21.83 [11.65-45.27] vs 5.55 [2.17-13.77], p=0.02), with worsening in socialization (-0.30/month, p=0.0008) over time. ChDM patients presented greater social-communication difficulties (SCQ total-scores 25.00 [24.00-25.00] vs 20.00 [16.00-22.50], p=0.01), a decline in perceptual-reasoning index (-0.68/month, p=0.04) and improvements in self-reported emotional-regulation (-0.59/month, p=0.005) and quality of life (+0.42/month, p=0.03) over time. Motor performance remained stable in both groups. CDM patients showed a slow decline in FVC, whereas ChDM patients remained stable. Speech, strength, and cognitive improvement were the most frequently reported therapeutic goals, with expectations depending on disease subtype.

Despite the relatively small cohort, these findings suggest marked heterogeneity between CDM and ChDM patients during the transition phase, with different patient and caregiver priorities, highlighting the need for subtype-specific care strategies.

85 - Respiratory Muscles Under the Microscope: MRI Biomarkers of Respiratory Impairment in Pediatric FSHD

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Background: Over half of individuals with facioscapulohumeral muscular dystrophy (FSHD) develop symptoms in childhood (≤ 18 years old), and those with early-onset disease (≤ 10 years old) are at increased risk of faster disease progression and a younger age at loss of ambulation. Neuromuscular weakness of the thoracic muscles contributes to spinal deformities, (e.g. scoliosis, lordosis) and impaired respiratory function. Children with FSHD are therefore at high risk for respiratory complications, yet respiratory dysfunction in pediatric-onset FSHD remains uncharacterized. Left untreated, respiratory dysfunction can cause dependence on non-invasive ventilation or death. Quantitative muscle fat fraction (qFF) as measured by whole-body magnetic resonance imaging (WB-MRI) has emerged as a promising biomarker that can predict functional decline but has not been applied to the muscles of respiration to understand how changes in qFF influence respiratory function.
Objective: To determine the impact of FSHD on the muscles of respiration and pulmonary function.
Methods: Baseline WB-MRI and PFT results from the first 10 pediatric participants enrolled in the MOVE Peds natural history study will be evaluated.
Results: qFF of select muscles of respiration (pectoralis, latissimus dorsi, serratus anterior, paraspinal muscles, obliques) will be determined and correlated with baseline PFT measurements. Quantification of percentage of affected muscles, percentage of asymmetry between the left and right side, and mean fat infiltration score for each muscle as determined using the modified Mercuri scale.
Conclusions: This evaluation will provide novel insight into how FSHD affects individual muscles of respiration and the impact this can have on respiratory function.

87 - The impact of prior traumatic experiences on later fatiguability and psychiatric burden in patients with motor neuron disease and muscular dystrophy

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Although fatigue is a frequent complaint associated with motor neuron disease (MND) and muscular dystrophy (MD), it is not clear if and to what extent prior trauma exposure contributes to worse clinical outcomes.
The goal of this study is to assess if prior trauma exposure has worse impact on fatigue in patients diagnosed with MND and MD.
Data extracted from de-identified EHRs from TriNetX database was utilized. After propensity score matching was used to minimize effects of demographic confounds, the final sample size included two matched cohorts of 450 adult patients with minimum 1 year history of MND or MD at index and exposure defined as documented trauma exposure within 5 years prior to index. Risk comparison was used to assess for the following outcomes within 5 years post-index: (a) psychiatric diagnoses and (b) secondary clinical outcomes.
Patients with pre-index documented trauma exposure were shown to have a significantly higher risk of reporting fatigue, mood, and anxiety, all with $p<.001$; and hyperlipidemia, both with $p < .01$. The strongest associations based on risk difference and odds ratio (OR) were observed for anxiety, mood, and fatigue, with ORs of 3.613, 3.492, and 2.296, respectively.
These findings suggests that prior chronic stress may exacerbate clinical symptoms. The results support the integration of mental health screenings and support within multidisciplinary care for those identified to have experienced an adverse event. Future studies should explore whether stress reducing therapies may help reduce fatigue severity in addition to anxiety and mood in this population.

Thirty-two nonambulatory males (weight range 22.6 to 93.0 kg) were included between March 21, 2024, and January 31, 2026. Twenty-eight males (87.5%) required dose modification, with thrombocytopenia (46.9%) and gastrointestinal intolerance (34.4%) being the most common reasons. Among these males, 6 (18.8%) discontinued therapy: 4 due to gastrointestinal intolerance, 1 due to thrombocytopenia, and 1 due to patient preference. At the end of follow up, only 10 males (31.3%) remained at the weight-based initial dose recommended by the study label.
Conclusions:
Among nonambulatory males treated with givinostat, dose modification was frequent and target dosing was often not tolerated. If confirmed in a larger population, findings indicate reduced tolerability in a real-world population that differs from the clinical trial population. Consideration might be given to a lower starting dose for older and heavier males.

94 - Longitudinal Exploratory Evaluation of Bulbar Function in Weaker Non-Ambulatory Adults with Spinal Muscular Atrophy (SMA)

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Disease modifying treatments (DMTs) have been associated with patient-reported changes in bulbar function in spinal muscular atrophy (SMA), yet validated tools to evaluate bulbar integrity remain limited. This study evaluated longitudinal bulbar function in weak, non-ambulatory adults with SMA receiving DMTs.
We recruited 37 non-ambulatory adults with SMA as part of a prospective study (mean [SD] age 36.3 [11.6] years; range 23.4-78.5) from 2022-2025. Bulbar measures included patient reported outcomes (PROs), maximal mouth opening (aMMO), tongue and lip strength (Iowa Oral Performance Instrument), and speech metrics via mobile application (Linus Health's Speech Vitals) in clinic and remotely. Associations were assessed using Wilcoxon rank-sum tests and Spearman correlation; linear mixed-effects models assessed longitudinal change.
Participants included individuals treated with DMT (nusinersen or risdiplam) with 54% male, 59.5% SMA Type 2, 78.4% had 3 copies of SMN2, 67.6% non-sitters, and 64.9% used respiratory support. The cohort were weaker individuals with RULM mean score 10/37 [6.99]) and limited perceived voice deficits (VHI 17.88 [19], mild-moderate). Speech collection included 242 sessions (160 remote, 82 in clinic), with mean follow-up 310 [165] days (range 158-831). Patient-reported and clinical measures differed significantly between functional groups, whereas speech metrics did not. Several speech metrics showed moderate correlations with bulbar measures. Longitudinally, the digital measure that showed significant change was pitch variability.
Speech metrics collected via a mobile application are feasible objective endpoints for assessing bulbar function. This data underscores the complexity of different methods of communication and compensatory mechanisms used by individuals with SMA.

95 - The Trial Sustainability Control Tower: A Finance-Led Decision Model for Sustainable Neuromuscular Trial Delivery Across UCLH & NIHR

Ahsan Ghafoor

Introduction:
Neuromuscular clinical trials are high-complexity, high-cost studies requiring coordinated delivery across investigators, trial coordinators, research nurses, pharmacy, imaging, laboratories, R&D, CRF operations and sponsors. While clinical and regulatory risks are closely monitored, financial sustainability risks often remain fragmented across budgets, contracts, invoices, amendments and operational activity. This can lead to missed income, unrecovered pass-through costs, delayed sponsor payments, unfunded work and hidden pressure on NHS research capacity.
Objectives:
To develop a finance-led Trial Sustainability Control Tower that gives UCLH R&D a single, proactive view of trial cost, income, risk and delivery sustainability.
Methods:
The model translates each protocol, contract, budget and schedule of events into a live sustainability map. Every activity is linked to its responsible team, funding source, invoice trigger, delivery milestone, pass-through cost, amendment status and risk rating. A red-amber-green framework identifies underfunded procedures, missing contract coverage, delayed income, unrecovered costs, unfunded amendments and studies at risk of becoming financially unsustainable.
Results:
The Control Tower creates one shared decision view across QSCTC, R&D and CRF teams. It enables earlier escalation, reduces missed billing opportunities, improves sponsor query resolution, strengthens audit readiness and provides evidence for budget renegotiations, contract amendments and resource planning. It also helps teams assess whether a trial is scientifically valuable, operationally deliverable and financially sustainable.
Conclusions:
This model transforms finance from retrospective reporting into a real-time delivery safeguard. By embedding financial intelligence into trial operations, it protects NHS research capacity, improves legitimate income recovery and supports continued patient access to complex neuromuscular therapies.

96 - LEOPARD-DMD: Interval Results from a Duchenne Muscular Dystrophy Natural History Study

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Introduction: In preparation for therapeutic trials in Duchenne Muscular Dystrophy (DMD), we need sensitive outcome measures that can detect clinically relevant changes in disease burden over time. To satisfy this need, we previously developed and validated the regulatory-grade DMD Caregiver Reported-Health Index (DMDCR-HI).

Objectives: To determine the longitudinal performance metrics of the DMDCR-HI.

Methods: We are conducting a 24-month longitudinal study with caregivers of individuals with DMD. Caregivers are completing a demographics form, DMDCR-HI, parent-reported PedsQL, instrument preference survey, and global impression of change questionnaire at 6-month intervals. We are evaluating: 1) the ability of the DMDCR-HI to measure disease progression, 2) participant preferences for the DMDCR-HI vs. the PedsQL, and 3) meaningful score differences of the DMDCR-HI and its subscales.

Results: We enrolled 92 caregivers of individuals with DMD; 65 caregivers completed the 18-month time point. From baseline to 18 months, caregivers identified significant worsening in the following DMDCR-HI subscales: shoulder and arm function (10.08 points, p=0.003), activity participation (4.92 points, p=0.048), mobility (6.72 points, p=0.024), ambulation (8.46 points, p=0.012), and extended ambulation for fully/partly ambulatory patients (6.02 points, p=0.043). The PedsQL did not detect any significant changes in disease. A total of 65% of caregivers thought the DMDCR-HI was better able to detect important changes in disease.

Conclusions: The DMDCR-HI is a validated outcome measure that can detect disease progression over an 18-month period and is preferred by users. Future analysis will provide insight into what a meaningful change in DMDCR-HI score is for upcoming clinical trials.

97 - Sensory Neuronopathy as a Presenting Manifestation of Pancreatic Ductal Adenocarcinoma

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Introduction: Sensory neuronopathy is an uncommon disorder of the dorsal root ganglia characterized by prominent large-fiber sensory loss, sensory ataxia, and gait instability. It is most often associated with autoimmune diseases or secondary to paraneoplastic etiology, classically small cell lung carcinoma. We present a case of sensory neuronopathy as the presenting syndrome of pancreatic adenocarcinoma.
Case report: A 77-year-old woman with type 2 diabetes presented with progressive gait instability, sensory loss, and leg weakness associated with unintentional weight loss. Examination demonstrated prominent large-fiber sensory loss in bilateral upper and lower extremities, appendicular and truncal ataxia, proximal-predominant lower extremity weakness, and diffuse areflexia. Electrodiagnostic study showed axonal sensory>motor polyneuropathy with diffuse loss of sensory nerve action potentials. Paraneoplastic antibodies were negative in the serum. CT abdomen identified a pancreatic mass, with biopsy confirming pancreatic ductal adenocarcinoma. The overall picture was most consistent with paraneoplastic sensory neuronopathy associated with pancreatic adenocarcinoma. She underwent resection followed by a 5-day course of IVIG.
Conclusion: Paraneoplastic sensory neuronopathy is a rare neurologic syndrome, and its association with pancreatic adenocarcinoma is particularly uncommon and only rarely described in the literature. This case adds to the reports of pancreatic cancer being associated with paraneoplastic neurological syndromes.

101 - Revelation of Occult Hypermagnesemia: A Case Series on Mg Toxicity Induced by Chronic Supplementation Following Established Guidelines

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Introduction: Increased magnesium (Mg) intake via diet and guideline-based supplementation is generally deemed safe, assuming healthy kidneys efficiently eliminate excess. This case report, supported by a historical patient cohort identified via literature review, challenges this dogma.
Case Reports: Two athletic patients with no prior medical history or medication use presented with a severe, diffuse neuromuscular symptom complex. Both had chronically supplemented Mg (200-300 mg/day).
Methods: A clinical work-up was performed, including an electrolyte panel with red blood cell magnesium (RBC-Mg) analysis, complemented by a literature review. Management involved a low-Mg diet combined with high-dose B-vitamin therapy.
Results: Initially, both patients exhibited elevated RBC-Mg alongside normal or low-normal serum Mg (sMg), in the index patient with sMg levels being inversely proportional to RBC-Mg. After five weeks of therapeutic Mg reduction and B-vitamin supplementation, the index patient showed a significant decrease in RBC-Mg, accompanied by a marked rise in sMg. This "scissors effect" was first described by Jean Durlach over four decades ago. Contrary to Durlach's original interpretation, it is posited that markedly elevated RBC-Mg indicates toxic intracellular Mg overload.
Conclusion: The findings augment the historical Durlach cohort and suggest current Mg guidelines may not be universally safe. RBC-Mg is a critical tool for detecting chronic tissue accumulation in exhaustion syndromes. The reciprocal drop in sMg presents a diagnostic pitfall, falsely suggesting deficiency when viewed in isolation. Symptom responsiveness to high-dose B-vitamin therapy implies the reactivation of respiratory chain enzymes previously blocked by Mg excess.

103 - Sensory-Predominant Inflammatory Axonal Neuropathy with Cauda Equina Root Enlargement and CSF HHV-6 Detection

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Background: Sensory-predominant inflammatory neuropathies are difficult to classify when inflammatory features coexist with electrodiagnostic findings that do not meet established demyelinating criteria.
Methods: We reviewed serial electrodiagnostic studies, neuroimaging, cerebrospinal fluid (CSF) analysis, infectious evaluation, and treatment response in a 34-year-old man with progressive distal sensory loss and paresthesias over 2.5 years without objective weakness.
Results: Neurologic examination demonstrated distal sensory loss with impaired vibration and proprioception while motor strength remained preserved. Serial nerve conduction studies showed reduced median, ulnar, radial, and lower-extremity sensory amplitudes with mild latency prolongation and conduction slowing. Motor studies were largely preserved, although delayed F-wave latencies suggested proximal nerve root involvement. Longitudinal review favored a sensory-predominant axonal neuropathy rather than a primary demyelinating process. Lumbar MRI demonstrated smooth enlargement and enhancement of the cauda equina nerve roots. CSF analysis revealed albuminocytologic dissociation (protein 55.5 mg/dL, 3 white blood cells/µL). Extensive metabolic, autoimmune, infectious, and neoplastic investigations were unrevealing. CSF PCR was positive for HHV-6, although infectious disease evaluation favored latent reactivation or chromosomal integration rather than active infection. Weekly pulse corticosteroid therapy resulted in approximately 40% improvement in sensory symptoms with interval electrophysiologic improvement.
Conclusions: This case highlights a sensory-predominant inflammatory neuropathy characterized by axonal sensory nerve involvement, albuminocytologic dissociation, and cauda equina root enlargement despite the absence of definitive electrodiagnostic demyelination. CSF HHV-6 detection raises the possibility of a postinfectious immune trigger in a susceptible host.

104 - Prevention of pathogenic Ataxin-1 phosphorylation by RNA trans-splicing ameliorates pathology in a mouse model of spinocerebellar ataxia type 1

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RNA-trans-splicing is an RNA-based gene therapy that creates a hybrid mRNA through a trans-splicing reaction between a target pre-mRNA and an exogenous RNA trans-splicing molecule (RTM). Our objective was to determine whether the pathogenic serine phosphorylation of Ataxin-1 in spinocerebellar ataxia type 1 (SCA1) can be converted to a nontoxic state using RNA trans splicing. Human and mouse FLAG-tagged RTMs were constructed using traditional cloning methods. Alanine substitutions at S776 (human) or S751 (mouse) were introduced using lentiviral RTM delivery in cells or via AAV2/8 delivery in the well-established $Sca1^{154Q/2Q}$ knock-in mouse model. Mice were treated via intracerebroventricular injections in neonates (P0-2) or with cerebellar stereotaxic injections at symptomatic stage (P100). Motor function and coordination were assessed every 15 days via rotarod. First, accurate *Ataxin-1* reprogramming was demonstrated *in-vitro* and *in-vivo*. Subsequently, a combination of western blot, filter-retardation and Thioflavin T assays of mouse P180 cerebellar lysates revealed diminished Ataxin-1 aggregation and reduction in S776/S751 phosphorylation upon treatment. Additionally, confocal imaging in fixed mouse cerebellar tissue (P150) demonstrated maintained synaptic integrity, with preserved excitatory and inhibitory inputs to Purkinje neurons. Longitudinal rotarod and leg-splaying-test assessment demonstrated marked preservation in motor function and coordination, suggesting a promising therapeutic potential. Finally, adopting a patient-centric view, we delivered the trans-splicing therapy at a symptomatic stage via cerebellar-targeted stereotaxic injections, revealing a significant functional improvement. Together, these findings support the potential of RNA trans-splicing as a promising and versatile therapeutic approach for SCA1.

106 - Atypical Primary Lateral Sclerosis Presenting with Binocular Diplopia: A Case Report

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Introduction: Primary lateral sclerosis (PLS) is an upper motor neuron (UMN) disorder with typically insidious onset of spasticity, most commonly beginning in the lower extremities. Ocular manifestations are rarely described and are not recognized as an initial presenting feature.
Objectives: To describe an atypical presentation of PLS with initial binocular diplopia, expanding the phenotypic spectrum of this disorder.
Methods: We report a 77-year-old woman with a 5-year history of progressive UMN symptoms beginning with binocular diplopia. She underwent extensive evaluation including serial electromyography/nerve conduction studies, single-fiber EMG, MRI of the brain and cervical spine, cerebrospinal fluid analysis, autoimmune and neuromuscular antibody panels, and genetic testing for hereditary spastic paraplegia, ALS genes, and spinocerebellar ataxia.
Results: Neurological exam demonstrated left esotropia with impaired right eye adduction, spastic dysarthria, facial and tongue weakness, diffuse hyperreflexia with pathological reflexes, and upper extremity spasticity. Diagnostic workup was unrevealing for alternative etiologies. Vestibular testing showed central oculomotor dysfunction. The patient met 2020 consensus criteria for definite PLS based on progressive UMN involvement in multiple regions, symptom duration greater than 4 years, absence of lower motor neuron findings on serial studies, and exclusion of mimics. The disease course showed slow progression without lower motor neuron involvement.
Conclusions: This case represents a rare presentation of PLS with binocular diplopia as the initial symptom. It highlights possible supranuclear oculomotor involvement and expands the clinical spectrum of PLS. Recognition of atypical presentations is essential to avoid diagnostic delay and to distinguish PLS from other motor neuron and hereditary disorders.

108 - Long-Read Amplicon Sequencing Method to Measure CTG Repeat Length and Mosaicism for Correlation to Disease Severity in Myotonic Dystrophy Type 1

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Introduction: Myotonic dystrophy type 1 (DM1) is a multisystemic disease caused by expansion of a CTG repeat in the *DMPK* gene, with repeats ranging from 100s to 1000s of triplets. Using current methods, the length of the inherited repeat in the blood is broadly correlated with disease severity (Pearson's R » -0.44; Age-of-onset x modal CTG length), but accurate measurement of individual repeat lengths has technical limitations, particularly with larger alleles.
Objectives: To develop a method to measure CTG repeat length and mosaicism that is amenable to low sample input, economically feasible for large-scale analyses, and allows for sequence-level data.
Methods: We compare (1) Southern blot of genomic DNA, (2) Southern blot of long-range PCR, (3) small-pool PCR, (4) Cas9-mediated genomic DNA enrichment followed by PacBio long-read sequencing, and (5) PacBio sequencing of long-range PCR products using a test-set of patient-derived blood gDNA samples with variable length and mosaicism, and gDNA mixes of known repeat lengths from patient-derived cell lines. Concordance between the methods, limitations of detection of longer or shorter alleles dependent on method, and quantification of mosaicism are measured.
Results: Long-range PCR can amplify highly expanded CTG repeat alleles and represent mosaicism with high concordance compared to gDNA Southern blot (ICC = 0.901 for modal repeat length; ICC 0.888 for range of repeat mosaicism). Long-read sequencing identifies repeat interruptions, and incorporation of unique molecular identifiers to perform bioinformatic amplification correction is explored.
Conclusions: Long-read sequencing of long-range PCR products is an economical alternative to measure CTG repeat length.

111 - A cross-sectional study exploring the alignment between patient-reported and biomechanical dysphagia outcomes in myotonic dystrophy type1 (DM1)

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Studies in myotonic dystrophy type 1 (DM1) consistently demonstrate poor association between patient-reported dysphagia symptoms and instrumental assessment findings. This disconnect complicates clinical assessment and may lead to underdiagnosis of dysphagia. We investigated relationships between biomechanical dysphagia severity and patient-reported symptoms.

Ninety-four adults with DM1 were recruited from across the UK to a tertiary neuromuscular centre. During the same visit, participants completed the Sydney Swallowing Questionnaire (SSQ) and Swallowing Quality of Life Questionnaire (SWAL-QOL), followed by a videofluoroscopic swallowing study using the Modified Barium Swallow Impairment Profile (MBSImP). Participants were stratified into three dysphagia severity groups based on MBSImP oral and pharyngeal sum score tertiles for comparison of symptom scores.

Median age was 45 years (IQR 38, 52); 52 were female. SSQ scores ranged from 20 to 1096 (max 1700), with higher scores indicating greater symptom burden; scores increased across oral dysphagia tertiles: median 136 (IQR 70, 350; n=27), 224 (84, 426; n=20), and 264 (106, 578; n=45), and pharyngeal dysphagia tertiles: median 152 (57, 270; n=22), 194 (78, 398; n=39), and 350 (183, 663; n=31). SWAL-QOL swallowing symptom scores (range 0-100, with higher scores indicating fewer symptoms) decreased across oral tertiles: median 68 (43, 81), 57 (41, 82), and 46 (34, 66), and pharyngeal tertiles: 68 (46, 86), 65 (38, 86), and 43 (30, 59). Individual questionnaire items will be presented, highlighting those with poor sensitivity for detecting differences in dysphagia severity.

Findings suggest that limitations in measurement sensitivity may explain previously observed disconnect between patient-reported and instrumental measures.

112 - Quantitative muscle ultrasound as an assessment and phenotyping tool for oro-pharyngeal dysphagia in myotonic dystrophy type 1

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Current dysphagia phenotyping focuses on biomechanical function while neglecting pathophysiology. This limits treatment selection in conditions like myotonic dystrophy type 1 (DM1), where dysphagia may result from central nervous system impairment, muscle abnormalities, or both. We integrated biomechanical and muscle pathophysiology assessments to characterise DM1 dysphagia phenotypes.

Ninety-four adults with DM1 and 63 healthy controls were recruited. Participants underwent videofluoroscopic swallowing study using the Modified Barium Swallow Impairment Profile (MBSImP) and quantitative muscle ultrasound (QMUS) of five swallowing-related muscles. Participants were stratified by MBSImP oral and pharyngeal sum score tertiles. QMUS echogenicity and thickness were converted to sex-, age-, and BMI-adjusted z-scores and compared between tertiles.

Median age was 45 years (IQR 38, 52) for DM1 participants and 43 years (IQR 30, 56) for controls. For pharyngeal dysphagia, median geniohyoid echogenicity z-scores decreased across MBSImP tertiles: 2.60 (IQR 2.25, 2.79; n=22), 2.34 (1.48, 3.05; n=38), and 1.73 (1.43, 2.31; n=30), while thickness was reduced in tertiles 1-2 (medians -1.09 and -1.06) but less affected in tertile 3 (-0.40). All oral dysphagia tertiles showed elevated echogenicity (2.18-2.30) and reduced thickness (-1.01 to -1.07).

For geniohyoid echogenicity, ICC ranged from 0.73-0.99 in controls and 0.80-0.97 in pwDM1, with 95% LoA of ±23 and ±34 grayscale units (scale 0-255) respectively. Results for remaining muscles will be presented.

QMUS indicators of altered muscle thickness and echogenicity were associated with biomechanical dysphagia in DM1, but the relationship was inconsistent, potentially indicating multifactorial dysphagia mechanisms beyond muscle abnormality alone.

115 - Development of a Specialist Research Delivery Unit Supporting Neuromuscular Clinical Trials Within a UK Tertiary Neuroscience Centre

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Introduction: Increasing complexity and volume of neuromuscular clinical trials places growing demands on disease-specific research teams. Limited capacity may affect study initiation, delivery and participant access to research opportunities. The Queen Square Clinical Trials Centre (QSCTC) was established to provide flexible late-phase clinical trial support across neurological specialties.
Objectives: To evaluate the contribution of a specialist research delivery unit to neuromuscular clinical trial activity during its first year of operation.
Methods: A retrospective service evaluation was undertaken of QSCTC activity during its first year of operation. Data collected included portfolio growth, investigator support, participant activity and geographical distribution of participants engaged in clinical research supported by the unit.
Results: During the evaluation period, the active portfolio expanded from 2 to 11 studies including motor neuron disease, Myasthenia gravis, Huntington's disease, multiple sclerosis and inherited neuromuscular disorders. Six principal investigators were supported across multiple neurological subspecialties. Thirty-four studies approached the unit for research support. A total of 83 participant visits were delivered including screening, follow-up and remote assessments. Several newly activated studies achieved first participant screening within 30 days of activation. Participants were recruited from Greater London and multiple counties across South East England including Hertfordshire, Buckinghamshire, Essex, Kent, Oxfordshire, Cambridgeshire and Sussex.
Conclusions: During its first year of operation, a specialist research delivery unit supported substantial growth in neuromuscular clinical trial activity across multiple disease areas and investigators. This model may provide a practical approach to supporting specialist neuroscience research delivery within large academic centres facing increasing research demand while maintaining flexibility across diverse portfolios.

116 - Early Motor Neuron Dysfunction Drives Age-Related Motor Decline: Longitudinal Insights and Therapeutic Modulation with 4-AP

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Introduction: Age-related decline in motor function is a major cause of disability and morbidity and is associated with premature death. While the mechanisms of motor function decline remain incompletely understood, our ongoing work suggests loss of motor neuron (MN) excitability is a major driver and potential therapeutic target. We hypothesize that 4-aminopyridine (4-AP), a potassium channel blocker, offers a translational approach to restore MN excitability.
Objectives: To define the temporal trajectory of MN excitability and neuromuscular decline during aging and evaluate whether 4-AP restores MN excitability.
Methods: Indices of MN and muscle membrane excitability in C57BL/6J mice (n=57) were assessed longitudinally across the natural trajectory of aging from 11-28 months. In a separate ongoing intervention study, aged mice (22-23 months; n=30) were randomized to 4-AP or vehicle to evaluate how acute administration of 4-AP alters these excitability indices.
Results: Longitudinal data showed early electrophysiological deficits, with cervical motor evoked potential (cMEP) and compound muscle action potential, representing indices of spinal MN and muscle excitability, declining at 14-16 months ($p<0.001$), preceding reductions in grip strength at 23-25 months ($p<0.0001$). Acute 4-AP treatment data in old mice showed a nearly two-fold increase in cMEP compared with saline.
Conclusions: Our findings suggest that MN excitability is an early driver of age-related motor decline and represents a modifiable therapeutic target. Furthermore, preliminary results suggest that 4-AP improves MN excitability, supporting this as a potential therapeutic approach. Ongoing chronic 4-AP studies will determine whether restoring MN excitability improves neuromuscular outcomes.

119 - Ulnar Neuropathy in Wild-Type Transthyretin Amyloidosis: A Retrospective Review

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Introduction: Transthyretin amyloidosis (ATTR) is a systemic disorder caused by misfolded transthyretin deposition in multiple organs, including the myocardium and peripheral nervous system. Wild-type transthyretin amyloidosis (ATTRwt) is increasingly recognized to have prominent extracardiac neurological manifestations. Although median nerve entrapment causing carpal tunnel syndrome is well recognized, the prevalence and significance of ulnar neuropathy remain poorly defined.
Objective: To determine the prevalence of ulnar neuropathy in patients with confirmed ATTRwt and characterize its clinical and electrodiagnostic features.
Methods: A retrospective cohort study was conducted of patients with ATTRwt evaluated by a neuromuscular specialist at a single tertiary-care academic medical center between March 2017 and December 2025. Patients were identified through electronic health record review and were included if they met established diagnostic criteria for ATTRwt. Clinical documentation and electrodiagnostic studies were reviewed for evidence of ulnar neuropathy. Ulnar neuropathy was defined by the presence of at least one accepted clinical or electrodiagnostic criterion.
Results: Ninety-four patients with ATTRwt were identified (mean age 81.5 +/- 7.7 years; 90.4% male). Among these, 55 patients (58.5%) demonstrated evidence of ulnar neuropathy based on clinical assessment or electrodiagnostic testing.
Conclusions: Ulnar neuropathy is a common but underrecognized manifestation of wild-type transthyretin amyloidosis. In this single-center cohort, its high prevalence suggests it may broaden the recognized neurologic spectrum of ATTRwt and represent an early clinical indicator. Greater recognition could facilitate earlier diagnosis and inform clinical management.

120 - From Injury to Compensation: Age-Dependent Neuromuscular Responses to CTB-Saporin

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Introduction: Motor neuron (MN) and motor unit (MU) degeneration or injury results in denervation and loss of function but compensation may occur through collateral sprouting of surviving MNs. Yet, prior work suggests that compensatory capacity is limited in the context of aging and neuromuscular diseases such as Amyotrophic Lateral Sclerosis (ALS), spinal muscular atrophy (SMA), and Charcot Marie Tooth and Kennedy's diseases. Ultimately, improving collateral sprouting capacity might offer a strategy to mitigate neuromuscular disease.
Objectives: To define the impact of aging on MU compensation response following CTB-Saporin-induced MN loss in wildtype mice.
Methods: Adult (8-10 months) and aged (26-28 months) mice were injected with 6μg CTB-Saporin and neuromuscular outcomes were assessed longitudinally. Further, a dose finding study was assessed using a range of CTB-Saporin doses in young animals (4 months) to determine the CTB-Saporin dose at which MU compensation is most complete.
Results: At 6μg, CTB-Saporin reduced compound muscle action potential (CMAP) and MU number estimation in both groups, with sustained torque and grip deficits; old mice showed greater repetitive nerve stimulation decrement. Across 0-6μg, CMAP declined dose-dependently. Two-way ANOVA showed a dose effect on CMAP ($p=0.040$); age explained 10.78% and 29.48% of CMAP and single motor unit potential variance, respectively.
Conclusions: Aged mice demonstrate loss of MU repair and compensation following MU disruption. Ongoing dose-ranging will define a submaximal injury level to test age-related limits in MU compensation, a process with potential therapeutic relevancy to disorders of neuromuscular denervation.

121 - Off-label givinostat therapy in a patient with Duchenne muscular dystrophy and early-childhood tuberculosis

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Introduction: Givinostat is a histone deacetylase inhibitor recently approved for Duchenne muscular dystrophy (DMD), an X-linked recessive neuromuscular disorder. This novel disease-modifying therapy prevents muscle damage and fibrosis. Individualized treatment strategies are required when standard corticosteroid regimens are contraindicated.
Methods: Case Report.
Results: An 8-year-old boy with genetically confirmed Duchenne muscular dystrophy was initiated on off-label givinostat therapy. At 2 years old, during active tuberculosis treatment, elevated transaminases were detected alongside calf hypertrophy, frequent falls and fatigue. Past medical history included an inguinal hernia, migrating testes, and a paternal history of Fabry disease. Further laboratory testing revealed markedly elevated CK levels. MLPA confirmed an exon 45 hemizygous deletion. Standard corticosteroid therapy was contraindicated due to repeated tuberculosis treatment and chemoprophylaxis, leaving him without disease-modifying therapy until age 8. Prior to givinostat initiation, neurological examination revealed lumbar hyperlordosis, positive Gower's sign, and impaired heel walking. After 6 months of treatment, functional assessments improved: the North Star Ambulatory Assessment score increased from 30 to 33/34, time to rise decreased from 4.0s to 2.7s, and 4-stair climb improved from 2.0s to 1.6s. The 6-minute walk test remained stable (439m to 425m). The therapy was well-tolerated with no side effects.
Conclusion: This case demonstrates the therapeutic challenge of managing DMD when corticosteroids are contraindicated, proposing that givinostat may remain a viable non-immunosuppressive alternative for patients precluded from standard therapy. While short-term assessment shows functional improvement and excellent tolerability, further follow-up remains necessary for evaluating clinical benefit.

127 - QTc Distribution in Duchenne Muscular Dystrophy Patients: Implications for Therapies with Potential Cardiac Effects

Maddalena Bianchetti[1, 2], Sophia Paolucci[2], Anna Capasso[1, 2], Chiara Arpaia[1, 2], Romina Venditti[1], Federica Mirra[2], Gianpaolo Cicala[1, 2], Martina Malaspina[1], Elena Sofia Spanò[3], Paolo Galletti[3], Rita Blandino[2], Angelica Bibiana Delogu[4], Enrica Rolle[5], Giulio Gadaleta[5], Tiziana Enrica Mongini[5], Federica Ricci[5], Sofia Maroni[6], Valeria Sansone[6], Marina Pedemonte[7], Federica Trucco[7], Claudio Bruno[7], Marika Pane[1, 2], Eugenio Maria Mercuri[1, 2]

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Background: Concerns have been raised regarding potential QT interval prolongation in patients affected by Duchenne muscular dystrophy (DMD), particularly following the recent approval of givinostat, a medication that may influence QT/QTc duration. This study aimed to characterize QTc values in a cohort of DMD patients not treated with givinostat, including a subgroup receiving medications known to potentially affect QTc.

Methods: The study included 279 patients aged 1.39-46.78 years followed at four neuromuscular referral centers across Italy. All participants underwent routine electrocardiographic (ECG) evaluation as part of standard clinical care. A subgroup of 108 patients received medications associated with increased QTc risk, including proton pump inhibitors, antiepileptic drugs, antidepressants, antipsychotics, stimulants, antihistamines, beta-blockers, diuretics, and antiarrhythmic agents.

Results: The cohort comprised 279 male patients (mean age 15.12 ± 7.41 years). QTc values ranged from 297 to 525 ms. Overall, 254 patients (91.04%) had QTc values <440 ms (mean 397.46 ± 25.28 ms), while 23 (8.24%) had QTc values >440 ms (mean 463.88 ± 24.94 ms). Four patients (1.43%) had QTc values >500 ms (mean 513 ± 8.83 ms). Among the 108 patients receiving medications associated with QT prolongation risk, 95 (87.96%) had QTc values <440 ms (mean 398.48 ± 24.30 ms), and 50 (46.30%) had QTc values <400 ms (mean 380.94 ± 18.78 ms).

Conclusions: In this cohort, only a small proportion of patients (8.24%) had QTc values >440 ms. Patients receiving medications potentially affecting QTc showed a similar prevalence of QTc prolongation, with 12.03% presenting QTc values >440 ms.

128 - Neuropathic Symptoms and Neuropathic Pain Treatment Practices in Patients Receiving Paclitaxel and Nab-Paclitaxel: A Single Center Study

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Introduction: Chemotherapy-induced peripheral neuropathy (CIPN) is a common dose-limiting toxicity affecting 60-70% of patients. Severe CIPN significantly impairs quality of life, making early recognition essential. Duloxetine is currently the only first-line therapy recommended by the American Society of Clinical Oncology.
Objective: This study characterized paclitaxel and nab-paclitaxel-associated neuropathic symptoms, evaluated subsequent chemotherapy regimen modifications, and described real-world pharmacologic management practices.
Methods: EMRs of adult cancer patients treated with paclitaxel or nab-paclitaxel at a single center between January-June 2023 were reviewed up to 2 years.
Results: Of 513 patients identified, 199 were evaluated: 169 (84.9%) paclitaxel and 32 (15.1%) nab-paclitaxel. Mean age 63.3 years; 70.1% female. Overall, 53.8% (n=107) developed symptoms: 84.1% (n=90/107) during active chemotherapy and 15.9% (n=17/107) within 3 months post-treatment. Incidence was 53.8% (n=91/169) for paclitaxel and 50.0% (n=16/32) for nab-paclitaxel.
Among 90 patients with active-treatment symptoms, numbness (78.9%, n=71/90) and tingling (45.6%, n=41/90) predominated, involving feet (62.9%), fingers (60.7%), toes (42.7%), and hands (32.6%). Neuropathic pain occurred in 37.9% (n=33/87). Chemotherapy modifications occurred in 46.1% (n=41/89), including dose reduction in 32.6% (n=29/89) and discontinuation in 13.5% (n=12/89). Pharmacologic therapy was initiated in 42 patients, including 33.3% (n=14/42) without documented pain. Gabapentin was the most common first-line agent (78.6%, n=33/42; median maximum 900 mg/day); duloxetine was used in 9.5% (n=4/42; median maximum 60 mg/day). Combination therapy was used in 19% (n=8/42).
Conclusion: CIPN affects over half of patients, frequently causing chemotherapy modification or discontinuation. Real-world practice heavily favors gabapentin over duloxetine, highlighting opportunities to optimize evidence-based management.

129 - Multidisciplinary Assessment of Brain Involvement in Duchenne Muscular Dystrophy

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Background: Duchenne muscular dystrophy (DMD) is a progressive disorder caused by pathogenic variants in the DMD gene, resulting in loss of dystrophin. Increasing evidence indicates that brain involvement is common in DMD, as dystrophin is expressed in both muscle and the central nervous system. Multiple brain dystrophin isoforms are differentially affected by mutation location, contributing to variability in cognitive, neurodevelopmental, and psychiatric manifestations.
Objectives: This project aims to expand knowledge of brain involvement in DMD through a multidisciplinary approach integrating clinical, neurophysiological, genetic, and computational tools. Specific objectives include characterizing central nervous system involvement, exploring genotype-epigenotype relationships, identifying genetic modifiers, and developing predictive models of neurodevelopmental outcomes.
Methods: The study will include boys older than 6 years with a genetically confirmed diagnosis of DMD followed at our center. Participants will undergo a structured assessment using clinical and neurophysiological tools, including high-density EEG. Genetic investigations will evaluate DMD variants and employ Third-Generation Whole-Genome Sequencing (TG-WGS) to identify modifier loci associated with central nervous system involvement. Machine learning approaches will integrate clinical, neurophysiological, and genetic data to develop algorithms identifying multifactorial risk factors for cognitive and neurodevelopmental disorders.
Expected Impact: This work addresses a major unmet need in DMD by improving understanding of the contribution of DMD mutations and additional genetic factors to brain involvement. It will help define the frequency and severity of neurodevelopmental and psychiatric comorbidities, support more accurate diagnoses and treatment selection, and inform the choice of outcome measures and surrogate endpoints for future interventional trials.

130 - Incidence and Dose-Response Relationship of Neuropathic Symptoms in Patients Receiving Paclitaxel or Nab-Paclitaxel: A Single Center Study

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INTRODUCTION:
Paclitaxel and nab-paclitaxel are widely used taxane chemotherapies for breast, ovarian, and lung cancers. Both are associated with chemotherapy-induced peripheral neuropathy (CIPN), which can impair quality of life and limit treatment. Paclitaxel causes neuropathy in ~60-70% of patients, while nab-paclitaxel rates may be similar or higher. Evaluating incidence and risk factors at our center is important for patient counseling and toxicity monitoring.
OBJECTIVE:
To determine the incidence of neuropathic symptoms with paclitaxel vs. nab-paclitaxel, assess cumulative dose at symptom onset, and evaluate the impact of pre-existing neuropathy.
METHODS:
This retrospective single-center study included adults treated with paclitaxel or nab-paclitaxel (Jan-Jun 2023). Patients were identified via SlicerDicer, with chart review up to 2 years for new or worsening neuropathic symptoms. Incidence and cumulative dose at onset were compared between groups and by neuropathy history.
RESULTS:
A total of 513 patients were identified, of whom 201 have been evaluated (paclitaxel n=169; nab-paclitaxel n=32). Around 53.8% (n=107) had new or worsening neuropathic symptoms, 84.1% (n=90/107) during chemotherapy and 15.9% (n=17/107) within 3 months of treatment. Incidence was similar (53.8% vs. 50%) between both groups. Mean cumulative dose at onset was 869.3±564.6 mg (paclitaxel) and 1,614.2±779.9 mg (nab-paclitaxel). Pre-existing neuropathy did not affect incidence (p=0.66). However, in nab-paclitaxel, it was associated with lower dose at onset (1,208.9 vs. 2,087 mg; p=0.035), but not in paclitaxel.
CONCLUSION:
Neuropathic symptoms are common (~50%) with both agents, with similar incidence. Pre-existing neuropathy may lower the dose threshold for nab-paclitaxel-related symptoms which warrants proactive counseling and monitoring.

131 - Baseline Characteristics and Preliminary Clinical Outcomes in an Observational Study of Advanced Glycation End Products and Chemotherapy-Induced Peripheral Neuropathy

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Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common and dose limiting toxicity. Informative biomarkers are lacking. Advanced glycation end products (AGEs) have been implicated in pathways associated with oxidative stress, inflammation, and neuronal injury and may contribute to CIPN risk. AGE reduction is a promising therapeutic strategy.
Objective: To develop an electronic health record driven strategy to identify and enroll patients before treatment with platin or taxane-based chemotherapy. This longitudinal cohort study examines the relationship between AGEs and CIPN risk and severity, laying the foundation for a future CIPN prevention trial.
Methods: Adult patients are prospectively enrolled prior to receiving chemotherapy and followed longitudinally. CIPN clinical assessments include a spectrum of symptom, sign and quality of life-based measures (BPI, CAPPRI, CIPN RODS, EORTC 20, mTCNS). Serum AGEs, metabolic measures and neurofilament light chain (NfL) are collected at baseline and at predefined times through 6 months post chemotherapy.
Results: 54 patients have been enrolled and 21 have completed chemotherapy. Twelve have developed CIPN. The median time to symptom onset was 69 days (range: 10-172 days). Collection of serum samples clinical assessments has been integrated into clinic and infusion visits.
Conclusions: These findings demonstrate the feasibility of this prospective recruitment strategy for biomarker development or CIPN prevention studies. Ongoing analyses will evaluate the relationship between serum AGEs and CIPN incidence and severity, with the goal of designing a trial of AGE reduction (e.g. time restricted eating) for CIPN prevention.

133 - Charcot-Marie-Tooth Disease, Sleep, and Fatigue: Exploring a Complex Interplay to Improve Patient Outcomes

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Introduction Charcot-Marie-Tooth (CMT) disease encompasses a heterogeneous group of inherited polyneuropathies. Fatigue is a prevalent and debilitating symptom that significantly impairs quality of life across CMT subtypes. While the pathophysiology of fatigue remains incompletely understood, sleep disturbances have been documented in CMT1A for approximately two decades; however, systematic characterization across other subtypes is lacking, representing a critical gap in clinical management.

Objective This cross-sectional study aimed to characterize sleep disturbances across genetically confirmed CMT subtypes and evaluate the effect of intervention on objective sleep parameters.

Methods Chart review was performed on 14 patients with genetically confirmed CMT who underwent polysomnography within the preceding ten years. Pre- and post-intervention apnea-hypopnea index (AHI), BMI, Epworth Sleepiness Scale (ESS) score, and mean nocturnal SaO_2 were recorded.

Results Mean age was 47.8 ± 18.0 years; mean BMI was 28.8 ± 4.7 kg/m^2; mean AHI was 10.8 ± 8.4 events/hour, and mean ESS was 12.4 ± 5.8. Subtypes included CMT1A (n=6), CMT2A (n=3), CMTX1 (n=3), CMT2D (n=1), and CMT2E (n=1). Of 14 patients with interpretable data, 85.7% demonstrated at least mild sleep-disordered breathing. Notably, AHI did not significantly correlate with age or BMI. Among 10 treated patients, 8 achieved AHI reduction following CPAP/BiPAP; ESS improvement was modest.

Conclusion CMT patients demonstrate objectively impaired nocturnal breathing responsive to CPAP/BiPAP therapy. The absence of correlation with conventional risk factors underscores the need for proactive, routine sleep screening in all CMT patients, independent of BMI or age. Whether treatment translates to fatigue reduction warrants a prospective study.

134 - Wearable Gait Assessment in Adults with SMA: Preliminary Findings from the SAFE SMA Study

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[1]The Ohio State University

Individuals with spinal muscular atrophy (SMA) experience progressive muscle weakness and fatigue leading to impaired gait and falls. Falls may result in injury and loss of ambulation, yet no validated tool exists to predict fall risk. Wearable gait devices provide objective gait measures and may help identify characteristics associated with falls and functional decline. This study aims to evaluate the feasibility of wearable devices in adults with SMA and characterize the relationship among gait parameters, muscle fatigability, and fall risk.

A 6-Minute Walk Test (6MWT) was completed in clinic while wearing OpalV2R® sensors to measure spatiotemporal measures. Preliminary analyses were performed on eight participants (5-women, 3-male; median age: 34.5; range 25-56). Participants demonstrated slower gait speeds (1.01±0.29 m/s), normal cadence (102.71±15.29 steps/min), and shortened stride length (1.17±0.23 m) compared to heathy. Participants spent 62.51%±3.12% of the gait cycle in stance phase and 37.47%±3.14% in swing phase, varying slightly from healthy norms of 60% stance and 40% swing. Slower gait speed was strongly associated with less swing phase time ($\rho=0.92$, $p=0.0011$), longer double support time ($\rho=-0.95$, $p<0.001$), and shorter stride length ($\rho=0.98$, $p<0.001$), whereas faster walkers exhibited opposite patterns. Lateral step variability showed significance with foot strike angle ($\rho=0.74$, $p=0.0366$) and stride length ($\rho=0.71$, $p=0.0465$). Left right gait measurement showed strong agreement for most parameters.

Preliminary findings demonstrate feasibility and suggest that wearable devices capture meaningful gait differences to target interventions and/or bracing. Ongoing data collection will determine whether gait metrics and fatigability measures can predict falls.

135 - Better Balance-CMT: Protocol for a randomised, controlled, efficacy and implementation trial of a home-based, balance training intervention for people with Charcot-Marie-Tooth Disease

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1. Introduction
Charcot-Marie-Tooth disease (CMT) is associated with sensory loss and impaired balance, increasing fall risk. Multi-sensory rehabilitation and resistance training have demonstrated benefits in improving balance and proximal muscle strength when delivered in specialist settings. A pragmatic, home-based programme, Better Balance-CMT, has been developed with proof-of-concept evidence of safety, acceptability, and good adherence.
2. Objectives
This study will evaluate the efficacy of the Better Balance-CMT home-based balance intervention compared with treatment as usual, and to explore factors influencing its real-world implementation.
3. Methods
A randomised, single-blind, two-arm trial will be conducted with a parallel implementation study and economic evaluation. The 12-week intervention will be delivered at home by trained physiotherapists through three face-to-face sessions, supported by web-based materials and remote guidance, using self-management principles. Eighty-four participants will be recruited from six NHS hospitals in England. The primary outcome is change in Berg Balance Scale score, analysed using linear regression adjusted for baseline. A 12-week control period and an additional open-label phase will assess sustained engagement and carry-over effects. Co-production with patients and stakeholders will inform the intervention delivery and implementation strategy.
4. Results
Digital resource development for Better Balance-CMT is underway, with ongoing co-production activities to optimise usability and engagement.
5. Conclusions
Better Balance-CMT will be a scalable rehabilitation approach with potential to improve balance in people with CMT. Funded by the National Institute for Health Research, the trial is scheduled to begin at the end of 2026 with findings expected to inform clinical practice and wider implementation.

136 - Allied Health Professionals Neuromuscular Hub: Empowering Allied Health Professionals to support adults living with neuromuscular conditions

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1. Introduction
Access to specialist knowledge is essential for allied health professionals (AHPs) managing adults with neuromuscular conditions, which are often rare and complex. Limited access to expert-led training can create gaps in care delivery. An online physiotherapy module developed in 2016 demonstrated the value of digital education, prompting expansion to a broader multidisciplinary AHP audience with updated, evidence-based content.
2. Objectives
To develop a comprehensive digital learning hub for AHPs that provides evidence-based guidance on assessment and management of adult neuromuscular conditions, promotes awareness of patient needs, and enables monitoring of engagement and learning through platform analytics.
3. Methods
An expert panel of AHPs specialising in neuromuscular diseases co-developed and updated educational content into 15 structured modules. The programme, funded by Muscular Dystrophy UK in partnership with Treat-NMD, is hosted on an online learning platform (POD-LMS) and accessible via a dedicated website. Resources include recorded lectures, downloadable materials, references, and links to supplementary media.
4. Results
The AHP Neuromuscular Hub has been completed and peer-reviewed. It comprises 15 modules covering key areas such as assessment, exercise, fatigue, orthotics, respiratory care, dietetics, and self-management. Each module includes supporting resources and assessments, with downloadable certification upon completion.
5. Conclusions
This digital hub provides an accessible, scalable approach to improving AHP knowledge and skills in neuromuscular care. Its launch in February 2026 will enable widespread uptake, with ongoing monitoring of engagement to inform further development and optimise impact on clinical practice.

137 - Developing a model of balance impairment for people living with CANVAS: Protocol for a cross-sectional observational study

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1. Introduction
Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) is a rare neurological condition characterised by combined sensory neuropathy, cerebellar and vestibular dysfunction, leading to significant balance impairment and increased risk of falls. Rehabilitation for CANVAS is limited by a lack of condition-specific evidence and an incomplete understanding of how multi-system deficits interact to affect postural control.
2. Objectives
This study aims to characterise postural instability in people with CANVAS and develop a pragmatic model of balance dysfunction to inform future rehabilitation strategies and identify modifiable treatment targets.
3. Methods
A cross-sectional observational study will recruit approximately 30 adults with CANVAS from specialist clinics. Guided by the WHO International Classification of Functioning, Disability and Health (ICF), assessments will examine both impairments and activity limitations. Body function measures include proprioceptive thresholds, vestibulo-ocular reflex parameters, and cerebellar function using smooth pursuit and the Scale for the Assessment and Rating of Ataxia (SARA). Postural control will be evaluated using posturography under varied sensory conditions and during dynamic tasks. Functional balance, patient-reported outcomes, and falls (recorded at baseline and over six months) will also be assessed.
4. Results
The study will generate an integrated profile of balance impairment, combining physiological, functional, and patient-reported data. This will enable identification of key contributors to postural instability and highlight phenotypic patterns relevant to rehabilitation.
5. Conclusions
Findings will provide CANVAS-specific evidence to support the development of a clinically meaningful model of balance dysfunction and guide targeted rehabilitation interventions and future feasibility studies.

138 - Social Determinants of Health in San Antonio Area Myasthenia Gravis Patients

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Introduction:
Generalized Myasthenia Gravis is an autoimmune neuromuscular junction disorder causing fluctuating muscle weakness and affecting >50,000 people in the US. Despite multiple available therapies, many patients face barriers to access to care, contributing to increased disease burden.
Objective:
This research seeks to explore barriers to access by identifying the social determinants of health faced by Myasthenia Gravis (MG) patients treated at a university academic center or a county hospital-affiliated safety-net clinic.
Methods:
We conducted a retrospective chart review and collected data on demographics, home address, employment status, insurance coverage, comorbidities, emergency department (ED) visits, hospitalizations, MG-ADL scores, and clinic no-shows. Data was also collected on antibody profile, time to diagnosis, and treatment types.
Results:
We compared 39 patients seen at the county-affiliated hospital clinic (Group A) with 330 seen at the university academic center (Group B). Group A had higher proportions of Hispanic/Latino and Spanish-speaking patients, higher unemployment and disability rates, and lower use of private insurance. Over half of group A lived in the most disadvantaged neighborhoods. Group A also had higher rates of clinic no-shows, ED visits, and hospitalizations. Antibody profiles and time to diagnosis were similar between groups, however, Group A had lower use of oral immunomodulatory agents and newer infusion therapies.
Conclusion:
The groups varied in demographics, socioeconomic factors, treatment types and health outcomes, despite similar antibody profiles and time to diagnosis, suggesting that differences in access likely drive these disparities. Next steps include implementing dedicated outreach for disadvantaged MG patients.

139 - Investigating Neuromuscular Junction defects in Spinal Muscular Atrophy following central and peripheral SMN restoration

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Introduction
Spinal muscular atrophy (SMA) is associated with impaired neuromuscular junction (NMJ) transmission. We previously demonstrated persistent NMJ defects in adults treated with nusinersen, suggesting that systemic SMN restoration may be required to optimize NMJ function.
Objectives
To evaluate the impact of risdiplam on NMJ transmission compared with historical nusinersen-treated controls and examine associations with strength, function, mobility, and fatigue.
Methods
Adults with 5q-SMA treated with risdiplam for ≥12 months. Abnormal repetitive nerve stimulation (RNS) was defined as >10% compound muscle action potential (CMAP) decrement. Assessments included handheld dynamometry, modified SMAFRS, RULM, FSS, HFMSE, 6MWT, ATEND, ulnar CMAP and MUNE.
Results
Eighteen participants were included (median age 31 years, 56% female, 72% non-ambulatory). Ten participants (56%) demonstrated abnormal RNS decrement. Participants with abnormal decrement had a significantly lower median BMI (22.1 vs 31.1 kg/m^2, p=0.026), whereas age, sex, disease duration, treatment duration, and motor function scores were similar between groups. RNS decrement correlated with 6MWT distance (r=0.90, p=0.037), elbow flexion strength (r=0.54, p=0.022), hip abduction strength (r=0.51, p=0.031), and knee flexion strength (r=0.55, p=0.018). No significant associations were observed between RNS decrement and SMAFRS, ATEND, fatigue, CMAP, MUNE, or SMUP. Compared with historical nusinersen-treated controls (n=16), risdiplam did not improve NMJ transmission (p=0.80).
Conclusions
NMJ transmission defects remain prevalent in adults with SMA despite long-term risdiplam treatment. Associations between RNS decrement, mobility, and select strength measures suggest that NMJ dysfunction may contribute to residual weakness. These findings support continued investigation of NMJ transmission as a therapeutic target in SMA.

140 - Evaluation of nutrition in a cohort of adult patients with Spinal Muscular Atrophy (SMA): A preliminary analysis

Laura Domrose[1], Sarah Heintzman[1], Gia Cinkay[1], Songzhu Zhao[1], Bakri Elsheikh[1]
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INTRODUCTION
Limited research examines the nutritional status of adults with SMA. Metabolic irregularities and SMA related physical limitations place patients at risk for nutritional deficiencies.
OBJECTIVES
Nutrition is a modifiable factor that may improve health outcomes. Managing nutritional intake and metabolic abnormalities may affect functional abilities and overall health outcomes in SMA. We conducted a cross-sectional study to evaluate the nutritional status of SMA patients.
METHODS
Anthropometric data were collected from the EMR, and patient-reported surveys were conducted including: DHQIII Food Frequency Questionnaire, EAT-10, general GI symptoms questionnaire, demographic questionnaire, GPAQ physical activity questionnaire, and SMAFRS. Data were collected through a one-time virtual encounter and recorded in REDCap.
RESULTS
Twenty patients enrolled. BMI data showed five patients were obese, six overweight, eight normal weight and one underweight (<18). Sixteen completed EAT-10 (abnormal ≥3). Ten had a median score of 0.5 (range 0-1); six had a median score of 7.5, indicating swallowing difficulties. Two had a percutaneous endoscopic gastrostomy and both were non-ambulatory. EAT-10 scores were negatively correlated with vigorous/moderate recreational physical activity ($r = -0.52625$, $p = 0.0363$), indicating greater swallowing difficulties were associated with less recreational activity.
CONCLUSIONS
Addressing weight and obesity in adult SMA patients may present an opportunity to optimize nutrition and improve overall health outcomes. These findings highlight the need for targeted interventions to manage weight and support swallowing function as well as physical activity engagement to enhance overall health and quality of life.

141 - Remote Assessment of Central Nervous System Symptoms in Myotonic Dystrophy Type 1

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Introduction: Myotonic dystrophy type 1 (DM1) is an autosomal dominant muscular dystrophy with significant phenotypic variability in severity, multi-systemic involvement, and age of onset. Central nervous system (CNS) symptoms are frequently reported and have significant impact on quality of life for patients.
Objectives: Evaluate the CNS phenotype of patients with DM1 using remote assessments.
Methods: As part of REACH-DM (NCT07505342) and REACH-DM Kids (NCT07630389), individuals with DM1 underwent structured interviews and completed observer-reported outcomes measures (affected children) and patient reported and performance outcome measures (affected adults). For children, these included assessments of adaptive function (Vineland), executive function (BRIEF2), and social skills (SRS). For adults, these included assessment of sleep (FDS), apathy (AES), and executive function (Trail Making Test). Subjects also completed functional assessments. Data was analyzed using descriptive statistics.
Results: Ninety patients with DM1 aged 1-81 years completed at least one remote assessment (19 pediatric and 71 adult patients). In children, memory/thinking problems were reported in 68% (n=13) and hypersomnolence in 26% (n=5). Clinically abnormal scores were noted in 72% (n=13) for the Vineland Composite, 75% (n=9) for BRIEF-2 composite, and 62% (n=8) for SRS-2 Total. In adults, memory/thinking problems were reported in 22.8% (n=24) and hypersomnolence in 80.3% (n=57). Mean FDS total was 14.81 (std=2.97) and mean AES total was 53.43 (std=6.33). Additional analyses are ongoing.
Conclusions: Remote assessments in DM1 reveal frequent neurobehavioral impairments in children and prominent hypersomnolence and apathy in adults. Remote assessments may represent a scalable framework for evaluating and tracking CNS symptom burden in DM1.

142 - AAV9-KIF5A Gene Therapy as a Strategy to Improve Motor Unit Repair and Recovery in a Peripheral Nerve Transection Mouse Model

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Kinesin family member 5A (KIF5A) is an anterograde motor protein that is implicated in the pathogenesis of hereditary neuropathies, hereditary spastic paraparesis, and amyotrophic lateral sclerosis (ALS). Recently, our laboratory reported the phenotype of the first mouse model of an ALS-associated KIF5A mutation, which had an impairment in motor unit recovery following peripheral nerve injury. We have extended these studies and find the impairment in motor unit repair is related to the protein expression levels of KIF5A in neurons, suggesting that ALS-associated KIF5A mutations result in a reduction of KIF5A availability. We hypothesize that restoration or upregulation of KIF5A may rescue this phenotype and that the increase of KIF5A may enhance motor unit repair. To directly evaluate the effect of KIF5A expression on motor unit repair, we have developed an adeno-associated virus (AAV)-based gene therapy approach to increase KIF5A expression in the central nervous system (CNS) of a mouse model of sciatic nerve transection. In our ongoing study, we have identified that AAV-mediated overexpression increases KIF5A levels in the CNS without any observed toxicity up to 8 weeks post-injection. Effects of supraphysiological KIF5A expression on electrophysiological and motor function behavioral assays will be presented. Data from this study will establish a strong proof-of-concept premise for the upregulation of KIF5A as a novel therapeutic target.

143 - Refractory Myasthenia Gravis Four Years After Stiff-Person Spectrum Disorder: Lessons for Malignancy Surveillance

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Introduction:
Stiff-person spectrum disorder (SPSD) is a rare autoimmune neurological disorder that may occur as a paraneoplastic syndrome, with thymoma representing an uncommon but increasingly recognized association. The coexistence of SPSD, thymoma, and myasthenia gravis (MG) remains particularly rare.
Case Report:
A patient with GAD65-positive SPSD responded well to intravenous immunoglobulin (IVIG) and remained clinically stable for four years before developing refractory MG. Evaluation revealed a giant thymoma (5.8 × 5.3 × 4.1 cm). The MG course was complicated by respiratory failure requiring mechanical ventilation and tracheostomy. Neuromuscular symptoms improved following thymectomy and initiation of efgartigimod. Unfortunately, our patient experienced a cardiac arrest and post-anoxic status epilepticus, passing away after transition to comfort care.
Methods:
Clinical data, laboratory studies, neuroimaging findings, treatment course, and relevant literature were reviewed.
Results:
The combination of SPSD, thymoma, and refractory MG represented a rare autoimmune overlap syndrome. Although SPSD symptoms remained stable on IVIG for several years, a giant thymoma was later identified, and the patient subsequently developed refractory MG. Neuromuscular symptoms improved following thymectomy and efgartigimod therapy.
Conclusions:
Standardized guidelines for malignancy screening in GAD65-positive SPSD are lacking. This case highlights the importance of malignancy screening at the time of SPSD diagnosis and continued surveillance during follow-up, as an underlying neoplasm may become clinically apparent years after the initial neurological presentation. Earlier identification and treatment of an underlying malignancy may influence clinical outcomes.

145 - Remote Monitoring and Management of Chemotherapy Induced Peripheral Neuropathy (CIPN-REMOTE), a Randomized Single Blinded Study of a Novel Remote Care Delivery Model

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Introduction: CIPN affects 40-60% of patients receiving neurotoxic chemotherapy and is a major cause of morbidity and reduced quality of life. CIPN-REMOTE aims to improve outcomes through app-based symptom monitoring with remote management by trained nurse practitioners (NPs) utilizing an evidence-based care algorithm.
Methods: CIPN-REMOTE is a 12-week single-blinded randomized controlled trial of a novel CIPN care model. Adults who completed neurotoxic chemotherapy within the last 18 months were randomized to Usual Care (UC) or Symptom Care at Home with NP follow up (SCH-NP). Participants log symptoms daily using an app, website or automated phone system. The clinical oncologist provides standard of care treatment to the UC group. In the SCH-NP group, any moderate to severe symptom triggers an NP call within 24 hours. The primary endpoint is change in NTSS-6 between a 7-day run-in and weeks 11-12. Secondary endpoints include CIPN specific sign, symptom and quality of life outcomes.
Results: 253 participants have completed the study. Preliminary blinded analysis using descriptive statistics alone reveals 125 were randomized to group 1 (G1) and 128 to group 2 (G2). G1 experienced a 1.09 +/- 4.27 and G2 a 2.26 +/- 3.81 improvement in NTSS-6. 49.6% of those in G1 had a clinically meaningful improvement compared to 59.4% in G2.
Conclusions: TREMOTE-CIPN has completed enrollment with the last participant expected to exit in Nov. 2026. Preliminary analysis indicates meaningful improvement in CIPN symptoms in both study groups suggesting the home monitoring and remote care delivery model is a promising approach.

II. Industry-Led Abstracts

2 - Post hoc analyses from the Phase 3 SAPPHIRE study evaluating apitegromab in patients with nonambulatory type 2 or 3 spinal muscular atrophy

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Introduction
The Phase 3 SAPPHIRE study (NCT05156320) showed 12mo of apitegromab, an investigational muscle-targeted treatment, reliably improved motor function outcomes for patients with SMA also receiving SMN-targeted treatments, nusinersen or risdiplam.
Objectives
Evaluate the impact of several baseline characteristics on HFMSE outcomes following apitegromab (10 and 20mg/kg) or placebo treatment.
Methods
Post hoc analyses were conducted for the SAPPHIRE population (aged 2-21y). Outcomes are reported as LSM difference (SE) in HFMSE change from baseline for apitegromab vs placebo.
Results
Following 12mo of treatment, the greatest change in HFMSE score was observed for patients with ≤2y of current SMN-targeted treatment: LSM difference (SE) of 2.9 (2.08), favoring apitegromab. For patients with longer treatment exposure (3-4y, 5-6y, and ≥7y), LSM difference (SE) was 1.7 (1.93), 0.8 (0.87), and 1.9 (1.44), respectively. Notable increases in HFMSE score were also observed in patients receiving apitegromab ≤5y since symptom onset: LSM difference (SE) of 2.1 (2.02). Functional improvements continued to favor apitegromab for patients treated 6-10y and ≥11y since symptom onset, with respective LSM differences (SE) of 0.8 (0.81) and 1.7 (1.10). Additionally, apitegromab was associated with greater functional benefit in patients with higher baseline motor function (HFMSE score ≥31): LSM difference (SE) of 2.6 (1.08). Patients with HFMSE baseline scores of ≤20 or 21-30 also experienced meaningful functional gains following apitegromab treatment: LSM difference (SE) of 0.8 (0.73) and 1.6 (1.93).
Conclusions
These data show that apitegromab treatment resulted in functional benefits regardless of SMN-targeted treatment exposure, SMA symptom onset, and motor function status.

3 - Assessing the impact of 'any point differences' or 'stability' in the Hammersmith Functional Motor Scale-Expanded on the quality of life of patients with SMA

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Introduction

Validated motor function assessments (eg, HFMSE) are essential for measuring SMA treatment efficacy; however, the meaningfulness of score changes often require patient/caregiver insights.

Objectives

To understand the real-world implications of improvement or stabilization in HFMSE related-tasks, we conducted 60-minute semi-structured qualitative interviews with patients living with SMA and/or their caregivers.

Methods

Using the constant comparative method, we identified four life domains that participants emphasized as being tied to motor function ability: ADLs, psychosocial wellbeing, independence, and QoL. Here we focus on perspectives from pediatric (caregiver proxy/patient-caregiver dyads; aged 2-17y; n=29) and adult (aged ≥18y; n=32) patients related to QoL.

Results

There was a general consensus among pediatric (mean age [SD], 9.2 [4.6]; current function: 'sitter' [59%] and 'walker' [41%]) and adult (mean age [SD], 44.0y [15.5]; current function: 'sitter' [72%] and 'walker' [28%]) patients that gaining or retaining the ability to eat, sleep, stretch/reposition, practice self-care, transfer, navigate their environment, work, and play/participate in daily activities would be important for their QoL. For example, improving by a single point in the props on arms HFMSE task would allow a pediatric patient (sitter; caregiver proxy) to participate in school activities, "She would be able to… prop up and color and things like that while on their stomach." Additionally, an adult patient (walker) highlighted the benefits of stability in HFMSE rolling tasks for sleep, "… I'm able to maneuver myself…get out of bed… get more comfortable."

Conclusions

These findings underscore the importance of integrating patient/caregiver perspectives for understanding clinically meaningful change.

10 - Evaluation of the Effect of Empasiprubart on Nerve Morphology in Multifocal Motor Neuropathy: Study Design

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Introduction: Multifocal motor neuropathy (MMN) is rare, chronic, autoimmune neuromuscular disease that is predominantly driven by immune-mediated complement deposition. Nerve enlargement is characteristic on ultrasound; however, post-treatment data are limited. Empasiprubart, a first-in-class, humanized, monoclonal antibody that binds complement factor C2, inhibits classical and lectin pathway activation. Empasiprubart showed a favorable safety profile and clinical proof-of-concept in the phase 2 ARDA trial. A phase 3 trial is ongoing.
Objectives: This study will evaluate the effect of intravenous (IV) empasiprubart on nerve morphology by ultrasound in MMN.
Methods: This phase 1b, open-label, single-treatment group study will enroll 30-60 adults. The main cohort includes participants with definite or probable MMN receiving maintenance IVIg. An ancillary cohort includes participants with possible MMN and/or those not meeting the IVIg inclusion criteria for the main cohort. Inclusion criteria include ultrasound-confirmed nerve enlargement and a Rasch-built Overall Disability Scale for Multifocal Motor Neuropathy (MMN-RODS) centile score ≤90. The study includes screening (≤8 weeks), treatment (48 weeks), and safety follow-up (60 weeks). IV empasiprubart will be administered on Days 1 and 8, then every 4 weeks. Nerve ultrasound will occur at screening and on Day 1 and Weeks 12, 24, and 48.
Results: The primary endpoint is change from baseline in nerve cross-sectional area at Week 24. Secondary endpoints include muscle strength/function/dexterity (modified Medical Research Council-14 sum score, grip strength, and 9-hole peg test), patient-reported outcomes (MMN-RODS), and safety.
Conclusion: This study will evaluate the empasiprubart's effect on nerve morphology by ultrasound and clinical outcomes in MMN.

11 - Long-Term Safety and Efficacy Data of Empasiprubart in Multifocal Motor Neuropathy: Phase 2 ARDA+ Study

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Introduction: Empasiprubart (EMPA) binds C2, inhibiting the classical and lectin complement pathways, leaving the alternative pathway intact.
Objectives: ARDA+ (NCT05405361) assesses long-term safety and efficacy of intravenous EMPA in adults with multifocal motor neuropathy (MMN).
Methods: Participants completing the 16-week, double-blind ARDA trial and entering the long-term open label-extension (ARDA+) received EMPA. Efficacy endpoints at Week 64 included changes from ARDA baseline in grip strength (GS, most-affected hand; kPa) and MMN Rasch-built Overall Disability Scale (MMN-RODS).
Results: Interim results are reported (cutoff: 4 June 2025 [1 year after the last participant rolled over]; median treatment duration: 74 weeks) for this analysis endpoint. Cohort 1: EMPA/EMPA (n=17; received EMPA in ARDA and continued in ARDA+) and placebo (PBO)/EMPA (n=7; received PBO in ARDA and switched to EMPA in ARDA+); cohort 2: EMPA/EMPA (n=18) and PBO/EMPA (n=9). At cutoff, 44/51 participants had ≥1 year with EMPA and remained on treatment. EMPA demonstrated a consistent safety profile, with no deaths/new safety concerns. At Week 64, median change (Q1-Q3) from ARDA baseline in GS (kPa) was 16.7 (2.7-30.7; EMPA/EMPA) and 8.3 (4.0-27.0; PBO/EMPA) in cohort 1, and 44.7 (18.0-53.3) and 10.2 (2.7-19.3) in cohort 2. Median MMN-RODS (Q1-Q3) increased by 9.0 (0.0-23.0; EMPA/EMPA) and 18.0 (-2.0-27.0; PBO/EMPA) in cohort 1, and 13.5 (6.0-32.5) and 0.5 (-2.0-4.0) in cohort 2.
Conclusion: In ARDA+, participants receiving EMPA maintained improvements across efficacy and safety endpoints; those switching from PBO experienced new improvements after EMPA initiation, supporting complement system involvement in MMN pathophysiology.

12 - Design of a Phase 2a Study to Evaluate the Safety, Efficacy, and Tolerability of Intravenous Empasiprubart as an Add-On Therapy to Intravenous Efgartigimod in Adult Participants With Generalized Myasthenia Gravis

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Introduction
Generalized myasthenia gravis (gMG) is an immunoglobulin G (IgG)-mediated disease that manifests differently in each patient. In some, a single therapy may insufficiently address all pathogenic mechanisms mediated by IgG autoantibodies, such as complement activation. Efgartigimod, an IgG1 Fc fragment, blocks neonatal Fc receptor-mediated IgG recycling. Empasiprubart, an IgG1 antibody, selectively inhibits complement C2. For patients with partial response to efgartigimod, empasiprubart add-on therapy could further improve outcomes.
Objective
To present the design of a Phase 2a, proof-of-concept study evaluating safety, efficacy, and tolerability of empasiprubart add-on therapy in participants with gMG who partially respond to efgartigimod. This is the first gMG regimen assessed within a platform study.
Methods
The study consists of 3 parts over ~54 weeks. Part A: ~50 adult participants with acetylcholine receptor antibody-positive (AChR-Ab+) gMG receive 1 efgartigimod treatment cycle (4 once-weekly intravenous infusions followed by a 4-week treatment-free period). Part B: participants with partial response to efgartigimod (Myasthenia Gravis Activities of Daily Living [MG-ADL] improvements ≥2 with total remaining ≥5) receive 2 cycles of efgartigimod with intravenous empasiprubart coadministered at the first and last infusions of each cycle. Part C (safety follow-up): 4 additional cycles with efgartigimod monotherapy. Participants not meeting partial response criteria during Part A proceed to Part C.
Results
Primary endpoints will evaluate safety and tolerability during Parts A and B. Secondary endpoints will evaluate efficacy, including MG-ADL.
Conclusions
Results of this study will provide proof-of-concept data on empasiprubart as an add-on therapy to efgartigimod for adults with AChR-Ab+ gMG.

14 - Pathway-Selective Complement Blockade and its Impact on Bacterial Cell Killing

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Introduction: The complement system plays a key role in innate immunity against gram-positive and -negative bacteria. Although inhibition of the terminal complement pathway may increase infection risk, selectively blocking activation pathways upstream of the central complement component C3 may better preserve innate activity.
Objectives: To evaluate how inhibition at different points in the complement cascade affects bacterial killing.
Methods: Four gram-negative species (*Neisseria meningitidis* [H44/76; 2996]; *Haemophilus influenzae* [Eagan; 2093117]; *Escherichia coli* [MG1655; EC014]; and *Klebsiella pneumoniae* [Kpn002 (SF002); Kpn007 (SF007)]) and two gram-positive species (*Streptococcus pneumoniae* [LAC002; TIGR4] and *Staphylococcus aureus* [Newman; Newman ΔSpA/Sbi]) were studied. The bacterial strains were incubated in pooled human serum and studied for C3b complement deposition and bacterial killing with and without complement blockade. For gram-negative species, bacterial killing by serum was assessed using two methods: bacterial survival was measured by enumerating colony-forming units, and complement-mediated membrane permeabilization was measured using the membrane-impermeable deoxyribonucleic acid dye SYTOX Green. *Streptococcus pneumoniae* killing and *Staphylococcus aureus* phagocytosis were assessed using freshly isolated human polymorphonuclear neutrophils. Four complement inhibitors targeting different complement pathway components were tested. These were preincubated in 80% serum for 30 minutes before diluting to 5% and 50% in the final assay conditions. Control conditions included buffer, serum without complement inhibitor, and heat-inactivated serum.
Results: Data will describe how inhibition of different complement components affects bacterial killing.
Conclusion: C2 inhibition preserved complement-mediated bacterial killing across diverse strains, offering insight into how targeting specific complement proteins can effectively modulate immune responses against bacterial pathogens.

18 - Quality of Life in Patients with Generalized Myasthenia Gravis Achieving Sustained vs Transient Minimal Symptom Expression in the Phase 3 Vivacity-MG3 Trial

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Background: In the Vivacity-MG3 trial (NCT04951622), generalized myasthenia gravis (gMG) patients receiving nipocalimab demonstrated improved and sustained efficacy vs placebo. Minimal symptom expression (MSE; MG-ADL score ≤1), is a treatment goal in gMG. However, outcomes associated with achieving sustained MSE have not been fully explored.
Objective: To evaluate MSE treatment response and quality-of-life (QoL) in patients achieving sustained vs transient MSE in Vivacity-MG3.
Methods: Participants were stratified into groups based on MSE status over the 24 week double-blind phase: never achieved MSE (No-MSE), achieved MSE sustained for ≥8 weeks (sustained-MSE), achieved MSE ≥1 times but not sustained for ≥8 weeks (transient-MSE). Analyses included likelihood (odds ratio [OR]) of achieving sustained or transient MSE (reference=No-MSE) for nipocalimab vs placebo and MG-QoL-15r total score least-squares mean (LSM) change from baseline (CFB) to week 24 (W24) compared across MSE groups.
Results: Of 153 patients, 35 achieved MSE by W24 (nipocalimab+SOC, n=24/77; placebo+SOC, n=11/76); 19 had sustained MSE (nipocalimab+SOC, n=15/77; placebo+SOC, n=4/76). Nipocalimab- vs placebo-treated patients were significantly more likely to achieve sustained MSE (OR [95% CI]: 4.35 [1.37,13.81], p=0.013). At W24, sustained vs transient MSE patients demonstrated significantly greater improvements in MG-QoL-15r (LSM CFB [95% CI]: −12.7 [−16.3,−9.2] vs −8.7 [−12.5,−5.0], p=0.016) and vs those with No MSE (−4.1 [−7.0,−1.3], p<0.001).
Conclusion: Nipocalimab-treated patients were 4-times more likely to achieve and sustain MSE for ≥8-weeks than placebo. Those achieving sustained vs transient MSE demonstrated greater improvements in QoL. Sustained MSE may be a more impactful treatment goal for gMG patients receiving advanced treatments.

19 - Long-term safety and efficacy of nipocalimab: Approximately 2 years follow-up results from the open-label extension phase of Vivacity-MG3 study

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BACKGROUND: Long-term sustained symptom control remains an important treatment goal in generalized myasthenia gravis (gMG). In a broad population of autoantibody-positive gMG patients, nipocalimab (neonatal Fc-receptor blocker) demonstrated substantial improvement in MG-Activities of Daily Living (MG-ADL) scores over the 24-week double-blind (DB) phase and over 60 weeks (W) of open-label extension (OLE) in Vivacity-MG3 (NCT04951622).
OBJECTIVE: To assess the long-term safety and efficacy of nipocalimab in gMG patients from the ongoing Vivacity-MG3 OLE phase through Week 96.
DESIGN/METHODS: Adult patients with gMG (MGFA Class II-IV), inadequately controlled (MG-ADL≥6) on standard-of-care (SOC) therapy were randomized 1:1 to nipocalimab+SOC or placebo+SOC in the 24-week Vivacity-MG3 DB, followed by an option to enter the OLE. Efficacy and safety were evaluated in seropositive (anti-AChR positive, anti-MuSK positive, and/or anti-LRP4 positive) patients who received ≥1 dose of study treatment.
RESULTS: In the efficacy analysis set (N=137) during OLE, median (range) total duration of treatment for placebo/nipocalimab (n=66) and nipocalimab/nipocalimab (n=71) groups was 69.1W (8-128W) and 62.1W (8-128W) respectively. Among patients with 96W of treatment, mean (SD) change from DB baseline (CFB) in MG-ADL for the placebo/nipocalimab and nipocalimab/nipocalimab groups was -6.69 (3.39) and -6.47 (4.62), CFB in Quantitative-Myasthenia-Gravis (QMG) was -5.81 (4.11) and -5.97 (4.97), and Mean (SD) percent CFB in IgG was -63.24 (14.31) and -64.06 (12.91), respectively. No new safety concerns were reported.
CONCLUSIONS: In autoantibody-positive patients with gMG, long-term treatment with nipocalimab demonstrated sustained disease control through the 24-week phase 3 Vivacity-MG3 study and the 96-week OLE (120 weeks total).

22 - Efgartigimod in Acetylcholine Receptor Antibody Negative Generalized Myasthenia Gravis: Efficacy and Safety Results from ADAPT SERON

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Introduction
Approximately 15%-20% of patients with generalized myasthenia gravis (gMG) are acetylcholine receptor antibody (AChR-Ab) negative. Approved treatment options for this population remain limited. Efgartigimod is a human immunoglobulin G1 (IgG1) antibody Fc fragment that reduces IgG levels via neonatal Fc receptor blockade.
Objective
To evaluate efficacy and safety of efgartigimod in AChR-Ab negative gMG in a Phase 3 trial (ADAPT SERON).
Methods
An MG diagnostic adjudication committee confirmed gMG diagnoses. In double-blind, placebo-controlled Part A, participants were randomized 1:1 to 4 once-weekly infusions of 10 mg/kg intravenous efgartigimod or placebo followed by 5-week follow-up. Part B is an ongoing open-label period.
Results
Overall, 119 participants (n=40, MuSK-Ab+; n=6, LRP4-Ab+; n=73, triple-seronegative) were randomized to efgartigimod (n=58) or placebo (n=61). Efgartigimod demonstrated significantly greater improvement in mean Myasthenia Gravis Activities of Daily Living (MG-ADL) total score from baseline to Week 4 (primary endpoint), relative to placebo (P=0.007), with least squares mean change from baseline (90% CI) of −3.35 (−3.98 to −2.72) and −1.90 (−2.51 to −1.28) in each group, respectively. Improvements in MG-ADL scores were observed across all three serostatus subgroups and 30.8% of participants achieved MSE at any time during their first 3 cycles of efgartigimod. Among participants initially treated with efgartigimod, 91.2% achieved clinically meaningful improvement (≥2-point MG-ADL reduction) at Week 4 of any of the first 3 cycles. Efgartigimod was well tolerated, consistent with prior studies.
Conclusions
Efgartigimod demonstrated statistically significant and clinically meaningful improvements in MG-ADL total scores and was well tolerated in AChR-Ab negative gMG.

23 - Durable Responses to Low-Dose Investigational Gene Therapy BB-301 in Patients with Oculopharyngeal Muscular Dystrophy (OPMD) with Dysphagia at 12-Months and 24- Months Post-Treatment and Improved Depth of Response to High-Dose BB-301

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OPMD is an autosomal-dominant degenerative muscle disorder characterized by progressive life-threatening dysphagia and ptosis. BB-301, a gene therapy designed to reduce dysphagic symptoms in OPMD, is being evaluated in a phase 1b/2a, first-in-human study (NCT06185673).
Patients diagnosed with OPMD who were enrolled into the Benitec Natural History (NH) study for ≥ 6 months are eligible to screen onto the BB-301 phase 1b/2a study. Each patient serves as their own control. Clinical and radiographic assessments conducted during the pre-treatment period are compared to an identical set of post-treatment assessments. Serial efficacy assessments comprise videofluoroscopic swallowing studies [VFSS] and a validated patient reported outcome instrument (Sydney Swallow Questionnaire [SSQ]).
A Responder Analysis was developed to facilitate standardized evaluation of BB-301 efficacy. Parameters underlying Response characterization were derived from literature-based methods and include SSQ, VFSS, and cold water timed drinking test.
Six Patients in cohort 1 safely received low-dose BB-301. Six cohort 1 Patients have completed the 12-month statistical follow-up period for the phase 1b/2a study (completers), with 24-month post-treatment results available for Patient 1.
All cohort 1 completers were formal Responders to BB-301, demonstrating durable response to BB-301. At 24-months post-BB-301 treatment, Patient 1 continued to demonstrate robust, disease-modifying outcomes, with deepening improvements in VFSS and SSQ assessments.
Patient 1 and Patient 2 of cohort 2 safely received high-dose BB-301. The interim clinical results demonstrate robust depth of response, with broad improvements in swallowing function.
There have been no treatment-related serious adverse events.

26 - Safety and Efficacy of Riliprubart in CIDP: 76-week Phase 2 Trial Results

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Introduction: Riliprubart, a first-in-class humanized IgG4-monoclonal antibody, selectively inhibits activated-C1s in the classical-complement pathway and can be self-administrated subcutaneously via an auto-injector.
Objective: To report efficacy and safety of riliprubart at Week-76 in participants with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP; NCT04658472).
Methods: This open-label, Phase-2 trial evaluates riliprubart in Standard-of-care (SoC)-Treated, SoC-Refractory, and SoC-Naïve participants for 24-weeks (Part-A) and 52-weeks (optional Part-B). Primary endpoint (Part-A): %-participants relapsing (SoC-Treated)/responding (SoC-Refractory/Naïve); defined as ≥1-point change in adjusted Inflammatory Neuropathy Cause and Treatment (aINCAT) score. Part-B: safety and efficacy-durability based on %-relapse-free participants (SoC-Treated)/sustained-response (SoC-Refractory/Naïve); defined as no-increase in aINCAT score ≥2-points at Week-76 relative to Week-24. Exploratory endpoints: additional efficacy measures, change in total-complement, and plasma NfL levels.
Results: At Week-24, 87% (N=42/48) SoC-Treated participants improved/remained stable (52% improved; N=25/48) after switching to riliprubart. 50% (N=9/18) SoC-Refractory, and 75% (N=9/12) SoC-Naïve participants responded. As of April-2025, 74% (N=58/78) entered and 83% (N=48/58) completed Part-B (ongoing:2% [N=1/58]; discontinued:16% [N=9/58]). In SoC-Treated group, at least 80% (N=32/40) who improved/remained stable in Part-A continued to be relapse-free. At least 78% (N=7/9) SoC-Refractory and 86% (N=6/7) SoC-Naïve participants who responded in Part-A had sustained-response. Improvement across all groups was consistent across several outcome measures. Sustained reduction of complement activity and 35% NfL reduction were demonstrated. At least one treatment-emergent adverse event was reported in 74% (N=58/78) participants. Full Part-B data will be presented at the meeting.
Conclusions: Week-76 results suggest sustained clinical benefits of riliprubart in broad spectrum of participants with CIDP, supporting development in Phase-3.

27 - Riliprubart in CIDP: Time and Magnitude of Response Analysis from a Phase-2 Trial

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Introduction: Riliprubart, a first-in-class humanized IgG4-monoclonal antibody, selectively inhibits activated-C1s in classical complement pathway and can be self-administered subcutaneously via auto-injector. In Phase-2 trial (NCT04658472), riliprubart demonstrated favorable safety and encouraging efficacy in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).
Objective: To present time and magnitude of response analyses to characterize clinical benefits of riliprubart.
Methods: The open-label Phase-2 trial evaluated riliprubart across three groups: Standard-of-care (SoC)-Treated, SoC-Refractory, and SoC-Naïve. Participants received 24-week treatment (Part-A), followed by optional 52-week treatment-extension (Part-B). Primary endpoint (Part-A) evaluated %-participants relapsing in SoC-Treated (≥1-point increase in adjusted Inflammatory Neuropathy Cause and Treatment [aINCAT] disability score) and %-participants responding in SoC-Refractory/Naïve groups (≥1-point decrease in aINCAT score). This post-hoc analysis focused on INCAT responders (≥1-point decrease) in Part-A, and evaluated time-to-first-response, and participant proportion with deep response (≥2-point decrease), overall, and by baseline INCAT score (3-4 versus ≥5).
Results: Among 43 INCAT responders in Part-A, first INCAT response was observed as early as Week-2 with ≥44% of first responses achieved by Week-4, and ≥89% by Week-12 in all three groups. At the last INCAT assessment through Week-24, 44% (19/43) responders achieved deep response with higher rates in participants with severe baseline impairment (INCAT ≥5: 69% [11/16]) versus moderate impairment (INCAT 3-4: 38% [8/21]).
Conclusions: Riliprubart provided rapid and substantial improvement in INCAT score with majority of responders achieving first response by Week-12 and nearly half of responders achieving deep response (≥2-point decrease); supporting Phase-3 development of riliprubart as a potential treatment for people with CIDP.

28 - Telemedicine-Based INCAT Assessment in CIDP: Reliability and Agreement Between Nurse and Neuromuscular Expert Virtual Evaluations

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Introduction:
Inflammatory Neuropathy Cause and Treatment (INCAT) scale is a validated disability measure in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Recent advances in telemedicine and patient-centric care have driven the demand for virtual-INCAT assessment to facilitate remote monitoring.
Objective:
To evaluate inter-rater reliability of virtual-INCAT assessments among multiple assessors and examine agreement between registered nurse (RN)-administered assessments and neuromuscular-experts' evaluations to establish if RN-assessments can reliably replicate expert findings.
Methods:
We conducted a virtual-INCAT validation sub-study as a part of the ORBIT-CIDP study (**O**bservational, **R**eal-world, Digital **B**iomarker, and **I**ntegrated **T**reatment Outcomes in CIDP; NCT06968975); planned to enroll 200 participants with ≥3 months of therapy and residual disability for virtual-INCAT assessments by RNs using a telehealth platform with 20 randomly selected participants at the time of evaluation. Sessions were video recorded and were subjected to independent INCAT scoring by 7 neuromuscular-specialists. Outcomes included general agreement and scoring reliability between RNs and other experts. Interobserver-agreement was measured using Kendall W coefficient, Fleiss-kappa, mean absolute deviation, and pairwise agreement reliability by interclass correlation coefficients. Pairwise RN vs expert agreement was measured similarly.
Results:
To be presented during the congress.
Conclusions:
This study will provide evidence on the reliability of virtual-INCAT assessments by establishing inter-rater concordance between clinical experts and RNs. If validated, this could transform CIDP patient evaluation by enabling remote monitoring in clinical trials, expanding access in resource-limited settings, and reducing patient burden. This study establishes groundwork for comparing virtual and in-person assessments to validate virtual-INCAT as a reliable and accessible standard-of-care.

29 - ORBIT-CIDP: A Real-World CIDP Study Leveraging Digital and AI-Powered Patient-Centric Innovation

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Introduction:
People with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) often experience residual disability, mobility limitations, and neurological deficits. These challenges increase the burden of regular, in-person clinical assessments required for clinical research. ORBIT-CIDP (**O**bservational, **R**eal-world, Digital **B**iomarker, and **I**ntegrated **T**reatment Outcomes; NCT06968975) addresses this gap by implementing telehealth-based approach integrating artificial intelligence (AI), digital biomarkers, and patient-centric data collection.
Objective:
To describe the ORBIT study, an innovative, first-of-its-kind study focused on patient-centric approaches to CIDP research.
Methods:
Study includes 200 US adults (≥18 years) with CIDP who have received therapy for ≥3 months, have residual disability, impairment, or neurologic deficits. Exclusion criteria include participation in interventional clinical trials. The primary objective is to characterize disability changes over up-to 2-years using the patient-reported Inflammatory Rasch-built Overall Disability Scale (IRODS) score.
The secondary objective is to characterize change in disability by the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) score, including assessing the reliability of virtually administered INCAT. The study will also assess novel digital biomarkers including video-AI movement assessments and insole-derived gait analysis.
Results:
To date, 124 participants have been enrolled in ORBIT-CIDP study. Of which 62.1% are female; 82.3% are white, and 89.5% are not Hispanic or Latino. Additional data will be presented at the congress.
Conclusions:
ORBIT-CIDP pioneers a direct-to-patient approach in CIDP research, enabling real-world disability assessment and feasibility of virtual INCAT administration. By integrating novel digital biomarkers, this study reduces the burden of clinical visits while potentially validating remote monitoring methods, ultimately accelerating patient-centered research in CIDP.

31 - Corticosteroid Usage in Patients with Generalized Myasthenia Gravis Receiving Nipocalimab: Findings from Open-Label Extension Phase of the Phase 3 Vivacity-MG3 Study

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Background: Nipocalimab demonstrated sustained disease control in generalized myasthenia gravis (gMG), improving MG-ADL and QMG scores versus placebo during the Vivacity-MG3 (NCT04951622) 24-week double-blind phase and through Week 60 of the open-label extension (OLE). Corticosteroid dose adjustment was prohibited during the double-blind phase but permitted in OLE, where all patients received nipocalimab.
Objective: To characterize corticosteroid usage, dose reduction/discontinuation, and symptom improvement during the Vivacity-MG3 OLE.
Methods: Corticosteroid dose reductions to ≤20, ≤15, ≤10, and ≤5 mg/day prednisone-equivalent were evaluated through OLE Week-60. Among patients achieving low corticosteroid dose (≤10 or ≤5mg/day), proportions achieving meaningful clinical improvement (MCI; ≥2-point MG-ADL improvement), minimum symptom expression (MSE; MG-ADL=0 or 1), and ≥8-week sustained outcomes were evaluated.
Results: Of 89 patients receiving corticosteroids at OLE baseline (placebo/nipocalimab:44 [49%], nipocalimab/nipocalimab:45 [51%]), 45% reduced/discontinued corticosteroids by Week-60; mean dose decreased from 23 to 10 mg/day prednisone-equivalent. Dose reduction to ≤20, ≤15, ≤10, and ≤5 mg/day prednisone-equivalent were achieved by 85.4%, 71.9%, 60.7%, and 33.7%, respectively. Among patients reaching ≤10 mg/day (n=54), 98.1% achieved MCI, 44.4% MSE, and 94.4% and 24.1% ≥8-week sustained MCI and MSE, respectively. For those reaching ≤5 mg/day (n=30), 100.0% achieved MCI, 60.0% MSE, and 93.3% and 33.3% ≥8-week sustained MCI and MSE, respectively.
Conclusion: Through OLE Week-60, nearly half of patients receiving corticosteroids at baseline reduced or discontinued corticosteroids. Many patients who tapered to low-dose corticosteroid (≤10 or ≤5mg/day) sustained MCI and/or MSE for ≥8-weeks, supporting the corticosteroid-sparing effect of nipocalimab and concurrent meaningful clinical improvement in nipocalimab-treated patients with gMG.

32 - Pregnancy Enhanced Tracking with Neonatal and Infant Assessment (PETUNIA): Design of a Safety Study for Nipocalimab in Generalized Myasthenia Gravis

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Introduction:
Generalized myasthenia gravis (gMG) is a rare autoantibody-mediated disease frequently affecting individuals of childbearing potential. Nipocalimab is a neonatal Fc receptor blocker currently approved in the U.S., Europe, and other regions globally for treatment of gMG. However, its safety has not been studied in pregnant individuals with gMG.
Objective:
Pregnancy Enhanced Tracking with Neonatal and Infant Assessment (PETUNIA) aims to determine the prevalence of pregnancy, maternal, and infant outcomes after exposure to nipocalimab during pregnancy.
Methods:
PETUNIA is a global, non-interventional study using an enhanced pharmacovigilance approach aiming to estimate the prevalence of pregnancy outcomes, maternal complications, and neonatal and infant health outcomes among pregnant individuals with gMG exposed to nipocalimab in the post-marketing setting. From time of first approval, prospective and retrospective reports of nipocalimab exposure during pregnancy will be followed through the end of pregnancy, and for corresponding live births, through one year of life, via structured, targeted questionnaires administered to healthcare providers. The projected sample size is ≥162 total pregnancies with 50 prospectively reported over a 10-year-period from geographies where nipocalimab is approved.
Results:
Primary endpoints include pregnancy outcomes and maternal complications (fetal growth restriction, hypertensive disorders of pregnancy, placental abruption, small for gestational age), serious infections in neonate/infant, and major congenital malformations. Proportions of nipocalimab-exposed pregnancies or neonates/infants with each endpoint will be calculated with 95% confidence intervals using exact methods.
Conclusion:
PETUNIA is designed to obtain real-world safety data on pregnant individuals with gMG exposed to nipocalimab in pregnancy to support clinical decision-making.

34 - Update on Phase 2 of KYSA-6, an Open-Label, Single-Arm, Multicenter Phase 2/3 Study of Miv-cel (Mivocabtagene Autoleucel; KYV-101), a Fully Human CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy in Generalized Myasthenia Gravis (gMG)

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Introduction: gMG is a neuromuscular autoimmune disease typically causing substantial disability. Novel therapies that provide greater absolute reduction in MG-ADL to minimize/eliminate disease symptoms are needed. Miv-cel is a fully human, autologous CD19 CAR T-cell therapy with CD28 costimulation, designed for potency and tolerability.
Objective: Evaluate clinical outcomes with miv-cel in patients with gMG in Phase 2 of KYSA-6 (NCT06193889).
Methods: Adults (18-75y) with gMG (MGFA class IIb-IV), a history of AChR or MuSK autoantibodies, an MG-ADL score ≥6, and ≥2 immunosuppressant/immunomodulator failures, received low-dose lymphodepletion and a single infusion of 1×10^8 CAR T cells.
Results: As of 2/25/2026, 7 patients were dosed (mean [range]: age 46.1y [21-62]; MG-ADL 10.6 [7-16]; QMG 16.9 [9-28]). Median follow-up was 10.2 months (range, 3.3-16.0; n=3 with ≥12 months). All patients had robust CAR T-cell expansion and B-cell depletion. With a single dose, all patients had ≥3-point MG-ADL improvement versus baseline; 57% (4/7) achieved MSE (MG-ADL ≤1) at their last follow-up. At 24-weeks (n=6), miv-cel treatment resulted in 8.5-point (range, 7-13) and 11.3-point (5-27) mean reductions from baseline in MG-ADL and QMG scores, respectively. All 7 patients became immunotherapy-free (86% at last follow-up). No ICANS or high-grade CRS occurred.
Conclusions: These findings support the potential of a single dose of miv-cel to deliver durable, drug-free, disease-free remission in patients with moderate to severe gMG. Miv-cel treatment resulted in robust, sustained improvements in disease severity with an acceptable safety profile and eliminated background immunosuppressants in the majority of patients. Phase 3 is ongoing.

38 - Phase 1 ASCEND Study Evaluating INS1201 Adeno-Associated Virus Serotype 9 (AAV9) Gene Therapy in Ambulatory Pediatric Males with Duchenne Muscular Dystrophy (DMD): Trial in Progress

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Introduction
INS1201 is an investigational intrathecally administered AAV9 vector-based micro-dystrophin gene therapy for potential treatment of DMD. Preclinical studies demonstrated histopathological improvement and functional efficacy in *mdx* mice, with efficient skeletal and cardiac muscle targeting, and high expression at low doses in mice and non-human primates.
Objectives
ASCEND is a phase 1, first-in-human, dose-escalation study assessing INS1201 safety and biodistribution in ambulatory males with DMD aged 3-<5 years (Part 1: Cohorts 1 and 2) and 2-<3 years (Part 2: Cohorts 3 and 4).
Methods
ASCEND (NCT06817382) will evaluate up to 12 participants across two parts, each comprising two sequential dose cohorts (each n=3): 5.0E+14 vector genomes (vg) in Cohorts 1 and 3, and 1.0E+15 vg in Cohorts 2 and 4. Enrollment is staggered, with a 30-day safety observation period between each participant; an independent data monitoring committee will convene following completion of the last participant's observation period in each of Cohorts 1, 2, and 3. Primary endpoint is incidence and severity of treatment-emergent adverse events (AEs), AEs of special interest, and serious AEs. Secondary endpoints include identification of a recommended phase 2 dose (RP2D) and change from baseline in micro-dystrophin DNA and expression. Exploratory endpoints include micro-dystrophin biodistribution and expression, functional outcomes, and caregiver-reported outcomes. Participants will be followed up for 96 weeks post-administration, followed by a 3-year safety extension study.
Results
As of May 2026, ASCEND is actively enrolling at 10 US sites.
Conclusions
ASCEND will assess INS1201 safety and biodistribution and will inform RP2D selection.

45 - ClC-1 inhibition improves neuromuscular function and accelerates reinnervation in pre-clinical models while sustained functional effects are observed clinically in CMT patients

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ClC-1 inhibition enhances muscle excitability and improves neuromuscular transmission; however, its ability to induce sustained biological effects beyond acute functional improvement remains unclear. Here, we investigated the effects of ClC-1 inhibition across complementary preclinical models of neuromuscular dysfunction and related these findings to emerging clinical observations.
In a CMT2D mouse model, repeated dosing with a ClC-1 inhibitor (NMD712) improved neuromuscular transmission, as evidenced by a reduction in CMAP decrement, and was associated with increased grip strength and body weight. These effects developed progressively with repeated dosing, suggesting a cumulative biological response beyond acute pharmacological action. Ex vivo analyses of muscle preparations obtained following repeated in vivo dosing further demonstrated reduced neuromuscular transmission failure, indicating improved reliability of nerve-driven muscle activation.
In a sciatic nerve crush model, ClC-1 inhibition significantly accelerated recovery of motor function, as assessed by gait parameters, and promoted restoration of muscle mass following denervation, consistent with enhanced reinnervation.
Importantly, recent data from an exploratory Phase 2 trial in CMT patients (SYNAPSE-CMT; NCT06482437) demonstrated improvements in muscle strength and motor function that persisted 7 days after treatment discontinuation. Together with preclinical evidence of improved neuromuscular function, reduced transmission failure, and accelerated reinnervation, these findings support the hypothesis that ClC-1 inhibition may underlie sustained biological effects beyond acute neuromuscular facilitation, consistent with disease-modifying effects and may be mediated by activity-dependent mechanisms linking muscle and nerve function.

46 - Clinical Validation of the Association Between Micro-Dystrophin Expression and Muscle MRI with Functional Outcomes: A Pooled Analysis of Delandistrogene Moxeparvovec in Patients Treated with Duchenne Muscular Dystrophy

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Introduction: Delandistrogene moxeparvovec, an approved gene transfer therapy, addresses the root cause of Duchenne Muscular Dystrophy (DMD) through targeted skeletal and cardiac muscle expression of micro-dystrophin protein containing key functional domains of dystrophin.

Objectives: To report correlations of micro-dystrophin expression and skeletal muscle magnetic resonance imaging (MRI) with functional outcomes post-treatment with delandistrogene moxeparvovec.

Methods: Data were pooled from Studies SRP-9001-102 (NCT03769116; N=40, 4-7 years, ambulatory), SRP-9001-103 (NCT04626674; N=40, 3-20 years, ambulatory), and SRP-9001-301 (NCT05096221; N=126, 4-7 years, ambulatory). Correlation of changes in functional outcomes (North Star Ambulatory Assessment [NSAA], Time to Rise [TTR], 10-meter Walk/Run [10MWR], 100-meter Walk/Run [100MWR]) with micro-dystrophin expression (western blot at Week 12), and change in skeletal muscle MRI fat fraction (FF) was measured at 1- and 2-years post-infusion.

Results: Micro-dystrophin expression and functional outcomes were significantly correlated at both 1-year (NSAA r=0.34, $P<0.001$; TTR r=-0.23, $P=0.018$; 10MWR r=-0.36, $P<0.001$; 100MWR r=-0.24, $P=0.016$) and 2-years (NSAA r=0.46, $P<0.001$; TTR r=-0.28, $P<0.03$; 10MWR r=-0.5, $P<0.001$; 100MWR r=-0.53, $P<0.001$) post-treatment, demonstrating durable treatment effect. MRI FF across all skeletal muscle tissues showed a statistically significant correlation ($P<0.05$) with all functional endpoints, with higher fat composition indicating worse functional efficacy.

Conclusions: These results provide confirmation on the mechanism of action, whereby delandistrogene moxeparvovec produces micro-dystrophin protein demonstrating functional benefit and slowing DMD disease progression. These findings are further supported by skeletal muscle MRI, a clinically meaningful endpoint for DMD disease progression, where levels of FF post-treatment show a strong association with functional efficacy.

47 - A Novel Guillain-Barré Syndrome Clinical Progression Scale to Characterize the Patient's Care Journey: Utilization in a Phase 3 Trial of Tanruprubart

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Introduction: Guillain-Barré syndrome (GBS) is a rare, acute, life-altering autoimmune polyneuropathy with rapidly progressive weakness and prolonged recovery. In GBS-02, a Phase 3, randomized, double-blind, placebo-controlled trial, tanruprubart (ANX005) 30 mg/kg led to rapid complement inhibition and clinical improvement with sustained clinical benefit over 6 months in patients aged ≥16 years (n=241) with GBS (NCT04701164).
Objective: Characterize the patient's care journey using a novel GBS Clinical Progression Scale (CLIPS).
Methods: CLIPS was adapted from the WHO Covid-19 Clinical Progression Scale by the study sponsor and GBS experts. This ordinal measure is based on 8 levels of care from 0 (discharged home, independent activities of daily living, capable of self-care) to 7 (death). During GBS-02, clinical status on the scale was physician-recorded weekly for 4 weeks and at 2, 3, 4, and 6 months in a subset of patients (tanruprubart 30 mg/kg n=41, 75 mg/kg n=45, placebo n=45). Treatment impact on level of care was evaluated using a proportional odds logistic regression adjusted for baseline covariates.
Results: All patients were hospitalized and most required medical intervention (Grade >=3). By Day 8, care requirements decreased. At Week 4, the odds of requiring less care favored tanruprubart 30 mg/kg (aOR 2.3, 95% CI (0.99-5.39; p=0.054) over placebo, consistent with overall clinical outcome.
Conclusions: CLIPS captured patients' transitions through levels of care, providing a pragmatic lens to interpret treatment benefit. Early separation at Week 4 favoring tanruprubart supports a clinically meaningful shift toward lower resource intensity during early GBS.

49 - Safety and Exposure of SRP-1003, an αvβ6 Integrin-Targeting siRNA Therapy for Patients With Myotonic Dystrophy Type 1: Interim Findings From a Phase 1/2 Study

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Introduction: Myotonic dystrophy type 1 (DM1) is an inherited, progressive, multi-system, autosomal dominant muscular dystrophy.
Objective: To present SRP-1003, an investigational alpha-v beta-6 (αvβ6) integrin-targeting ligand-conjugated small interfering RNA (siRNA) that knocks down *DMPK* messenger RNA in the nucleus by targeting toxic RNA for degradation.
Methods: This ongoing, phase 1/2, randomized, placebo-controlled, 2-part trial (NCT06138743) includes patients aged 18–65 years. In part 1, randomized (2:1) patients receive a single ascending siRNA SRP-1003 dose [approx. 1 mg/kg (n=12); 2 mg/kg (n=6)] or placebo. In part 2, randomized (2:1) patients receive multiple ascending siRNA SRP-1003 doses [approx. 3 mg/kg (n=6); 4 mg/kg (n=6); or 8 mg/kg (n=12)] or placebo. Primary/secondary endpoints: safety and tolerability/plasma pharmacokinetics. Key exploratory endpoint: siRNA muscle concentration.
Results: The mean (standard deviation) participants' age was 39.1 (10.32; N=36) years. Overall, 28 patients experienced treatment-emergent adverse events (TEAEs); mostly mild to moderate and not dose dependent. Two patients experienced severe serious TEAEs unrelated to study drug (patient 1: limb abscess, fatal arrythmia; patient 2: emotional distress [leading to study discontinuation]). The most common TEAEs were headache and upper respiratory tract infections (13.9% each). SRP-1003 had a half-life of ~5 hours and showed consistent dose-dependent increase in plasma exposure, supportive of overall pharmacokinetic linearity. A single low dose (approx. 1 mg/kg) yielded robust muscle siRNA delivery (12 nM; n=7).
Conclusions: SRP-1003 showed an acceptable safety and tolerability profile without dose-limiting safety signal. Plasma exposure increased proportionally with high-level muscle delivery using the αvβ6 integrin-targeting approach, supporting continued investigation of SRP-1003.

50 - Safety and Exposure of SRP-1001, an αvβ6 Integrin-Targeting siRNA Therapy for Patients with FSHD1: Interim Findings From a Phase 1/2 Study

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Introduction: SRP-1001 is an investigational αvβ6 integrin-targeting ligand-based siRNA therapy designed to silence aberrant *DUX4* expression in facioscapulohumeral dystrophy type 1 (FSHD1).
Objectives: To present the preliminary data from the first-in-human trial for SRP-1001 in patients with FSHD1.
Methods: This ongoing, phase 1/2, randomized placebo (PBO)-controlled trial (NCT06131983) included patients aged 16-70 y. In part 1, patients had a single ascending dose (mg/kg) of siRNA (approx. 1 mg/kg, n=5; 2 mg/kg, n=4; 4 mg/kg, n=4; or 8 mg/kg, n=5) or PBO (n=9). In the 12-month part 2, patients had multiple ascending doses (approx. 4 mg/kg, n=11; 8 mg/kg, n=11) or PBO (n=7). Primary and secondary endpoints were safety and tolerability, and plasma pharmacokinetics, respectively. Other endpoints were siRNA muscle concentration, levels of *DUX4*-regulated gene expression, and serum creatine kinase (CK).
Results: The mean (standard deviation) age at baseline was 44.9 (12.75; N=56) years. Overall, 43 patients had any treatment-emergent adverse events (TEAEs). Most were mild to moderate in severity, with 1 serious, unrelated TEAE (chest discomfort) reported. SRP-1001 showed consistent dose-dependent increase in plasma and muscle exposure with no evidence of saturation. Compared with PBO, pooled SRP-1001 single doses suppressed *DUX4*-regulated gene expression by ~90% and reduced CK levels by ~33%.
Conclusions: SRP-1001 suppressed *DUX4*-regulated genes while showing an acceptable safety profile and dose-dependent increases in plasma and muscle concentration.

51 - The Long-Term Safety and Efficacy of Efgartigimod PH20 SC in Adult Participants with Active Idiopathic Inflammatory Myopathy: Results from the Phase 2 Randomized ALKIVIA and Open-Label Extension ALKIVIA+ Trials

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Introduction: Idiopathic inflammatory myopathy (IIM) is a rare, systemic, rheumatic disease. Immunoglobulin G (IgG) autoantibodies may drive several IIM subtypes. Efgartigimod, an IgG1 antibody Fc fragment, has demonstrated clinically meaningful improvements in IIM.

Objectives: Describe efficacy and safety results from phase 2 of ALKIVIA (NCT05523167) and ALKIVIA+ (NCT05979441).

Methods: In ALKIVIA (a phase 2/3, randomized [1:1], double-blinded, placebo-controlled trial), adults with IIM received weekly subcutaneous efgartigimod co-formulated with recombinant human hyaluronidase (EFG) or placebo plus background therapy (PBO). After 24 weeks, eligible participants continued into ALKIVIA+. The primary endpoint was Total Improvement Score (TIS) per 2016 American College of Rheumatology/European Alliance of Associations for Rheumatology Myositis Response Criteria. Changes in Physician Global Assessment of Disease Activity (MDGA), Patient Global Assessment of Disease Activity (PGA), and Manual Muscle Testing-8 (MMT8) were evaluated.

Results: In ALKIVIA, 89 participants received EFG (n=47) or PBO (n=42); 69 switched from PBO to EFG (PBO-EFG; n=34) or continued EFG (EFG-EFG; n=35) in ALKIVIA+. At Week 24, mean TIS was higher with EFG vs PBO (50.67 vs 38.96) and more EFG participants achieved improvements (TIS ≥20: 91.5% vs 73.8%, TIS ≥40: 78.7% vs 47.6%, TIS ≥60: 34.0% vs 9.5%). Greater mean improvements were observed with EFG vs PBO in MDGA (-3.06 vs -2.36), PGA (-2.88 vs -1.11), and MMT8 (15.2 vs 10.8) scores. At Week 52, PBO-EFG and EFG-EFG groups achieved similar improvements. Safety remained consistent.

Conclusion: Clinically meaningful efficacy and consistent safety were observed with EFG, supporting its continued evaluation.

53 - Tanruprubart in GBS: Targeting Early Complement-Associated Inflammation Conserved Across the Clinical Spectrum and Regions

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Introduction: Guillain-Barré syndrome (GBS) is an acute, immune-mediated polyradiculoneuropathy resulting in mild weakness to severe paralysis. Converging evidence supports a short pathogenic window where classical complement activation and innate immune effector mechanisms drive neuroinflammation and early nerve injury.
Objective: To Investigate acute inflammatory effectors in GBS and assess their modulation by upstream complement inhibition.
Methods: Unbiased serum proteome-wide longitudinal profiling (Olink® Explore HT) was conducted in GBS patients from a Phase 3, randomized, placebo-controlled study of anti-C1q therapy tanruprubart in Asia (n=115), an IVIg/PE-treated US cohort (n=14) and healthy controls (n=10). Longitudinal analyses and pathway-based interpretation were performed.
Results: Across tanruprubart Phase 3 and IVIg/PE US cohorts, 352 proteins were elevated at baseline, with 2- to 4-fold higher levels versus healthy controls. The top 3 Reactome pathways were all inflammation-related and included 81 unique proteins. In placebo-treated patients, this signature remained high, peaking at ~Day 8, then declining by Day 29, consistent with a transient, early inflammatory phase. In contrast, tanruprubart produced rapid, broad suppression of the inflammatory signature by Day 8, confirmed in a panel of the top 12 inflammatory proteins spanning cytokine signaling, interferon signaling, innate immune pathways, and neutrophil activation. The IVIg/PE US cohort did not demonstrate a comparable early reduction.
Conclusion: These findings identify a temporally defined early inflammatory phase in GBS across geographically and clinically distinct cohorts. Rapid suppression of complement-linked inflammatory pathways following C1q inhibition supports a mechanism-aligned therapeutic approach and suggests a window during which upstream complement targeting may have greatest biological impact.

54 - A First-in-Human Dose-Escalation Study of Intrathecal INS1202 Gene Therapy in Adults with Amyotrophic Lateral Sclerosis (ALS): Trial in Progress

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Introduction
ALS is characterized by progressive brain and spinal cord motor neuron degeneration. Misfolded mutant superoxide dismutase 1 (SOD1) protein aggregates are a pathological hallmark of SOD1-ALS, and misfolded wild-type SOD1 has been observed in sporadic ALS (sALS). INS1202 is an investigational, intrathecally administered, adeno-associated virus serotype 9 (AAV9) vector-based gene therapy that delivers a short hairpin RNA which selectively targets *SOD1* mRNA, ultimately reducing toxic SOD1 protein aggregates. INS1202 improved muscle function and survival in SOD1-mutant mice and reduced toxicity of sALS patient-derived astrocytes in co-culture with healthy mouse motor neurons, supporting evaluation of INS1202 in humans.
Objectives
ARMOR (NCT07290062) is a first-in-human, multi-center, phase 1 study evaluating safety, tolerability, and pharmacodynamics of a one-time intrathecal administration of INS1202 in participants aged 18 to <80 years with ALS who carry *SOD1* mutations or harbor no known ALS-related genetic mutation. Eligible participants meet Gold Coast diagnostic criteria with ALS Functional Rating Scale-Revised (ALSFRS-R) score ≥24, disease duration ≤42 months, and predicted vital capacity ≥50%.
Methods
Three ascending dose cohorts are planned. Dose escalation includes a 30-day safety monitoring period between initial patients and cohorts, with Independent Data Monitoring Committee review and endorsement.
Results
The primary study period is 48 weeks with long-term safety assessed in a 4-year extension study. Endpoints include incidence and severity of adverse events (primary); identifying recommended phase 2 dose and evaluating viral vector shedding (secondary); assessing SOD1 and neurofilament light chain protein levels, clinical efficacy including ALSFRS-R score, and patient-reported outcomes (exploratory).
Conclusions
ARMOR is actively recruiting.

56 - PGN-EDODM1: Data from the FREEDOM-DM1 single-ascending dose study and the initial cohort of the FREEDOM2-DM1 multiple-ascending dose trial.

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1. Introduction: PGN-EDODM1 is an investigational peptide-conjugated oligonucleotide in clinical trials for myotonic dystrophy type 1 (DM1). PGN-EDODM1 binds to pathogenic CUG trinucleotide repeat expansions in *DMPK* mRNA, liberating MBNL1 protein through steric blocking, and is expected to restore mis-splicing of downstream transcripts.
2. Objectives: Data from a single-ascending dose study and the interim readout of Cohort 1 of a multiple-ascending dose study will be presented.
3. Methods: FREEDOM-DM1 is a completed Phase 1 randomized, double-blind, placebo-controlled, single ascending dose (SAD) study of PGN-EDODM1 (NCT06204809). FREEDOM2-DM1 is an ongoing multiple ascending dose study (NCT06667453) with 3 ascending dose levels (n=8, randomized 3:1); each cohort receives 4 doses administered every 4 weeks. Endpoints include safety, tolerability, pharmacokinetics, pharmacodynamics (correction of mis-splicing), and multiple measures of function.
4. Results: FREEDOM-DM1 demonstrated dose-dependent improvements in mean splicing correction of 12.3%, 29.1%, and 53.7% 28 days after single doses of 5 mg/kg, 10 mg/kg, and 15 mg/kg, respectively (22-gene panel). Following a single dose, improvements in functional measures were not observed. PGN-EDODM1 was generally well-tolerated, with one serious treatment-related adverse event (abdominal pain) at 10 mg/kg. Transient mild-moderate changes in renal biomarkers were observed, which met dose-limiting toxicity criteria in one participant at 15 mg/kg. These were asymptomatic and resolved without intervention.
In FREEDOM2-DM1 4 doses of 5 mg/kg PGN-EDODM1 resulted in mean splicing improvement of 7.3% (n=6) vs. 6.8% in the 2 placebos. Middle finger vHOT in treated participants showed a positive trend towards improvement. PGN-EDODM1 was well-tolerated with no cumulative toxicity.
5. Conclusions: Data are encouraging and support escalation to higher doses in the ongoing FREEDOM2-DM1 study.

57 - HARMONIA STUDY DESIGN: A GLOBAL PHASE 3 TRIAL ASSESSING THE EFFICACY AND SAFETY OF Z-BASIVARSEN IN MYOTONIC DYSTROPHY TYPE 1 (DM1)

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DM1 is a spliceopathy that results in multi-system clinical manifestations. Zeleciment basivarsen (Z-basivarsen or DYNE-101) consists of a TfR1-binding Fab conjugated to an ASO designed to target mutant nuclear *DMPK* RNA in both muscle and CNS with the goal of correcting the underlying spliceopathy.
Data from the ongoing Phase 1/2 ACHIEVE trial informed the initial safety and efficacy of z-basivarsen, which will continue to be evaluated in HARMONIA, a Phase 3, placebo-controlled, randomized, double-blind study to assess the efficacy, safety, and tolerability of z-basivarsen in participants with DM1.
HARMONIA plans to enroll ~150 participants aged ≥16 years. Participants will be randomized 1:1 to receive either z-basivarsen 6.8 mg/kg Q8W or placebo during the 48-week placebo-controlled period, after which they will be eligible to enter an LTE portion. The primary objective is to evaluate the effect of z-basivarsen compared with placebo on improvement in muscle function as measured by the change from baseline in 5 Times Sit-to-Stand (5xSTS). 5xSTS is a validated and reliable measure of lower-extremity strength and functional mobility. It measures the ability to perform activities of daily living and has been shown to be an independent predictor of fall risk. Key secondary objectives include measures of myotonia, muscle strength and function, and patient and clinician-reported outcomes. Given DM1's significant CNS component, the study will evaluate potential effects on CNS-related disease burden, using actigraphy, clinical, and patient-reported outcome measures. HARMONIA is designed to evaluate the multi-systemic impact of spliceopathy correction using functional endpoints related to activities of daily living.

60 - Impact of delandistrogene moxeparvovec treatment delays for ambulatory patients with Duchenne muscular dystrophy

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Introduction: Delandistrogene moxeparvovec is approved in the U.S. to treat ambulatory patients ≥4-years-old with Duchenne muscular dystrophy (DMD). Given the progressive muscle damage in DMD, it is important to understand how treatment delays impact functional outcomes.
Objectives: To model the clinical impact of delandistrogene moxeparvovec treatment delay versus standard of care (SoC) or immediate treatment (no delay).
Methods: A health-state simulation of a prevalent DMD population (ambulatory patients, ≥4-years-old, range of baseline ages) was used. Patients were simulated to receive SoC (corticosteroids and/or medical management), immediate delandistrogene moxeparvovec treatment, and delayed (0.5-2 years from baseline) treatment. Clinical outcomes included 5-year cumulative incidence of loss of rise from floor (RFF), ambulation (LoA), and overhead reach to the scalp or higher with compensation (Brooke score ≥3). Delandistrogene moxeparvovec was simulated to delay progression based on hazard ratios (HRs) by age from EMBARK (NCT05096221) Year 3 data on RFF loss and RFF loss <5 seconds. Both HRs were used to simulate LoA and Brooke ≥3, accounting for outcome uncertainty when extrapolating to other clinical milestones.
Results: At 5 years, RFF loss incidence was 69.6% with SoC, 24.0% with no treatment delay, and 28.8-43.4% with 0.5-2-year delays. LoA incidence was 55.7% (SoC), 17.4-27.2% (no delay), and 21.0-37.8% (0.5-2-year delays). Brooke ≥3 incidence was 44.8% (SoC), 4.8-15.1% (no delay), and 8.3-25.5% (0.5-2-year delays).
Conclusions: Applying 3-year EMBARK data, this model estimates lower clinical event incidence with delandistrogene moxeparvovec treatment regardless of administration timing. However, even short delays have a noticeable impact on incidence versus SoC.

64 - U.S. Healthcare Provider Consensus on Definitions of Delayed Diagnosis, Misdiagnosis, and Suboptimal Management in Myasthenia Gravis

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Introduction: Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disease associated with disparities in care across patient subpopulations. Lack of consensus among healthcare providers (HCPs) on definitions of medical unmet needs limits standardized assessment of care quality in clinical practice and research.
Objectives: Develop consensus-based definitions of delayed diagnosis, misdiagnosis, and suboptimal management in MG among U.S. HCPs.
Methods: A two-round Delphi process was conducted among U.S. HCPs experienced in managing MG. In Round 1, participants rated agreement with proposed definitions and provided qualitative feedback. In Round 2, definitions were re-evaluated after review of aggregated responses and themes of disagreement. Consensus was predefined as ≥70% agreement.
Results: 110 HCPs (91% MD, 90% neuromuscular specialty, 85% with >5 years managing MG) completed both rounds. Consensus agreement was achieved for definitions of delayed diagnosis (>90 days from first healthcare contact for MG-related symptoms; 96%) and misdiagnosis (alternative neurological or unrelated diagnosis preceding MG; 99%), and for multiple indicators of suboptimal management, with low-to-moderate variance (0.219-0.566). Highest consensus indicators of suboptimal management (>95% agreement) spanned aspects of care, including delayed diagnostic imaging, lack of timely thymectomy, prolonged high-dose prednisone use without immunosuppressive or other therapy, and failure to adjust treatment with worsening symptoms. Maintenance IVIg monotherapy >3 months did not reach consensus as suboptimal management (42% agreement).
Conclusions: This Delphi study establishes consensus-derived definitions for key diagnostic and management gaps in MG. These standardized definitions have potential to improve assessment of high-quality care in MG and thereby demonstrate and reduce gaps in care.

67 - Treatment Patterns and Clinical Outcomes in Multifocal Motor Neuropathy: Descriptive Insights from the iMMersioN Study

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Introduction: Multifocal motor neuropathy (MMN) is a rare, chronic, autoimmune neuromuscular disease that is predominantly driven by immune-mediated complement deposition that drives pathophysiology. iMMersioN (NCT05988073) is a global, prospective, longitudinal study to characterize disease course, management, and burden in adults with MMN.
Objectives: Describe the baseline characteristics, treatment patterns, and clinical outcomes of participants enrolled in iMMersioN.
Methods: Outcome measures (MMN-Rasch-built Overall Disability Scale [MMN-RODS]; modified MRC-10 [mMRC-10]) and the impact on health-related quality of life (chronic acquired polyneuropathy patient-reported index [CAP-PRI]) will be assessed for ≥48 months. Site visits coincide with existing treatment visits (approximately every 3 months).
Results: Of 400 participants, 65.8% had definite, 17.6% probable, and 16.6% possible MMN. Mean (standard deviation [SD]) age was 56.8 (13.0) years; 34% were female and 73% were White. Mean (SD) time since initial symptoms and diagnosis was 13.7 (10.2) and 9.5 (8.3) years, respectively. At study entry, 64.8% of participants were receiving intravenous immunoglobulin (IVIg) monotherapy, 15.5% no MMN treatment, and 13.5% subcutaneous immunoglobulin (SCIg) monotherapy. At data cutoff (January 8, 2026) or study discontinuation, 63.5%, 18.3%, and 13.5% were receiving IVIg, no MMN treatment, and SCIg, respectively. At 12 months, mean (SD) changes from baseline in MMN-RODS centile score (n=259), mMRC-10 sum score (n=251), and CAP-PRI (n=258) were -2.6 (10.5), 0.5 (6.6), and -0.4 (4.4), respectively.
Conclusion: This analysis provides insights into treatment patterns and clinical outcomes in MMN. Although most participants were receiving treatment, changes in outcome measures were modest, highlighting an unmet need for additional therapeutic options.

68 - Interim Analysis from the Ongoing Phase 3 FORTIFY Study of BBP-418 Shows Significant Improvements Across Biomarker and Functional Endpoints in LGMD2I/R9

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Introduction: Limb-girdle muscular dystrophy 2I/R9 (LGMD2I/R9), an autosomal recessive disorder caused by pathogenic variants in *FKRP* impairing α-dystroglycan (αDG) glycosylation, leads to progressive, irreversible muscle damage and cardiopulmonary decline. No approved therapies exist.
Objective: FORTIFY (NCT05775848) is an ongoing randomized, double-blind, placebo-controlled, phase 3 study evaluating BBP-418, an oral small molecule designed to restore αDG glycosylation and maintain muscle integrity during contraction.
Methods: An interim analysis assessed change from baseline (CFB) in αDG (% of control) in muscle at Months 3 and 12; CFB at Month 12 in serum creatine kinase (CK), 100MTT (m/s), and forced vital capacity (FVC; % predicted, seated); and responder rates for NSAD, PUL 2.0, 10MWT, and 10MTT. Safety was assessed.
Results: BBP-418 increased glycosylated αDG 1.8-fold at 3 months, which was sustained at 12 months (both $P<0.0001$) vs. placebo. CK decreased 82% at Month 12 ($P<0.0001$). Improvements were observed in 100MTT velocity (+0.14 m/s from baseline; +0.27 m/s vs. placebo; $P<0.0001$) and FVC (+3% predicted from baseline; +5% predicted vs. placebo; $P=0.0071$). At Month 12, more participants treated with BBP-418 vs. placebo achieved improvement/stability in NSAD (72.3% vs. 37.5%; $P=0.0028$), PUL 2.0 (80.0% vs. 53.8%; $P=0.0224$), 10MWT (86.5% vs. 23.8%; $P<0.0001$), and 100MTT (81.0% vs. 22.7%; $P<0.0001$). FVC response rates numerically favored BBP-418. No participants treated with BBP-418 discontinued due to adverse events; serious adverse events were infrequent and balanced.
Conclusions: BBP-418 demonstrated benefit across multiple endpoints with a favorable safety profile, supporting its potential as the first disease-modifying therapy for LGMD2I/R9.

69 - Tanruprubart Monotherapy in Guillain-Barré Syndrome: Early Week 1 Improvement in MRC Sum-Score in FORWARD Study

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Introduction:
Guillain-Barré syndrome (GBS) is a rare, life-altering, neuromuscular emergency where classical complement activation contributes to progressive muscle weakness. Although intravenous immunoglobulin (IVIg) and plasma exchange (PE) are recommended treatments, early clinical progression may still occur and recovery is often incomplete. Tanruprubart is a monoclonal antibody that inhibits C1q, the initiating molecule of the classical complement pathway.
Objective: To describe muscle strength changes through Week 1 in GBS patients treated with tanruprubart in the ongoing FORWARD study.
Method: FORWARD is an open-label, single-arm study of a single intravenous tanruprubart 30 mg/kg dose in recently diagnosed GBS (onset within 10 days; baseline GBS-Disability Score [GBS-DS] 3-5) without prior or planned IVIg/PE. Change in Medical Research Council Sum-Score (MRCss) from baseline through day 7 was summarized.
Results: Among the first 4 treated participants, baseline GBS-DS was 3 in 1 patient and 4 in 3 patients; baseline MRCss ranged from 39 to 53. By Week 1, all patients showed improved muscle strength, with MRCss gains of 7 to 19 points from baseline. Improvement started the day after infusion in all patients. No IVIg/PE was administered during the first week. Tanruprubart was generally well tolerated.
Conclusion: In these initial FORWARD cases, rapid improvement in MRCss was observed by Week 1, following tanruprubart monotherapy. These early findings are consistent with data from the pivotal Phase 3 study conducted in Bangladesh and the Philippines where tanruprubart treatment resulted in highly consistent, rapid improvement. Longer-term and functional outcomes remain important to assess clinical benefit.

70 - Design of a Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Adimanebart in Adult and Pediatric Participants with DOK7-, MUSK-, AGRN-, or LRP4-CMS

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Introduction: Congenital myasthenic syndromes (CMS) are caused by mutations at the neuromuscular junction (NMJ) that impair neuromuscular signal transmission, resulting in muscle weakness and fatigability. CMS include subtypes affecting the acetylcholine receptor (AChR)-clustering pathway, such as DOK7-, MUSK-, AGRN-, and LRP4-CMS. Targeting this pathway represents a potential therapeutic approach in CMS. Adimanebart (ARGX-119) is an agonistic monoclonal antibody that targets and activates MuSK to promote AChR clustering, potentially stabilizing the NMJ and improving muscle weakness, fatigability, and performance across daily activities. Positive Phase 1b results in DOK7-CMS support investigation of adimanebart in additional CMS subtypes.

Objectives: To assess efficacy and safety of intravenous (IV) adimanebart in adult and pediatric participants (aged ≥12 years) with DOK7-, MUSK-, AGRN-, or LRP4-CMS.

Methods: This Phase 3 global, multicenter, randomized, double-blind, placebo-controlled study comprises a 24-week double-blind treatment period (DBTP) and 104-week open-label extension (OLE). In the DBTP, all participants will be randomized 1:1 to adimanebart IV or placebo IV. Participants who complete the DBTP will continue to the OLE. The study will include ~105 participants.

Results: The primary endpoint is change from baseline in Six-Minute Walk Test (6MWT) distance. Key secondary endpoints include change from baseline in PROMIS Physical Function-10b T-score, Quantitative Myasthenia Gravis Key Component Composite Score, and 6MWT cadence. Safety, tolerability, pharmacokinetics, and immunogenicity will also be assessed.

Conclusion: This Phase 3 study will confirm efficacy and safety of adimanebart IV in adult and pediatric participants with DOK7-, MUSK-, AGRN-, or LRP4-CMS.

73 - Preliminary baseline demographic and safety data from the first-in-human ArthemiR trial of a novel antimiR drug, ATX-01, for the treatment of DM1

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Introduction
ATX-01 is a novel anti-microRNA in clinical development for the treatment of Myotonic Dystrophy (DM). ATX-01 has a dual mechanism of action as a result of the inhibition of miR-23b, a key player in DM1 pathophysiology. In preclinical experiments, ATX-01 increases translation of the important RNA binding protein MBNL and decreases levels of toxic DMPK RNA foci, leading to an improvement in mis-splicing events characteristic of DM1. Preclinical pharmacology demonstrated broad tissue distribution, including to skeletal and cardiac muscle, and to the central nervous system, supporting the potential for ATX-01 to address the multisystemic manifestations of DM1.
Objectives
ArthemiR is a first-in-human randomized, double-blind, placebo-controlled clinical trial to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary clinical efficacy of ascending single and multiple doses of ATX-01 in adult participants with DM1.
Methods
ArthemiR is an integrated single-ascending dose (Part 1) and multiple-ascending dose (Part 2) trial in participants with DM1 aged 18 to 64 years old. Key inclusion criteria include a CTG repeat count of >150 in the DMPK gene, the presence of grip myotonia of >3 seconds, and ability to walk. Key exclusion criteria include congenital DM1, moderate-advanced cardiac disease, and use of anti-myotonia medication. The ArthemiR study is ongoing at 12 sites across Canada, France, Italy, the Netherlands, Spain, the U.K., and the U.S.
Results and Conclusions
Preliminary baseline demographic and safety data from the initial cohorts of the single-ascending dose part (Part 1) of the trial will be presented.

74 - Effect of Subcutaneous Self-Administered Gefurulimab on Ocular Muscle Function in Myasthenia Gravis in the PREVAIL Trial

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Introduction: Gefurulimab, a novel dual-binding nanobody, blocks complement component 5 activation. The phase 3 PREVAIL trial, assessing the efficacy and safety of gefurulimab in adults with anti-acetylcholine receptor antibody-positive (AChR-Ab+) generalized myasthenia gravis (gMG) (NCT05556096), met all primary and secondary endpoints and demonstrated clinically meaningful improvement from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) total score at week 26 compared with placebo.
Objective: To evaluate the effect of gefurulimab on ocular symptoms in adults with AChR-Ab+ gMG.
Methods: Adults with AChR-Ab+ gMG were randomized 1:1 to weekly subcutaneous self-administration of gefurulimab or placebo. The primary endpoint was change from baseline in MG-ADL total score at wk26. MG-ADL and Quantitative Myasthenia Gravis (QMG) subdomain scores were assessed.
Results: 260 patients were randomized (gefurulimab: n=131; placebo: n=129). Mean±SD baseline MG-ADL and QMG total scores were 9.0±2.16 and 14.8±4.37, respectively. Improvements in ocular subdomain scores were observed at first assessment after treatment initiation (MG-ADL, wk1; QMG, wk4) and sustained through wk26. Least squares mean±SEM change from baseline at wk26 in MG-ADL and QMG ocular subdomain scores for gefurulimab versus placebo were -1.2±0.14 versus -0.6±0.13 (treatment difference, -0.6±0.19; 95% CI: -1.0, -0.2; P=0.0016) and -1.7±0.14 versus -0.9±0.14 (treatment difference, -0.7±0.19; 95% CI: -1.1, -0.4, P=0.0002), respectively. Improvements were also observed in other MG-ADL and QMG subdomains. Adverse events were similar between groups; no meningococcal infections were reported.
Conclusion: Gefurulimab, self-administered once weekly via subcutaneous injection, showed early and sustained improvements in MG-ADL and QMG ocular subdomain scores, demonstrating benefits for patients with gMG experiencing ocular symptoms.

75 - Delivering for DMD: Leveraging the FORCE platform to deliver exon skipping oligonucleotides for a broad set of DMD patients

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Introduction
Approved exon skipping therapies for Duchenne muscular dystrophy (DMD) are designed to restore the reading frame of *DMD* transcripts, enabling translation of near-full length, functional dystrophin. Insufficient delivery to muscle and CNS leads to the modest efficacy of these therapies. FORCE was designed to solve delivery of oligonucleotides by leveraging TfR1 biology. Data in *mdx* mice and the zeleciment rostudirsen clinical program in exon 51 skip amenable DMD demonstrate that the FORCE platform enhances delivery to muscle, leading to functional improvement.
Objectives
Leverage FORCE to assess skipping of exon 44, 45, 53, or 55 in preclinical cell and mouse DMD models.
Methods
Exon 44, 45, 53, or 55-skipping payloads conjugated using FORCE were evaluated in DMD-relevant cell models. Subsequently, efficacy was evaluated in the hTfR1/hDMD$_{WT/}$*mdx* mouse. Additionally, a FORCE-PMO was assessed in the DMD relevant hTfR1/hDMD$_{Del52}$/*mdx* mouse model amenable to exon 53 skipping.
Results
All four FORCE-PMOs induced nearly complete exon skipping in mutant myotubes, including nearly complete skipping of exon 44 at a very low dose. In the hTfR1/hDMD$_{WT}$/*mdx* mouse, a single dose of FORCE-PMO provided exon skipping in skeletal and cardiac muscle. Repeat dosing of the exon 53 skipping FORCE-PMO in the hTfR1/hDMD$_{Del52}$/*mdx* mouse led to dystrophin restoration in muscle and localization to the sarcolemma.
Conclusions
Preclinical data support FORCE-PMO delivery of exon skipping and expression of near-full length, functional dystrophin protein. Four development candidates are in the IND-enabling phase and represent opportunities to improve exon skipping therapies for a larger population of people living with DMD.

76 - Global Phase 3 Study to Evaluate the Efficacy and Safety of Telitacicept in Patients with Generalized Myasthenia Gravis (UPSTREAM MG)

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Introduction: Generalized myasthenia gravis (gMG) is an autoimmune disease that affects the postsynaptic membrane of the neuromuscular junction. Current therapies treat the symptoms of gMG through nonspecific immunosuppression or downstream removal of antibodies and inhibition of complement activation.
Telitacicept is a novel TACI-Fc fusion protein that targets B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) and may reduce B-cell survival and pathogenic antibody production in autoimmune diseases such as gMG.
Data from phase 2 (NCT04302103) and phase 3 (NCT05737160) studies of telitacicept showed efficacy and safety in adults with acetylcholine receptor (AChR) autoantibody-positive gMG.
Objectives: To present the study design of our global, pivotal, phase 3, double-blind, placebo-controlled study with an open-label extension (OLE) in adult patients with gMG.
Methods: The study will enroll ~180 adult patients with a confirmed diagnosis of gMG, Myasthenia Gravis Foundation of America (MGFA) class II-IV, Myasthenia Gravis Activities of Daily Living (MG-ADL) score ≥6 with <50% of the total score due to ocular symptoms, and Quantitative MG (QMG) score ≥8, with 4 items having a score ≥2 at screening and baseline. After screening, participants will enter a 24-week, double-blind, placebo-controlled phase with 1:1 randomization to either placebo or telitacicept subcutaneous weekly, followed by an OLE period. The primary outcome is the mean change from baseline in MG-ADL score at week 24.
Results: Study enrollment is currently ongoing.
Conclusions: This study will assess the efficacy, safety, and pharmacokinetics/pharmacodynamics of telitacicept in adult patients with gMG.

77 - Reduced Clinical Deteriorations and Healthcare Resource Utilization After Switching from Efgartigimod to Ravulizumab in Patients with Generalized Myasthenia Gravis in the United States

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Introduction: Generalized myasthenia gravis (gMG) remains suboptimally controlled in patients receiving conventional immunosuppressants and oral corticosteroids (OCS). Efgartigimod (FcRn-antagonist) and ravulizumab (C5-inhibitor) have distinct mechanisms of action, and may be switched in clinical practice when symptoms, exacerbations, or dependence on OCS persist. Real-world evidence evaluating outcomes during these transitions remains limited.
Objective: Estimate clinical deteriorations and healthcare-resource-utilization (HCRU) in patients with anti-acetylcholine-receptor-antibody-positive gMG who switched from efgartigimod to ravulizumab.
Methods: A retrospective cohort study of adults with gMG who transitioned from efgartigimod to ravulizumab was conducted using Veeva Compass US claims data. Outcomes: gMG exacerbations, OCS dose escalations, HCRU endpoints. Incidence rates compared across three periods: conventional therapy ("baseline"), efgartigimod (pre-switch), and ravulizumab (post-switch). Multivariable-adjusted generalized estimating equations to estimate incidence-rate-ratios (IRRs).
Results: 107 eligible patients with median follow-up of 19, 13, and 14 months during baseline, efgartigimod, ravulizumab periods, respectively. After initiation of efgartigimod, there were no differences versus baseline in rates of MG exacerbation (IRR=0.63 [0.33-1.19]; p=0.152) or OCS dose escalation (IRR=1.09 [0.81-1.47]; p=0.561). After switching from efgartigimod to ravulizumab, gMG exacerbation rates decreased by 60% (IRR=0.40 [0.20-0.80]; p=0.009); OCS dose escalation rates decreased by 55% (IRR=0.45 [0.31-0.65]; p<0.001). There were similar reductions for Emergency Department visits and total inpatient days. Neurology outpatient visits increased by 38% during the efgartigimod period (IRR=1.38 [1.06-1.80]; p=0.018) followed by a 63% reduction after switching to ravulizumab (IRR=0.37 [0.28-0.48];p<0.001).
Conclusions: In patients with gMG, switching from efgartigimod to ravulizumab was associated with reduced clinical deteriorations and HCRU. These findings suggest complement inhibition with ravulizumab may reduce disease burden and HCRU.

79 - Safety Analysis Following Real World Use of Delandistrogene Moxeparvovec for Duchenne Muscular Dystrophy (DMD): Interim Analysis of the Phase 4 ENDURE Study

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Introduction

The US, Phase 4, observational ENDURE study (NCT06270719) measures the effectiveness and safety of delandistrogene moxeparvovec versus standard of care (SOC).

Objectives

In this planned interim analysis, patient characteristics, adverse events (AEs), and the impact of prophylactic immunosuppression on acute liver injury (ALI) are described among participants receiving delandistrogene moxeparvovec.

Methods

Participants were enrolled after the clinical decision to initiate delandistrogene moxeparvovec or if they were receiving SOC. Baseline characteristics, AEs, and adjudicated treatment-related ALI stratified by prophylactic immunosuppressant use are descriptively reported.

Results

Fifty-six delandistrogene moxeparvovec-treated participants (45 baseline ambulatory [mean age 9.4 years], 11 non-ambulatory [mean age 16.0]) and 24 SOC participants (all ambulatory [mean age 9.9]) were enrolled (02/2024-02/2026). Vomiting (30.4%; 17/56) and nausea (25.0%; 14/56) were the most frequent treatment-related AEs among treated participants. Treatment-related ALI occurred in 9/56 (16.1%) treated participants (ranging 33-53 days post-infusion), 7 (12.5%) of which were serious (5 ambulatory, 2 non-ambulatory). Eleven treated participants received prophylactic immunosuppression (all sirolimus; initiation ranging 43 days pre-infusion to 14 days post-infusion [before any ALI signs/symptoms]). No ALI cases were observed in treated participants who received prophylactic sirolimus. Two deaths occurred in treated participants, one from acute liver failure (previously disclosed; treatment-related) and one from empyema 8 months post-treatment (unrelated).

Conclusion

There were no new safety findings in this interim analysis of ENDURE. ALI frequency was consistent with prior disclosures. Preliminary findings of prophylactic sirolimus in a limited number of patients suggest protection against ALI; however, ongoing evaluation is warranted.

81 - Baseline Glycolipid IgG Autoantibodies in GBS are Prevalent and Show Cross-Regional Pattern Concordance

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Introduction: Guillain-Barré syndrome (GBS) is an acute, immune-mediated polyradiculoneuropathy resulting in mild weakness to severe paralysis. Autoantibodies target peripheral nerve glycolipids, triggering complement activation, neuroinflammation, and axonal damage. Diverse antibody reactivity patterns underlie the spectrum of phenotypes e.g. acute motor axonal neuropathy (AMAN) and acute inflammatory demyelinating polyneuropathy (AIDP). Recent studies highlight the mechanistic and clinical significance of these complex profiles, emphasizing the need to define antibody-driven disease biology to guide therapies addressing GBS presentations and outcomes.
Objective: Investigate underlying autoantibody patterns in GBS.
Methods: Baseline serum samples from patients with GBS (n=239) in a Phase 3 trial with tanruprubart (GBS-02), conducted in Bangladesh and the Philippines, and an independent US cohort (n=142) were analyzed. Autoantibody profiling was performed using a harmonized glycolipid microarray.
Results: IgG reactivity to glycolipids/complexes was found in >90% of GBS-02 participants. High-abundance/high-affinity IgG signatures were observed in both cohorts, with broad reactivity to GM1, GD1b, GT1a, GD1a, and/or GalNAc-GD1a. The broad, predominant reactivity pattern was present in 51% of GBS-02 participants and 90% of the US cohort. Although frequencies differed across regions, antigen-specific features were concordant. In GBS-02, AMAN (54%), AIDP (28%), and equivocal electrophysiologic subtypes (18%) were observed in the predominant broad reactivity pattern. US cohort electrophysiologic data were unavailable.
Conclusions: Autoantibodies to glycolipids/complexes were detected in most patients. Data from the pivotal Phase 3 population suggests that key baseline IgG reactivity patterns are shared across regions, supporting the external relevance of the enrolled population. Further studies are warranted.

82 - PROMIS Parent Proxy Mobility Scores in Patients Treated with Delandistrogene Moxeparvovec in EMBARK Part 2 Compared with External Controls

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Introduction: Duchenne muscular dystrophy (DMD) causes progressive muscle weakness, leading to ambulatory function loss. Patient- or caregiver-reported outcomes provide meaningful insight into disease progression to help evaluate a treatment's ability to slow functional decline.
Objectives: This study compared changes in Patient-Reported Outcomes Measurement Information System Parent Proxy Mobility scores (PROMIS Mobility) in patients with DMD treated with delandistrogene moxeparvovec in Part 2 of the EMBARK (NCT05096221) trial to external controls (ECs) treated at Nationwide Children's Hospital.
Methods: Inverse probability of treatment weighting was used to adjust for non-randomized treatment assignment and baseline differences between delandistrogene moxeparvovec-treated and EC groups. Rate of change in PROMIS Mobility mean raw score was evaluated across groups using a linear mixed-effects model. An exploratory analysis assessed the proportion of patients from each group that reached a meaningful improvement in PROMIS Mobility, defined using EMBARK Part 1 data with anchor-based methods.
Results: Patients treated with delandistrogene moxeparvovec (n=60; mean [SD] baseline age=7.18 [1.06]) had a nominally significant and clinically meaningful slower PROMIS Mobility rate of decline versus ECs (n=25; mean [SD] baseline age=6.97 [1.15]; difference in linear mixed-effects model slope, 0.281; 95% CI, 0.041-0.520; P=0.022). A Kaplan-Meier analysis showed meaningful PROMIS Mobility improvement events occurred earlier in patients treated with delandistrogene moxeparvovec and more frequently (48% [29/60] versus 12% [3/25]; log-rank P=0.0246).
Conclusions: Patients treated with delandistrogene moxeparvovec experienced a nominally significant slower change in PROMIS Mobility and more improvement events versus ECs, consistent with earlier findings and further demonstrating its potential to slow disease progression.

86 - Effect of zilucoplan stratified by age of myasthenia gravis onset: RAISE-XT 120-week post hoc analysis

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Introduction:
RAISE-XT (NCT04225871), a Phase 3 open-label extension study, demonstrated sustained improvements in myasthenia gravis (MG)-specific outcomes in patients with generalized MG (gMG) during zilucoplan treatment up to Week 120.
Objective:
To evaluate the efficacy of zilucoplan by age of gMG onset.
Methods:
In RAISE-XT, adults with gMG who completed RAISE (double-blind; NCT04115293) self-administered daily subcutaneous zilucoplan 0.3 mg/kg. Change from double-blind baseline (CFB) in efficacy outcomes to Week 120 and safety were evaluated post hoc (cut-off: 11 November 2023) in early (≤50 years) and late (>50 years) age-of-onset subgroups.
Results:
Mean (standard deviation) age (early onset [N=106] and late onset [N=77]) was 43.9 (12.4) and 66.2 (5.6) years. At Week 120, mean (standard error) CFB (early versus late) was: MG Activities of Daily Living, −7.47 (0.53) versus −6.66 (0.75); Quantitative MG, −10.14 (0.77) versus −9.39 (1.15); MG Quality of Life 15-item revised, −12.55 (1.18) versus −7.68 (1.73); Quality of Life in Neurological Disorders Short Form Fatigue, −11.34 (1.61) versus −9.65 (2.22). Serious and treatment-related treatment-emergent adverse events occurred in 34.0% (n/N=36/106) and 38.7% (n/N=41/106) of patients (early subgroup) and 49.4% (n/N=38/77) and 33.8% (n/N=26/77) of patients (late subgroup), respectively.
Conclusions:
Zilucoplan demonstrated long-term efficacy irrespective of age at gMG onset.

88 - Response to Rozanolixizumab Across Treatment Cycles in Patients with Generalized Myasthenia Gravis: A Post Hoc Analysis of Final Pooled Phase 3 Data

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Introduction:
In MycarinG (Phase 3, NCT03971422), one cycle of six once-weekly subcutaneous rozanolixizumab (7mg/kg or 10mg/kg) infusions demonstrated clinically relevant improvements in MG-specific outcomes versus placebo. Patients could subsequently enroll in open-label extension studies MG0004 (NCT04124965), then MG0007 (NCT04650854), or MG0007 directly.
Objective:
To evaluate response to rozanolixizumab over multiple treatment cycles in patients with generalized myasthenia gravis (gMG), based on Cycle 1 responder status.
Methods:
In MG0004, patients received chronic once-weekly rozanolixizumab (7 mg/kg or 10 mg/kg) for ≤52 weeks. In MG0007, after an initial cycle of rozanolixizumab 7 mg/kg or 10 mg/kg, subsequent cycles were administered at the investigator's discretion. Data were pooled across MycarinG, MG0004 (first 6 weeks), and MG0007 (final data) for patients with ≥2 symptom-driven cycles. MG Activities of Daily Living (MG-ADL) responders (≥2-point improvement) and Quantitative MG (QMG) responders (≥3-point improvement) at Day 43 of each cycle were assessed. *Post hoc* analyses were conducted by Cycle 1 responder status.
Results:
Overall, 129 patients had ≥2 symptom-driven cycles. In Cycle 1, 74.4% (96/129) were MG-ADL responders and 68.2% (88/129) were QMG responders at Day 43. Among MG-ADL responders, response rates remained consistent across subsequent cycles (74.4% to 88.2% up to Cycle 13). Among QMG responders, rates ranged from 61.0% to 83.3% up to Cycle 13. Among MG-ADL non-responders, 63.6% (21/33) became responders at Cycle 2. Among QMG non-responders at Cycle 1, 50.0% (20/40) became responders at Cycle 2.
Conclusions:
Cycle 1 responders had broadly consistent response rates in subsequent cycles of rozanolixizumab. Non-responders may benefit from additional treatment cycles.

89 - Update on the INSPIRE DUCHENNE Phase 1/2 Study of the Next-Generation Microdystrophin Gene Therapy Candidate SGT-003 for Duchenne Muscular Dystrophy

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Introduction

SGT-003 is a next-generation AAV-based microdystrophin gene therapy candidate that uses a novel muscle-tropic capsid, POLARIS-101™ (formerly known as AAV-SLB101), to deliver a functional replacement for dystrophin. This capsid was designed to improve muscle targeting compared to first-generation capsids. SGT-003 microdystrophin includes the R16/R17 nNOS binding domain, enabling stabilization of the muscle membrane and restoration of local signaling pathways.

Objectives

INSPIRE DUCHENNE is a Phase 1/2, open-label, first-in-human trial designed to evaluate the safety, tolerability, and efficacy of SGT-003 in participants with Duchenne muscular dystrophy.

Methods

Safety and tolerability were assessed through adverse event monitoring. Muscle biopsy analyses were conducted to evaluate vector transduction and microdystrophin expression, and biomarkers of muscle integrity were measured over time.

Results

As of May 12, 2026, 47 total participants received SGT-003 across an age range of 1 to 10 years. Treatment has been generally well tolerated, with the most frequent treatment-related adverse events including nausea, vomiting, and decreased appetite. As of a data cutoff of February 23, 2026, robust transduction and microdystrophin expression were observed in Day 90 muscle biopsies (n=17-20 per method), with means of 11 vector copies per nucleus, 60% of normal expression, and 63% positive fibers. Biomarkers of muscle integrity all demonstrated consistent improvements at Day 90 and were sustained through Day 360 post-dosing.

Conclusions

SGT-003 has demonstrated a favorable safety profile and evidence of robust microdystrophin expression, with associated improvements in biomarkers of muscle integrity. These findings support a positive biological impact of SGT-003 treatment in participants with Duchenne.

90 - SGT-003 gene therapy stabilizes the DAPC and improves muscle integrity in Duchenne muscular dystrophy

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Introduction
Duchenne muscular dystrophy is caused by the absence of functional dystrophin, leading to destabilization of the dystrophin-associated protein complex (DAPC), compromised sarcolemmal integrity, and myofiber degeneration. Persistent muscle injury results in elevated serum biomarkers of membrane damage and, in muscle, increased expression of embryonic myosin heavy chain (eMHC), a marker of active degeneration/regeneration.
Objectives
SGT-003, Solid Biosciences' next-generation AAV microdystrophin gene therapy, was evaluated for its ability to restore DAPC integrity and improve muscle health.
Methods
Sarcolemmal localization of DAPC components were assessed in muscle biopsies obtained pre- and post-treatment with SGT-003. An extensive range of muscle integrity biomarkers including serum CK and titin fragments were quantified as biomarkers of sarcolemmal damage. eMHC expression was measured to assess active muscle degeneration/regeneration cycling.
Results
Treatment with SGT-003 resulted in robust sarcolemmal localization of all sarcoglycans and enzymatically active nNOS, consistent with reconstitution of the DAPC. These changes were accompanied by improvements in biomarkers of muscle integrity including reductions in serum CK and titin fragments. Importantly, a marked decrease in eMHC-positive fibers was observed, indicating protection from myofiber necrosis and regenerative cycling.
Conclusions
SGT-003 demonstrated compelling biological evidence of functional microdystrophin activity, including restoration of the DAPC, enhanced sarcolemmal integrity, and attenuation of chronic muscle injury. The reduction in eMHC suggests protection from the pathological degeneration/regeneration loop that drives disease progression in Duchenne. Together, these findings underscore the potential of SGT-003 to meaningfully alter the disease trajectory in Duchenne muscular dystrophy.

91 - PIERRE Clinical Trial Update: Safety and Performance of ThecaFlex DRx™ for Repeated Intrathecal Delivery of Nusinersen

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Neurological therapeutics often require intrathecal (IT) dosing via lumbar puncture (LP). Use may be constrained by contraindications and barriers, including complex spinal anatomy and procedural anxiety. Repeated LPs add cumulative burden and increase exposure to radiation and anesthesia, limiting tolerability. These challenges highlight the need for alternative IT delivery approaches that reduce procedural complexity and burden. The ThecaFlex DRx™ System is an implantable subcutaneous port and IT catheter designed to expand access to patients requiring repeated LP by providing an easier approach to CSF sampling and therapeutic delivery.

PIERRE (NCT05866419) is an ongoing study assessing implantation and infusion success, along with safety, following ThecaFlex implantation and nusinersen administrations.

As of March 2026, 42 participants underwent device implantation. ThecaFlex was successfully implanted in all attempted participants (100%) with no device implantation failures. Nusinersen administration via device was attempted in 39 of 42 participants, consistent with the dosing schedule as of March 30, with successful delivery in 34/39 attempted participants (87.2%). The safety profile remained consistent with earlier findings, with no deaths or unanticipated adverse device effects observed. Additional data from the March 2026 study synopsis, including a larger cohort and longer follow-up, will be presented to further characterize safety and performance.

Preliminary results suggest acceptable safety and support the feasibility of this unique implantable device for repeat IT therapy delivery in patients with SMA. ThecaFlex may improve the patient experience of repeat IT drug administration and may be clinically useful to utilize with other neurological therapeutics.

93 - Comparing Longitudinal Treatment-related Adverse Risks of Infection in Generalized Myasthenia Gravis

Svetlana Faktorovich[1], Phuong Phan[2], Shirali Pandya[2], Casey Church[3], Dongxiao Zhang[3], Michael Blackowicz[2]
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Introduction: Myasthenia gravis (MG) is a neuromuscular disorder characterized by fluctuating muscle weakness. Approved biologic options for generalized MG (gMG) include complement inhibitors (e.g., ravulizumab) and FcRn antagonists (e.g., efgartigimod), while B-cell-targeted agents (e.g., rituximab) are used off-label. While safety of these approved agents has been characterized in clinical trials, additional real-world evidence is needed to evaluate longer-term infection risks.
Objective: The objective of this study is to estimate and compare the real-world infection rates associated with gMG treatments.
Methods: This study was a retrospective longitudinal cohort study of patients with MG initiating ravulizumab, efgartigimod, rozanolixizumab, or rituximab using the Veeva Compass claims database from January 2017 to August 2025. Generalized estimating equations was used to compare annual infection rates across cohort, with adjustment for known and suspected confounders.
Results: Of 1,515 patients, 689 (46.1%) initiated rituximab, 555 (36.6%) efgartigimod, 218 (14.4%) ravulizumab, and 53 (3.5%) rozanolixizumab. After confounder adjustment, both efgartigimod and rituximab showed statistically significantly higher infection rates versus ravulizumab-efgartigimod by 47% (IRR=1.47, 95% CI: 1.17-1.84, $p<0.001$) and rituximab by 46% (IRR=1.46, 95% CI: 1.23-1.72, $p<0.001$). Rozanolixizumab suggested a similar trend but was underpowered to detect differences due to small sample size (IRR=1.34, 95% CI: 0.85-2.11, $p=0.208$).
Conclusions: This study observed lower infection rates in patients receiving ravulizumab compared to those receiving other biologic therapies for gMG. Understanding real-world, long-term infection risk profiles for these drugs could help inform treatment decisions for MG, particularly for patients at higher risk of infection or infection-related complications.

98 - Clinical Relevance of Minimal Symptom Expression (MSE) in Efgartigimod-Treated Patients with Generalized Myasthenia Gravis (gMG)

James F. Howard Jr.[1], Cynthia Z. Qi[2], Hongbo Yang[3], Akiyuki Uzawa[4], Kristin Heerlein[2], Qing Liu[3], Yujie Wu[3], Glenn Phillips[2], Andreas Meisel[5]

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Introduction: Minimal Symptom Expression (*MSE; MG-ADL 0-1)* has emerged as a patient-centric treatment goal in gMG and has been reported in efgartigimod-treated patients. Additional evidence is needed to evaluate long-term symptom trajectories following MSE achievement and whether MSE reflects meaningful gains in quality of life (QoL) and clinician-assessed outcomes.

Objectives: To evaluate MG-ADL trajectories in efgartigimod-treated patients by MSE status and assess associations with QoL and clinician-assessed outcomes.

Methods: *Post-hoc* analyses pooled AChR-Ab+ patients across ADAPT/ADAPT+, ADAPT-SC/ADAPT-SC+, and ADAPT-NXT. Cumulative MSE attainment and time to first MSE were summarized. MG-ADL trajectories were standardized to 4-week intervals using the lowest score per interval. Concurrent associations between MSE and MG-QoL15r, EQ-5D utility, Quantitative Myasthenia Gravis (QMG), and Myasthenia Gravis Composite (MGC) scores were assessed using linear mixed-effects models.

Results: Among 225 efgartigimod-treated participants, 132 (58.7%) achieved MSE, with a median time to first MSE of 1.2 months. With continued efgartigimod treatment, achievers sustained low disease burden over ~3 years, while non-achievers also experienced sustained, clinically meaningful MG-ADL improvements exceeding the minimal clinically important difference. Estimated concurrent mean scores were significantly better during MSE versus non-MSE intervals: EQ-5D utility (0.84 vs. 0.71), MG-QoL15r (7.03 vs. 10.86), QMG (7.48 vs. 11.95) and MGC (5.48 vs. 13.40) (all $p<0.001$).

Conclusions: MSE is achieved early following efgartigimod and is associated with sustained low disease burden and QoL scores approaching healthy population. Patients not achieving MSE still derive meaningful benefit, supporting MSE as an aspirational - but not exclusive - treatment target in gMG.

99 - Alglucosidase Alfa to Avalglucosidase Alfa Switch Improves Biomarkers in Infantile-Onset Pompe Disease: Pompe Registry Analysis

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Introduction: Avalglucosidase alfa (Ava), approved for infantile-onset (IOPD) and/or late-onset Pompe disease, contains bis-mannose-6-phosphate, improving cellular uptake and clinical efficacy.
Objectives: This analysis describes outcomes in patients with IOPD from the Pompe Registry (NCT00231400) who switched from Alg (≥1-year) to Ava (≥3-months).
Methods: Registry data were analyzed to estimate annual changes in creatine kinase, alanine aminotransferase, aspartate aminotransferase (CK, ALT, AST, U/L), and urine hexatetrasaccharide (Hex4, mmol/mol creatinine) using linear mixed models during the last 5 years of Alg and first 3.5 years of Ava. Results were stratified by last Alg dose (label-dose: ~20 mg/kg EOW, or high-dose: ~40 mg/kg EOW, ~20 or ~40 mg/kg weekly).
Results: 47 patients with IOPD (49% male) were included. Median ages at Alg and Ava initiation were 0.6 and 8.5 years, respectively, and median time on Ava was 2.2 years. Before switching, 66% received high-dose Alg, and 87% started Ava at 40 mg/kg EOW.
In label-dose Alg patients, CK, Hex4, ALT, and AST significantly increased on Alg and significantly decreased on Ava (differences in pre vs. post slopes all; $P<0.0001$). In high-dose Alg patients, CK, ALT, and AST decreased during both treatments, with a significantly greater rate of decrease on Ava (differences in pre vs. post slopes; all $P<0.0001$). Hex4 remained elevated/stable in high-dose Alg patients but decreased significantly after switching to Ava (difference in slopes $P<0.0001$).
Conclusions: Patients with IOPD showed improved CK, Hex4, ALT, and AST trajectories after switching to Ava, regardless of their Alg dose prior to the switch.

105 - Efficacy and cumulative safety of cemdisiran in adults with generalized myasthenia gravis (gMG): Results from the phase 3 NIMBLE trial

Ali Habib[1], Saiju Jacob[2], Tuan Vu[3], Renato Mantegazza[4], Hiroyuki Murai[5], John Vissing[6], Aziz Shaibani[7], Todd Levine[8], Yessar Hussain[9], Andreas Meisel[10], Rodrigo Pavani[11], Umesh Chaudhari[11], Neda Jalali[11], Michelle DeVeaux[11], Karoline A Meagher[11], Steven Sherman[11], Dipti Pawaskar[11], Amal Souttou[11], Lorah Perlee[11], James F Howard Jr[12]
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Introduction: Autoantibody-mediated terminal complement activation damages neuromuscular junctions in gMG, resulting in fatigable muscle weakness.
Objectives: The phase 3 NIMBLE trial evaluated cemdisiran (siRNA inhibiting hepatic C5 production) as subcutaneous monotherapy or in combination with pozelimab (monoclonal antibody targeting C5) in participants with gMG.
Methods: In this double-blind, placebo-controlled trial, 288 participants with gMG were randomized to cemdisiran monotherapy (600 mg Q12W), pozelimab monotherapy (200 mg Q4W), combination (both 200 mg Q4W), or placebo. We present key results (based on database lock on July 8, 2025) for the primary efficacy endpoint, change from baseline in MG-ADL total score at Week 24 (n=239), terminal complement inhibition, and the rate of TEAEs (n=277).
Results: NIMBLE met its primary endpoint. In the cemdisiran (n=64) and combination (n=67) arms, the least-squares mean (SE) change from baseline at Week 24 in MG-ADL was −4.5 (0.4) and −4.0 (0.4), with placebo-adjusted differences of −2.3 (P=0.0005) and −1.7 (P=0.0086), achieving 76.6% (n=60) and 99.6% (n=66) terminal complement inhibition, respectively. TEAEs occurred in 69% (54/78), 82% (40/49), 81% (65/80), and 77% (54/70) of participants in the cemdisiran, pozelimab, combination, and placebo arms, respectively. No meningococcal or serious infections occurred in the cemdisiran arm during the double-blind treatment period (DBTP); SAEs of infections in other arms were low. There were 2 deaths (pneumonia [cemdisiran], septic shock [combination]) after the DBTP in participants on concomitant immuno-suppressive therapies with comorbidities.
Conclusions: Quarterly, subcutaneous cemdisiran was generally well-tolerated, with rapid, sustained symptom improvement following partial complement inhibition in participants with gMG.

109 - Impact of Time Since Diagnosis on Efficacy of Inebilizumab: A Post Hoc Analysis of Phase 3 Myasthenia Gravis Inebilizumab Trial (MINT) Data

Ali A. Habib[1], James F. Howard, Jr[2], Michael Benatar[3], Emma Ciafaloni[4], Maria Isabel Leite[5], Kimiaki Utsugisawa[6], John Vissing[7], Sarah Bray[8], Michaela Schlader-Ratzinger[9], Catherine Najem[9], Sue Cheng[9], Richard J. Nowak[10]
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Introduction: The MINT study (NCT04524273) met its primary endpoint (Myasthenia Gravis Activities of Daily Living [MG-ADL]), demonstrating the efficacy of inebilizumab in the AChR$^+$ and MuSK$^+$ seropositive patients with generalized myasthenia gravis (gMG).
Objectives: To determine if response to inebilizumab differs by time since the diagnosis of gMG in the MINT phase 3 trial.
Methods: Patients (AChR$^+$ or MuSK$^+$) underwent a protocol-specified glucocorticoid taper to ≤5 mg/day and were randomized 1:1 to 300 mg inebilizumab or placebo for 26 (MuSK$^+$) or 52 (AChR$^+$) weeks. Changes from baseline (CFBs) in MG-ADL and Quantitative Myasthenia Gravis (QMG) scores by time since diagnosis were examined.
Results: Overall, 238 patients (AChR$^+$, 190; MuSK$^+$, 48) were enrolled and randomized to inebilizumab or placebo. The least squares mean (LSM) CFB in MG-ADL score was numerically greater for inebilizumab versus placebo at week 26 for patients with time since diagnosis of <1 year (-5.4 vs. -3.0), ≥1-<4 years (-4.3 vs. -1.8), and ≥4 years (-3.7 vs. -2.5); the LSM CFB in QMG score was also numerically greater for inebilizumab versus placebo at week 26 (-5.2 vs. -4.0; -6.4 vs. -2.2; -4.0 vs. -1.9, respectively). Improvements from baseline with inebilizumab versus placebo were observed at week 52 for MG-ADL (AChR$^+$:-5.7 vs. -2.3, -5.0 vs. -2.7, -4.0 vs. -1.5, respectively) and QMG (AChR$^+$:-7.4 vs. -1.8, -8.3 vs. -2.9, -3.9 vs. -0.5, respectively) scores.
Conclusions: Efficacy of inebilizumab appears independent of time since diagnosis, although the small size of subgroups limits firm conclusions.

110 - Myasthenia Gravis Inebilizumab Trial (MINT): Adverse Events of Special Interest During the Randomized Controlled Period

Richard J. Nowak[1], Kimiaki Utsugisawa[2], Michael Benatar[3], Emma Ciafaloni[4], Maria Isabel Leite[5], John Vissing[6], Fengming Tang[7], Blanca Canales[7], Qing Li[7], Sue Cheng[7], James F. Howard Jr.[8]
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Introduction: B cells play a key upstream mechanistic role in autoimmune generalized myasthenia gravis (gMG) pathogenesis through the production of antibodies targeting the acetylcholine receptor (AChR$^+$), muscle-specific kinase (MuSK$^+$), or other related proteins. Inebilizumab is a monoclonal antibody targeting CD19$^+$ B cells.
Objectives: To examine whether inebilizumab is associated with an increased risk of adverse events of special interest (AESIs) in participants with gMG.
Methods: MINT (NCT04524273) was a phase 3 trial in adults with gMG. During the randomized controlled period (52 weeks for AChR$^+$; 26 weeks for MuSK$^+$), participants were randomized (1:1) to receive inebilizumab 300 mg or placebo on Day-1, Day-15, and Day-183 (AChR$^+$ only). Subsets of adverse events were identified as AESIs due to their relevance to inebilizumab's mechanism of action.
Results: A total of 238 participants were randomized to receive inebilizumab 119 (95 AChR$^+$, 24 MuSK$^+$) and placebo 119 (95 AChR$^+$, 24 MuSK$^+$). Baseline demographics and disease characteristics were balanced between the two treatment groups. AESIs were infrequent, occurring in 10.1% (n=12) of the inebilizumab- and 16% (n=19) of the placebo-treated group. Cytopenias occurred in 2.5% (n=3) of inebilzumab-treated and 9.2% (n=11) of placebo-treated participants. Serious and/or opportunistic infections were infrequent (inebilizumab: 3.4% [n=4]; placebo: 5.0% [n=6]), with COVID-19 being the most common (inebilizumab: 2/4; placebo: 3/6) and no instances of progressive multifocal leukoencephalopathy. Infusion related reactions occurred in 5.0% (n=6) of the inebilizumab- and 2.5% (n=3) of placebo-treated participants.
Conclusions: These results support a favorable safety profile of inebilizumab over a 26-52-week period.

113 - Real-world safety profile of delandistrogene moxeparvovec in the US postmarketing setting

Vannary Pizzo[1], Preeti Singh[1], Damon Asher[1], Randal Richardson[2]
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Introduction: Delandistrogene moxeparvovec, an rAAVrh74 vector-based gene therapy approved in the US, slows Duchenne muscular dystrophy progression in ambulatory patients. Clinical studies demonstrated the safety and tolerability of delandistrogene moxeparvovec to be manageable with appropriate monitoring and treatment of adverse events (AEs), typically occurring within 90 days post-infusion.
Objectives: Evaluate real-world postmarketing safety of delandistrogene moxeparvovec from commercially-treated patients in the US.
Methods: Patients who experienced AEs were identified from the Sponsor's (Sarepta Therapeutics) safety database (cutoff: 2 November 2025).
Results: This analysis included 715 patients (n=338 [4-7 years]; n=377 [>7 years]). Most common treatment-related treatment-emergent AEs (≥15% [events/total exposure]) were vomiting (n=141 [19.7%]), nausea (n=139 [19.4%]), and liver injury (n=132 [18.5%]). There were 57 (7.9%) events of serious acute liver injury (ALI) reported and 50 (7.0%) hospitalizations due to ALI. Serious ALI frequency and hospitalizations were similar in patients aged 4-7 and >7 years (n=26 [7.7%] vs. n=30 [8.0%] and n=23 [6.8%] vs n=26 [6.9%], respectively). One event (0.1%) of acute liver failure was reported (previously disclosed, resulting in death). Other treatment-related serious AEs included myocarditis (n=5), immune-mediated myositis (n=2), and infusion-related reactions (n=2). Limitations include incomplete, biased or under-reporting, and difficulties in attributing causality.
Conclusions: Overall safety of delandistrogene moxeparvovec in a large population of US commercially-treated patients is consistent with clinical trial results to date. Frequency of serious ALI and hospitalizations was comparable in patients aged 4-7 and >7 years, highlighting similar safety and tolerability in younger and older ambulatory patients.

124 - Indirect Treatment Comparisons of Nusinersen Versus Intrathecal Onasemnogene Abeparvovec-brve in Treatment Naïve, Later-Onset Spinal Muscular Atrophy Patients

Camilla Woodsmith[1], Jessica Owen[1], Kurt Taylor[1], Xiaomeng Liao[1], Philipp Arnold[2], Nadia Tavares[2], Chrysanthe Peteros[2], Dajun Tian[2], Catherine Mak[2]
[1]Petauri Evidence, [2]Biogen

Introduction
Nusinersen is the first approved treatment for spinal muscular atrophy (SMA) - a severe rare neuromuscular disorder causing progressive motor neuron decline and eventual death. Intrathecal onasemnogene abeparvovec-brve (OAV101 IT) is a recently approved gene therapy for SMA. In the absence of head-to-head trials comparing nusinersen with OAV101 IT, indirect treatment comparisons can estimate comparative efficacy.
Objectives
This analysis compared the efficacy of nusinersen (CHERISH (NCT02292537), DEVOTE Part B (NCT04089566)), with OAV101 IT, using data from STEER (NCT05089656), in treatment naïve, later-onset SMA patients.
Methods
Anchored matching-adjusted indirect comparisons (MAIC) compared CHERISH data to STEER in participants aged 2 to <5 years. DEVOTE Part B and STEER were compared using unanchored MAIC. Comparative efficacy was assessed using change from baseline (CFB) in Hammersmith Functional Motor Scale-Expanded (HFMSE) and Revised Upper Limb Module (RULM). Reduced effective sample sizes following weighting limited statistical power.
Results
Month 12 (CHERISH)/Week 52 (STEER) results numerically favored nusinersen 12 mg in improved CFB compared to OAV101 IT in both HFMSE (mean difference [MD]: 1.86; 95% confidence intervals [CI]:-1.08,4.80; effective sample size [ESS]/starting sample [N]:58.2/97) and RULM (MD: 1.52; CI:-0.57,3.61; ESS/N: 58.2/97). After MAIC weighting, the DEVOTE Part B (nusinersen 28 mg) versus STEER (OAV101 IT) comparison was not feasible.
Conclusions
Nusinersen may be associated with numerically greater improvements in functional outcomes compared to OAV101 IT in treatment-naïve, later-onset SMA patients. As CHERISH evaluated a lower 12-month cumulative dose (48 mg) than the licensed regimens (72 mg or 156 mg), observed results may underestimate its full efficacy.

125 - Indirect Treatment Comparison of Nusinersen 50/28 mg Versus Intrathecal Onasemnogene Abeparvovec-brve in Treatment Experienced Spinal Muscular Atrophy Patients

Camilla Woodsmith[1], Jessica Owen[1], Kurt Taylor[1], Xiaomeng Liao[1], Philipp Arnold[2], Nadia Tavares[2], Chrysanthe Peteros[2], Dajun Tian[2], Catherine Mak[2]
[1]Petauri Evidence, [2]Biogen

Introduction
Nusinersen is the first approved treatment for spinal muscular atrophy (SMA) - a severe rare neuromuscular disorder causing progressive motor neuron decline and eventual death. Intrathecal onasemnogene abeparvovec-brve (OAV101 IT) is a recently approved gene therapy for SMA, and nusinersen 50/28 mg was also recently approved for SMA. In absence of head-to-head trials, indirect treatment comparisons can estimate comparative efficacy.
Objectives
This analysis compared the efficacy of high dose nusinersen (50/28 mg) with OAV101 IT using data from DEVOTE Part C (NCT04089566) and STRENGTH (NCT05386680) in treatment-experienced SMA patients.
Methods
The DEVOTE Part C population was trimmed to sitting, non-ambulatory, <18 years-old participants for alignment with STRENGTH, following which an unanchored matching-adjusted indirect comparison was conducted. Comparative efficacy was assessed using Hammersmith Functional Motor Scale-Expanded (HFMSE) and Revised Upper Limb Module (RULM) change from baseline (CFB) at Week 42 and last observation (Week 52) in STRENGTH compared with Day 302 (DEVOTE). Reduced effective sample sizes following weighting limited statistical power.
Results
From week 42 onwards, nusinersen showed numerically greater improvements in HFMSE and RULM than OAV101 IT. Mean differences (nusinersen vs OAV101 IT) at Week 42 were 0.48 (95% confidence intervals [95%CI]: −2.26, 3.22) for HFMSE and 1.85 (95%CI: −2.18, 5.88) for RULM; and at Week 52 were 1.28 (95%CI: −1.19, 3.75) for HFMSE (effective sample size [ESS]/starting sample [N]:4.3/10) and 1.90 (95%CI: −2.10, 5.91) for RULM (ESS/N: 6.1/10).
Conclusions
In treatment-experienced patients, findings suggest that high dose nusinersen may be associated with greater functional improvements compared to OAV101 IT.

126 - Interim 1-Year Open-Label Results from the Myasthenia Gravis Inebilizumab Trial (MINT)

Richard J. Nowak[1], Michael Benatar[2], Maria Isabel Leite[3], Emma Ciafaloni[4], Kimiaki Utsugisawa[5], Sarah Bray[6], Kristina Patterson[7], Ankur Bhambri[7], Arati Kiran Kanchi[7], Sue Cheng[7], John Vissing[7], James F. Howard Jr.[8]
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Introduction: Myasthenia Gravis Inebilizumab Trial (MINT; NCT04524273), a placebo-controlled, phase 3, randomized trial, demonstrated significant improvements in Myasthenia Gravis Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG) scores in participants treated with inebilizumab versus placebo in the randomized, controlled period (RCP).
Objective: To evaluate 1-year efficacy and safety results of inebilizumab during the 3 MINT open-label period (OLP).
Methods: Participants with generalized myasthenia gravis were randomized 1:1 to receive 300 mg of intravenous inebilizumab or placebo for 52 weeks (participants with anti-acetylcholine receptor antibodies; AChR$^+$) or 26 weeks (participants with anti-muscle-specific kinase antibodies; MuSK$^\pm$) during the RCP, followed by an optional 3-year OLP wherein all participants received inebilizumab. This 1-year interim analysis includes participants who received inebilizumab during the RCP or OLP.
Results: Overall, 238 participants were enrolled in MINT; 208 entered the OLP (inebilizumab, 109; placebo, 99), and 188 completed 1 year. Baseline RCP MG-ADL and QMG scores were similar among participants. Mean improvements continued from baseline of the RCP to 1 year of the OLP for participants treated with inebilizumab/inebilizumab (MG-ADL, -6.1; QMG, -7.3) and placebo/inebilizumab (MG-ADL, -5.9; QMG, -6.9) in the combined AChR$^+$ and MuSK$^+$ populations. The safety profile in the OLP was consistent with that in the RCP.
Conclusions: During 1 year of the OLP, participants experienced sustained improvements in MG-ADL and QMG scores with inebilizumab, supporting durability of response for participants originally randomized to inebilizumab and consistency of efficacy and tolerability regardless of initial treatment in the RCP.

Neuromuscular Study Group

27th Annual Scientific Meeting

SEPTEMBER 25-27, 2026

The Historic Menger Hotel
204 Alamo Plaza, San Antonio, TX 78205

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Welcome

Dear Colleagues,

On behalf of the Neuromuscular Study Group (NMSG), we are delighted to welcome you back to San Antonio, Texas, for our 27th Annual Scientific Meeting.

For nearly three decades, the NMSG has united researchers from around the world to collaborate on advancing neuromuscular science. This meeting in particular has become a unique opportunity for our community to come together for a vibrant exchange of ideas that reinforces our commitment to progressing innovation in our field. Whether you are presenting a poster or discussing trials between sessions, we encourage you to engage fully with your colleagues and our industry partners, as your active participation will greatly strengthen the value of our time together.

A few meeting highlights for this year.

- *Emerging Investigators: We welcome back this valuable session where emerging talent can connect with and learn from established leaders in the field. Join us at 3:40 pm on Friday.*
- *Abstract Poster Presentations: We had 138 submissions this year. Please stop by to see their work at 5 pm on Friday in the Minuet and Patio Rooms.*
- *Industry Partners: We appreciate the immense industry involvement. Please join us for their presentations starting at 2:00 pm on Saturday and visit their tables daily in the Grand Ballroom.*
- *Shark Tank: In its seventh year, the Shark Tank session will feature four exciting proposals, with the winner receiving a $10,000 grant. New this year: Everyone who attends the session will be able to score the presentations. Join us at 9:00 am on Sunday.*

Outside of the scientific program, take time to enjoy the history and charm of the Alamo here in San Antonio. Starting at the historic Alamo, with its cypress-shaded River Walk and tucked-away patios just steps away, San Antonio offers a truly welcoming setting. We hope you will soak in the rich heritage, savor South Texas hospitality and cuisine, and make the most of this charming location during your visit.

We are excited for the continuing opportunity to share breakthroughs, clinical insights, and new ideas that can improve the treatment and care of our patients. Let us continue to embrace the spirit of collaboration as we explore the latest research and inspire one another with our findings.

Sincerely,

Richard J. Barohn, M.D.
Professor of Neurology, Immediate Past Executive Vice Chancellor of Health Affairs, University of Missouri
Distinguished Emeritus Professor, University of Kansas
Co-Chairman of the Neuromuscular Study Group

Professor Michael G. Hanna
Director, UCL Institute of Neurology
Co-Chairman of the Neuromuscular Study Group

RICHARD J. BAROHN, M.D.
Co-chairman,
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Professor of Neurology, Immediate Past Executive Vice Chancellor for Health Affairs, University of Missouri;
Distinguished Emeritus Professor, University of Kansas

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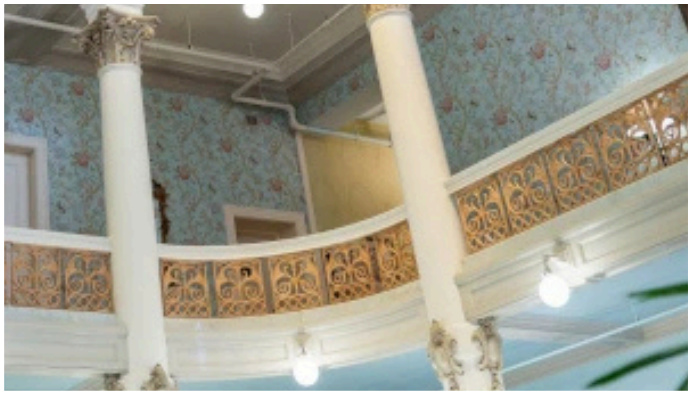
Co-chairman,
Neuromuscular Study Group

Director, University College London
Institute of Neurology

Committees



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Information

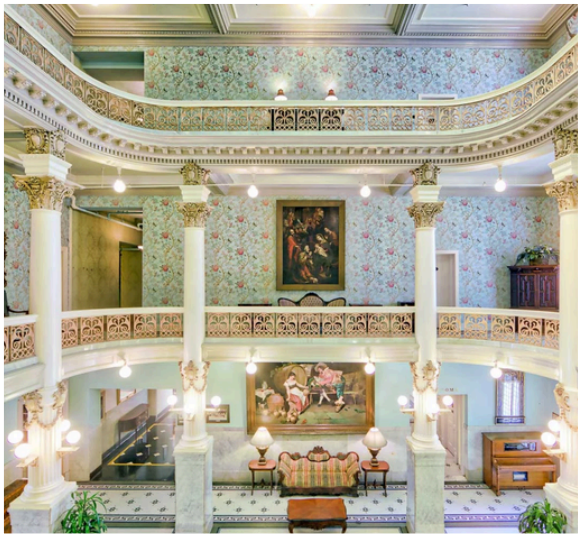
WIFI
The NMSG has special WiFi access for meeting attendees. This network can be used throughout the hotel.
Network name: NMSG2026
Password: RememberTheAlamo!

WATER AND COFFEE
Water and coffee will be provided all day in the Colonial Room.

SPEAKERS
Please provide your presentation on a USB drive to Amardeep Gill, our onsite AV expert, as early as possible so your slides can be loaded into our laptop computer.

PRESENTATION QUESTIONS
If you have a question after a presentation, raise your hand and a microphone will be brought to you.

QUESTIONS
If you have questions not related to a presentation, please ask a member of our staff at the table just outside the Poolside room.



2026 CONTINUING EDUCATION

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

JOINT ACCREDITATION STATEMENT
In support of improving patient care, this activity has been planned and implemented by Amedco LLC and Neuromuscular Study Group (NMSG). Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.
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Amedco LLC designates this live activity for a maximum of **11.75** credits *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
*All sessions are granted CME, except **Session 6** and the **Industry Presentations**, both on Saturday afternoon.

GROUP PICTURE
Don't miss the group picture on Friday, September 25th at 7:15 PM in the Victorian Lobby

Agenda

THURSDAY AGENDA

September 24, 11am-6:30pm

11:00 AM - 1:00 PM	***Executive Committee Meeting Lunch***	Cavalier Room
1:00 PM - 4:00 PM	***Clinical Trial Breakout***	Renaissance Room
4:00 PM - 5:00 PM	***CRC Meeting***	Renaissance Room
5:00 PM - 6:30 PM	***Welcome Reception***	Main Lobby

FRIDAY AGENDA

September 25, 6:30am-11:30pm

6:30 AM - 8:30 AM	***Breakfast***	Colonial and Minuet Rooms
6:30 AM - 8:30 AM	***Breakfast - ALS Military Meeting***	Cavalier Room
8:30 AM	***Welcome***	Grand Ballroom
8:30 AM	***State of the NMSG*** Richard J. Barohn, M.D., Professor of Neurology, Immediate Past Executive Vice Chancellor of Health Affairs, University of Missouri; Distinguished Emeritus Professor, University of Kansas; NMSG Board Chair Professor Michael Hanna, M.D., University College London, NMSG Board Co-Chair	Grand Ballroom
8:45 AM	***Today's Agenda*** Natalie Katz, M.D., Duke, NMSG Planning Committee Co-Chair Matt Wicklund, M.D., University of Texas Health/San Antonio, NMSG Planning Committee Co-Chair	Grand Ballroom

FRIDAY AGENDA

September 25, 6:30am-11:30pm

SESSION ONE	***GENETIC THERAPEUTICS*** Moderators: Natalie Katz and Valeria Sansone	Grand Ballroom
8:50 AM	***Triumphs, Trials, and Future Considerations in Genetic Therapies for Hereditary Neuromuscular Diseases*** Andrea Sierra Delgado, M.D., University of Missouri	Grand Ballroom
9:15 AM	***Update on Congenital Myopathies in the Genomic Era: From (Rapid) Diagnosis to Trial Readiness*** Anna Sarkozy, M.D., Dubowitz Neuromuscular Center, Great Ormond Street Hospital for Children	Grand Ballroom
9:40 AM	***Spinal Muscular Atrophy: A Journey from Fatal Disease to Fetal Therapy*** Richard Finkel, M.D., St. Jude Children's Research Hospital	Grand Ballroom
10:05 AM	***Merging Concepts in Biomarkers and Therapeutics for ALS*** Andrea Malaspina, Ph.D., FRCP, University College London	Grand Ballroom
10:30 AM - 10:55 AM	***BREAK***	Grand Ballroom Pre-Function

FRIDAY AGENDA

September 25, 6:30am-11:30pm

SESSION TWO	***BIOMARKERS*** Moderators: Matthew Birkbeck, Ph.D., Newcastle University and Andrea Sierra Delgado, M.D., University of Missouri	Grand Ballroom
10:55 AM	***Biomarkers in Myasthenia Gravis*** Pushpa Narayanaswami, M.D., Harvard Medical School	Grand Ballroom
11:20 AM	***Clinical and Genetic Heterogeneity in Facioscapulohumeral Muscular Dystrophy: Implications for Biomarkers and Trials*** Enrico Bugiardini, M.D., Ph.D., University College London	Grand Ballroom
11:45 AM	***Peripheral Immune Activation Reflecting CNS Barrier Dysfunction in ALS*** Robert Bowser, Ph.D., Barrow Neurological Institute, St. Joseph's Hospital and Medical Center	Grand Ballroom
12:10 PM	***Biomarkers in Myotonic Dystrophy*** Nicholas E. Johnson, M.D., M.Sci., FAAN, Virginia Commonwealth University	Grand Ballroom
12:30 PM - 1:30 PM	***LUNCH***	Colonial and Minuet Rooms

FRIDAY AGENDA

September 25, 6:30am-11:30pm

SESSION THREE	***ABSTRACT PRESENTATIONS*** Moderators: James Lilleker and Karen Suetterlin	Grand Ballroom
1:30 PM	***Multilevel Neurophysiologic Assessment of Cortical and Peripheral Motor System Dysfunction in Amyotrophic Lateral Sclerosis*** Arsh Ketabforoush, M.D., University of Missouri	Grand Ballroom
1:45 PM	***Clinical Outcomes and Safety of Nucleoside Therapy for Thymidine Kinase 2 Deficiency in a Brazilian Cohort*** Cristiane Araujo Martins Moreno, M.D., Ph.D, Universidade de São Paulo, Brazil	Grand Ballroom
2:00 PM	***Longitudinal assessment of motor function in Duchenne Muscular Dystrophy in a pediatric cohort: development of Italian centile curves for the North Star Ambulatory Assessment, 10-Meter Walk/Run Velocity and Rise from Floor Velocity*** Sophia Paolucci, TNPEE, Fondazione Policlinico Universitario Agostino Gemelli IRCCS	Grand Ballroom
2:15 PM	***Neuromuscular junction failure in sarcopenia is linked to NaV1.4 loss and reversed by ClC-1 inhibition*** Hiroshi Nishimune	Grand Ballroom
2:30 PM	***Real-World Givinostat Tolerability and Dose Modification in Nonambulatory Males with Duchenne Muscular Dystrophy*** Abigail B. Crowner, PharmD, MPH, University of Iowa Health Care	Grand Ballroom

SESSION THREE, CONTINUED	***ABSTRACT PRESENTATIONS*** Moderators: James Lilleker and Karen Suetterlin	Grand Ballroom
2:45 PM	***Lysosome Remodeling in CMT1A Neuropathy: Pathogenic Mechanism or Compensatory Response?*** Abigail Chischolm, M.S., University of Missouri, Columbia	Grand Ballroom
2:52 PM	***Manifesting dystrophinopathy in a girl with Williams-Beuren syndrome: a dual molecular diagnosis supported by skewed X-inactivation*** Wiktoria Błachut, medical student, Jagiellonian University Medical College, Cracow, Poland	Grand Ballroom
3:00 PM	***Near infrared spectroscopy during non-ischaemic handgrip exercise reveals distinct muscle oxygenation signatures in mitochondrial disease and sarcopenia*** Helen Devine, Newcastle University	Grand Ballroom
3:07 PM	***Retrospective Analysis of MG-ADL Data Outcomes Following Zilucoplan Treatment in Myasthenia Gravis*** Carson Barnard, M.D., University of Kansas Medical Center	Grand Ballroom
3:12 PM	***Dose-Finding Safety and Tolerability Study of Clenbuterol in Facioscapulohumeral Muscular Dystrophy (FSHD)*** Rebecca Clay, CCRP, University of Kansas Medical Center	Grand Ballroom
3:20 PM - 3:40 PM	***Break***	Grand Ballroom Pre-Function

FRIDAY AGENDA

September 25, 6:30am-11:30pm

SESSION FOUR	***EMERGING INVESTIGATORS WORKSHOP, SPONSORED BY argenx*** Moderator: Matthew Birkbeck, Ph.D., Newcastle University	Grand Ballroom
3:40 PM - 4:50 PM	***Moderator: Matthew Birkbeck, Ph.D., Newcastle University*** Mentors: Gita Ramdharry, Ph.D., Karen Suetterlin, MBBS, MRCP, Ph.D., David Arnold, M.D., Jasper Morrow, MBChB, Ph.D., Abdus S. Wahed, Ph.D., Margaret Duku	Grand Ballroom

EVENING ACTIVITIES	***EVENING ACTIVITIES***	
5:00 PM - 7:00 PM	***POSTER PRESENTATIONS***	Minuet and Patio Rooms
7:15 PM	***GROUP PICTURE***	Menger Hotel Victorian Lobby
7:30 PM - 9:30 PM	***DINNER***	The Crockett Hotel
9:30 PM - 11:30 PM	***RECEPTION***	The Menger Bar

SATURDAY AGENDA

September 26, 6:30am-11:30pm

6:30 AM - 8:30 AM	***Breakfast***	Colonial and Minuet Rooms
6:30 AM - 8:30 AM	***Journal Breakfast***	Cavalier Room
8:00 AM	***Welcome***	Grand Ballroom
8:00 AM	***State of the NMSG*** Richard J. Barohn, M.D., Professor of Neurology, Immediate Past Executive Vice Chancellor of Health Affairs, University of Missouri; Distinguished Emeritus Professor, University of Kansas; NMSG Board Chair Professor Michael Hanna, M.D., University College London, NMSG Board Co-Chair	Grand Ballroom
8:15 AM	***Today's Agenda*** Dr. Miriam Freimer, M.D., Ohio State University Matt Wicklund, M.D., University of Texas Health/San Antonio, NMSG Planning Committee Co-Chair	Grand Ballroom
8:20 AM	***Robert C. Griggs Keynote Lecture*** ***What exactly are we estimating in a randomized, controlled clinical trial?*** Professor Michael McDermott, Ph.D., University of Rochester	Grand Ballroom
9:10 AM	***NMSG Fellowship Update*** Sophie Rengarajan, M.D., Ph.D., UCLA Medical Center	Grand Ballroom
9:25 AM - 9:45 AM	***Break***	Grand Ballroom Pre-Function

SATURDAY AGENDA

September 26, 6:30am-11:30pm

SESSION FIVE	***GENETIC THERAPEUTICS*** Moderators: Matt Wicklund and John Vissing	Grand Ballroom
9:45 AM	***Genetic Nerve Diseases Across the Lifespan/CMT*** Michael Shy, M.D., University of Iowa	Grand Ballroom
10:10 AM	***CAR-T Cell Therapy in MG*** Ali Habib, M.D., UCI Health	Grand Ballroom
10:35 AM	***Precision Diagnostics and Targeted Therapies in Primary Mitochondrial Diseases*** Professor Robert Pitceathly, MBChB, Ph.D., University College London	Grand Ballroom
11:00 AM	***Fellowship Committee Meeting for Endowment possibility***	Grant Room
11:25 AM - 12:30 PM	***LUNCH***	Colonial and Minuet Rooms

SATURDAY AGENDA

September 26, 6:30am-11:30pm

SESSION SIX - NO CME	***TECHNOLOGICAL ADVANCEMENTS*** Moderators: Gita Ramdharry and Megan Iammarino	Grand Ballroom
12:30 PM	***Engineered GM1 (TLN): From Preclinical ALS Studies to Clinical Evaluation in Parkinson's Disease*** Smita Saxena, Ph.D., University of Missouri	Grand Ballroom
12:55 PM	***Spinal Cord Stimulation in Spinal Muscular Atrophy*** Marco Capogrosso, Ph.D., University of Pittsburgh	Grand Ballroom
1:20 PM	***Psychometric Testing of Functional Outcome Measures*** Katy Eichinger, Ph.D., DPT, University of Rochester	Grand Ballroom
1:45 PM - 2:00 PM	***BREAK***	Grand Ballroom Pre-Function

SATURDAY AGENDA

September 26, 6:30am-11:30pm

INDUSTRY PRESENTATIONS - NO CME	***INDUSTRY PRESENTATIONS*** Moderators: Matt Wicklund and Miriam Freimer	Grand Ballroom
2:00 PM	***Catalyst*** ***Vamorolone, a Delta-9,11 Corticosteroid: Exploring the Structural-Activity Relationship*** Keri Kasun, PharmD, Sr Medical Science Liaison – Rare Neuromuscular Disease	Grand Ballroom
2:25 PM	***Johnson & Johnson*** ***Pregnancy Enhanced Tracking with Neonatal and Infant Assessment (PETUNIA): Design of a Safety Study for Nipocalimab in Generalized Myasthenia Gravis*** Ashley Anderson, Associate Medical Director, Autoantibody, Johnson & Johnson	Grand Ballroom
2:50 PM	***UCB*** ***Understanding FcRn Biology, Treatment Durability, Steroid-Sparing Evidence, and Albumin Considerations in gMG*** Amanda Hernandez, M.D., Ph.D., Assistant Professor of Neurology, Chief of Neuromuscular Medicine, Farmington, CT	Grand Ballroom
3:15 PM	***MLBIO*** ***LGMD2I/R9 (FKRP-related) — Disease Overview and Interim Results from the FORTIFY Phase 3 Study*** Douglas Sproule, M.D., M.Sc.	Grand Ballroom
3:40 PM	***argenx*** ***From strength to function: Understanding the clinical relevance of grip strength in CIDP and MMN*** Dr. Allison Crowell, General Neurologist, Clinical Neurophysiology Penn Medicine Lancaster General Hospital	Grand Ballroom

INDUSTRY PRESENTATIONS, CONTINUED - NO CME	***INDUSTRY PRESENTATIONS*** Moderators: Matt Wicklund and Miriam Freimer	Grand Ballroom
4:05 PM	***Sanofi*** ***Riliprubart Phase 2 data and Phase 3 trial design.*** Asif Paker, M.D., M.P.H.	Grand Ballroom
4:30 PM	***Sarepta*** ***Advancing Genetic Medicine Research for Rare Neuromuscular and Central Nervous System Diseases*** Elisabeth McGee, APRN, Sarepta Therapeutics, Inc.	Grand Ballroom
4:55 PM	***Scholar Rock*** ***Going Beyond the Motor Neuron to the Muscle: Expanding the Focus of SMA Care*** Natalie Katz, M.D., Ph.D., Assistant Professor of Pediatrics (Neurology) Co-Director, Duke Children's Neuromuscular Program	Grand Ballroom
5:20 PM	***VOR Bio*** ***Our Investigational BAFF/APRIL Inhibitor: Evaluating Telitacicept in Generalized Myasthenia Gravis and Beyond*** Nolan Campbell, Ph.D. - Medical Director - Myasthenia Gravis	Grand Ballroom
5:45 PM	***Pepgen*** **FREEDOM2-DM1: Interim results of a multiple-ascending dose clinical trial of PGN-EDODM1 in people with myotonic dystrophy type 1** Paul Streck, M.D., MBA, Executive Vice President, Head of Research & Development, PepGen	Grand Ballroom

SATURDAY AGENDA

September 26, 6:30am-11:30pm

EVENING ACTIVITIES	***EVENING ACTIVITIES***	The Buckhorn Saloon
7:30 PM - 9:30 PM	***DINNER***	The Buckhorn Saloon
9:30 PM - 11:30 PM	***RECEPTION AND DANCING***	The Buckhorn Saloon

SUNDAY AGENDA

September 27, 6:30am-12:30pm

6:30 AM - 8:30 AM	***Breakfast***	Colonial and Minuet Rooms
8:30 AM	***Welcome***	Grand Ballroom
8:30 AM	***State of the NMSG*** Richard J. Barohn, M.D., Professor of Neurology, Immediate Past Executive Vice Chancellor of Health Affairs, University of Missouri; Distinguished Emeritus Professor, University of Kansas; NMSG Board Chair Professor Michael Hanna, M.D., University College London, NMSG Board Co-Chair	Grand Ballroom
8:45 AM	***Today's Agenda*** Dr. Natalie Katz Matt Wicklund, M.D., University of Texas Health/San Antonio, NMSG Planning Committee Co-Chair	Grand Ballroom
SESSION SEVEN	***SHARK TANK, SPONSORED BY ALEXION*** Francesco Sacca', M.D., FAAN, Senior Medical Director, GMA Rare Neurology, Alexion Pharmaceuticals Moderator: James Lilleker	Grand Ballroom
9:00 AM	***2025 Shark Tank Winner Update*** Grace McMacken, MBBCh, Ph.D., Queen's University Belfast	Grand Ballroom
9:20 AM	***Introduction of Sharks*** Moderators: James Lilleker, MBChB, MRCP, Ph.D., Jasper Morrow, MBChB, Ph.D., Paloma Gonzalez Perez, M.D., Ph.D.	Grand Ballroom
9:30 AM	***Shark Tank Presentations***	Grand Ballroom
11:00 AM - 11:15 AM	***BREAK***	Grand Ballroom Pre-Function

SUNDAY AGENDA

September 27, 6:30am-12:30pm

SESSION EIGHT	***THE CLINIC AND BEYOND*** Moderators: Jacqueline Montes and Nicholas Streicher	Grand Ballroom
11:15 AM	***Advancing Our Knowledge of Clinical Phenotypes Using Standardized Outcome Assessments*** Megan Iammarino, DPT, University of Texas/San Antonio	Grand Ballroom
11:40 AM	***Dysphagia in Myotonic Dystrophy Type 1: A Multidimensional Profile and Practical Approach for the Neuromuscular Clinician*** Jodi Allen, Ph.D., University College London	Grand Ballroom
12:05 PM	***Adaptive and Sequential Multiple Assignment Randomized Trials in Neuromuscular Diseases*** Abdus S. Wahed, Ph.D., University of Rochester	Grand Ballroom
12:30 PM	***Announce Shark Tank Winner***	Grand Ballroom
12:30 PM	***LUNCH***	Colonial and Minuet Rooms
AFTER LUNCH	***END OF CONFERENCE***	THANK YOU!

Notes

DOWNTOWN
SAN ANTONIO
History • Culture • River Walk
W. HOUSTON ST.
N. ALAMO ST.
BROADWAY
BUCKHORN
U.S. Federal Courthouse & Post Office
3RD ST.
E. HOUSTON ST.
San Antonio Visitor Center
Buckhorn Saloon & Museum
318 E. Houston St.
ENTRANCE ON E. HOUSTON ST.
COLLEGE ST.
The Crockett Hotel
320 Bonham St.
Hyatt Regency San Antonio Riverwalk
1
The Alamo
300 Alamo Plaza
LOSOYA ST.
2
San Antonio River Walk
PLAZA DE VALERO
BONHAM ST.
CROCKETT HOTEL
3
La Villita
Historic Arts Village
E. CROCKETT ST.
ENTRANCE ON BONHAM ST.
4
Shops at Rivercenter
THE RIVER WALK
The San Antonio River flows naturally through downtown and passes beneath several streets and bridges, including Losoya St. and E. Crockett St.
MOTOR ENTRANCE & VALET DROP-OFF ON E. CROCKETT ST.
MENGER HOTEL
Torch of Friendship
The Menger Hotel
204 Alamo Plaza
E. COMMERCE ST.
WALKING ROUTES
FROM THE MENGER HOTEL
To Crockett Hotel
~ 1 minute walk
To Buckhorn Saloon & Museum
~ 7 minutes walk
All distances are approximate.
Wear comfortable shoes and enjoy the walk!
E. MARKET ST.

Don't miss LGMD2I/R9.

Genetic testing can guide care planning[1,2]

When to suspect LGMD2I/R9

Consider LGMD2I/R9 when patients present with[2,3]:

- Pelvic and shoulder muscle weakness[2,4]
- Scapular winging[5]
- Calf hypertrophy[4,5]
- Gait disturbance, frequent falls[1,4,6]
- Elevated serum creatine kinase (CK)[4]
- Cardiac or respiratory complications over time[7]

Unexplained elevated CK?

Episodic or persistent CK elevation may be an early sign of neuromuscular disease.[8]
Avoid missed or delayed diagnosis—consider genetic testing[9]

Why test early?

- Reduce time to diagnosis in rare muscle diseases[1,9]
- Enable accurate subtype identification[1,8,9]
- Support family risk assessment and counseling[1,9]
- Inform appropriate management and referrals[1,9]

A simple path to diagnosis

1. Suspect LGMD2I/R9
Based on clinical presentation and/or elevated CK

2. Order genetic testing
Use a neuromuscular NGS panel that includes *FKRP*[2,4,8,10]

3. Results inconclusive?
Consider whole exome sequencing (WES) or genetics consultation[7,9,11]

4. Confirm diagnosis and next steps
Connect patients to appropriate specialist care and resources[2,7,9]

CK=creatine kinase; FKRP=fukutin-related protein; LGMD2I/R9=limb-girdle muscular dystrophy type 2I/R9; NGS=next-generation sequencing; WES=whole exome sequencing.

References: 1. Osman H, et al. *Health Expect*. 2025;28(3):e70271. 2. Vissing J, et al. *Neurol Genet*. 2026;12(2):e200370. 3. Murphy LB, et al. *Ann Clin Transl Neurol*. 2020;7(5):757-766. 4. Belhassen I, et al. *Acta Myol*. 2023;42(4):106-112. 5. Jensen SM, et al. *Neuromuscul Disord*. 2023;33(2):119-132. 6. Coffey LN, et al. *Neuromuscul Disord*. 2021;31(12):1235-1240. 7. Narayanaswami P, et al. *Neurology*. 2014;83(16):1453-1463. 8. Ng KWP, et al. *Front Neurol*. 2022;13:997551. 9. Georganopoulou DG, et al. *Protein J*. 2021;40(4):466-488. 10. Uzan GS, et al. *Mol Syndromol*. 2024;15(1):14-21. 11. Caramizaru A, et al. *Clin Genet*. 2026;110(1):46-63.

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(nipocalimab-aahu)

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AGAMREE® is FDA approved for the treatment of Duchenne muscular dystrophy (DMD) in patients 2 years of age and older[1]

aGamree® (vamorolone) oral suspension 40mg/mL

GAVEN
Actual AGAMREE patient

Tough on Duchenne.

"Now that we've been on it for 6 months...he's growing again, and he's happier overall." —Jessica, mother of Gaven

Visit us at the 2026 Annual Neuromuscular Study Group Scientific Meeting or learn more at **AGAMREEhcp.com**

IMPORTANT SAFETY INFORMATION

Contraindications

AGAMREE is contraindicated in patients with known hypersensitivity to vamorolone or any of the inactive ingredients in AGAMREE.

Warnings & Precautions

- **Alterations in Endocrine Function:** Corticosteroids, such as AGAMREE, can cause serious and life-threatening alterations in endocrine function, especially with chronic use. Monitor patients receiving AGAMREE for Cushing's syndrome, hyperglycemia, and adrenal insufficiency after AGAMREE withdrawal. In addition, patients with hypopituitarism, primary adrenal insufficiency or congenital adrenal hyperplasia, altered thyroid function, or pheochromocytoma may be at increased risk for adverse endocrine events. Acute adrenal insufficiency can occur if AGAMREE is withdrawn abruptly, and could be fatal. The risk of adrenal insufficiency is reduced by gradually tapering the dose when withdrawing treatment. For patients already taking corticosteroids during times of stress, the dosage may need to be increased.
- **Immunosuppression and Increased Risk of Infection:** Use of corticosteroids, including AGAMREE, increases the risk of new infection, exacerbation of existing infections, dissemination, and reactivation or exacerbation of latent infection and may mask some signs of infection; these infections can be severe, and at times fatal. Tell patients and/or caregivers to inform their healthcare provider if the patient has had recent or ongoing infections or has recently received a vaccine. Advise patients taking AGAMREE to avoid exposure to chickenpox or measles and to alert their healthcare provider immediately if they are exposed.
- **Alterations in Cardiovascular/Renal Function:** Monitor for elevated blood pressure and monitor sodium and potassium levels in patients chronically treated with AGAMREE.
- **Gastrointestinal Perforation:** Use of corticosteroids increases the risk of gastrointestinal perforation in patients with certain gastrointestinal disorders, such as active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and non-specific ulcerative colitis. Signs and symptoms of gastrointestinal perforation may be masked.
- **Behavioral and Mood Disturbances:** Potentially severe psychiatric adverse reactions may occur with systemic corticosteroids, including AGAMREE, and may include hypomanic or manic symptoms (eg, euphoria, insomnia, mood swings) during treatment and depressive episodes after discontinuation of treatment. Encourage patients to seek medical attention if psychiatric symptoms develop.
- **Effects on Bones:** Prolonged use of corticosteroids, such as AGAMREE, can lead to osteoporosis, which can predispose patients to vertebral and long bone fractures. Monitor bone mineral density in patients on long-term treatment with AGAMREE.
- **Ophthalmic Effects:** The use of corticosteroids, such as AGAMREE, may increase the risk of cataracts, ocular infections, and glaucoma. Monitor intraocular pressure if treatment with AGAMREE is continued for more than 6 weeks.
- **Vaccination:** Do not administer live-attenuated or live vaccines to patients receiving AGAMREE. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting AGAMREE.
- **Effects on Growth and Development:** Long-term use of corticosteroids, including AGAMREE, can have negative effects on growth and development in children.
- **Thromboembolic Events:** Observational studies have shown an increased risk of thromboembolism. Use AGAMREE with caution in patients who have or may be predisposed to thromboembolic disorders.

Adverse Reactions

The most common adverse reactions (>10% for AGAMREE and greater than placebo) are cushingoid features, psychiatric disorders, vomiting, weight increased, and vitamin D deficiency.

Use in Specific Populations

- In patients with mild to moderate hepatic impairment, the recommended daily dose of AGAMREE is 2 mg/kg, preferably with a meal, up to a maximum daily dosage of 100 mg for patients weighing more than 50 kg.
- When used concomitantly with strong CYP3A4 inhibitors, the maximum recommended daily dose of AGAMREE is 4 mg/kg, preferably with a meal, up to a maximum daily dosage of 200 mg for patients weighing more than 50 kg.
- The safety and effectiveness of AGAMREE have not been established in pediatric patients below the age of 2 years.

Scan to view full Prescribing Information at AGAMREEhcp.com/hcp-pi/.

To report SUSPECTED ADVERSE REACTIONS, contact Catalyst Pharmaceuticals, Inc. at 1-844-347-3277 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Reference: 1. AGAMREE (vamorolone) Oral Suspension [prescribing information]. Catalyst Pharmaceuticals, Inc.; 2024.

Catalyst pharmaceuticals

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AGA-0908-1 August 2026

Visit the Catalyst Pharmaceuticals table to learn more about LEMS.

When your patients are experiencing refractory symptoms,

LOOK OUT FOR LAMBERT-EATON MYASTHENIC SYNDROME (LEMS)[1-4]

LEMS is an underrecognized autoimmune neuromuscular disorder with symptoms that overlap with myasthenia gravis (MG).[1,5,6] However, LEMS can often be identified by autonomic symptoms, including dry mouth, constipation, and orthostatic hypotension.[2,6] Distinguishing LEMS is critical as up to 60% of cases are associated with an underlying malignancy—most commonly small cell lung cancer.[2,7-9]

Scan the QR code to learn more about anti-voltage-gated calcium channel antibody testing and a free testing option.

LEMS aware

LEMSawarehcp.com

References: 1. Merino-Ramirez MA, et al. *Can J Neurol Sci.* 2016;43(5):635-647. **2.** Titulaer MJ, et al. *Lancet Neurol.* 2011;10(12):1098-1107. **3.** Evoli A, et al. *Neuromuscul Disord.* 2024;44:104468. **4.** Evoli A, et al. Supplementary material. In: 275th ENMC international workshop: Seronegative myasthenia gravis: An update paradigm for diagnosis and management, 9–11 February 2024, Hoofddorp, the Netherlands. *Neuromuscul Disord.* 2024;44:104468. **5.** Harms L, et al. *J Med Econ.* 2012;15(3):521-530. **6.** Titulaer MJ, et al. *Lancet Neurol.* 2011; Appendix:1-4. **7.** Kesner VG, et al. *Neurol Clin.* 2018;36(2):379-394. **8.** Wirtz PW, et al. *Clin Neurol Neurosurg.* 2002;104(4):359-363. **9.** Titulaer M, et al. *J Clin Oncol.* 2008; 26(26):4276-81.

Catalyst pharmaceuticals

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PepGen™

Transforming the lives of people living with myotonic dystrophy type 1 (DM1).

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Want to learn more?

Visit our booth.

Visit our website at **www.PepGen.com** or scan the QR code.

Email us: **clinicaltrials@pepgen.com**

Our mission

Armed with the most advanced science in genetic medicine, we are in a daily race to rescue lives otherwise stolen by rare disease.

At Sarepta, every day is another twenty-four hours to stand up for patients, advance technology, challenge convention and ***DRAG TOMORROW INTO TODAY.***

SAREPTA THERAPEUTICS

SETH
Living with Duchenne muscular dystrophy

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Sanofi is Honored to Sponsor the 2026 NMSG Annual Meeting

Breaking Ground in CIDP with Complement Inhibition

Scan the QR code to learn more about our actively recruiting Phase 3 trial

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Come visit UPLIZNA at Booth #12

Scan to learn how UPLIZNA can help your patients or visit UPLIZNAhcp.com

AMGEN

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USA-335-82351 06/26

argenx-sponsored presentation

From strength to function: Understanding the clinical relevance of grip strength in CIDP and MMN

Saturday, September 26; 3:40–4:05 pm CDT
Grand Ballroom, Menger Hotel,
San Antonio, Texas

Join us on Saturday, September 26, for a symposium about grip strength in neuromuscular diseases.

Expert faculty will explore the clinical relevance of grip strength as a sensitive, objective measure of upper limb muscle function and overall muscle strength in neuromuscular diseases, such as CIDP and MMN. Faculty will also discuss insights derived from grip strength data generated in clinical trials and considerations for the use of this measure in future clinical practice.

Save the date to your calendar!

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MMN, multifocal motor neuropathy.
This event is funded and organized by argenx and is intended for healthcare professionals only.
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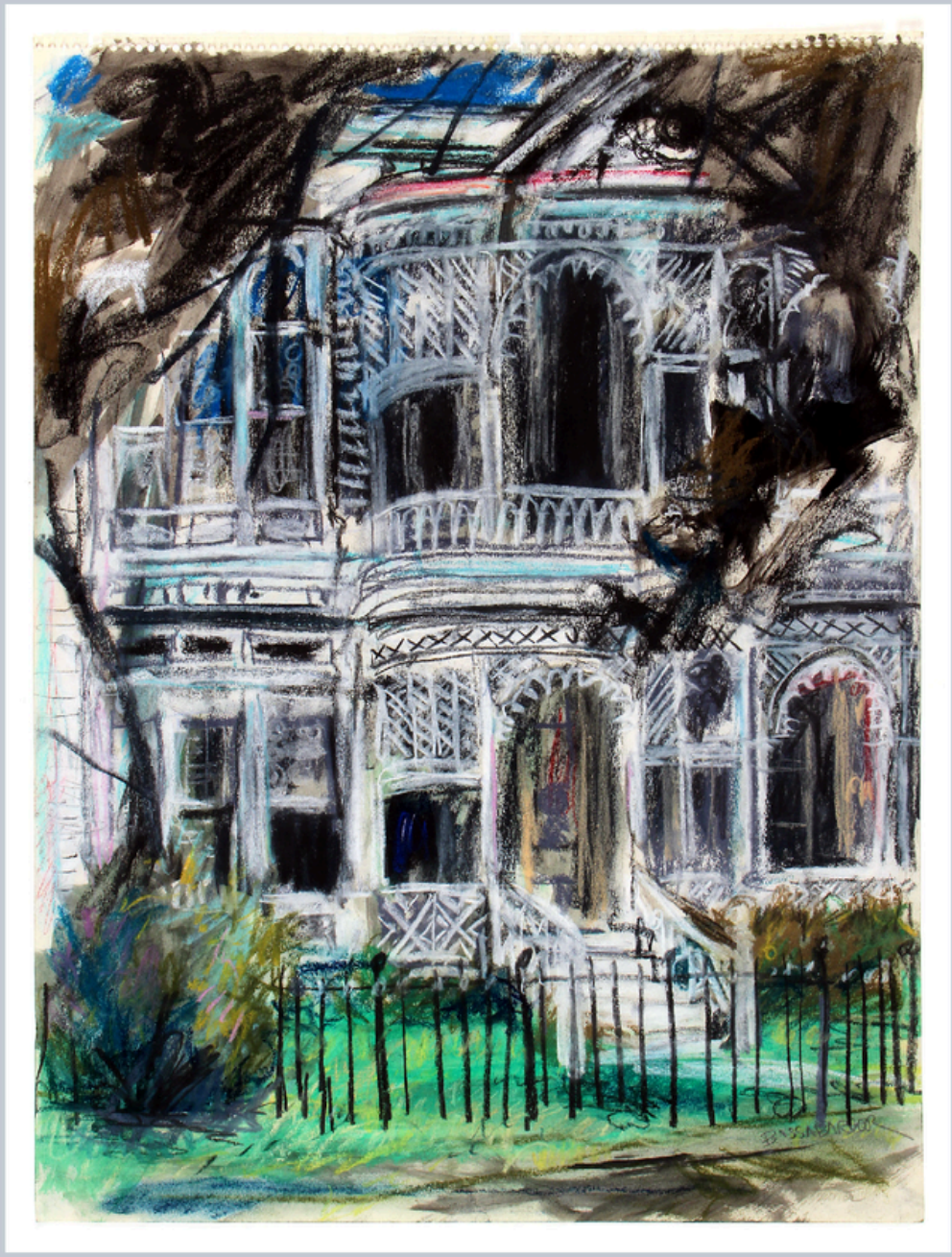
US-SRK-0060

Ben Gabelman
Living with SMA

RRNMF Neuromuscular Journal

vol. 7:2 September 2026



SAVE THE DATE!

September 17-19, 2027

27th Annual NMSG Scientific Meeting

Day One: Friday, September 25, 2026

Welcome & Meeting Overview

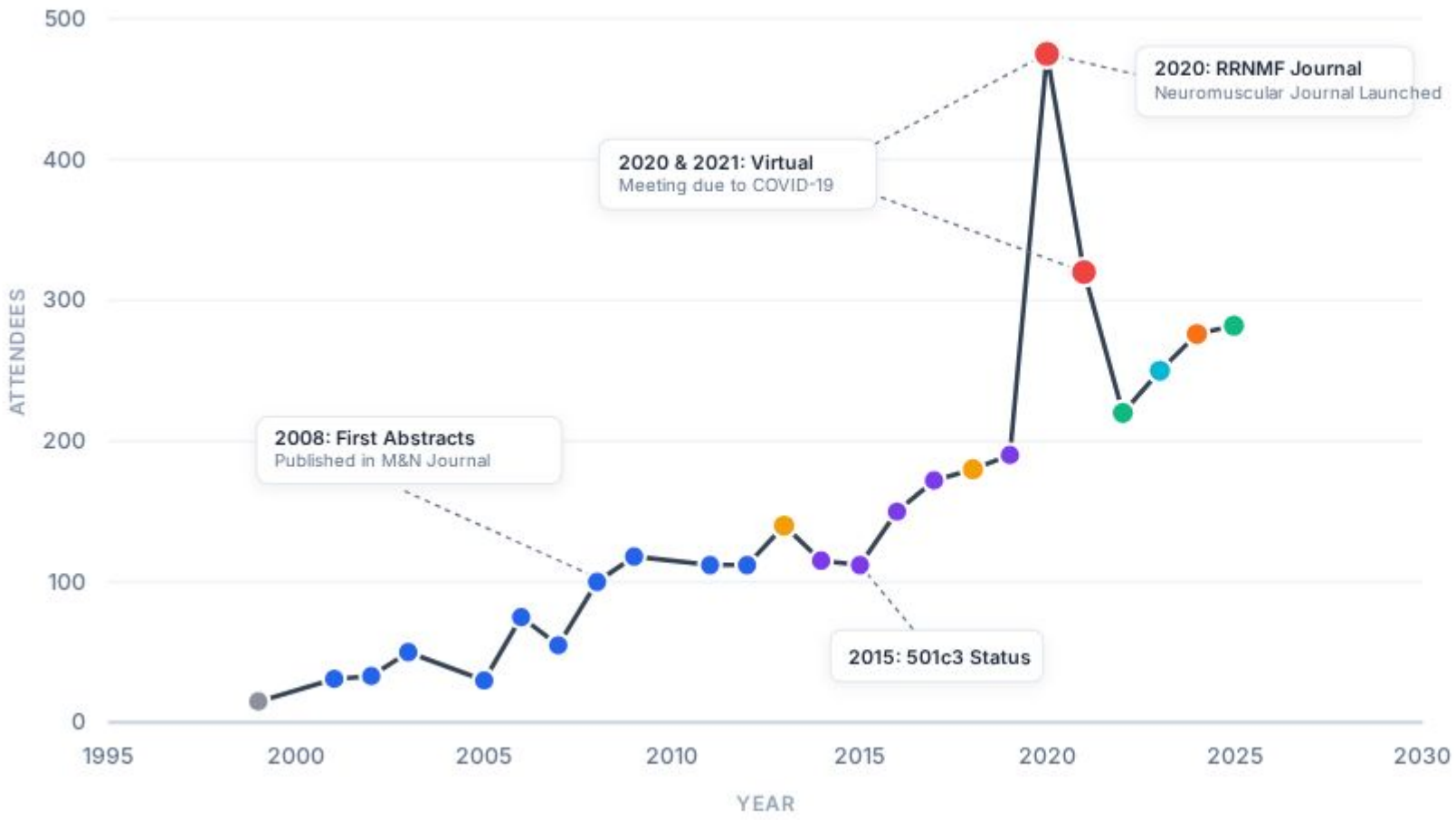
280+
REGISTERED ATTENDEES

50+
JUNIOR INVESTIGATORS

12
PARTICIPATING COUNTRIES

- Brazil
- Canada
- Denmark
- England
- Italy
- Japan
- Netherlands
- Poland
- Singapore
- Switzerland
- United Kingdom
- United States

History of the NMSG Annual Meeting



PEAK ATTENDANCE
475 (Virtual)

IN-PERSON RECORD
282 (Stresa '25)

Meeting Locations

- Chicago, IL
- Beaver Hollow
- England
- Snowbird, UT
- Remote
- Stresa, Italy
- Orlando, FL
- Tarrytown, NY
- San Antonio, TX

NMSG Strategic Goals

Premier Organization & Clinical Trials
Maintain position as the premier organization and annual meeting for neuromuscular clinical trials.

Support Young Investigators
Support and develop young investigators in the field to foster next-generation leadership.

International Collaboration
Foster global partnerships and international clinical trial collaboration.

Pre-Clinical Discovery
Connect to pre-clinical investigators who are exploring potential pathways for new treatments.

Industry Engagement
Engage effectively with pharmaceutical and industry partners to accelerate therapies.

2026 NMSG Planning Committee

Vino Vivekanandam, Ph.D., 2026 Planning Chair
University College London
Matthew Wicklund, MD, FAAN, 2026 Planning Chair
University of Texas Health - San Antonio
David Arnold, MD
University of Missouri
James Lilleker, MBChB, MRCP, Ph.D.
University of Manchester
Gina Ramdharry, Ph.D.
University College of London
Nicholas Streicher, M.D.
University of Michigan

Prof John Vissing, M.D.
Copenhagen University Hospital
Matthew Birkbeck, Ph.D.
University of Michigan
Heidi Fuller, Ph.D.
Keele University
Megan Iammarino, DPT
University of Texas Health - San Antonio
Valeria Sansone, M.D., Ph.D., Co-Chair
NeMO, Milan
Karen Suetterlin, MBBS, MRCP, Ph.D.
Newcastle University
Richard J. Barohn, M.D., NMSG Chair
University of Missouri

2026 NMSG Executive Committee

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University of Missouri
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University of Rochester School of Medicine
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Valeria Sansone, M.D., Ph.D., Incoming Investigator Member,
NeMO Milan
James Lilleker, MBChB, MRCP, Ph.D., Investigator Member,
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Bhaskar Roy, MBBS, MHS, Young Investigator Member, Yale School of Medicine

Michael Hehir, M.D., Outgoing Investigator Member,
University of Vermont Medical Center
Michaela Walker, MPH, CCRP, Coordinator Member, University of Kansas Medical Center
Abdus Wahed, PhD, Director, NMSG Biostatistics Center, University of Rochester Medical Center
Emma Ciafaloni, M.D., FAAN, Director, NMSG Coordination Center
University of Rochester Medical Center
Mazen Dimachkie, M.D., Treasurer
University of Kansas Medical Center
Karen Mul, M.D., Ph.D., Incoming Investigator Member,
Radboud University Medical Center
John Vissing, M.D., Outgoing Investigator Member,
University of Copenhagen

2026 NMSG Special Thanks

Amardeep Gill, *Livestream Director, StreamGuru.net*, *AV*

Liz Russo Paulk, *NMSG Administrative Manager*

Kelly Gregory, *University of Missouri*

J. Andrea Sierra Delgado, M.D., *University of Missouri*

Susanna Pozzi, *NeMO Milan*

General Meeting Information

RESTROOMS are located just outside Ballroom C.

WATER AND COFFEE all day in the Grand Ballroom pre-function space.

SPEAKERS - Please provide your presentation on a USB drive to Amardeep Gill, our onsite AV expert, as early as possible so your slides can be loaded into our laptop computer.

QUESTIONS AFTER A PRESENTATION? Raise your hand and we'll bring a microphone to you.

OTHER QUESTIONS? Please ask a member of our staff at the table just outside Ballroom C.

WI-FI ACCESS Network: **NMSG2026** | Password: **RememberTheAlamo!**

Abstracts

NMSG Abstracts

The accepted abstracts for this conference are published in **RRNMF Neuromuscular Journal**. Use the QR code in your agenda book to retrieve them.

Scan QR Code in Agenda Booklet

Fellowship

Our **Neuromuscular Review Course** returns this spring with a new set of virtual continuing education courses!

Designed with neurologists, physicians, primary care providers, physical medicine specialists, and advanced practice professionals in mind, this course will provide you with up-to-date insights into the clinical approach of diagnosing and managing neuromuscular diseases.
The 2027 Next Generation Research Grant in Neuromuscular Disease will open for applications in mid-June. This early-career research grant consists of a commitment of $150,000 over two years, and is awarded in partnership between the NMSG and the American Brain Foundation. Applications are due October 1, 2026, and funding begins on July 1, 2027. For additional details and to apply, visit ***https://www.americanbrainfoundation.org/for-researchers/#ngrg.***

- **June 2026: Fellowship applications open, watch June newsletter for details**
- **October 1, 2026: Applications close**
- **October – December 2026: Reviewers evaluate applications**
- **Mid-January 2027: Reviewers meet to discuss applications and select recipients**
- **July 1, 2027: Fellowship begins**

AMERICAN BRAIN FOUNDATION

Continuing Education

- In support of improving patient care, this activity has been planned and implemented by Amedco LLC and Neuromuscular Study Group (NMSG). Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.
-
- Amedco Joint Accreditation #4008163
-
- Physicians (ACCME) Credit Designation Amedco LLC designates this live activity for a 14.25 credits AMA PRA Category 1 CreditsTM. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Friday Highlights

- 9:00 am - Genetic Theraputics
- 10:45 am - Biomarkers
- 1:30 pm - Abstract Presentations
- 3:40 pm - Early Investigators Workshop sponsored by argenx
- 5:00 pm - Poster Presentations
- 7:15 pm - Group Picture
- 7:30 pm - Dinner at the Crockett Hotel
- 9:30 pm - Reception at the Menger Bar

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- UCB/Medical
  - Poster Session

Thank you again all sponsors

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- PTC Bio
- Sanofi
- Sarepta Therapeutics
- Scholar Rock
- Solid Biosciences Inc.
- UCB/Commercial
- UCB/Medical
- VOR Bio

Closing Remarks

One Last Thought

"Whether you are presenting a poster or discussing trials between sessions, we encourage you to engage fully with your colleagues and our industry partners as your active participation will greatly strengthen the value of our time together."

27th Annual NMSG Scientific Meeting

Day Two: Saturday, September 26, 2026

Reminders

- If you have a question after a presentation, raise your hand and we'll bring a microphone to you.
- If you have questions not related to the presentation, please ask a member of our staff at the table just outside the sponsor room.
- The NMSG has a special WiFi access for meeting attendees. This network can be used throughout the hotel.
  Network name: NMSG2026
  Password: RemembertheAlamo!

Become a NMSG Member!

1. On the NMSG website the application is under the membership tab.
2. The NMSG Executive Committee will review your application and contact you with any questions.
3. If your site is approved, we will invoice you for $500 which is good for the calendar year and includes all researchers at your site.

Questions?

Ask our group's administrator

Kelly Gregory

NMSG Member Benefits

- Discounted registration to this meeting
- Brainstorming potential study ideas
  - Steering committee input
- Critiquing grant submissions
- Mentorship
- Database management
- Statistical support
- Funding assistance
- Shark Tank competition
- Hang out in cool places with other neuromuscular academics and industry partners

NMSG Member Sites – Current on Dues

- Beth Israel Deaconess
- Cedar-Sinai Los Angeles
- Common Spirit
- Indiana University
- Northwestern University
- Univ of MASS Medical School
- University of California, Irvine
- University of Kansas Medical Center
- University of Milan
- University of Missouri
- University of Nebraska
- University of Pittsburgh
- University of Rochester Medical Center
- University of Texas Health Science Center, San Antonio
- University of Vermont

Thanks Again to:

- Amardeep Gill, *Livestream Director, StreamGuru.net*
- Liz Russo Paulk, *NMSG Administrative Manager*
- J. Andrea Sierra Delgado, M.D., *University of Missouri*
- Megan Galmiche, *University of Missouri*
- Birda Lewis, *University of Missouri*
- Kayla Bunch, *University of Missouri*
- Kelly Gregory, *University of Missouri*

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Continuing Education

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- Physicians (ACCME) Credit Designation Amedco LLC designates this live activity for a 14.25 credits AMA PRA Category 1 CreditsTM. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Saturday Highlights

- 9:30 am - Genetic Therapeutics
- 12:30 pm - Technological Advancements
- 2:00 pm - Industry Presentations
- 7:30 pm - Dinner at the Buckhorn Saloon
- 8:30 pm - Buckhorn Museum
- 9:30 pm - Dancing at the Buckhorn

27th Annual NMSG Scientific Meeting

Day Three: Sunday, September 27, 2026

Sunday Highlights

- 9:00 am - Shark Tank sponsored by Alexion
- 11:15 am - The Clinic and Beyond
- 12:20 pm - Shark Tank Winner Announcement
- 12:30 pm - Lunch

Continuing Education

- In support of improving patient care, this activity has been planned and implemented by Amedco LLC and Neuromuscular Study Group (NMSG). Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.
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Thanks Again to:

- Amardeep Gill, *Livestream Director, StreamGuru.net*
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- Megan Galmiche, *University of Missouri*
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Sponsors – Thank You!

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Sponsors – Thank You

And thanks again to our 2026 sponsors!

Join us next year in Tarrytown, NY, from September 17-19, 2027

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