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RICK'S REAL NEUROMUSCULAR
Friends

FACILITATORS

Cover Image: *The School of Athens* by Raphael, c. 1509-1511.
Fresco, Apostolic Palace, Vatican City

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Message from the Founding Facilitator for Volume 4, Issue 4

Richard J. Barohn MD

For Volume 4, Issue 4 we have a number of outstanding contributions to the RRNMF Neuromuscular Journal. In the "What's on your mind?" category, once again Drs. Freeman and Frey have thought provoking articles on the nature of health care delivery in the United States. Dr. Bill Campbell gives his empathetic view on a neuromuscular neurologist, Dr. Rick Olney, who was diagnosed with and died from ALS. Medical student Vincent Czerwinski provides insight into both how the care giver and the child patient must feel in the clinical setting in the face of a rare muscle disease.

In Clinic Stuff, Dr. Mahmoud and colleagues at the University of Missouri-Kansas City and Saint Luke's Hospital describe a case of pembrolizumab-induced myasthenia, myocarditis and myositis. Dr. Savaj and colleagues at Hinduja hospital, Mumbai report a case of neurolymphomatosis infiltrating the brachial plexus. The neurology group at the Medical University of South Carolina led by Drs. Rajan, Ruzhansky and others present a fascinating case and family with an autosomal dominant ATXN2 gene mutation that presented with either an ALS or a spinocerebellar atrophy phenotype in various family members. Dr. Morena and colleagues in both New York and Pennsylvania report a case of an intra neural ganglion cyst of the perineal nerve at the lateral knee and review the literature. Finally, Medical student Vincent Czerwinski (who wrote the What's on Your Mind piece) and his mentors at the University of Kansas Medical Center describe a child with an RYR1 mutation who was managed for respiratory failure and exhibited imaging evidence of leukoencephalopathy in the caudate and putamen that they suggest cannot be explained by hypoxia.

In the New Stuff section, Dr. Pasnoor and my colleagues at Kansas, Texas, Ohio and Buffalo at long last report a project we began in the early 1990s. We created a detailed coding system for neuromuscular disorders and five institutions utilized this for a number of years, both prior to the advent of electronic medical records (EMR) and during the early years of EMR. The goal was to categorize patients better than the ICD9 and subsequently the ICD10 could. I think our attempt was a valiant one and there are some lessons learned. I still believe this system or a modification of it could be useful on a wider basis, but it would have to be embedded into the EMRs, which seems unlikely to happen.

Finally, we have a Meeting Stuff section for this issue in which we publish the abstracts presented at the annual NMSG meeting. This organization used to be called the MSG and a year ago we officially changed the name. This year the meeting will be held in Orlando, Florida. Our goal is to publish the abstracts just before the meeting is held.

I once again would like to thank our lead medical student editor, Jihane "Jiji" Oufattole who works tirelessly to copyedit manuscripts and also sends notices to authors on the status of their papers. Jiji is now in her fourth year of medical school at the University of Missouri and she has been assisting us for several years. She is training a new group of MIZZOU medical students to take over for when she graduates in 2024. I also want to thank our superb digital press editors, Marianne Reed and Eric Bader. We cannot get an issue out without them.

Since we began the journal, Drs. Michael Pulley and Yuebing Li have served as associate facilitators. They also deserve a huge "Thank You" from me. I am pleased to announce we have a new associate facilitator, Dr. Salman Bhai from UT Southwestern Medical Center in Dallas. Dr. Bhai represents the next generation of leaders for this journal. Also, Lauren Peck, an undergraduate at the University of Missouri, is now officially our undergraduate facilitator. Lauren has been helping with various journal functions and we greatly appreciate her involvement.

For this issue's cover art, we are reproducing the incomparable painting in the Vatican by Raphael, "School of Athens." This amazing true classic work of art is appropriate for the issue that houses our annual NMSG proceedings. The fictitious school of Athens with Socrates, Aristotle, and other scholars is a nice image symbolizing how thought leaders gather to advance knowledge. This can happen at academic meetings of any kind: Athens or Orlando. Gatherings of academics and their sponsors can occur anywhere. Recall Raphael was sponsored by the Vatican to make this work of art, just as the NMSG has sponsors to make it possible to hold our annual meetings. It is also appropriate to use this cover after the successful publication of the proceedings of the Myasthenia Gravis Foundation of America meeting in Volume 4, Issue 3 of this journal. We would like this journal to become a place for neurologic scholars to publish their meeting proceedings—just like the School of Athens!

Richard J Barohn MD
Founding and Chief Facilitator

Profits Over Patients

Joshua Freeman, MD

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

The *New York Times'* exposé (one of several) on the despicable actions of large, ostensibly "non-profit" health systems, 'How a Sprawling Hospital Chain Ignited Its Own Staffing Crisis', examines Ascension Health, one of the largest such systems in the US. It is definitely worth reading, although you may want to try deep breathing first. Ascension owns hospitals over a wide area of the US, mainly in the Midwest, and took a bow in 2019 when it "*was trumpeting its success at reducing its number of employees per occupied bed, a common industry staffing metric,*" saving $500M! Unfortunately, cutting the number of employees to bare bones limited the quality of care available to patients. And when the COVID pandemic hit, and occupancy rates skyrocketed, they were woefully understaffed – except that the woe was experienced by the patients who sought, and to one degree or another, received care in those hospitals. It was and remains a disaster. Among the impacts cited in the article: at one hospital *"there were so few nurses that psychiatric patients with Covid were left waiting a full day for beds, and a single aide was on hand to assist with 32 infected patients;"* at another "*Chronic understaffing meant that patients languished in dried feces, while* robots *replaced nursing assistants who would normally sit with mentally impaired patients.*" Think about that patient being your parent! Disgusting? Upsetting? Dangerous? How about downright evil?

But, you might think, the cost cutting was necessary. After all we read about hospitals that are on the brink, are barely surviving, needing government bailouts to keep serving their communities. Oh, wait, those are different hospitals. Those are rural safety net hospitals. Ascension, on the other hand, has $18 Billion in the bank. **$18 Billion!** In a "non-profit" hospital system! Boy, I'm sure that those C-suite execs who oversaw that got big 7-figure bonuses! And now? With that much in the bank, I doubt they are going to suffer much just because people are getting terrible care and dying in their hospitals.

So how are these systems non-profit? The *Times* does a good summary:

> *In exchange for avoiding taxes, the Internal Revenue Service requires them to offer services, such as free health care for low-income patients, that help their communities.*

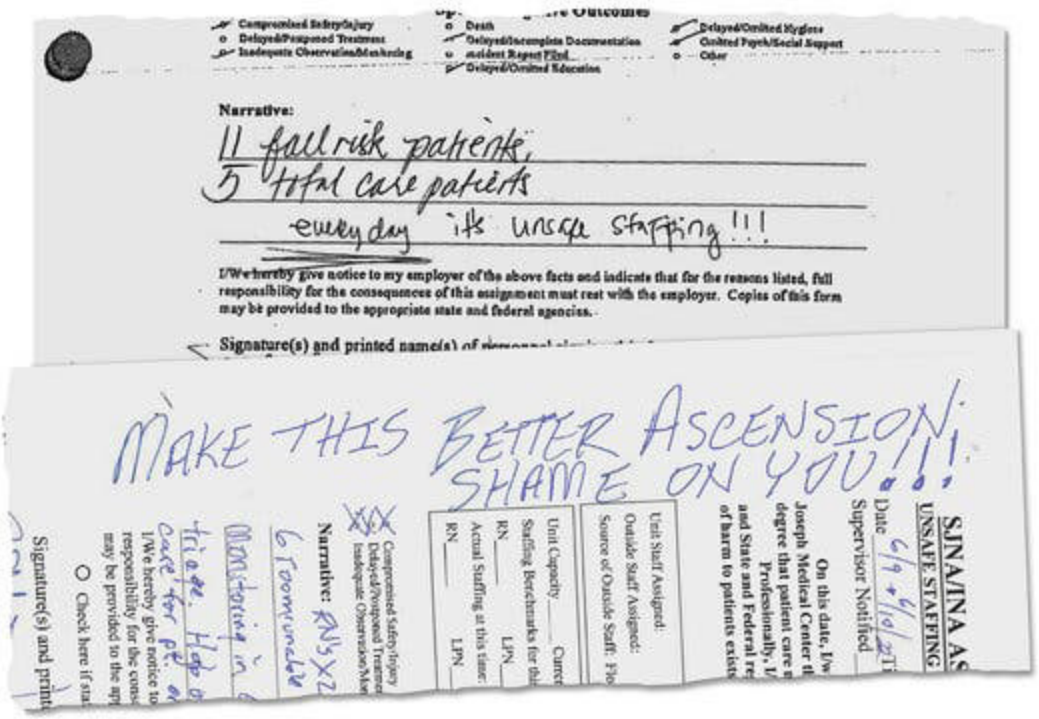
But...

> *The* Times *this year has documented how large chains of nonprofit hospitals have moved away from their charitable missions. Some have skimped on free care for the poor,* illegally *saddling tens of thousands of patients with debts. Others have plowed resources into affluent suburbs while siphoning money from poorer areas. And many have cut staff to skeletal levels, often at the expense of patient safety.* (And see this article on rural hospitals shutting their maternity care units.)

Oh. That doesn't sound so good. And, to be sure, Ascension is far from the only "non-profit" hospital chain to behave in this manner; most of the big and "successful" ones do so. The West's Providence Health System, the focus of a previous *Times* exposé and post on this blog ("Non-profit" hospital systems behaving worse than for-profits: No end to the scams," October 1, 2022), ironically started by an order of nuns to care for the poor and underserved, also gets coverage in this article.

There is so much evil here it is hard to know where to start. Certainly, a key part is running networks of institutions ostensibly created to heal the sick and injured ("hospitals") as if they were manufacturing businesses and employing *au courant* management strategies designed for manufacturing, such as "just in time" supply chains and cutting staff down to the bone. This is absurd; hospitals, to be effective, to be able to meet regular seasonal changes, not to mention disasters or pandemics, need to have excess capacity at all times. Running "lean and mean" is wrong on many levels. It is exploitive of the staff, and indeed puts staff in the position of providing poor-quality care to their patients, compromising their professionalism and commitment; the testimonies of the nurses at Ascension are the most damning part of the report. It makes it difficult to impossible to gear up in times of need. And it um, kills people. You cannot have a potential staff of on-again-off-again health care workers to be employed just when needed "just in time". If you could, if such excess capacity existed in the society, it would be yet another sign of perversion, of oppressing people and their families and communities to make more money – profit for "non-profits".

Another way that this is, to put it gently, inequitable, is described in the *Times* article: cutting back on



services in high-need-but-low-income communities and reallocating them to wealthier neighborhoods. And, of course, emphasizing and marketing high profit-margin services (cancer care, orthopedics, neurosurgery, cardiac interventions). Again, a morally bankrupt strategy to meet not the health needs of our country but rather the dollar desires of a board of directors!

So what do I have to add to the excellent coverage given to this issue by the *NY Times*? They even call it "Profits over Patients," which it is. I think I can give the problem a name that the *Times* will not: Capitalism. Capitalism is the problem. And it is not just any capitalism, it is not the capitalism of mom-and-pop stores or small businesses or making a reasonable profit, it is the capitalism-run-amok, it is the capitalism of anything-for-a-buck, full-speed-ahead, don't-care-who-gets-hurt, bigger-is-better, I-want-to-be-a-billionaire-too that we have seen increasingly over the last decades. It is the capitalism that Noam Chomsky calls "gangster capitalism", but in many ways what these folks do worse than what gangsters do, because it threatens not only people but all of our society. Sure, a gangster may threaten or even kill you. These systems are *designed* in a way that will kill thousands! But you know what? That seems to be the end point of capitalism. That is the Gordon Gekko, greed-is-good, result of capitalism that is not only unfettered by government regulation (especially with the elimination of many of the best parts of the New Deal) but that is actively enabled by a government that is willing to let private companies take all the profits when they make them and bail them out when they lose. And it is arguably even more evil that the hospitals described in the *Times* article are large "non-profits" which behave exactly like for-profits except that they don't pay taxes! Who would have thought I'd be arguing for for-profits? Well, I'm not; they actually provide even worse care for the community because there are almost no regulations governing what they do. But at least they pay taxes.

So what can be done? A great deal actually.

- Ban for profit corporations, or any entity controlled by private equity, from health care delivery. Yes, hospitals, but also clinics, urgent care centers, nursing homes, etc.
- Require not-for-profit entities to behave like non-profits are supposed to, with community benefit being the SOLE criterion by which they are judged. Do not allow building of facilities, expansion, or the dissolution of "product lines" except when it can be demonstrated that this will benefit the health of the overall community. Not allow "we're moving into/building into this prosperous expanding suburb because, you know, they will need health care" if it means there will be inadequate resources to serve the people in the most needy, sickest, and poorest communities. No cannibalizing inner-cities to feed wealthier suburbs. And while it may not be possible to directly regulate the income (salary and

bonuses) of C-suite executives of non-profits, the requirements should ensure that they cannot make loads of money and build huge reserves ($18 billion! Come on!) If they won't do this, tax them!

Ensure that the communities most in need, especially in rural areas, have their needs met on a case-by case-basis. The absurd Hobson's Choice the federal government is offering rural hospitals, crystallized in the headline of the article cited in the second paragraph, "A Rural Hospital's Excruciating Choice: $3.2 Million a Year or Inpatient Care?" must be changed so that each hospital, and the larger community it serves (sometimes geographically enormous), gets support for what it needs, inpatient care, outpatient care, and usually both.

Even better, while eliminating private for-profit ownership, discourage misbehavior by non-profit owners by creating and implementing a single payer health system, such as Medicare for All, which as the sole payer would be able to regulate these health systems for the benefit of the health care of the people of our country.

Drugs, Guns, Geezers, and Money

Donald R. Frey, MD

Originally published in Dr. Frey's blog "A Family Doctor Looks at the World."
https://afamilydoctorlooksattheworld.com/

For a lot of reasons, I haven't had a chance to write much lately. In the meantime, lots of things are crashing all around us—some good, some not so good. For now, let's focus on three (actually, any one of these three could be a topic in and of itself, but time grows short).

Older readers will recognize the title of this piece as a play on the old song title "Lawyers, Guns, and Money" by an off-the-wall songwriter named Warren Zevon, who, like Jimmy Buffett, is no longer with us. But references aside, let's look at what recent news has to say about the cost of prescription drugs, the fall-out from new gun laws, the outlook for the future of older Americans, and what all of this is costing.

And if you're younger? Sorry, but you can't relax. All of this will hit you a lot sooner than you can imagine.

PRESCRIPTION DRUG COSTS

Let's say you walk into a grocery store with a list of items you need to pick up. You grab what's on the list, toss them into your cart, and get in line at the checkout counter. You notice that the person in line just ahead of you is your neighbor Charlie. He has exactly the same items in his cart as you.

The cashier rings up Charlie's groceries. "That'll be $49.15," the cashier says with a smile. Charlie pays for the groceries, and leaves. The cashier next rings up yours.

"That'll be $112.08," she says, with the same smile she gave Charlie.

You're stunned. "Wait, I got the same things as Charlie! This has to be a mistake!"

"No mistake," she says. "That was Charlie's price. This is yours."

"But you can't do that! I shop here all the time!"

"I know," the cashier politely says. "But we always charge you more than double everyone else. Edna, Frank, Bill, Lucy—all of your neighbors. We'd charge them $49.15. Just not you."

"Why?"

The cashier shrugs. "Because we can get away with it, I guess. You don't seem to notice. And we have lots of expenses that people don't realize, and we don't want to trouble your neighbors. But if we didn't charge you a lot more, we just couldn't stay open.

"That's bullshit!" You rage. "This store makes plenty of money! I see where the store's owner lives and the kind of car he drives. You're just gouging me to make even more!"

The cashier smiles. "Well, maybe. But you keep paying it, don't you?"

Tell me—if that happened to you, would you ever shop there again?

But this is exactly what you're doing when you pay for prescription medications. The same drugs, manufactured by the same companies, rolling off the same production lines are sold to you for over twice the price paid in other countries. And those drugs aren't some kind of cheap, dangerous knock-offs. They're the same pills, gels, and liquids.

Why? Keep in mind that drug companies are multinational. Pfizer (an American based company), sells Lipitor all over the world. Novo Nordisk (a Danish company), sells Ozempic all over the world—and not just to rich Americans. In fact, of the twenty largest pharmaceutical companies in the world, the majority aren't even based in the U.S.

It's important to point this out, because the excuse we always hear for high drug costs is that companies need to charge through the ceiling in order to fund their research. The facts, however, tell a different story.

Pharmaceutical companies spend more on marketing than on development. In other words, they spend more money trying to *convince* you to take the blue pill than they spent actually *developing* the blue pill in the first place. In addition, they make more in actual profit than what they have put into research. And more often than not, the basic research behind the drug was actually government funded (either by the U.S. or elsewhere).

But as long as they can convince you that if you don't overpay for your prescriptions, then all research will vanish and it will be the end of the world as we know it, they'll keep making out like bandits .

So let's go back to the grocery store example. What if you found out that the reason your neighbors could pay so much less was because they got together and negotiated with the store for a lower price? You'd insist that you should be included, too. Why should you foot the bill when they don't?

This is what happens virtually everywhere else in the world. The country negotiates directly with a drug company, uses its group purchasing power, and drives down the costs to its citizens. It works. But in the U.S, it's illegal.

Why? Because in 2003, President George W. Bush signed the Medicare Modernization Act, which, with the backing of the pharmaceutical industry, outlawed direct negotiations. With the stroke of a pen, Bush insured that Americans would overpay for medications for decades to come.

But that's beginning to change, and the drug companies are throwing a fit. The Biden administration recently announced they would negotiate directly for ten costly drugs to bring down costs, Eliquis, Jardiance, Xarelto, Januvia, Farxiga, Entresto, Enbrel, Imbruvica, Stelara, and Fiasp.

You've heard of most of them. They're advertised constantly on TV, but according to their manufactures, allowing American consumers to pay less—and to pay no more than the rest of the world is paying—is just asking too much! And all the while, these same companies are spending billions of your money on marketing.

Let's face it. There are only two real possibilities. Either the drug companies are right, and they have to charge us more for the same medications as anywhere else in the world to fund research (which is highly doubtful), or they're deliberately misleading us as an excuse to charge us more and rake in more profit (which is far more likely).

Take your pick. But either way, we're being taken for a ride. And if we allow this to continue, we should just get a big ink pad and stamp the word "STUPID" in all caps in the middle of our forehead. We have no one to blame but ourselves.

THE NO-PERMIT NO-QUESTIONS NO-THINKING CONCEALED CARRY LAWS

Earlier this month, Nebraska joined an increasing number of states (including my childhood home of Missouri) in allowing anyone to carry pretty much any gun any place at any time without a permit. The thinking, beyond the usual "this is my right and I don't give a damn how it affects anyone else but me!" reasoning is that carrying a gun will somehow make society safer. I've already written here and here about the serious flaws in this logic.

Ironically enough, almost to the day that Nebraska changed its law, a major study was published which reviewed gun deaths in West Virginia before and after institution of a law allowing permit-less concealed carry. It found that firearms mortality jumped by 48% after their law was passed. Whatever you might want to believe, the law didn't make things safer.

No, West Virginia isn't every state. But it gives us a cautionary message that gun laws make a difference. I've already talked about Florida, where gun deaths have increased 32% since the passage of so-called "stand your ground" laws. As the data keeps coming in, it's becoming clearer and clearer that America's gun fetish is actually killing more and more of us.

All of this has enormous implications for all of us, but especially our police officers who now must confront the fact that our streets may be loaded with untrained, angry, uninformed people who are packing loaded handguns. They will have to weigh this fact every time they approach a citizen.

Is this the kind of country we want? We should think about that long and hard. That is, if we still care about the truth.

GEEZERS AND MONEY

I don't think any textbook explicitly states when geezerhood begins, but there's no question that I am there. Knee replacements, hearing aids, and dental implants. It's not great, but it does beat the alternative. As someone who's lectured for decades on the topic of geriatric medicine, the fact that all this stuff is now happening to me frankly sucks.

As many of you know, and others will one day find out, Medicare was created to be a safety net for medical expenses for geezers like me. For many of us, it's been a godsend.

But Medicare has been scapegoated by the political right for generations (at least since 1965). Conservatives have been decrying the program since it began. All along, they've claimed the program's costs would destroy it.

They've also tried to kill it through various other means, the leading ones being bleeding the program through the promotion of so-called Medicare Advantage, and as I mentioned at the top of this article, funneling Medicare money to boost pharmaceutical profits.

Regardless, Medicare has continued to meet its commitments, despite all of the doomsday pronouncements. But last month, financial reports revealed something no one saw coming. Over the past ten years, Medicare spending per enrollee has stopped growing. In fact, it's actually receded.

In 2011, Medicare spent $13,159 per recipient. At that rate, it was expected to hit $22,006 by 2023. Instead, current spending is flat at $12,459—barely half of the predicted sum, and even less than 2011.

What happened? We simply don't know. Are geezers like me using fewer services? Probably not.

Is America's declining life expectancy a factor? After all, if people aren't living as long, they won't be going to the doctor as often. This might be a small issue but can't really explain the $10,000 per person gap.

Here's a possible reason. The Affordable Care Act (ACA) or Obamacare, if you'd prefer. 20 million Americans who previously had no insurance now are covered. The ACA requires that preventative services are paid for. As a result, millions who might have forgone care in their 40's and 50's because they couldn't afford it, now have access. Could they be entering the Medicare program with fewer delayed (and more expensive) health care problems? After all, the more cases of high blood pressure you can detect and treat early on, the fewer strokes you'll have to treat later. The more cases of diabetes you can detect and treat early, the fewer amputations you'll have to do later.

How long this will last is uncertain. Right now, a far-right Trump appointed judge in Texas is doing everything he can to strike the provision down. Apparently, he doesn't

think screening for cancer, diabetes, etc., is something worth paying for.

At some point, Medicare costs will once again start rising, as everything ultimately does. But in the meantime, despite hemorrhaging money to private insurers through Medicare Advantage, paying exorbitant dollars to big pharma, and being nickel and dimed by the far right, Medicare is holding its own. Get rid of the twin impediments of Advantage plans and overpayment for medications (as the new rule allowing direct Medicare drug negotiations is intended to do) and Medicare's outlook is even better.

That's good news if you're a geezer like me. But even better news for all of you future geezers who may be out there.

Flouting the rules

William W. Campbell, MD, MSHA

There should be a rule in medicine: cardiologists shouldn't have heart attacks, oncologists shouldn't get cancer, lupus should spare rheumatologists. Why? Because they know too much. They can see what's coming. They know the complications. They know the drug side effects.

Following this rule, neurologists should never develop ALS.

Unfortunately, there is no such rule.

Other rules also apply. ALS only affects nice people. The disease has a peculiar predilection to attack nice people and spare mean people. And ALS loves the ironic twist.

Another rule: when you hear hoofbeats, think horses, not zebras. This maxim reminds physicians that common things are common. A patient with fever and a cough probably has a viral upper respiratory infection, not anthrax. The aphorism is all well and good, except when the horse is an inexorably progressive and inevitably fatal disease—when the horse is ALS. Then you have to be absolutely certain this thing that appears to be a horse is not a zebra in disguise.

We know that certain diseases can mimic the clinical picture of ALS. Some of these mimickers are treatable. The evaluation of an ALS patient includes a search for conditions known to mimic it, but all of them are rare and the search is usually futile.

A new mimicker appeared on the scene in the late 1980's, a condition called multifocal motor neuropathy (MMN). Researchers from Johns Hopkins University described two patients with a disorder involving the motor fibers of multiple peripheral nerves in the upper extremities, sparing sensory fibers.[1] Both patients had presented with painless, progressive, asymmetric upper extremity weakness, and both were initially diagnosed as having ALS. But their nerve conduction studies showed striking abnormalities not typical of ALS.

Temporal dispersion refers to the normal tendency of things moving at different velocities to spread out over distance. Runners of differing footspeed will separate further from each other the longer the race. The same phenomenon normally occurs with a compound muscle action potential (CMAP) because not all motor nerve fibers conduct at the same velocity. Conduction block refers to the failure of a nerve potential to transmit, analogous to a runner spraining an ankle and never finishing the race. Both temporal dispersion and conduction block affect the amplitude of the CMAP, and distinguishing between the two may prove difficult.

The patients in the Hopkins paper describing MMN had conduction block in the involved nerves on nerve conduction studies. Conduction block never occurs in ALS. These patients also had high titers of antibodies to GM1ganglioside.

Crucially, the Hopkins MMN patients responded to treatment with cyclophosphamide. So, the Hopkins researchers had reported patients initially thought to have ALS who had conduction block on nerve conduction studies and antibodies to GM1 ganglioside, and who responded to treatment with cyclophosphamide.

In the late 1980s and 1990s, papers appeared with titles such as: *Chronic multifocal demyelinating neuropathy simulating motor neuron disease, Multifocal motor neuropathy mimicking motor neuron disease* and *Motor neuropathies mimicking amyotrophic lateral sclerosis/motor neuron disease*.[2-4] In a large Irish study, the most common ALS mimic was MMN.[5]

Neurologists around the world became obsessed with not missing MMN in patients who appeared to have ALS.

The American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) convened a panel to develop consensus criteria for distinguishing between temporal dispersion and true conduction block. The head of the panel and lead author of the paper that followed was Dr. Richard K. Olney, the Director of the ALS Treatment and Research Center at UCSF.[6] Rick was a stellar physician and researcher and an esteemed colleague, highly regarded yet unpretentious and always amiable. He was universally recognized as a very nice guy.

The conduction block paper was published in 1999. In 2003, Rick noticed problems with his right leg. His doctors at first thought he had a lumbar disk herniation and he underwent surgery, but the weakness progressed and Rick soon knew he had ALS.

Rick was cared for in his own ALS center by physicians he had trained. Even as his personal illness progressed, he continued to study it.[7] He enrolled as the first patient in a clinical trial he had designed before his diagnosis. Rick Olney died in 2012, at age sixty-four. The AANEM honored his memory by creating the Richard K. Olney Lecture, given annually at its association meeting.

Rick survived eight years. Another ALS researcher, Dr. Lisa Krivickas of Harvard, wasn't as lucky. Lisa and I were colleagues on the Board of Directors of the American Board of Electrodiagnostic Medicine. From the time Lisa told us in a board meeting that she had ALS until she was gone was only a little over two years. She was forty-five. The disease had taken her mother when Lisa was young.

In 2017, Dr. Rahul Desikan, a prominent researcher in the field of neurodegenerative diseases, including ALS, at UCSF, found he had ALS. He died in July 2019 of a rapidly progressive form of the disease. He was forty-one.

It almost seems as if the disease is an evil, sentient entity intent on tracking down and eliminating the specific people trying to find a cure for it. It appears to have license to flagrantly flout the rules.

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RYR1: A story about calcium channels and the people who have them

Vincent Czerwinski

RYR1 encodes the ryanodine receptor – a calcium channel found in skeletal muscles which opens in response to sarcolemma depolarization allowing calcium to move from the sarcoplasmic reticulum into the cytoplasm. Those with *RYR1* mutations experience central core disease, a congenital myopathy which is characterized by profound muscular flaccidity. To a young medical student this phenomena is 'interesting', a label reserved for the few and far between cases in medicine when a clear cellular mechanism produces intuitive effects phenotypically. However, no amount of intellectualization can prepare medical students for the sight of a four-year old girl on an intubator who sits completely still in her room- the only movement coming from her eyes as she tracks the new presence in her space. Students may find this sight so uncanny that they quickly scan the patient's medications to check for paralytics having already forgotten what they've just looked up regarding the effects of *RYR1* mutations.

Students are encouraged to push this unease to the side and proceed with their duties, checking with the mother for overnight updates and performing a physical exam. Diligently collecting data points for the all-important presentation: one of the many metrics by which students are measured.

Speaking of that all-important evaluation, when rounding in the pediatric ICU, students may be surprised to find that their attendings call the parents to listen in while presenting outside the patient's room. Students may find the presence of a parent to be abnormal, and their presentations may suffer for it- punctuated by pauses that linger slightly too long. Pauses in which the movie playing in the patient's room can be heard. She's watching Moana.

> "*See the line where the sky meets the sea? It calls me*
> *And no one knows how far it goes*
> *If the wind in my sail on the sea stays behind me*
> *One day I'll know-*
> "

But this isn't the time for listening to songs or watching movies. There are attendings to impress, patients to round on, and maybe even lives to save. And reader, if this choice of movie seems inappropriate or cruel, worry not- according to Glenwright et al. in the Journal of Child Language, we do not develop a sense of irony until age 5-7. That means, at least for the next 12 months, your hospitalized patient with an RYR1 mutation will be untethered by anchor of prognosis. She'll watch Moana and think to herself, "when I go there's just no telling how far I'll go."

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A severe case of Pembrolizumab-induced triad of myasthenic crisis, myocarditis, and anti-SSA myositis

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Introduction

Myasthenia gravis (MG) is an autoimmune neuromuscular disorder characterized by fatigable weakness involving ocular, bulbar, respiratory, and/or limb muscles. The weakness is due to an antibody-mediated immunologic attack directed at acetylcholine receptors or receptor-associated proteins in the postsynaptic neuromuscular junction.

Immune-related myasthenia gravis (irMG) is one of the rare but life-threatening immune-related adverse events (irAE) described with the use of immune checkpoint inhibitors (ICI). There appears to be an intimate link between autoimmunity and anti-tumor effect elicited by immune checkpoint inhibitors such as pembrolizumab. Onset of immune-related adverse events appears to be more strongly associated with anti-PD-1 (like pembrolizumab) and anti-PD-L1 antibody response than to other types of ICI. As such, reports of immune-related adverse events including potentially devastating side effects and their management are important.

We report a case of a man in his late 70s who presented with one week of progressive chest and muscle pain, generalized weakness, and fatigue. He received a single infusion of pembrolizumab three weeks prior as adjuvant immunotherapy for stage IIb malignant melanoma after undergoing wide local surgical excision. He was started on steroids for pembrolizumab-induced myositis and myocarditis. Symptoms progressed to include severe dyspnea, dysphagia and eyelid ptosis requiring tracheostomy and PEG tube placement. Serologic studies ultimately confirmed myasthenia gravis and anti-SSA myositis.

He was emergently treated with plasma exchange, pyridostigmine, Intravenous Immunoglobulin (IVIG) and is making gradual improvement with physical therapy and oral prednisone taper.

This case study presents a severe case of Pembrolizumab-induced triad of myasthenic crisis, myocarditis with myositis specific anti-SSA 52kD Ab IgG autoantibody for the first time. More studies are needed to assess the clinical significance and prognostic value of this autoantibody in patients presenting with Pembrolizumab-induced triad.

Case Presentation

This is a case of a man in his late 70s with hypertension and COVID-19 four months prior from which he recovered without residual respiratory symptoms. He is a nonsmoker who exercises regularly, doing home yoga and going to the gym three times a week.

He was diagnosed with malignant melanoma of his left lateral neck and underwent wide lateral surgical excision of a T4a, pN0, cM0 lesion, which was stage IIb on pathologic staging with negative sentinel lymph nodes. Adjuvant immunotherapy was recommended, and he received a single infusion of pembrolizumab. Two weeks later, he presented with cough, generalized body aches, fatigue and profuse sweating. The following day, he reported chest pain, generalized muscle pain, shortness of breath, hot flashes, nausea, vomiting, extreme fatigue, and poor appetite. In the emergency room, he was noted to be afebrile with hypertension, tachycardia and tachypnea. Labs were notable for elevated troponin (3881), liver enzymes (ALT 338 U/L, AST 439 U/L), and creatine kinase (4142 U/L). He was admitted to the hospital and started on intravenous fluids and heparin drip for the troponin elevation. Overnight, he developed dyspnea on exertion and labored breathing with worsening chest pain. EKG revealed sinus rhythm with right bundle branch block. Coronary angiogram identified two-vessel nonobstructive stenosis for which medical management was recommended. He was started on prednisone 100 mg daily due to concern for pembrolizumab-induced myositis and myocarditis. Transaminases and CK were improving on prednisone. On hospital day 4, he had progressive and persistent dyspnea with associated hypoxia, tachypnea and accessory respiratory muscle use, increased supplemental oxygen requirement, dysphagia and bilateral ptosis. Respiratory vitals revealed negative inspiratory force (NIF) -25 with vital capacity (VC) 1000 mL. He was transferred to ICU and placed on bilevel positive airway pressure (BiPap) ventilator. Emergent plasma exchange was initiated for suspected myasthenic crisis, and he was started on pyridostigmine and switched to IV methylprednisolone. He developed neck extensor muscle weakness and hypophonia before making gradual improvement in NIF and VC. After the 4th plasma exchange, NIFs were consistently -40. Dyspnea and dysphagia was subjectively improving and he was off BiPap, on 2-3 liters of nasal cannula supplemental oxygen. Walking distance was increasing with physical therapy, but he developed acute worsening of dyspnea with lethargy, NIF of -20, VC 1100 mL, respiratory acidosis with hypoxemia on arterial blood gas, worsening leukocytosis (WBC 37.02), acute kidney injury, and decreased urine

output. Pressors and broad-spectrum antibiotics were started due to concern for sepsis secondary to pneumonia. BiPap was resumed and the 5th plasma exchange was completed.

With worsening respiratory function (NIF -15, VC 750 mL), he was treated with IVIG (1 gram /kg daily) for 2 days with gradual improvement in NIF to -40. BiPap was discontinued but he subsequently developed worsening leukocytosis, elevated lactate and procalcitonin. CT chest revealed worsening bilateral lower lobe consolidations, concerning for mucus plugging. He required intubation for worsening hypoxia. Hypothermia and hypotension were noted, requiring broader spectrum antibiotic coverage for septic shock and vasopressors for hemodynamic support. Continuous renal replacement therapy (CRRT) was initiated for renal failure. Once renal function was recovering, a second round of plasma exchange was initiated but terminated after 3 exchanges due to thrombocytopenia and anemia requiring transfusion. Ultimately, percutaneous endoscopic gastrostomy (PEG) tube and tracheostomy were placed. Patient was discharged in a stable condition to a long-term acute care facility on hospital day 37.

Investigations

As part of his oncology workup for his malignant melanoma, he underwent whole-body PET scan. No focal metastatic disease identified. MRI head with and without contrast revealed no intracranial metastatic disease.

During admission, troponin peaked at 7359. EKG for chest pain revealed sinus rhythm with premature atrial complexes and right bundle branch block. Subsequent coronary angiography was nonischemic, revealing a normal left main trunk, 50% stenosis of the mid LAD with 30% stenosis distally, normal circumflex artery and mild atherosclerosis of the RCA. Echocardiogram revealed normal biventricular size, ejection fraction 65%, no regional wall motion or valvular abnormalities. CT angiography of the chest revealed no aortic dissection or pulmonary embolism.

Serologic studies revealed positive acetylcholine binding antibody at 2.84 (reference range 0.00-0.24), positive acetylcholine modulating antibody at 58% (reference range 0-45%) and negative MuSK antibody. Myositis panel revealed an elevated anti-SS-A 52kD antibody IgG of 31 (reference range <20) and negative antibodies for Jo-1, PL-7, PL-12, EJ, OJ, SRP, Mi-2, TIF-1gamma, MDA-5 (CADM-140), NXP-2 (P140), PM/Scl-100, Ku, U1 RNP, U2 RNP and U3RNP (Fibrillarin). Serum paraneoplastic antibodies were negative. No thymoma on CT chest. Electromyography was not available during hospital admission. Creatinine kinase was elevated at 4142 on admission, which normalized prior to discharge.

Fluctuating leukocytosis with recurrent concerns for sepsis with white blood cell count 14.25 on admission, peaking at 37.02, normal at discharge. Platelets were normal at 279 on admission and as low as 33 after the development of thrombocytopenia with plasmapheresis, improving to upper 60s at time of discharge.

Treatment

He was started on prednisone 100 mg (1 mg/kg) daily due to concern for ICI-related myositis and myocarditis. After the development of ptosis, dysphagia and deterioration of respiratory status, he was started on pyridostigmine 60 mg three times daily and emergent plasma exchange was initiated for presumed ICI-related myasthenia gravis. With worsening dysphagia, prednisone was transitioned to IV methylprednisolone. Five plasma exchanges were completed with some recovery of respiratory muscle strength and ability to come off BiPap support. This improvement was followed swiftly by the development of pneumonia with septic shock and subsequent worsening of respiratory function. He received 2 days of IVIG 1 gram/kg/day and respiratory muscle weakness again improved followed by acute respiratory acidosis with hypoxemia, requiring intubation and tracheostomy. He required supportive treatments with broad-spectrum antibiotics, vasopressors, and CRRT. A second round of plasma exchange was initiated, and he underwent 3 exchanges before developing significant anemia and thrombocytopenia requiring transfusion. He remained on methylprednisolone 40 mg IV and pyridostigmine 90 mg four times daily on discharge to long-term acute care facility. Shortly after transition to long-term facility, methylprednisolone was changed to prednisone 30 mg daily. He is currently on prednisone 10 mg daily.

Outcome and Follow-up

Patient was discharged to long-term acute care facility after a 37-day admission. At the time of his discharge, he had tracheostomy and PEG tube placement. His anemia, thrombocytopenia and renal functions were improving. Troponin and creatine kinase elevations had normalized. After 7 weeks in rehab, he was discharged home with home health. He was seen in follow up in the neuromuscular clinic and is doing very well with oral prednisone taper.

Discussion

The use of immune checkpoint inhibitors as standard of care and as an adjuvant immunotherapy has been a major breakthrough in several types of malignancy, and its use is expected to expand. Neurological complications and life-threatening immune-related adverse events (irAEs) including immune-related myasthenia gravis (irMG) and immune-related myositis are very well described and can limit their clinical use.[1-3]

Pembrolizumab is one of the immune checkpoint inhibitors which can be used as adjuvant immunotherapy in some forms of malignancy. Mechanism of action includes interference of binding of PD-L1, the ligand for

the programmed death 1 protein to PD-1 on T-cells. This normally blocks T-cell activated destruction of the cell, and by blocking this process PD-1 and PD-L1 inhibitors permit T-cell mediated destruction of malignant cells. This process can cause a range of irAEs, however.[4]

The neurological autoimmune side effects can be mild to life threatening in some cases. The central and the peripheral nervous system can be affected, and side effects include seizures, encephalitis, leukoencephalopathy, myelopathy, polyneuropathy, MG and myositis.[1] In many reported cases of irMG, patients were older males who presented with myasthenia gravis, myositis and/or ptosis that followed soon (about a month) after they received pembrolizumab. They can have severe clinical presentations, rapid clinical deterioration with long-term sequela and high mortality rates.[5] Some patients present with a triad of MG, myositis and myocarditis and seem to develop respiratory failure more frequently than those with MG alone. Most of the death from MG complications was seen in those with elevated CK levels with MG overlapping with myositis and myocarditis. Patients with elevated CK seemed to develop respiratory failure more than those with normal levels. Overall, patients who were tested for CK and/or troponin seemed to have a higher MG deterioration rate and a higher mortality rate primarily because of MG complications. Patients with irMG who present with more than one organ involvement such as myositis, myocarditis, pneumonitis, hepatitis, and peripheral neuropathy have higher mortality.[6,7]

Our patient presented with the clinical triad of myositis and myocarditis followed by severe life-threatening bulbar myasthenia gravis requiring intubation, tracheostomy, and PEG placement. He developed his symptoms 2 weeks after his first dose of pembrolizumab and was found to be positive for acetylcholine-binding antibody, acetylcholine-modulating antibody and anti-SSA 52kD antibody.

Anti-acetylcholine receptor antibodies were the most commonly found antibodies followed by anti-MuSK and anti-striated muscle antibodies in patients with overlapping MG, myocarditis and myositis.[5] However, no cases have been reported regarding the type of myositis antibodies seen in pembrolizumab-induced myositis or the triad of MG, myositis, and myocarditis. We report positive anti-SSA antibody for the first time in a patient with this triad. Anti-Ro/SSA antibody, mostly directed against the Ro52 subunit, is the most prevalent myositis-associated antibody and is found in more than 30% of patients with myositis.[8] A systematic review in 2019 reported poor prognosis in MG combined with hyperCKemia with immune checkpoint inhibitors but no myositis antibody panel was performed.[9] In most of cases with ICI-related myositis, myositis-specific (MSAs) or myositis-associated (MAAs) antibodies were undetected.[10]

The use of low-dose steroids can prove to be effective for patients with irMG.[11] Early use of IVIG and PLEX have led to favorable outcomes in most patients with severe iMG, and their early use is recommended preceding or simultaneously with steroids to overcome the risk of a transient worsening, especially in patients with severe disease.[6,7,12]

Based on American Society of Clinical Oncology (ASCO) guidelines our patient meets definition of grade 4 myasthenia gravis (MG-G4) and given the significant risk of mortality associated with MG- G4, it is recommended that immune checkpoint inhibitors be discontinued permanently.[13]

Permanent discontinuation of therapy should also be considered in grade 2 or greater myocarditis (with abnormal cardiac biomarker testing with mild symptoms or new ECG abnormalities without conduction delay defining grade 2 myocarditis) and grade 4 myositis (severe weakness limiting self-care activities of daily living). There have been a few studies evaluating recurrence of ICI-related irAEs after rechallenging of ICI therapy. Recurrence of irAEs seem to vary from 28.8% to around 60% after rechallenging.[14-18]

Oncologists, Neurologists and Internists should have a high index of suspicion to recognize the neurological complications of immune checkpoint inhibitors, discontinue the medication as soon as possible and start aggressive immunosuppressive modalities to reduce mortality.

Learning Points/Take Home Messages

- With increasing applications for immune checkpoint inhibitors, their use is expected to increase. It is important for patients to be educated regarding the risks, benefits, and potential severe side effects related to these therapies, including the potential for developing myasthenic crisis, myocarditis and myositis.
- ICI-related myasthenia gravis overlapping with myositis/myocarditis has more severe symptoms, worse clinical outcomes and higher mortality than patients with MG alone and requires aggressive management with IVIG or PLEX as first line regimen in addition to steroids.
- Further studies are needed to assess if anti-Ro52 antibody could have a prognostic value for higher risk of respiratory failure in patients presenting with the triad of MG, myocarditis and myositis

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A rare case report of neurolymphomatosis with NK-T-cell lymphoma

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Neurolymphomatosis (NL) is a rare neurological association in patients with non-Hodgkin's lymphoma.[1,2] It involves infiltration of peripheral nerves by lymphoma. The most common presentations of NL include painful polyneuropathy or radiculopathy, cranial neuropathy, painless polyneuropathy, and mononeuropathy or mononeuropathy multiplex.[1] It is important to distinguish neurolymphomatosis from other types of neuropathies, particularly treatable infectious and inflammatory causes such as CIDP. However, it is difficult to differentiate a cancer-related inflammatory vasculitis causing mononeuritis multiplex from infiltrative etiology without definitive histopathologic examination. In this report, we describe a rare case of non-Hodgkin's T-cell lymphoma (nasal NK–T cell lymphoma) presenting as neurolymphomatosis involving the brachial plexus and multiple peripheral nerves.

Case History

A 72-year-old male, with past medical history of diabetes mellitus, hypertension, and ischemic heart disease was treated for nasal NK-T cell lymphoma in November 2021 with excision surgery followed by radiation therapy. He had been in remission since then.

6 months later in June 2022, he presented with an acute painful left wrist drop. For which he received 30 mg of oral prednisolone which was tapered to 10 mg over the next 3 months. After the steroid taper, he developed a painful left foot drop followed by left shoulder pain with weakness and 15 days later, painful right wrist-drop. There was hyperalgesia to pin-prick in distribution of radial, superficial peroneal and sural nerves. Bilateral biceps and supinator deep tendon jerks (DTR) and left triceps DTRs were absent. Right triceps DTR and both knee jerks were normal. Both ankle DTRs were absent.

Electrophysiological studies revealed multiple mononeuropathies with severe axon loss in an asymmetric pattern. Needle electrode examination revealed severe axon loss in the muscles supplied by the affected nerves in upper and lower extremities as described in Table 3. In addition, there was involvement of proximal upper extremity muscles, severe in degree electrically which suggested involvement of upper trunk of brachial plexus on either side. (Refer table 2 and table 3)

Whole body PET-CT done 2 months into illness showed diffuse low grade increased metabolic activity in head of right humerus and left infraclavicular region. MRI spine with brachial plexus revealed T2 hyperintensity in left C6, C7, C8, D1 nerve roots. Divisions and cords of brachial plexus also showed mild thickening and hyperintensity bilaterally. Cerebrospinal fluid examination (CSF) revealed 7 cells (73% lymphocytes), protein 113, glucose 63 and no malignant cells. Inflammatory markers were elevated, erythrocyte sedimentation rate (ESR) was 24 and C-reactive protein (CRP) was 96.

He underwent biopsy of the left brachial plexus as it was the only area that showed increased metabolic activity on whole body-PET-CT which confirmed the diagnosis of neurolymphomatosis. Biopsy was suggestive of hypertrophied fascicles and prominent endoneurial lymphoid infiltration extending up to perineurium, lymphoid cells are small with dark nuclei and scanty cytoplasm. IHC was positive for CD3, CD8, CD56, Ki67 (figure A to H).

He was treated with intravenous immunoglobulins (2 gm/kg) over 5 days with minimal improvement in his neurological symptoms, his shoulder pain improved and he could feed himself with his right hand. He was offered palliative treatment in view of poor prognosis seen in neurolymphomatosis. He succumbed to the illness 3 months later.

Table 1: Muscle Strength assessment according to MRC grade:

		Right	Left			Right	Left
Shoulder	**Flexion**	**2**	**3**	**Hip**	**Flexion**	**4**	**4**
	Extension	**0**	**0**		**Extension**	**4**	**4**
	Abduction	**1**	**3**		**Abduction**	**4**	**4-**
	Adduction	**2**	**3**		**Adduction**	**4**	**4-**
Elbow	**Flexion**	**2**	**2**	**Knee**	**Flexion**	**4+**	**3**
	Extension	**2**	**2**		**Extension**	**4+**	**4-**
Wrist	**Flexion**	**4-**	**2**	**Ankle**	**Dorsiflexion**	**3**	**0**
	Extension	**2**	**1**		**Plantarflexion**	**4**	**1**
	Intrinsic hand muscles	**2**	**1**				

Table 2: Nerve conduction study

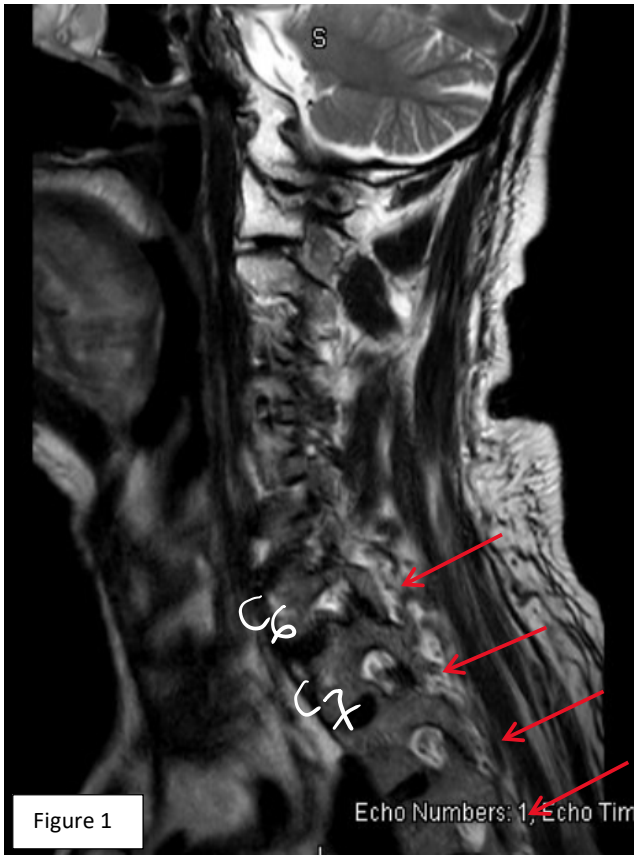
Nerve	Site	Latency (ms)		Amplitude (μV)		Conduction velocity (m/s)		F- latency	
		Right	Left	Right	Left	Right	Left	Right	Left
Sural sensory	Ankle	NR	NR	NR	NR	-	-	-	-
Superficial peroneal sensory	Dorsum of foot	4.4	NR	5	NR	-	-	-	-
Median sensory	Digit 2	3.3	3.2	17	10	-	-	-	-
Ulnar sensory	Digit 5	3.2	2.9	12	22	-	-	-	-
Radial sensory	Wrist	2.9	2.5	10	2	-	-	-	-
LABC	Forearm	NR	NR	NR	NR				
MABC	Forearm	NR	NR	NR	NR				
Peroneal motor	EDB	6.5	NR	1.7	NR	30	NR	73.1	
Tibial motor	Abductor hallucis	6.8	6.7	0.3	0.6	28	32	-	68.9
Median motor	APB	3.7	3.4	6.1	2.8	50	48	-	-
Ulnar motor	ADB	3.0	2.6	3.2	5	49	54	39.3	32.2
Radial motor	EIP	2.8	NR	6	NR	50	NR	32	NR

Abbreviations: LABC - Lateral antebrachial cutaneous sensory, MABC - Medial antebrachial cutaneous sensory

Table 3: Needle Electromyography study.

Muscle	Spontaneous activity	Recruitment	Duration	Amplitude	Polyphasia
Left deltoid	Nil	Severely reduced	Increased	Increased	Present
Left infraspinatus	Nil	Normal	Normal	Normal	No
Left biceps	Fibs +++	No motor units			
Left triceps	Fibs ++	Severely reduced	Increased	Increased	Present
Left FDI	Normal	Normal	Normal	Normal	No
Left EIP, EDC	Fibs ++	Severely reduced	Increased	Increased	Present
Right deltoid	Fibs +++	No motor units			
Right triceps	Fibs +++	No motor units			
Right FDI	Nil	Mildly reduced	Increased	Increased	No
Right EIP	Fibs ++	Moderately reduced	Increased	Increased	Present
Left TA	Fibs +++	No motor units			
Left MG	Fibs +++	No motor units			
Right TA	Fibs ++	Moderately reduced	Increased	Increased	Present
Right MG	Fibs ++	Moderately reduced	Increased	Increased	Present

FDI: first dorsal interossei, EIP: extensor indicis proprius, EDC: extensor digitorum communis, TA: tibialis anterior, MG: medial head of gastrocnemius, Fibs: fibrillation potentials



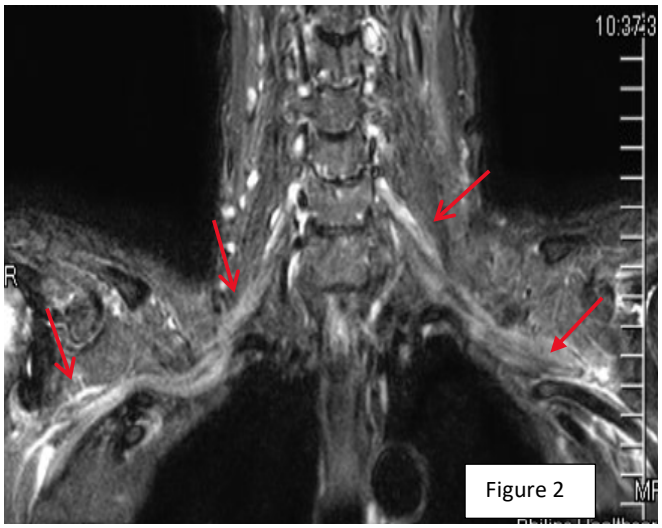


Figure 1: T2 weighted MRI cervical spine saggital section showing increased hyperintensity of left C6,C7,C8 and D1 exiting nerve roots.

Figure 2: Coronal STIR sequence of MRI suggestive of incresed thickeness of brachial plexus, cords and divisions on both sides.

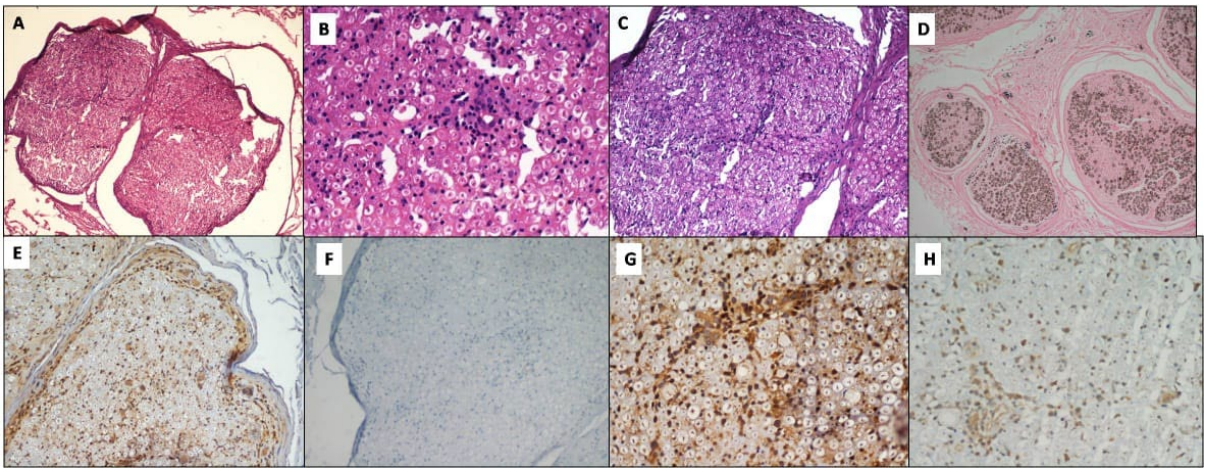


Figure 3: (A) The cross-section of the nerve showing endoneurium and perineurial thickening and (B&C) endoneurial lymphoid infiltrate. (D) Kapl stain showing non uniform involvement of the fascicles with multifocal fibre loss. Immunohistochemistry showing (E) positive CD3 in almost all lymphoid cells whereas (F) CD20 was negative. (G) The cells were positive for CD8 and (H) high proliferation index highlighted by Ki67

Discussion

Neurolymphomatosis is a rare entity. It is usually a manifestation of B-cell lymphoma. Our patient had nasal NK-T cell lymphoma, which itself is extremely rare. It has a rare association with neurolymphomatosis. In a series described by International Primary Central Nervous System Lymphoma Collaborative Group (IPCG) (Grisariu et al.), only one of 166 patients had NK cell lymphoma.[8] It affects the peripheral nervous system especially the spinal ganglia, nerve roots and nerve plexuses. it presents with progressive, severely painful sensori-motor peripheral neuropathy.[2] It can also present with cranial neuropathies.

Neurolymphomatosis can be confused with mononeuropathy, polyneuropathy, polyradiculopathies, Guillain-Barre syndrome, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), arachnoiditis, paraneoplastic neuropathy, leptomeningeal lymphomatosis, nerve root compression, vasculitic neuropathy, or secondary effects of chemotherapy or radiation.[3]

Our patient presented with asymmetric painful proximal and distal weakness in the upper extremities and left foot drop. Clinically the differentials considered were asymmetric CIDP and mononeuritis multiplex as his lymphoma was in remission and NK/T cell lymphoma is not commonly known to cause nerve infiltration. Autoimmune work up was unremarkable. He was treated empirically with steroids at an outside hospital. However, he did not improve. Since nerve conduction studies and needle electromyography were consistent with bi-brachial plexopathy, and whole-body PET-CT revealed increased uptake in the left infraclavicular area, an MRI brachial plexus was done. It showed T2/STIR hyperintensity in the brachial plexus on both sides (Figure 1,2). Hence, he underwent left brachial plexus biopsy to look for evidence of neurolymphomatosis. Biopsy was consistent with hypertrophied fascicles and prominent endoneurial lymphoid infiltration extending up to perineurium. Lymphoid cells were small with dark nuclei and scanty cytoplasm. Immuno-histochemistry was positive for CD3, CD8, CD56, Ki67. This confirmed the diagnosis of neurolymphomatosis and he was then offered palliative care.

MRI neurography and FDG-PET scan is helpful in diagnosis. The International Primary Central Nervous System Lymphoma Collaborative Group has stated that FDG PET and FDG PET/CT might be more sensitive than MRI in the diagnosis of neurolymphomatosis. NL has a characteristic appearance on 18F-FDG PET/CT. It generally presents as a linear or fusiform FDG-avid mass, following a neuronal path. Although, FDG activity can be variable (SUVmax range 1.5–17.0), NL is most often quite FDG-avid (average SUVmax 7.1).[4] CSF examination may show neoplastic cells, CSF protein may be elevated due to root involvement. Nerve biopsy is diagnostic.

Once diagnosed, the prognosis of neurolymphomatosis is poor, with a median survival of 10 months from initial diagnosis.[5] Our patient partially responded to IVIG with reduction in pain scores and was able to feed himself with his right hand due to some improvement in the strength in right shoulder abduction. This was probably more subjective improvement in pain scores than an actual objective improvement in strength. Strength improved very minimally, which may have been due to an inflammatory component that responded to IVIG. However, there was no further improvement and his strength remained more or less same. He succumbed to his illness 3 months after the diagnosis.

Neurolymphomatosis is treated similarly as CNS lymphoma with systemic and intrathecal methotrexate and radiotherapy.[1] In a case series by Alazawi et al., 3 patients were given high dose Methotrexate based chemotherapy and after salvage therapy with high-dose methotrexate regimen, one patient received autologous stem cell transplant. 2 out of 3 patients survived.[7] The prognosis is usually poor but high-dose methotrexate as well as high-dose chemotherapy and autologous stem cell transplant may be an effective way to treat NL.[7] There are few case reports demonstrating effectiveness of bendamustin in neurolymphomatosis.[6]

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Amyotrophic lateral sclerosis and spinocerebellar ataxia type 2: A familial case report

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Introduction

While separate and phenotypically distinct diseases, spinocerebellar ataxia type 2 (SCA2) and amyotrophic lateral sclerosis (ALS) share a genetic association via a trinucleotide (CAG) repeat expansion in the *ATXN2* gene [1,2]. While ubiquitin-positive cytoplasmic inclusions of trans-activate response DNA-binding protein (TARDBP or TDP-43) are known to be pathognomonic for ALS, these TDP-43 inclusions are also seen in the cytoplasm of motor neurons in SCA2. This elucidates an interconnected pathway of gene overexpression and protein toxicity [2,3]. Full expansion is associated with an increased presence of TDP-43 inclusions in the cytoplasm of degenerating neurons [4].

While the genetic association between ALS and SCA2 via the *ATXN2* gene is well established, there are few reports demonstrating intrafamilial phenotypic variability of *ATXN2* mutations. Here we report a family with separate and distinct phenotypes via repeat expansions in *ATXN2*, whose presentations do not align with their expected phenotypes based on CAG repeat size.

Case Description

A 36-year-old female presented to Neuromuscular Neurology clinic with painless bilateral arm weakness for 7 months. Physical examination revealed tongue fasciculations, and mild dysarthria on cranial nerve testing. Upper extremity strength showed 3/5 strength (Muscle Power Assessment MRC Scale) in the right deltoid, 4/5 strength in the right biceps, triceps, wrist flexors, extensors and abductor pollicis brevis (APB), and 1/ 5 strength in the right first dorsal interosseous (FDI) muscle. Left upper extremity strength testing showed 4/5 strength in the deltoid, 4+/5 in the biceps, triceps, wrist flexors, extensors, APB, and 1/5 strength in the FDI. Lower extremity strength testing was 5/5 throughout on initial examination. Finger contractures were noted. Sensory examination was normal. Reflex testing showed 2+ reflexes throughout, which were deemed pathologic in the upper extremities for degree of weakness. There was a positive right pectoralis, right Hoffmann, and mute toes. Cerebellar testing was not done on initial assessment, and as the patient progressed became not possible due to weakness. Diagnostic evaluation included MRI of the brain and cervical spine, which were normal. Laboratory work-up included normal thyroid function tests, normal serum angiotensin-converting enzyme level, absent monoclonal on serum protein electrophoresis with immunofixation, serum creatinine kinase of 334 U/L, normal serum copper and paraneoplastic panels. Electrodiagnostic testing showed evidence of a widespread neurogenic process with active and chronic denervation seen in the tested muscles of the right arm, leg and trapezius. Subtle sensory nerve abnormalities in the right median, ulnar, radial and sural nerves were of unclear clinical significance. The patient underwent genetic testing which included *SOD1* gene sequencing and *C9orf72* plus *ATXN2* repeat expansion analysis. Her *SOD1* sequencing was normal, as well as her *C9orf72* analysis which revealed G4C2 repeat sizes of 6 and 7. Her *ATXN2* analysis revealed a heterozygous, pathogenic repeat expansion of 40 CAG repeats. Based on her clinical symptomatology, work-up, and electrodiagnostic testing, a diagnosis of ALS was made. Over the next year, the weakness progressed to include dysarthria, dysphagia, leg weakness with loss of ambulation, and respiratory failure. When still ambulatory, she was noted to have wide-based gait, which might have been related to a lack of arm movement. She progressed to quadriplegia and died at age 39.

Family history revealed olivopontocerebellar degeneration (OPCD) and SCA type 2 (SCA2) in her brother, diagnosed at 16. He presented with symptoms such as falls and dysarthria and became wheelchair bound. Per chart review provided by the patient's mother, the brother's physical exam showed horizontal nystagmus, right nasolabial fold flattening, leftward tongue deviation with 3+ reflexes at the ankle and knees, and bilateral extensor response. He was noted to have wide based stance, ataxic gait, and positive Romberg. His brain MRI showed olivopontocerebellar atrophy. He died 9 years post-diagnosis and 13 years prior to the presentation of our patient. Our patient's father had a reported history of gait imbalance, ataxia, tremor, dysarthria, and a possible prior diagnosis of OPCD. He died at age 50 of an unknown cardiac condition. Our patient's paternal aunt was also suspected to have SCA. There was an additional report of ALS on the paternal side although it was unclear who was affected. The pattern of familial inheritance is regarded as autosomal dominant (Figure 1).

Figure 1. Family Pedigree

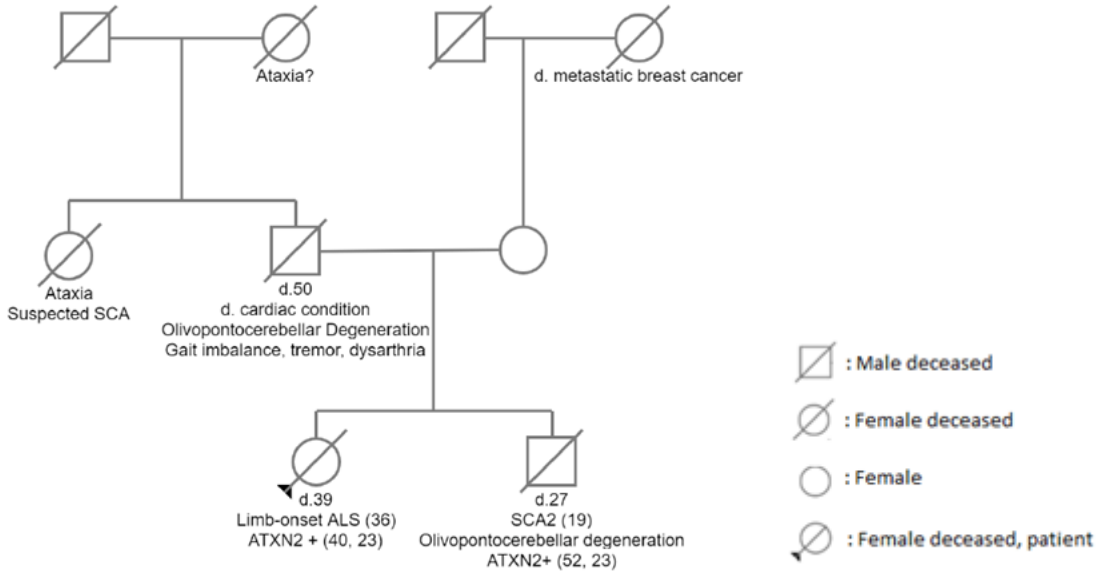
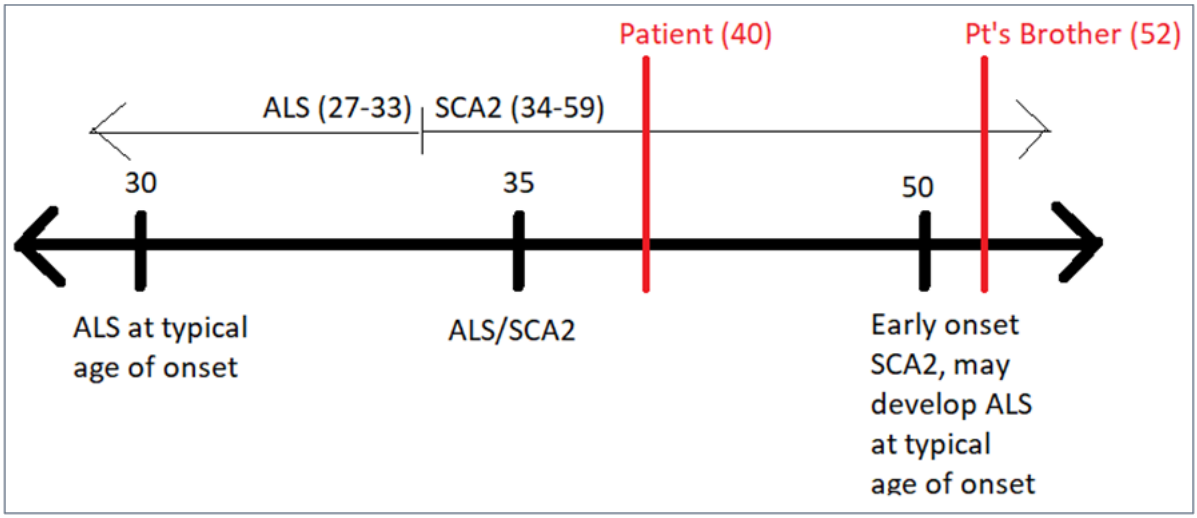


Figure 2. Variability of ALS and SCA2 by Expansion length



Patient: ATXN2 Positive (Allele 1 :40 repeats, Allele 2: 23 repeats), Patient's brother: ATXN2 Positive (Allele 1: 23 repeats, Allele 2: 52 repeats). Amyotrophic Lateral Sclerosis (ALS), Spinocerebellar Ataxia Type 2 (SCA2)

Discussion

The length of CAG repeat expansion in the *ATXN2* gene is directly related to the age of onset and severity of SCA2. There is also evidence to suggest that CAG repeat length correlates with the expected phenotype (ALS vs. SCA2). Development of SCA2 is typically associated with CAG repeat sizes of 33 or greater, while the development of ALS is typically associated with an intermediate length of CAG repeat expansion (27-33) [1,5]. ALS and SCA2 share a genetic basis consisting of expanded CAG repeats in the *ATXN2* gene and TDP-43-positive neuronal cytoplasmic inclusions, but few cases of families affected by both diseases have been reported [3,6]. This case documents a patient who was diagnosed with ALS without manifested signs of spinocerebellar ataxia despite having full CAG repeat expansion 40/23, and a sibling with SCA2 (Figure 2). Prior reports proposed that SCA2 onset age is inversely proportional to expansion length [1]. In this familial case, this is less relevant to the patient, but it does apply to her sibling. The number of CAA interruptions to the CAG expansion has been shown to be inversely associated with the age of ALS onset in patients with an average repeat length of ~27 [1,7]. In this case, the 40-repeat expansion bodes an increased risk of SCA2 and not necessarily ALS. Our patient's development of early-onset ALS may be explained at least partly by CAA interruptions. As CAA interruptions increase the stability of CAG expansion [1], thus expressivity may be influenced by the degree of CAA codon interruption to the CAG repeat. However, CAA interruption data was unavailable for review.

Despite attempts to characterize a distinction between disease entities by mutation history, this case highlights heterogeneity in the genetic background and development of ALS versus SCA2. Understanding the genotype-phenotype correlation of *ATXN2* mutations has implications for neuromuscular and movement disorder neurologists and genetic counselors, specifically in ordering appropriate genetic testing, providing accurate risk assessment for relatives, and providing access to genetically targeted therapies. Identification of ataxia, olivopontocerebellar atrophy, or Parkinsonian disease in the family history of an individual with ALS warrants analysis of *ATXN2*. When providing risk assessment for family members at risk of an *ATXN2* repeat expansion, it is crucial to consider and advise that family members may present differently based on repeat size and degree of CAA codon interruption.

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Intraneural ganglion cyst of the peroneal nerve at the lateral knee: A case report and literature review

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Abstract

Introduction: Intraneural ganglion cysts can arise from the peroneal nerve at the lateral knee secondary to synovial fluid tracking along the articular branch and transforming within the nerve into a mucinous cyst, resulting in nerve compression.

Case Report: A 17-year-old right-handed male presented with a four-month history of right foot drop. He is physically active and attributed the foot drop to a sprained ankle. EMG/NCS showed a right common peroneal neuropathy distal to the innervation of the biceps femoris short head with active denervation. MRI showed an intraneural ganglion cyst in the common peroneal nerve starting at the level of biceps femoris. On exam, he had right foot drop and sensory deficits referable to the peroneal distribution, along with a right steppage gait. He had successful decompression of the ganglion cyst, excision of the articular branch and resection of the proximal tibiofibular joint, with clinical improvement.

Conclusion: Early recognition and surgical treatment leads to better outcomes for patients when an intraneural ganglion cyst results in neurologic deficits. Physical activities and trauma, which increase stress on the knee joints, may predispose ganglion cyst formation within peroneal nerves. Fibers of the deep peroneal nerve may be preferentially affected when compared to the superficial peroneal nerve. Disconnection of the articular branch and proximal tibiofibular joint resection may decrease risk of recurrence.

Introduction

Patients with foot drop complain of difficulty walking, recurrent falls, and limitations in daily activities. The differential diagnosis is broad, from central causes such as stroke to peripheral ones such as lumbar radiculopathy or neuropathy; timely diagnosis is critical as early intervention/treatment can improve deficits in some cases. One uncommon cause of focal peroneal neuropathy mimicking entrapment neuropathy is an intraneural ganglion cyst. The cyst can arise from the peroneal nerve at the lateral knee secondary to synovial fluid tracking through the articular branch and transforming within the nerve into a mucinous cyst. If sufficiently large, it may compress the peroneal nerve resulting in neurologic deficits. Electrodiagnostic and imaging studies such as ultrasonography (US) and MRI aid in localization and diagnosis. Early recognition and surgical treatment lead to better neurologic outcomes for patients.

We report a patient with foot drop due to an intraneural ganglion cyst of the common peroneal nerve and discuss the multimodal approach to diagnosis through electromyography/nerve conduction study (EMG/NCS), US, and MRI. We also discuss the surgical treatment technique and how recurrence of the cyst can be minimized.

Case Description

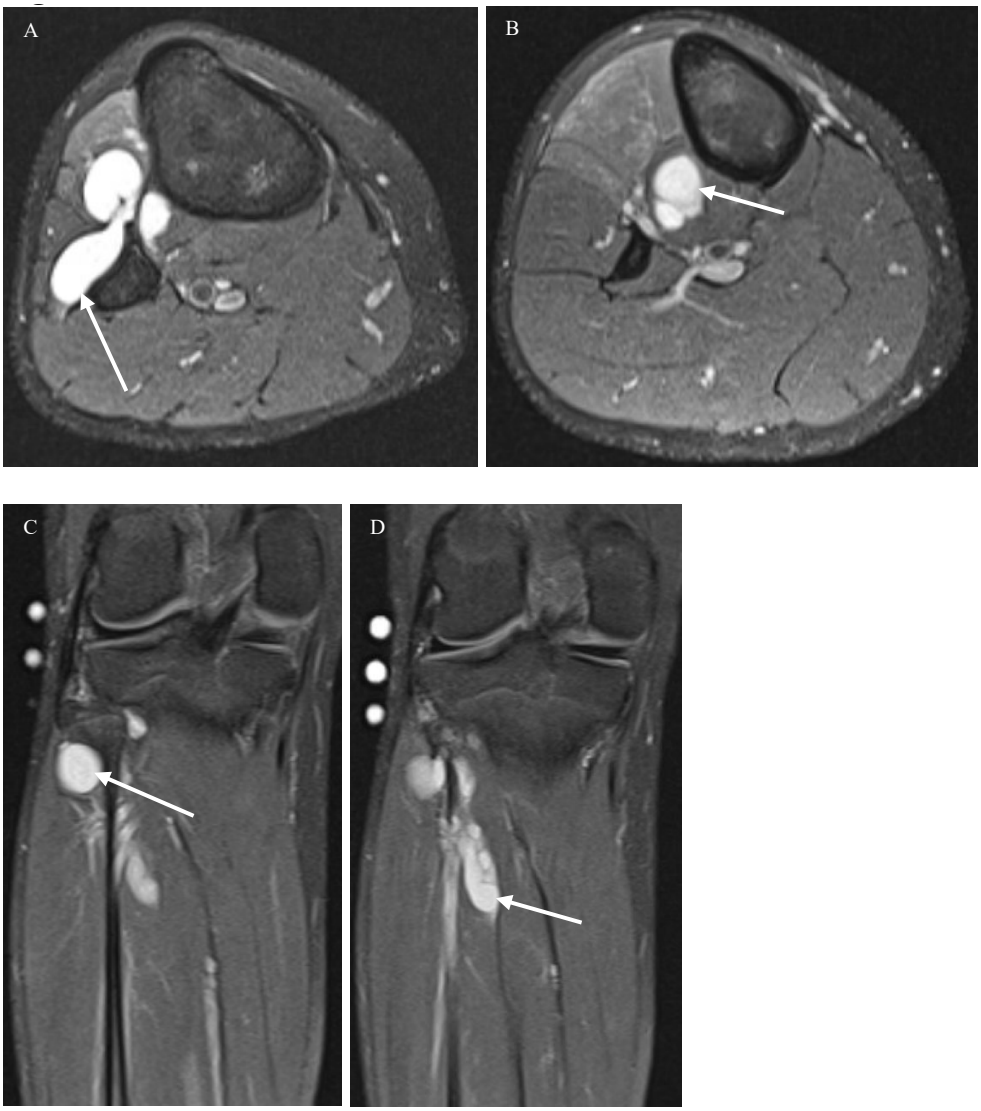
A 17-year-old right-handed male presented with a four-month history of right foot drop. He rode mountain bikes frequently and attributed his weakness to an ankle sprain sustained two weeks prior. He saw his pediatrician who diagnosed right sciatica as there was positive straight leg raise test and prescribed physical therapy. He was noted to have a progressive foot drop with therapy, so he consulted a pediatric neurologist. He had evaluation with EMG/NCS which showed an active and chronic common peroneal neuropathy at the fibular head. MRI of the right knee showed an intraneural ganglion cyst involving the common peroneal nerve from the medial head of the biceps femoris to just below the bifurcation of the superficial and deep peroneal nerves, with deep peroneal greater than superficial peroneal involvement (Figure 1). He was referred to our institution for further treatment.

In addition to right leg weakness and numbness, the patient noted pain at the lateral right knee and popliteal fossa. On exam, he had weakness in right foot dorsiflexion (MRC grade 2), extensor hallucis longus (EHL) (MRC grade 1), and foot eversion (MRC grade 4), with intact strength at ankle and toe plantarflexion and ankle inversion. There was decreased sensibility to light touch and pin on the dorsal aspect of the right foot including the webspace between the first and second toe. He had a right steppage gait and inability to heel walk on the right. Reflexes were intact. Repeat electrodiagnostic studies

showed an active right common peroneal neuropathy distal to the innervation of the biceps femoris short head with worsened axon loss across the fibular neck. He was referred for surgical removal of the intraneural ganglion cyst causing his peroneal neuropathy. He had aspiration of the cyst under ultrasound guidance for temporary decompression of the cyst prior to resection. Sonographic images demonstrated a large multiseptated intraneural ganglion cyst involving the common peroneal and deep peroneal nerves, largest foci measuring up to 3.4 x 1.5 cm distal to the proximal tibiofibular joint (Figure 2). 15 mL of thick gelatinous fluid was aspirated and there was complete collapse of the distal portion of the cyst. However, attempt of aspiration failed to return fluid in the proximal segment of the cyst. The patient did not have clinical improvement after cyst aspiration. About 5 months from onset of his right foot drop, he had surgical decompression of the ganglion cyst, with excision of the articular branch and resection of the proximal tibiofibular joint. At two-week follow up, he had stable motor examination with improved sensation and pain. At five-month follow up, his dorsiflexion improved to MRC grade 4 strength, with stable EHL (MRC grade 1) and eversion (MRC grade 4) weakness and normal sensation. He had no pain or symptoms from the proximal tibiofibular joint resection.

At eleven-month follow up (nine months post surgery), his EHL improved to MRC grade 3 strength and eversion improved to normal strength. His dorsiflexion MRC grade strength was stable and his gait improved to a minimal right steppage gait only seen with longer distances.

Figure 1: MRI of intraneural ganglion cyst (arrows) at the lateral knee in the axial (A) and coronal (C) view. The cyst tracks distally predominantly involving the deep peroneal nerve (B and D).



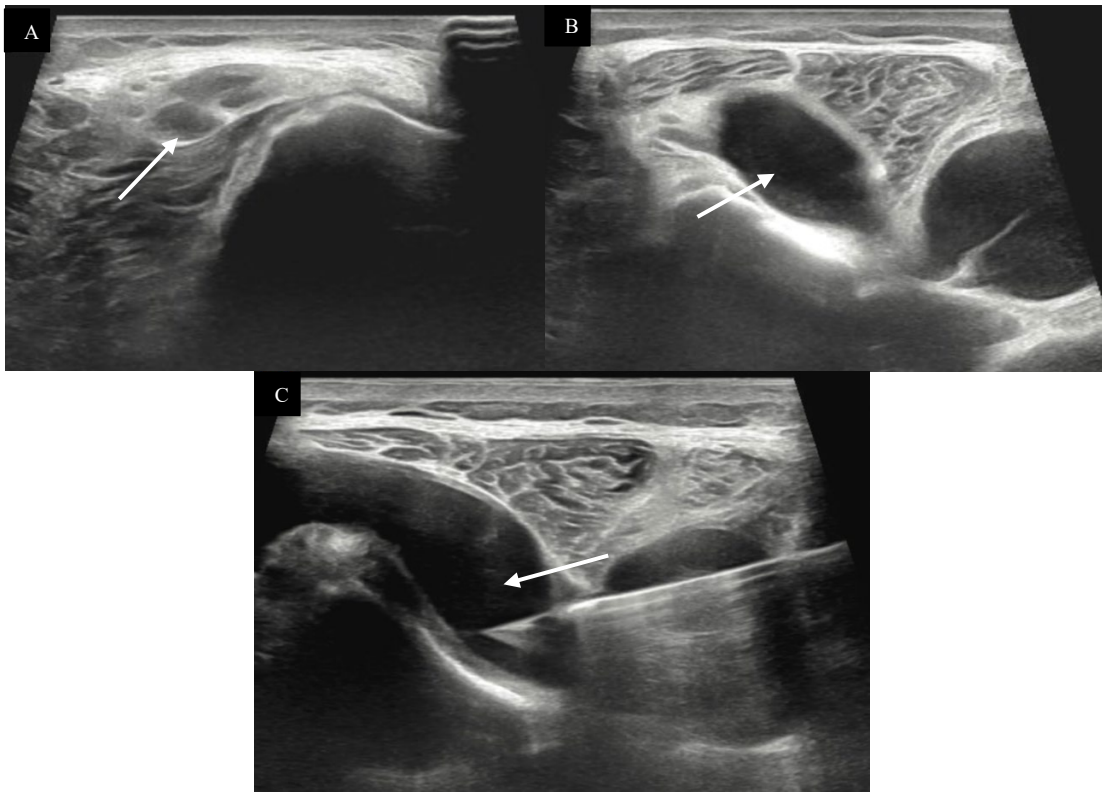


Figure 2:
A) Ultrasound of intraneural ganglion cyst (arrow) of the common peroneal nerve around the fibular head.
B) Large multiseptated intraneural ganglion cyst (arrow) distal to the proximal tibiofibular joint.
C) Needle placement leading to aspiration of the distal portion of the cyst (arrow).

Discussion

Peroneal nerve palsy is a common cause of foot drop, typically from external compression, trauma, or complication post-surgery.[1] Intraneural ganglion cyst is an uncommon cause of peroneal nerve palsy, but has been reported in 18% of patients with an isolated peroneal mononeuropathy.[2] Intraneural ganglion cysts are non-neoplastic mucinous cysts within the peripheral nerve arising from an adjacent joint. Under the mechanism of formation proposed by the unified articular theory for those involving the peroneal nerve, there is a capsular defect of the neighboring superior tibiofibular joint that allows synovial fluid to track along the articular branch through the path of least resistance within the epineurium, and through a one-way valve mechanism to the common peroneal nerve.[3] The more medially located deep peroneal nerve is affected first, followed by the more lateral superficial peroneal nerve fascicles, then cutaneous sensory nerves.[4] This is likely why foot and toe dorsiflexion and EHL weakness are more prominent compared to eversion weakness, as seen in our patient. Frequent activities leading to pressure on the knee joints and trauma may be potential causes of the initial capsular defect and leakage of synovial fluid.

Symptoms of intraneural ganglion cysts of the common peroneal nerve are typical of peroneal neuropathy – weakness in foot dorsiflexion and eversion, pain and possibly Tinel sign around the lateral knee, and numbness and tingling in the lateral distal leg and dorsum of the foot. EMG/NCS abnormalities are consistent with those of common peroneal neuropathy across the fibular neck, including velocity slowing or a decrease in amplitude/conduction block across the fibular neck. Comparison to the contralateral asymptomatic side can help approximate the amount of axonal loss. In some patients, conduction block can be seen when recording at tibialis anterior (TA) but not at extensor digitorum brevis (EDB), reflecting the propensity for early involvement of deep peroneal nerve fibers. Peroneal F responses and superficial peroneal sensory responses are typically prolonged or absent. Needle EMG abnormalities can be seen in TA, EHL, and peroneus longus with sparing of short of the biceps femoris if the lesion is not proximal to the fibular head.[4] US of the nerve at the lateral knee is a useful adjunct to electrodiagnostic studies to provide direct structural assessment of the nerve for intrinsic or extrinsic lesions. Intraneural ganglion cysts on US typically appear as an anechoic or hypoechoic mass with well-defined margins and occasional internal septations. US has been shown to be more sensitive (93% vs 67%) and similarly specific (86%) compared to MRI in detecting nerve pathologies in

patients with mononeuropathies or brachial plexopathies.[5] US can be used as the initial radiographic evaluation as it can be performed at bedside and is less expensive than MRI. MRI, however, can image deeper structures with more clarity and can identify cyst connections to a joint, helping guide surgical planning. MRI is more likely to identify a joint connection compared to US. Surgical resection of a cyst without identifying and treating the feeding joint connection can risk cyst recurrence.[6] Intraneural ganglion cysts on MRI appear as T2 hyperintense lesions tracking along the course of the nerve.

In a study of 100 patients with tibiofibular ganglion cysts, recurrence rate after aspiration of the ganglion cyst was 81.8%. Recurrence was reduced to 27.4% with cyst excision, and 8.3% with additional proximal tibiofibular joint resection.[7] Historically, there has been a high recurrence rate with revision surgery required. A more recent surgical technique utilizing the consistent U-shape of the articular branch of the common peroneal nerve leads to a more efficient dissection. It consists of disconnection of the articular branch which removes the tract that the synovial fluid takes to reach the common peroneal nerve. Additional resection of the superior tibiofibular joint removes the synovium to prevent cyst recurrence. This technique can minimize risk of cyst recurrence, improving odds of recovery.[8]

Conclusion

In summary, for peroneal neuropathy caused by intraneural ganglion cyst, prompt, and accurate diagnosis is important, as earlier recognition and surgical treatment leads to better outcomes for patients. Dorsiflexion and EHL weakness can be affected disproportionately to eversion. US and MRI are both useful imaging techniques in evaluating intraneural ganglion cysts at the lateral knee, and furthermore MRI can help guide surgical planning. Cyst aspiration should not be used as a definitive treatment plan as there is a high risk of recurrence. Disconnection of the articular branch and proximal tibiofibular joint resection may decrease risk of recurrence.

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RYR1 myopathy complicated by RSV bronchiolitis requiring intubation leading to post-hypoxic leukoencephalopathy in a 4-year-old.

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Introduction

Mutations in *RYR1* lead to a variety of clinical syndromes including central-core disease: an autosomal dominant or autosomal recessive myopathy which affects skeletal muscles. Baseline respiratory weakness due to central-core disease makes these patients more susceptible to respiratory failure due to what would often be incidental insults–such as bronchiolitis caused by RSV. Despite the frequency of respiratory insult requiring hospitalization in these patients, no specific guidelines exist regarding their respiratory support, largely due to the fact that central-core disease is a rare and vastly heterogeneous condition. We present the intensive care unit (ICU) management of respiratory failure in a patient with central-core disease and outline a unique radiographic finding which to date has not been described in the *RYR1* myopathy literature.

Case Presentation

A 4-year-old, ex-33 week, medically fragile female with a history of central core disease secondary to autosomal recessive *RYR1* mutation presented to our institution with respiratory distress. Her baseline physical examination was significant for facial elongation and high arching palate. Skeletal muscle involvement of her myopathy included neuromuscular scoliosis, hypotonia, and bilateral hip subluxation. With respect to her activities of daily living, she was gastrostomy tube dependent; she was able to speak and sit on her own but required assistance in standing; she was unable to walk and had a power wheelchair. She was cognitively intact and able to use an iPad. Prior to hospitalization, the patient required nightly nasal BiPAP without oxygen supplementation as well as daily cough assist, albuterol, and glycopyrrolate.

Our patient initially presented to an outside emergency department with a three-day history of cough and hypoxia. Her brother who was ill earlier in the month, was a notable sick contact. Upon initial evaluation, the patient was afebrile with a temperature of 99.1F, tachycardic with a heart rate of 175, and tachypneic with a respiratory rate of 22. Laboratory workup was significant for a venous blood gas of 7.29/58.3/32/28 on BiPAP with an FiO2 of 60%. Her complete blood and comprehensive metabolic panel were both unremarkable. Respiratory viral panel was positive for respiratory syncytial virus (RSV). Chest X-ray demonstrated left sided superimposed pneumonia. Blood cultures were drawn and were ultimately negative.

Initial treatment in the emergency department included ceftriaxone and vancomycin. The patient was quickly transferred to our institution due to hypoxemic respiratory failure requiring pediatric ICU care.

In transit, the patient's respiratory status deteriorated and her respiratory rate rose to the 60s with subcostal and intercostal retractions. Bag mask ventilation required two nurses due to dolichocephaly and elongated facial structure with successful endotracheal intubation.

On hospital day one, the patient required ETT replacement over a bougie due to the cuff on the ETT malfunctioning. The bougie was unable to be advanced fully into the tube due to resistance distal to cords. The patient's oxygen saturation dropped and bag mask ventilation met very high pressures and poor compliance. Eventually, resistance rapidly decreased indicating a likely displacement of a mucous plug. Saturations first improved, and then became unreadable and the patient entered asystole. A code was activated and ROSC was achieved after four minutes following three doses of epinephrine.

Over the next fourteen days, the patient had persistent pneumonitis with worsening infiltrates despite negative blood, urine, and respiratory cultures. Furthermore, the patient remained in relatively deep sedation despite discontinuation of dexmedetomidine. After fourteen days, the patient was deemed stable enough for an MRI to assess for anoxic brain injury following cardiac arrest. MRI and findings depicted in Figure 1.

Over the next three months the patient continued to have a protracted ICU course. She developed multiple endotracheal tube-associated pseudomonas infections. She also had multiple failed extubations. She was successfully extubated after three months in the ICU and was eventually transferred to a local children's hospital for closer management from pediatric pulmonology. Prior to transfer, the patient had another MRI performed which is depicted in Figure 2.

At the children's hospital, the patient was gradually weaned down from her BiPAP requirement and eventually was stable on room air during the daytime. Her respiratory cares were gradually weaned and at discharge she was getting cough assist, vest therapy, 3% hypertonic saline, and levalbuterol Q 8 hours. For sialorrhea she was getting 1 mL of atropine per cheek Q 12 hours. Her neurological status was subdued following the hypoxic brain injury, for which

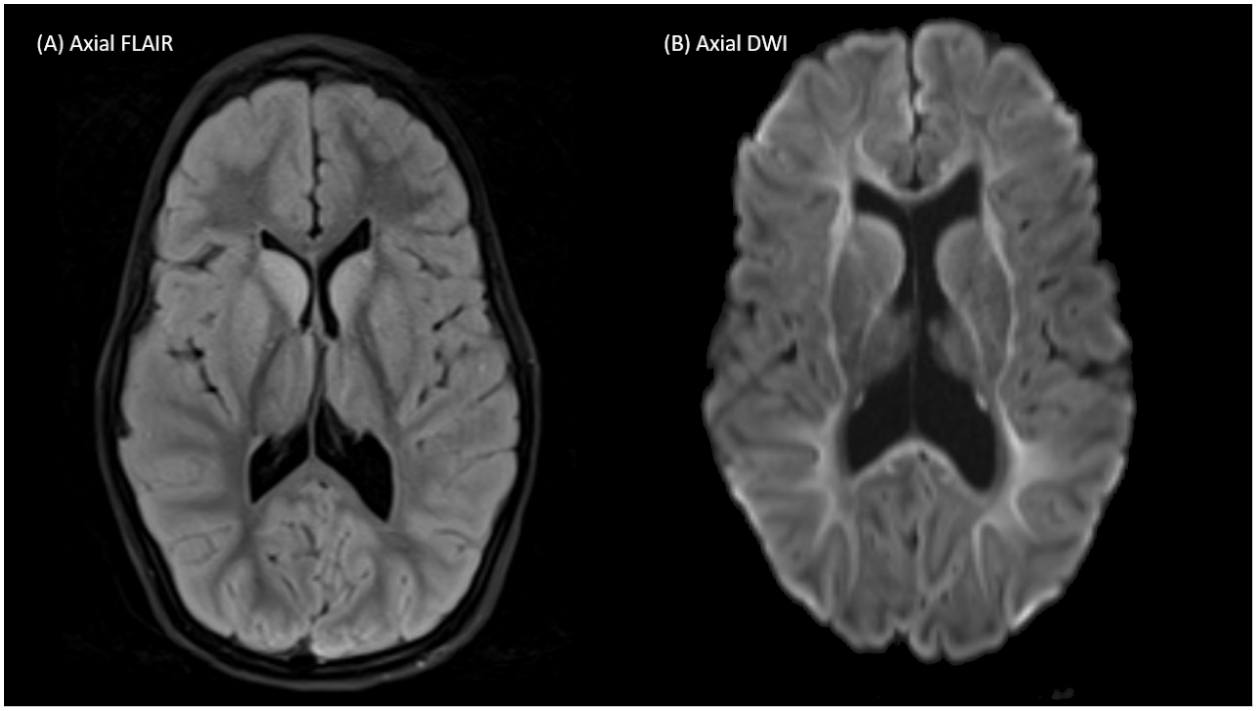

Figure 1. MRI brain obtained fourteen days following cardiac arrest.
Axial FLAIR (a) and DWI (b) images through the basal ganglia demonstrates symmetric FLAIR-DWI hyperintense signal abnormality predominantly involving the deep gray nuclei, consistent with sequelae of hypoxic ischemic injury, with extensive confluent DWI hyperintensity and diffusion restriction involving the deep cerebral white matter typical for post anoxic leukoencephalopathy.

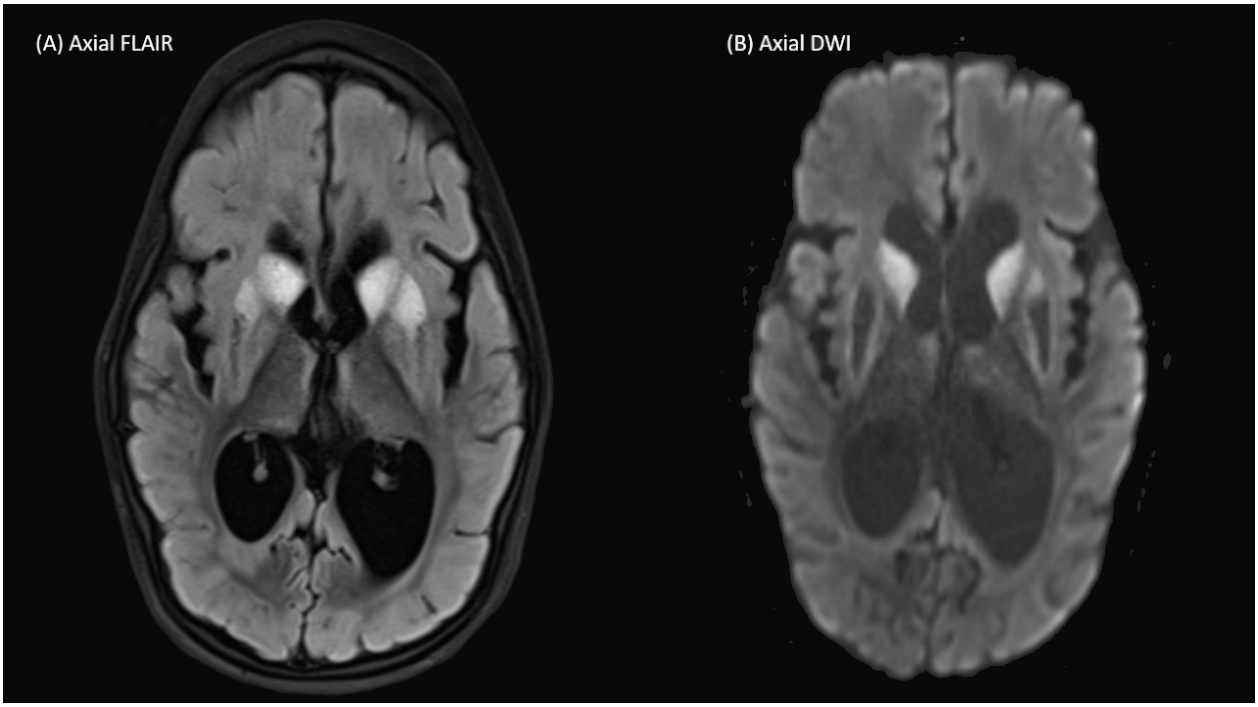

Figure 2. MRI brain obtained two months following cardiac arrest.
Development of central volume loss with persistent FLAIR (a) and diffusion (b) hyperintense signal abnormally in the bilateral caudate and anterior putamen. New symmetric T1 hyperintensity was present in the striatum (not shown) consistent with superimposed mineralization. While volume loss and mineralization are likely attributable to the previous hypoxic-ischemic insult, persistent FLAIR-DWI signal abnormality is atypical in this timeframe and may reflect cell injury related to clinically reported genetic susceptibility to malignant hyperthermia (RYR1 gene mutation) or other toxic metabolic insult.

Table 1: Summary of respiratory management.

Time	Secretion management	Respiratory inhaler	Mechanical respiratory assistance	Humidifiers / nebulizers
Prior to hospitalization	Glycopyrrolate 1 mg/ 5 mL oral; 4 mL by mouth TID	Levalbuterol 45 mcg / inhalation. 2 puffs q6hrs, PRN	BiPAP	3% NaCl inhalation solution. 240 mL via nebulizer 2 times/day.
ICU stay	Dornase alfa 1 drop six times / day. Cough assist six times / day. Vest therapy BID. Atropine 1% ophthalmic solution 1 drop q12 hours.	albuterol (PROVENTIL) oral syrup 0.8 mg, 0.8 mg, Per G Tube, TID	Invasive ventilation => BiPAP	3% NaCl inhalation solution. 240 mL via nebulizer 4 times/day. 7% NaCl inhalation solution. 240 mL via nebulizer 2 times/day.
Upon discharge	Atropine 1% ophthalmic solution q12 hours.	Albuterol 90 mcg / inhalation. 2 puffs p4hrs, PRN	BiPAP	Levalbuterol .63 mg / mL inhalation via nebulizer. 3% NaCl inhalation solution. 240 mL via nebulizer 2 times/day.

she was discharged on amantadine to improve alertness. Two months post hospitalization, the patient had returned to her baseline neurologic function and motor function. A summary of the patient's respiratory management is presented in Table 1.

Discussion

Central core disease is a congenital myopathy histologically characterized by cores of type 1 muscle fibers present in the center of myocytes.[1] Central core disease is caused by *RYR1* mutations, can be inherited in either an autosomal dominant or autosomal recessive fashion, and exhibits a relatively large spectrum of phenotypic manifestations.[2, 3] Up to one third of patients with central cores due to *RYR1* mutation are asymptomatic and live normal lives.[4] In the mild form, muscular weakness has an adult onset, and patients have normal life expectancy. In more severe autosomal recessive cases, myopathy and weakness develop early in a patient's life.[2] In these cases, weakness accompanies a host of other aberrations including external ophthalmoplegia, bulbar involvement, scoliosis, and hip dislocation. A review of twenty-three patients with central core disease identified respiratory weakness in only 22% of those affected.[5]

Two features of the described case make it useful to the broader literature. First, the specific details of respiratory management utilized in our patients' care may serve as a model for future instances of children with severe *RYR1* myopathy hospitalized with bronchiolitis. Secondly, our case features the unique MRI brain finding of persistent bilateral caudate and putamen hyperintensity which cannot be explained by our patients' post-hypoxic leukoencephalopathy.

Post-hypoxic leukoencephalopathy is an entity characterized by neurological regression following an episode of hypoxia.[6] Diffusion-weighted imaging (DWI) has allowed for greater characterization of post-hypoxic leukoencephalopathy as extensive restricted diffusion constitutes the most characteristic feature.[6] Our patient's initial MRI represented a typical signal of post-hypoxic leukoencephalopathy; however, persistence of signal abnormality in the deep gray nuclei two months following initial insult is unlikely to be attributable to her hypoxic insult. At the present time, there is not an obvious etiology of her abnormal signal persistence, and it may represent a sequela of her underlying *RYR1* myopathy, although this has not been reported. Comparisons with brain MRI of other children with *RYR1* myopathy may reveal an unreported susceptibility of the deep gray nuclei which would augment the current understanding of this condition.

There are no specific guidelines regarding the respiratory ICU management of patients with autosomal recessive *RYR1* myopathy. Much of the literature regarding ICU management of the neuromuscular patient comes from amyotrophic lateral sclerosis (ALS).[7] The manifestations of muscle weakness from ALS include diaphragmatic respiratory failure, inability to manage respiratory secretions, and bulbar weakness leading to aspiration.[7] Our patient had similar manifestations of muscular weakness. We found a combination of atropine drops and dornase alfa to be effective agents in controlling our patient's oral secretions. While these interventions cannot be directly attributed to our patient's recovery, this instance serves as an example of their successful use.

Learning Points

1. Hypoxic leukoencephalopathy may have persistent MRI signal abnormalities in patients with *RYR1* myopathy.
2. Amantadine may improve decreased mental status due to hypoxic leukoencephalopathy.

3. Atropine and dornase alfa are agents to consider for management of copious secretions in the context of respiratory failure associated with *RYR1* myopathy.

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Clinical outcomes in COVID-19 patients with pre-existing myasthenia gravis: A systematic analysis of reported cases

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ABSTRACT

INTRODUCTION: Myasthenia gravis (MG) presents an additional challenge in managing COVID-19 as outcomes potentially depend on prior disease control and treatment. Yet the role of pre-existing MG in COVID-19 outcomes has not been established.

METHODS: We searched PubMed, Scopus, and Web of Science databases for reports of MG patients with confirmed COVID-19 until March 2022. We analyzed data on patient demographics, chronicity, and MG control at baseline pre-COVID, treatment history and outcome following COVID infection.

RESULTS: Twenty-nine publications with 119 patients (females n=75, age range 20-93 years, AChR Ab positive n= 65, MuSK Ab positive n= 5, seronegative n=14, unknown n=35) were included. Eighty-three (70%) were hospitalized, more than half with MG exacerbation. There was no significant difference in disease duration or control of MG symptoms at baseline between hospitalized and non-hospitalized. Hospitalization was associated with higher dose of daily prednisone, but a comparable proportion of patients were on steroid-sparing agents. Among hospitalized patients, 40% were intubated uncorrelated with MG baseline control. Unfavorable outcomes were not always associated with MG exacerbation. Amongst those discharged, 75% received intravenous immunoglobulin (IVIG) or plasmapheresis (PLEX) for MG exacerbation as compared to 67% with a fatal outcome didn't receive either.

CONCLUSION: Preexisting MG does not appear to be associated with severe COVID-19 outcomes. A higher dose of prednisone prior to COVID-19 infection is associated with increased risk of hospitalization but MG control at baseline did not determine worse outcome. IVIG/PLEX appear safe in patients with COVID-19 experiencing MG exacerbation.

Introduction

Myasthenia gravis (MG), an autoimmune disease affecting the neuromuscular junction, commonly requires immunosuppressive treatment putting patients at a potentially increased risk for infections.[1] Patients with MG are susceptible to respiratory infections such as COVID-19 due to their neuromuscular weakness.[2] These patients can develop respiratory insufficiency, which could lead to a perilous clinical course from COVID-19 pneumonia. Furthermore, COVID-19 can itself precipitate MG exacerbation since infections are known to be common triggers.[3] Antibiotics used to treat secondary pneumonia and possibly medications such as hydroxychloroquine, used early in the pandemic, can potentially worsen MG.[4] Given the uncertainties surrounding COVID-19, especially at the beginning of the pandemic and the persistent emergence of new variants and treatment protocols, treating COVID-19 patients with known MG has remained an ongoing challenge.[5] The fluctuating course of MG and the wide variations seen between MG patients further complicated this challenge.

Over the course of the pandemic, several case reports of COVID-19 in patients with known MG have been described. These have suggested highly variable clinical courses with some attributing pre-existing myasthenia to worse COVID-19 outcomes, whereas others speculate that COVID-19 itself was responsible for the eventual outcome. Yet systematic evidence on the factors such as the role of steroids taken for MG control, which could alter COVID-19 outcomes in this population, remains scarce. This study thus attempts to aggregate information presented across all such published cases in order to investigate predictors of outcomes in MG patients with concomitant COVID-19 infection.

We performed a systematic review of the relevant literature with key aims to assess two specific outcomes of COVID-19 in patients with pre-existing MG. The first outcome is hospitalization, for which we compared clinical characteristics of patients who were hospitalized with those who did not require hospitalization. Second, among hospitalized patients, we identified factors associated with severe outcomes requiring subsequent invasive ventilation and/or mortality.

Methods

Following the recommendations of Preferred Reporting Items for Systematic Review and Meta-Analysis checklist (PRISMA)[6] for conducting systematic reviews, we searched PubMed, Scopus, and Web of Science databases for reports of MG patients with confirmed COVID-19 infection until March 2022 with keywords "COVID-19" and "myasthenia gravis." For our analysis, we excluded registries or studies with little detail of individual patients which were insufficient to answer our

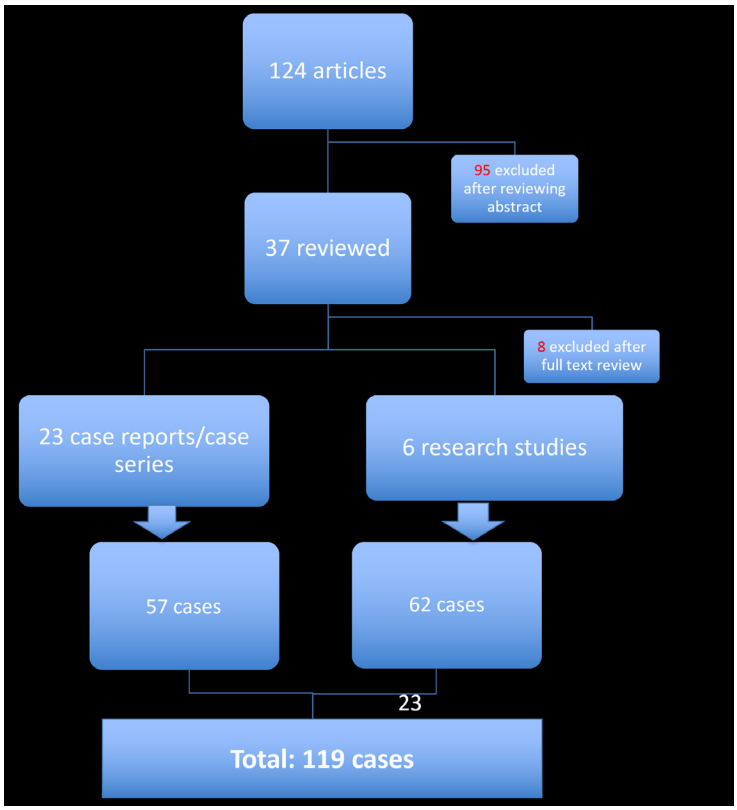

Figure 1: Flowchart showing search process, outcomes and included studies conducted in accordance with PRISMA guidelines for systematic reviews[6]

research question. Additionally, exclusion of those studies helped us to ensure we were not including duplicate cases. We systematically collated a dataset including patient demographics, chronicity, and MG control at baseline pre-COVID, treatment history and outcome following COVID infection.

We used two widely accepted MG outcome measures, Myasthenia Gravis Foundation of America (MGFA) class and Myasthenia Gravis Activities of Daily Living (MGADL) scores, to define MG control.[7] Patients with MGFA classes I, IIA and IIB or MGADL score of <6[8,9] were classified as MG controlled at baseline or having milder disease. Further, to determine favorable vs unfavorable outcome amongst hospitalized patients, we defined favorable outcome as patients who were discharged to home or facility. Death and continued hospitalization with intubation were considered unfavorable outcomes. When information was inadequate or unavailable for certain parameters for individual cases, those were excluded from the denominator for analysis.
Statistical analyses were performed with the following details. For continuous variables of normal distribution, the statistic reported is mean ± standard deviation, while the median is reported for variables with skewed distributions. For categorical variables frequencies and percentages are reported. Continuous variables were compared by Student's t-test and categorical variables were compared by two sample Z-test of proportions. A p-value < 0.05 was considered statistically significant.

Results

We found a total 124 articles based on keyword search and after reviewing all abstracts, following the criteria described in methods, 37 were reviewed in detail (Figure 1). Eight of these were further excluded because they were aggregated analyses of registries or studies with little details of individual patients. Finally, we were able to include 23 publications with case reports or case series, and 6 studies (observational or cross-sectional) describing 62 patients cumulatively with individual details. The final dataset comprised of 119 patients (Figure 1) whom we analyzed assessing their outcome and potential predictors for Covid-19 outcomes.

Out of 119 patients, the majority (N=83 (70%) was hospitalized (median age of 56 years, 54% females) (Table 1). Non-hospitalized patients were more commonly females (83%, p <0.05) and younger (median age 43.5 years, p <0.05) and more frequently noted to have a history of thymectomy (94%. p <0.05). Patients who were hospitalized more likely had comorbidities (72%, p<0.05). Although a comparable proportion of patients were on

Table 1: Comparison between hospitalized and non-hospitalized patients

Demographic and clinical characteristics	Non hospitalized N=36	Hospitalized N=83	p value
Female	30/36 (83)	45/83(54)	0.003
Mean Age (Range) (yrs)	48.1 (21-86) (Median 43.5) (N=36)	56.4 (25-93) (Median 56) (N=68)	0.013
Mean Duration of MG (Range) (yrs)	8.7 (0.75-35) (Median 6) (N=24)	6.7 (0.25-25) Median (4.2) (N=64)	0.126
AChR Ab positive	17/23 (74)	48/61 (79)	0.638
MuSK Ab positive	0/23 (0)	5/61(8)	0.156
Double seronegative	6/23 (26)	8/61 (13)	0.156
History of thymoma	9/16 (56)	6/24 (25)	0.045
History of thymectomy	15/16 (94)	25/61 (41)	0.001
Comorbidities	11/36 (31)	48/67 (72)	<0.001
On oral steroids at baseline	21/36 (58)	59/83 (71)	0.174
On high dose prednisone or equivalent (>20mg/day)	5/24 (21)	32/60 (53)	**0.007**
On steroid sparing agent	18/36 (50)	47/83(57)	0.503
MG controlled at baseline	28/35 (80)	60/69 (87)	0.352
Evidence of MG exacerbation	1/36 (3)	45/80 (56)	<**0.001**
Received antibiotic or antiviral	18/36 (50)	64/81 (79)	**0.0015**
Received HCQ for COVID?	0/37 (0)	12/82 (15)	**0.014**
Received tocilizumab for COVID?	0/37 (0)	5/82 (6)	0.126
Intubation	0/37 (0)	38/83 (46)	<**0.001**

Ab: antibody, AChR: Acetylcholine receptor, HCQ: Hydroxychloroquine, IVIG: Intravenous immunoglobulin, MuSK: Muscle specific kinase, PLEX: Plasma exchange

steroid-sparing agents for both groups, hospitalization was associated with a higher dose (prednisone>20mg/day or equivalent) of daily oral steroids (53% vs 21%, $p<0.05$). Unlike age, disease duration of myasthenia was not different between hospitalized and non-hospitalized patients (Figure 2).

Among hospitalized patients, males (86%) and elderly (median age 68yrs, $p<0.05$) were more likely to have unfavorable outcomes and prior disease duration was unrelated (Table 2, Figure 3). Usage of antibiotics or antivirals was not significantly different amongst hospitalized patients with favorable or unfavorable outcomes. Interestingly, 18/30 (60%) patients who received azithromycin and 4/5 (80%) patients who received fluoroquinolones showed evidence of MG exacerbation. However, only 4/12 patients who took HCQ reported MG exacerbation.

Forty six percent of hospitalized patients required intubation, but this was not associated with MG baseline control (68% vs 76%, $p > 0.05$). More than half (56%) of the hospitalized patients showed evidence of MG exacerbation. Unfavorable outcome was not always associated with MG exacerbation (62% vs 77%, $p<0.05$). Amongst 38 hospitalized patients with MG exacerbation whose outcomes could be determined, 28 had a favorable outcome with 21 (75%) of them having received either IVIG or PLEX. On the contrary, only four out of 10 with unfavorable outcome received either therapy (40%). Among the remaining six with unfavorable outcome who received neither, death was confirmed for 4 patients.

Discussion

MG patients who contract COVID-19 are expectedly at increased risk of hospitalization and likely to have longer duration of hospital stay, which recent studies analyzing data from registries have confirmed.[10-12] However, determinants for risk of hospitalization and poor outcome in hospitalized MG patients were not well-established. The limited studies on MG patients with COVID-19 have documented diverse clinical course with only few potential predictors of outcome.[13,14] To address this gap, we compared hospitalized and non-hospitalized patients and further compared between hospitalized patients with or without favorable outcomes. There was no significant difference in MG disease duration (Figure 2) and antibody positivity status between hospitalized and non-hospitalized groups. We found male and elder myasthenics are more likely to be hospitalized and more likely to have poor outcome when hospitalized. Studies worldwide similarly have shown elderly[15] and men are likely to have worse COVID-19 outcomes[16-18] including patients with neuromuscular disorders.[19] On the contrary, myasthenia tends to have a more severe course in females.[20] Thus, COVID-19 appears to be the dominant factor in shaping outcomes in patients with concomitant MG and COVID infection. Unsurprisingly, comorbidities found previously to be significant risk factors for severe COVID-19 infection[21,22] were more common amongst hospitalized MG patients in our dataset. Additionally, MG control at baseline was unrelated to hospitalized patients being intubated. Unfavorable outcome in hospitalized patients was not always associated with MG exacerbation. Our analysis thus suggests pre-existing MG did not appear to be a major factor in worsening outcome from COVID-19 infection.

We found high dose of oral steroids to be associated with increased risk for hospitalization. Baseline long-term corticosteroid treatment, especially in high dose, has been noted to predict severe course of COVID-19 in a study on MG patients.[23] This highlights why reducing or discontinuing steroids without losing MG control should be the therapeutic goal when managing MG. Interestingly high dose of prednisone at baseline did not predict poor outcome amongst hospitalized patients in our analysis. Furthermore, administration of extra steroids during hospitalization also did not seem to affect the outcome (Table 2). The lack of such association could possibly be explained by the potential beneficial role of steroids in severe COVID-19 infection[24] but not in mild COVID.[25] The majority of non-hospitalized patients had h/o thymectomy and 85% patients with thymectomy in our cohort had MG controlled. While a protective role of thymus gland has been suggested in viral infection like COVID-19,[26] thymectomy is known to render improved clinical outcome in MG[27] and perhaps accounted for a lesser risk of a severe clinical course. No significant association of poor outcome was noted with non-steroid sparing agents, as observed in COVID-19 and other autoimmune conditions.[28]

Both IVIG and PLEX are effective treatments for myasthenic crisis. The beneficial role of therapeutic plasma exchange[29] and IVIG[30] also has been observed in severe COVID-19 infection, although debate continues with concern for increased thromboembolic events particularly in relation to IVIG.[31,32] In the cases we reviewed, most hospitalized patients with COVID-19 appeared to have benefitted from IVIG/PLEX for MG exacerbation. These regimens appear safe in COVID-19 patients who experience MG exacerbation.

One of the major limitations of the study is reporting bias since our review is primarily based on published case reports and case series. Given the publishing bias in case reports and high incidence of hospitalization in our cohort, the findings of the study perhaps can be interpreted as characterizing severe COVID-19 infection among MG patients. Additionally, marked heterogeneity of study population due to variation in geographical origin, practiced standard of care, as well as often limited information due to non-uniform reporting could not be adjusted for. Nevertheless, several of our study findings,

including more favorable COVID-19 outcomes in females and increased risk for hospitalization due to comorbidities, lend face validity to our dataset. Additional studies may utilize data from MG cohorts from individual institutions or databases. None of the studies we reviewed reported whether patients were vaccinated. Given these studies were published prior to March 2022, it is highly plausible that most cases occurred before vaccines for COVID-19 were widely available around the world. While it is true that vaccines could alter the course of COVID-19 in MG patients and having that information would be helpful, studies like ours provide clinical implications of managing MG should any future pathogens result in epidemics for whom vaccines may not become immediately available.

Conclusion

Pre-existing myasthenia gravis is potentially a risk factor for worse outcomes in COVID-19. Yet, given MG itself is a disease with a highly variable course, it is important to establish the specific factors among MG patients that could alter COVID-19 outcomes. We aggregated data combining a large number of published cases of MG patients diagnosed with COVID-19 and found that pre-existing MG itself does not predict a worse COVID-19 outcome. Rather, the factors typically associated with worse COVID-19 outcomes, irrespective of MG diagnosis, also led to poorer outcomes in MG patients who contracted COVID-19.

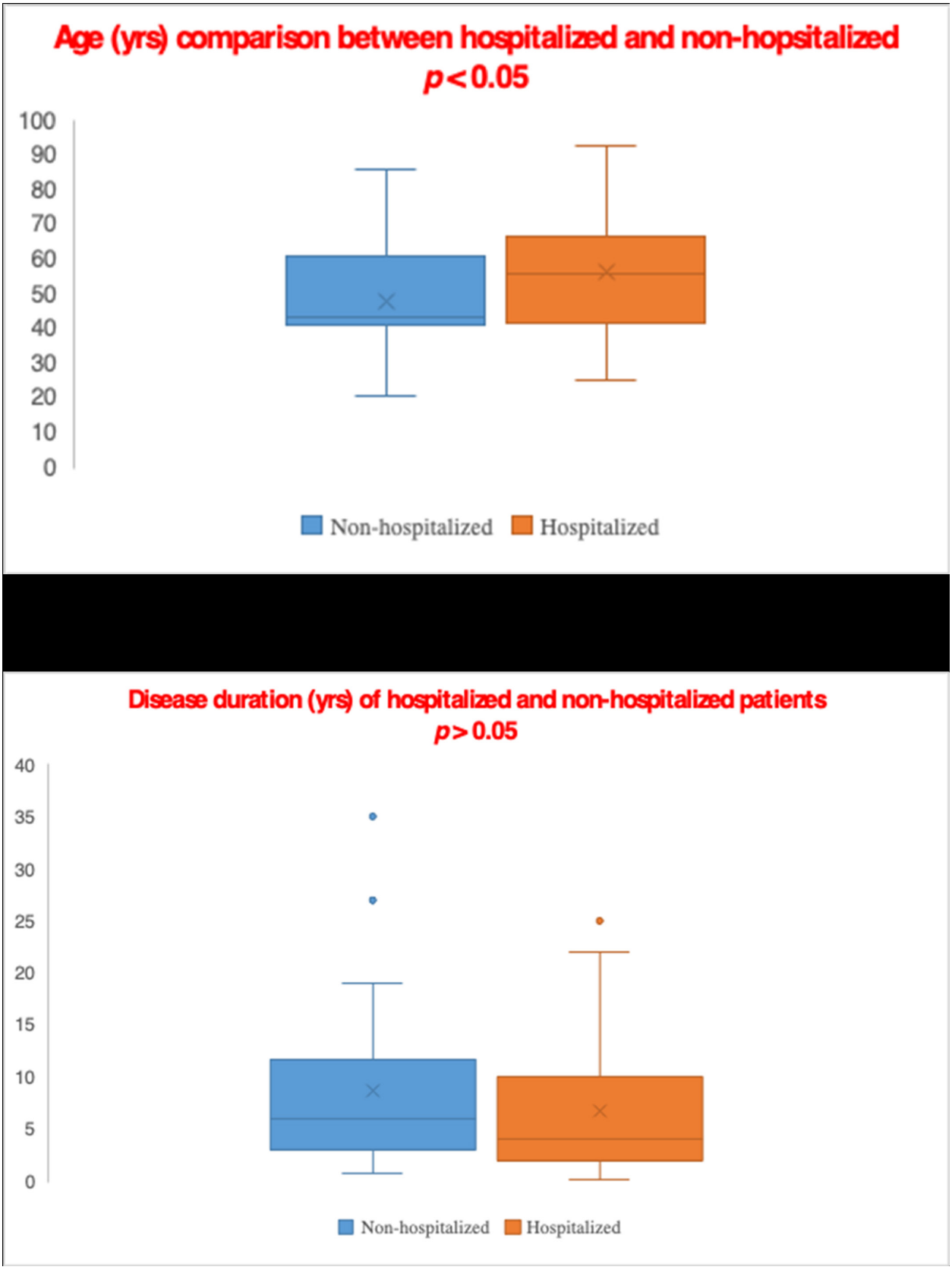

Figure 2: Differences in hospitalized vs non-hospitalized patients based on age (top) and disease duration (bottom)

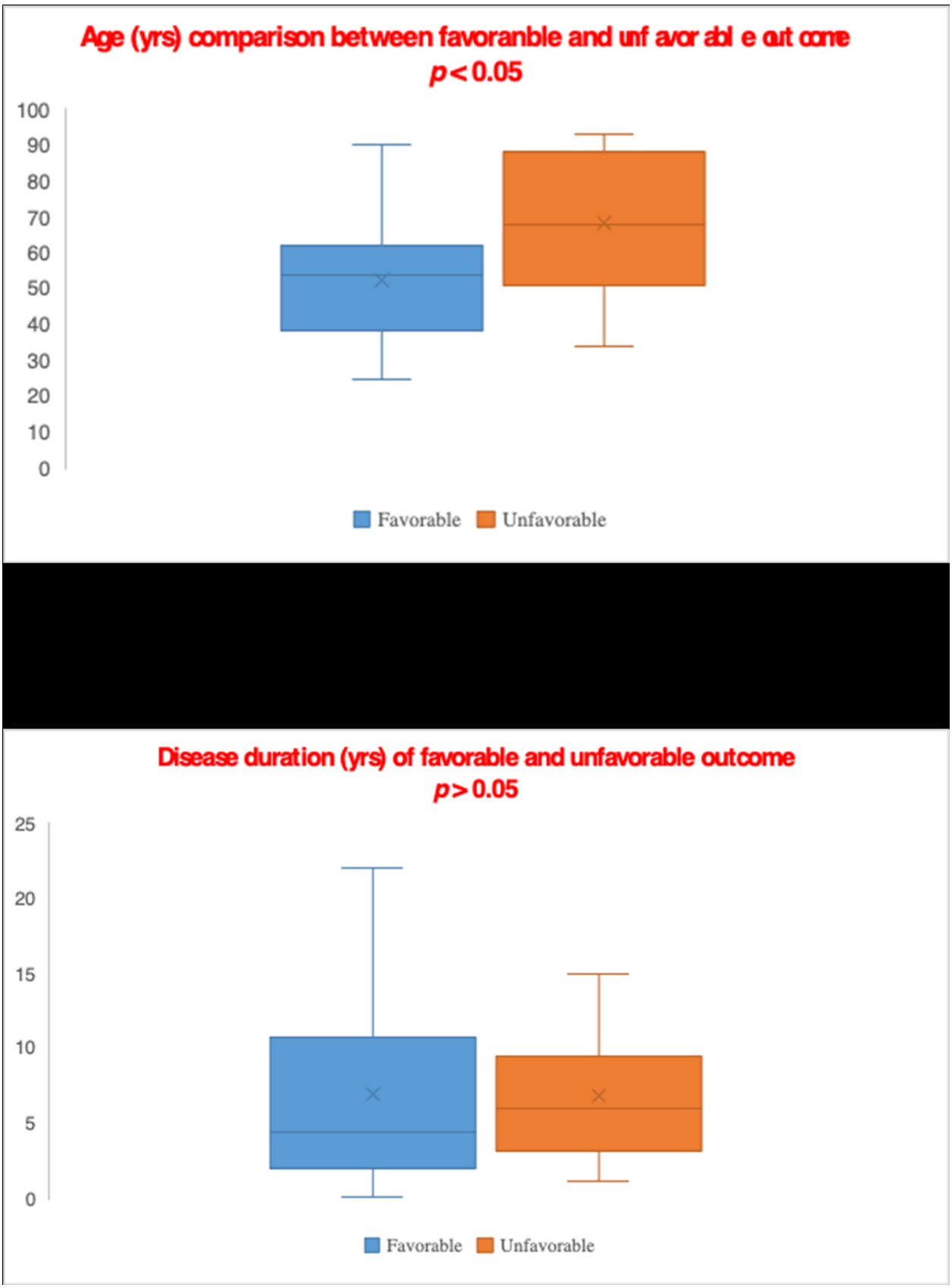

Figure 3: Differences in hospitalized patients' favorable vs un-favorable outcomes based on age (top) and disease duration (bottom)

TABLE 2 Comparison between favorable and non-favorable outcome among hospitalized patients

Demographics and clinical characteristics	Favorable outcome N=49	Non favorable outcome N=17	*p* value
Female	20/36 (56)	1/7 (14)	0.046
Mean Age (Range) (yrs)	52.4 (25-90) (Median=54) N=40	68.5 (34-93) (Median=68) N=16	**0.007**
Duration of MG (Range) (yrs)	6.9 (0.16-22) (Median=4.5) N=44	6.8 (1.2-15) (Median=6) N=12	0.493
AChR Ab positive	31/41 (76)	11/12 (92)	0.226
MuSK Ab positive	3/41 (7)	1/12 (8)	0.904
Double seronegative	7/41 (17)	0/12 (0)	0.124
History of thymoma	3/15 (20)	1/4 (25)	0.825
History of thymectomy	16/38 (42)	2/9 (22)	0.271
Comorbidities	22/34 (65)	13/16 (81)	0.234
On oral steroids at baseline	33/48 (69)	13/17 (77)	0.548
On high dose prednisone or equivalent (>20mg/day)	21/37 (57)	9/17 (53)	0.795
On steroid sparing agent	25/48 (52)	9/17 (53)	0.952
MG controlled as baseline	36/41 (88)	11/14 (79)	0.395
Evidence of MG exacerbation	28/45 (62)	10/13 (77)	0.327
Received antibiotic or antiviral	34/48 (71)	15/16 (94)	0.061
Received tocilizumab/HCQ	9/48 (19)	2/16 (13)	0.569
Extra steroids administered during hospitalization	25/40 (63)	6/14 (43)	0.201
Received IVIG or PLEX For MG exacerbation	21/28 (75)	4/10 (40)	**0.045**
Intubation	19/48 (40)	15/17 (88)	**0.001**

Ab: antibody, AChR: Acetylcholine receptor, HCQ: Hydroxychloroquine, IVIG: Intravenous immunoglobulin, MuSK: Muscle specific kinase, PLEX: Plasma exchange

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Isolated hypoglossal nerve palsy secondary to basilar artery compression: A case report and reviewing of electrodiagnostic evaluation of the hypoglossal nerve

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ABSTRACT

Introduction: Hypoglossal nerve palsy causes ipsilateral tongue weakness, commonly presenting with dysphagia, dysarthria, or perceived tongue weakness. Vascular compression is a rare cause of isolated hypoglossal nerve palsies. Imaging and serologic labs are common parts of the evaluation of hypoglossal nerve palsies. Though less commonly used, electrodiagnostic studies can be important in the diagnostic evaluation of hypoglossal nerve palsies.

Case: We report a case of a 53-year-old man with dysphagia found to have a left hypoglossal nerve palsy secondary to vascular compression from the basilar artery confirmed by electrodiagnostic and radiographic studies and we provide a review of the electrodiagnostic evaluation of the hypoglossal nerve.

Keywords: Vascular compression, isolated hypoglossal nerve palsy, basilar artery

Introduction

The hypoglossal nerve is a pure motor nerve innervating the intrinsic and extrinsic muscles of the tongue. It can be divided into 5 sections: medullary (nuclear), cisternal (extramedullary intracranial), skull base, nasopharyngeal/oropharyngeal carotid, and sublingual.[1] Hypoglossal nerve deficits that are distal to the nucleus cause ipsilateral tongue weakness. The most common initial symptoms of an isolated hypoglossal nerve palsy are dysphagia (38.5%), dysarthria (28.3%), tongue weakness (22.3%), headache (14.2%), and hoarseness (6.5%).[2] Isolated hypoglossal nerve palsies are rare. Causes of hypoglossal nerve palsies are extensive with common causes including carotid endarterectomy (15.2%), primary tumors (14.2%), including squamous cell carcinoma of the tongue, parotid tumors, tongue adenoid cystic carcinoma, and brain stem gliomas, metastatic tumors (13%) including lung cancer, renal cell carcinoma, rectal and pancreatic, prior radiation (6.2%), and inflammatory conditions (7.3%) including vasculitic multiple mononeuropathy, post-surgical inflammatory mononeuropathy, rheumatoid arthritis pannus, neurosarcoidosis, and Sjogren's syndrome. More rare causes of hypoglossal nerve palsies include trauma (4.1%), vascular (excluding post-op) causes (3.3%), congenital (2.8%), cystic (2.4%), and motor neuron disease (1.6%).[3]

Case presentation

A 53-year-old right-hand dominant male with a history of hypertension, hyperlipidemia, diabetes, and atrial fibrillation status post an atrial ablation 13 years prior, presented to the neurology clinic with a 4-5 month duration of difficulty initiating swallowing. He had previously been evaluated by an otolaryngologist and speech therapist with unremarkable modified barium swallow testing. His initial exam was significant for left tongue deviation both at rest and with protrusion, mild left-sided tongue atrophy without other cranial nerve deficits. His extremity muscle strength was normal, with decreased distal lower extremity reflexes and decreased sensation in a glove and stocking distribution. He had unremarkable serum inflammatory and autoimmune laboratory workup with normal erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, and rheumatoid factor as well as normal serum Lyme titers. A non-contrast head computed tomography (CT) scan was normal. Magnetic resonance imaging (MRI) of the brain with and without contrast (Figure 1) revealed mass effect of the basilar artery on the left upper medulla at the region of the left 12th cranial nerve without evidence of infarct or space-occupying lesions in the brainstem.

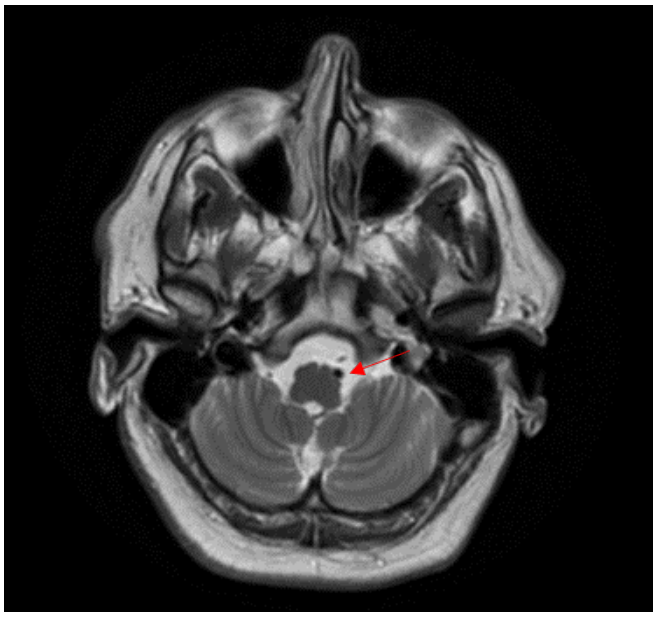
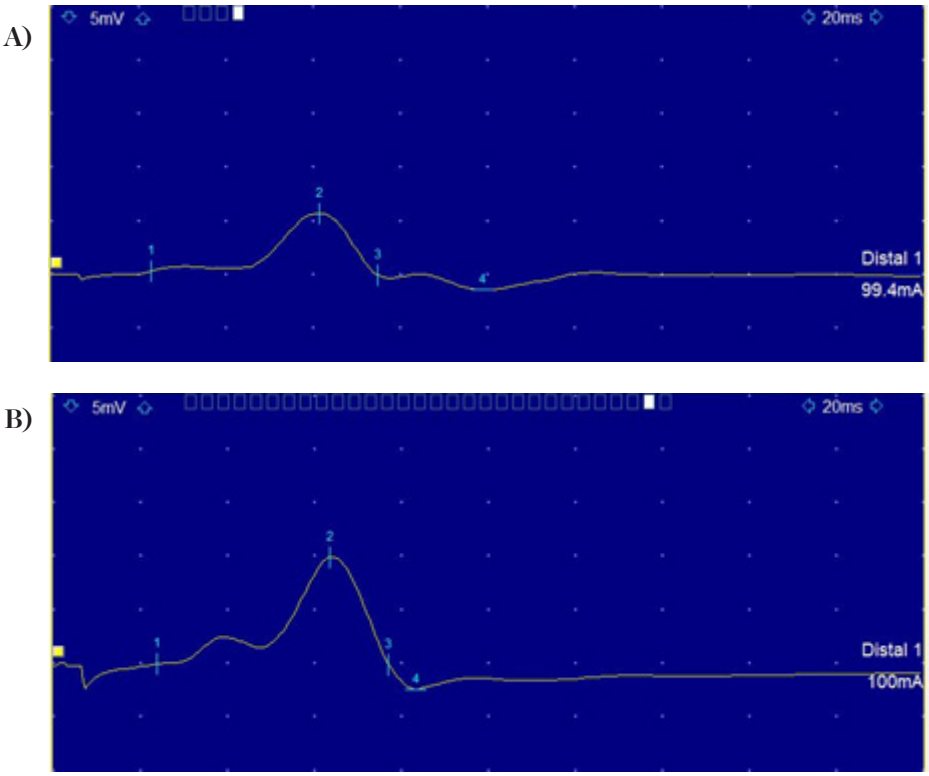


Figure 2: A) Left hypoglossal nerve conduction study at the intrinsic tongue muscle B) Right hyoglossus nerve conduction study at the intrinsic tongue muscle

On needle exam of the genioglossus muscle long duration and high amplitude motor unit action potentials (MUAP) were observed on the left without abnormal spontaneous activities .Needle examination of the right genioglossus muscle and left mentalis was normal. The facial motor NCS were normal and symmetrical bilaterally.



Subsequent nerve conduction studies (NCS) were completed by stimulating the hypoglossal nerve and recording over the dorsal surface of the tongue over the intrinsic tongue muscles. Findings were significant for relative decreased amplitude of the left hypoglossal motor nerve response compared to the right (right: amplitude of 10.0 mV with a latency of 2.4 ms, left: amplitude of 5.4 mV, latency of 2.3 ms) [Figure 2].

The patient had improvement in activation and protrusion of his left tongue between the initial exam and electrodiagnostic testing with persistent prominent tongue deviation. He continued to participate in speech therapy using compensatory and rehabilitative techniques and reported symptomatic improvement in dysphagia at a 6-month virtual follow-up.

Discussion

Vascular (excluding post op) causes of isolated hypoglossal nerve palsy are rare, accounting for 3.3% of all cases.[3] Vascular compression is a known non-surgical vascular cause of hypoglossal nerve palsy. Previous case reports detail hypoglossal nerve compression from persistent primitive hypoglossal artery[4] intracranial vertebral artery,[5] adherent fusiform PICA aneurysm[6] and basilar artery compression[7]. Treatment for vascular compression included spontaneous resolution or surgical decompression.

Initial evaluation of isolated hypoglossal nerve palsies entails evaluation of inflammatory, infectious, and compressive causes via serum and cerebrospinal fluid testing for inflammatory and infectious markers, and brainstem and cerebral vessel imaging. Though less commonly used, electrodiagnostic studies can be used to confirm and further evaluate hypoglossal nerve palsies. Electrodiagnostic evaluation of the hypoglossal nerve was first reported by Skorpil and Zverina in 1962 and later refined at Walter Reed Army Medical Center by Redmond and Di Benedetto in 1988.[8,9] Nerve stimulation is performed along the mandible, one-third from the angle of the jaw to the mental protuberance and 1 cm medial to the mandibles. The recording electrode is positioned 1 cm posterior to the lower incisors and the reference electrode is positioned 2

cm posterior to the recording electrode. The electrodes can be held on the anterior surface of the tongue via a special mouthpiece or a tongue depressor. Of the 30 subjects sampled, Redmond and Di Benedetto reported a mean latency of 2.2 +/- 0.4 ms (range 1.4-3.2 ms) and a mean amplitude of 3.8 +/- 1.6 mV (range 1.0-8.0 mV).[8] Needle electromyography of the genioglossus muscle can be used to evaluate hypoglossal nerve function, which is achieved by needle insertion intraorally or inferiorly via a subcutaneous approach from the medial angle of the mandible.[10] Electrodiagnostic testing can be easily completed on the hypoglossal nerve to assess motor function as an adjunct to serologic and radiographic evaluation of hypoglossal nerve palsies. This case reports an important cause of hypoglossal nerve palsies and reviews the potential utility in electrodiagnostic studies during evaluation.

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Database Evaluation for Muscle and Nerve Diseases – DEMAND: An academic neuromuscular coding system

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ABSTRACT

Background: A database which documents the diagnosis of neuromuscular patients is useful for determining the types of patients referred to academic centers and for identifying participants for clinical trials and other studies. The ICD-9 or ICD-10 numeric systems are insufficiently detailed for this purpose.

Objective: To develop a database for neuromuscular diagnoses

Methods: We developed a detailed diagnostic coding system for neuromuscular diseases called DEMAND: Database Evaluation for Muscle and Nerve Diseases that has been adopted by neuromuscular clinics at University of Texas Health Science Center San Antonio (UTHSCSA), Ohio State University (OSU), University of Kansas Medical Center (KUMC), and University of Texas Southwestern (UTSW). At the initial visit, patients are assigned a diagnostic code which can be revised later if appropriate. Fields include patient's name, date of birth, and diagnostic code. The neuromuscular database consisted of 457 codes. Each code has a prefix (MUS or PNS) followed by a three-digit number. Depending on whether muscle or nerve is primarily involved, there are eight broad groups: motor neuron disease (MUS codes 100-139); neuromuscular junction disorders (MUS 200-217); acquired and hereditary myopathies (MUS 300-600s); acquired and hereditary polyneuropathies (PNS 100-400); mononeuropathies (PNS 500s); plexopathies (PNS 600s); radiculopathies (PNS 700s); and mononeuritis multiplex (PNS 800s).

Results: During a period of 10 years, 17,163 of patients were entered (1,752 at UTHSCSA, 1,840 at OSU, 3,699 at KUMC, 9,872 at UTSW). The number of patients in several broad categories are: 3,080 motor neuron disease; 1,575 neuromuscular junction disease; 1,851 muscular dystrophies; 633 inflammatory myopathies; 1,090 hereditary neuropathies; 1,001 immune-mediated polyneuropathies; 620 metabolic/toxic polyneuropathies; 535 mononeuropathies; 296 plexopathies; and 769 radiculopathies.

Conclusion: A detailed diagnostic neuromuscular database can be utilized at multiple academic centers. The database should be simple without too many fields to complete, to ensure compliance during busy clinic operations. This database has been very useful in identifying groups of patients for retrospective, observational studies and for prospective treatment studies including trials for Amyotrophic Lateral Sclerosis (ALS), Muscular Dystrophies (MD), Myasthenia Gravis (MG), and retrospective studies of Primary Lateral Sclerosis (PLS), chronic inflammatory demyelinating neuropathy (CIDP), etc.

Introduction

Even when the ICD-9 transitioned to ICD-10, there was still not enough precision for academic purposes. The ICD system is primarily a billing system and not an academic classification system. A database which documents the diagnosis of neuromuscular patients is valuable for determining the types of patients referred to academic centers and for identifying participants for future studies and clinical trials. The ICD-9 or ICD-10 numeric system is poorly suited for this purpose. For instance, all forms of muscular dystrophy and hereditary neuropathy are assigned one code in the ICD-9 or ICD-10 system (Myotonic dystrophy type 1 and Myotonic dystrophy type 2 are assigned the same codes in ICD-9 or ICD-10 system). Due to the wide variety of different muscle disorders and the myriad etiologies for polyneuropathies, the neuromuscular database is poorly served by the ICD-9 or ICD-10. In addition, the ICD-9 and ICD-10 system may encounter difficulty incorporating new genetic and other diagnoses as they are recognized over time. We developed a database for neuromuscular diagnoses. Our goal was to develop a comprehensive uniform database to diagnose neuromuscular patients for all study designs which can also be adapted to allow mapping to new nomenclature and reclassification. We have called this coding system DEMAND: Database Evaluation for Muscle and Nerve Disease.

Methods

We developed a comprehensive diagnostic coding system for neuromuscular diseases. The system was first developed at University of Texas Southwestern (UTSW) in 1993. It was later adopted at University of Texas Health Science Center San Antonio (UTHSCSA), Ohio State University (OSU), and University of Kansas Medical Center (KUMC). The neuromuscular database initially consisted of fewer codes but over time has expanded to 457 codes. Each code has a prefix (MUS or PNS) followed by a three-digit number. There are eight broad groups:

Motor Neuron Disease	MUS 100-139
Neuromuscular Junction	MUS 200-217
Acquired and Hereditary Myopathies	MUS 300-600
Acquired and Hereditary Polyneuropathies	PNS 100-400
Mononeuropathies	PNS 500
Plexopathies	PNS 600
Radiculopathies	PNS 700
Mononeuritis Multiplex	PNS 800

For reference purposes, the corresponding ICD-10 and ICD-9 numbers for each MUS and PNS code are listed. For details regarding all the individual codes in each broad group along with the corresponding ICD-10 and ICD-9 numbers, see Appendix 1 for each MUS code and Appendix 2 for each PNS code. At the time of collection of this data, only the ICD-9 codes were available. However, since then the ICD-10 codes have also been released. If a disease diagnosis is not apparent, the database allows the option by symptoms or lab findings. Examples of symptoms are Fatigue – MUS 811, Numbness – PNS 835, Myalgias – MUS 301, and Pain – PNS 820.

Neuromuscular Clinical Database Collection form (Appendix 3)

The neuromuscular clinical database contains patient's names, ID, date of birth, social security number, neuromuscular code (MUS or PNS), ICD code, date of visit, and new or follow-up visit. We ask physicians to complete these after they see the patient. The information is then transferred to a computerized spread sheet at each site. With the introduction of the electronic health record some sites determined ways to enter the PNS/MUS code directly in the electronic medical record. This required some IT support and this capability varied at each site.

Neuromuscular Consent Form

This consists of informed consent about the participation in the database study for the patients with a neuromuscular disorder. At KUMC, the HSC-approved consent form is signed by the patient at the initial visit (Appendix 4). Other universities exempt the consent form in the initial visit and go to their HSC (IRB) for specific projects.

Codes for Muscular/Neuromuscular Junction Disease/ Peripheral Nervous System Disorders

Patients are assigned a diagnostic code at the initial visit. The database fields are minimal: patient's name, date of birth, and diagnostic code. These are entered into an Excel spreadsheet by a clinic clerk. If on the next visit there is a change of working diagnosis, the new code is entered into the computer spreadsheet.

At KUMC, the HSC-approved consent form is signed by the patient at the initial visit. Our goal is for all new clinic patients to sign the consent. This form states, "The database may be used to identify patients for research studies."

Results

Over 10 years, 17,163 of patients have been entered (Table 1). Table 2 shows the number of patients in several broad categories. In the motor neuron disease category, 2,023 of the 3,080 patients had amyotrophic lateral sclerosis (ALS) (Table 3). Of the 1,575 patients in the neuromuscular junction category, 1,368 had myasthenia gravis (Table 2). Of the 1,851 patients with muscular dystrophy, 258 had Duchenne muscular dystrophy and 330 had myotonic dystrophy (Table 3). Of the 633 inflammatory myopathy patients, 102 had dermatomyositis; 200 had inclusion body myositis; and 188 had polymyositis. Within the PNS group of patients with peripheral neuropathy, 1,090 had hereditary neuropathies; 1,001 had immune-mediated polyneuropathy; 620 had metabolic/toxic polyneuropathy; 535 had mononeuropathies; 296 had plexopathies; and 769 had radiculopathies. Table 4 shows the sum of related muscle disorders with the number of cases seen in this reporting period.

Discussion

Categorizing neuromuscular patients in tertiary care clinics is challenging. Although the ICD-10 numeric system is available, this is too crude and not sufficiently discriminating. For instance, both Myotonic dystrophy type 1 and type 2 have the same codes in the ICD-10 system.

This neuromuscular database is useful for determining the types of patients referred to tertiary care academic centers and more specific differentiation of the neuromuscular disorders. In the ICD-10 system, PLS, lower motor neuron disease and focal motor neuron disease have the same G12.29 codes whereas these have different codes in our neuromuscular database. Our database shows that in our tertiary care clinics, ALS is the most common occurring motor neuron disease. ALS was seen 13 times more than PLS. The database also reflects regional referral patterns. For example, because UTSW has a leprosy referral clinic, this diagnosis was unique to the Dallas clinic. Therefore, at UT San Antonio, these patients and diabetic patients tend to be seen in the general neurology clinic, which accounts for fewer patients in these categories in

this database.

The most common neuropathy seen in all four centers surprisingly was cryptogenic sensory polyneuropathy. This can be attributed to the tertiary care referral pattern. Within the diabetic neuropathy category, diabetic distal sensory polyneuropathy is seen three to four times more often than diabetic lumbosacral radiculoplexus neuropathy. This diagnostic frequency of diabetic polyneuropathy is still more common than would occur in a general medicine or neurology clinic and again indicates the tertiary care referral pattern. This also accounts for the many chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy cases in the immune-mediated PNS group.

As expected, within the neuromuscular junction disorders, the most common neuromuscular junction disease was myasthenia gravis. MG is about 50 times more common than the Lambert-Eaton syndrome in our centers. The most common inflammatory myopathy disease seen was inclusion body myositis. Surprisingly, polymyositis cases were seen more often than dermatomyositis.[1,2]

Benefits of the neuromuscular database are:

1. Comparison of data between different hospitals.
2. Comparison between the initial visit diagnosis and final working diagnosis.
3. This intuitive and instinctive database is user friendly.
4. Allows continuous addition of new entities as they are discovered and reported.
5. Allows more precise coding of neuromuscular disorders beyond what can be done using the ICD system.

Finding an easy solution to enter the codes in the electronic medical record remained a barrier.

In summary, our experience shows that a diagnostic neuromuscular database can be utilized at multiple academic tertiary care centers. The database should be simple without too many fields to ensure compliance. This database has been very practical in identifying groups of patients for retrospective, observational studies and for prospective treatment studies (see tables 1-5).

Table 1. Total number of patients coded in four different hospitals of United States

Hospitals	Number of patients
UTHSCSA (1995-2005)	1,752
OSU (1995-2005)	1,840
KUMC (2001-2005)	3,699
UTSW (1993-2005)	9,872
TOTAL PATIENTS	17,163

Table 2. Total number of cases in different major categories seen in four hospitals.

Groups	UTSW	KUMC	OSU	UTHSCSA	Total
MOTOR NEURON DISEASE (MUS 100S)	1734	582	263	501	3080
NEUROMUSCULAR JUNCTION (MUS 200s)	1020	248	102	205	1575
MUSCULAR DYSTROPHIES (MUS 400s)	893	386	176	396	1851
HEREDITARY NEUROPATHIES (PNS 100s)	591	223	142	134	1090
IMMUNE MEDIATED POLYNEUROPATHY (PNS 200s)	285	225	257	234	1001
RADICULOPATHIES (PNS 700s)	542	206	6	15	769
INFLAMMATORY MYOPATHIES (MUS 500s)	375	88	96	74	633
METABOLIC/TOXIC POLYNEUROPATHY (PNS 300s)	368	131	112	9	620
MONONEUROPATHIES (PNS 500s)	221	209	48	57	535
PLEXOPATHIES (PNS 600s)	178	59	54	5	296

Table 3. Total number of cases in neuronopathies and neuropathies category seen in four hospitals.

DISEASE	UTSW	KUMC	OSU	UTHSCSA	TOTAL
ALS (MUS 101)	1051	414	147	411	2023
PLS (MUS 104)	86	31	12	19	148
CRYPTOGENIC SENSORY POLYNEUROPATHY (PNS 409)	191	210	270	24	695
DIABETES MELLITUS NEUROPATHY DSPN (PNS 309)	168	83	61	8	320
DIABETIC LUMBOSACRAL PLEXOPATHY (PNS 625)	41	29	20	0	90
CIDP (PNS 206)	177	72	61	32	342
MMN (PNS 209)	59	23	8	2	92

Table 4. Total number of cases in neuromuscular and myopathic category seen in four hospitals.

DISEASE	UTSW	KUMC	OSU	UTHSCSA	TOTAL
MYASTHENIA GRAVIS (MUS 201)	883	198	92	195	1368
LAMBERT EATON MYSTHENIC SYNDROME (MUS 202)	19	4	3	4	30
INCLUSION BODY MYOSITIS (MUS 504)	119	36	21	24	200
POLYMYOSITIS (MUS 501)	116	27	27	18	188
DERMATOMYOSITIS (MUS 502)	56	5	20	21	102
DUCHENNE MD (MUS 401)	42	53	35	128	258
BECKER MD (MUS 402)	35	11	2	26	74
FSH MD (MUS 405)	78	49	29	27	183
LGMD (MUS 404)	92	58	29	42	221
MYOTONIC DYSTROPHY (MUS421)	163	78	16	73	330
MYOTONIA CONGENITA (THOMSEN'S) (MUS 422)	26	8	4	13	51

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2. Van der Meulen MGF, Bronner IM, Hoogendijk JE, Burger H, Van Venrooij WJ, Voskuyl AE, et al. Polymyositis: an overdiagnosed entity. *Neurology* 2003;61:316-21.

Appendix 1: Current MUS Codes

Category	Code		ICD-9	ICD-10
MUS	100	Motor Neuron Disorder	335.29	G12.29
MUS	101	Amyotrophic Lateral Sclerosis	335.2	G12.21
MUS	102	Familial ALS	335.2	G12.21
MUS	103	Lower Motor Neuron-MND	335.29	G12.29
MUS	104	Primary Lateral Sclerosis	335.24	G12.29
MUS	105	Familial Spastic Paraplegia	335.29	G11.4
MUS	106	Focal Motor Neuron Disease	335.29	G12.29
MUS	107	Stiff-Man Syndrome	333.91	G25.82
MUS	108	Isaac's Syndrome (Neuromyotonia NMT)	359.3	G71.19
MUS	109	Sequelae of Poliomyelitis	45.9	A80.9
MUS	110	Post-Polio Syndrome	138	G14
MUS	111	Benign Fasciculations	781	R25.3
MUS	112	ALS with frontotemporal dementia	335.2	G31.09
MUS	113	Other MND With frontotemporal dementia	335.29	G12.29/G31.09
MUS	120	Spinal Muscular Atrophy	335.1	G12.9
MUS	121	Infantile Onset SMA	335	G12.0
MUS	122	Childhood Onset SMA	335.11	G12.1
MUS	123	Adolescent Onset SMA	335.11	G12.1
MUS	124	Adult Onset SMA	335.19	G12.8
MUS	125	Distal SMA	335.1	G12.1
MUS	126	X-Linked SMA | Bulbospinal | Kennedy Syndrome	335.1	G12.2
MUS	130	Other Motor Neuron Disorder	335.29	G12.29
MUS	131	West Nile Virus Neuronopathy	335.29	A92.32
MUS	133	Hirayama’s Disease [Monomelic Amyotrophy]	335.29	G12.8
MUS	135	Hopkins Syndrome	335.29	Q87.0
MUS	136	IBALS [Isolated Bulbar ALS, MND]	335.22	G12.21
MUS	137	BAD [Brachial Amyotrophic Diplegia, MND]		
MUS	138	LAD [Leg Amyotrophic Diplegia, MND]		G82.20
MUS	139	Radiation-induced motor neuron disease	335.2	G12.29
MUS	200	Neuromuscular Junction Disorder	358.8	G70.89
MUS	201	Myasthenia Gravis [AchR Positive] (see 210 series)	358	G70.2
MUS	202	Lambert-Eaton Syndrome in neoplastic disease	358.1	G73.1

MUS	202	Lambert-Eaton Syndrome, unspecified	358.30	G70.80
MUS	202	Malignant Neoplasm		C80.1
MUS	203	Myasthenia Gravis [MuSK Positive]		
MUS	204	Magnesium Induced MG	358.2	G70.1
MUS	205	Antibiotic Induced MG	358.2	G70.1
MUS	206	Organophosphate Induced MG	358.2	G70.1
MUS	207	Organophosphate Induced Neuropathy	989.5	T63.89XA
MUS	208	Tick Paralysis	358.8	T48.1X#
MUS	209	Congenital Myasthenia Gravis	358	G70.2
MUS	210	MG, Ocular	358	G70.01
MUS	211	MG Status Post Thymectomy	358	G70.00
MUS	212	MG with Thymoma	358	G70.00
MUS	213	MG, in Remission	358	G70.00
MUS	214	MG, Asthenic bulbar	358	G70.00
MUS	215	MG, Crisis	358.01	G70.01
MUS	216	MG, Seronegative	358	G70.00
MUS	217	MG, Distal	358	G70.00
MUS	300	Muscle Disorder	359.9	G72.9
MUS	301	Myalgia	729.1	M79.1
MUS	301	Fibromyalgia	729.1	M79.7
MUS	302	Malignant Hyperthermia	995.86	T88.3
MUS	303	Rhabdomyolysis	728.88	M62.82
MUS	303	Myoglobinuria	791.3	R82.1
MUS	304	Fasciitis	729.4	M72.9
MUS	305	Hyper-CK-emia	790.5	R74.9
MUS	400	Muscular Dystrophy (MD)	359.1	G71.0
MUS	401	Duchenne MD	359.1	G71.0
MUS	402	Becker MD	359.1	G71.0
MUS	403	Other Dystrophinopathies	359.1	G71.0
MUS	404	Limb-Girdle MD (see 490 series)	359.1	G71.0
MUS	405	Facioscapulohumeral MD	359.1	G71.0
MUS	406	Scapuloperoneal MD	359.1	G71.0
MUS	407	Emery-Dreifuss MD	359.1	G71.0

MUS	408	Oculopharyngeal MD	359.1	G71.0
MUS	409	Distal MD	359.1	G71.0
MUS	410	Ocular Myopathy MD	359.1	G71.0
MUS	411	Other Muscular Dystrophy	359	
MUS	412	Muscular Dystrophy, Congenital	359	G71.2
MUS	413	Bethlem Myopathy	359	G71.0
MUS	414	Tubular Aggregate Myopathy	359	G71.2
MUS	415	Ulrich's Muscular Dystrophy	359.2	G71.0
MUS	420	Myotonic Disorders	359.2	G71.19
MUS	421	Myotonic Dystrophy, Type 1	359.2	G71.11
MUS	422	Myotonia Congenita, aut dominant	359.2	G71.12
MUS	423	Myotonia Congenita, aut recessive	359.2	G71.12
MUS	424	Paramyotonia Congenita	359.2	G71.19
MUS	425	Schwartz-Jampel (myotonic chondrodystrophy)	359.2	G71.13
MUS	426	Myotonic Dystrophy, Type 2	359.2	G71.11
MUS	427	Myotonic Dystrophy, unspecified	359	G72.9
MUS	430	Congenital Myopathy	359	G72.9
MUS	431	Centronuclear	359	G71.2
MUS	432	Nemaline Myopathy	359	G71.2
MUS	433	Central Core Myopathy		G71.2
MUS	434	Congenital Fiber Type Disproportion	359	G71.2
MUS	435	Hyaline Body Myopathy	359	G71.2
MUS	436	Congenital Hypotonia	359	P94.2
MUS	437	Reducing Body Myopathy	359	G71.2
MUS	438	Multi-Core	359	G71.2
MUS	439	Desmin Myopathy (SEE MUS 453 & 514)	359	G71.0
MUS	460	Metabolic Myopathy	359.8	E88.9
MUS	461	McArdle's Disease	271	E74.04
MUS	462	Other Glycogenoses	271	E74.09
MUS	463	Myoadenylate Deaminase Deficiency	359.8	E79.2
MUS	464	Muscle Carnitine Palmitoyltransferase Deficiency	272.9	E71.314
MUS	465	Other Lipid Disorders	272.9	E78.9
MUS	466	Kearns-Sayre Syndrome	359.8	H49.819
MUS	467	Other Mitochondrial Disorders	359.8	E88.49
MUS	468	Acid Maltase Deficiency [Pompe Disease]	359.8	E74.02

MUS	469	Danon Disease	359.8	E74.0
MUS	470	XEMA (X-Linked myopathy with excessive autophagy)	359	
MUS	471	CPEO (Chronic progressive external ophthalmoplegia)	378.72	H49.40
MUS	480	Periodic Paralysis (PP)	359.3	G72.3
MUS	481	Hypokalemic PP	359.3	G72.3
MUS	482	Hyperkalemic PP	359.3	G72.3
MUS	483	Normokalemic PP	359.3	G72.3
MUS	484	Andersen Tawil Syndrome	359.3	G72.3
MUS	485	Thyrotoxic PP	359.3	G72.3
MUS	486	LGMD, Type 1a	359.1	G71.0
MUS	487	LGMD, Type 1b	359.1	G71.0
MUS	488	LGMD, Type 1c	359.1	G71.0
MUS	489	LGMD, Type 1d	359.1	G71.0
MUS	490	LGMD, Type 2a	359.1	G71.0
MUS	491	LGMD, Type 2b / Miyoshi	359.1	G71.0
MUS	492	LGMD, Type 2c	359.1	G71.0
MUS	493	LGMD, Type 2d	359.1	G71.0
MUS	494	LGMD, Type 2e	359.1	G71.0
MUS	495	LGMD, Type 2f	359.1	G71.0
MUS	496	LGMD, Type 2g/ Distal myopathy / Telethonin	359.1	G71.0
MUS	497	LGMD, Type 2h	359.1	G71.0
MUS	498	LGMD, Type 2i	359.1	G71.0
MUS	499	LGMD, Type 2j	359.1	G71.0
MUS	500	Inflammatory Myopathies	710.4	G72.49
MUS	501	Polymyositis (organ involvement unspecified)	710.4	M33.20
MUS	502	Dermatomyositis	710.3	M33.90
MUS	503	Polymyositis with Connective Tissue Disease	710.4	M33.22
MUS	504	Inclusion Body Myositis (IBM)	359.71	G72.41
MUS	505	HIV Polymyositis	728	B20
MUS	506	Polymyalgia Rheumatica	725	M35.3
MUS	507	Sarcoid Myopathy (myositis)	135	D86.87
MUS	508	Viral Myositis	728	B97.89
MUS	509	Other Infectious Myopathies	728	M60.009
MUS	510	Eosinophilic Polymyositis	710.4	M33.20
MUS	511	Focal Myositis	729.1	M60.9

MUS	512	Necrotizing Myopathy	359.8	G72.89
MUS	513	Granulomatous Myositis	728.82	M60.20
MUS	550	LGMD 1F / TNPO3	359.1	G71.0
MUS	551	LGMD 1G / HNRPDL	359.1	G71.0
MUS	552	LGMD 1H / 3p23	359.1	G71.0
MUS	553	2K / MDDGC1 / POMT1	359.1	G71.0
MUS	554	2L / ANO5	359.1	G71.0
MUS	555	2M /MDDGC4 / Fukutin	359.1	G71.0
MUS	556	2N / MDDGC2 / POMT2	359.1	G71.0
MUS	557	2O / MDDGC3 / POMGnT1	359.1	G71.0
MUS	558	2P /MDDGC9 / DAG1	359.1	G71.0
MUS	559	2Q / Plectin 1f	359.1	G71.0
MUS	560	2R / Desmin	359.1	G71.0
MUS	561	2S / TRAPPC11	359.1	G71.0
MUS	570	HIBM1 / MFM1 / LGMD 1D / Desmin	359.71	G72.41
MUS	571	HIBM2 / Nonaka / GNE	359.71	G72.41
MUS	572	HIBM3 / Myosin heavy chain IIa	359.71	G72.41
MUS	573	HIBM with Paget disease & Dementia / VCP	359.71	G72.41
MUS	574	MFM2 / αB-crystalline	359	G72.89
MUS	575	MFM3 / LGMD 1A / Myotilin	359	G72.89
MUS	576	MFM4 / Markesbery-Griggs / ZASP	359	G72.89
MUS	577	MFM5 / Filamin C	359	G72.89
MUS	578	MFM6 / BAG3	359	G72.89
MUS	579	Myopathy & Respiratory Δ Type 1 / Udd / Titin	359	G72.89
MUS	580	Myopathy & Respiratory Δ Type 2 / 2q21	359	G72.89
MUS	581	Scapuloperoneal MD / Hyaline body myopathy / FHL-1	728.9	G71.0
MUS	582	Polyglucosan body / RBCK1	271	E74.09
MUS	583	Welander / TIA1	359.1	G71.0
MUS	584	Gowers-Laing / MPD1 / MYH7		G71.0
MUS	585	CMD with Desmin inclusions / SEPN1	359.1	G71.0
MUS	586	Distal Myopathy w/ vocal cord & Pharyngeal paralysis/ MPD2/ Matrin 3	359	G71.0
MUS	587	Miyoshi-like muscular dystrophy 2 / ? 10p	359.1	G71.0

MUS	588	Miyoshi-like muscular dystrophy 3 / Anoctamin 5 / ANO5	359.1	G71.0
MUS	589	Distal Nebulin myopathy / NEM2 Rod myopathy / Nebulin	359	G71.0
MUS	600	Other Myopathies	359.8	G72.89
MUS	601	Diabetic Muscle Infarction	359.8	
MUS	602	Toxic Myopathy	359.4	G72.2
MUS	603	Hyper Thyroid Myopathy		E05.90
MUS	603	Hypo Thyroid Myopathy		E03.90
MUS	604	Other Endocrine Myopathies	259.9	E34.9
MUS	605	Steroid Myopathy	359.4	G72.2
MUS	606	Amyloid Myopathy	277.3	E85.8
MUS	607	Muscle Tumors	239.3	C49.9
MUS	608	Alcoholic Myopathy	359.4	G72.2 (T51)
MUS	609	Thyroid Eye Disease [Graves' Eye Disease]	259.4	E05.00
MUS	610	Cholesterol Lowering Agent Myopathy [CLAM]	359.4	T46.6X#
MUS	611	Critical Illness Myopathy	359.8	G72.81
MUS	612	Isolated Neck Extensor Myopathy [INEM]	359.8	
MUS	613	[Statin-Associated] Autoimmune Necrotizing Myopathy		G72.81
MUS	700	EMG Abnormalities		
MUS	701	Martin-Gruber Anastomosis		
MUS	702	Accessory Peroneal Nerve		S84.10
MUS	703	Other Anomalous Innervation		
MUS	704	Conduction Block		R94.131
MUS	705	Pseudo-Conduction Block		
MUS	710	Abnormal Spontaneous Activity, Unspecified		R94.131
MUS	711	Cramps [General]	729.82	R25.2
MUS	712	Doublets/Multiplets		R94.131
MUS	713	Facial Myokymia		G51.4
MUS	714	Complex Repetitive Discharge [CRD]		R94.131
MUS	715	Neurotonia [on EMG]		G11.8
MUS	716	Myotonic Discharges		R94.131
MUS	717	Iterative Discharges		R94.131
MUS	718	Abnormal Insertional Activity		R94.131
MUS	719	Fasciculations	781	R25.3

MUS	720	Axon Reflex		R94.131
MUS	721	Stimulus Induced Repetitive Discharges		R94.131
MUS	722	Cramps Fasciculation Syndrome		R25.3
MUS	800	Limb-Girdle Syndrome	728.9	G71.0
MUS	801	Dropped Head Syndrome	780.79	M62.81
MUS	802	Dropped Body Syndrome	780.79	M62.81
MUS	803	Ptosis	378.9	H02.40
MUS	804	Ophthalmoplegia	378.9	H51.9
MUS	805	Dysarthria	784.5	R47.1
MUS	806	Dysphagia	784.5	R13.10
MUS	807	Ataxia	781.2	R27.0
MUS	808	Diplopia	368.2	H53.2
MUS	809	Bulbar Palsy	352.5	G12.22
MUS	810	Pseudobulbar Palsy	335.23	G12.8
MUS	811	Fatigue, NOS	780.79	R53.83
MUS	812	Upper Extremity Weakness	728.9	G83.20
MUS	813	Lower Extremity Weakness	728.9	G83.10
MUS	814	Hand Weakness	728.9	M62.81
MUS	815	Neck Weakness	728.9	M62.81
MUS	816	[Neuromuscular] Respiratory Weakness	780.79	R53.83
MUS	817	Exercise-Induced Weakness	780.79	R53.83
MUS	818	PEO [Progressive External Ophthalmoplegia]		H49.4
MUS	900	Neuromuscular Disorders		G70.9
MUS	901	Chronic Fatigue Syndrome	780.71	R53.82
MUS	910	Related to Cancer	239.9	D49.9
MUS	911	Thymoma [Benign]	212.6	D15.0
MUS	911	Thymoma [Malignant]	164.0	C37
MUS	920	Hereditary		
MUS	921	Dominant		
MUS	922	Recessive		
MUS	923	X-Linked		
MUS	930	Myelopathy	336.9	G95.9
MUS	931	B12 Deficiency	266.9/281.1	E53.8
MUS	932	Vitamin E Deficiency	269.1	E56.0
MUS	933	HIV Related	42	B20

MUS	934	HTLV-1 Related [Myelopathy]	42	C91.50
MUS	935	Cervical Myelopathy	336.9	M47.12
MUS	936	Thoracic Myelopathy	336.9	M47.14
MUS	937	Lumbosacral Myelopathy	336.9	M47.16
MUS	938	Cauda-Equina Syndrome	344.6	G83.4
MUS	939	Syringomyelia & syringobulbia	336	G95.0
MUS	940	Degenerative Spine Diseases [Spondylosis]	722.6	M51.9
MUS	941	Meningomyelocele [Spina Bifida]	741.9	Q05.9
MUS	942	Spinocerebellar Degeneration	334.9	G11.9
MUS	943	Traumatic [Injury]	959.9	T14.90
MUS	944	Spasticity, NOS	781.2	R25.2

Appendix 2: Current PNS Codes

Category	Code		ICD-9	ICD-10
PNS	100	Inherited Polyneuropathy	356	G60.0
PNS	101	CMT Type 1, (see PNS 130 series)	356.1	G60.0
PNS	102	CMT Type 2, (see PNS 140 series)	356.1	G60.0
PNS	103	CMT Type 3	356.1	G60.0
PNS	104	X-Linked CMT	356.1	G60.0
PNS	105	Familial Amyloidosis	277.3	E85.9
PNS	106	Porphyria	277.1	E80.2
PNS	107	Leukodystrophy	330	E75.29
PNS	108	Refsum disease	356.3	G60.1
PNS	109	Glycogen Storage Disease	330.9 (271.0)	E74.00
PNS	110	Hereditary Neuropathy with Pressure Palsies [HNPP]	356.9	G60.0
PNS	111	Friedreich's Ataxia	334	G11.1
PNS	112	Neuropathy in Olivopontocerebellar Atrophy [OPCA]	333	G62.9 / G23.8
PNS	113	Neuropathy in Other Multiple System Degeneration	337.9	G62.9 / G90.3
PNS	115	Neuropathy in Neurofibromatosis		G62.9 / Q85.00
PNS	116	Polyglucosan Body Disease		E74.09
PNS	117	Fabry Disease	272.7	E75.21
PNS	120	Hereditary sensory/autonomic neuropathy (HSN/HSAN)	356	G60.9
PNS	130	CMT 1A	356.1	G60.0
PNS	131	CMT 1B	356.1	G60.0
PNS	132	CMT 1C	356.1	G60.0
PNS	133	CMT 1D	356.1	G60.0
PNS	134	CMT 1E	356.1	G60.0
PNS	135	CMT 1F	356.1	G60.0
PNS	140	CMT 2A	356.1	G60.0
PNS	141	CMT 2B	356.1	G60.0
PNS	142	CMT 2C	356.1	G60.0
PNS	143	CMT 2D	356.1	G60.0
PNS	144	CMT 2E	356.1	G60.0
PNS	145	CMT 2F	356.1	G60.0
PNS	146	CMT 2G	356.1	G60.0
PNS	147	CMT 2H	356.1	G60.0
PNS	148	CMT 2I	356.1	G60.0
PNS	149	CMT 2J	356.1	G60.0

PNS	150	CMT 2I	356.1	G60.0
PNS	160	CMT Type 4, (autosomal recessive)	356.1	G60.0
PNS	170	HMSN 5	356.1	G60.0
PNS	180	HMSN 6	356.1	G60.0
PNS	181	Hereditary Neuralgic Amyotrophy	356.1	G54.5
PNS	182	Familial Amyloid Neuropathy	277.3	E85.1
PNS	190	HMN	335.29	G60.0
PNS	200	Immune Mediated/Inflammatory/Infectious Polyneuropathy	357.8	G61.89
PNS	201	Guillain-Barre Syndrome	357	G61.0
PNS	202	Recurrent GBS	357	G61.0
PNS	203	Miller-Fisher Syndrome	357	G61.0
PNS	204	Axonal GBS	357	G61.0
PNS	205	Acute Paralytic Poliomyelitis	357	A80.30
PNS	206	Chronic Inflammatory Demyelinating Polyneuropathy	357.81	G61.81
PNS	207	Neuropathy Due to Vasculitis	357.1	G63
PNS	208	Neuropathy Due to other Connective Tissue Disease (see 212 series)	357.1	G63
PNS	209	Multifocal Motor Neuropathy	357.9	G60.9
PNS	210	CIDP with CNS Overlap	357.8	G61.81
PNS	211	MADSAM neuropathy (Multifocal Acquired Demyelinating Sensory and Motor neuropathy)	357.81	G61.8
PNS	212	Neuropathy Due to SLE	357.1	M32.19
PNS	213	Neuropathy Due to RA	357.1	M05.50
PNS	214	Neuropathy Due to Sjogren's Syndrome	357.1	M35.00
PNS	215	Neuropathy Due to Peripheral Vascular Disease	357.4	G63
PNS	220	Neuropathy Due to Infection	357.9	G61.9
PNS	221	Neuropathy Due to Lyme Disease	357.9	A69.22
PNS	222	Neuropathy Due to Herpes Zoster	357.9	B02.23
PNS	223	Neuropathy Due to HIV	357.9	B20
PNS	224	Neuropathy Due to Leprosy	357.9	A30.9
PNS	225	Sarcoid neuropathy		D86.87
PNS	239	DADS neuropathy (Distal Acquired Demyelinating Symmetric neuropathy)		
PNS	240	Neuropathy Associated with Monoclonal Protein	357.9	G61.9
PNS	241	Neuropathy Associated with MGUS	357.9	G61.9
PNS	242	Neuropathy Associated with POEMS	357.9	G61.9
PNS	243	Neuropathy Associated with Anti-MAG	357.9	G61.9
PNS	244	Neuro. Assoc. w/ Monoclonal Protein Due to Amyloidosis	277.3	E85.1, 3, 8

PNS	245	Neuropathy Associated with GM-1 Antibody	357.9	G61.9
PNS	246	Neuropathy Associated with Multiple Myeloma	357	C90.00
PNS	247	Neuropathy Associated with Anti-Hu Antibody	357.9	G61.9
PNS	248	Paraneoplastic Neuropathy [non-Hu]	357.9	G61.9
PNS	249	Anti-AchR Antibody Neuropathy		
PNS	250	Multiple Sclerosis	340	G35
PNS	251	Neuropathy Due to Hepatitis B	357.4	G63
PNS	252	Neuropathy Due to Hepatitis C	357.4	G63
PNS	255	Neuropathy Due to Prior GVHD	357.4	G63
PNS	260	Neuropathy Due to Celiac Disease	357.4	G63
PNS	261	Neuropathy Due to Inflammatory Bowel Disease	357.4	G63
PNS	262	CANOMAD syndrome	357.81	G61.8
PNS	270	Neuropathy Due to Myelodysplasia	357.4	G63
PNS	271	Potassium channel antibody syndrome		
PNS	300	Metabolic Neuropathy	357.9	G61.9
PNS	301	Renal Disease Neuropathy	357.9	G61.9
PNS	302	Hepatic Disease Neuropathy	357.9	G61.9
PNS	303	Thyroid Disease Neuropathy	357.9	G61.9
PNS	304	Pregnancy Neuropathy	357.9	G61.9
PNS	305	Critical-Illness Neuropathy	357.9	G61.9
PNS	306	Nutritional Neuropathy	263.8	E46
PNS	307	Vitamin B12 Deficiency Neuropathy	266.2/281.1	E53.8
PNS	308	Vitamin E Deficiency Neuropathy	269.1	E56.9
PNS	309	Diabetes Mellitus Sensorimotor Polyneuropathy	357.2/250.6	E11.40
PNS	311	Diabetic Neuropathic Cachexia	250.9	E11.40
PNS	312	Impaired Glucose Tolerance Neuropathy		R73.02
PNS	320	Toxin Neuropathy	357.7	G62.2
PNS	321	Alcohol Neuropathy	357.5	G62.1
PNS	322	Heavy Metals Neuropathy	357.7	G62.2
PNS	323	Copper/Zinc-related Myeloneuropathy	357.4	
PNS	330	Drug Neuropathy	357.6	G62.0
PNS	331	Chemotherapeutic Drug Neuropathy	357.6	G62.0
PNS	332	Dilantin Neuropathy	357.6	G62.0
PNS	333	Hypertriglyceridemia Neuropathy		E78.1

PNS	400	Polyneuropathy, NOS	357.9/356.4	G62.3
PNS	401	Sensory Neuropathy	357.9/356.4	G60.8
PNS	402	Acute Motor Neuropathy	357.9/356.4	G62.81
PNS	403	Sensorimotor Neuropathy	357.9/356.4	G60.8
PNS	404	Autonomic Neuropathy	337	G90.9
PNS	405	Axonal Neuropathy	357.9/356.4	G61.9
PNS	406	Demyelinating Neuropathy	357.9/356.4	G61.9
PNS	407	Mixed Axonal Demyelinating Neuropathy	357.9/356.4	G61.9
PNS	408	Sensory Neuronopathy (Ganglionopathy) - autoimmune autonomic ganglionopathy	357	G90.0
PNS	409	Cryptogenic Sensory Polyneuropathy (CSPN)	357.9/356.4	G61.9
PNS	410	Small-Fiber Neuropathy	357.9/356.4	G61.9
PNS	411	DADS Neuropathy (Distal acquired demyelinating)	357.81	G61.81
PNS	412	MAMA (Multifocal acquired motor axonal)	357.81	G61.81
PNS	413	POTC		
PNS	500	Mononeuropathy	355.9	G58.9
PNS	501	Radial Neuropathy	354.3	G56.3
PNS	502	Posterior Interosseous Neuropathy	354.3	G56.3
PNS	503	Axillary Neuropathy	353	G56.90
PNS	510	Median Neuropathy	354.1	G56.1
PNS	511	Carpal Tunnel Syndrome	354	G56.0
PNS	512	Median Neuropathy in the Arm	354.1	G56.10
PNS	513	Anterior Interosseus Neuropathy	354.8	G56.80
PNS	520	Ulnar Neuropathy	354.2	G56.20
PNS	521	Ulnar Neuropathy at the Wrist	354.2	G56.20
PNS	522	Ulnar Neuropathy at the Ulnar Grove	354.2	G56.20
PNS	530	Peroneal Neuropathy	355.36	G57.30
PNS	531	Peroneal Neuropathy at the Knee	355.36	G57.30
PNS	540	Facial Neuropathy	351.9	G51.9
PNS	541	Bell's Palsy	351	G51.0
PNS	542	Facial Neuropathy-Traumatic	351.9	G51.9
PNS	543	Facial Neuropathy Due to Surgery	351.9	G51.9
PNS	544	Facial Neuropathy Due to Infection	351.9	G51.9
PNS	545	Pain due to Neuropathy of Facial Nerve	351.8	G51.8
PNS	546	Hemifacial Spasm	351.8	G51.3
PNS	550	Trigeminal Neuropathy	350.1	G50.0

PNS	551	Trigeminal Neuropathy-Herpes Zoster	53.1	B02.29
PNS	552	[Spinal] Accessory Neuropathy	352.4	G52.8
PNS	553	Hypoglossal Neuropathy	352.5	G52.3
PNS	554	Cranial Neuropathy	352.9	G52.9
PNS	560	Musculocutaneous Neuropathy	354.8	G56.80
PNS	561	Suprascapular Neuropathy	354.8	G56.80
PNS	562	Long Thoracic Neuropathy	354.8	G56.80
PNS	563	Upper Extremity Neuropathy	354.9	G56.90
PNS	570	Tibial Neuropathy	355.79	G56.80
PNS	571	Sciatic Neuropathy	355	G57.00
PNS	572	Femoral Neuropathy	355.2	G57.20
PNS	572	Femoral Neuropathy [R lower limb]		G75.21
PNS	572	Femoral Neuropathy [L lower limb]		G75.22
PNS	573	Saphenous Neuropathy	355.79	G57.80
PNS	574	Obturator Neuropathy	355.79	G57.80
PNS	575	Sural Neuropathy	355.79	G57.80
PNS	576	Plantar Neuropathy	355.79	G57.60
PNS	577	Other Lower Extremity Neuropathy	355.79	G57.90
PNS	578	Lateral Femoral Cutaneous Neuropathy	355.1	G57.10
PNS	579	Peroneal Neuropathy	355.9	G57.30
PNS	580	Phrenic Neuropathy	G58.8	
PNS	600	Celiac Plexopathy		G54.8
PNS	610	Brachial Plexus Neuropathy	353	G54.0
PNS	611	Idiopathic Brachial Plexus Neuropathy	353.8	G54.0
PNS	612	Traumatic Brachial Plexus Neuropathy	353.8	G54.0
PNS	613	Radiation Brachial Plexus Neuropathy	353.8	G54.0
PNS	614	Malignancy Brachial Plexus Neuropathy	353.8	G54.0
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PNS	616	Hematoma Brachial Plexus Neuropathy	353.8	G54.0
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PNS	625	Diabetic Lumbosacral Plexus Neuropathy, (Amyotrophy)	358.1	G54.1

PNS	626	Hematoma Lumbosacral Plexus Neuropathy	353.8	G54.1
PNS	627	Hereditary Lumbosacral Plexus Neuropathy		G54.1
PNS	700	Radiculopathy	729.2	M54.10
PNS	710	Cervical Radiculopathy	723.4	M54.12
PNS	711	Cervical Radiculopathy - Disc	722	M50.10
PNS	712	Cervical Radiculopathy - Degenerative Spine Disease	722	M50.10
PNS	713	Cervical Radiculopathy - Diabetes	723.4	M54.12
PNS	714	Cervical Radiculopathy - Tumor	723.4	M54.12
PNS	715	Cervical Radiculopathy - Trauma	722	M54.12
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PNS	720	C5 Cervical Radiculopathy	722	M50.12
PNS	721	C6 Cervical Radiculopathy	722	M50.12
PNS	722	C7 Cervical Radiculopathy	722	M50.12
PNS	723	C8 Cervical Radiculopathy	722	M50.13
PNS	730	Thoracic Radiculopathy	724.4	M54.14
PNS	731	Thoracic Radiculopathy - Disc	722.11	M51.14
PNS	732	Thoracic Radiculopathy - Degenerative Spine Disease	722.11	M51.14
PNS	733	Thoracic Radiculopathy - Diabetes	724.4	M54.14
PNS	734	Thoracic Radiculopathy - Tumor	724.4	M54.14
PNS	735	Thoracic Radiculopathy - Trauma	722.11	M51.34
PNS	736	Thoracic Radiculopathy - Herpes Zoster	53.19	B02.29
PNS	740	Lumbosacral Radiculopathy	724.4	M54.17
PNS	741	Lumbosacral Radiculopathy - Disc	722.1	M51.17
PNS	742	Lumbosacral Radiculopathy - Degenerative Spine	722.1	M51.17
PNS	743	Lumbosacral Radiculopathy - Diabetes	724.4	M54.17
PNS	744	Lumbosacral Radiculopathy - Tumor	724.4	M54.17
PNS	745	Lumbosacral Radiculopathy - Trauma	722.1	M51.27
PNS	746	Lumbosacral Radiculopathy - Herpes Zoster	53.19	B02.29
PNS	747	Lumbosacral Radiculopathy - Other	724.4	M54.17
PNS	748	Lumbosacral Radiculopathy - HIV	724.4	M54.17
PNS	750	Lumbosacral Radiculopathy - L1	722.1	M51.27
PNS	751	Lumbosacral Radiculopathy - L2	722.1	M51.27
PNS	753	Lumbosacral Radiculopathy - L3	722.1	M51.27
PNS	754	Lumbosacral Radiculopathy - L4	722.1	M51.27
PNS	755	Lumbosacral Radiculopathy - L5	722.1	M51.27

PNS	756	Lumbosacral Radiculopathy - S1	722.1	M51.27
PNS	757	Lumbosacral Spinal Stenosis	724.02	M48.07
PNS	758	Spinal AVM	G27.39	
PNS	800	Mononeuritis Multiplex	354.5	G58.7
PNS	801	Mononeuritis Multiplex - Vasculitis	354.8	G58.7
PNS	802	Mononeuritis Multiplex - Diabetes	354.8	G58.7
PNS	803	Mononeuritis Multiplex - HIV	354.8	G58.7
PNS	804	Mononeuritis Multiplex - CMV	354.8	G58.7
PNS	805	Mononeuritis Multiplex - Other Infectious	354.8	G58.7
PNS	806	Mononeuritis Multiplex - Collagen Vascular Disease	354.8	G58.7
PNS	807	Mononeuritis Multiplex - Tumor	354.8	G58.7
PNS	808	Mononeuritis Multiplex - HNPP	356.1	G58.7
PNS	820	Pain, NOS	729.1	R52.0
PNS	821	Hand Pain	729.5	M79.64
PNS	822	Shoulder Pain	719.41	M25.51
PNS	823	Upper Extremity Pain, NOS	729.5	M79.609
PNS	824	Foot Pain	729.5	M79.67
PNS	825	Knee Pain	719.46	M25.56
PNS	826	Hip Pain	719.45	M25.55

PNS	827	Lower Extremity Pain, NOS	729.5	M79.609
PNS	828	Neck Pain	729.1	M54.2
PNS	829	Back Pain	724.2	M54.9
PNS	830	Abdominal Pain	789	R10
PNS	831	Chest Pain	786.59	R07.9
PNS	832	Cephalgia	784	R51
PNS	833	Reflex Sympathetic Dystrophy (RSD)	337.2	G90.59
PNS	834	Painful Legs Moving Toes	729.5	M79.609
PNS	835	Numbness, NOS/Parasthesias	782	R20.2
PNS	836	Upper Extremity Numbness	782	R20.2
PNS	837	Lower Extremity Numbness	782	R20.2
PNS	838	Face Numbness	782	R20.2
PNS	839	Ataxia	781.2	R27.0
PNS	840	Conversion Disorder	300.11	F44.4
PNS	841	Somatic Complaints	300.81	F45.0
PNS	842	Erythromelalgia	443.82	I73.81
PNS	910	Neuropathy Associated with Cancer	199.1	C80.1
PNS	911	Lymphoma Related Neuropathy	202.8	
PNS	912	Small-Cell Tumor Related Neuropathy	199.1	C80.1
PNS	920	Hereditary		
PNS	921	Dominant		
PNS	922	Recessive		
PNS	923	X-Linked		
CNS	100	Movement Disorders	333.9	G25.9
CNS	110	Tremor	333.1	R25.1
CNS	120	Parkinsonism	332	G20.0
CNS	130	Dystonia	333.6	G24.9
CNS	140	Chorea	333.5	G25.5
CNS	141	Restless Legs Syndrome (RLS)	333.99	G25.81
CNS	200	Seizure Disorders	345.9	G40.909
CNS	300	Dementia	290	F03.90
CNS	301	Alzheimer Disease	331	G30.9
CNS	302	Frontotemporal dementia	290	G31.09
CNS	400	Gait Disturbance	781.2	R26.9

CNS	500	Cerebral Palsy	343.9	G80.9

Appendix 3: Data Collection Sheet

Neuromuscular Clinical Data Base

Patient Name: _____

KU ID #: _____

DOB: _____

SS #: _____

NM Code: _____

ICD-10 Code: _____

Date of Service: _____

Signature: _____

Date: _____

Appendix 4: KUMC IRB consent form

Please feel free to read but DO NOT SIGN until your doctor has discussed this with you.

Thank you

Neuromuscular Database Project Informed Consent

INTRODUCTION

I understand that I am being asked to participate in a database study for patients with a neuromuscular disorder. If I consent, the information collected during my clinic visits will be entered into a database. This information is gathered in the form of medical record number, name, date of birth, date of visit, and diagnosis code. An arbitrary neuromuscular code will be assigned based on my diagnosis. Dr. Mazen Dimachkie is conducting this study at the KUMC Center for Neuromuscular Disease. Every patient who presents in the neuromuscular clinic will be asked to participate.

You do not have to participate in this research study. It is important that before you make a decision to participate, read the rest of this form. You should ask as many questions as needed to understand what will happen to you if you participate in this study.

BACKGROUND

The Neuromuscular Clinic offers diagnostic and treatment services for persons with Neuromuscular disease and other related conditions. Patients may also participate in clinical research pertaining to investigational medications.

PURPOSE

The purpose of this project is to collect information on neuromuscular patients into a database and to use this information for scientific study and improvement of treatment procedures. This database may be used to identify patients for research studies.

If I am identified through this database for potential participation in a research study, I:

____ give my permission
____ do not give my permission

to be contacted regarding these studies. By signing this consent form, I am under no obligation to participate in any future research study. I would be contacted by the neuromuscular research nurse, solely under the direction of one of the doctors treating me in the neuromuscular clinic.

PROCEDURE

Should I decide to participate in this database study, information collected during my normal clinic visits will be entered into a computer database along with information from other patients from the Neuromuscular Clinic. Information obtained during routine clinic visits may be entered into a separate database for study purposes. This includes any testing performed by members of the clinic staff; i.e. speech therapist, social worker, and others that I see during the course of the clinic visit. Other information in my KU records related to my neuromuscular disease may be entered into the research database. Participating in this study will not add to the length of my normal clinic visit. If I consent, the

data will be collected during my initial visit and then at each follow-up visit.

Information in the Neuromuscular Database will be analyzed for research purposes. Researchers may at various times study topics such as aspects of my disease, effects of standard medications, and quality of life.

Researchers at KUMC will analyze information in the database and they may share it with researchers at other universities. If study data is shared outside KUMC, individual identifiers will be removed so that the participants' identities are not known.

RISKS

I am taking no foreseeable risks by participating in this study. The information I disclose will remain confidential.

NEW FINDINGS STATEMENT

I will be informed if any significant new findings develop during the course of the study that may affect my willingness to participate in this study.

BENEFITS
I will not directly benefit from participating in this study, however the information collected will be used for scientific study and may result in improved treatment of neuromuscular disorders.

PAYMENT TO THE SUBJECT
I will not receive payment for participating in this study. Also, I will retain my current financial responsibility for my visits to the Neuromuscular Clinic.

COSTS

There is no additional cost to me for participating in this study.

ALTERNATIVES

My alternative is to not participate in the Neuromuscular Database Project.

INSTITUTIONAL DISCLAIMER STATEMENT

If you think you have been harmed as a result of participating in research at the University of Kansas Medical Center (KUMC), you should contact the Director, Human Research Protection Program, Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160. Under certain conditions, Kansas state law or the Kansas Tort Claims Act may allow for payment to persons who are injured in research at KUMC.

CONFIDENTIALITY AND PRIVACY AUTHORIZATION

My name or information identifying me will not be released without my written permission unless required by law. Study data will be recorded on the Neuromuscular Database form and entered into the database by the Research Instructor. Researchers cannot guarantee absolute confidentiality. If any information obtained from this database is published or presented in public, information that identifies me will be removed.

The privacy of my health information is protected by a federal law known as the Health Insurance Portability and Accountability Act (HIPAA). If I choose to participate in this study, I will be asked to give permission for researchers to use and disclose my health information.

To perform this study, researchers will collect health information about me from my medical record and from the study activities that are listed in the Procedures section of the consent form. My study-related health information will be used at KU Medical Center by Dr. Mazen Dimachkie, members of the research team, the KU Hospital Medical Record

Department, the KUMC Research Institute and officials at KUMC that oversee research, including the KUMC Human Subjects Committee, and federal officials who oversee research, if a regulatory review takes place.

All study information that is sent outside KU Medical Center will have my name and other identifying characteristics removed, so that my identity will not be known. Because identifiers will be removed, my health information will not be re-disclosed by outside persons or groups and will not lose its federal privacy protection.

Permission granted on this date to use and disclose my health information remains in effect indefinitely. By signing this form I give permission for the use and disclosure of my information for purposes of the study at any time in the future. Any research information that is placed in my medical record will be kept indefinitely.

QUESTIONS

I have read the information in this form. The investigators have answered my questions to my satisfaction. I know if I have any more questions after signing this form, I may contact Mazen Dimachkie, MD at (913) 588-6970. If I have any questions about my rights as a research subject, I may call (913) 588-1240 or write the Human Subjects Committee at Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160.

SUBJECT RIGHTS AND WITHDRAWAL FROM THE STUDY

I understand that my participation in this study is voluntary and that the choice not to participate or to quit at any time can be made without penalty or loss of benefits. Deciding not to participate or quitting will have no effect upon the medical care or treatment I receive now or in the future at the University of Kansas Medical Center.

If I want to cancel permission to use your health information, I should send a written request to Dr. Mazen Dimachkie. The mailing address is Mazen Dimachkie, M.D., University of Kansas Medical Center, 3599 Rainbow Blvd, Mail Code 2012, Kansas City, KS 66160. If I cancel permission to use my health information, the research team will stop collecting any additional information about me. All of the data collected on me will be removed from the database if I request it.

CONSENT

The investigators gave me information about what will be done to me in this research study. The also told me how it will be done, what I will have to do, and how long the research will take. They told me about any inconvenience, discomfort or risks I might experience due to this research. They explained to me how this research might affect my health or me. I agree to take part in this study as a research subject. I am aware that I may quit or refuse any part of this research study at any time. I understand that quitting will have no effect upon this medical care or treatment I receive in the future.

By signing this form, I give my permission for my health information to be used and disclosed for the purposes of this research study. If I choose not to sign this form, my information will not be entered into the database. The research team may use and share information that was gathered before they received your cancellation.

I understand that the investigators will give me a signed copy of this form to keep for my records.

Message from the NMSG Chair and Co-Chair:

We are once again very pleased to publish the abstracts and agenda for the annual NMSG meeting that will be held in Orlando, Florida on Sept 22, 23 and 24, 2023. This year's meeting again will highlight many cutting-edge advances in the field of neuromuscular disease. We also give students, residents, fellows, and junior faculty the opportunity to meet with established leaders in the field, present their projects, and get advice on career advancement in academics.

At the time we write this introduction, over 225 individuals have registered for the meeting. We also have a record number of representatives from industry attending and we are proud to have many of them as sponsors for the three-day event. Five years ago, we established a Shark Tank session in which a NMSG member can pitch their research idea to a panel of neuromuscular sharks. The top project receives a grant to carry out their project. An instantly funded research grant!

This year the planning committee was led by Dr Dave Arnold, who is now at the University of Missouri in Columbia where he is the Executive Director of the NextGen Precision Health Initiative. Dave led an engaged group of NMSG members that put together an outstanding. program. In addition, we had great work put in by Ladan Bigdeli, NMSG Student Doctor Editor, from The Ohio State University College of Medicine working with all 92 abstracts submitted.

We and the planning committee would like to thank the sponsors for generously supporting the meeting again including our top sponsors of UCB, Argenx, Catalyst Pharmaceuticals, Fulcrum, Pfizer and Sarepta Therapeutics.

We also want to thank Liz Paulk, the administrative manager of the NMSG. Liz works tirelessly year round with the NMSG leadership, planning committee, members, sponsors, and representatives at the site the meeting is held to make these meetings appear to come off seamlessly. The amount of work involved is enormous. And while Liz and her new assistant, Missy Apel are getting one meeting off the ground, they are already planning for the 2024 and the 2025 meetings. It is an ongoing dynamic process and that is a very good thing.

We are already planning the meeting for 2024 that will be in Tarrytown, New York at the Tarrytown House Estates on September 20-22nd.

We hope that many of the abstracts and presentations are ultimately transitioned to full articles that will be submitted to the RRNMF Neuromuscular Journal in the upcoming months.

Richard J Barohn MD
Chair, NMSG
Columbia, Missouri, USA

Michael Hanna MD
Co-Chair NMSG
London, UK

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Pharmacological and Non-Pharmacological

#812- Long-Term Safety, Tolerability, and Efficacy of Efgartigimod in Patients With Generalized Myasthenia Gravis: Concluding Analyses From the ADAPT+ Study

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Introduction: Efgartigimod, a human IgG1 antibody Fc-fragment, reduces total IgG (including pathogenic autoantibodies) through neonatal Fc receptor blockade.

Objectives: Evaluate long-term safety, tolerability, and efficacy of efgartigimod in generalized myasthenia gravis (gMG).

Methods: ADAPT, a 26-week, global, randomized, placebo-controlled, phase 3 trial, evaluated efgartigimod in adults with gMG; those completing ADAPT were eligible for the ADAPT+ open-label extension. Efgartigimod (10 mg/kg IV) was administered in cycles of once-weekly infusions for 4 weeks, with subsequent cycles initiated based on clinical evaluation. Primary objective was assessment of long-term safety and tolerability. Long-term efficacy was also assessed by Myasthenia Gravis Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG) scores.

Results: 90% (151/167) from ADAPT entered ADAPT+, and 145 (111 anti-AChR-Ab+/34 anti-AChR-Ab-) received ≥1 cycle by January 2022. With 229 patient-years of follow-up (mean duration per patient: 610 days), the most common AEs were headache (25%), COVID-19 (16%), nasopharyngitis (14%), diarrhea (10%), and urinary tract infection (9%), mostly mild-moderate and did not increase in frequency with subsequent cycles. AChR-Ab+ patients with ≥1 year follow-up across ADAPT/ADAPT+ (n=103) received median(range) 5.2(0.5-7.5) cycles/y. All anti-AChR-Ab+ patients (n=111) showed consistent, repeatable improvements in MG-ADL (mean[SE] change week 3, cycle 1: -5.0[0.33]; ≤11 cycles) and QMG (-4.7[0.41]; ≤7 cycles) during each cycle, mirroring repeatable reductions in total IgG (mean[SE] reduction, -55.9%[1.15]; ≤7 cycles) and anti-AChR autoantibody levels (-56.1%[1.43]). AChR-Ab- patients experienced similar results.

Conclusions: Long-term efgartigimod treatment is well tolerated, resulting in consistent, repeatable improvements in clinical outcomes in adults with gMG.

#813- Long-Term Safety, and Efficacy of Subcutaneous Efgartigimod PH20 in Patients With Generalized Myasthenia Gravis: Interim Results of ADAPT-SC+

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Introduction: In ADAPT-SC, subcutaneous (SC) efgartigimod PH20 (coformulated with recombinant human hyaluronidase PH20) demonstrated total IgG reduction noninferior at Day 29 to intravenous efgartigimod (approved in US and EU for AChR-Ab+ generalized myasthenia gravis [gMG], and in Japan regardless of antibody status), resulting in similar gMG improvement. Patients completing ADAPT-SC or enrolled in ADAPT+ could enroll in ongoing open-label extension ADAPT-SC+.

Objectives: Evaluate long-term safety, tolerability, and efficacy of efgartigimod PH20 SC in gMG.

Methods: Efgartigimod PH20 SC 1000 mg was administered in cycles of 4 weekly injections, with subsequent cycles initiated ≥28 days from last dose based on clinical evaluation. Clinical efficacy was assessed via Myasthenia Gravis Activities of Daily Living (MG-ADL). By March 2022, 164 participants received ≥1 dose of efgartigimod PH20 SC. Patients received approximately 3 cycles over a mean(SD) study duration of 170(59) days and 72 patient-years' observation.

Results: AEs were predominantly mild/moderate. The most frequent AEs were injection site erythema (25.6%), headache (15.2%), and COVID-19 (11.6%). Injection site reactions (ISRs) were mild/moderate and did not lead to treatment discontinuation. Most ISRs occurred within 24 hours and resolved spontaneously, with decreasing incidence in subsequent cycles. Two deaths occurred (metastatic renal cancer, COVID-19); neither were efgartigimod related per investigator. Consistent improvement from baseline in MG-ADL total score (mean[SE] improvement at week 4) was observed in cycles 1 (–4.0[0.25]), 2 (-3.8[0.29]), and 3 (-4.1[0.31]).

Conclusions: Multiple efgartigimod PH20 SC cycles were well tolerated with no new safety signals compared to ADAPT-SC. Safety and efficacy profiles were consistent with ADAPT/ADAPT+.

#798- Clinical-based prediction models for gastrostomy in patients with amyotrophic lateral sclerosis

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Introduction: Malnutrition and weight loss are negative prognostic factors for survival in patients living with amyotrophic lateral sclerosis (ALS). Dysphagia plays a prominent role and accelerate the disease. Early nutritional management is recommended but the exact time for placing gastrostomy is still debated.

Objectives: to identify the best easily collectable clinical variables to build a predictive model able to foresee the need for gastrostomy in ALS patients.

Methods: ALS patients followed at the NEMO Centre were retrospectively recruited. For each patient, anamnestic information and functional and nutritional assessment were identified and in order to predict the risk of PEG placement within 6 months from evaluation.

Results: A total of 263 ALS patients (median age of evaluation: 63.76 years [54.48 – 70.25], spinal/bulbar ratio of 2.25) were retrospectively recruited. Of these, 138 (52.47%) underwent a PEG placement within 6 months from evaluation, while 125 (47.53) did not. The Anamnestic Prediction Model (APM) resulted in a not well calibrated model (HL test, p=0.0117), with fair discriminatory ability (c-index: 0.6943). The Anamnestic and Functional Prediction Model (A-FPM) resulted in a well calibrated model (HL test, p=0.5913), with excellent discriminatory ability (c-index: 0.9063). The Anamnestic and Nutritional Prediction Model (A-NPM) resulted in a well calibrated model (HL test, p=0.4755), with good discriminatory ability (c-index: 0.8074).

Conclusions: The models built and described in the present study, based on different clinical variables that might be easily recordered in a outpatient setting, might predict the time for gastrostomy and help clinicians in defining a specific patient-centered care plan.

#796- MEND: MExiletine versus lamotrigine in Non-Dystrophic Myotonia

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Introduction: Non-dystrophic myotonias (NDM) are rare genetic neuromuscular disorders causing symptoms including stiffness. While there are currently no curative therapies, there are symptomatic treatments. Use of the gold standard therapy, mexiletine, can be limited in situations including cost restrictions, cardiac morbidity and pregnancy. A clinical trial has recently demonstrated efficacy of lamotrigine in NDM.

Objectives: We undertook a randomized, double-blind, cross-over trial to determine whether lamotrigine was not inferior to mexiletine. The primary outcome was a participant-reported stiffness severity score measured daily on a 0-9 scale and averaged over the last two weeks of each treatment period.

Methods: Patients were recruited via the National Hospital for Neurology and Neurosurgery Highly Specialised Services for Muscle Channelopathies. Participants were randomised to lamotrigine followed by mexiletine or mexiletine followed by lamotrigine. Each treatment period consisted of eight weeks with one-week washout in-between. Anti-myotonic treatments were washed out prior to commencement. The primary outcome was recorded daily using an IVR diary with email/phone check-ins. Adverse events were also recorded.

Results: Sixty participants were enrolled. A total of 14 participants (23%) withdrew due to loss to follow-up (n = 3), adverse events (n = 7), inability to consistently swallow trial capsules (n = 1), and inability to tolerate the up-titration protocol (n = 3). Analysis of primary outcome data is currently being undertaken. When taking Lamotrigine the primary outcome measure reduced from baseline by 2.83, while when taking Mexiletine a reduction from baseline by 3.32 was seen. Analysis of primary outcome data is currently being undertaken.

Conclusions. Further data analysis is ongoing and results will be presented at the NMSG meeting.

#741- Investing to Save: Evaluation of Unplanned Hospital Admissions of Neuromuscular Patients in Greater Manchester, UK.

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Background: Unplanned hospital admissions for people with neuromuscular diseases (pwNMDs) are associated with morbidity, mortality, and carry financial implications for the healthcare system. Such admissions may be avoidable, and frequency influenced by the quality of routine care services.

Objectives: To examine the characteristics of unplanned admissions of pwNMDs in Greater Manchester, and investigate factors associated with their occurrence.

Methods: Retrospective case-note evaluation of 97 randomly selected pwNMD and their corresponding 120 unplanned admissions to the Northern Care Alliance NHS Foundation Trust 2017-2019. Potential preventability and predisposing factors for each admission were assessed.

Results: At first admission, 56.7% (55/97) of patients had a prior NMD diagnosis, while only 21.6% (21/97) were known to a NM service. Of the 78.4% (76/97) patients not known to NM services, 44.7% (34/76) had a prior NMD diagnosis at first admission. Of all 120 admissions, 35.8% (43/120) were potentially preventable. Of the 63 admissions related to the underlying NMD, 55.6% (35/63) were potentially preventable. The most frequent cause for preventability was admission for a known potentially preventable complication of NMD. The median length of stay was 4 and 6 days, for total (n=120) and potentially preventable (n=43) admissions respectively. A delayed discharge was recorded in 28% (12/43) of potentially preventable admissions. No emergency plans were found in the notes for any patient.

Conclusions: A significant burden of potentially preventable unplanned admissions of pwNMDs were identified. Improvements in the routine provision of long-term care for these patients could reduce this risk and improve outcomes.

#764- Development of prediction models based on respiratory assessments to determine the need for Non-Invasive Ventilation in patients with Myotonic Dystrophy type 1.

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ABSTRACT

Introduction: Myotonic dystrophy type 1 (DM1) is a slowly progressive, multisystem, autosomal dominant disorder, in which the impairments of respiratory systems representing one of the main causes of death.

Objective: The aim of our study was to develop prediction models to identify the most appropriate test(s) providing indication for NIV.

Methods: DM1 patients attending the NEMO Clinical Center (Milan) between January 2008 and July 2020, who had been subjected to a complete battery of respiratory tests were retrospectively recruited. Demographic, clinical and anthropometric characteristics were collected, as well as arterial blood gas analysis, spirometry, respiratory muscle strength, cough efficacy and nocturnal oximetry as respiratory assessments. Patients were stratified in those requiring NIV and those with normal respiratory function.

Results: Out of 151 DM1 patients (median age: 44yrs [35.00 – 53.00], male/female ratio: 0.80 (67/84)), 76 had an indication for NIV initiation (50.33%). ABG, spirometry and nocturnal oximetry prediction models resulted in an excellent discriminatory ability in distinguishing patients who needed NIV from those who did not (AUC of 0.818, 0.808 and 0.935; respectively). An easy-to-use calculator was developed to automatically determine a score of NIV necessity based on the prediction equations generated from each aforementioned prediction model.

Conclusions: The proposed prediction models may help to identify which patients are at a higher risk of requiring ventilator support and therefore help in defining individual management plans and criteria for specific interventions early in the disease course. As future steps, although internally validated, an external validation of the proposed prediction models will be necessary to evaluate their generalizability.

#746 A UK experience of symptomatic treatment of myotonia with Lamotrigine

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Introduction: Lamotrigine has recently been shown to be effective for symptomatic treatment for non-dystrophic myotonia; little data on real-world clinical experience exists.

Objectives: To report our clinical experience of using Lamotrigine for treatment using the Myotonia-Behaviour-Score (MBS) in patients with myotonia.

Methods: We retrospectively evaluated the MBS from a UK single-centre of patients attending the Nationally Commissioned Highly Specialised Service for Channelopathies. The MBS was collected at pre treatment, six months follow up and after the highest dose increase was reached.

Results: Out of 26 patients on Lamotrigine, 12 were evaluated to date. Of those half (6) had *CLCN1* mutations and other half (6) *SCN4A* mutations, with mean (SD) age of 43.4 (15.6) years. Mean reduction in MBS of seven patients after six months of treatment was from 3.6 to 1.7, which was statistically significant (p=0.0176). There was no significant difference in MBS reduction in five patients with average treatment duration of 2.4 (± 1.3) (range 1-3.7) years after the highest dose increase (range 3 to 1.8, p=0.2). One patient experienced nausea, which ceased after stopping the medication.

Conclusions: These preliminary data suggest that treatment with Lamotrigine effectively reduce myotonia in selected patients with non-dystrophic myotonia. Further data analysis is ongoing.

#750 Safety and efficacy of ataluren in nmDMD patients from Study 041, a phase 3, randomized, double-blind, placebo-controlled trial

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Introduction: Study 041 (NCT03179631) is a phase 3, double-blind, placebo-controlled 72-week ataluren trial in nonsense mutation Duchenne muscular dystrophy (nmDMD) patients followed by a 72-week open-label period.

Objectives: To describe efficacy and safety results from the placebo-controlled phase.

Methods: Boys with nmDMD aged ≥5 years, on corticosteroids, and with a 6-minute walk distance (6MWD) ≥150m were eligible. The primary objective was to determine ataluren's effect on ambulatory function, assessed by the 6-minute walk test. Boys were randomized 1:1 to ataluren:placebo. The intention-to-treat (ITT) population comprised randomized boys who received ≥1 dose of study treatment. Predefined subgroups included boys with ≥300m 6MWD and ≥5s stand from supine (primary) and those with 300-400m 6MWD.

Results: Ataluren and placebo groups in the ITT population and key subgroups were balanced according to enrolment age, baseline 6MWD, corticosteroid use and time to stand from supine. Significant differences in mean 6MWD change from baseline and rate of change favored ataluren in the ITT population (14.4m; 0.20m/week; p=0.0248) and 300-400m 6MWD subgroup (24.2m; 0.34m/week; p=0.0310), representing a 21% and 30% slowing of the decline rate in 6MWD in these groups, respectively. There were significant treatment benefits in time to 10% worsening of 6MWD. The number of ITT patients who lost ambulation receiving placebo was almost double of those receiving ataluren. Ataluren was well tolerated, had no probable drug-related serious adverse events (AEs), and AE frequency (85.3%) was similar to placebo (84.7%).

Conclusions: Study 041 confirms ataluren's favorable risk-benefit as shown in previous clinical and real-world evidence studies.

#752 Ataluren preserves upper limb function in nmDMD patients from Study 041, a phase 3 placebo-controlled trial, and the STRIDE Registry

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Introduction: Study 041 (NCT03179631) is a phase 3, double-blind, placebo-controlled 72-week ataluren trial in nonsense mutation Duchenne muscular dystrophy (nmDMD) patients. The STRIDE Registry (NCT02369731) is an ongoing, long-term, real-world evidence study.

Objectives: To assess performance of upper limb (PUL) function in nmDMD patients receiving ataluren+standard of care (SoC).

Methods: In Study 041, nmDMD boys aged ≥5 years, on stable corticosteroid regimen, and with 6-minute walk distance (6MWD) ≥150m were randomized 1:1, ataluren:placebo. The intention-to-treat (ITT) population comprised randomized boys who received at least one dose of study treatment (N=359; mean age 8.1 years); baseline 300-400m 6MWD (n=169) was a key subgroup. STRIDE patients were propensity-score matched to patients receiving SoC alone in CINRG DNHS (NCT00468832), yielding a comparable population (N=261). Kaplan-Meier analyses estimated age at loss of upper limb function.

Results: Least-squares mean PUL total score change from baseline to week 72 (by MMRM analysis) numerically favored ataluren vs placebo (0.44, p=0.1059) in the Study 041 ITT population and was significant in the 300–400m 6MWD subgroup (1.02, p=0.0165).
In matched STRIDE vs CINRG patients (mean last assessment age, 13.1 vs 14.6), ataluren preserved hand-to-mouth function by 3.4 years (p=0.0046) as assessed by entry level items of PUL vs Brooke Scale, respectively. Median age at loss of overhead reach numerically favored STRIDE, consistent with the overall trend (15.8 vs 12.6; p=0.2872). Median age at loss of distal hand function was non-estimable for STRIDE patients.

Conclusions: Results indicate that ataluren may help preserve upper limb function in advanced nmDMD patients.

#756 A Phase 1/2 Study of DYNE-251 in Males with DMD Mutations Amenable to Exon 51 Skipping: DELIVER Study Design

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Background: Approved therapies for Duchenne muscular dystrophy (DMD) use exon skipping phosphorodiamidate morpholino oligomers (PMOs) that enable the translation of a shortened, functional dystrophin protein, but their success has been hampered by poor muscle delivery and uptake. DYNE-251 is an exon 51 skipping PMO conjugated to an antigen-binding fragment targeting the transferrin receptor 1 (TfR1) which is expressed on muscle. Robust preclinical data have supported the clinical development of DYNE-251 for the treatment of DMD.

Objectives: To evaluate the safety, tolerability, and dystrophin levels in muscle following treatment with DYNE-251.

Methods: DELIVER is an ongoing randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) study of DYNE-251 administered intravenously to ambulant and non-ambulant males (4-16 years) with exon 51 skip-amenable mutations (NCT05524883). The study consists of a MAD/placebo-controlled period (24 weeks), open-label extension (OLE, 24 weeks), and long-term extension (LTE) period (96 weeks). Primary outcomes are the number of participants with treatment-emergent adverse events and the change from baseline in dystrophin levels in muscle at Week 25.

Results: The DELIVER trial is expected to enroll ~48 males across 7 cohorts – 0.7, 1.4, 2.8, 5, 10, 20, and 40 mg/kg approximate PMO equivalent doses of DYNE-251. Participants will be randomized in a 2:1 or in a 3:1 ratio of DYNE-251 to placebo administered every 4 weeks during the MAD/placebo-controlled period. All participants will receive the highest safe and tolerable dose during the OLE and LTE periods.

Conclusions: Initial data from the MAD portion of the study are expected in H2 2023.

#757 A Phase 1/2 Randomized, Placebo-Controlled, Multiple Ascending Dose Study (ACHIEVE) of DYNE-101 in Individuals with Myotonic Dystrophy Type 1 (DM1)

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Introduction: Myotonic dystrophy type 1 (DM1) is caused by expansion of CUG repeats in the dystrophia myotonica protein kinase (*DMPK*) RNA which sequester splicing regulators into toxic nuclear foci, leading to a spliceopathy that drives DM1 clinical manifestations. DYNE-101 is a transferrin receptor (TfR)1-targeting antigen-binding fragment conjugated to a gapmer antisense oligonucleotide (ASO) that targets nuclear *DMPK* RNA. Preclinical data show that DYNE-101 reduces mutant *DMPK* RNA, foci formation, and corrects splicing, suggesting a potential effect in individuals with DM1. DYNE-101 was well-tolerated in non-human primates.

Objectives: To evaluate the safety, tolerability, pharmacodynamics, efficacy, and pharmacokinetics of DYNE-101 administered intravenously to adults with DM1 aged 18-49 years.

Methods: ACHIEVE is an ongoing, randomized, double-blinded, placebo-controlled, multiple ascending dose (MAD) Phase 1/2 trial (NCT05481879). The primary outcome is the number of participants with treatment-emergent adverse events. Change from baseline in splicing index in skeletal muscle assessed by biopsies at baseline, 12, and 24 weeks is a secondary outcome.

Results: The study will enroll ~72 participants in 4 cohorts of ascending doses of DYNE-101 (1.8, 3.4, 6.8, and 10.2 mg/kg approximate ASO-equivalent doses). Participants who receive 1.8 mg/kg DYNE-101 will be dosed every 4 weeks. Participants who receive 3.4, 6.8, and 10.2 mg/kg DYNE-101 will be dosed every 4 or 8 weeks. All participants will receive the highest safe and tolerable dose of DYNE-101 during the subsequent 24-week open-label and 96-week long-term extension periods.

Conclusions: Initial safety, tolerability, and splicing data from the MAD portion are expected in H2 2023.

#780 FREEDOM-DM1: Phase 1 Study to Assess Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of PGN-EDODM1 in Adults with Myotonic Dystrophy Type 1 (DM1)

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Introduction: PepGen's enhanced delivery oligonucleotide cell-penetrating peptide technology is engineered to optimize tissue delivery and cellular uptake of therapeutic oligonucleotides. PGN-EDODM1 is being developed for the treatment of myotonic dystrophy type 1 (DM1). PGN-EDODM1 is designed to bind to pathogenic CUG trinucleotide repeat expansion in *DMPK* mRNA, thereby liberating MBNL1 protein through steric blocking and without degrading *DMPK* transcript. The release of MBNL1 protein is hypothesized to correct DM1 spliceopathy, the root cause of DM1 pathology. Nonclinical data demonstrated that PGN-EDODM1 reduced the number of myonuclear foci (DM1 cells), liberated MBNL1 (DM1 cells), corrected mis-splicing (DM1 cells, HSA^{LR} mouse) and normalized myotonia (HSA^{LR} mouse).

Objectives: Evaluate the safety and tolerability (primary objective) and plasma pharmacokinetics (secondary objective) following a single dose of PGN-EDODM1 in adults living with DM1. Exploratory objectives include the concentration of PGN-EDODM1 in skeletal muscle, pharmacodynamics (changes in the splicing pattern of affected transcripts), pharmacokinetics in urine, and functional measures (including video hand opening time to assess myotonia) to inform future studies.

Methods: Males and females 18-50 years of age, inclusive, with genetically confirmed diagnosis of DM1 will be randomized 3:1 (6 PGN-EDODM1 and 2 placebo) in each dose cohort. A muscle needle biopsy (tibialis anterior) will be performed at baseline, Week 4, and Week 16 for measurement of tissue drug concentrations and splicing of selected transcripts.

Conclusion: The Phase 1 study FREEDOM-DM1 will evaluate the continued development of PGN-EDODM1 for the treatment of the root cause of DM1. The study design of FREEDOM-DM1 will be presented.

#781 CONNECT-EDO51: Nonclinical and Phase 1 Data Support Phase 2 Trial Designs to Continue Evaluating Safety and Efficacy of PGN-EDO51 for Duchenne Muscular Dystrophy (DMD) Amenable to Exon 51 Skipping

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Introduction: PepGen's enhanced delivery oligonucleotide cell-penetrating peptide technology is engineered to optimize tissue delivery and cellular uptake of therapeutic oligonucleotides. PGN-EDO51 is being evaluated for the treatment of DMD amenable to exon 51 skipping.

Objectives: Evaluate efficacy (exon skipping and dystrophin production), safety, and tolerability of PGN-EDO51 in people with DMD.

Methods: Nonclinical studies and a Phase 1 single-dose study in healthy adult male volunteers (HVs) informed the design of Phase 2 studies.

Results: A single dose of 15 mg/kg PGN-EDO51 in HVs attained the highest published levels of oligonucleotide (50nM) and exon skipping (2% skipping, ddPCR) in biceps reported after a single dose in HVs and that were sustained up to 28 days postdose. PGN-EDO51 was generally well tolerated. In monkeys, a single 20 mg/kg dose resulted in similar exon skipping levels in the biceps (2.5%, ddPCR); and four repeat monthly doses (20 mg/kg) showed accumulation of exon skipped transcripts (34.9% skipping, ddPCR): a 14-fold increase compared to single doses. In *mdx* mice, exon skipping and dystrophin were observed 4 weeks after a single 30 mg/kg dose of PGN-EDO23 (murine analogue); and four repeat monthly doses resulted in 91.5% exon skipping (RT-PCR) and 82.3% dystrophin.

Conclusions: The data support that monthly repeat PGN-EDO51 dosing may result in the accumulation of skipped transcripts and dystrophin protein. Two Phase 2 clinical studies will assess the safety and efficacy of repeat doses of PGN-EDO51 in males living with DMD amenable to exon 51 skipping: CONNECT1-EDO51 is an open-label trial in Canada; CONNECT2-EDO51 is a multinational, randomized placebo-controlled trial. Study designs will be presented.

#792 Phase 3b Extension Study Evaluating Superiority of Daily vs Approved On/Off Oral Edaravone Dosing in Patients With Amyotrophic Lateral Sclerosis

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Introduction: Intravenous edaravone (Radicava®/Radicut) was shown to slow the rate of physical functional decline in amyotrophic lateral sclerosis (ALS). Oral edaravone (Radicava ORS® [edaravone] oral suspension) was approved by the US Food and Drug Administration for use in patients with ALS in May 2022 and has since gained approval in Canada, Japan, and Switzerland.

Objectives: Study MT-1186-A04 (NCT05151471) is an ongoing, multicenter, phase 3b, double-blind, parallel group, randomized extension study evaluating and comparing the long-term safety, efficacy, and tolerability of 2 oral edaravone dosing regimens for up to an additional 48 weeks following the end of Study MT-1186-A02 in patients with ALS, comprising a total duration of up to 96 weeks.

Methods: Study MT-1186-A04 will evaluate 2 oral edaravone dosing regimens (105-mg dose). Group 1 will have oral edaravone administered once daily for each 28-day cycle. Group 2 will have oral edaravone administered for 10 days followed by placebo for 18 days in each 28-day cycle. Dosing in both groups will continue up to 48 weeks. Study MT-1186-A04 is anticipated to include approximately 300 adult patients who have completed Study MT-1186-A02. The primary objective is to evaluate the efficacy of each dosing regimen based on the randomization date in Study MT-1186-A02 to at least a 12-point Revised ALS Functional Rating Score decrease or death, whichever happens first, over the course of the study.

Results: Ongoing.

Conclusions: This extension study will provide important information on the safety, efficacy, and tolerability of 2 oral edaravone dosing regimens in patients with ALS.

Sponsorship: Mitsubishi Tanabe Pharma America, Inc.

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Disclosure:

JR is a consultant for Expansion Therapeutics, National Institutes of Health, Department of Defense, F Prime, The ALS Association. SD and MC have nothing to disclose. LZ has received honoraria for consulting with

MTP, Biogen, Amylyx and Cytokinetics. AC serves on scientific advisory boards for Mitsubishi Tanabe, Roche, Biogen, Denali Pharma, AC Immune, Biogen, Lilly, and Cytokinetics and has received a research grant from Biogen. ACL has served as a scientific consultant for Mitsubishi Tanabe Pharma America, Inc. GS has served as a medical advisor for Mitsubishi Tanabe Pharma Corporation. MD is a medical advisor for MT-1186-A02 study. DS, TF, AW, AS and SA are employees of Mitsubishi Tanabe Pharma America, Inc. VT is an employee of Mitsubishi Tanabe Pharma Europe Ltd. MH is an employee of Mitsubishi Tanabe Pharma Corporation.

Encore of 2023 ENCALS, 2023 Neuromuscular Study Group (NMSG) Annual Meeting

#804 Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamic Effects of AOC 1020 Administered Intravenously to Adult Patients with Facioscapulohumeral Muscular Dystrophy (FORTITUDE™) Trial Design

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San Diego, CA; *Rochester, NY; **Kansas City, KS

Introduction: FSHD is a rare, progressive, often asymmetric, genetic disease caused by aberrant expression of DUX4 in skeletal muscle, leading to a series of downstream events that result in degeneration and wasting. Strategies targeting DUX4 expression in skeletal muscle of individuals with FSHD via oligonucleotides are promising therapeutic approaches.

AOC 1020 is an antibody-oligonucleotide conjugate (AOC™) comprised of a humanized anti-transferrin receptor 1 (TfR1) antibody conjugated to a DUX4-targeting siRNA.

Objective: To evaluate the safety and tolerability of AOC 1020 in participants with FSHD.

Methods: This phase 1/2 study (NCT05747924) is a randomized, placebo-controlled, double-blind trial. The study will enroll 72 adults aged 18 to 65 years with a genetic diagnosis of FSHD1 or FSHD2. All participants will receive 5 doses of study medication administered quarterly with 1 booster at 6 weeks. Part A utilizes a dose-titration design to evaluate the safety of AOC 1020 at 2 low doses. Part B is a nested single/multiple-ascending dose design evaluating 2 higher doses. Staggered cohorts will be initiated based on a safety data review of the preceding cohorts. Part C is a parallel, placebo-controlled design to be conducted with 2 selected doses to evaluate exploratory clinical outcomes. After their final dose, participants enter a 3-month follow-up period. The total duration is 12 months. Eligible participants may enroll in an open-label extension study.

The primary objective of the study is to evaluate safety and tolerability. Secondary objectives include PK of AOC 1020. Exploratory measures of efficacy will be evaluated.

Results/Conclusions: N/A

#805 Phase 1/2 Trial Evaluating AOC 1044 in Healthy Volunteers and Participants with DMD Mutations Amenable to Exon 44 Skipping (DMD44): EXPLORE44™ Trial Design

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Introduction: Duchenne muscular dystrophy (DMD) is a X-linked muscular disease caused by mutations in the DMD gene that prevent the expression of a functional dystrophin protein. Oligonucleotide-mediated skipping of DMD exons can restore the reading frame and dystrophin protein expression.
AOC 1044 is an antibody-oligonucleotide conjugate (AOC™) comprised of a humanized anti-transferrin receptor 1 (TfR1) antibody conjugated to phosphorodiamidate morpholino oligomers (PMOs).

Objective: To evaluate the safety and tolerability of single and multiple ascending doses of AOC 1044

Methods: EXPLORE44™ (NCT05670730) is a randomized, placebo-controlled, double-blind phase 1/2 trial conducted in two parts. Part A assesses the effects AOC 1044 in 5 single-dose cohorts of healthy volunteers, who are monitored for 3 months. Part B will assess the effects of AOC 1044 in 3 multiple-ascending dose-level cohorts of participants with DMD44, dosed no more frequently than once every 6 weeks for 3 months, with 3 months of follow-up.
The primary objective is safety and tolerability of single doses in healthy volunteers and multiple doses in participants with DMD44. Secondary objectives include pharmacokinetics and pharmacodynamics with exon 44 skipping (parts A and B) and dystrophin protein levels (part B). Exploratory objectives include measures of clinical activity, patient-reported outcomes, and quality of life in participants with DMD44.
Part A will enroll 40 healthy male volunteers (18-45 years). Part B will enroll 24 ambulatory or non-ambulatory males (7-27 years) with genetically confirmed DMD44. Eligible participants from part B will have the option to enroll in a planned open-label extension study.

Sponsorship: Avidity Biosciences, Inc

#772 Longer Milestone-Free Time in IV Edaravone–Treated vs Non–IV Edaravone-Treated Patients With Amyotrophic Lateral Sclerosis: An Administrative Claims Analysis

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[*]Former employee

Introduction: Intravenous (IV) edaravone was US Food and Drug Administration-approved for the treatment of amyotrophic lateral sclerosis (ALS) and was shown in clinical trials to slow the rate of physical functional decline.

Objectives: To estimate time to progression milestones in IV edaravone–treated vs IV edaravone–naïve patients with ALS in a real-world, retrospective observational analysis.

Methods: Patients with ALS who were continuously enrolled in Optum's de-identified Clinformatics® Data Mart between 8/8/2017–12/31/2021. IV edaravone–treated patients (cases) and non–IV edaravone-treated patients (controls) were propensity score-matched for the following covariates: age, race, geographic region, sex, insurance, riluzole prescription; and pre-index disease duration, cardiovascular disease, gastrostomy tube, artificial nutrition, noninvasive ventilation, and hospitalization. The index date was the first IV edaravone claim or when IV edaravone was available on the market, for cases or controls, respectively. Restricted mean time lost (RMTL) was calculated for the following milestones: use of canes/walkers/wheelchairs, artificial nutrition, noninvasive ventilation, invasive ventilation, speech-generating devices, and hospice.

Results: Cases (n=360) were matched to controls (n=360). For most reported milestones, cases had a longer milestone-free time than controls based on RMTL, except for speech-generating devices and invasive ventilation. More cases than controls reported no milestones and had fewer deaths from 0-12 months and 0-24 months, respectively, after the index date.

Conclusions: This analysis describes the time to milestones in IV edaravone–treated and IV edaravone–naïve patients with ALS in a real-world setting. This information may be useful to payers and clinicians in evaluating IV edaravone use.

Sponsorship: Mitsubishi Tanabe Pharma America, Inc.

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J.D. Berry reports research funding from Genentech, Alexion, Anelixis, Biogen, MTPA, Brainstorm Cell Therapeutics, Amylyx Pharmaceuticals, nQ Medical, MT Pharma Holdings of America (MTPHA), Transposon Therapeutics, RAPA Therapeutics, National Institute of Neurological Disorders and Stroke, Muscular Dystrophy Association, ALS Finding a Cure, ALS Association, and ALS One. He has served as a member of scientific advisory boards for Biogen, Clene Nanomedicine, Janssen, MTPA, MTPHA, Sawai, and Regeneron; holds equity in ReactNeuro; and has been an educational speaker for Projects in Knowledge, Inc. M. Hagan is a former employee of Mitsubishi Tanabe Pharma America, Inc. M. Ciepielewska is an employee of Mitsubishi Tanabe Pharma America, Inc. J. Zhang and Y. Liu are employees of Princeton Pharmatech, which has received consultancy fees from Mitsubishi Tanabe Pharma America, Inc.

#773 PGN-EDO51, an Enhanced Delivery Oligonucleotide (EDO) Candidate for the Treatment of Duchenne Muscular Dystrophy (DMD): Positive Results from a Phase 1 Study in Healthy Volunteers

Jane Larkindale, Pallavi Lonkar, Jaya Goyal, Ashling Holland, Jeffrey Foy, Brijesh Garg, Shaoxia Yu, Anthony Frank, Chris Abbott, Niels Svenstrup, Sarah Vacca, Michelle Mellion

(PepGen Inc., Boston, MA)

Introduction: PepGen's enhanced delivery oligonucleotide cell-penetrating peptide technology is engineered to optimize tissue delivery and cellular uptake of therapeutic oligonucleotides. PGN-EDO51 is being evaluated for the treatment of DMD amenable to exon 51 skipping.

Objectives: To evaluate the safety, tolerability, pharmacokinetics (plasma, urine, muscle), and pharmacodynamics (exon skipping) of single-ascending doses of PGN-EDO51 administered intravenously to healthy adult male volunteers (HV).

Methods: HVs were randomized (3:1 ratio) to receive a single dose of PGN-EDO51 or placebo. Biceps biopsies were performed.

Results: 32 HVs received PGN-EDO51 (1, 5, 10, or 15 mg/kg, n=6 per cohort) or placebo (n=8), and all completed the study. Majority of treatment-related adverse events were mild and resolved without intervention, including transient, reversible changes in kidney biomarkers (n=9) and hypomagnesemia (n=2) at the highest doses, with no significant clinical sequelae. On Day 28 following 15 mg/kg dose, dose-dependent and sustained concentrations of PGN-EDO51 up to 50 nM and dose-dependent increases in mean exon skipping of up to 2.0% (by ddPCR) were measured in biceps biopsies.

Conclusions: PGN-EDO51 demonstrated a generally tolerable profile at clinically relevant doses and exhibited high levels of muscle oligonucleotide delivery and exon 51 skipping. When compared to publicly available clinical data for other approaches, these are the highest levels measured in a clinical study after a single dose of oligonucleotide in HVs, supporting the hypothesis of enhanced delivery. Potential accumulation of exon 51 skipped transcripts and dystrophin protein with repeat dosing in people with DMD amenable to exon 51 skipping support the design of Phase 2 studies.

#809 Preliminary Results from MLB-01-003: An Open Label Phase 2 Study of BBP-418 in Patients with Limb-girdle Muscular Dystrophy Type 2I

Amy Harper[1], Ruby Langeslay[1], Thulashitha Rajasingham[2,3], Hector M Rodriguez[2,3], Athiwat Hutchaleelaha[2,3], Tricia Blankenbiller[2,3], Doug Sproule[2,3]

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Introduction: Limb-girdle Muscular Dystrophy (LGMD) Type 2I, also called LGMDR9 FKRP-related, is caused by bi-allelic partial loss-of-function of the fukutin-related protein (FKRP) gene, which results in hypoglycosylation of alpha-dystroglycan (αDG). BBP-418 is an oral substrate supplementation therapy intended to saturate the partially functional FKRP enzyme, driving increased glycosylation of αDG, and potentially ameliorating the root cause of LGMD2I.

Objectives and Methods: The ongoing Phase 2 is an open label dose escalation study investigating the safety and tolerability of BBP-418. Part 1 involved three dose cohorts (6 g QD, 6 g BID, 12 g BID BBP-418) treated for 3 months. During Part 2 and OLE (Part 3), all patients received 12 g BID of BBP-418, dose adjusted for weight.

Results: 14 patients with LGMD2I (aged 12-53, 8/14 homozygous for the L276I mutation) were enrolled. Participants showed increased levels of glycosylated αDG after 90 days of dosing, median 33.4% of normal with BBP-418 compared to a baseline of 7.4%, which was sustained through 15 months. A sustained reduction in creatine kinase (CK) of >75% was observed through 15 months. Following 15 months of dosing with BBP-418, increased NSAD (+0.80 points) and 10MWT velocity (+0.12 m/s) and decreased 100MTT time (-2.82 seconds) were observed. BBP-418 was well-tolerated with no observed treatment-related serious adverse events, dose limiting toxicities or discontinuations. Updated data will be provided at the meeting.

Conclusions: Preliminary data from patients with LGMD2I suggest a positive effect of BBP-418 on levels of glycosylated αDG, CK, NSAD, 100MTT, and 10MWT velocity. A global, double-blind placebo-controlled Phase 3 is ongoing.

#818 Empasiprubart (ARGX-117) in Multifocal Motor Neuropathy: Interim Baseline Characteristics of the Phase 2 ARDA Study

W. Ludo van der Pol[1], Stojan Peric[2], Luis Querol[3], Yessar Hussain[4], Paul Duncombe[5], Inge Van de Walle[5], Emma Persson[5], Sergio Barrera-Sierra[5], Iris Van Hoomissen[5], Miodrag Vujcic[5], Olivier Van de Steen[5], Jeffrey A. Allen[6]

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Introduction: Multifocal motor neuropathy (MMN) is a chronic, immune-mediated neuropathy characterized by progressive asymmetric weakness. MMN is often associated with anti-GM1 IgM autoimmunity, leading to activation of the classical complement pathway, drivingsubsequent axon damage. Empasiprubart (ARGX-117), an antibody that inhibits complement factor 2, was shown *in vitro* to block IgM-mediated classical pathway complement activation targeting motor neurons in MMN. This Phase 2, multicenter, randomized, placebo controlled, double-blinded, parallel-group study (ARDA, NCT05225675) will assess safety, efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity of empasiprubart in adults with MMN.

Objective: To present baseline characteristics of the to date randomized patients

Methods: ARDA will recruit 48 participants with probable or definite MMN (per 2010 EFNS/PNS guidelines). All must have proven IVIg dependency and on a stable IVIg regimen. MMN diagnosis and IVIg dependency must be confirmed by a MMN confirmation committee. Enrolled participants will be assigned to one of two dosing cohorts (16 randomized to empasiprubart, 8 to placebo per cohort).

Results: As of 1 March 2023, 16 participants were randomized (7-USA, 9-Europe). Most (12) were classified as definite MMN. The median age was 55 (range 37-76) years, 68.8% were male. Pre-randomization IVIg intervals were every 2 weeks (5 patients), 3 weeks (4) and 4 weeks (7) with a median dose of 1.60 g/kg (range 1.25-1.97). Of the 16 randomized patients, 9 completed a formal IVIg dependency period and 7 were determined to be IVIg dependent and were allowed to bypass the dependency phase

Conclusions: This ongoing ARDA study will inform future complement-inhibition studies in patients with MMN.

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LvdP employer received fees for ad hoc consultancy from Argenx, Takeda, Biogen, Roche and Novartis gene therapies.
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LQ received research grants from Instituto de Salud Carlos III – Ministry of Economy and Innovation (Spain), CIBERER, Fundació La Marató, GBS-CIDP Foundation International, UCB and Grifols. Received speaker or expert testimony honoraria from CSL Behring, Novartis, Sanofi-Genzyme, Merck, Annexon, Alnylam, Biogen, Janssen, Lundbeck, ArgenX, UCB, LFB, Avilar Therapeutics, Octapharma and Roche. Serves at Clinical Trial Steering Committee for Sanofi Genzyme, and was Principal Investigator for UCB's CIDP01 trial.

YH reports no disclosures
IVW, IVH, EP, SBS are employees of argenx
OVS works as a consultant for argenx.
MV, PD works as a consultant for argenx and PPD.
JA has received consulting honoraria from argenx, Alexion, Akcea, CSL Behring, Johnson & Johnson, Grifols, Takeda, and Sanofi.
Marc: 413-265-1121

#825- DESIGN OF A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY OF NIPOCALIMAB IN PARTICIPANTS WITH ACTIVE IDIOPATHIC INFLAMMATORY MYOPATHIES (SPIREA)

Catherine E. Najem,[1] Zia Choudhry*,[2] Jagriti Craig,[1] Lisa Christopher-Stine,[3] Federico Zazzetti,[4] Wim Noel,[5] Christopher Blango Sr.,[1] Chetan S. Karyekar,[1] Rohit Aggarwal[6]

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Introduction: Idiopathic inflammatory myopathies (IIM) are a rare group of systemic autoimmune diseases characterized by progressive muscular weakness and internal organ involvement, often leading to physical disability and decreased quality of life. Nipocalimab is designed to address the underlying disease pathology by selectively blocking the neonatal Fc receptor to reduce pathogenic autoantibodies. In a phase 2 study of generalized myasthenia gravis (NCT03772587), nipocalimab lowered pathogenic IgG autoantibody levels with significant clinical benefit, acceptable safety, and a favorable benefit-risk profile.

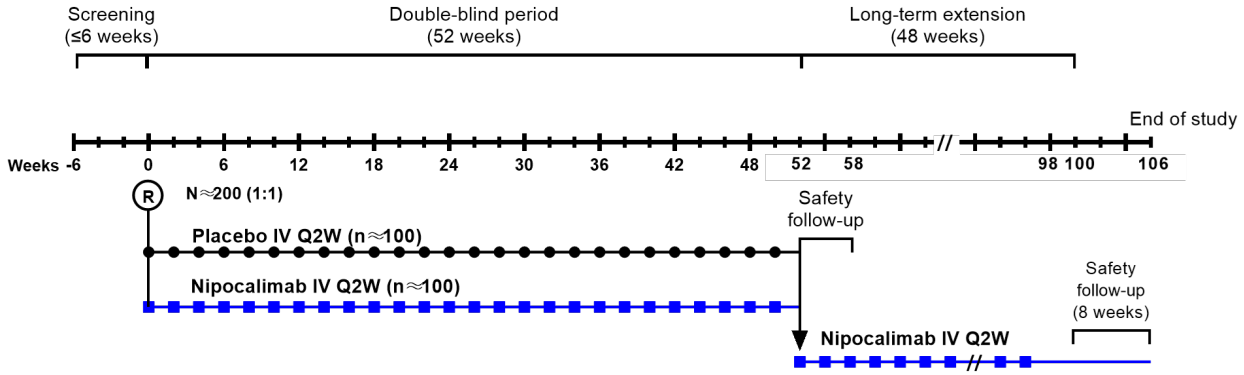
Objective: To describe the study design of SPIREA (NCT05379634) which aims to evaluate the efficacy and safety of nipocalimab in patients with IIM.

Methods: SPIREA is a phase 2, double-blind, placebo-controlled, randomized clinical trial enrolling adults (N≈200) with active IIM. The study comprises screening, double-blind treatment, long-term extension, and follow-up periods (**Figure 1**). Randomized participants are treated every 2 weeks with intravenous nipocalimab or placebo through Week 50. Background oral glucocorticoid (GC) doses will be tapered from Weeks 24–44.

Results: The primary endpoint is the proportion of participants who achieve at least minimal improvement (≥20) in American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Total Improvement Score (TIS) at Week 52 and on ≤5 mg/day of oral GC from Weeks 44–52. Secondary endpoints include the proportion of participants who achieve ≥20-point improvement in TIS at Weeks 24 and 52.

Conclusions: The ongoing SPIREA study evaluating nipocalimab's safety and efficacy in patients with IIM will help to validate the ACR/EULAR-TIS endpoint in IIM and the role of nipocalimab as a steroid sparing agent in IIM.

Figure 1. Study Design.



IV, intravenous; Q2W, every 2 weeks; R, randomization.

#737 Design of REACH: Phase 3 Randomized, Double-Blind, Placebo-Controlled, 48-Week Study of the Efficacy and Safety of Losmapimod in FSHD

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FSHD is a chronic, variably progressive disease leading to accumulation of disability over decades. Nonclinical studies have shown that losmapimod (a small molecule p38 α/β MAPK inhibitor) reduces the aberrant expression of DUX4, the underlying cause of FSHD. Two Phase 2 clinical studies, a 48-week randomized controlled study (ReDUX4, FIS-002-2019) and a 52-week open-label study (OLS, FIS-001-2019) demonstrated evidence of benefit of treatment with losmapimod on muscle structure and function, as well as FSHD-relevant clinical endpoints that are recognized by patients and favorable safety and tolerability, supporting continued development. Fulcrum has initiated a Phase 3 double-blind, placebo-controlled trial to support the development of losmapimod in FSHD. Approximately 230 people with FSHD, 210 with genetically confirmed FSHD1 and 20 with FSHD2, will be randomized 1:1 to receive losmapimod or placebo orally, twice daily for 48-weeks. The primary endpoint is reachable workspace quantification of total relative surface area (Q1-Q5) with 500 g wrist weight in the dominant arm, with secondary efficacy endpoints of quality of life in the neurological disorders upper extremity scale (Neuro-QoL UE), patient global impression of change (PGIC), and muscle fat infiltration (MFI) using whole-body musculoskeletal MRI (WB-MSK MRI). Exploratory assessments include muscle fat fraction, muscle strength by hand-held dynamometry, and patient reported outcomes (PROs) including patient global impression of severity (PGIS), a novel FSHD PRO, numeric pain rating scale (NPRS), 5-level EQ-5D (EQ-5D-5L) and healthcare utilization questionnaire. The design of this Phase 3 study will be presented.

#738 Safety and Tolerability of Losmapimod for the Treatment of FSHD

Marie-Helene Jouvin[1], Vivekananda Ramana[1], John Jiang[1]

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FSHD is a variably progressive disease leading to accumulation of disability over decades. Fulcrum has assessed losmapimod, a small-molecule p38 α/β MAPK inhibitor, in FSHD in one completed Phase 1 study (FIS-001-2018) and two ongoing Phase 2 studies (FIS-001-2019, FIS-002-2019) in the open-label extension period. Subjects aged 18-65 years with genetically confirmed FSHD1, Clinical Severity Score 2-4, and MRI-eligible muscles for biopsy were exposed to losmapimod 7.5 or 15 mg BID PO for 14 days and up to 96 weeks. In Study FIS 001-2018, 6 subjects were exposed to 7.5 mg and 11 subjects to 15 mg BID dosing for 14 consecutive days. In Studies FIS-001-2019 and FIS-002-2019, 14 and 77 subjects respectively, received at least one dose of losmapimod 15 mg BID for up to 96 weeks. A total of 108 subjects with FSHD1 have been exposed to losmapimod. Most AEs observed during the studies were considered mild to moderate in severity. Most common AEs were eczema, dry skin, ALT increase, rash, headache, and myalgia. Most AEs resolved with continued dosing. Dosing was paused for 14 days in four subjects (3 in FIS 001-2019, 1 in FIS-002-2019) due to COVID-19 infection. No drug-related SAEs, deaths, discontinuations due to AEs, or clinically significant changes in vital signs, clinical laboratory results, or ECG parameters were reported. Losmapimod administered up to 15 mg BID in >100 subjects with FSHD1 for up to 96 weeks has been generally well-tolerated; the benefit-risk profile of losmapimod for treatment of FSHD remains positive and favorable.

#734 A Phase 1/2a, Randomized, Double-Blind, Placebo-Controlled, First-in-patient Study of JM17 To Evaluate safety, Tolerability, Pharmacokinetics, and Pharmacodynamics in Adults with Spinal and Bulbar Muscular Atrophy

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Introduction: Spinal and Bulbar Muscular Atrophy (SBMA) is a rare, X-linked lower motor neuron disease with an abnormal expansion of CAG repeat in the androgen receptor (AR) gene. JM17 is a novel Nrf2 activator that was shown to reduce accumulation of mutant polyQ AR protein in muscles and to improve motor functions in SBMA mouse model. Previous Phase 1 study in healthy volunteers has demonstrated a favorable safety and drug-like profile of JM17 (NCT04392830).

Objectives: This study aims to further characterize the safety, tolerability, pharmacokinetics, pharmacodynamics of JM17 in adult male SBMA patients (NCT05517603).

Methods: This is an international multicenter study. Approximately 24 subjects with SBMA aged ≥18 years will be randomized in 3:1 ratio to receive either 600 mg of JM17 or placebo once daily in oral suspension for 12 weeks. A safety follow-up visit will be scheduled 4 weeks after the end of treatment. The primary objectives are the safety of JM17. The secondary objectives are the pharmacokinetics and the pharmacodynamics of JM17 as evaluated by the level of mutant AR protein and the transcriptome in skeletal muscles. Exploratory objectives included clinical assessments in muscle strength, volume, and function as well as patient reported outcomes.

Results: Topline data are expected to be available in 2024.

Conclusions: This is the first-in-patient proof-of-mechanism study to demonstrate the therapeutic potential of JM17 in SBMA. The results from the Phase 1 study and this study will provide important information to optimize dose selection in the next efficacy study.

#806 Rozanolixizumab in Muscle-specific Kinase Autoantibody-positive Myasthenia Gravis: Further Analyses from MycarinG Study

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Introduction: Muscle-specific kinase autoantibody-positive (MuSK-Ab+) generalized myasthenia gravis (gMG) is usually more clinically severe than acetylcholine receptor autoantibody-positive (AChR-Ab+) gMG.

Objectives: To evaluate clinical outcomes of rozanolixizumab in MuSK-Ab+ gMG using data from the Phase 3 MycarinG study.

Methods: MycarinG (MG0003/NCT03971422) randomized adults with Myasthenia Gravis Foundation of America Class II–IVa, AChR-Ab+ or MuSK-Ab+ gMG to weekly rozanolixizumab 7mg/kg, 10mg/kg or placebo for 6 weeks. The primary endpoint was Day 43 change from baseline (CFB) in Myasthenia Gravis Activities of Daily Living (MG-ADL).

Results: 200 patients (21 MuSK-Ab+) were randomized to rozanolixizumab 7mg/kg (n=66 [5 MuSK-Ab+]), 10mg/kg (n=67 [8]) or placebo (n=67 [8]). Among patients with MuSK-Ab+ gMG, a higher proportion experienced prior MG crisis and a lower proportion had thymectomy than the overall population, and baseline MG-ADL score was higher (Table 1). Day 43 least-squares mean CFB in MG-ADL for 7mg/kg, 10mg/kg and placebo groups were −7.28, −4.16 and 2.28, respectively, in patients with MuSK-Ab+ gMG and −3.37, −3.40 and −0.78 in the overall population (Figure 1). Mean percentage CFB in total immunoglobulin G (IgG) and IgG4 for patients with MuSK-Ab+ gMG and the overall population are presented in Table 2. Treatment-emergent adverse events occurred in 81.3% (7mg/kg), 82.6% (10mg/kg) and 67.2% (placebo) patients in the overall population and most were mild-to-moderate in severity.

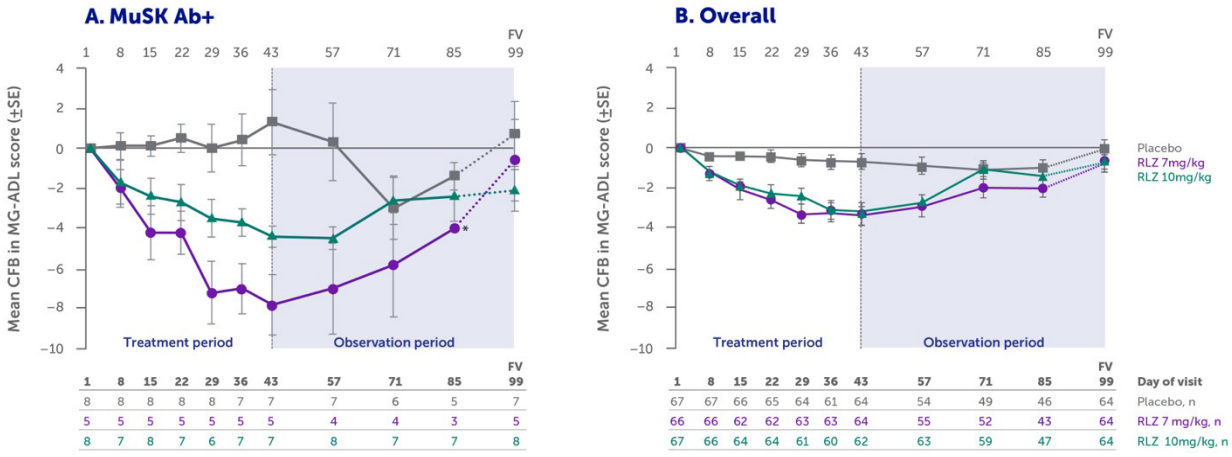
Conclusion: Rozanolixizumab lowered total and subclass IgG levels and improved MG-specific outcomes in MuSK-Ab+ gMG, consistent with the overall study population. Funding: UCB Pharma.

Table 1: Baseline characteristics of patients with MuSK-Ab+ gMG and in the overall population

		MuSK-Ab+*			Overall population†		
		Placebo (n=8)	RLZ 7mg/kg (n=5)	RLZ 10mg/kg (n=8)	Placebo (n=67)	RLZ 7mg/kg (n=66)	RLZ 10mg/kg (n=67)
Age at initial diagnosis, years, mean (SD)		37.1 (10.0)	37.2 (13.7)	43.6 (16.9)	41.4 (19.1)	46.6 (16.0)	42.6 (19.1)
Race, n (%)	Asian	0	2 (40.0)	2 (25.0)	5 (7.5)	9 (13.6)	7 (10.4)
	Black	0	0	1 (12.5)	1 (1.5)	0	4 (6.0)
	Native Hawaiian or other Pacific Islander	0	0	0	1 (1.5)	0	0
	White	8 (100)	3 (60.0)	5 (62.5)	46 (68.7)	41 (62.1)	49 (73.1)
	Missing‡	0	0	0	14 (20.9)	16 (24.2)	7 (10.4)
Duration of disease, years, mean (SD)		10.2 (9.8)	13.9 (7.6)	5.2 (5.0)	9.4 (9.3)	6.9 (6.8)	9.6 (9.9)
MG-ADL score at baseline, mean (SD)		8.8 (3.7)	11.0 (3.5)	9.3 (2.7)	8.4 (3.4)	8.4 (3.8)	8.1 (2.9)
QMG score at baseline, mean (SD)		17.9 (4.0)	17.0 (5.8)	14.0 (3.6)	15.8 (3.5)	15.4 (3.7)	15.6 (3.7)
MGFA disease class at baseline, n (%)	Class II	1 (12.5)	3 (60.0)	3 (37.5)	23 (34.3)	29 (43.9)	26 (38.8)
	Class III	4 (50.0)	2 (40.0)	5 (62.5)	41 (61.2)	34 (51.5)	39 (58.2)
	Class IVa/b§	3 (37.5)	0	0	3 (4.5)	3 (4.5)	2 (3.0)
Prior MG crisis, n (%)		5 (62.5)	3 (60.0)	4 (50.0)	23 (34.3)	19 (28.8)	17 (25.4)
Baseline medications, n (%)	1 baseline MG-specific therapy (excluding AChEI)	1 (12.5)	1 (20.0)	4 (50.0)	23 (34.3)	19 (28.8)	26 (38.8)
	≥2 baseline MG-specific therapies (excluding AChEI)	4 (50.0)	3 (60.0)	4 (50.0)	27 (40.3)	30 (45.5)	34 (50.7)
Thymectomy at baseline, n (%)		3 (37.5)	1 (20.0)	0	31 (46.3)	32 (48.5)	20 (29.9)
Total IgG, g/L, mean (SD)		9.5 (3.0)	9.2 (1.0)	9.3 (2.2)	10.2 (2.6)	10.2 (3.2)	9.7 (2.6)

*Includes two patients who had positive AChR and MuSK autoantibody status.
†Includes both patients with AChR-Ab+ and MuSK-Ab+ gMG.
‡Data on race were not permitted to be collected in certain countries.
§Only 1 patient, who was randomised to the placebo group, had Class IVb disease.
AChEI, acetylcholinesterase inhibitor; AChR-Ab+, acetylcholine receptor autoantibody-positive; gMG, generalised myasthenia gravis; IgG, immunoglobulin G; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MuSK-Ab+, muscle-specific kinase autoantibody-positive; QMG, quantitative myasthenia gravis; RLZ, rozanolixizumab; SD, standard deviation.

Fig 1: Mean change from baseline in MG-ADL in (A) patients with MuSK-Ab+ gMG and (B) the overall population



*SD was not calculated for populations with n less than 3.
FV, final visit; gMG, generalised myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MuSK Ab+, muscle-specific kinase autoantibody-positive; RLZ, rozanolixizumab; SE, standard error.

Table 2: Mean percentage change from baseline in total IgG and IgG4 for patients with MuSK-Ab+ gMG and in the overall population

	MuSK-Ab+*			Overall population†		
	Placebo (n=8)	RLZ 7mg/kg (n=5)	RLZ 10mg/kg (n=8)	Placebo (n=67)	RLZ 7mg/kg (n=66)	RLZ 10mg/kg (n=67)
Total IgG (%)	−1.3	−75.9	−77.6	−4.2	−69.1	−71.4
IgG4 (%)	10.14	−69.47	−66.95	−5.29	−56.57	−59.87

*Includes two patients who had positive AChR and MuSK autoantibody status.
†Includes both patients with AChR-Ab+ and MuSK-Ab+ gMG.
AChR, acetylcholine receptor; gMG, generalised myasthenia gravis; IgG, immunoglobulin G; MuSK-Ab+, muscle-specific kinase autoantibody-positive; RLZ, rozanolixizumab.

#751 Ataluren preserves muscle function in nmDMD patients: a pooled analysis of results from three randomized, double-blind, placebo-controlled trials

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Introduction: Study 041 (NCT03179631) is a phase 3, randomized, placebo-controlled 72-week ataluren trial in nonsense mutation Duchenne muscular dystrophy (nmDMD) patients.

Objectives: To describe results of a pooled analysis of ataluren muscle function efficacy results from Study 041 and two randomized, placebo-controlled 48-week ataluren trials (Study 007 [phase 2b] and Study 020 [phase 3]).

Methods: Patients were eligible if they were male, had phenotypic evidence of DMD, and had an nmDMD diagnosis confirmed by genetic testing. Patients were randomized 1:1 (ataluren:placebo).
Pooled efficacy results for 48-week change in 6-minute walk distance (6MWD), North Star Ambulatory Assessment (NSAA) total and linear scores (where available), and timed function tests (TFTs; 10m walk/run, 4-stair ascent and 4-stair descent) are described for the overall pooled study population; and 48-week change in 6MWD for a key subgroup with baseline 6MWD 300–400m.

Results: The pooled study population included 354 patients receiving ataluren and 347 patients receiving placebo. Treatment with ataluren significantly reduced mean change from baseline in all measures vs placebo for the overall population (6MWD: 19.3m, p=0.0002; NSAA total score: 1.07, p=0.0010; NSAA linear score: 2.70, p=0.0031; 10m walk/run time: -1.31s, p=0.0001; 4-stair ascent time: -1.45s (p=0.0003); 4-stair descent time: -1.54s, p=0.0003). The pooled subgroup with baseline 6MWD 300–400m included 155 patients receiving ataluren and 157 patients receiving placebo. Ataluren preserved 32.1m of 6MWD in this subgroup vs placebo (p=0.0005)

Conclusions: Pooled placebo-controlled clinical trial data from 701 patients demonstrate that ataluren preserves muscle function, assessed by clinical meaningful endpoints, in nmDMD patients.

#739 Therapeutic Play Gym: A caregiver-mediated exercise system for infants and young children with severe neuromuscular weakness- Feasibility and Extension Study

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Introduction: Children need stability, self-produced sensorimotor experiences, and variable practice to master developmental skills in supine, side-lying, prone, and supported seated positions.

Objective: To evaluate the effect, safety, and the feasibility of caregiver-mediated exercise training using a novel Therapeutic Play Gym (TPG).

Methods: Nine children ages 4-58 months (ventilation dependence=9, G-tube dependence=6) with diagnoses of Spinal Muscular Atrophy (SMA) Type 0, SMA Type 1, X-Linked Myotubular Myopathy, and Nemaline Rod Muscular Dystrophy and their caregivers enrolled in the study. Dyads completed baseline (BL), Month 3, and Month 6 end of study (EOS) testing with the exploratory TPG-specific FUNctional Measure (FUNM), Neuromuscular Gross Motor Outcome (GRO), and Caregiver Impression of Change Questionnaire (CICQ). Testing was performed in the home environment or during naturally occurring episodes of care at The University of Florida.

Study results: Participants logged 28,642 training minutes with no TPG-related adverse events (AEs). All outcomes captured a statistically significant change in function: BL FUNM (not in TPG) to EOS FUNM (in TPG) $p = 0.013$, No TPG at BL to EOS $p = .0087$, Neuro GRO BL to EOS $p = .0264$, CGIC $p < .0001$.

Conclusion: Exercise training using the TPG device is yielding promising in functional ability and caregiver reported quality of life. 8 dyads are enrolled in a 2-year extension study.

#732 Endosomal Escape Vehicle (EEV™) - Oligonucleotide Conjugates Produce Exon Skipping and Dystrophin Production in Preclinical Models of Duchenne Muscular Dystrophy

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Introduction: Antisense phosphorodiamidate morpholino oligomer (PMO)-mediated exon skipping therapies for Duchenne muscular dystrophy (DMD) produce only a very modest amount of dystrophin in skeletal and cardiac muscle. To enhance PMO delivery to target tissues, we designed a family of proprietary cyclic cell-penetrating peptides that form the core of the Endosomal Escape Vehicle (EEV™) platform.

Objective: Assess the therapeutic potential of EEV-PMO conjugates for exon 44 and 45 skip amenable DMD in preclinical models.

Methods: Efficacy of EEV-PMO conjugates were assessed in several cell and animal models. EEV-PMO-23 (EEV-exon 23 skipping PMO conjugate) was administered to D2-*mdx* mice intravenously (IV). Efficacy of ENTR-601-44 (EEV-exon 44 skipping PMO conjugate) and ENTR-601-45 (EEV-exon 45 skipping PMO conjugate) were also assessed in several cell and animal models.

Results: D2-*mdx* mice administered EEV-PMO-23 demonstrated robust exon skipping and dystrophin production in both skeletal and cardiac muscle and improved skeletal muscle contractile force to wild type levels. Next, efficacy of exon 44 and 45 skip amenable EEV-PMO conjugates were assessed. ENTR-601-44 showed durable exon skipping in skeletal and cardiac muscle in non-human primates for at least 12 weeks following a single IV dose. Additionally, ENTR-601-45 produced robust exon skipping and dystrophin production in skeletal and cardiac muscle cells derived from patients with exon 45 skip amenable DMD.

Conclusions: These results demonstrate the ability of the EEV platform to efficiently deliver exon skipping oligonucleotides to skeletal and cardiac muscle in preclinical models of DMD and support the potential for further study in patients with DMD amenable to exon 44 and 45 skipping.

#842 Matching-adjusted indirect comparison of ravulizumab/efgartigimod in generalized myasthenia gravis: Timepoint challenges

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[1]University of Münster, Münster, Germany; [2]University Hospital Essen, Essen, Germany; [3]University of Tennessee, Knoxville, TN, USA; [4]Tokyo Medical University, Tokyo, Japan; [5]Alexion Pharmaceuticals Inc., Boston, MA, USA; [6]Broadstreet Health Economics & Outcomes Research, Vancouver, BC, Canada

Introduction: Matching-adjusted indirect comparisons (MAICs) may be used to assess the benefits of different treatments for symptom control. In this MAIC, we built on findings from previous comparisons of ravulizumab and efgartigimod and used mean changes from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) scores from the CHAMPION-MG and ADAPT trials to assess the effects ofthese treatments on symptom control in patients with gMG at different timepoints.

Methods: Individual patient-level data from CHAMPION-MG were weighted to match summary baseline characteristics from the acetylcholine receptor antibody-positivesubset of patients in ADAPT at the trial-arm level, and mean changes in MG-ADL scores from baseline to different timepoints were compared. Anchored comparisons were performed at Weeks 4 and 10, and at Week 8 (efgartigimod) vs Week 26 (ravulizumab).

Results: Baseline characteristics of the patients before and after matching are shown in Table 1. The timepoints chosen to assess the impact of ravulizumab and efgartigimod on MG-ADL were found to affect the results. Improvements in MG-ADL scores appeared to favour efgartigimod vs ravulizumab at Week 4, whereas at Week 10, and Week 8 (efgartigimod) vs Week 26 (ravulizumab), the results trended in favour of ravulizumab (Table 2).

Conclusion: Outcomes of indirect comparisons of the effects of efgartigimod and ravulizumab on symptom control in patients with gMG can vary depending on the chosen timepoints and matching methodology. The consistency of symptom control achievable over a prolonged period should be considered, alongside efficacy and tolerability, when assessing treatment options for patients with gMG.

Disclosures:
S. Meuth: Received speaker fees and advisory honoraria from Almirall, Amicus Therapeutics Germany, Bayer Health Care, Biogen, Celgene, Diamed, Genzyme, MedDay Pharmaceuticals, Merck Healthcare, Novartis, Novo Nordisk, ONO Pharma, Roche, Sanofi-Aventis, Chugai Pharma, QuintilesIMS and Teva; research funding from the German Ministry for Education and Research, Deutschen Forschungsgesellschaft, Else Kröner Fresenius Foundation, German Academic Exchange Service, Hertie Foundation, Interdisciplinary Center for Clinical Studies Muenster, German Foundation Neurology and by Almirall, Amicus Therapeutics Germany, Biogen Idec, Diamed, Fresenius Medical Care, Genzyme, Merck Healthcare, Novartis, ONO Pharma, Roche, and Teva
T. Hagenacker: Received speaker fees and advisory honoraria from Alexion, Hormosan, Roche, Biogen and Argenx
C. Scheiner: Consultant for Alexion and CSL Behring Gmbh
M. Masuda:
A. Kielhorn: Employee of Alexion
B. Werneburg: Employee of Alexion at the time of the study
L. Powell: Employee of Broadstreet HEOR which received funding from Alexion to conduct this work
B. Rogula: Employee of Broadstreet HEOR which received funding from Alexion to conduct this work
K. Johnston: Employee of Broadstreet HEOR which received funding from Alexion to conduct this work

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Tables:

Table 1. Baseline characteristics before and after matching

	CHAMPION						ADAPT (AChR-Ab+ patients)		
	Ravulizumab (n=86)		Placebo (n=89)		Total (n=175)		Efgar-tigimod (n=65)	Placebo (n=64)	Total (n=129)
	Unmatched	Matched	Unmatched	Matched	Unmatched	Matched			
Mean age, years	58.0	44.7	53.3	49.2	55.6	47.0	44.7	49.2	46.9
Female, n (%)	44 (51.2)	61 (70.8)	45 (50.6)	56 (62.5)	89 (50.9)	116 (66.6)	46 (70.8)	40 (62.5)	86 (66.7)
MGFA class II, n (%)	39 (45.3)	37 (43.1)	39 (43.8)	35 (39.1)	78 (44.6)	72 (41.0)	28 (43.1)	25 (39.1)	53 (41.1)
MGFA class III, n (%)	41 (47.7)	46 (53.8)	45 (50.6)	50 (56.3)	86 (49.1)	96 (55.1)	35 (53.8)	36 (56.3)	71 (55.0)
MGFA class IV, n (%)	6 (7.0)	3 (3.1)	5 (5.6)	4 (4.7)	11 (6.3)	7 (3.9)	2 (3.1)	3 (4.7)	5 (3.9)
Mean years since diagnosis	9.8	9.7	10.0	8.9	9.9	9.3	9.7	8.9	9.3
Mean MG-ADL score	9.1	9.0	8.9	8.6	9.0	8.8	9.0	8.6	8.8
Steroid use at study entry, n (%)	56 (65.1)	61 (70.8)	65 (73.0)	71 (79.7)	121 (69.1)	132 (75.3)	46 (70.8)	51 (79.7)	97 (75.2)
NSIST use at study entry, n (%)	56 (65.1)	53 (61.5)	63 (70.8)	51 (57.8)	119 (68.0)	104 (59.6)	40 (61.5)	37 (57.8)	77 (59.7)

AChR-Ab+, acetylcholine receptor antibody-positive; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; NSIST, non-steroidal immunosuppressant therapy.

Table 2. Mean (95% confidence interval) MG-ADL changes from baseline to different timepoints

Timepoint	Efgartigimod–placebo	Ravulizumab–placebo	Efgartigimod–ravulizumab
At Week 4	−2.8 (−3.8, −1.8)	−1.1 (−2.0, 0.3)	−1.6 (−3.0, −0.3)
At Week 10	−0.6 (−1.9, 0.6)	−1.6 (−2.6, −0.7)	1.0 (−0.5, 2.5)
At Week 8 (efgartigimod) vs Week 26 (ravulizumab)	−0.5 (−1.5, 0.6)	−1.7 (−2.7, −0.7)	1.2 (−0.2, 2.7)

MG-ADL, Myasthenia Gravis Activities of Daily Living.

#843 Assessing the extent of symptom control provided by ravulizumab or efgartigimod to patients with generalized myasthenia gravis (gMG)

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Introduction: The levels of gMG symptom control achievable with ravulizumab and efgartigimod have been shown with Myasthenia Gravis Activities of Daily Living (MGADL) scores in the CHAMPION-MG and ADAPT trials, respectively.[1,2] This analysis used 10-week trajectories post-baseline in MG-ADL total scores to estimate the time patients spent in different health states with each treatment over 12 months.

Methods: Mean changes from baseline in MG-ADL over 26 weeks with ravulizumab and over 10 weeks with efgartigimod were extracted from the CHAMPION-MG and ADAPT, respectively. Changes were categorized into different health states: improvements or deteriorations (≥0.5-point difference) or steady (<0.5-point difference) vs the previous observation (Figure 1). These observations were extrapolated to estimate trends over 12 months.

Results: Of 9 mean MG-ADL changes observed in patients on efgartigimod, 2 were improvements, 4 were steady (with statistically significant difference vs placebo; $p<0.0001$) and 3 were deteriorations vs the previous observations. Of 7 observations in patients on ravulizumab, 3 were improvements and 4 were steady (including 3 with statistically significant difference vs placebo; $p<0.0030$) vs the previous observations (Figure 2). After extrapolation, patients on ravulizumab were estimated to spend most (87.9%) of their time in the steady state, while those on efgartigimod were more widely distributed across health states (Figure 3).

Conclusion: Levels of symptom control were more widely distributed in patients treated with efgartigimod than ravulizumab. This should be considered with other factors, such as the burden of treatment administration, when selecting therapies for patients with gMG.

Disclosures:
T. Hagenacker: Received speaker´s fees as well as advisory honoraria from Alexion, Hormosan, Roche, Biogen and Argenx
S. Meuth: Received speaker fees and advisory honoraria from Almirall, Amicus Therapeutics Germany, Bayer Health Care, Biogen, Celgene, Diamed, Genzyme, MedDay Pharmaceuticals, Merck Healthcare, Novartis, Novo Nordisk, ONO Pharma, Roche, Sanofi-Aventis, Chugai Pharma, QuintilesIMS and Teva; research funding from the German Ministry for Education and Research, Deutschen Forschungsgesellschaft, Else Kröner Fresenius Foundation, German Academic Exchange Service, Hertie Foundation, Interdisciplinary Center for Clinical Studies Muenster, German Foundation Neurology and by Almirall, Amicus Therapeutics Germany, Biogen Idec, Diamed, Fresenius Medical Care, Genzyme, Merck Healthcare, Novartis, ONO Pharma, Roche, and Teva
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A. Kielhorn: Employee of Alexion
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L. Powell: Employee of Broadstreet HEOR which received funding from Alexion to conduct this work
P. Jayasinghe: Employee of Broadstreet HEOR which received funding from Alexionto conduct this work
K. Johnston: Employee of Broadstreet HEOR which received funding from Alexion to conduct this work

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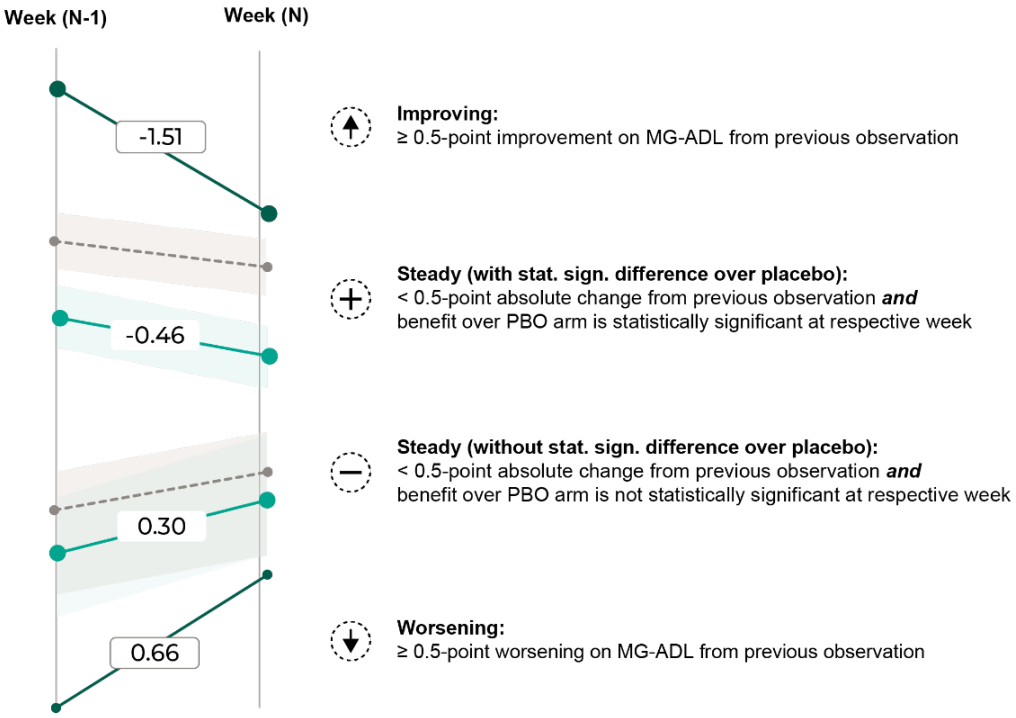
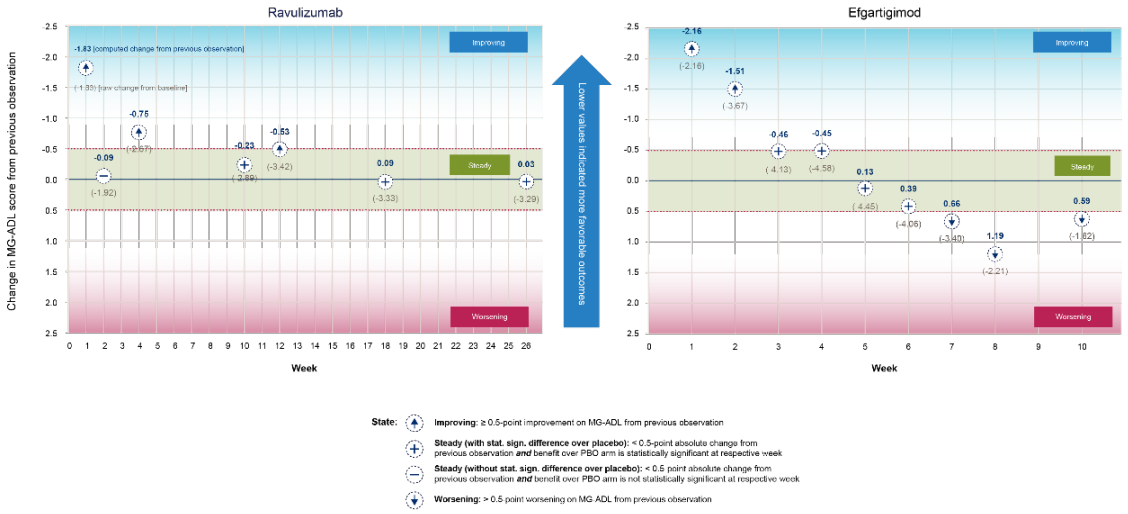
Figures:

Figure 1. Definitions of the different health states



MG-ADL, Myasthenia Gravis Activities of Daily Living; PBO, placebo.

Figure 2. Health states according to change in mean MG-ADL score from the previous observation for patients treated with ravulizumab or efgartigimod



State:

Improving: ≥ 0.5-point improvement on MG-ADL from previous observation

Steady (with stat. sign. difference over placebo): < 0.5-point absolute change from previous observation ***and*** benefit over PBO arm is statistically significant at respective week

Steady (without stat. sign. difference over placebo): < 0.5 point absolute change from previous observation ***and*** benefit over PBO arm is not statistically significant at respective week

Worsening: > 0.5-point worsening on MG ADL from previous observation

Grey values in parentheses show raw change from baseline; values in blue show the calculated change from the previous observation.
MG-ADL, Myasthenia Gravis Activities of Daily Living.

	All zilucoplan doses (N=200)
Any TEAE, n (%)	188 (94.0)
Serious TEAE, n (%)	64 (32.0)
TEAE resulting in permanent withdrawal from IMP, n (%)	17 (8.5)
Treatment-related TEAE, n (%)	67 (33.5)
Severe TEAE, n (%)	57 (28.5)
TEAEs leading to death, n (%)	4 (2.0)

#808 Long-term safety, efficacy & self-injection satisfaction with zilucoplan in myasthenia gravis: RAISE-XT interim analysis

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Introduction: Long-term data from RAISE-XT (NCT04225871), a Phase 3, multicenter, open-label extension study, will evaluate zilucoplan, a C5 complement inhibitor, in patients with generalized myasthenia gravis (gMG).

Objectives: To evaluate the long-term safety, efficacy, and self-injection satisfaction of zilucoplan in gMG.

Methods: Adults (aged 18–75 years) with gMG who completed a qualifying zilucoplan study (NCT03315130/NCT04115293 [RAISE]) self-administered daily subcutaneous injections of zilucoplan 0.3 mg/kg. Primary outcome was incidence of treatment-emergent adverse events (TEAEs). Secondary efficacy outcomes included change from qualifying study double-blind baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) score. The Self-Injection Assessment Questionnaire (SIAQ; scores 0–10; higher scores indicate more positive experience) was completed by US patients directly after self-injection and measured patient satisfaction with self-injection.

Results: At data cut-off (September 8, 2022), 200 patients had enrolled in RAISE-XT. Median (range) exposure was 1.2 (0.11–4.45) years. TEAEs occurred in 188 (94.0%) patients; 64 (32.0%) patients experienced a serious TEAE (Table). Mean (standard deviation) changes from double-blind baseline MG-ADL score continued to decrease through Extension Week 12 and were maintained through to Extension Week 48 (Week E48) for the zilucoplan and placebo-switch groups: −5.95 (4.14) and −6.85 (5.13) at Week E48, respectively (Figure 1). In the SIAQ domain of satisfaction with self-injection, median score was 8.20 (range: 3.9–10.0; n=63; Figure 2).

Conclusions: In this interim analysis of RAISE-XT, zilucoplan demonstrated a favorable long-term safety profile and sustained efficacy through to Week E48. High satisfaction rates with self-injection were reported.
Funding: UCB Pharma.

Table: Overview of TEAEs

Safety set.
IMP, investigational medicinal product.

	All zilucoplan doses (N=200)
Any TEAE, n (%)	188 (94.0)
Serious TEAE, n (%)	64 (32.0)
TEAE resulting in permanent withdrawal from IMP, n (%)	17 (8.5)
Treatment-related TEAE, n (%)	67 (33.5)
Severe TEAE, n (%)	57 (28.5)
TEAEs leading to death, n (%)	4 (2.0)

Figure 1: Mean CFB in MG-ADL score to Week E48

mITT population. Baseline is defined as the baseline before entering the double-blind study.
CFB, change from baseline; MG-ADL, Myasthenia Gravis Activities of Daily Living; mITT, modified intention-to-treat; SE, standard error.

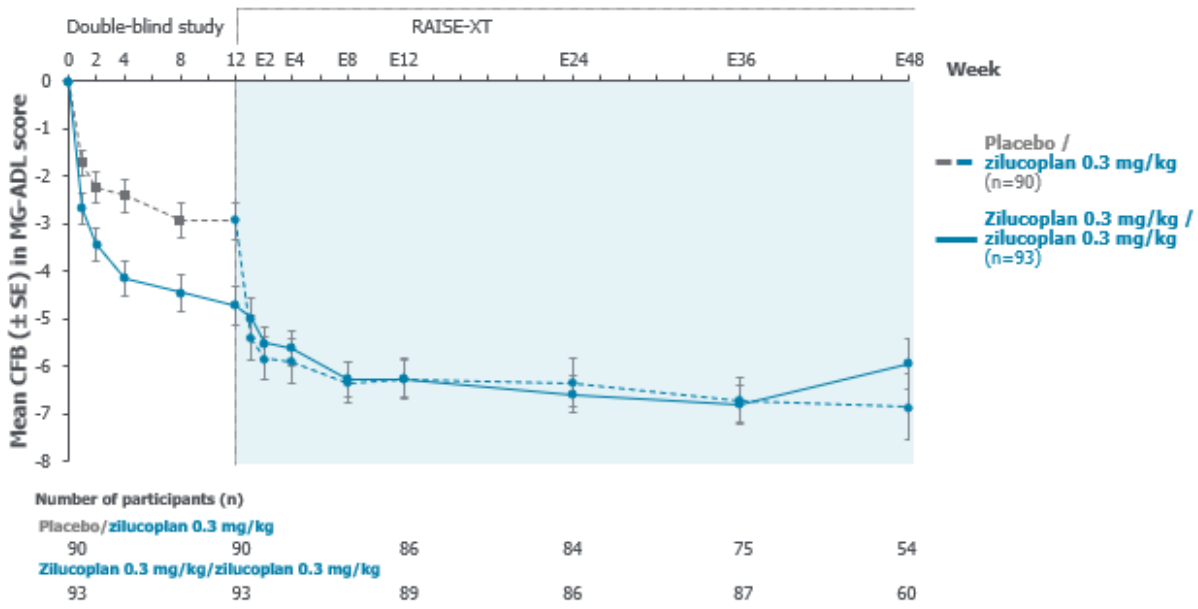
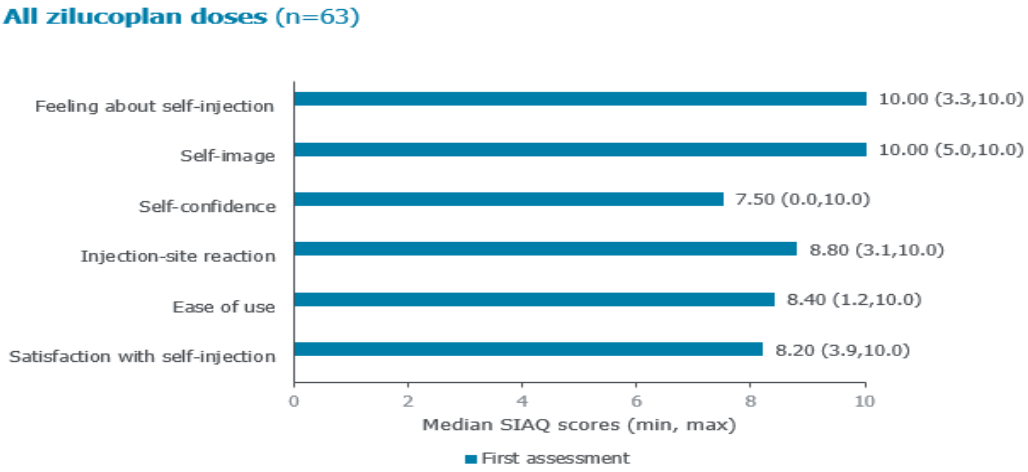


Figure 2: SIAQ reported outcomes

All zilucoplan doses, n=63.
For the domain of 'Satisfaction with self-injection', scores ≥8 are indicative of high or very high satisfaction.



#793- Interim Analysis of Evolve: Evaluating Eteplirsen, Golodirsen, or Casimersen Treatment in Patients <7 Years Old in Routine Clinical Practice

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Introduction: Clinical trial 4658-102 (NCT03218995) demonstrated the safety and tolerability of eteplirsen in 6–48-month-old patients with Duchenne muscular dystrophy (DMD).

Objective: Describe patients' (<84 months) experience with phosphorodiamidate morpholino oligomer (PMO) treatment (eteplirsen, golodirsen, or casimersen) in routine clinical practice from the ongoing phase 4, observational, EVOLVE study.

Methods: Patients were stratified by age at PMO initiation: <24, 24 to <48, and 48 to <84 months. The interim analysis included treatment patterns, safety, and functional assessments.

Results: As of December 2021, 32 patients <84 months were enrolled; eteplirsen-treated (n=30): mean (SD) age (years) at treatment initiation was 1.8 (0.05), 3.3 (0.42), and 5.7 (0.74), and mean (SD) duration (years) was 2.5 (1.45), 2.8 (1.66), and 4.6 (1.54) for the <24-, 24- to <48-, and 48- to <84-month-old groups, respectively. Steroid usage before eteplirsen initiation was 0/3, 1/7 (14.3%), and 12/20 (60.0%) for the 3 age groups. Three serious adverse events (SAEs) occurred in 2/30 (6.7%) eteplirsen-treated patients; none were deemed treatment related. Eteplirsen was well tolerated with no treatment-related discontinuations or interruptions. Two patients, 1 golodirsen-treated and 1 casimersen-treated, were enrolled (ages 6.4 and 6.2 years at PMO initiation, respectively; treatment duration was 0.7 years for each). Neither had prior steroid use nor reported SAEs.

Conclusion: These real-world data are consistent with the safety of previous clinical studies and further support early initiation of PMOs in young patients.

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Disclosures: SG, SS, IS, JK: Employees of Sarepta Therapeutics, Inc. **MAW:** Received research funding as site or study principal investigator from Sarepta Therapeutics, Inc., Novartis Gene Therapies, and Alcyone Therapeutics, Inc., and serves as consultant for Sarepta Therapeutics, Inc. **KM:** Received research support as site principal investigator from Sarepta Therapeutics, Inc., Italfarmaco, Retrotope, Reata, Catabasis, and Santhera Pharmaceuticals, and received research support from NIH (5 U54 NS053672, U24 NS-10718), CDC (U01 DD001248), and FARA. **FA:** Served on advisory boards for NS Pharma, PTC Therapeutics, Santhera Pharmaceuticals, Mallinckrodt, and Sarepta Therapeutics, Inc. **LMRP:** Served on advisory boards for NS Pharma, PTC Therapeutics, Santhera Pharmaceuticals, Mallinckrodt, and Sarepta Therapeutics, Inc., and received research support as principal investigator from Capricor, PTC Therapeutics, Catabasis, Fibrogen, Santhera Pharmaceuticals, and Sarepta Therapeutics, Inc. **RS:** Received research funding from Genentech, Sarepta Therapeutics, Inc., Novartis, Fibrogen, Capricor, argenx BVBA, and Biohaven. **CZ:** Received research support from Biogen and Novartis, served on advisory boards for Biogen, Optum, and Sarepta Therapeutics, Inc. **CM:** Serves as consultant for Astellas/Mitobridge, Bristol Myers Squibb, Capricor, Catabasis Pharmaceuticals, Edgewise Therapeutics, Eli Lilly, Epirium Bio (formerly Cardero Therapeutics), Gilead, Halo Therapeutics, Italfarmaco, Novartis, Pfizer, Prosensa, PTC Therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics, Inc., and receives research funding and speaking fees from Sarepta Therapeutics, Inc.

Prior Presentation: MDA Clinical and Scientific Conference, 2023; 28th International Annual Congress of the World Muscle Society, 2023

#795- Patient satisfaction following Phase I and Phase II/III primary mitochondrial myopathy trials

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Introduction: Primary mitochondrial myopathies (PMMs) are emerging as a major target for drug development. However, inherent challenges to trial design in this group of rare disease remain. Increasingly, patient preference concerning symptom management is used to inform trial design. Nevertheless, there is limited data for patient-reported experience during participation in PMM drug studies.

Objective: To explore patient satisfaction during Phase I and Phase II/III clinical trials in PMMs.

Methods: Data was collected from people with PMMs who had previously participated in Phase I and Phase II/III clinical trials at The National Hospital for Neurology and Neurosurgery, using a patient-administered survey with the Likert scale 0-10.

Results: Seventeen participants responded. Mean age was 55.9 years The main reason provided for joining a trial was to improve health outcomes in others The least important factor was receiving compensation for participating. The most burdensome factor was traveling to site while the least burdensome was too much contact with the study team
Seventy one per cent of participants considered questionnaires, and 65% thought assessments, were relevant to PMMs. Weekend visits were suggested to improve accessibility compared with home/remote visits.
Nineteen per cent of participants received information about publications and 22% had received information on whether they had the drug or placebo post-trial.

Conclusion: Improved accessibility could potentially enable a more diverse PMM population to participate in clinical trials. There is also an opportunity for assessments and questionnaires to be more relevant to participants with PMM. Nevertheless, overall satisfaction was rated high for trial visits.

#748- Safety and Tolerability of Phenylbutyrate in Inclusion Body Myositis

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Introduction: Phenylbutyrate (PBA) showed positive effect on the muscle cell model of Inclusion Body Myositis (IBM) by improving lysosomal activity, ameliorating consequences of impaired autophagy, and decreasing vacuolization. This provides rational to study this medication in patients with IBM.

Objectives: To evaluate the safety and tolerability of phenylbutyrate in IBM and monitor for any early signal of effectiveness.

Methods: Open-label study of 10 subjects with IBM who received treatment with PBA for 3 months after a 3 month run-in period. The PBA dose was 3 gm twice daily. The primary outcome measure was adverse event reporting. Secondary outcome measures included manual muscle testing, timed up and go test, IBM functional rating scale, and grip strength, along with exploratory biomarkers evaluating the mitochondrial function, stress response, degenerative process and apoptosis.

Results: Ten subjects completed the study. PBA was well tolerated with no serious adverse events related to it. The most common adverse events were GI related and did not require stopping treatment. One of the biomarkers (MitoTracker) showed a statistically significant drop over the treatment period of the study (p-value of 0.03 for the mean change). There were no statistically significant changes in other secondary outcome measures, but the study was limited by a small sample size and short treatment period.

Conclusions: Phenylbutyrate was safe and well tolerated in patients with IBM in this pilot study. The change in the MitoTracker suggests target engagement, but a Phase II study is needed to confirm and study the efficacy of PBA in IBM

#767- A systematic review and meta-analysis of the placebo effect in inclusion body myositis

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Introduction: Inclusion body myositis (IBM) is characterized by slowly progressive muscle weakness, making it challenging to detect clinically-meaningful changes in motor function in prospective interventional clinical trials. Furthermore, medical, psychological, and logistic factors may impact trial outcomes, and are grouped under the term "placebo effect".
Objectives: To quantify the change in motor function of IBM patients receiving placebo during prospective interventional clinical trials.

Methods: Systematic review and meta-analysis according to the PRISMA guidelines. A comprehensive search of several databases was performed to identify randomized placebo-controlled trials that reported motor outcome measures in the placebo group. Change from baseline was used for effect size, and was converted to standardized mean differences (SMD). DerSimonian-Laird continuous random effect model was used to combine SMD from the different studies. Meta-regression analysis was performed to detect change over time. Heterogeneity was evaluated using the I2 indicator.

Results: 10 eligible studies were identified with overall a low risk of bias. During the trial period, participants with IBM receiving placebo had a measurable decline in their motor function, with SMD of – 0.341 (95% CI: -0.624, -0.057; p=0.018). Heterogeneity was acceptable (I2= 36.9%, p=0.113). Meta-regression equation for change in SMD over time (measured in weeks) was: SMD = 0.179 – 0.015 x Follow-up time (p=*0.028*).

Conclusions: Patients with IBM displayed measurable decline in their motor function during clinical trials period. Meta-regression equation can help estimating decline in motor function over time.

#787- The effect of corticosteroid treatment on cardiac function in adults with Duchenne Muscular Dystrophy

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Introduction: Duchenne Muscular Dystrophy (DMD) is a progressive genetic disorder of skeletal muscles resulting in muscle degeneration, loss of ambulation in early adolescence and premature death due to cardiorespiratory complications. While the rate at which cardiomyopathy (CM) progresses in corticosteroid (CS) Naïve patients is understood, there is an ongoing debate regarding the extent of protection provided by CS.

Objectives: To evaluate the effect of continuing CS treatment on cardiac function in adults with DMD.

Methods: A retrospective case note review was conducted at the National Hospital in London, Queen Square. Data on cardiac function and age at start of cardioprotective medication was collected. Patients were stratified into 3 groups: CS Naïve (never had CS or CS treatment <12 months), CS stopped (CS >12 months but stopped prior to transition to adult services) and CS continued (CS continued into adulthood).

Results: Data were collected between February 2020 and July 2022. 149 patients were included (77 CS continued, 31 CS stopped, 41 CS Naïve). Mean age at the last assessment was 21.34 (±2.70) in CS continued, 22.34 (±4.10) in CS stopped and 24.40 (±4.82) in CS Naïve group. Age at CM onset (defined as Left Ventricular Ejection Fraction (LVEF) <45% or Left Ventricular Fraction Shortening (LVFS) <28%) was 12.77y (±3.79) in CS continued (N=25), 13.13y (±3.23) in CS stopped (N=16) and 14.34y (±2.59) in CS Naïve (N=18). All individuals were on variety of cardioprotective medications.

Conclusions: Longitudinal data of LVEF and LVFS and other statistical analyses are in progress and will be presented and results discussed.

#718- Effectiveness of conservative non-pharmacological interventions in people with muscular dystrophies (MD): a systematic review and meta-analysis

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Introduction: Muscular dystrophies (MD) are managed with conservative non-pharmacological interventions, but evidence of their effectiveness is limited.

Objective: To investigate the effectiveness of such interventions for MD physical management.

Methods: PRISMA guidelines were followed. MEDLINE, CINHAL, Embase, AMED and CENTRAL (inception to August 2022) were searched. Effect size (ES) and 95% confidence intervals quantified treatment effect.

Results: Of 31,285 identified articles, 39 studies (957 participants), mostly at high risk of bias, were included. For children with Duchenne muscular dystrophy (DMD), trunk-oriented strength exercises and usual care were more effective than usual care alone in improving distal upper-limb function, sitting and dynamic balance; physiotherapy plus aerobic treadmill training was more effective than physiotherapy plus-ergometer training for anterior-posterior stability; arm ergometer training was more effective than range-of-motion exercises for arm elevation movement quality. For adults with Facioscapulohumeral dystrophy (FSHD), Limb-girdle muscular dystrophy (LGMD) and Becker muscular dystrophy (BMD), strength-training improved dynamic balance and self-perceived physical condition. A multicomponent program improved gait in adults with Myotonic dystrophy type 1 (DM1). ESs varied from -1.26 to 2.29.

Conclusions: Strength-training, with or without other forms of exercise, may improve function and well-being in MD. Although evidence quality was low, strength-training should be considered in MD management, as it was found to be safe.

#735- Mycophenolate is better tolerated than azathioprine in myasthenia gravis

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Introduction: Azathioprine is generally considered the first-line steroid-sparing immunosuppressive agent for myasthenia gravis (MG). Mycophenolate and methotrexate are often reserved as second-line choices due to lack of randomised controlled trial evidence, despite widespread consensus on their efficacy.

Objectives: We aimed to gather real-world data on the side effects of steroid sparing agents, their use in United Kingdom (UK) clinical practice, and the reasons for discontinuation in the UK.

Methods: We performed a national survey of side effects and reasons for discontinuation of immunosuppressants in patient with MG in the UK. 235 patients who completed the survey; 166 had taken azathioprine, 102 mycophenolate, and 40 methotrexate.

Results: High proportions of patients reported side effects from their medications for MG; 90% of those on prednisolone, 79% pyridostigmine, 78% azathioprine, 62% methotrexate, and 60% mycophenolate. Side effects of treatments for MG led to admission to accident and emergency (n=7) or hospital (n=33) in 17% of patients. Azathioprine was discontinued by 66% of patients who started it (53% of these due to side effects), compared to only 19% mycophenolate (26%), and 32% methotrexate (25%). Azathioprine was significantly more likely to be discontinued than mycophenolate due to side effects ($p<0.0001$). There was no significant difference in treatment cessation due to lack of effect.

Conclusions: This real world data highlights the significant burden of treatment for MG. Mycophenolate appears to be better tolerated than azathioprine. Strategies to optimise azathioprine dosing such as azathioprine metabolite testing should be utilized to reduce the risk of treatment failure.

Stratification of NMD & Disease Burden

#740- Compound Muscle Action Potential Amplitude as a Biomarker of Myasthenia Gravis

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Introduction: Myasthenia gravis (MG) is an autoimmune disorder that results in failure of the neuromuscular junction (NMJ). Compound muscle action potential (CMAP) is an electrodiagnostic (EDX) test that measures muscle excitation after nerve stimulation, and reduced CMAP amplitude during repetitive nerve stimulation (RNS) is a standard diagnostic test for MG. Single fiber electromyography (SFEMG) is another EDX test that is more sensitive but less commonly used.

Objectives: To explore correlations between clinical severity, serological titers, and EDX profiles in MG.

Methods: A chart review of patients aged >18 years with an MG diagnosis to analyze acetylcholine antibody titer (AChR), EDX results (CMAP, RNS, SFEMG) of hand, trapezius, and facial muscles, and MG Foundation of America (MGFA) clinical severity.

Results: 18 male, 34 female (55 +/- 16 years, range: 20-81 years) were categorized into ocular-MGFA 1, mild generalized-MGFA 2, and moderate-severe generalized-MGFA 3-5 groups. CMAPs exhibited differences between MGFA groups, indicating smaller CMAPs with more severe MG (one-way ANOVA, $p<0.05$). RNS and SFEMG results were similar across groups. AChR titers were comparable between MGFA groups and negatively correlated with average RNS decrement (Spearman, $p<0.05$), but not with CMAP or SFEMG.

Conclusions: Correlation between MGFA and CMAP, but not other standard MG diagnostic tests (RNS, SFEMG), may suggest that functional impairment in MG may be driven by the accumulation of static rather than variable NMJ failure. AChR and RNS decrement showed a correlation, implying a relationship between AChR and variable NMJ failure. Prospective studies could investigate CMAP as a biomarker for MG.

#776- Burden of Myasthenia Gravis (MG) Based on Sentiment Analysis of Patients' Digital Conversations

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Introduction: MG is a rare, chronic autoantibody neuromuscular disease with profound patient burden. Data from digital conversations can highlight areas most concerning to patients.

Objectives: To describe sentiments towards MG and compare males vs females on the most frequent themes.

Methods: One year [8/2021–8/2022) of MG-focused public domain conversations from US internet protocol addresses were tagged based on self-identification in the conversations or public profiles. Advanced search techniques and artificial intelligence powered algorithms were used to extract and organize data by topics into an unstructured dataset. Sentiment analysis via natural language processing was used to classify conversations as positive, negative or neutral and analyzed to derive the most frequent drivers of sentiment.

Results: Of 13,234 conversations (from topical sites, message boards, social networks and blogs), the most frequent conversation topic categories were diagnosis (29%), living with MG (28%), symptoms, (24%) and treatment (19%). Of 3176 conversations on symptoms, eye problems (21%), facial muscle problems (18%), and fatigue (18%) featured most frequently. Most conversations (59%) were negative in tone and meaning, 39% were neutral and only 2% were positive. Negative conversations were dominated by themes of impact on life (29%), misdiagnosis problems (27%), treatment issues (24%), and symptom severity (20%). Males had more conversations with negative sentiment vs females while females seemed more pragmatic in their outlook on MG.

Conclusions: Digital conversations reveal a high degree of concern among patients with MG most specifically related to symptoms, life impact, misdiagnosis and MG treatments. Therapies providing better symptom control could positively affect many aspects of patient's lives.

#770- Remote Monitoring and Management of Myasthenia Gravis (REMOTE-MG): A Pilot Feasibility Study

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Introduction: Time while myasthenia gravis (MG) patients are symptomatic is critical due to inability to work, perform activities of daily living, or care for families. MG patients are often evaluated every 3 – 6 months. Physicians are blind to fluctuations in patient function between visits unless patients call to report changes. Given the national shortage of neurologists, more frequent follow-up is not feasible.

Objectives: Evaluate the feasibility and utility of measuring MG patient symptoms using a web-based or app-based MG monitoring system.

Methods: We designed a prototype remote monitoring tool in REDCap; the tool measures MG-ADL, MG-QOL15r, global visual analogue scale, patient acceptable symptom state, and presence/absence of side effects. Enrolled MG patients (target N=50) in the Northern New England Clinical and Translational Research Network (Vermont, Northern New York, and Maine) will remotely report MG symptoms weekly for 8 weeks. The primary outcome is >= 75% patient completion rate and >= 75% secure transfer of data to treating physicians. Change in treatment plan based on data is an exploratory outcome.

Results: 10 patients are currently enrolled. Preliminary study results and study design will be presented.

Discussion: Given the fluctuating nature of MG, prolonged periods of treatment adjustments, shortage of neuromuscular physicians, now is the time to revolutionize MG care and pivot to a care model adapted for the current times and technology. If this study is successful, a future protocol to act on remotely collected data will be designed with an ultimate goal of reducing time with symptoms for MG patients.

#771- Measuring Adverse Event Burden in Myasthenia Gravis: Retrospective Validation of the Adverse Event Unit (AEU) with MGTX Trial Data

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Introduction: The Adverse Event Unit (AEU) is a patient and physician weighted consensus unit that quantifies and compares adverse event (AE) burden among any group of medications in neurologic patients. A recent single-center, prospective, study demonstrated feasibility and preliminary validity of utilizing the AEU to measure AE burden in myasthenia gravis (MG).

Objectives: Evaluate feasibility of assigning AEU scores retrospectively from AE data recorded in the MGTX randomized trial of thymectomy in MG. Quantify differences in AE burden utilizing the AEU in MGTX trial participants treated with different dosages of prednisone.

Methods: Serious and non-serious AE were recorded at all MGTX visits. AEU scores were assigned by matching each MGTX AE to the best matched category in the AEU scale; death and MG worsening were not coded as side effects. AEU scores will be compared among participants receiving varied doses of prednisone and for participants receiving prednisone for different durations.

Results: The MGTX trial randomized 126 patients at 36 sites. All patients received prednisone; prednisone dosage was adjusted during the trial. Non-severe AE were reported at 747/2187 (34%) of study visits (Median AEU score 3 IQR 3-7). Severe AE were reported at 46 study visits (2%) (Median AEU score 7.5 IQR 7-12).

Discussion: This study demonstrates feasibility of assigning AEU scores retrospectively from clinical trial data. MGTX Median AEU scores are similar to UVM prospective study MG median AEU score (5 IQR 0-8). AEU scores in relation to prednisone dose and thymectomy status will be presented.

#727- Treatment Preferences of Patients with Myasthenia Gravis

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Introduction: The patient burden of MG is often underestimated. New MG treatments, such as biologics, may increase the proportion of patient symptom-free patients. However, these new treatments have potential side effects and associated costs. Understanding the treatment preferences of people with MG will help inform patients, clinicians, and policy makers.

Objectives: We aim to study how people with MG make decisions regarding new interventions--considering trade-offs between potential side effects and efficacy.

Methods: Fifteen patients with a wide range of MG severity participated in semi-structured interviews. Interviews were recorded and transcripts were analyzed using line-by-line open coding, to generate themes. We used these themes to identify treatment characteristics to develop a discrete choice experiment to study how people with MG make treatment decisions.

Results: Four themes were identified: MG symptoms and burdens, patient experience with treatment side effects, patient treatment preferences and patient treatment goals. Most patients preferred treatments in the form of pills (67%). The greatest reported treatment goals were returning to normal or zero symptoms (40%), discontinuation of prednisone (40%), and a preference to take less pills (33%). Double vision was the most bothersome symptom for 33% of patients and 33% reported weight gain as the most bothersome side effect.

Conclusion: We identified relevant characteristics for potential MG treatments. The attributes for the ongoing discrete choice experiment are: improvement in eye function, improvement in bulbar symptoms, improvements in arms/legs function, ability to reduce prednisone dose, risk of infections, administration mode, and out-of-pocket cost to estimate willingness to pay.

#779- Summated Compound Muscle Action Potential Amplitude as a Biomarker of Amyotrophic Lateral Sclerosis

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Introduction: With the evolving amyotrophic lateral sclerosis (ALS) therapeutic landscape, there is a growing need for diagnostic, prognostic, and treatment response biomarkers.

Objectives: The aim of this study was to explore summated compound muscle action potential amplitude (CMAP) as a candidate biomarker.

Methods: ALS patients (El Escorial definite and probable) were recruited at diagnosis. Bilateral median, ulnar, peroneal, and tibial nerves CMAPs were assessed as individual and summated values and compared with other clinical ALS assessments. A small healthy control cohort was included for CMAP comparison.

Results: Forty ALS patients (21 males, 19 females, mean age of 55.9 ± 12.8 years) and controls (3 males, 3 females, mean age of 33.2 ± 3.4 years) were enrolled. Mean duration (symptom onset to diagnosis) was 7.9 ± 5.2 months, and the ALS Functional Rating Scale-revised (ALSFRS-R) was 37 ± 7.6. Summated CMAP was significantly reduced (>40%) in ALS versus controls (36.2 ± 13.9 vs. 63.7 ± 11.2, $p < 0.0001$) and similarly all individual CMAPs were significantly reduced ($p < 0.05$) except for the left tibial motor ($p=0.14$). Summated CMAP correlated with ALSFRS-R, total manual muscle testing score, and disease duration ($r = 0.36$, $p = 0.023$; and $r = 0.32$, $p = 0.045$, and $r = -0.33$, $p = 0.039$, respectively).

Conclusions: Most individual CMAP responses were reduced indicating significant generalized lower motor neuron disease burden at time of diagnosis. Summated CMAP could be a potential biomarker of ALS, and future studies should investigate change longitudinally and with therapeutic interventions.

#783- Factors Influencing Genetic Testing Uptake in Amyotrophic Lateral Sclerosis (ALS) Patients

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Amyotrophic lateral sclerosis (ALS) is a debilitating neurodegenerative disease, and the role of genetic counseling and testing in ALS clinics remains underexplored. This study aimed to assess the value of incorporating genetic counseling and testing in a multidisciplinary ALS clinic and identify factors influencing the uptake of genetic testing.

A chart review was conducted to gather clinical and demographic data of ALS patients seen at MUSC between July 1, 2021, and July 1, 2023, who were offered genetic testing. Additionally, a survey was sent to 60 living patients to assess their decision to undergo genetic testing and rate the importance of various factors on a scale of 1 to 5.

Out of the 24 respondents (40% response rate), 17 patients (70.83%) underwent genetic testing, while 7 patients (29.17%) did not. Participants who underwent genetic testing consistently rated the influencing factors higher than those who did not. In Group 1, the most important factor was family risk assessment (median: 5), followed by clarity regarding the disease's origin and diagnosis confirmation. Similarly, in Group 2, family risk assessment ranked highest (median: 1), even among those who chose not to undergo genetic testing.

These findings emphasize the perceived significance of family risk assessment in decision-making related to genetic testing for ALS. The study underscores the potential value of integrating genetic counseling and testing into multidisciplinary ALS clinics, providing insights for healthcare professionals, genetic counselors, and researchers involved in ALS care.

Further analysis is ongoing, and this study contributes to our understanding of the factors influencing the decision to undergo genetic testing in ALS patients. The results hold implications for improving ALS diagnosis, treatment, and patient support by considering the factors that influence genetic testing uptake.

#761- Utility of genetic panels for neuromuscular disorders in a tertiary referral center neurology clinic in Central Pennsylvania

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Introduction: Genetic testing panels have become frequently utilized in the neurology clinic. Recent AANEM guidelines state these tests are essential to diagnosis of a neuromuscular disease. Despite the overall benefit in uncovering a genetic diagnosis, previous studies have shown a wide range in utility.

Objectives: Our aims are to determine our yield from genetic panel testing, uncover specific patient presentation patterns and diagnostic studies to aid in genetic testing.

Methods: Data will be collected from a single site, tertiary referral center in central Pennsylvania. Gene panel results from Invitae (San Francisco, California) and GeneDx (Gaithersburg, Maryland) of roughly 900 patients will be evaluated in correlation with demographic data, presentation, family history, and electrodiagnostic (EDX) studies.

Results: Preliminary data comprising results of 109 patients were categorized based on presenting symptoms as follows: myopathic 21.1%, neuropathic 24.8%, motor neuron disease 29.4%, upper motor neuron 2.8%, other 29.4% which is comprised of vague muscle weakness, muscle stiffness/cramps, small fiber neuropathy, dysautonomia, hyperCKemia, referral for genetic symptoms in asymptomatic patients. Of those presenting with neuropathic, myopathic, and motor neuron features with a positive gene panel result, 60%, 50%, and 100% respectively had a positive family history/electrodiagnostic study compared to uncertain results with 2%, 15%, and 12% for positive family history and 36%, 15%, and 88% for positive electrodiagnostics.

Conclusions: Preliminary data demonstrates a greater percentage of positive gene panel results with positive family history and EDX. This data collection will enable the development of an algorithmic approach for genetic testing based on phenotypic presentation, family history, and EDX studies.

#755- Relationships of Lower Leg Fat Fraction among antagonistic and synergistic muscles and a potential Fat Fraction threshold for functional performance in Myotonic Dystrophy Type 1

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Introduction: Quantitative Magnetic Resonance Imaging (qMRI) is an objective, sensitive tool for assessing fat fraction (FF) in patients with Myotonic Dystrophy Type 1 (DM1). However, no research has explored the correlation of FF in antagonistic and synergistic muscles and the impact of FF on functional tests.

Objective: To investigate the relationships of lower leg FF in antagonistic and synergistic muscles in DM1, the effect of FF on functional mobility, and if there is a threshold for FF to distinguish between functional performance.

Methods: Eighteen ambulatory, adult DM1 subjects (11 females) were tested. FF was determined via qMRI for six lower leg muscles from Dixon imaging using a 3T scanner, and mobility was assessed via various walking tests. Associations were identified via correlation coefficients. We also examined the performance in mobility based on FF to investigate whether a threshold could be defined to discriminate functional abilities.

Results: Strong correlations were found between FF in the antagonist ($r=0.77$) and synergist groups ($r=0.80$-0.89) of the lower leg. FF of the lower leg muscles also correlated with walking and mobility tests ($r=0.61$-0.90). Lower leg FF of 0.2 appeared to discriminate for functional mobility performance.

Conclusions: Strong relationships between lower leg muscle FF may be more indicative of the disease process affecting all lower leg muscles rather than selective involvement based upon muscular function. qMRI used to assess lower leg FF revealed that 0.2 appears to be a potential threshold for functional abilities in DM1 patients that should be explored further in future studies.

#821- USE OF GAS SCALE TO IDENTIFY RELEVANT CENTRAL NERVOUS SYSTEM DOMAINS IN MYOTONIC DYSTROPHY TYPE 1: DIAGNOSTIC AND OUTCOME MEASURE PROSPECTIVE FOR CLINICAL CARE AND TRIALS

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Introduction: Myotonic Dystrophy Type 1 (DM1) is a multisystem disorder, and central nervous system (CNS) dysfunction is one of its core and most heterogeneous clinical manifestations. Heterogeneity and multi-domain involvement make CNS functions assessment challenging, and – despite the progress made – current tests and scales neither can detect what is clinically relevant and matters to the patient nor can capture changes over time. The Goal Attainment Scale (GAS) is a validated scale centered on patient's goals, offering an opportunity to reflect clinically meaningful data which are individualized and potentially useful to derive a semi-quantitative patient-generated outcome.

Objectives: The aim of this study is to explore the use of a revised version of the GAS in DM1 as a potential patient-centered semi-quantitative outcome measure to engage patients, measure clinically meaningful changes and monitor patients perception of change over time.

Methods: Patients who underwent a full battery of validated patient-reported outcome measures (PROMs) in the last year were recruited. The GAS scale was revised and adapted for DM1.

Results: 73 adult patients (median age 45 [39 – 53], median MIRS 4 [4 – 4]) were recruited, 5 different SMART goals were identified: 1. cognitive impairment with executive dysfunction and lack of attention, 2. visuospatial deficits 3. social dysfunction, 4. personality abnormalities and 5. excessive daytime sleepiness (EDS) and fatigue. Data are under analysis.

Conclusions: Assessment, data collection and monitoring can be challenging when it comes to CNS in DM1: ongoing analysis will provide insight about GAS adequacy and consistency in this field.

#789- Natural history of pulmonary function in adult patients with Spinal Muscular Atrophy type 2 and 3

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Introduction: The respiratory natural history in adult patients with Spinal muscular atrophy (SMA), particularly relevant considering the availability of disease-modifying treatments, is currently undefined.

Objectives: To describe the annual progression of pulmonary function (forced vital capacity, FVC) and non-invasive ventilation (NIV) requirement across in adults with SMA type 2 and 3.

Methods: Retrospective observational natural history study of adult patients followed by five Italian centres and by one US centre of the International SMA Consortium (iSMAc).
Patients' anthropometrics, FVC absolute, FVC% pred., NIV requirement were collected.

Results: One hundred seventy-four patients were included. The median follow-up duration was 38.3 months. Seventy-four were SMA type 2, median (IQR) age was 25.9(19.2-35.3). One hundred were SMA type 3, median (IQR) age was 35.5(24.4-45.2).
SMA type 2 had a significantly lower FVC absolute (0.9 vs 3 L, $p<0.0001$), FVC% pred. (28 vs 87%, $p<0.0001$) and PCF (145 vs 361 l/min, $p<0.0001$) than SMA type 3 at first assessment. Respiratory function significantly differed across motor functional status groups within SMA type 2 and 3.
FVC% progressed annually by 0.10% and 0.48% in SMA type 2 and 3, respectively and did not differ according to motor functional groups suggesting stability.
Conversely, due to the different lung volumes at first assessment, the median age when FVC% pred. fell below 60%, 40% and 20% was significantly lower in SMA type 2 than type 3.

Conclusions: These novel results will serve as benchmark to assess the impact of disease-modifying treatments in the adult SMA population.

#803- Scoliosis progression in type II SMA at the time of treatment: a comparative study with untreated patients

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Introduction: Scoliosis is a significant complication in individuals with Type II Spinal Muscular Atrophy (SMA), affecting their quality of life. While pharmacological treatments have demonstrated efficacy in improving motor and respiratory function in type II SMA, there is limited information available regarding their impact on scoliosis.

Objective: The objective of this prospective study was to examine the impact of pharmacological treatment on scoliosis progression in Type II SMA patients and compare it to untreated individuals.

Methods: Treatment effect on Cobb's angle annual changes and on reaching a 50° Cobb angle was analysed in treated and untreated Type II SMA patients with a minimum 1.5-year follow-up. A sliding cut-off approach identified the optimal treatment subpopulation based on age, Cobb angle, and HFMSE at the initial visit.

Results: No significant difference was found in mean Cobb variation between untreated (n=46) and treated (n=39) groups (p=0.4). Optimal cut-off values for a better outcome were Cobb angle <26° and age <4.5 years. In this resampled population, the untreated group had a mean Cobb variation of 10.05 (SD 6.38) degrees/year, while the treated group had 5.61 (SD 4.72) degrees/year (p=0.01). Cox regression analysis indicated a protective treatment effect in reaching a 50° Cobb angle, significant in patients <4.5 years old (p=0.016).

Conclusions: This study highlights that pharmacological treatment, if initiated early, may slow down the progression of scoliosis in Type II SMA patients. Larger studies are warranted to further investigate the effectiveness of individual pharmacological treatment on scoliosis progression in this patient population.

#797- Assessment of Patient-Reported Physical Fatigue in Spinal Muscular Atrophy (SMA): Insights from a Pilot Study

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Introduction: Fatigue is a disabling symptom in SMA routinely assessed with multidimensional patient-reported outcome measures (PROMs). The current approach to perceived fatigue assessment eludes meaningful association with performance due to current multidimensional methods and disease confounders. Perceived fatigability, a whole-body measure of experienced physical fatigue, has not been studied in SMA.

Objective(s): Develop an SMA-specific PROM to measure perceived fatigability.

Methods: English-speaking individuals across three international SMA registries, ≥12 years with confirmed SMA, completed an anonymized self-survey. The scale included 108 items organized across 33 activity groupings. Experienced or imagined fatigue with current or previously performed activities were rated from 0=No Fatigue to 5=Extreme Fatigue. We identified items that ≥80% of participants reported minimal fatigue (score=0/1) for each functional group.

Results: One-hundred and eighteen participants with a mean age of 41.3 years (range 14-78; 48% male; 61% receiving disease-modifying therapy) completed the survey. Current functional status included sitters (45%), non-sitters (40%), and walkers (15%). Forty participants (33%) had achieved walking with or without support but were no longer able to at time of survey.
Minimal fatigue was reported in 2 items for non-sitters, 15 for sitters, and 19 for walkers. On average, participants rated their "usual energy" 6.2 out of 10 (range 0-9) during the past month, with no associations with age, function, or SMA type ($p>0.05$).

Conclusions: We developed a perceived fatigability scale, with activity intensity and duration anchors to measure experienced physical fatigue across SMA phenotypes. This may help to elucidate the impact of therapies on subjective patient well-being and function.

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#745 Relationship of autoantibody status in dermatomyositis patients to response to IVIG treatment. A post-hoc analysis of the ProDERM study

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Introduction: Dermatomyositis (DM) is an immune-mediated idiopathic inflammatory myopathy (IIM). Two subsets of autoantibodies have been identified in patients with IIM: myositis-specific antibodies (MSA, such as anti-Jo-1, anti-TIF-1 and anti-MDA-5) and myositis-associated antibodies (MAA, such as anti-PM-SCL, anti-Ku and anti-Ro). The ProDERM study recently demonstrated the efficacy and safety of intravenous immunoglobulin (IVIG) in 95 DM patients.

Objectives and Methods: In this post-hoc analysis of the randomized, placebo-controlled ProDERM study the autoantibody status at baseline and its relationship to treatment response to IVIG were investigated. Baseline serum samples were analyzed for MSA and MAA by the Oklahoma Medical Research Foundation. Treatment response was measured by TIS (Total Improvement Score).

Results: At baseline, 49 (52%) patients were MSA-positive, 13 (14%) MAA-positive, and in 33 (35%) no antibody was detected.
In the MSA group, 71% showed at least minimal TIS response (score ≥20) at week 16, compared to 55% in the "no-autoantibody-detected" group and 38% in the MAA+ group. TIS response was more common in the MSA+ group than the MAA+ group at Week 16 (p=0.03).
In the MSA+ group 24 patients were randomized to IVIG and of these 83% showed at least minimal TIS response (score ≥20) at week 16 compared to 60% of the MSA+ patients randomized to placebo.
More data on TIS response in patients with specific MSA autoantibodies (such as anti-TIF-1, antisynthetase or anti-Mi-2) will be presented at the meeting.

Conclusion: IVIG appears to be an effective agent for treatment of dermatomyositis, regardless of autoantibody status for the majority of autoantibodies. Further analyses will determine if specific MSA play a role in treatment response to IVIG.

#819- GETTING READY FOR TRIALS INVESTIGATING DYSFAGIA DIAGNOSTIC AND OUTCOME MEASURES IN MYOTONIC DYSTROPHY TYPE 1 (DM1): A SINGLE-CENTER RETROSPECTIVE LONGITUDINAL STUDY

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Introduction: Pneumonia is the main cause of death in DM1 and aspiration may play an important role. Yet dysphagia is a seldom complaint, is poorly studied in the initial stages of disease and consensus about assessment and management is scanty in this disease.

Objectives: The aim of our study was to assess swallowing function of patients with DM1 using a multimodal approach, focusing on the feasability and consistency of the tests and measures adopted.

Methods: Dysphagia was assessed in adult patients with DM1 with fiberoptic endoscopic evaluation (FEES) and validated questionnaires such as the symptom specific semi-quantitative scale Eating Assessment Tool 10 (EAT 10) and the qualitative survey SWAL-Qol.

Results: FEES showed that out of 113 patients (mean age: 49 years [42.50 – 57.50], mean disease duration: 16.76 years [9.56 – 23.72] ; mean MIRS: 4 [3 – 4]) 27 (24%) had a normal swallowing function (Dysphagia Outcome Severity Scale (DOSS): 6-7), 81 (72%) had mild-moderate impairment (DOSS: 3-5) and 5 (4.5%) had severe impairment (DOSS: 1-2). The EAT-10 score was ≥ 3, indicative of a swallowing involvement, in 65% of the patients, showing good association with the DOSS as the difficulty in swallowing increased. The SWAL-Qol showed a mild association with the DOSS and only for severe dysphagia.

Conclusion: Dysphagia had a high prevalence in our cohort and most of our patients showed mild-moderate swallowing impairment. According to the patient-reported questionnaires the awareness of the problem was scarce in the initial stages, and showed only mild association with the endoscopic scale scores with the worsening in the swallowing function, possibly leading to unexpected complications. A multi-modal approach is crucial to evaluate properly swallowing in DM1, and further effort needs to be addressed to patient-reported outcomes due to their potential clinical impact.

#816- Evaluation of ankle reflex and sural sensory nerve action potentials in a large patient cohort with cryptogenic peripheral polyneuropathy

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Introduction: Two common initial symptoms for peripheral neuropathy (PN) are a reduced Achilles tendon reflex (ATR) and a reduced sensory nerve action potential (SNAP) of the sural nerve. However, both can also be observed in otherwise healthy older or taller individuals.

Objectives: This study aims to investigate the prevalence of absent or reduced ATRs and SNAPs in a large patient cohort with cryptogenic sensory peripheral neuropathy (CSPN).

Methods: The records from 829 patients enrolled in the Peripheral Neuropathy Research Registry (PNRR) were evaluated and stratified into five subgroups for age (<50, 50-59, 60-69, 70-79, and ≥80 years) and height (<160, 160-169, 170-179, 180-184, and ≥185 cm) to search for correlations in regard to age, height, age at time of PN onset, PN duration, BMI and other factors that could influence PN-severity

Results: The likelihood of an absent ATR was associated with taller ($p=0.0002$) and older subjects ($p<0.0001$). ATR was found to associate with age at the time of symptom onset ($p<0.0001$), time since PN-symptom onset ($p<0.0001$), and height ($p<0.0001$). Sural SNAP was found to be consistently absent in taller ($p<0.0001$) and older subjects ($p<0.0001$), and was associated with age at time of symptom onset ($p<0.0001$), time elapsed since PN-symptom onset ($p<0.0001$), height ($p<0.0001$), and BMI ($p<0.0001$).

Conclusions: Age and height both contributed to likelihood of a reduced/absent ATR and sural SNAP. In addition, the time since onset of neuropathy as well as age at the time of onset also increased the likelihood of absent or reduced ATRs and sural SNAPs.

#774- Development of a Novel, Disease-Specific, Patient-Reported Outcome Measure; the Myotonic Dystrophy Type 2 Health Index (MD2HI)

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Introduction: There is a need for reliable, sensitive, disease-specific, patient-reported outcome measures capable of detecting clinically relevant changes in myotonic dystrophy type 2 (DM2) disease progression, as well as therapeutic gain over time.

Objectives: To develop and validate the Myotonic Dystrophy Type 2 Health Index (MD2HI) for use in DM2 therapeutic trials and clinical monitoring.

Methods: We conducted semi-structured qualitative interviews and a cross-sectional study with DM2 patients to determine the most common and impactful symptoms. We selected questions for the first version of the MD2HI based on their relevance, as determined by the cross-sectional study results. We used factor analysis to generate instrument subscales, which measure granular areas of symptomatic health. We performed beta testing to optimize the instrument usability and clarity resulting in the second version of the MD2HI.

Results: Fifteen individuals with DM2 participated in qualitative interviews and 74 participants completed the cross-sectional study. Additional individuals with DM2 participated in beta testing and reported that the instrument was straight forward and easy to use. Following beta interviews, modifications were implemented based on participant feedback, resulting in a more efficient version of the MD2HI.

Conclusions: The development and validation of the updated MD2HI provides researchers and clinicians with a valid, reliable, and efficient tool to measure relevant changes in DM2 disease burden over time or in response to therapeutic intervention.

#769- Motor Outcomes to Validate Evaluations in Facioscapulohumeral muscular dystrophy (MOVE FSHD): Preliminary Baseline Characteristics

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The MOVE FSHD study aims to determine the predictive value of clinical and motor assessments, patient-reported outcomes, imaging, and tissue biomarkers on disease progression in FSHD. This comprehensive study is important not only for improving patient care, but to understand what kind of change would be meaningful for clinical trials. Study will evaluate 450 FSHD participants over three years with 200 participating in a MRI and muscle biopsy sub-study to validate FSHD evaluations. Annual visits collect FSHD history, physical examination, patient reported outcomes, strength, timed functional tasks, and respiratory parameters. Sub-study participants will have additional biomarkers collected, including reachable workspace at every visit, whole body MRI at Baseline and 12-Month visits, muscle biopsy at Baseline and at 4-months (n=40). The MOVE FSHD study has over 240 participants who have completed their Baseline visit, more than 140 have returned for annual follow-up visits and sites have also begun enrolling MOVE+ sub-study participants. Our cohort is predominantly non-Hispanic white with 58% being male, 88% FSHD Type 1, and 92% are ambulatory. We currently have 12 individuals enrolled under the age of 18. Lastly, more than 50 of our previous 161 US participants from the ReSolve FSHD study have enrolled in the MOVE study with the remainder expected to roll-over within the next 1-2 years. MOVE FSHD addresses barriers to clinical trials by validating motor, clinical, and patient reported outcomes, as well as potential biomarkers. The data from MOVE FSHD can also improve our understanding of FSHD and directly impact patient care.

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Reference: Statland JM, Tawil R. Facioscapulohumeral Muscular Dystrophy. Continuum (Minneap Minn). 2016;22(6, Muscle and Neuromuscular Junction Disorders):1916-31. Epub 2016/12/07. doi: 10.1212/CON.0000000000000399. PubMed PMID: 27922500; PMCID: PMC5898965.

#820- Examining Recovery from Maximal Exercise Testing in Patients with Neuromuscular Disease

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Introduction: Patients with neuromuscular diseases (NMD) have decreased physical activity increasing the risk of cardiovascular and pulmonary disease. Assessing cardiorespiratory fitness via cardiopulmonary exercise testing (CPET) is an important factor in determining exercise and functional capacity. Evaluating recovery kinematics can provide insight into disease mechanisms and recovery from activity.
Objectives: The objective of the study is to evaluate recovery metrics in NMD compared to controls.

Methods: This is a prospective study in individuals with NMD and controls. CPET was performed using a Cosmed K5 metabolic system and a wheelchair-accessible Keiser M7i total body trainer. Recovery was defined as the period when workload ended until participants returned to within 10% of resting heart rate and oxygen consumption. Analysis on recovery metrics was performed at the time of 50% peak oxygen after peakVO2 (T1/2) over a duration of 3 minutes.

Results: Forty-nine participants were included: 15 controls and 34 NMD. The 34 participants with NMD were recruited from the Stanford Neuroscience Health Center. No significant demographic differences were found between groups. Peak exercise variables showed significant differences between groups, with controls demonstrating higher values. NMD had longer recovery times for oxygen, lower overshoot values for respiratory exchange ratio and ventilation/VO2.

Conclusion: NMD demonstrates different recovery metrics post CPET compared to controls. Results indicate impairments in recovery in patients with NMD, demonstrating limitations in exercise capacity and recovery. Understanding differences in recovery can optimize exercise prescriptions, improve prognostication, and diagnostic methods for patients with NMD.

#791- Improving diagnostic rates for mitochondrial diseases using enhanced WGS analysis and RNA-seq

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Introduction: Despite recent improvements in genomic technologies and increased use of whole genome sequencing, many patients with suspected mitochondrial myopathies (MMs) remain without a diagnosis, precluding access to precision care.

Objectives: We sought to boost diagnostic rates by combining bespoke bioinformatic analysis, based on deep phenotyping and RNA sequencing for a subset of cases.

Method: After an initial semiautomated analysis of WGS data all undiagnosed cases were reviewed by a clinician to guide bespoke analysis and RNA-sequencing was undertaken in cases with tissue samples (muscle or fibroblasts) available, with analysis including manual inspection of Sashimi plots and DROP pipeline analysis.

Results: We included 102 WGS cases and 55 RNA-Seq analyses. By enhancing analysis and including RNA-Seq we were able to boost diagnostic rates from 16.6% to 39.2%. Analysis of new diagnoses shows a high proportion are not in mitochondrial genes, despite patients having respiratory chain enzyme and histological results supportive of an MM. Mitochondrial genes, and those MM mimic genes are best expressed in muscle and fibroblasts but not blood. The study has led to the identification of novel genetic causes of non-mitochondrial myopathy and neuropathy.

Conclusions: MM presentations are non-specific and even biochemical abnormalities and pathological changes e.g., COX negative fibres and ragged red fibres, can be secondary to non-mitochondrial disease. The overlap with a broad range of alternative diagnoses means one size does not fit all for these patients, and greater emphasis needs to be put on a clinician-led bespoke analysis of data, supplemented with RNA-Seq where possible.

#747- Introducing routine diagnostic Whole Genome Sequencing into the clinic

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Introduction: Recruitment to the 100,000 Genomes Project (100KGP) was completed in December 2018. This project has provided thousands of families with a genetic diagnosis, allowing development in all areas of genomic medicine. Since April 2022, whole genome sequencing (WGS) has been introduced as a diagnostic test in the UK National Health Service (NHS) for certain disease groups including Charcot-Marie-Tooth disease (CMT). However, in order to effectively use WGS, clinicians must overcome certain challenges in the clinical setting.

Objectives: To asses the introduction of routine WGS for inherited neuropathy panel testing in our peripheral nerve clinics with special reference to clinician understanding and patient consent.

Methods: We describe our experience of introducing routine diagnostic WGS into our Peripheral Neuropathy Clinics since April 2022.

Results: All clinicians (including six consultants) needed updated training in consent for WGS. This was achieved by online information being made available by the NHS diagnostic laboratory, by a virtual training seminar and through face-to-face training by a dedicated inherited neuropathy specialist nurse. All 6 consultants are now trained and comfortable obtaining consent for WGS. We have requested 88 WGS tests including 68 singleton, one duo and 19 trio. One patient declined testing and two patients agreed to WGS but declined participation in research.

Conclusion: Utilising WGS requires expert training for clinicians, particularly in the consent process with regards unexpected findings. Dedicated time in clinic is needed to achieve this and hence a specialist nurse or equivalent is essential for delivering this service safely and effectively.

#784- GENETIC AND EPIDEMIOLOGY CHARACTERIZATION OF A LARGE COHORT OF PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS: TEN YEARS OF EXPERIENCE IN A DEDICATED NEUROMUSCOLAR CLINIC IN ITALY (The NEMO Clinical Center)

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Introduction : The extensive genetic and clinical characterization of patients with Amyotrophic lateral sclerosis (ALS) in the era of upcoming targeted trials is mandatory, due to the intrinsic etherogeneity of the disorder .

Objectives: to depict the genetic and epidemiologic characteristics of a cohort of ALS patients regularly followed at one single italian neuromuscular center in the last 10 years.

Methods: 1729 ALS patients were screened for SOD1, FUS, TDP43, C9ORF72 genes.

Results: mutations were found in 188/1729 (10.8%), 61.5% fALS patients and in 9,5% sALS cases. Out of 188 mutated patients, 37 (19.6%) were SOD1, 111 (59%) C9orf72 and 26 (13.8%) TDP43 mutated. Among the 14 (7.4%) FUS mutated patients 3 had a juvenile onset ALS while 11 adult onset ALS. The mean age of symptoms onset and median tracheostomy free survival time were respectively 53.72 years+8.75 and 125.87 months among SOD1 mutated patiens; 57.1y+8.7 and 42.2m among C9Orf72; 55.1y+11.84 and 54.5m among TDP43; 18.5y+10.4 and 45.6m among juvenile FUS and 54.3y+10.44 and 57.5m (8.3-90.4) among adult onset FUS. 63 mutated ALS patient are still alive and regularly followed up: 19 SOD1, 33 C9Orf72, 3 FUS, 8 TDP43.

Conclusions: Our data confirm the high incidence of the four most common gene mutations with the prevalence of C90rf72 expansions. The clinico-genetic correlation is fundamental in order todefine disease trajectory and better finalized tailored therapeutic intervention. Thus, we are developing a predictive model to combine genetic outputs and extensive clinical evaluations in order to implement the knoweldge on ALS natural history.

#785- Magnetic resonance imaging and spectroscopy biomarkers for primary mitochondrial myopathies: preliminary results of a longitudinal study

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Introduction: Primary mitochondrial myopathies (PMM) are genetic disorders with defects of the oxidative phosphorylation affecting predominantly the skeletal muscles. Currently, there are no disease modifying therapies for PMM. One major difficulty to clinical trials in PMM is the lack of reliable and reproducible biomarker that can catch the disease severity and progression.

Objectives: This is the first study aiming to examine the validity of MRI quantified muscle volume, fat fraction, and 31 phosphorous magnetic resonance spectroscopy (31P-MRS) of thigh muscles before, during, and after exercise as outcome measures with a direct correlation of clinical and functional measures used in PMM.

Methods: This is a prospective observational cohort study of patients with genetically confirmed PMM. Age and sex-matched healthy subjects (HS) are also recruited. Assessments are done at baseline and 12 months. Correlations between MRI outcomes and clinically relevant outcome measures are performed.

Results: Only baseline results are reported. Twenty adults with PMM (10 m.3243A>G and 10 single deletion of mitochondrial DNA) were recruited, 6 females and 5 males in each group, mean ages of 51.2±9.3 and 48.2±14.4 years, respectively. They were matched with 10 HS, with mean age of 47.9±14.3 years. All patients had fatigue. A direct correlation between age and fat fraction in thigh muscles in PMM patients was present. Muscle strength was reduced in those with increased fat fraction. The vastus lateralis 31P-MRS showed a more profound normalised phosphocreatine signal reduction during knee extension exercise, and a slower recovery time compared to HC.

Conclusions: MRI and 31P-MRS might be valuable biomarkers in clinical trials.

#775- The Inclusion Body Myositis Health-Index (IBM-HI): Development of a Novel, Disease Specific Patient-Reported Outcome Measure for IBM in Clinical Trials

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Introduction: This study outlines the development and validation of a new, multifactorial patient-reported outcome (PRO) tool called the Inclusion Body Myositis-Health Index (IBM-HI).

Objective: To create a fully validated, disease-specific PRO for IBM that is capable of detecting clinically relevant changes in disease burden over time and satisfying FDA criteria for use in therapeutic trials and labeling claims.

Methods: We conducted qualitative interviews with individuals with IBM to identify potential symptoms of importance and used a cross-sectional study to determine the prevalence and impact of these symptoms. We selected symptom questions for IBM-HI based on their frequency and importance to study sample as well as their potential to respond to therapeutic intervention. Using factor analysis, we grouped questions into subscales. We performed beta testing, test-retest reliability assessments, and known groups analysis to optimize the clarity, usability, meaningfulness, responsiveness, reliability, and differential ability of the IBM-HI.

Results: Ten individuals with IBM participated in initial interviews; 569 participants completed the cross-sectional study and known group's analysis; 15 participants completed beta testing; and 20 participants completed reliability evaluations. The Final IBM-HI measures a patient's perception of their multifactorial disease burden using 13 subscales. Average time of completion of IBM-HI was 11 minutes and reported that it was easy to complete. Validation testing showed the IBM-HI to be relevant, understandable, and reliable. IBM-HI total and subscale scores effectively distinguished between individuals with differing levels of disease severity.

Conclusions: IBM-HI is a fully validated PRO, ready for use in IBM clinical trials and patient monitoring.

#807- Investigation into the Long-Term Prognosis of Patients with Sporadic Inclusion Body Myositis

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Information and Objectives: Sporadic inclusion body myositis (IBM) is the most common inflammatory myopathy in individuals over the age of 50. IBM is slowly progressive and leads to pronounced weakness in finger flexors, knee and ankle extensors, impairing the patient's abilities to perform activities of daily living in advanced stages. Often, patients initially seek care with a myositis specialist, but are lost to follow-up when ambulation becomes difficult, limiting our knowledge on late-stage IBM.

Methods: Patients enrolled in the Johns Hopkins Myositis Research Registry between 2003-2018 with a confirmed diagnosis of IBM were contacted via phone and invited to participate in a 40-minute phone interview conducted via standardized questionnaire. The questionnaire assessed the presence of other autoimmune conditions, the severity of common IBM symptoms, exercise habits, past hospitalizations and current living arrangements and contained validated scales such as the IBMFRS, PGIS and PGIC.

Results: A total of 103 interviews were conducted with IBM patients. The mean age of the cohort was 72 years, ranging from 48 to 87 years. The mean time elapsed since onset of symptoms was 15.5 years, ranging from 3 to 35 years, and two thirds (67%) of the interviewed patients were male, and 85% were white, and about 10% African American.

Conclusions: Data analysis for this project has just started and will be conducted over this summer in an attempt to identify factors that will predict long-term prognosis in IBM.

#777- Rasch Analysis of the Patient-Reported Outcomes Measurement Information System (PROMIS) Parent Proxy (PP) Upper Extremity (UE) Item Bank Administered to Caregivers of Patients With Duchenne Muscular Dystrophy at Nationwide Children's Hospital

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Introduction: There is growing emphasis on health-related quality of life (HRQoL) as an important outcome in rare diseases. Central to assessing HRQoL are patient-reported outcome (PRO) measures that evaluate aspects of the disease and treatment meaningful to patients. The "patient voice" has been challenging to incorporate in practice because generic PROs frequently fail to reliably quantify changes important to individuals with rare diseases.

Objective: To describe the process for evaluating utility of PROs in a rare disease and identify modifications that improve the responsiveness of the instrument in the target population. We explored psychometric properties of the generic PROMIS PP UE v1.0 (29 items) through Rasch analysis for suitability of use in DMD.

Methods: Caregivers of patients with DMD ≥8 years of age at Nationwide Children's completed PROMIS PP UE (N=206). Rasch analysis assessed the internal functioning of items and scores. Statistics yielded from this analysis provided detailed measurement and diagnostic information to identify problematic items and improve the scale's performance.

Results: The final Rasch model included 21 items, with response options regrouped when necessary. Customized PROMIS PP UE satisfied all Rasch model assumptions, with a nonsignificant item-trait interaction (P=0.095). The scale's power to discriminate among respondents with different levels of UE function was very satisfactory (Person Separation Index = 0.947). This process could be used by other researchers to improve the sensitivity of PROs for their field of interest.

Conclusion: This is the first study that assessed psychometric properties of PROMIS PP UE in DMD.

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Disclosures: IA, SP: Employees of Sarepta Therapeutics, Inc., and may hold stock/options in the company. **CL:** Independent biostatistician who received funding from Sarepta Therapeutics, Inc., to help with the analysis. **TC:** Employee of F. Hoffmann-La Roche Ltd. **LA, NR, MI, LL:** Employees of the Nationwide Children's Hospital and have provided the data for this study. Nationwide Children's Hospital receives grant funding for other research initiatives from Sarepta Therapeutics, Inc.

#778 Comparison of Functional Ability Between 4–7 Years of Age (YOA) Children With Duchenne Muscular Dystrophy (DMD) to that of Typically Developing Age-Matched Children Using the Patient-Reported Outcomes Measurement Information System (PROMIS) Parent Proxy (PP) Mobility and Upper Extremity (UE) Questionnaires

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Introduction: DMD is a rare, progressive neuromuscular disorder characterized by diminishing functional ability. PROMIS are generic patient-reported outcomes quantifying the impact of disease on physical, social, or cognitive function. PROMIS PP Mobility and UE questionnaires are administered in DMD studies. Comparison with typically developing children allows for a comprehensive view of disease severity and exploration of scale responsiveness in a population of interest.

Objective: To compare PROMIS PP Mobility and UE questionnaires administered to boys with DMD versus typically developing children, both 4–7 YOA.

Methods: Nationwide Children's recruited caregivers of DMD and typically developing children (both 4–7 YOA) to complete PROMIS PP Mobility (v1.0) (n=73, n=182, respectively) and UE (v1.0) (n=73, n=176, respectively) questionnaires. Total raw and T-scores were calculated.

Results: Boys with DMD scored numerically lower than typically developing age-matched peers. The difference in scores between boys with DMD and typically developing children became greater at older ages. Specifically, the ability to perform functions such as "walk more than one block," "walk upstairs without holding on," "carry books in backpack," "open rings in a school binder," "take a bath," and "pour drink from full pitcher" became increasingly harder to complete for DMD boys.

Conclusion: From early childhood, boys with DMD perform worse than typically developing peers in terms of physical abilities. Pattern of differences indicates deterioration in lower and upper body function, consistent with DMD disease, which demonstrates that PROMIS PP Mobility and UE questionnaires can capture change in physical function in DMD boys 4–7 YOA.

Sponsorship: The publication was funded by Sarepta Therapeutics, Inc.

Disclosures: SP, IA: Employees of Sarepta Therapeutics, Inc., and may hold stock/options in the company. **CL:** Independent biostatistician who received funding from Sarepta Therapeutics, Inc., to help with the analysis. **TC:** Employee of F. Hoffmann-La Roche Ltd. **LA, NR, MI, LL:** Employees of the Nationwide Children's Hospital and have provided the data for this study. Nationwide Children's Hospital receives grant funding for other research initiatives from Sarepta Therapeutics, Inc.

#788- Pre- and post-natal outcomes in congenital and childhood onset DM1 - the impact of parental diagnostic delay

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Introduction: Myotonic dystrophy type 1 (DM1) is often diagnosed during pregnancy in women or after the development of symptoms in one parent. This reflects in missed prenatal diagnosis. However, the impact of the parental diagnostic delay on the prognosis of their children is not established.

Objectives: To describe the perinatal characteristics and the developmental outcomes of patients with congenital (CDM) and childhood (ChDM) DM1 in relation to the timing of diagnosis of the affected parent.

Methods: Retrospective study of patients with CDM and ChDM followed by 13 Italian centres. Children's disease type and parental timing of diagnosis were recorded. CTG expansions were classified as E1=<500,E2=500–1.000,E3=1.000–1.500,E4>1.500.Perinatal features, motor and cognitive development were collected.

Results: Seventy-one children were included, 41CDM, mean(±SD)age 12.0±5.1y, 30ChDM mean age 12.7±4.8y. All CDM had maternal inheritance. Only 6/41 were tested antenatally given the known maternal diagnosis; 2/41 children born to known affected mothers were only diagnosed at birth.
Perinatal information was available for 21 children;4 were born preterm, 15/21 required NICU>48 hours, 16/19 had ambulation and 14/18 speech delay. 2/21 had normal QI.
Of the 30 ChDM, 17 had paternal inheritance. 6/30 were diagnosed in-utero given the known parental diagnosis. Perinatal information was available in 19 children. All were born at term, one required NICU. 1/19 had ambulation and 4/19 speech delay. Only 7/13 had normal QI.

Conclusions: Diagnostic delay in DM1 is well-described but when this occurs in child-bearing age the impact on the pre- and perinatal outcome of the affected children is high.

#673- MR Neurography and Quantitative Muscle MRI of Parsonage Turner Syndrome Involving the Long Thoracic Nerve

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Introduction: Parsonage-Turner Syndrome (PTS) is characterized by severe, acute upper extremity pain and subsequent paresis and most commonly involves the long thoracic nerve (LTN). MR neurography (MRN) can detect LTN hourglass-like constrictions (HGCs) and quantitative muscle MRI (qMRI) can quantify serratus anterior muscle (SAM) neurogenic changes.

Objective: 1) To characterize MRN/qMRI findings in LTN-involved PTS. 2) To investigate associations between qMRI biomarkers and EMG motor unit recruitment (MUR) levels.

Methods: We retrospectively investigated 30 PTS subjects (25M/5F, mean/range age=39/15-67 years) with scapular winging who underwent 3.0 Tesla bilateral chest wall qMRI and unilateral brachial plexus MRN. EMG was performed on average 185 days from symptom onset (all ≥two weeks from symptom onset) and 5 days preceding MRI.

Results: The LTN was identified on MRN in 23/30 patients and HGCs were seen in 91% of cases (21/23). All 30 subjects had diffuse SAM edema on the affected side compatible with active denervation. Additionally, qMRI was significantly different to the contralateral, uninvolved side: increased T2 ($p<0.001$) and fat fraction ($p=0.013$), and decreased muscle diameter ($p=0.003$) and cross-sectional area ($p<0.001$). There were no significant associations between individual qMRI biomarkers and EMG MUR levels.

Conclusion: MRN can confirm PTS by identifying HGCs in most cases of LTN involvement. qMRI provides an objective measure of SAM changes. Lack of association between qMRI and EMG MUR levels for the SAM, as has been previously reported for other denervated muscles, could be related to MRI breathing artifacts and EMG sampling error. Further investigation and analysis are warranted.

#733-Not just liver enzymes: Transaminitis as a marker of Immune Mediated Necrotizing Myopathy

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Introduction: Immune mediated necrotizing myopathy (IMNM) is an autoimmune disease affecting skeletal muscles resulting in elevated markers of muscle injury including CK, AST and ALT. For patients who present with transaminitis, IMNM diagnosis can be delayed by extensive evaluation for liver pathology.

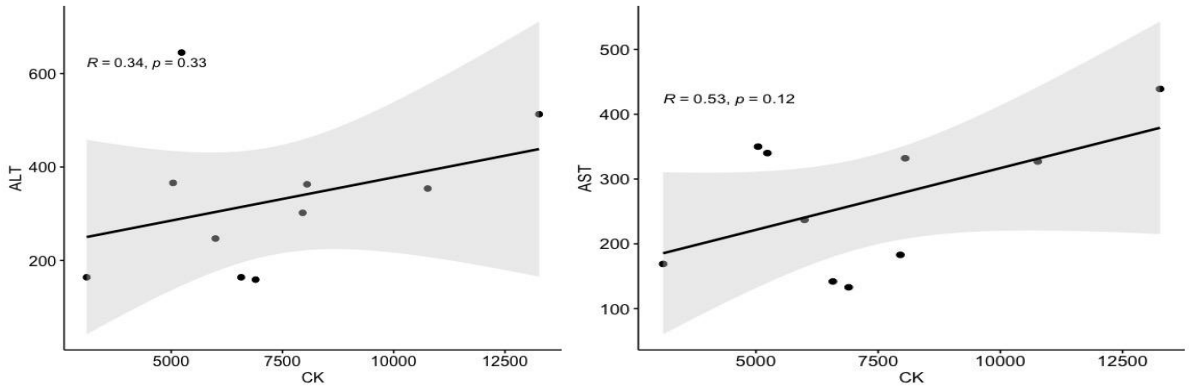
Objectives: Investigate levels of AST and ALT and their correlation with CK in IMNM.

Methods: A retrospective review of patients evaluated at UNC with a new diagnosis of IMNM was completed. Values for CK, AST and ALT at the time of diagnosis were extracted. Group mean and standard deviations were calculated and Pearson correlations were calculated between CK and transaminase levels.

Results: 10 patients were identified (4 female). Mean age at time of diagnosis was 68.7 years (SD 10 y). All patients had elevated CK (mean 7288 U/L, SD 2943 U/L), AST and ALT levels (AST mean 265 U/L, SD 105 U/L; ALT mean 327 U/L, SD 159 U/L) at initial presentation. There was a positive correlation trend between CK and AST (r 0.53, p=0.12) and ALT (r 0.34, p=0.33) (Figure 1). AST/ALT ratio was 0.8.

Conclusions: We demonstrated that transaminases in patients with initial diagnosis of IMNM can be elevated more than 5 times the upper limit of normal and show higher levels of ALT compared to AST; both parameters typically considered to be markers of primary liver disease. These findings can potentially impact existing protocols for evaluation of patients with elevated transaminases and expedite diagnosis for patients with IMNM.

Figure 1:



Pearson correlations between CK and AS and ALT levels in patient with IMNM.

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Mechanism of Disease and Less Common Disease Presentations

#810- Nematodes deficient in TANGO2 homologs exhibit strong neuromuscular phenotype suggestive of bioenergetic dysfunction

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Introduction: Rhabdomyolysis occurs through a convergent pathway involving sarcolemmal calcium influx and protease activation; however, how defects in several rhabdomyolysis-associated genes upstream of this pathway cause myocyte dysfunction remains unknown. TANGO2-deficiency disorder (TDD) is a poorly-understood autosomal recessive condition associated with a multitude of symptoms including rhabdomyolysis in the setting of metabolic crisis. Adult patients with TDD have been recently reported to have substantial limb-girdle weakness.

Objectives: Our overall aim is to elucidate the function of TANGO2 protein using *C. elegans* as a model system. In this study, we characterized the phenotype of nematodes deficient in hrg-9 and hrg-10, two homologs of TANGO2.

Methods: Double knockout worms (*hrg-9*$^{-/-}$*/hrg-10*$^{-/-}$) were generated using CRISPR-Cas9 genome editing techniques. We assessed 1) exercise tolerance by counting the number of swimming worms after 20 minutes in an isotonic buffer solution; 2) brood size, and 3) intestinal fluorescence following exposure to a fluorescent substrate, as a proxy for eating behavior.

Results: *hrg-9*$^{-/-}$*/hrg-10*$^{-/-}$ worms exhibited markedly reduced exercise tolerance (X^2=22.53; p<0.0001) and brood size ($\bar{x}$=112+/-28.2) compared to wildtype controls (40.8+/-20.9; t=6.0; p<0.0001). They also exhibited lower intestinal fluorescent intensity (t=2.8; p=0.0067) suggestive of reduced ingestion.

Conclusions: Nematodes deficient in TANGO2 homologs exhibit a strong phenotype reminiscent of other *C. elegans* strains with known bioenergetic dysfunction. These findings are in line with other work implicating TANGO2 as a potential regulator of lipid homeostasis and mitochondrial beta-oxidation and support additional studies focused on the localization and function of TANGO2 homologs in *C. elegans* body wall muscle.

#766- Amyotrophic Lateral Sclerosis and Spinocerebellar Ataxia Type 2: A Familial Case Report

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Spinocerebellar Ataxia Type-2 (SCA2) and Amyotrophic Lateral Sclerosis (ALS) are genetically linked through a trinucleotide (CAG) repeat expansion in the ATXN2 gene. The length of CAG repeat expansion in the ATXN2 gene is directly related to age of onset and severity of SCA2. There is also evidence to suggest that CAG repeat length correlates with expected phenotype (ALS vs. SCA2). There are few reports demonstrating intrafamilial phenotypic variability of ATXN2 mutations. Here we report a family with separate and distinct phenotypes via repeat expansions in ATXN2, whose presentations do not align with their expected phenotypes based on CAG repeat size. A patient, diagnosed with ALS at 36-year-old, exhibited painless bilateral arm weakness, dysarthria, and progressive motor impairment leading to quadriplegia and respiratory failure. Her brother was diagnosed with SCA2 at 16-year-old, presenting with falls, dysarthria, and ataxic features. The family history included olivopontocerebellar degeneration, suspected SCA, and possible ALS.

This case documents a patient who was diagnosed with ALS without manifested signs of SCA2 despite having full CAG repeat expansion 40/23. Despite attempts to characterize a distinction between disease entities by mutation history, this case highlights heterogeneity in the genetic background and development of ALS versus SCA2.

This case highlights the need for a deeper understanding of the complex relationship between ATXN2 mutations and disease presentation. Clinicians, genetic counselors, and researchers should consider the potential variations in disease expression based on repeat. This knowledge has important implications for appropriate genetic testing, accurate risk assessment for family members, and access to targeted therapies.

#786- Characterization of TDP-43 cryptic splicing

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TDP-43 is an RNA-binding protein with a prominent role in mRNA splicing, that mislocalises and forms aggregates in the cytoplasm in neurodegenerative disorders affecting both brain and muscle. The concomitant loss from the nuclei leads to the inclusion of non-conserved cryptic exons (CEs), which often contain premature stop codons or induce frameshift, causing degradation of the CE-containing transcripts through nonsense-mediated decay (NMD).
The aim of this work is to characterise CEs, their sensitivity to differential TDP-43 loss of function and to NMD, and their tissue-specificity.
Thus, we gathered previously published data and generated cell lines as models for TDP-43 loss of function, and performed RNA-sequencing on them.
First, we analysed the impact of increasing levels of TDP-43 knockdown, discovering patterns of response and maximal expression for different CEs. Later, we inhibited NMD both with cycloheximide and through the knockdown of the key NMD factor UPF1, showing that some CEs are spared from NMD and therefore have the potential to be translated and used as biomarkers. Moreover, we found CEs that are masked by NMD, and orthogonally validated them through qPCR, proteomics, and post-mortem RNA-sequencing data. Finally, we report on the ongoing effort to assess TDP-43 cryptic splicing and impaired RNA processing in muscle tissue and diseases.
Overall, this study expands our knowledge of the TDP-43 CE biology and provides evidence for novel biomarkers and therapeutic targets in TDP-43 proteinopathies.

#763- Evaluation of the Role of Glial Factors in the Pathogenesis of Spinal Muscular Atrophy

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Introduction: Diagnostic and therapeutic biomarker studies for spinal muscular atrophy (SMA) patients have gained momentum after novel disease modifying treatments. There are growing evidence that the glial cells and related neuroinflammation play role in SMA-related neurodegeneration.

Objectives: To investigate the role of glial factors in the pathogenesis of SMA.

Methods: Cerebrospinal fluid (CSF) levels of glial-derived neurotrophic factor (GDNF) and glial fibrillar acidic protein (GFAP) were measured by ELISA in treatment-naive SMA adult patients. CSF of patients undergone lomber punction with the suspicion of pseudotumor cerebri (PTC) were used as control.

Results: Twenty-two SMA patients and ten PTC patients were analyzed. GFAP levels were higher in SMA group compared to controls ($p<0.05$), while GDNF levels were found to be significantly lower ($p<0.05$) in SMA group.

Conclusions: This study supports the hypothesis that glial cells play a role in the pathogenesis of SMA. Considering the studies in literature, lower levels of GDNF in this study may highlight its biologically active role in the pathogenesis of SMA. Lower levels of GDNF accompanying with elevated levels of GFAP may be used as a diagnostic biomarker for SMA.

#762- Proteomic characterisation of molecular pathways involved in Type III Spinal Muscular Atrophy

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Introduction: Spinal muscular atrophy (SMA) is classified into four clinical sub-types, from Type I (severe), to Type IV (adult-onset). There is no cure for SMA, but gene-based treatment options have recently become available. Almost all pre-clinical work, however, has focused on identification and characterisation of molecular pathways associated with severe SMA.

Objectives: To determine whether similar molecular pathways are involved in Type III SMA compared to those detected in Type I and II SMA.

Methods: Using quantitative proteomics analysis, protein extracts from fibroblasts, myoblasts and induced pluripotent stem (iPS) cell-derived motor neurons from SMA Type III patients were compared with age-matched controls. Datasets were interrogated to identify commonalities between them and were then compared to datasets generated from SMA Type I and II fibroblasts and iPS cells using bioinformatics analysis.

Results: Dysregulated proteins were identified in the SMA Type III fibroblasts (n=77), iPS-derived motor neurons (n=71) and myoblasts (n=363) compared to control cells, but only one protein was consistently dysregulated in all three cell types from SMA Type III patients. Bioinformatics analysis indicated that some cellular and molecular pathways in Type II and III SMA were a protraction of that seen in Type I SMA, but strongly suggested that different SMA severities are associated with distinct molecular processes.

Conclusions: This work highlights new avenues for future work aimed at developing severity-specific therapies for SMA. Future work will also focus on validating the protein consistently dysregulated across the SMA Type III cells as a potential biomarker for Type III SMA.

#724- Atypical presentation of chronic inflammatory demyelinating polyneuropathy

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Introduction: We present a unique acute onset chronic inflammatory demyelinating polyneuropathy (CIDP) with multiple cranial nerves and bulbar involvement.

Case Presentation: 28-year-old woman presented to our hospital with 14-day history of numbness and tingling, impaired coordination, hoarseness and areflexia 3 weeks after a viral infection. MRI lumbar and lumbar puncture were consistent with acute inflammatory demyelinating polyneuropathy (AIDP) and she was treated with intravenous immune globulin (IVIG) and discharged with moderate improvement in her symptoms. She returned 2 weeks later with worsening of neck and proximal muscles weakness and bilateral facial nerve and vocal cord paralysis. She received five sessions of plasma exchange (PLEX) for possible recurrent AIDP and discharged with significant improvement of her symptoms. She returned to the hospital after a week with mild to moderate dysarthria, mild anisocoria, reduced sensation to pinprick in the right V3 distribution and tongue weakness in addition to worsening of prior symptoms. The patient admitted with CIDP diagnosis and received PLEX. Work ups looking for diseases mimicking CIDP were negative. Electrodiagnostic study revealed a chronic, inactive, demyelinating, motor>sensory polyneuropathy affecting upper>lower extremities. The patient was placed on PLEX, prednisone and CellCept with significant improvement of her symptoms.

Conclusion: CIDP typically does not present acute onset and multiple cranial nerves involvement and bulbar symptoms are very rare. The findings in this case report may prompt further understanding of clinical and imaging characteristics associated with acute onset CIDP and care measures that could help identifying patients at risk of severe course of the disease.

#760- Critical illness polyneuropathy/myopathy are associated with exposure to respiratory illness during critical care stays

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Introduction: Critical illness polyneuropathy and myopathy (CIP/CIM) are debilitating complications that may follow intensive/critical care (ICU) hospitalizations. Known risk factors include ventilator use, multiple organ failure, hyperglycemia, neuromuscular blockade, and potentially respiratory illnesses such as COVID-19.

Objectives: Examine associations between ICU-concurrent respiratory illnesses and CIP/CIM.

Methods: Propensity score matching (1:1) utilizing TriNetX integrated analytics controlled for known CIP/CIM risk factors in data from 80 healthcare organizations (100.8M adults). Odds ratios (OR) with 95% confidence intervals (CI) for a CIP and/or CIM diagnosis within 3 months of an ICU-concurrent respiratory illness were calculated.

Results: For CIP and/or CIM, the OR for any ICU-concurrent respiratory illness (N=937,162) was 19.5 (95% CI 16.4, 23.2). ORs were 6.91 (6.10, 7.82) for COVID-19 (N=251,298), 2.91 (2.65, 3.18) for influenza (N=254,096), and 3.05 (2.78, 3.34) for pneumonia (N=251,652). For exposure comparisons ORs were 1.60 (1.47, 1.74) for COVID-19 versus influenza (N=181,074), 1.57 (1.44, 1.71) for COVID-19 versus pneumonia (N=178,494), and 0.991 (0.918, 1.07) for influenza versus pneumonia (N=253,524).

Conclusion: CIP/CIM diagnoses are associated with elevated odds of exposure to respiratory illnesses, particularly COVID-19, during ICU hospitalizations. The cause of CIP/CIM remains unknown, but improving treatments for respiratory illnesses and optimizing recognized interventions such early rehabilitation and glycemic control may reduce occurrence.

#720- Review of Acute Rhabdomyolysis in Genetic Disorders vs Unaccustomed Exercise

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Aims: The aim of this study was to identify whether presenting features of patients presenting with AR due to unaccustomed exercise (UE) can be distinguished from those presenting with metabolic myopathies.

Methods/Materials: We retrospectively reviewed case notes of 51 patients presenting with AR between January 2020 and December 2022. A questionnaire was sent to patients to complete. The study was approved by our hospital internal review board.

Results: Of 51 patients included in this study 19 (37%) were diagnosed with AR due to UE, 10 (20%) with GSDV, 10 (20%) with CPT-2 deficiency and 12 (23%) with RYR-1-related AR. Investigation included testing on a panel of 65 genes associated with AR or targeted single gene testing. The mean age was 37 years (19-75); 84% were males. Median serum CK during AR episodes was 55 000iu/L (8 000-300000 iu/L). GSDV patients had highest baseline CK (mean CK:1980) (p=0.05). 30 patients (59%) were admitted hospital of whom 7 (14%) went to ITU and 6 (12%) required renal dialysis. None of these were UE patients... ITU admission/ renal dialysis were most likely in CPT-2 deficiency (p=0.014, p=0.049). Triggers for AR were exercise, heat, fasting, fever and coffee. Neck muscle involvement occurred in CPT-2 deficiency (p=0.05). Onset of AR was within minutes of exercising GSDV, after 2-36 hours inCPT-2 & RYR-1, where and more than 36 hours after exercise in UE (p<0,001).

Conclusion: Timing of onset of AR can help to differentiate specific underlying metabolic disorders from UE. This may be useful in guiding diagnostic investigations.

#814- Late-onset autophagic vacuolar myopathy with sarcolemmal features

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Introduction: Autophagic vacuolar myopathies with sarcolemmal features (AVSF) include Danon disease, X-linked myopathy with excessive autophagy (X-MEA), X-linked congenital autophagic vacuolar myopathy, infantile autophagic vacuolar myopathy, and adult-onset autophagic vacuolar myopathy with multiorgan involvement.

Case Report: A 63-year-old man with history of diabetes and intestinal metaplasia presented an eight-year history of severe, progressive and generalized myalgias. There was no family history or consanguinity, history of toxic exposure or infection.

Methods and Results: Exam did not reveal muscle weakness although it was limited by pain, there was no muscle atrophy or myotonia, and deep tendon reflexes were normal. Creatine kinase (800IU/L), aldolase, ESR and CRP were elevated. Antinuclear antibodies, rheumatoid factor, PM1/Scl and Pl-7 antibodies were elevated. Electromyogram revealed an irritable myopathy. Two muscle biopsies with an eight-year interval were concerning for progression of an autophagic vacuolar myopathy with complement deposition in sarcolemma of non-necrotic muscle fibers. A two-phase whole body bone scan (99mTc-HDP) showed increased tracer uptake in muscles of upper and lower extremities. Whole body PET did not show any malignancy. Cardiac evaluation revealed a non-obstructive hypertrophic cardiomyopathy. Neuromuscular Comprehensive genetic panel did not identify mutations in *GAA*, *LAMP2* or *VMA21* but a pathogenic variant in *RYR1* gene (c.6640 G>A, p.Val2214Ile) and a VUS in *SLC16A1* (c.10G>A, p.Ala4Thr). Steroids and IVIG infusions did not provide benefit. Whole genome sequencing (WGS) was performed (pending).

Conclusions: Myalgias may be the main symptom of AVSF. Unless WGS reveals another cause, we wonder whether this clinico-pathological phenotype is a manifestation of *RYR1*-related myopathy.

#743- Hemodynamic response to exercise and mechanisms of exercise intolerance in patients with Myositis

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Introduction: Exercise intolerance is a common symptom in patients with inflammatory myopathies (IIMs), yet the hemodynamic response to exercise and the mechanisms contributing to intolerance remain unclear.

Objective: To characterize the hemodynamic response to exercise and confirm the specific mechanisms of impaired oxygen transport/utilization using both whole body (cardiopulmonary exercise testing [CPET]) and isolated single-knee extension (IKE) exercise in patients with IIMs.

Methods: 5 patients (3M including DM/IMNM/IBM) with IIMs (52±13 yrs, 33.5±8.3 kg/m^2) and 9 (3M) controls (CON; 68±8 yrs, 25±3 kg/m^2) underwent CPET to determine peak oxygen uptake ($\dot{V}O_2$; indirect calorimetry), cardiac output ($\dot{Q}c$; acetylene rebreathe), and arterial-venous O_2 difference ($\Delta a\text{-}vO_2$). Leg blood flow (LBF; ultrasound) was measured during IKE at 5, 10, and 15 Watts (W). In IIMs, blood was collected from the common femoral vein of the exercising leg to calculate leg $\dot{V}O_2$ ($L\dot{V}O_2$; LBF x $\Delta a\text{-}vO_2$). Data were compared between-groups via t-tests and within-groups via repeated-measures ANOVA.

Results: Peak $\dot{V}O_2$ was not different between IIMs and CON (P=0.124), but peak $\dot{Q}c$ (P=0.042) was elevated and $\Delta a\text{-}vO_2$ (P=0.019) was diminished in IIMs; the $\dot{Q}c\text{-}\dot{V}O_2$ slope was higher in IIMs (7.2±1.6 vs 5.8±1.1 L/min/L/min, P=0.080). During IKE, LBF (both, P<0.001) increased from rest to 5W, but only increased thereafter in CON (Δ595.2±385.5 ml/min, P=0.011; IIMs: Δ129.6±221.4 ml/min, P=0.976), likely because IIMs failed to increase in $L\dot{V}O_2$ from 5-15W (Δ13.87±29.8 ml/min P=0.869).

Conclusion: Despite similar $\dot{V}O_2$, IIMs showed a hyperdynamic circulatory response to exercise and impaired muscle oxygen diffusion and/or mitochondrial capacity that limits oxygen transport and utilization.

#709- Myasthenic Syndrome Due to Tubular Aggregate Myopathy: A Case Report

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Introduction/Background: Tubular aggregate myopathies are a rare group of disorders with characteristic accumulation of densely packed tubules in skeletal muscle fibers. As a descriptive pathologic diagnosis, it includes a heterogeneous array of phenotypic presentations including exertional myalgia, muscle cramping and stiffness, progressive proximal weakness, fatigability, as well as periodic paralysis.

Case Report: A 55 year old woman presented with 2 to 3 years of generalized fatigable weakness. Over the course of a year, she developed progressive decline in respiratory function from 90% to 42% upright forced vital capacity. Initial EMG showed only mild polyphasia; repeat EMG showed nonirritable myopathy. Genetic testing showed heterozygous variants of uncertain significance in ACADM, CAPN3, COLG6A2, GFER, GOSR2, PLEC, and SMN1/SMN2. A right biceps muscle biopsy showed a tubular aggregate myopathy. Notably, genes known to be associated with tubular aggregate myopathy were negative, including CASQ1, STIM1, RYR1, ORAI1. Empiric use of pyridostigmine enabled the patient to walk for longer distances, though repetitive nerve stimulation and single fiber EMG were both negative for neuromuscular junction abnormalities.

Conclusion: 1) muscle biopsy should be considered in atypical cases of myasthenic syndromes, 2) symptomatic improvement with pyridostigmine is not specific for or diagnostic of myasthenia gravis, and 3) tubular aggregate myopathies are rare, and as a descriptive pathological diagnosis, consist of a heterogenous group of phenotypes. Negative genetic testing for known genetic causes of tubular aggregate myopathy does not exclude the diagnosis.

#666- Late onset CMT2A can be a diagnostic challenge when presenting with vague sensory symptoms

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Introduction: Mutations in the Mitofusion 2 gene have been reported to cause CMT2A. Mitofusion 2 is a protein that is important in mitochondrial fusion. It is well known that CMT2A can have both early onset more severe phenotypes and late onset milder phenotypes. This abstract investigates the clinical features of the late onset subset.

Methods: 4 subjects were evaluated using clinical, laboratory, electrophysiological and genetic data .

Results: All four subjects had a challenge to get to a diagnosis given the vague sensory nature of their presentation. One presented with sharp pains in his hands, confused for carpal tunnel syndrome. Another had a sunburn sensation in her legs and the last two had diffuse whole body parestheias which were all attributed to possible psychogenic causes. Two out of the four electrodiagnostic testing resulted in borderline abnormalities, which could be considered within normal limits including very mild delayed latencies in the sural and peroneal nerves. After extensive evaluations for all subjects, an MFN2 mutation was found and simple interventions such as gabapentin, alpha lipoic acid and Cymbalta helped control the symptoms. Genetic testing results revealed the following: subject 1, pathogenic deletion of exons 7-8, MFN2 c.749G>A reported as a suspected mutation, 881G>A variant of uncertain significance and C2119C> T pathogenic mutation.

Conclusion: Late onset MFN2 mutations can present with mild vague sensory complaints that can be a diagnostic challenge, but can be treated if recognized.

#730- A stable human Schwann cell model of Charcot-Marie-Tooth disease type 1A

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Introduction: Charcot-Marie-Tooth disease 1A (CMT1A) is caused by *PMP22* gene duplication leading to peripheral myelin protein 22 overexpression in Schwann cells. This results in myelin sheath defects and axonal loss, leading to muscle weakness and wasting. Therapy development is hindered by limited insights into the molecular pathways involved in PMP22 accumulation and clearance and by limitations of current disease models.

Objectives: To produce a stably transfected, clonal, immortalized human Schwann cell model of CMT1A and to identify potential targets for therapy design to promote degradation or enhanced PMP22 trafficking.

Methods: Human immortalised Schwann cells from healthy sural nerve were stably transfected with PMP22 and a promiscuous biotin ligase (BioID2) tag for labelling and identification of proteins in close proximity of PMP22 using mass spectrometry.

Results: Indicative of the myelinating Schwann cell dysfunction in CMT1A, transfectants overexpressing PMP22 had a spiky irregular morphology with intracellular, asymmetric aggregates of PMP22, which was not evident in control transfectants. Several hundred proteins in proximity of PMP22 were identified from BioID2 pulldowns which were associated with enriched molecular pathways including regulation of Schwann cell expansion, survival, and myelination. Close association between PMP22 and the endoplasmic reticulum membrane was evident, likely reflecting processing of the overexpressed protein.

Conclusion: Identification of proteins in proximity of overexpressed PMP22 has generated insights into potential pathological mechanisms associated with CMT1A. Future work aims to determine whether these proteins represent targets for therapy design aimed at promoting degradation and enhanced trafficking of PMP22.

#736- Defining paretic neuromuscular pathophysiology in a mouse model of spinal cord injury

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Introduction: The neuromuscular system demonstrates remarkable plasticity in response to changes in activity level, injury, and aging. Maladaptive remodeling of the motor unit (MU) or neuromuscular junction (NMJ) after injury may exacerbate disability and hinder recovery. Prior clinical/preclinical studies indicate substantial MU alterations in paretic muscle following stroke. Here, we investigated whether similar changes occur after spinal cord injury (SCI).

Objective: Characterize paretic neuromuscular pathophysiology in a mouse model of SCI, using in vivo longitudinal assessments and histological analyses.

Methods: Muscle physiology and MU electrophysiology were assessed weekly in SCI (T9 Transection) or control (Sham) mice, caudal to injury. Five weeks post-injury (wpi), NMJ transmission was evaluated using single-fiber electromyography (SFEMG), and tissue was collected to examine lumbar motoneurons and hindlimb NMJs.

Results: After SCI, paretic muscle weight markedly decreased, and tetanic contractility was reduced by ~45%. Electrophysiology indicated rapid, sustained MU loss. SFEMG revealed no difference in NMJ transmission at 5wpi. Though number of axonal inputs per NMJ was unchanged, NMJ size and colocalization of pre- and postsynaptic structures were reduced.

Conclusions: Similar to stroke, SCI prompts loss of functional MUs and contractility in paretic muscle caudal to injury. Findings of smaller NMJs with less pre-/postsynaptic overlap suggest reduced innervation. Forthcoming quantification of motoneuron size and counts will inform whether neuronal loss is occurring. Future studies will map evolution of NMJ morphology following SCI, assess synaptic transmission at earlier timepoints, and explore physiological silencing of MUs as an alternative explanation for the observed functional loss.

#765- Paramyotonia congenita in Zambia:A case report with broader implications for rare disease capacity building in sub-Saharan Africa

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Introduction: Paramyotonia congenita (PMC) is a rare disease caused by SCN4A gene mutations. We describe a genetically-confirmed case in Zambia and consider the broader need for and impact of rare disease identification and diagnosis in resource-constrained settings.

Case Report: A 6-year-old male patient presented to the University Teaching Hospital, Lusaka, Zambia with complaints of extremity stiffness and fatigue exacerbated by exercise. Symptom onset was nine-months. The father and two male siblings had less severe symptoms.
Exam findings included facial stiffness, palpebral fissure narrowing, generalized muscular hypertrophy, hand-grip and thenar percussion myotonia, and a bradyphrenic and lumbering gait. EMG of father's right anterior tibialis confirmed the presence of electrical myotonia.

Methods: After parental written informed consent, a blood sample was sent for genetic testing through the International Centre for Genomic Medicine in Neuromuscular Disease.

Results: A SCNA4 gene mutation was found, alongside a CLCN4 mutation. Given the severe clinical phenotype, the possibility of the CLCN4 mutation as a modifying factor is under further investigation. Analysis of mutations in afflicted family members are forthcoming.
Carbamazepine, available on Zambian government formularies at no patient cost, was prescribed for symptomatic management. At the first follow-up visit, the father noted patient symptom improvement, including ability to ambulate to school.

Conclusion: Rare disease treatments may be readily available in resource-constrained settings, but models for identification and diagnosis are lacking. Such models become increasingly urgent as gene-targeted therapies become available. Rare disease research in such settings may also fuel scientific discovery for the benefit of patients globally.

#817- Novel Mutations in the PLEC Gene: A Case of Epidermolysis Bullosa Simplex with Muscular Dystrophy

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Introduction/Background: Plectin is a giant cytoskeleton-crosslinker protein that connects actin microfilaments, microtubules, and intermediate filaments. Mutations in the *PLEC* gene lead to disorganization of myofibrils and sarcomeres, and phenotypically are associated with epidermolysis bullosa simplex (EBS) with muscular dystrophy.

Case Report: A 21-year-old woman presented with progressive bilateral upper extremity weakness. She was born with EBS with significant airway involvement and mechanical blistering on her hands and feet. She noted bilateral upper extremity proximal weakness at 15 years of age, which continued to progress over time, limiting her ability of carrying and lifting. On exam, she had bilateral ptosis without limitations of extraocular movements, mild lower facial weakness, and preferential weakness of biceps (3/5 in biceps, 4/5 triceps, 4/5 wrist extension/flexion, 4/5 finger flexion/extension) and mild distal lower extremity weakness. Electromyography exhibited low amplitude, polyphasic motor unit action potentials with early recruitment, consistent with myopathy. Interestingly, there was suggestion of muscle membrane irritation on EMG. Low frequency repetitive nerve stimulation of the right median nerve showed significant amplitude decrement. She underwent sequencing of the *PLEC* gene, revealing variants in c.4687C>T (p.Gln1563) and c.5251C>T (p.Gln1751), neither of which have been previously reported, but both were classified as pathogenic due to their creation of premature stop codons, resulting in expected loss of protein function. She was trialed on pyridostigmine and amifampridine with minimal benefit.

Summary/Conclusion: These novel mutations in the *PLEC* gene expands our knowledge of plectinopathies and their heterogenous clinical phenotypes. Clinical trial examining new therapies for this spectrum of disorders is ongoing.

Academic Registries and Patient Organizations

#753- Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG Natural History Study: a matched cohort analysis

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Introduction: STRIDE (NCT02369731) is an ongoing registry providing data on ataluren use in nonsense mutation Duchenne muscular dystrophy (nmDMD) patients.

Objectives: We examined if nmDMD patients receiving ataluren+standard of care (SoC) in the STRIDE Registry experienced a delay in age at loss of ambulation (LOA) versus DMD patients receiving SoC alone in the CINRG Duchenne Natural History Study (NCT00468832).

Methods: Data were extracted on January 31, 2022. Propensity score matching identified STRIDE and CINRG patient cohorts (N=260) comparable in established predictors of disease progression: age at first symptoms; age at initiation of corticosteroid use; duration of deflazacort use; and duration of other corticosteroid use. Kaplan–Meier analyses were used to estimate age at LOA.

Results: The mean (SD) ages at first symptoms in the STRIDE and CINRG cohorts (N=260 per cohort) were 2.8 (1.7) and 2.8 (1.5) years, respectively. Most patients (STRIDE vs CINRG) received corticosteroids for ≥12 months (85.0% vs 83.8%), with a similar proportion receiving deflazacort (47.7% vs 44.2%) or other corticosteroids (41.9% vs 43.5%). In the STRIDE cohort, 26.5% (69/260) of patients lost ambulation compared with 54.6% (142/260) of patients in the CINRG cohort. The median (95% confidence interval) ages at LOA (STRIDE vs CINRG) were 17.9 (14.8, not estimable) and 12.5 (12.0, 13.5) years, respectively. Kaplan–Meier analyses showed that ataluren+SoC delayed age at LOA compared with SoC alone ($p<0.0001$).

Conclusions: These Kaplan–Meier analyses showed that in routine clinical practice ataluren+SoC delayed age at LOA by 5.4 years compared with SoC alone in nmDMD patients.

#754- Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Natural History Study: a matched cohort analysis

Már Tulinius,[1] Filippo Buccella,[2] Isabelle Desguerre,[3] Janbernd Kirschner,[4] Eugenio Mercuri,[5] Francesco Muntoni,[6] Andrés Nascimento Osorio,[7] Lauren P. Morgenroth,[8] Heather Gordish-Dressman,[9] Shelley Johnson,[10] Christian Werner,[11] Panayiota Trifillis,[10] Karyn Koladicz,[10] Nicholas Mastrandrea,[10] Jonathan Blaize,[10] Bethany Freel,[10] and Craig M. McDonald[12]

[1]Department of Pediatrics, Gothenburg University, Queen Silvia Children's Hospital, Gothenburg, Sweden; [2]Parent Project APS Italy, Rome, Italy; [3]Hôpital Necker – Enfants Malades, Paris, France; [4]Medical Center – University of Freiburg, Freiburg, Germany; [5]Department of Pediatric Neurology, Catholic University, Rome, Italy; [6]University College London, Great Ormond Street Institute of Child Health, London, United Kingdom; [7]Hospital Sant Joan de Déu, Unidad de Patología Neuromuscular, Universidad de Barcelona, Barcelona, Spain; [8]Therapeutic Research in Neuromuscular Disorders Solutions, Pittsburgh, PA, USA; [9]Center for Genetic Medicine, Children's National Health System & the George Washington, Washington, DC, USA; [10]PTC Therapeutics Inc., South Plainfield, NJ, USA; [11]PTC Therapeutics Germany GmbH, Frankfurt, Germany; [12]University of California Davis School of Medicine, Davis, CA, USA

Word count=245/250

Introduction: STRIDE (NCT02369731) is an ongoing, multicenter, observational registry providing data on ataluren use in nonsense mutation Duchenne muscular dystrophy (nmDMD) patients in routine clinical practice.

Objectives: We investigated if nmDMD patients receiving ataluren+standard of care (SoC) in the STRIDE Registry experienced a lesser decline in pulmonary function versus DMD patients receiving SoC alone in the CINRG Natural History Study (NCT00468832).

Methods: Data were extracted on January 31, 2022. Propensity score matching identified STRIDE and CINRG patient cohorts (N=260) comparable in established predictors of disease progression: age at first symptoms; age at initiation of corticosteroid use; duration of deflazacort use; and duration of other corticosteroid use. Kaplan–Meier analyses were used to estimate ages at %-predicted forced vital capacity (FVC) <60% and <30%.

Results: The mean (standard deviation) ages at onset of first symptoms (STRIDE vs CINRG; N=260 per cohort) were 2.8 (1.7) and 2.8 (1.5) years, respectively. Most patients (STRIDE vs CINRG) received corticosteroids for ≥12 months (85.0% vs 83.8%), with a similar proportion receiving deflazacort (47.7% vs 44.2%) or other corticosteroids (41.9% vs 43.5%). Median (95% confidence interval [CI]) ages at %-predicted FVC <60% (STRIDE vs CINRG) were 17.7 (16.8, not estimable) and 15.3 (14.9, 16.5) years, respectively (p=0.0053). Median (95% CI) ages at %-predicted FVC <30% (STRIDE vs CINRG) were not estimable and 22.5 (20.3, 25.4) years, respectively (p=0.0008).

Conclusions: These interim registry data suggest that treatment with ataluren+SoC in routine clinical practice slows disease progression in pulmonary function in nmDMD patients.

#794- MGBase: The launch of an international electronic database for patients with Myasthenia Gravis

Stephen W Reddel, Sidney, Australia.
Carolina Barnett Tapia, Toronto, Canada.
Helmut Butzkueven, Melbourne, Australia
Katherine Buzzard, Melbourne, Australia
Gary Cutter, Alabama, USA.
Henry Kaminski, Washington, D.C. USA.
Anneke Van der Walt, Melbourne, Australia.
WenWen Zhang, Melbourne, Australia.

Introduction: There is no globally accessible Myasthenia Gravis (MG) database for real world outcomes research. Longitudinal outcome data including physician reported, patient-reported and safety outcomes are limited in MG.

Objective: To develop and implement the first international observational database for patients with MG to advance collaborative outcome-based research and improve quality of care.

Design/Methods: MGBase was developed from the successful Multiple Sclerosis registry, MSBase (>80,000 patients), with support of the MSBase Foundation. This leverages existing IT infrastructure, data security, privacy compliance and governance structures of MSBase. A minimum data set and extended options enable data quality.
Designed for use during outpatient consultations, MGBase provides a longitudinal display of the patient disease course, therapies and outcomes. The development of MGBase was guided by international MG experts. Members of this group have subsequently formed the MGBase scientific leadership group responsible for determining the overall direction and scope of the MGBase registry.

Results: MGBase launched in December 2021 in Australian pilot centers. By August 2022 there were 53 patients enrolled, with mean age of 59 years (67% male), mean disease duration of 9.7 years. Disease subtype was AChR += 29, MuSK +=3, seronegative = 14, unknown =3. Longitudinal data (yearly outcomes, treatment and safety) are available.

Conclusions: MGBase is the first observational international registry launched for patients with MG. The MGBase registry is dedicated to evaluating outcomes data in MG and making this available for scientific and health outcomes research within an international collaboration. Updated data will be presented at the conference.

#799- Patients in the Pompe Registry Who Switched From Alglucosidase Alfa to Avalglucosidase Alfa: Real-world experience

Carolina Tesi Rocha[1], Benedikt Schoser[2], Antonio Toscano[3], Meredith Foster[4], Magali Periquet[5], Susan Sparks[4], Priya S. Kishnani[6]; on behalf of the Pompe Registry Sites
[1]Department of Neurology, Stanford University School of Medicine, Palo Alto, CA, USA; [2]Friedrich-Baur-Institute, Department of Neurology, LMU Klinikum München, München, Germany; [3]Department of Clinical and Experimental Medicine, Reference Center for Rare Neuromuscular Disorders, University of Messina, Messina, Italy; [4]Sanofi, Cambridge, MA, USA; [5]Sanofi, Berlin, Germany; [6]Duke University Medical Center, Durham, NC, USA

Introduction: Avalglucosidase alfa (AVA), a recombinant human acid α-glucosidase enzyme replacement therapy, has marketing authorization in several countries for infantile-onset (IOPD) and/or late-onset Pompe disease (LOPD).

Objectives: Describe characteristics of IOPD and LOPD patients who switched from alglucosidase alfa (ALG) to AVA enrolled in the international, observational, voluntary Pompe Registry (NCT00231400).

Methods: For this analysis, patients had ≥1 ALG record immediately pre-switch to AVA. Demographic and treatment histories were summarized. Respiratory, ambulatory, and biomarker data were assessed pre- and post-switch for LOPD only.

Results: As of April 7, 2023, 119 patients were identified (LOPD, 104 [87%]; IOPD, 15 [13%]). Females: LOPD 49 (47%); IOPD: 9 (60%). Patients switched to AVA at mean ± SD age: LOPD 44.0 ± 21.86 (range, 1.0–83.0) y; IOPD: 9.9 ± 4.31 (range, 3.0–17.6) y. Pre-switch, 59 [57%] LOPD and 10 [67%]) IOPD patients had received ALG for ≥5 y. For LOPD, last assessments pre-switch were upright FVC % predicted: 59.5 ± 23.71 (n=84), 6MWT: 351.3 ± 160.03 m (n=52), urine Hex4: 9.9 ± 17.07 mmol/mol creatinine (n=62), and serum CK: 542.0 ± 454.93 U/L (n=81). Mean changes in LOPD patients with both pre- and up to 1-y post-switch assessments showed stabilization in respiratory and ambulatory function, and biomarker improvement.

Conclusions: The Pompe Registry continues to accrue data for patients switching from ALG to AVA, which will support our understanding of AVA's effectiveness on respiratory and ambulatory outcomes and biomarker levels in the real-world. **Funding:** Sanofi.

#841 - CHANGE IN CONCOMITANT THERAPIES FOR GENERALIZED MYASTHENIA GRAVIS IN PATIENTS RECEIVING ECULIZUMAB: A RETROSPECTIVE ANALYSIS OF REGISTRY DATA

Michael Pulley (Jacksonville, FL),[1] Samir Macwan (Rancho Mirage, CA),[2] Richard J. Nowak(New Haven, CT),[3] Tahseen Mozaffar (Orange, CA),[4] Ema Rodrigues (Boston, MA),[5] HouariKorideck (Boston, MA),[5] Brian Werneburg (Boston, MA),[5] Pushpa Narayanaswami (Boston, MA)[6]*

[1]University of Florida, Jacksonville, FL, USA, [2]Eisenhower Health, Rancho Mirage, CA, USA, [3]Yale School of Medicine, New Haven, CT, USA, [4]University of California, Irvine, Orange, CA, USA, [5]Alexion, AstraZeneca Rare Disease, Boston, MA, USA, [6]Beth Israel Deaconess Medical Center/ Harvard Medical School, Boston, MA, USA

*Affiliation at time of study.

CONFIDENTIAL
Registry change in concomitant ISTsNMSG 2023 encore abstract

Introduction: A range of treatments are available for patients with generalizedmyasthenia gravis (gMG) such as typical immunosuppressive therapies and complement C5 inhibitors, including eculizumab.

Objective: To assess concomitant therapy use at and after eculizumab initiation in patients with gMG.

Methods: US patients enrolled in a global gMG registry that collects data on eculizumabuse were included if they were treated with eculizumab for ≥ 1 year and had data on concomitant therapy use 12 months before eculizumab initiation. Azathioprine (AZA), mycophenolate mofetil (MMF), IVIg/plasma exchange (PLEX), and oral corticosteroid use at initiation of and during eculizumab treatment were analyzed. Data cutoff was July 5, 2022.

Results: Of the 94 patients included, 25 (27%), 40 (43%), 25 (27%) and 4 (4%) were receiving zero, one, two, or three concomitant therapies investigated at eculizumab initiation, respectively. Nine (10%) patients received AZA, 26 (28%) MMF, 19 (20%) IVIg/PLEX and47 (50%) oral corticosteroids. In 57 (61%) patients, the number of concomitant therapies did not change after eculizumab initiation. The number of concomitant therapies decreased in 24(26%) patients. Thirteen (14%) patients received more treatments after eculizumab initiation. Of the patients using each treatment at eculizumab initiation, AZA was discontinued in 2/9 (22%) patients, MMF in 8/26 (31%), IVIg/PLEX in 5/19 (26%) and oral corticosteroids in 11/47 (23%).

Conclusions: One or more concomitant therapy was discontinued in approximately onequarter of patients with gMG treated with eculizumab, providing evidence from clinical practice that eculizumab may enable patients with gMG to reduce concomitant therapies.

Acknowledgments: Writing assistance was provided by Vikte Lionikaite, PhD and Rebecca Hornby, PhD of Oxford PharmaGenesis, Oxford, UK, with funding from Alexion, AstraZeneca Rare Disease.

Author disclosures:
MP has received compensation for medical advisory board membership from Alexion and for regional advisory board participation from Alexion, Argenx, Immunovant, CSL/Behring, Catalyst, and UCB.
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Pharmaceuticals, Inc., argenx, Cabaletta Bio, Inc., CSL Behring, Grifols, S.A., Ra Pharmaceuticals, Inc. (now UCB S.A.), Immunovant, Inc., Momenta Pharmaceuticals, Inc., and Viela Bio, Inc. (Horizon Therapeutics plc).
TM has no disclosures.
ER has received personal compensation for serving as an employee of Alexion Pharmaceuticals and has received stock or an ownership interest from Alexion Pharmaceuticals, Inc.
HK was an employee of Alexion, AstraZeneca Rare Disease at time of study.
BW is an employee of Alexion, AstraZeneca Rare Disease.
PN has received research support from PCORI, Momenta/Janssen, Alexion/Astra Zeneca, and Ra/UCB, has served on advisory boards for Janssen, DMC Chair, and Sanofi, and has been a speaker for Argenx, Alexion, and UCB.

Funding statement: This study was sponsored by Alexion, AstraZeneca Rare Disease.
CONFIDENTIAL

#815- Introduction of the Peripheral Neuropathy Research Registry

S. Thomas[1], S. Ajroud-Driss[2], M. Dimachkie[3], R. Freeman[4], S. Geisler[5], D. Simpson[6], R. Singleton[7], G. Smith[8], A. Stino[9], and A. Höke[1]
([1]Baltimore, MD; [2]Chicago, IL; [3]Kansas City, KS; [4]Boston, MA; [5]St. Louis, MO; [6]New York City, NY; [7]Salt Lake City, UT; [8]Richmond, VA; [9]Ann Arbor, MI)

Information and Objectives: Peripheral polyneuropathy (PN) is a condition that affects approximately 8% of the population over 55 in the United States, which is often associated with intense neuropathic pain. In order to advance the knowledge about PN and to develop more efficient treatments, researchers need to have access to both clinical data and biospecimen for laboratory testing. In order to boost PN research efforts, the Foundation for Peripheral Neuropathy (FPN) started the Peripheral Neuropathy Research Registry (PNRR) to have both data and biospecimen readily available for researchers.

Methods: The PNRR data set includes neurological examination, Nerve Conduction Studies, laboratory testing results, as well as patient history questionnaire that catalogues PN symptoms and their severity, medication intake and medical and family history. In addition, plasma, serum and DNA are collected from each patient and stored in the biorepository.

Results: Currently, 1450 patients with idiopathic PN are enrolled in the database, 660 with diabetic PN, 150 with HIV-induced PN and 185 with Chemotherapy-induced PN. DNA was collected for all of them, and for 1650 serum and plasma is also available.

Discussion: The Foundation for Peripheral Neuropathy (FPN) makes both biospecimen and data available to researchers who want to advance the knowledge about PN. Requests for either biospecimen or data access can be submitted via the FPN website through the PNRR portal for researchers https://redcap.uits.iu.edu/surveys/?s=XLX8APCJWY

#811- Comparison of Nerve Conduction Studies: Prediabetes, Type 2 Diabetes, Metabolic Syndrome and Cryptogenic Sensory Neuropathy

Morgan Hamersky, Simone Thomas, Drs. Ahmet Höke, Amro Stino, Heyrettin Okut, and Mazen M. Dimachkie

Background: Diabetes mellitus (DM) is the most common identifiable etiology for polyneuropathy. Most patients with diabetic peripheral neuropathy (DPN) and cryptogenic sensory peripheral neuropathy (CSPN) demonstrate axonal injury, with some data suggesting increased likelihood of demyelination in DPN.

Objectives: In this study, we evaluated electrodiagnostic (EDX) parameters across the glycemic spectrum in patients with and without metabolic syndrome.

Methods: The Peripheral Neuropathy Research Registry is a cohort of well characterized patients with DPN and CSPN. 994 patients were grouped based on glycemia (type 2 diabetes, prediabetes, or normoglycemia) and presence or absence of metabolic syndrome. We evaluated peroneal motor and sural sensory nerve EDX data normalized across institutions, including conduction velocities, action potential amplitudes, and latencies. The normoglycemic CSPN cohort without metabolic syndrome served as disease control.

Results: Both DM and metabolic syndrome were more likely to associate with abnormal NCS findings. DM patients had significantly slowed peroneal motor conduction velocities, reduced sural sensory nerve action potential amplitude, and reduced sural nerve velocities. DM subjects were more likely to have both axonal and demyelinating pathology compared to CSPN subjects. Prediabetic subjects did not differ significantly from CSPN subjects on EDX parameters. Metabolic syndrome was associated with significant slowing of conduction velocity and reduction of action potential amplitude of both sural and peroneal nerves when compared to those without metabolic syndrome.

Conclusions: DPN appears to associate with more advanced axonal and demyelinating changes on EDX studies as compared to CSPN, particularly in the presence of metabolic syndrome.

#802- Prevalence of Neuropathies and amyotrophic lateral sclerosis among adults in the United States: A cross-sectional study using the All of Us Research Program Database

Adeel S. Zubair[1], Shani Evans[1], Bhaskar Roy[1]
1. Yale School of Medicine, Department of Neurology, New Haven, CT, USA

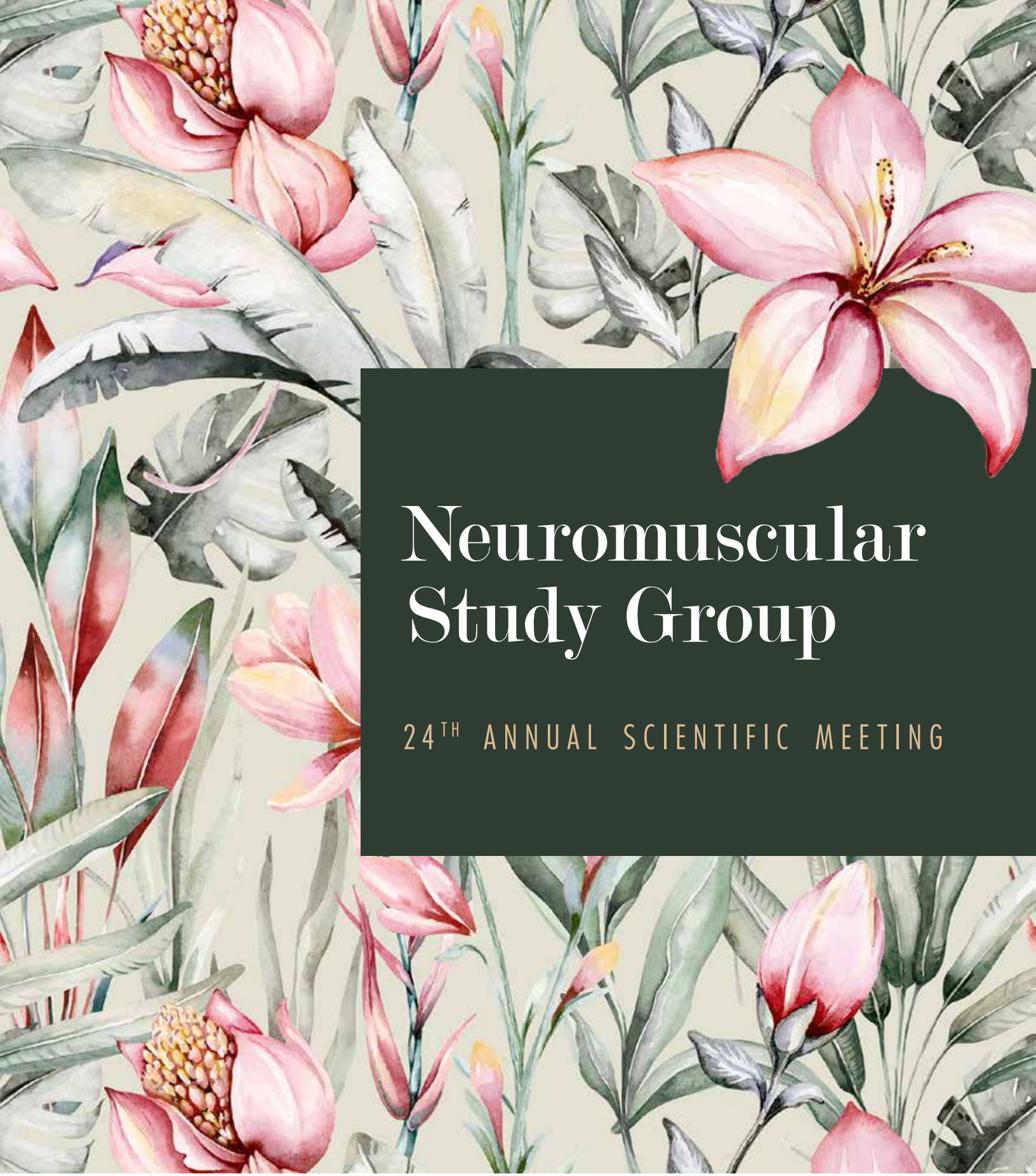
Introduction: The All of Us research program by the National Institutes of Health (NIH) was created to build a diverse health database of patients across the United States, aiming to represent the diversity of the population, including race, ethnicity, sex, gender, and sexual orientation.

Objectives: To examine the prevalence of amyotrophic lateral sclerosis (ALS) and neuropathies using the inclusive and diverse All of Us research program.

Methods: A cross-sectional analysis utilizing the electronic health records (EHRs) of 369,297 All of US adult participants was performed. Participants with a neuropathy diagnosis were identified by observational medical outcome partnership (OMOP) concept IDs for each condition, which includes Systemized Nomenclature of Medicine (SNOMED) and International Classification of Diseases (ICD) codes.

Results: This is ongoing research. The initial analysis reflected a similar prevalence of ALS (0.038 percent (95% CI 0.032-0.045)) based on the most recent estimate from the *Global Burden of Disease Study*, but the prevalence of chronic inflammatory demyelinating polyneuropathy (0.084% [95% CI 0.075-0.094]) was higher, and prevalence of diabetic neuropathy (2.7% [95% CI 2.7-2.8]) was lower than previous reports.

Conclusions: Updated prevalence of ALS and neuropathies based on a US-based database is important to understand the disease burden of these conditions. The differences noted in terms of the prevalence of CIDP and diabetic neuropathy can be specific to this database, but may also reflect increased awareness and diagnosis of CIDP, and further investigations are warranted.



Neuromuscular Study Group

24TH ANNUAL SCIENTIFIC MEETING

ORLANDO, FLORIDA | SEPTEMBER 22-24, 2023

Contents

Welcome

On behalf of your Neuromuscular Study Group (NMSG), we would like to welcome each of you to the 24th Annual Neuromuscular Study Group Scientific Meeting.

As we prepare to embark on this year's conference, we cannot help but look back with pride at the resounding success of our 2022 meeting in Italy. It was an extraordinary event, and we are thrilled to share that it marked our largest attendance to date with over 225 attendees with 141 submitted abstracts. After two years of adapting to online meetings, coming together in person once again was a great atmosphere rekindling of scientific exchange and networking.

The infamous Shark Tank session has gained momentum and we will host our 5th event during the meeting with 3 proposals being presented. The winner will receive a $10K grant to use towards their study. Last year's winners will be present at the meeting, and we look forward to learning how their funded proposals have progressed.

We are proud to continue to fund our Neuromuscular Research 2-year Fellowship program partnering with the American Brain Foundation. Both of our current Fellows will be presenting during the meeting.

As the Co-Chairs of the Neuromuscular Study Group, we would like to thank this year's planning committee with W. David Arnold serving as chair for putting together an excellent agenda that covers such a broad range of topics and interests within the neuromuscular field. This is a volunteer committee and they have worked especially hard to make the Young Investigator session new and exciting (and not scary!) Our heartfelt gratitude to the planning committee and to each chosen presenter for their invaluable contributions to making our conference such a success.

This year we continue to have industry involvement from both Europe and the U.S., many supporting the NMSG for the first time. Thank you so much to our sponsors for the support, please stop by their tables and look for their abstracts in the poster session. All the accepted abstracts are published in the current RRNMF Journal.

We also want to thank Liz Paulk, NMSG Administrative Manager, for organizing another successful and large event. The planning committee and Liz all have spent much time planning this years' meeting, making it exciting and fresh for the entire group.

RICHARD J. BAROHN, M.D.

Chair, Neuromuscular Study Group

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

PROF MICHAEL G. HANNA, M.D.

Co-chair, Neuromuscular Study Group

Director, University College London Institute of Neurology

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UCL Institute of Neurology

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Massachusetts General Hospital

Valeria Sansone, M.D., Ph.D. (outgoing)
Massachusetts General Hospital

Michael Hehir, M.D.
University of Vermont

John Vissing, M.D. (incoming)
Copenhagen Neuromuscular Center

Evaluator Member
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University College London

Information

WIFI

The NMSG has a special wifi access for meeting attendees.
This network can be used in the Conference Center.
Network name: Neuromuscular2023 | Password: StudyNM23

Wifi is also available in the hotel.
Network name: Caribe Network | Password: Room number, first and last name

SATURDAY DINNER

Dinner on Saturday night will be in the Carribean VI and VII Ballroom after the conclusion of the Key Note Speaker. After dinner we will have dessert and a reception outside at the Boca Patio.

Dress for the evening is business attire.

All are welcome.

SPEAKERS/PRESENTERS

Please bring your presentation to Amardeep Gill, our onsite AV expert, at the back of the Caribbean IV general session room the morning of your session.

Our technical staff will assist you with any audio/visual needs you may have. You will not need your own laptop as we have one available.

POSTERS

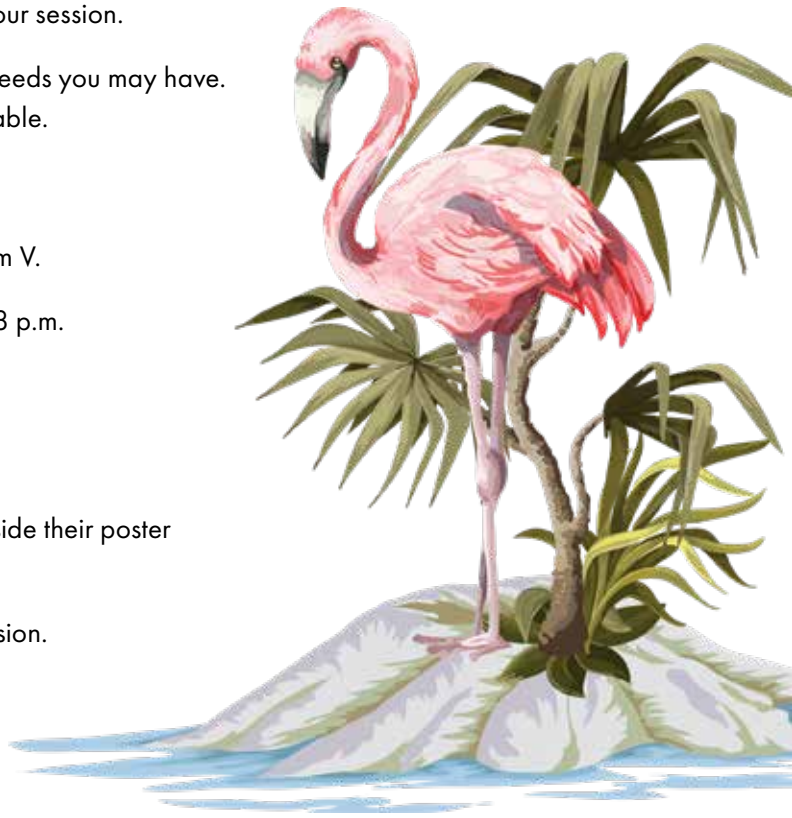
The poster exhibition is located in the Caribbean Ballroom V.

Walk through poster session is Friday, September 22, 6-8 p.m.

Please set up your poster in the Caribbean Ballroom V
after 7 p.m. on Thursday, or first thing Friday morning.
Posters will be displayed all day and evening on Friday.

Important note: Poster presenters are requested to be beside their poster during the walk though session.

Please remove your poster after the conclusion of the session.



Agenda

24TH ANNUAL NEUROMUSCULAR STUDY GROUP SCIENTIFIC MEETING

DAY 1: FRIDAY, SEPTEMBER 22	
6:30-8 a.m.	**Buffet Breakfast and Check-In** | *Caribbean VI and VII*
8-8:20 a.m.	**Welcome and State of the Neuromuscular Study Group** Dr. Richard Barohn and Prof Michael Hanna | *Caribbean III and IV*
SESSION I: MOTOR NEURON AND NEUROMUSCULAR JUNCTION	Heidi Fuller, M.D., Moderator | *Caribbean III and IV*
8:20-8:40 a.m.	**Unravelling Inflammatory Neuropathies** Simon Rinaldi, MBChB, Ph.D. | *University of Oxford*
8:45-9:05 a.m.	**Towards Clinical Trial Readiness for Charcot Marie Tooth Neuropathies** David Hermann, MBBCh | *University of Oxford*
9:10-9:30 a.m.	**Respiratory Updates in CANVAS** Riccardo Zuccarino, M.D. | *NEMO Milan*
9:35-9:55 a.m.	**Recent Learnings from Non-Coding Genome Investigations** Stephan Zuchner, M.D., Ph.D. | *University of Miami*
10-10:15 a.m.	**Refreshment/Exhibitor Break**
10:15-10:35 a.m.	**Expanding Therapeutic Options in Myasthenia Gravis** James Howard, M.D. | *The University of North Carolina at Chapel Hill*
10:40-11 a.m.	**Updates on ALS** Jon Katz, M.D. | *Sutter Health, California Pacific Medical Center, The Forbes Norris MDA/ALS Research and Treatment Center*
SESSION II: FLASH PRESENTATIONS	Dr. Michael Pulley, Moderator | *Caribbean III and IV*
11:05-11:15 a.m.	**Investing to Save: Evaluation of Unplanned Hospital Admissions of Neuromuscular Patients in Greater Manchester, UK** Marwah Almadhi, BSc Biomedical Sciences, MBChB Medicine (current) | *University of Manchester*
11:17-11:27 a.m.	**Measuring Adverse Event Burden in Myasthenia Gravis: Retrospective Validation of the Adverse Event Unit (AEU) with MGTX Trial Data** Michael Hehir, M.D. | *University of Vermont*
11:29-11:39 a.m.	**A Systematic Review and Meta-Analysis of the Placebo Effect in Inclusion Body Myositis** Elie Naddaf, M.D. | *Mayo Clinic*
11:41-11:51 a.m.	**The Inclusion Body Myositis Health-Index (IBM-HI): Development of a Novel, Disease Specific Patient-Reported Outcome Measure for IBM in Clinical Trials** Shaweta Khosa, M.D. | *University of Rochester, Center of Health and Technology Outcomes Division (CHeT)*
11:53 a.m.-12:03 p.m.	**Relationships of Lower Leg Fat Fraction Among Antagonistic and Synergistic Muscles and a Potential Fat Fraction Threshold for Functional Performance in Myotonic Dystrophy Type 1** Zhihao He, MS | *University of Florida*
12:05-12:15 p.m.	**Mycophenolate is Better Tolerated Than Azathioprine in Myasthenia Gravis** Katy Dodd, MBChB, MRCP | *University of Manchester*

12:17-12:27 p.m.	**A UK Experience of Symptomatic Treatment of Myotonia with Lamotrigine** Iwona Skorupinska, MSc, BSc | *University College London*
12:30-1:30 p.m.	**Lunch** | *Caribbean VI and VII*
	Neuromuscular Study Group Executive Committee Meeting Breakout Lunch | *Governor's Board Room*
SESSION III: PLATFORM PRESENTATIONS Kris Kelly, DPT, MS, EdM, Moderator | *Caribbean III and IV*	
1:30-1:45 p.m.	**Improving Diagnostic Rates for Mitochondrial Diseases Using Enhanced WGS Analysis and RNA-seq** William Macken, M.D., Ph.D. | *University College London*
1:50-2:05 p.m.	**MEND: MExiletine versus lamotrigine in Non-Dystrophic Myotonia** Vinojini Vivekanandam, MBBS(Hons) | *University College London, Queen Square*
2:10-2:25 p.m.	**Scoliosis Progression in Type II SMA at the Time of Treatment: A Comparative Study with Untreated Patients** Giorgia Coratti, Ph.D. | *Catholic University of Sacred Heart*
2:30-2:45 p.m.	**Remote Monitoring and Management of Myasthenia Gravis (REMOTE-MG): A Pilot Feasibility Study** Michael Hehir, M.D. | *University of Vermont*
2:50-3 p.m.	**Refreshment/Exhibitor Break**
SESSION IV: YOUNG INVESTIGATOR/EVALUATOR/COORDINATOR *ALL NEW* Session Moderators: Dr. W. David Arnold, Dr. Karen Suetterlin, Dr. Katherine Dodd, Dr. Heidi Fuller, Prof Valeria Sansone, Marie Wencel, CCRP *Caribbean III and IV*	
3-5 p.m.	**How to Give an Effective Elevator Pitch**
	Failing Well, Overcoming Rejections, Criticisms and Changing Direction
	Networking
POSTER SESSION *Caribbean V*	
6-8 p.m.	**Poster Walk Through and Reception**
	Reception
8-9 p.m.	**Dinner** | *Caribbean VI and VII*
9-11:30 p.m.	**Reception** | *Atrium East, Main Hotel Lobby, Lower Level*

DAY 2: SATURDAY, SEPTEMBER 23	
7-8 a.m.	**Buffet Breakfast** | *Caribbean VI and VII*
8-8:15 a.m.	**Opening** Dr. Richard Barohn and Prof Michael Hanna | *Caribbean III and IV*
SESSION V: BIOMARKERS Donovan Lott, PT, Ph.D., CSCS, Moderator | *Caribbean III and IV*	
8:15-8:35 a.m.	**Shear Wave Elastography in Neuromuscular Disease** Lisa Hobson-Webb, M.D. | *Duke University*
8:40-9 a.m.	**Unveiling the Hidden Regulators: Circulating MicroRNAs as Biomarkers in Myasthenia Gravis** Professor Anna Rostedt Punga, M.D., Ph.D. | *Uppsala University*
9:05-9:25 a.m.	**Neurofilament as a biomarker in ALS clinical trials** Robert Bowser, Ph.D. | *Barrow Neurological Institute*
9:30-9:50 a.m.	**Alternative Splicing DM** Eric Wang, Ph.D. | *University of Florida*
9:55-10:15 a.m.	**MRI as a Biomarker in the Muscular Dystrophies** Glenn Walter, Ph.D. | *University of Florida*
10:15-10:30 a.m.	**Refreshments/Exhibitor Break**
SESSION VI: AGING W. David Arnold, M.D., Moderator | *Caribbean III and IV*	
10:30-10:50am	**Proteomic Analysis of Differentially Vulnerable Synaptic Populations to Identify Regulators of Stability** Thomas Wishart, BSc., M.B.A., Ph.D. | *University of Edinburgh*
10:55-11:15am	**Motor Unit Magnetic Resonance Imaging (MUMRI) in Ageing Skeletal Muscle** Matthew Birkbeck, Ph.D. | *Newcastle University/Newcastle Upon Tyne Hospitals NHS Foundation Trust*
11:20-11:40am	**Clinical Aspects of Sarcopenia** Roger Fielding, Ph.D. | *Tufts University*
11:45 a.m.-1 p.m.	**Lunch** | *Caribbean VI and VII*
SESSION VII: EXERCISE Dr. Miguel Chuquilin, Moderator | *Caribbean III and IV*	
1-1:20 p.m.	**Effect of exercise on functional outcomes and disease pathophysiology in DM1** Elisa Duchesne, PHT, Ph.D. | *Université du Québec à Chicoutimi*
1:25-1:45 p.m.	**Exercise in SMA: More Than Just an Intervention** Jackie Montes, PT, EdD, NCS | *Columbia University Irving Medical Center*
1:50-2:10 p.m.	**Exercise as medicine for DMD** Tanja Taivassalo, Ph.D. | *University of Florida*
2:15-2:35 p.m.	**Exercise, Rehabilitation and Physical Activity in Charcot-Marie-Tooth Disease** Gita Ramdharry, Ph.D. | *University College London*
2:40-3:10 p.m.	**Refreshments/Exhibitor Break**
SPONSOR PRESENTATIONS W. David Arnold, M.D., Moderator | *Caribbean III and IV*	
3:10-3:30pm	**NMJ damage in MG: Point of no return or potential for repair?** James F. Howard, Jr., M.D., FAAN | *The University of North Carolina at Chapel Hill*
3:35p-3:55pm	**Innovation in the Development of Treatments for Neuromuscular Diseases** Jeffrey Guptill, M.D., MA, MHS, FAAN | *Efgartigimod Neuromuscular Franchise Lead Clinical Development, Argenx*
4:00-4:20pm	**Advancing Precision Genetic Medicine Through Innovative Technologies for Neuromuscular Diseases** Teji Singh, M.D. | *Sarepta Therapeutics*
4:25-4:45pm	**Addressing unmet needs in FSHD: Data from the losmapimod Phase 2 trial** Olga Mitelman, M.D. | *Head of Medical Affairs, Fulcrum Therapeutics*
4:50-5:10pm	**Lambert-Eaton Myasthenic Syndrome is Underrecognized in Small Cell Lung Cancer: An Analysis of Real-World Data** Nicholas Streicher, M.D., MPH | *MedStar Georgetown University Hospital*
5:15-5:35pm	**At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development, and manufacture of health care products, including innovative medicines and vaccines**
ROBERT C. GRIGGS ANNUAL NMSG KEYNOTE SPEAKER | *Caribbean III and IV*	
7:30-8:30 p.m.	**The Circle of Translation** Professor Mary M. Reilly | *UCL Queen Square Institute of Neurology*
8:30-9:30 p.m.	**Dinner** | *Caribbean VI and VII*
9:30-11 p.m.	**Evening Reception** | *Boca Patio*

DAY 3: SUNDAY, SEPTEMBER 24

7-8 a.m.	**Buffet Breakfast** | *Caribbean VI and VII*
8-8:10 a.m.	**Opening** Dr. Richard Barohn and Prof Michael Hanna | *Caribbean III and IV*
SESSION VIII: NMSG YOUNG INVESTIGATORS PROJECTS Dr. Karen Suetterlin, Moderator | *Caribbean III and IV*	
8:10-8:25 a.m.	**Neuromuscular Ultrasound as a Biomarker to Improve Clinical Trial Readiness in Charcot Marie Tooth Neuropathies** Tyler Rehbein, M.D., 2022 NMSG Fellow | *University of Rochester*
8:30-8:45 a.m.	**Development of Novel Imaging Biomarkers for use in Pediatric Facioscapulohumeral Muscular Dystrophy** Natalie Katz, M.D., 2023 NMSG Fellow | *Duke University*
8:50-9:05 a.m.	**2022 Shark Tank Award Update: Quantifying Idiopathic Inflammatory Myopathy-Associated Cancer Risk via Comprehensive Phenotyping of a Large UK-Wide Cohort** Alex Oldroyd, MBChB, Ph.D., MSc, MRCP | *University of Manchester*
9:10-9:25 a.m.	**2022 Shark Tank Award Update: Predictive Models in Spinal Muscular Atrophy Treated Patients Using Machine Learning** Giorgia Coratti, Ph.D. | *Pediatric Neurology and Centro Clinico Nemo Rome*
SHARK TANK SESSION Aziz Shaibani, M.D., FACP, FAAN, FANA, Moderator | *Caribbean III and IV* Shark Panel: Mazen Dimachkie, M.D., Amanda Guidon, M.D., MPH, Laurie Gutmann, M.D.	
9:30-10:40 a.m.	**Perceived Fatigability Tracker: Improving Assessment to Enhance Spinal Muscular Atrophy (SMA) Patient Outcomes** Rafael Rodriguez-Torres DPT | *Columbia University Irving Medical Center*
	Are patients with IIM at a greater risk of developing PCC than healthy controls at six months after COVID infection Tulika Chatterjee, M.D. | *University of Illinois College of Medicine at Peoria, IL*
	LITEBulb SMA - Lingual Intervention of Tongue Exercises for BULBar SMA Carla Zingariello, DO | *University of Florida College of Medicine*
10:40-10:55 a.m.	**Refreshments/Exhibitor Break**
SESSION IX: EMERGING PHENOTYPES Dr. Katy Dodd, Moderator | *Caribbean III and IV*	
10:55-11:20 a.m.	**Neuromuscular Implications of Placebo Research** Aziz Shaibani, M.D., FACP, FAAN, FANA | *Nerve and Muscle Center of Texas*
11:25-11:45 a.m.	**Treating Adults with SMA in the UK** James Lilleker, MBChB, Ph.D. | *University of Manchester*
11:50 a.m.-12:10 p.m.	**Neuromuscular Complications of Cancer Immunotherapy** Amanda Guidon, M.D., MPH | *Mass General Hospital, Harvard University*
12:15-12:35 p.m.	**Pediatric FSHD, overview and gaps in knowledge** Katherine Mathews, M.D. | *University of Iowa Carver College of Medicine*
12:35-1:45 p.m.	**Closing** | *Caribbean III and IV*
	Lunch | *Caribbean VI and VII*

Meeting Support

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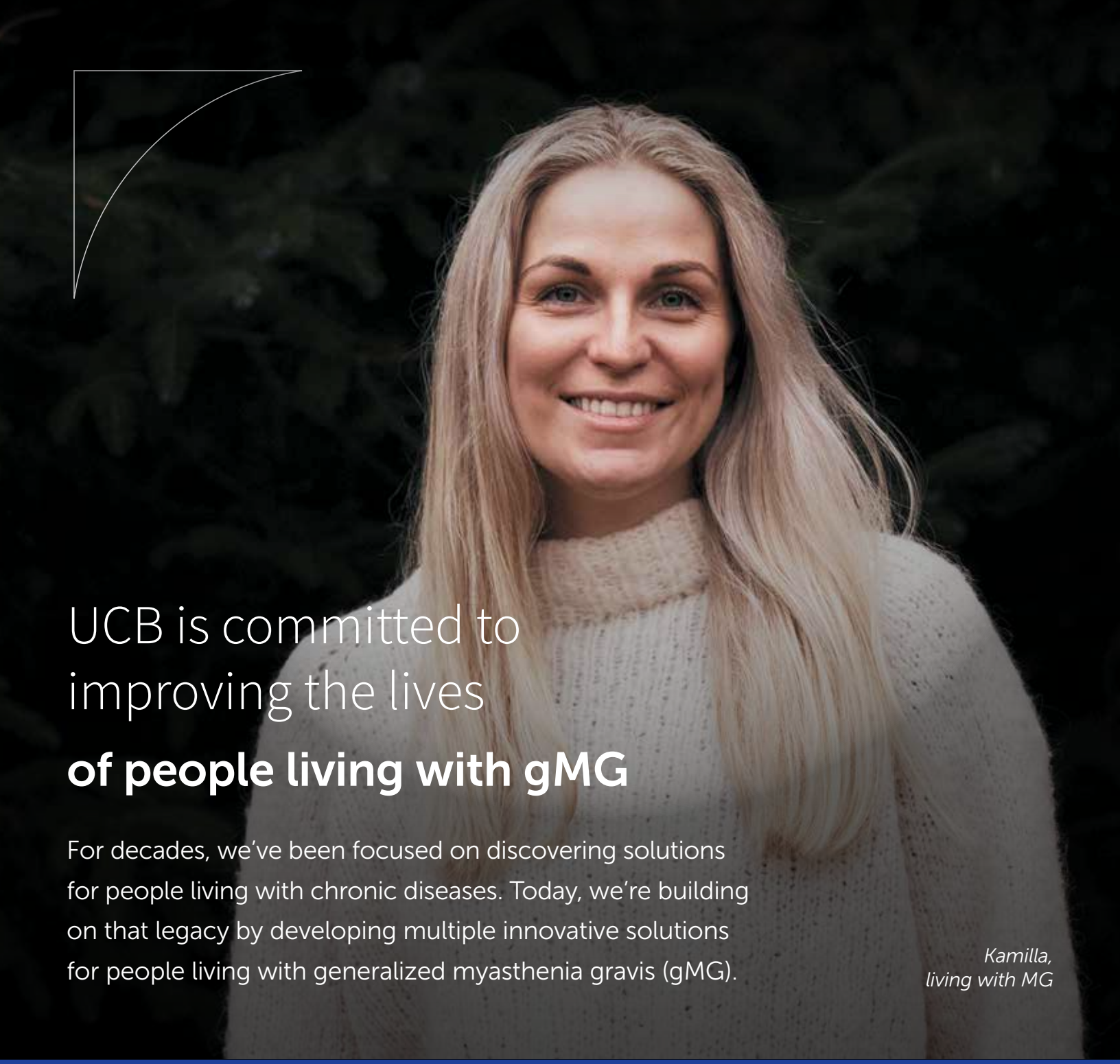


UCB is committed to improving the lives **of people living with gMG**

For decades, we've been focused on discovering solutions for people living with chronic diseases. Today, we're building on that legacy by developing multiple innovative solutions for people living with generalized myasthenia gravis (gMG).

Kamilla, living with MG

Join UCB at the 2023 Neuromuscular Study Group Annual Scientific Meeting to learn more about our recent advancements for patients living with gMG.

Inspired by **patients.**
Driven by **science.**

LEMS aware

JOIN US FOR A POSTER PRESENTATION UNCOVERING NEW DATA REGARDING THE PREVALENCE OF LAMBERT-EATON MYASTHENIC SYNDROME (LEMS) IN PATIENTS WITH SMALL CELL LUNG CANCER (SCLC)

Nicholas Streicher, MD, MPH
Assistant Professor of Neurology
Georgetown University Hospital

2023 Neuromuscular Study Group (NMSG) Annual Scientific Meeting
Saturday, September 23, 2023
5:10 PM-5:30 PM | 5-minute Q&A to follow

We hope to see you at this special presentation.
Preregistration is not required. A member of our staff will be on-site to assist with check-in.

Catalyst pharmaceuticals

This activity is not part of the official scientific program of the NMSG and is not available for Continuing Medical Education (CME) credit.

Join argenx for an Update at the 2023 NMSG Scientific Meeting

See You There!

Saturday,
September 23

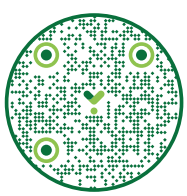
3:35 PM to 3:55 PM

Conference Center
Caribbean III and IV

Caribe Royal Hotel
Orlando, FL

Innovation in the Development of Treatments for Neuromuscular Diseases

Join us as we discuss novel targets for the treatments of neuromuscular diseases (NMDs).



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Visit Pfizer at the NMSG Annual Scientific Meeting

With our 170-year legacy of helping patients, Pfizer is providing Ig treatments to patients who rely on them[1]

- Pfizer's portfolio of SCIg and IVIg treatments supports a growing need for Ig therapy[2]
- Pfizer will continue to support the Ig community with a portfolio of Ig therapies

Pfizer

Pfizer is proud to support the Ig community with a commitment to helping meet the diverse treatment needs of patients

Visit us at our exhibit booth

Ig=immunoglobulin; IVIg=intravenous immunoglobulin; SCIg=subcutaneous immunoglobulin.

References: 1. Pfizer Inc. Company fact sheet. Accessed March 10, 2023. https://www.pfizer.com/news/media-resources/press-kits/corporate-media-kit. **2.** Fortune Business Insights. Report ID: FBI100571. February 2023. Accessed March 10, 2023. https://www.fortunebusinessinsights.com/industry-reports/immunoglobulins-market-100571.

Advance your diagnosis coding for limb-girdle muscular dystrophy

New ICD-10 codes as of October 2022

Have you been using G71.00 ("Muscular dystrophy, unspecified") or G71.09 ("Other specified muscular dystrophies") for your LGMD patients? There are more specific codes available.

Support clinical and research communities in ongoing efforts to:

- Understand LGMD epidemiology
- Assess disease progression
- Understand economic burden of LGMD
- Help manage care of patients
- Facilitate reimbursement and patient access when targeted therapies become available in the future

Diagnosis Code	Description	Subtype, if applicable
G71.031	Autosomal dominant LGMD	LGMD1/D
G71.032	Autosomal recessive LGMD due to calpain-3 dysfunction (calpainopathy)	LGMD2A/R1
G71.033	LGMD due to dysferlin dysfunction (dysferlinopathy)	LGMD2B/R2
G71.0340	LGMD due to sarcoglycan dysfunction, unspecified (sarcoglycanopathy)	
G71.0341	LGMD due to alpha sarcoglycan dysfunction (alpha-sarcoglycanopathy)	LGMD2D/R3
G71.0342	LGMD due to beta sarcoglycan dysfunction (beta-sarcoglycanopathy)	LGMD2E/R4
G71.0349	LGMD due to other sarcoglycan dysfunction	LGMD2C/R5* LGMD2F/R6*
G71.035	LGMD due to anoctamin-5 dysfunction (anoctaminopathy)	LGMD2L/R12
G71.038	Other LGMD	
G71.039	LGMD, unspecified	

*LGMD2C/R5 is caused by mutations in the SGCG gene, which encodes gamma-sarcoglycan. LGMD2F/R6 is caused by mutations in the SGCD gene, which encodes delta-sarcoglycan.

G71.038 is intended for all other forms of autosomal recessive LGMD. G71.039 is intended for patients that do not have a genetically confirmed LGMD diagnosis. If your patient has not yet received genetic testing to confirm their LGMD diagnosis, explore no-charge sponsored genetic testing options.

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NOW ENROLLING

REGENXBIO, a global leader in AAV gene therapy, is currently enrolling participants in a clinical trial of RGX-202, an investigational, one-time gene therapy for the potential treatment of Duchenne muscular dystrophy (DMD). The clinical trial will evaluate the effect of RGX-202 in boys with DMD between the ages of 4 - 11 years.

Find a study location near you!

Visit ClinicalTrials.gov (identifier # NCT05693142) for a full list of trial sites.

Find a study location

Questions?

If you would like to get in touch with a member of our Patient Advocacy team, you may email us at **Duchenne@regenxbio.com.**

If you are a healthcare provider and would like more information on our studies for patients with Duchenne, please contact us at **medinfo@regenxbio.com.**

Visit us at our NMSG Booth

REGENXBIO

ALEXION
AstraZeneca Rare Disease

Transforming Lives. Every Day.

At Alexion, our mission is to transform the lives of people affected by rare diseases and devastating conditions through the development and delivery of innovative medicines, as well as through supportive technologies and healthcare services.

Abstracts

Abstracts for research presented at this year's NMSG scientific meeting can be viewed online by scanning the QR code or visiting:
doi.org/10.17161/rrnmf.v4i4

Continuing Education

NEUROMUSCULAR STUDY GROUP (NMSG) ANNUAL SCIENTIFIC MEETING

September 22-24, 2023
Orlando, FL

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 **12.00 credits** *AMA PRA Category 1 Credits*™.
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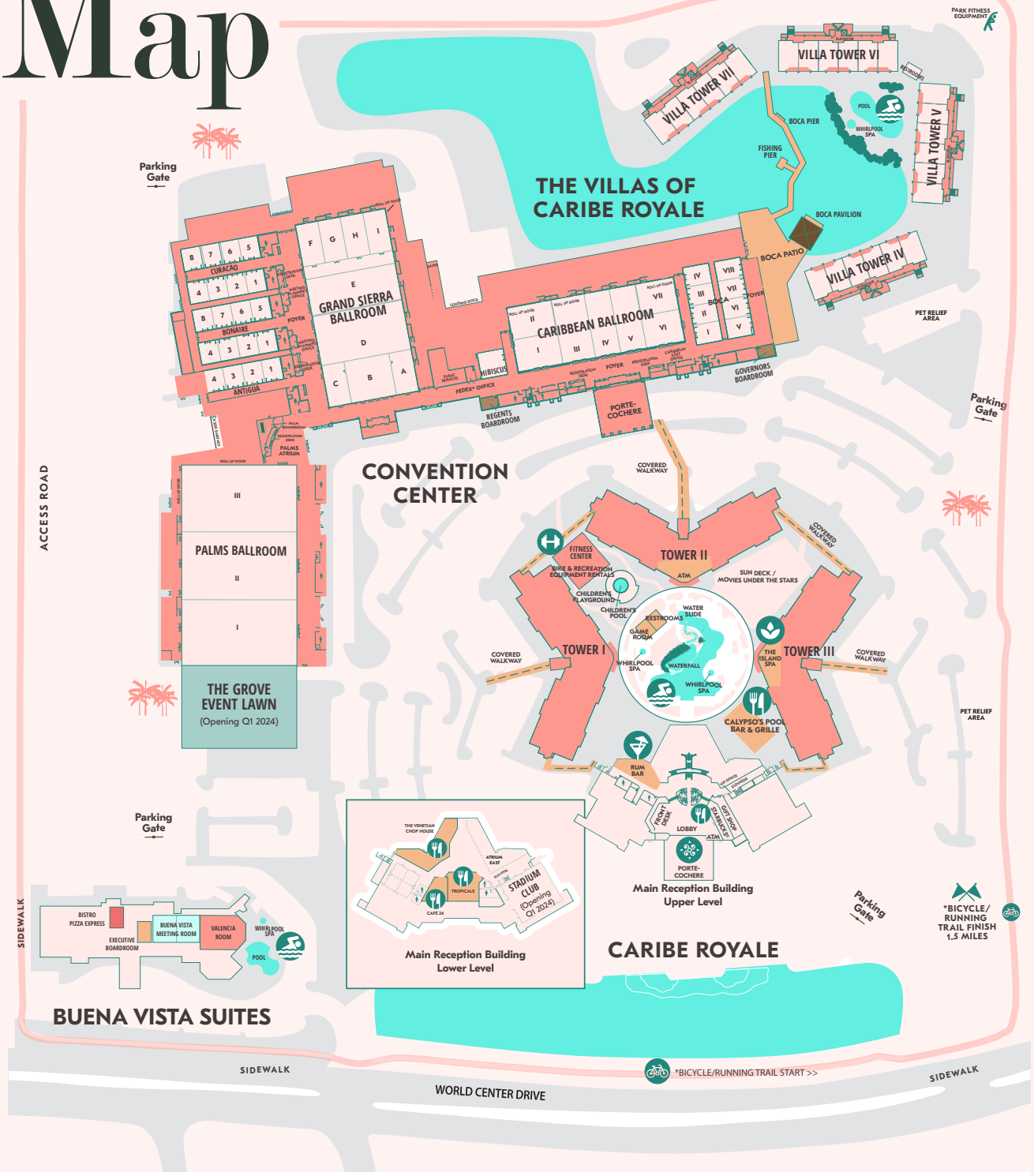
Map



Map Legend

- Entrance
- Restrooms
- Restaurants
- Bars
- Pools
- Bike Trail
- Resort Spa
- Fitness Center