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Cover image: Follower of Pieter Pourbus (Flemish, 1523/1524-1583); *Portrait of a Lady*, mid 16th century; Oil on canvas; Gift of Museum Associates (2015.8)

The painting featured on the journal's cover is from the permanent collection of the University of Missouri's Museum of Art and Archaeology (MA&A). The MA&A is located in the lower east level of Ellis Library on MU's campus, and boasts more than 16,000 objects, spanning six continents and 6,000 years. For more information, visit maa.missouri.edu. Admission to the MA&A is always free.

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Letter from the Founding Facilitator for RRNMF Volume 5, Number 2

Richard J. Barohn, MD

In this issue of our journal, we have a number of editorials that we refer to as "What's on your mind" pieces. Dr. Josh Freeman gives his views on universal health care (he is pro!). Dr. Donald Frey has a wonderful piece reflecting on the adventures of Huckleberry Finn by Samuel Clemens (aka Mark Twain). I have been re-reading all of Twain's works over the last year and Frey's views on Twain message struck a chord. Twain in his masterpiece was focused on the humanity and compassion of the relationship between Huck and Jim. I then have two editorials I first sent by email to my team at the University of Missouri about Black History month and Woman's History month. In the Women's History month piece, I co-wrote it with Grace Ashraf, a sixth grader on her way to "becoming a physician."

In the New Stuff category, Pedro Machado, Mazen Dimachkie, and others have agreed to publish the actual protocol, study design, and rational for the important randomized control trial of arimoclomol in inclusion body myositis. While the study was negative and did not show that arimoclomol could slow the course of progression of IBM, the design of the trial was sound and can be used as a blueprint for future trials. Also under New Stuff is a very nice analysis by Dr. Yuebing Li and his group reviewing the published experience of the new biologic treatments for MG (complement inhibitors and Fc receptor inhibitors) in the setting of myasthenic crisis.

Two cases are published in the Clinic Stuff category. Dr. Conway and colleagues in Cleveland describe a case of paraneoplastic anti-Hu antibody syndrome of jaw dystonia. Drs. Lizarraga and Harada from the University of Rochester and the neuromuscular group describe a case of necrotizing myopathy with anti-SRP antibodies that responded to subcutaneous methotrexate injections when other therapies had failed. And Suzann Beaupark describes a myasthenia gravis case utilizing the Mary Walker Effect to develop a new test to elicit fatigable myasthenia gravis eye signs. Suzann Beaupark, who has myasthenia gravis herself, provides an excellent historical account of Mary Walker's contribution to our understanding of MG.

In the Looking Back/Looking Forward section, the team behind the neuromuscular update course (directed by Dr. Mazen Dimachkie) publish the next in a series of lectures from the course on the pattern recognition approach to myopathy and neuromuscular junction disorders. In the last issue we published the pattern recognition approach to neuropathy and neuronopathy as well as the laboratory approach to these conditions. We are planning to publish further lectures from this popular course.

In the Other Stuff category, we are grateful that Dr. Michael Abraham has allowed us to publish another of his wonderful poems. This one is titled Culmination. Michael is an interventional neuroradiologist and neurocritical care physician at the University of Kansas Medical Center.

In the Meeting Stuff category, there are two meetings we are highlighting. The first is the recent Festschrift for Dr. Robert Griggs, aka "Berch." I am publishing the comments I made at the meeting. This was a special event that was put on by the department of neurology at the University of Rochester in Rochester, New York. I am also including the program from this event and some information on Dr. Griggs. The event also marked the delivery of the Dr. Richard Moxley endowed annual lecture, which was delivered by Dr. Griggs. Drs. Moxley and Griggs have been giants in the field of neuromuscular disease and many of us have had the privilege of working with them over our careers. And in the case of Dr. Griggs, to say that I worked with him is an understatement as he truly has been my primary "long distance mentor" for almost 40 years and I talk about some of the ways I have benefited from this mentor-mentee relationship. To be successful you must have good mentors, and I have been very fortunate in that regard.

The second meeting stuff piece is the abstracts, agenda, and welcome comments for the annual Neuromuscular Study Group meeting that is going to held in Tarrytown, New York on September 20 to 22. This is the 25th anniversary meeting! This year we have an all-time high number of participants and submitted abstracts. This meeting continues to expand and be a major academic highlight of the year where junior and senior neuromuscular clinician researchers gather to discuss progress on their work and develop new projects. A big part of the meeting is the interaction with representatives from industry. With all the major advances in new drugs for neuromuscular disorders, there are more opportunities than ever for the academic clinician scientists and the industry scientists to work together and develop new therapeutic approaches for our patients.

The cover of this issue is a work of art from the University of Missouri Museum of Art and Archaeology. I have been frequenting the museum on the MU campus since I arrived four years ago, and it recently reopened in new digs in the classic Ellis Library on our campus. I am always struck by the gems of art in this small but mighty museum. The work of art on the cover is one of my favorites, even though the artist is unknown. It is a portrait of a woman from the sixteenth century. While the artist is "anonymous," the museum has enough information to say the artist is a "follower of Pieter Pourbus (Dutch/Flemish, 1523/1524-1583)." The title is simply "Portrait of a Lady." It was a gift to the Museum of Art and Archaeology at the University of Missouri-Columbia by the Museum Associates in 2015. I think it is an exquisite work of art.

Once again, I want to thank all our authors for submitting manuscripts. And our reviewers and faculty facilitators and student editors. Jiji Oufattole MD has graduated and is now becoming a surgeon. Dr. Oufattole has worked on the journal with me since I arrived at the University of Missouri in 2020. Over the last two years she has served as the senior student editor and has trained the other student editors who are now active in the journal. I cannot thank Jiji enough for the amazing work she has done on the journal for four years. And Lauren Peck, our undergraduate facilitator, has graduated and will soon be going to school to become a physician assistant. Lauren has also provided enormous help on the journal and review articles. And of course, we are always grateful to Marianne Reed and Eric Bader in the digital publishing unit at KU. We are so grateful to have the publishing platform and their expertise to publish these issues.

Rick

Racism and lack of social services: The status of women's health care in the US

Joshua Freeman, MD

Originally published in Dr. Freeman's blog "Medicine and Social Justice." https://medicinesocialjustice.blogspot.com/

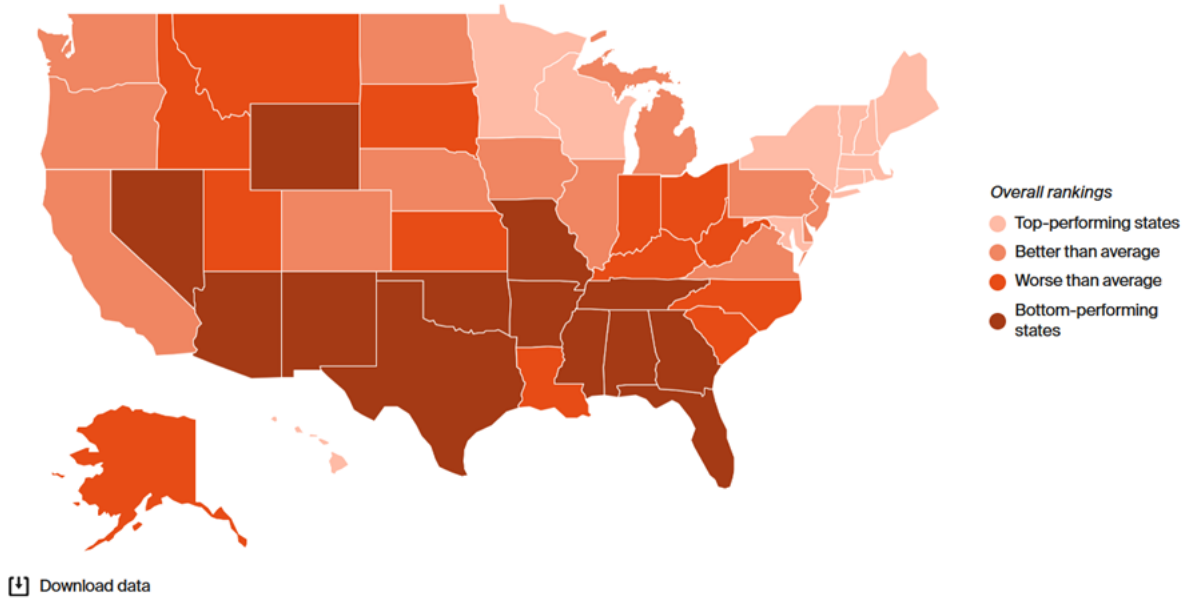
A recent publication from the Commonwealth Fund is the 2024 State Scorecard on Women's Health and Reproductive Care in which they rank all the states (plus DC) for how well that care is provided and the health status of women that results. The map below gives an overall sense (darker is worse), and the entire ranked list can be found in an interactive table in the document.

The first thing that we see is that there are no real surprises. Massachusetts is at the top and Mississippi is at the bottom. The other top and bottom states are the usual suspects for almost anything that is beneficial to people, with the Northeast doing best and the old Confederacy doing the worst. There are always some minor shifts within those groups, and in this ranking we see that Louisiana* and South Carolina are only "worse than average" not in the "bottom performing states", while disappointing to me, Arizona and New Mexico are in the lowest group. The reasons are a little different in different states; the Arizona legislature is (narrowly; we hope to flip it this year) controlled by Republicans who are as mean and nasty as those in the deep south. New Mexico is controlled by Democrats, but it is very poor. Poor is a big component of health status, and its fingerprints are all over this data on women's health. 'Despite a small rebound in women's life expectancy in 2022, it remains at its lowest since 2006,' says the report.

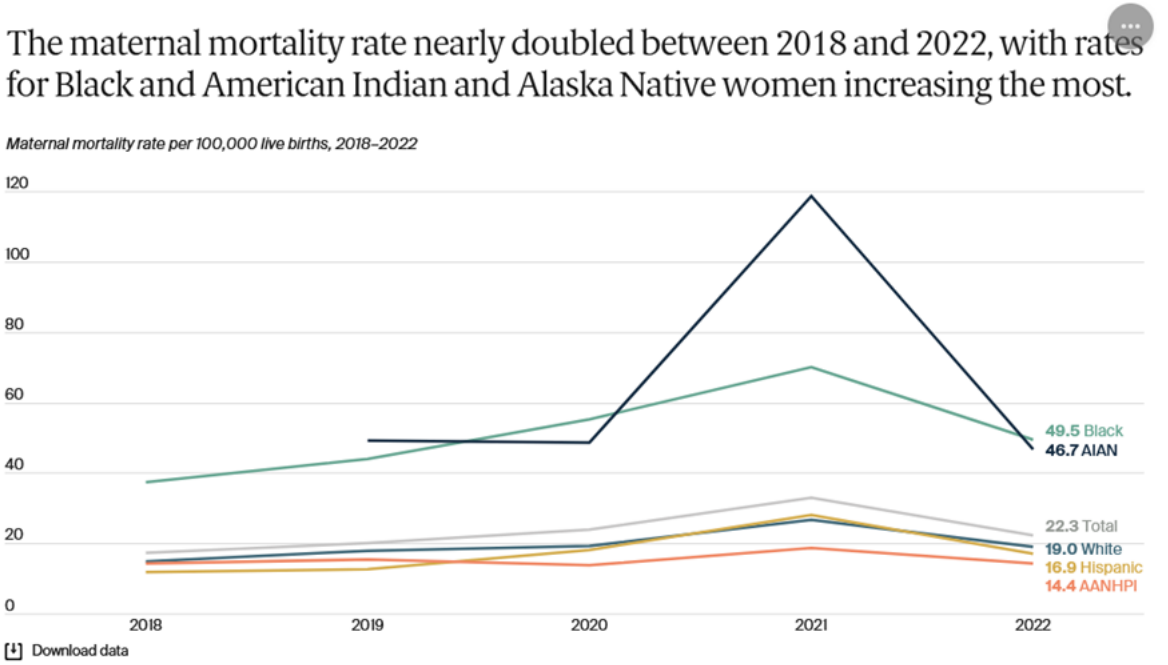
Abortion care – access to it and the quality of it – has dominated the national political discussion. I don't want to minimize it; it is incredibly important that women can have abortions, it is a privacy issue, and it will hopefully have major negative repercussions for the party whose agenda is to limit it. That the greatest restrictions on abortion are in the same states that have the worst women's health status is neither a coincidence nor a surprise; the people who control these states and are anti-abortion are also racists and are unwilling to provide funds to improve the health standards of people who are women, minority, or poor – and especially all three. But it goes far beyond abortion:

> For health outcomes, we measured all-cause mortality, maternal and infant mortality, preterm birth rates, syphilis among women of reproductive age, infants born with congenital syphilis, self-reported health status, postpartum depression, breast and cervical cancer deaths, poor mental health, and intimate partner violence.

Abortion is not the major component of poor reproductive health status. Maternal mortality rates are shockingly high in the southeast, and worst in the Mississippi Delta. The US overall does not do very well in this area, especially as it is the richest country in the world. Data from the CIA (!) shows that in 2020, the US maternal mortality rate overall was 21/100,000, tied with Lebanon, Grenada, and Malaysia and just slightly worse than the West Bank or (pre-war) Gaza Strip. This was (and



Data: Overall performance scores from the Commonwealth Fund 2024 State Scorecard on Women's Health and Reproductive Care.



remains) much higher than Canada (11), UK (10), and most of Europe, including eastern Europe at 5 or less! (Note, showing the same dramatic racist differences as in the US, Israel is at 3). Of course, this overall rate in the US is driven by the states with the highest rates, with the worst states having a range of 34.1-51.7! While this is largely the result of excessively high rates in minority women, it is worth noting that the maternal mortality rate for white women in the US is over 19!

This is a good time to discuss the segmentation of results for maternal mortality (and all-cause mortality, and really most things) by race or ethnicity. In the bizarre, perverted, and of course racist excuse provided by many (racists) for why the US' maternal mortality is so high compared to civilized countries, it is often said "it's the minorities that drive the rate up". In addition to ignoring the excessively high rate for US whites (19) it is scarcely an excuse; indeed, it is an indictment. It is not only that the US, unlike civilized countries, does not provide health care for everyone, essentially free of charge at the time of service (that is, paid for by tax revenues, as well as costing a lot less because of the elimination of the incredible profits extracted by middlemen such as insurance companies in the US). It also provides lousy social services of all kinds, not ensuring, as civilized countries do, housing, food, and education for everyone. These (the "social determinants of health") are even more important than medical care in creating improved health status. And, while other countries do spend much more money than we do on providing them, the total cost per capita is probably less than what the US spends on health care alone! Of course, much of the spending (particularly on social services and health care for the poor, like Medicaid) is on a state basis; that is why there are such differences between the Massachusetts' and Mississippi's in this Commonwealth Fund study. And what are the practices that work? Again, no surprise:

In our scorecard, states with the lowest rates of maternal mortality had:

- more maternity care providers (Vermont #2, Connecticut #3)
- fewer women with no prenatal care (Vermont #1, California #3, Connecticut #5)
- fewer women with no postpartum checkups (Vermont #1)
- fewer uninsured women ages 19–64 (Vermont #3)

It cannot be stated too strongly that public funds should support a public social safety net, not bloat the profits of private companies as they do here in the US! This is most well-documented for the piggish pharmaceutical

industry and the entirely unnecessary (indeed, far worse than unnecessary, destructive and evil) for-profit health insurance industry, which I have discussed many times. But it is also the other parts of the health care industry, particularly delivery systems (e.g., hospitals). Yes, the for-profits, hospitals and nursing homes and other facilities, especially those run by corporations. But it is also the ostensible "non-profits", which do their best to emulate for-profits by doing everything possible to exclude patients without insurance or with Medicaid, pay their CEOs (and other C-suite executives) exorbitant salaries, and channel huge earnings into subsidiaries that actually own or invest in for-profit enterprises! This is documented in Why many nonprofit (wink, wink) hospitals are rolling in money by Elisabeth Rosenthal (Washington Post, July 29, 2024) and discussed by Don McCanne in Health Justice Monitor 'Not-for-profit care begets profits'. Dr. McCanne cites a study by KFF showing even a program providing "street medicine", healthcare for the homeless, in California is making money by getting huge amounts of Medicaid funds. Providing health care to homeless people is a good thing, something we need more of. If I had my druthers, I would rather see them making money than huge "non-profit" hospital systems (or of course straight for-profits, although those at least pay taxes), but they shouldn't be either.

In health care, and in all social service, all the public money should go to providing direct care (OK, maybe with a 2% overhead, like Medicare – but NOT Medicare (Dis) Advantage – has). Zero dollars should go to profits (or "excess" income that can be invested for profit), bloated salaries, and the like.

We have too many people, women and others, dying because of the lack of such care.

*Louisiana just put the two drugs used for medication abortion, mifepristone and misoprostol, on its state's controlled dangerous substances list, like narcotics. So look for LA's ranking to drop!

Spring Rain and Mark Twain

Donald R. Frey, MD

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

Without getting into details, I've had to deal with some health issues this past month. I haven't written a damn thing.

Any Midwesterner can tell you that once you've lived through a drought, those first drops of rain that hit your face feel so good they almost make you dizzy. So it is with writing, I guess. I don't know when I'll write again. But right now, it feels pretty good.

My home state of Missouri has produced an array of authors. Langston Hughes, T.S. Eliot, Tennessee Williams, Dick Gregory, and of course, Chuck Berry. Most came from the more cultured Eastern side of the Show-Me State. My own Northwestern corner, in contrast, is better known for Harry Truman, Walter Cronkite, and everyone's favorite outlaws, the James boys.

But of all the Missourians who ever touched their pen to a page, none could really hold a candle to Samuel Clemens, aka Mark Twain.

Volumes have been written about Twain. They sit alongside the volumes he himself wrote. There's no need to recapitulate his life here. Suffice it to say he ranged from Hannibal, Missouri to Nevada to California to Connecticut to New York and eventually throughout the world. From the time he could walk, he soaked up everything he saw. And in his work, he spilled it all out like a flood.

He wrote compulsively, page after page. Editing carefully, he never minced words, but never strung them out either. In language as plain as worn denim and manure-stained boots, he threw the world at his readers. The joy and the pain. The humor and the tragedy. The humane and the inhumane. The racism and the kindness. The people who were beaten down and the people who were incredibly wealthy for no other reason than just being lucky as hell.

Yes, he made damn good money doing it. Much of it he blew. But in the end, he was someone who simply had to write.

And all of it in longhand, thousands of words each day. As he aged, his dominant right arm became so arthritic he could barely use it. So he forced himself to learn to write with his left.

Faulkner called him the Father of American Literature. Hemmingway went further. "All modern American literature comes from one book by Mark Twain called *Huckleberry Finn*," he declared. "It's the best book we've had. All American writing comes from that. There was nothing before. There has been nothing as good since."

And Twain did it all with no formal training in the art of writing. No classes in literature. No creative writing courses. He was forced to drop out of school in the fifth grade to support his family. All he could do was devour every book he could get his hands on.

He's often remembered for a sarcastic wit that could to make you fall out of your chair. But beneath it all, was the pain of someone who'd seen tragedy after tragedy after tragedy.

"The source of all humor," he wrote, "is not laughter, but sorrow."

He hated racists, colonialists, and imperialists. He raged against the Spanish-American War. He insisted Teddy Roosevelt was a bag of hot air, who didn't do nearly enough to reign in turn-of-the-century Wall Street financiers.

His words could cut down the high and mighty like a scythe through ripe wheat. "What if I were an idiot?" he once asked. "And what if I were a member of Congress? But I repeat myself."

Later it was "First God made idiots. Then he made School Boards."

Wouldn't he have a field day with those two institutions today.

The human ego was likewise his target, as was religious pomposity. "I believe the only reason God created man was because he was disappointed with the monkey," he quipped.

He travelled to Hawaii, and couldn't understand why Christian missionaries couldn't just leave the Islanders alone. In Australia, India, and South Africa, he was outraged at how Europeans treated native peoples. "Man is the only animal that loves his neighbor as himself, and then cuts his throat if his theology isn't straight," he grumbled.

In what many consider the greatest novel ever written, a young boy named Huckleberry Finn rafts down the Mississippi River with a runaway slave named Jim. Over time, they bond, and Huckleberry learns the reason Jim has run away–he learned that he was about to be sold down river, and possibly separated forever from his wife and daughter.

Jim misses his wife and daughter terribly and worries about their future. The pain is so powerful Jim sometimes cries himself to sleep at night. He's determined to somehow gain his freedom, find a job, and save enough money to buy his family out of bondage.

But Huckleberry is terrified by what his religious upbringing has taught him. Preachers in Missouri insisted that slavery was ordained by the Almighty, and to assist a runaway slave was sure to bring about the wrath of God. Hell and damnation would be waiting.

This makes Huck tremble. An eternity in hell? He's torn as to what to do. Finally, while Jim is sleeping, Huck

writes out a letter to give to the authorities explaining that Jim is a runaway.

But after the most intense soul-searching a young boy can do, Huck makes his decision. He tears up the letter, and refuses to betray Jim. In what may be the most profound seven words ever written, Huck says simply, "All right, then, I'll go to hell."

In an era of hypocrisy, extreme nationalism, and wild-eyed religiosity, how many today would have the courage and insight of that scruffy kid from Missouri?

Since his death, Twain has been both praised and scorned, his books sometimes promoted and too often banned. He's been called a saint, a sage, and a genius by some and a scoundrel, a blasphemer, and a hypocrite by others.

But through it all, his words still stand. Plain, often unsophisticated, sometimes vulgar, and frequently uncomfortable. Just like he was.

We could only wish that another like him would emerge at time when this world needs them most.

And if any of you would like to respond, and have your own favorite quote(s) by Twain to add, feel free to do so.

Recognizing Black History Month 2024

Richard J. Barohn, MD

Over the years, I have shared the work of Black physician scientists like Dr. Louis Tompkins Wright and Dr. Charles Richard Drew who have made significant contributions to the medical field in the United States. Recently, I came across this information highlighting other influential African American physicians and scientists.

In addition to these physician scientist leaders, there are numerous outstanding African American nurses whose contributions are also important to commemorate. I would like to recognize just a few of these nurses and their lasting contributions.

Harriet Tubman, 1822-1913

Harriet Tubman, photo courtesy of the Library of Congress

Many of us are familiar with the name Harriet Tubman, a formerly enslaved woman who was instrumental in leading slaves to freedom as a conductor on the Underground Railroad. Tubman served the Union Army during the Civil War, and while many of us are familiar with her story, her service as a nurse is often overlooked.

In 1862, Tubman served as a nurse in Beaufort, South Carolina, and was appointed matron of a hospital in Fort Monroe in Virginia where she cared for sick and wounded Black soldiers. Unfortunately, Tubman did not receive pay or pension as a nurse during the Civil War.

In the book *Harriet: The Moses of Her People*, author Sarah H. Bradford wrote this of Tubman: "She nursed our soldiers in the hospitals, and knew how, when they were dying by numbers of some malignant disease, with cunning skill to extract from roots and herbs, which grew near the source of the disease, the healing draught, which allayed the fever and restored numbers to health."

Despite her service, Tubman was denied a nurse's pension, even after the petitioning of then U.S. Secretary of State William H. Seward. The only monetary acknowledgment she received for her service was through her widow's pension based on her husband's service in the Civil War, which was increased from $8 to $20 a month in consideration of her personal services to the country.

Estelle Massey Osborne, 1901-1981

Estelle Massey Osborne, photo courtesy of the New York University Rory Meyers College of Nursing

Estelle Osborne attended nursing school in St. Louis at a time when only 14 of the 1,300 nursing schools in the country admitted Black students. During this time, the American Nursing Association refused membership to Black nurses. Osborne studied at St. Louis City Hospital, which later became known as the Homer G. Phillips Hospital. This hospital was the largest exclusively Black, city-operated general hospital in the world and at the time, served more than 70,000 people.

Over the next few years, Osborne earned several accolades, including being the first Black nurse to receive the Julius Rosenwald Fund Scholarship and the first Black nurse to earn a master's degree, receiving a Master of Arts from Columbia University Teachers College in New York City.

She then became a researcher for the Rosenwald Fund, where she studied rural life in the deep South, with a focus on ways to improve health education in rural Black communities. Following a five-year period as president of the National Association of Colored Graduate Nurses, Osborne returned to the Homer G. Phillips Hospital as its first Black superintendent of nurses as well as the first Black female director of the hospital's nursing school.

In 1943, to address a shortage of nurses both in the U.S. and overseas in the military, Congress enacted the Bolton Act, which appropriated $160 million in federal funding to nursing schools across the country. Osborne played a key role in ensuring funds from the Bolton Act benefited Black nurses. She would go on to serve in several prominent national leadership positions and helped pave the way for generations of Black nurses.

Mary Eliza Mahoney, 1845-1926

Mary Eliza Mahoney, photo courtesy of the National Women's History Museum

Mary Mahoney was the first Black nurse to graduate from nursing school and receive a professional nursing license in the U.S. Born in 1845 in Boston to freed slaves, she studied at Phillips School in her hometown, which in 1855, became one of the first integrated schools in the country.

As a teenager, Mahoney began working at the New England Hospital for Women and Children, where she worked for 15 years in a variety of roles, including as a nurse's aide. In 1878, a 33-year-old Mahoney was admitted to the hospital's nursing school. It was a demanding program and few who began their studies graduated. Though in 1879, Mahoney completed the program and became the first African American in the country to earn a professional nursing license.

Following her training, she continued a 40-year-career in the profession. In 1896, she joined the Nurses Associated Alumnae of the United States and Canada, the precursor to the American Nurses Association. Upon her retirement, she continued to fight for women's rights and was among the first women who registered to vote in Boston following the ratification of the 19th Amendment.

As we take just a glimpse into the lives of these distinguished leaders in nursing, it is important for us to recognize and reflect upon their important contributions.

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Recognizing Women's History Month 2024

Richard J. Barohn, MD
Grace Ashraf

For the last several years, I have highlighted prominent women in medicine like Dr. Rosalind Franklin, Florence Nightingale and Dr. Jane Cooke Wright.

I was recently made aware of another prominent female physician, Dr. Elizabeth Blackwell, the first woman in America to receive a medical degree. She was a strong advocate for women in medicine and eventually opened a medical college for women.

Dr. Elizabeth Blackwell, Feb. 3, 1821 - May 31, 1910

In the early 1800s, there were few medical colleges in our country--and none that accepted women. Despite this, Blackwell was inspired to pursue an education in medicine after a dying friend shared that her experience would have been better if she had a female physician.

After applying to several medical schools without success, Blackwell was admitted into Geneva Medical College in rural New York. Still, she faced discrimination and was shunned by her fellow students who felt she should pursue a more traditional career path. Undeterred, she eventually gained the respect of her colleagues and professors and received her medical degree from Geneva Medical College in 1849, graduating first in her class.

Her education took her to Europe, where she took an interest in preventive care and personal hygiene as a means to prevent outbreaks often caused by male physicians who did not wash their hands between patients.

Following her additional training, she returned to New York where she continued to face discrimination, this time from patients who did not want to be treated by a female physician. Nevertheless, she continued to rally and opened her own clinic to treat impoverished women before eventually helping to open the New York Infirmary for Women and Children and a medical college to help provide opportunities for fellow female physicians.

It was great to learn more about Dr. Blackwell and her impact on medical education. Please join me in celebrating and recognizing women in medicine during Women's History Month.

I used this story about Dr. Elizabeth Blackwell in my every two-week Executive Vice Chancellor/Dean column at the University of Missouri. I received a number of compliments on the piece. My favorite was from one of the neurologists at MU, Komal Ashraf DO. She told me her daughter Grace wrote her own piece on Dr. Blackwell for a fifth-grade milestone project. Grace brought another perspective on Dr. Blackwell. I asked Dr. Ashraf and Grace if I could publish her piece along with mine in this issue of RRNMF Neuromuscular Journal. I was happy they said yes. So here is my co-author's part of the story on Dr. Elizabeth Blackwell.

Elizabeth Blackwell, by Grace Ashraf

Did you know that Elizabeth Blackwell was the first female physician and doctor? She convinced male doctors and teachers that women could participate in more than house-related activities such as cooking and sewing. Elizabeth had many hardships throughout her life. Elizabeth was very brave.

Elizabeth Blackwell was born on February 3rd,1821, in Bristol, England. She was raised by her dad, Samuel Blackwell, and her mom, Hannah Blackwell. She was also raised by her Aunt Bar and a governess. Her mom was very busy with nine kids and Elizabeth was the third oldest. When Elizabeth's dad died when she was seventeen, her mom turned their house into a boarding school for girls, Elizabeth never married, but she adopted a girl named Katherine "Kitty" Barry from an Irish orphanage.

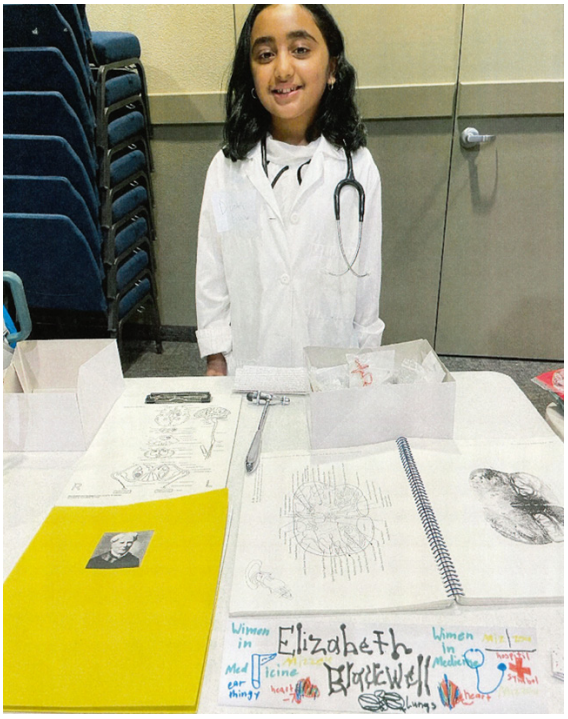
Elizabeth Blackwell's major accomplishment was that she became the first woman doctor. She is famous because of her strong character traits such as bravery and perseverance. Elizabeth even became someone special to America by also going through very hard and tough times. Elizabeth was an amazing person.

Elizabeth Blackwell made it possible for women to realize that they could do more than domestic activities, she made this possible by becoming the first woman doctor and surgeon. She did this by working very hard. She pushed through adversity, she had to advocate for herself, she studied diligently, and she persevered. She changed history by empowering other women to go into medicine. Elizabeth showed powerful men that women were able to use their intellect for helping to heal people and have similar jobs as them. She was the first female to publish a medical article, and she was a leader in organizing healthcare providers during the American Civil War.

Elizabeth Blackwell burned her eyes when she was treating someone with medicine. From that time until her death, she was blind in one eye. After that, Elizabeth wanted to quit her efforts to become a doctor, but her sister encouraged her to keep going. Elizabeth regained her strength and confidence. She was brave, confident, loving, and convincing.

Elizabeth was also strong and smart. In London, she helped start a medical school for women. One of her quotes is "It is not easy to be a pioneer- but oh, it is fascinating!"

Elizabeth Blackwell died on May 31st, 1910, in her house in Hastings, Sussex, after suffering a stroke that paralyzed half of her body. Fifteen years before she died, Elizabeth published her autobiography, *Pioneer Work in Opening the Medical Profession to Women*. In 1906, Elizabeth took her first and last car ride while visiting the United States of America.



Grace Ashraf and her mother, UMHC neurologist Dr. Komal Ashraf, DO at Grace's 5th grade Milestone Project presentation

Design and Rationale for a Randomized, Double-blind, Placebo-controlled Phase 2/3 Trial of Oral Arimoclomol in Inclusion Body Myositis

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*Members of the Arimoclomol in IBM Investigators of the Muscle Study Group are listed in Appendix 1 at the end of this document

ABSTRACT

Introduction/Aims: Inclusion body myositis (IBM) is the most common progressive, debilitating muscle disease in people over the age of 50 years, for whom there is no effective treatment. Here, we present the design and rationale for one of the largest clinical studies conducted in IBM to date, to evaluate the efficacy, safety, and tolerability of arimoclomol, a novel, oral amplifier of the cellular heat shock response.

Methods: This is a randomized, double-blind, placebo-controlled, parallel group trial conducted at 11 centers in the US and one center in the UK. Eligible patients had a diagnosis of IBM fulfilling European Neuromuscular Centre 2011 criteria, with onset of weakness at > 45 years of age. Enrolled participants were randomized 1:1 to receive either oral arimoclomol citrate 1,200 mg/day or matching placebo for up to 20 months. The primary endpoint is the change from baseline to Month 20 in the IBM functional rating scale (IBMFRS) total score. The secondary efficacy endpoints include evaluations of participants' functional abilities, strength, and physical health-related quality of life (HRQoL). A sub-study was planned to characterize muscle changes using MRI in a subset of participants.

Discussion: This study will generate important clinical data on a novel therapeutic strategy for patients with IBM, a population with no current treatment options.

Key words: heat shock response; IBMFRS; inclusion body myositis; MRI, muscle atrophy.

Introduction

Sporadic inclusion body myositis (IBM) is the most common progressive, debilitating muscle disease in people over the age of 50 years. IBM typically presents with insidious, asymmetric weakness that predominantly affects the quadriceps and/or finger flexors.[1] The epidemiology of IBM varies between and within countries, with an estimated overall prevalence of 46 per million (increasing to 139 per million for people above the age of 50 years).[2] The pathogenesis of IBM is complex and remains poorly understood but is thought to consist of an interplay between inflammatory and degenerative pathways.[3] The degenerative theory of IBM hypothesizes that the disease is driven by aging of the muscle fiber associated with accumulation and aggregation of misfolded, ubiquitinated, multiple-protein aggregates in a genetically susceptible individual.[4] Accumulation of these protein aggregates within muscle fibers is considered likely to trigger an inflammatory/immune response as a secondary consequence of muscle degeneration.[5]

Arimoclomol is a hydroxylamine derivative that acts as a co-inducer of the natural cellular 'heat shock response.'[6] The heat shock response enhances expression of heat shock proteins (HSPs), including 'molecular chaperones,' so called because they promote natural folding of new proteins and refolding of damaged or mutated proteins.[7] Activation of the heat shock response may be beneficial in diseases characterized by toxic protein aggregates, such as IBM. In fact, levels of HSP70 have been shown to be increased in IBM muscle biopsies.[8] Arimoclomol has been shown to co-induce molecular chaperone genes in cell lines and in isolated cells/tissues, meaning that it further elevates chaperone protein levels that are already increased by physiological or metabolic stresses.[9] It accomplishes this by prolonging activation of the transcription factor heat shock factor-1 (HSF-1).[6,10] Arimoclomol may inhibit the process of protein misfolding and aggregation in IBM by helping muscle fibers to up-regulate inducible HSPs.[9] As a result, arimoclomol may slow or prevent muscle degeneration in this otherwise relentlessly progressive, debilitating disease.

A preliminary study was performed in which 24 participants were randomly assigned in a 2:1 ratio to receive either arimoclomol 300 mg/day or matching placebo in a double-blind manner.[9] The data suggested that arimoclomol was safe and well tolerated in IBM.[9] In

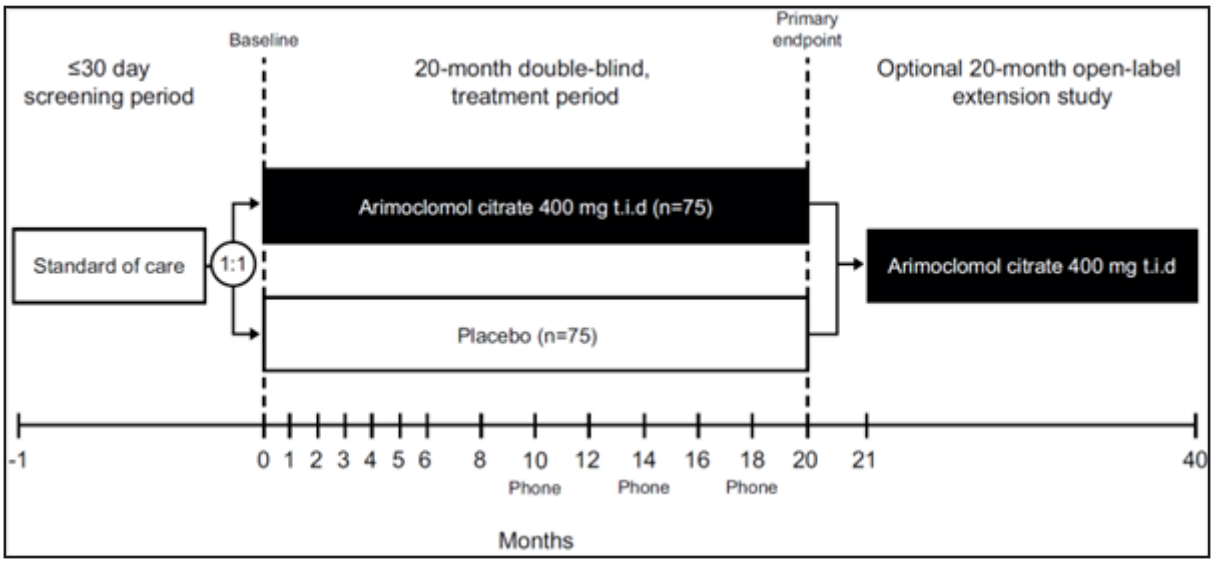

Figure 1: Trial Design

parallel, arimoclomol reduced key pathologic markers of IBM in two robust rat myoblast *in vitro* models representing the degenerative and inflammatory components of IBM.[9] Arimoclomol also improved disease pathology and muscle function in mutant valosin-containing protein (VCP) mice, which develop IBM-like muscle histopathologic features.[9]

Based on these data, the lead investigator group (primary investigator [PI]: M.M.D., and co-PIs: R.J.B., P.M.M., and M.G.H.) from the Neuromuscular Study Group (NMSG, musclestudygroup.org) secured funding from the United States Food and Drug Administration Office of Orphan Products Development in 2015 for a larger-scale clinical trial of arimoclomol in patients with IBM. With funding secured, the commercial developer of arimoclomol, Orphazyme A/S, expressed interest in increasing their collaborative role and this trial became a joint industry-academia co-funded study. This collaborative partnership with Orphazyme A/S has been fundamental not only for providing the experimental drug but also for assuming the operational trial conduct and ensuring compliance with International Council for Harmonization (ICH) guidelines.[11] This strong partnership drove regulatory interactions and processes and allowed for the initiation of add-on studies to investigate pharmacokinetics, perform further validation studies of clinical endpoints, assess muscle magnetic resonance imaging (MRI) outcomes, and provide for an open-label extension trial.

The resulting study is a randomized, double-blind, placebo-controlled trial of arimoclomol in patients with IBM. With planned enrollment of 150 patients and follow-up duration of up to 20 months, it represents one of the largest and longest studies ever conducted in an IBM population. We recently published the study results.[12] Here, we provide a summary of the rationale for the study and overview of its design.

Methods

The objectives of this study are to evaluate the efficacy, safety, and tolerability of arimoclomol citrate 1,200 mg/day (400 mg three times daily [t.i.d.]; equivalent to 744 mg/day arimoclomol free base) compared with placebo in participants with IBM over 20 months. An exploratory sub-study was planned to characterize muscle changes using MRI in a subset of participants from the main study.

Study design

This is a randomized, double-blind, placebo-controlled, parallel-group, Phase 2/3 trial conducted at 11 centers in the U.S. and one center in the U.K. (**Figure 1**; ClinicalTrials.gov no. NCT02753530). The MRI sub-study is being conducted at one center in the U.S. (University of Kansas Medical Center) and one in the U.K. (University College London), using the UCL Queen Square quantitative muscle MRI protocol.[13] Eligible participants were randomized 1:1 to receive either oral arimoclomol citrate 400 mg t.i.d. or matching placebo for up to 20 months. Randomization was computer generated using a permuted block algorithm to randomly allocate study drug to randomization numbers. Study medication bottle numbers to be dispensed at the baseline visit were distributed to centers in advance of randomization. Randomization was stratified by study center.

In response to the COVID-19 pandemic restrictions, the study protocol was amended after study initiation to allow additional phone visits (beyond those prospectively planned), home health nursing visits for safety laboratory blood-draws, and delivery of study medication to participants unable to attend the clinic. On completion of follow-up in this study, qualified participants will be offered the opportunity to enter a separate 20-month, single-arm, open-label extension study (IBM-OLE study; ClinicalTrials.gov no. NCT04049097).

Governance of study conduct and scientific direction is provided by a Scientific Steering Committee comprising the authors M.M.D. (Chair), M.G.H., P.M.M., R.J.B., and M.P.M. (MSG Biostatistician), and a representative of the study sponsor, Orphazyme A/S. The study protocol was approved by the relevant Institutional Review Board (IRB)/Research Ethics Committee, utilizing a single IRB review via the SMART IRB platform for the 11 US centers,[14] and the Health Research Authority approval process for the U.K. center. The trial is being conducted in accordance with the protocol, the principles of the Declaration of Helsinki, the ICH Good Clinical Practice guidelines, and all applicable laws and regulations, including local laws and guidance. An independent Data Monitoring Committee was established to assess study drug safety and tolerability at regular intervals. Informed consent was provided by all participants prior to any study procedure; the signature of an impartial witness was permitted for those with impaired manual dexterity. Consent for blood samples to be stored in the Biobank for future use was voluntary. Separate informed consent was also provided by participants included in the optional MRI sub-study.

Participants

A full summary of inclusion and exclusion criteria is provided in **Table 1**. Eligible participants had a diagnosis of clinicopathologically defined IBM, clinically defined IBM, or probable IBM as defined by the European Neuromuscular Centre IBM research diagnostic criteria 2011,[15] with onset of weakness at >45 years of age. Participants were also required to demonstrate the ability to rise from a chair without support from another person or device and to walk at least 20 feet / 6 meters with or without an assistive device. Patients were excluded if they were taking >7.5 mg/day prednisolone or equivalent, taking intravenous immunoglobulin (IVIg), or other immunosuppressants, within the last 3 months. A short course (up to 4 weeks) of systemic prednisolone >7.5 mg/day or equivalent was allowed during the study for conditions not related to IBM (e.g., asthma). Topical, nasal, and ocular corticosteroids were permitted unless they were being widely applied or the severity of the underlying condition made them unsuitable in the investigator's opinion. Local steroid injections were allowed.

Table 1: Participant eligibility criteria

Inclusion criteria	Exclusion criteria
1. Meet any of the European Neuromuscular Centre IBM research diagnostic criteria 2011 categories for IBM.[15]	**1.** History of any of the following: • Chronic infection, particularly HIV or hepatitis B or C • Cancer other than basal cell cancer <5 years prior • Other chronic serious medical illnesses
2. Demonstrate the ability to rise from a chair without support from another person or device.	**2.** Presence of any of the following on routine blood screening: • White blood cells <3,000/µL • Platelets <100,000/µL • Hematocrit <30% • Blood urea nitrogen >30 mg/dL • Creatinine >1.5 times the ULN • Serum albumin <3 g/dL with symptomatic liver disease
3. Able to walk ≥20 feet / 6 meters with or without an assistive device. Once arisen from the chair, the participant may use any walking device (i.e., walker/frame, cane, crutches, or braces). They cannot be supported by another person and cannot use furniture or a wall for support.	**3.** History of most recent creatine kinase >15 times the ULN without any other explanation besides IBM.
4. Age at onset of weakness >45 years.	**4.** History of non-compliance with other therapies.
5. Body weight ≥40 kg.	**5.** Use of testosterone except for physiologic replacement doses in case of androgen deficiency. The participant must have documented proof of the androgen deficiency.
6. Able to give informed consent.	**6.** Coexistence of any other disease that would be likely to affect outcome measures.
	7. Drug or alcohol abuse within the past 3 months. The participant has recent history (within 6 months before the screening visit) of chronic alcohol or drug abuse that may compromise the participant's safety or ability to participate in study activities. Cannabis for IBM symptoms is allowed (where legal).
	8. Participation in a recent drug study ≤30 days prior to the screening visit or use of a biologic agent <6 months prior to the screening visit.
	9. Women who are lactating or pregnant, or sexually active female participants of childbearing potential who intend to become pregnant or are unwilling to use a highly effective method of contraception during the trial through 1 month after the last dose of trial medication. Sexually active males with female partners of childbearing potential who are unwilling to use a condom with or without spermicide in addition to the birth control used by their partners during the trial until 3 months after the last dose of trial medication unless surgically sterile (vasectomy).
	10. Participants taking >7.5 mg prednisolone or equivalent, or participants on IVIg or other immunosuppressants within the last 3 months. Topical, nasal, and ocular corticosteroids are allowed unless they are being widely applied or the severity of the underlying condition makes them unsuitable in the investigator's opinion. Local steroid injections are allowed.
	11. Clinically significant renal or hepatic disease, as indicated by clinical laboratory assessment (results ≥3 times the ULN for alanine aminotransferase combined with bilirubin ≥2 times the ULN; symptomatic liver disease with serum albumin <3 g/dL; or creatinine ≥1.5 times the ULN). Laboratory tests may be repeated once at the screening visit. Reasons to repeat laboratory tests may include suspension of the medication causing the laboratory abnormality, any other suspected cause no longer existing, or ruling out laboratory error.

HIV, human immunodeficiency virus; IBM, inclusion body myositis; IVIg, intravenous immunoglobulin; MRI, magnetic resonance imaging; ULN, upper limit of normal.

Participant criteria for the MRI sub-study were the ability to give informed consent, the ability to have a baseline MRI performed prior to or within 4 weeks of starting treatment, and the absence of an issue that would prevent MRI (such as a heart pacemaker or other metallic implant, or uncontrollable claustrophobia). The investigator was responsible for evaluating each participant for potential MRI contraindications prior to each MRI.

Study treatment and dosing

Study treatment consists of two 200 mg arimoclomol citrate capsules administered orally t.i.d. (total daily dosage of 1,200 mg/day), or matching placebo, for up to 20 months. Study drug dosing can be interrupted for up to 4 weeks if a participant experiences an intolerable adverse event (AE). If the same AE persists on rechallenge with the full dosage, the dosage can be reduced by half (i.e., one 200 mg capsule t.i.d.) for the remainder of the study, or the treatment is permanently discontinued if this lower dosage is not tolerated.

We selected the arimoclomol citrate dosage of 1,200 mg/day for this study based on FDA guidance for a dosage approaching the maximum tolerated dose. Phase 1 studies showed that arimcolomol was tolerated at dosages up to 1,800 mg/day for 5 days and well tolerated at a dosage of 1,200 mg/day over 28 days (data on file).

Arimoclomol and matching placebo can be administered in multiple ways to accommodate increasing dysphagia associated with disease progression. Capsules can either be swallowed whole or opened and dispersed in 10–30 mL of liquid or soft food. Once dispersed in water, the capsule contents can also be administered via a feeding tube.

Study procedures and outcomes

All study objectives and endpoints are summarized in **Table 2**. The primary endpoint is the change from baseline to Month 20 in the IBM functional rating scale (IBMFRS) total score. Initially derived from the amyotrophic lateral sclerosis functional rating scale, the IBMFRS is a quickly administered (10-minute) rating scale used to determine participants' assessment of their capability and independence.[16] It includes 10 items, graded on a Likert scale from 0 (being unable to perform) to 4 (normal) (**Appendix 2**). These include one item for swallowing, three items for upper limb function (handwriting; cutting food and handling utensils; and fine motor tasks), three items for activities of daily living (dressing; hygiene; and turning in bed and adjusting covers) and three items for leg function (changing position from sitting to standing; walking; and climbing stairs). The sum of the 10 items yields a value between 0 and 40, with a higher score representing less functional limitation. The IBMFRS has been shown to correlate well with strength measures derived from maximum voluntary isometric contraction testing (MVICT), manual muscle testing (MMT), and handgrip dynamometry, while being a more sensitive gauge of participant functional change than these measures.[16] The IBMFRS has also been shown to correlate well with HRQoL as assessed by the 36-item Short Form Health Survey (SF-36).[16]

Key secondary endpoints include evaluations of participants' functional abilities and strength as listed in Table 2. Evaluators are undergoing periodic training throughout the study to maintain proficiency in study assessments.

Study procedures and assessments were performed over the course of 16 visits, as outlined in **Table 3**. The study was prospectively designed so that in-person visits become less frequent over time, with use of phone calls for visits at Months 10, 14, 18, and 21 to reduce the burden of participation.

Table 2: Study objectives and endpoints

Objectives	Endpoints
Primary objective	***Primary endpoint***
To evaluate the efficacy of arimoclomol citrate at a daily dose of 1,200 mg (400 mg t.i.d.) compared with placebo in the treatment of sporadic IBM at 20 months.	Change from baseline to Month 20 in the IBMFRS total score
	Secondary efficacy endpoints include changes from baseline to Months 12 and 20 in the following measures: • IBMFRS total score (Month 12) • Hand grip strength using the Jamar device • Modified Timed Up and Go (mTUG) • Manual Muscle Testing total score (24 muscles) • 6-min walk test (6MWT) distance • Physical component score of the Short-Form 36 health survey (SF-36) • Knee extensor strength (strongest knee at baseline) • Health Assessment Questionnaire-Disability Index (HAQ-DI) • 2-min walk test (2MWT) distance • Mental component score of the SF-36 • Patient Global Impression of Severity (PGIS) • Patient Global Impression of Change (PGIC) • Clinician Global Impression of Severity (CGIS) • Clinician Global Impression of Change (CGIC) • Accumulated number of falls and near-falls
Safety objective	***Safety endpoints***
To evaluate the safety and tolerability of 1,200 mg/day arimoclomol citrate (400 mg three times daily) compared to placebo in the treatment of sporadic IBM over 20 months.	Safety was assessed at scheduled visits and by recording adverse events and serious adverse events throughout the study. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1.
MRI sub-study objective	***Primary MRI sub-study endpoint***
To characterize muscle changes using MRI in a subset of participants	Change from baseline to Month 20 in the MRI whole fat fraction of the thigh
	Secondary MRI sub-study endpoints
	Secondary endpoints will be the change from baseline to Month 12 in whole fat fraction of the thigh, and the changes from baseline to Months 12 and 20 in magnetization transfer ratio (MTR), cross-sectional area (CSA), remaining muscle area (RMA), and muscle volume of the thigh. Changes from Month 12 to Month 20 in each of these endpoints will also be explored.

FET, Force Evaluation and Testing; MRI, magnetic resonance imaging; SF-36, 36-Item Short-Form Health Survey; t.i.d., three times daily.

Table 3: Schedule of study procedures

Visit #	1	2	3	4	5	6	6a	7	8	9	10	11	12	13	14	15
Month	-1 (Sc)	0 (Base)	1	2	3	4	5	6	8	10	12	14	16	18	20 ‡	21
Consent	X															
Eligibility	X															
Medical History	X															
IBM History	X															
Vital signs, including weight	X	X	X	X		X			X		X		X		X	
Physical Exam	X		X	X	X	X	X	X	X		X		X		X	
Safety Labs**	X		X	X	X	X	X	X	X		X		X		X	
Urine Preg***		X	X	X		X			X		X		X		X	
Blood for CN1A Ab levels	X										X				X	
Blood for biobanking	X					X			X		X				X	
POP PK			X						X							
ECG	X										X				X	
Randomization****	X															
Dispensing of Medication		X	X			X			X		X		X			
Return of Medication			X			X			X		X		X		X	
PGIS/PGIC		X				X			X		X		X		X	
C-SSRS	X		X	X	X	X	X	X	X		X		X		X	
Muscle Testing (MMT, MVICT)		X				X			X		X		X		X	
6 min walk test		X				X			X		X		X		X	
SF-36		X				X			X		X		X		X	
HAQ-DI		X				X			X		X		X		X	
Falls diary		X	X	X		X			X		X		X		X	
Grip		X				X			X		X		X		X	
IBMFRS		X	X	X	X	X		X	X	X	X	X	X	X	X	
mTUG		X				X			X		X		X		X	
CGIS/CGIC		X				X			X		X		X		X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X*

Phone visits are shaded gray.
Note: Visit windows for all visits are ± 7 days relative to baseline.
* = Only stop dates for ongoing AEs and new SAEs
** = Full Safety Labs
*** = Urine pregnancy prior to dispensing study medication
**** = Randomization procedure
‡ = Upon completion of this study, qualified patients may provide informed consent and enter an open label extension study at the Month 20 visit. Assessments recorded at this visit will also constitute the first assessments of such open-label extension study.

Sample size calculations

The standard deviation of the change from baseline to Month 12 in the IBMFRS total score was estimated to be 2.9 based on data from the preliminary trial of arimoclomol.[9] Assuming a 12-month IBMFRS total score change of −3.5 in the placebo group, similar to what was observed in the preliminary arimoclomol trial, a total of 136 participants (68 per treatment group) would provide 80% power to detect a treatment group difference in mean response of 1.4 points at Month 12 (representing a 40% slowing of the rate of decline) using a two-sample t-test and a 5% significance level (two-tailed). To account for an anticipated 10% dropout rate, the planned sample size was inflated to 150 participants (75 per group).

This calculation was performed in the absence of preliminary data on changes in the IBMFRS total score over a 20-month period, so it strictly applies only to a trial with 12-month follow-up. However, it will also apply to this trial with a 20-month follow-up if, as expected, the magnitude of the treatment effect relative to the standard deviation of the change in IBMFRS total score does not diminish over time.

Statistical methods

The primary efficacy endpoint was analysed using the restricted maximum likelihood-based approach of mixed model for repeated measurements, implemented using PROC MIXED in SAS. This approach included all observed follow-up data from visits originally intended to take place in person (months 1, 2, 3, 4, 6, 8, 12, 16, and 20), even if the visits were done remotely owing to the COVID-19 pandemic. It also accommodated missing data under the missing-at-random assumption. The statistical model included terms for treatment group, visit, centre, baseline IBMFRS total score, the interaction between treatment group and visit, and the interaction between baseline IBMFRS total score and visit. An unstructured covariance matrix was used to model dependence of the IBMFRS measurements within the same participant. The Satterthwaite approximation was used to estimate the denominator degrees of freedom. This model was used to estimate the adjusted group mean changes from baseline at each timepoint, as well as the treatment group difference in adjusted group means at month 20 along with its associated 95% CI and p value. For participants with no post-baseline observations, the baseline value was carried forward to month 1 to permit inclusion of those participants in the analysis.

All secondary efficacy endpoints were analysed in a similar way to the primary endpoint; a sequential hierarchical testing procedure was used for the primary and confirmatory secondary endpoints, using the hierarchy specified previously in the Outcomes section, to control the overall type I error probability at 5%. The confirmatory testing stopped at the first endpoint not meeting statistical significance.

Discussion

Given the severe disability and QoL impairment associated with advanced IBM, there is a substantial unmet need for effective treatment capable of altering the disease course.[17] Arimoclomol amplifies the cellular heat shock response to promote natural folding of new proteins, and refolding or degradation of damaged proteins associated with the degenerative component of the disease. This large-scale, controlled study was planned to provide a rigorous assessment of the efficacy and safety of that strategy in IBM.

This ultimately negative trial occurred against a backdrop of repeated failure for investigational IBM therapies in previous clinical studies.[12] Despite a clear inflammatory component of disease pathology, multiple studies of immunosuppressive agents (including corticosteroids, IVIg, methotrexate, and azathioprine) have shown no beneficial effect.[3] Similarly, trials of immune system cytokines and cytokine receptor inhibitors in IBM have failed to show clinically meaningful benefit.[3] The failure of targeting inflammation was one of the main arguments in favour of a predominantly degenerative mechanism of IBM disease.

Consequently, research has turned to other strategies, namely those combating muscle wasting and atrophy, such as modulation of the myostatin pathway. The human monoclonal antibody bimagrumab is an inhibitor of activin type 2 receptor signalling that blocks the action of activin and myostatin and significantly improves lean muscle mass in patients with IBM.[18] However, the RESILIENT study of 251 IBM participants showed that improvements in muscle mass with bimagrumab (3 or 10 mg/kg dosages) failed to translate into a significant improvement relative to placebo in the primary endpoint of change from baseline to Week 52 in 6MWT distance, as well as in multiple other secondary endpoints (isometric quadriceps muscle strength, hand grip and pinch strength, number of falls, swallowing efficiency, and short physical performance battery).[18,19]

It has been noted that the 6MWT may not be an optimal primary outcome measure for IBM, given that performance on the test is dependent on multiple factors other than leg muscle function, including cardiopulmonary function, fatigue, skeletal pain, motivation and general physical fitness.[20] The IBMFRS, used in this study, is a broader assessment of 10 distinct functional activities relevant to the overall impact of IBM on participants' lives.[16,21] Therefore, it may be a more sensitive and reliable tool than the 6MWT for assessing clinical benefit in IBM. The IBMFRS has also been shown to correlate well with measures of muscle strength and HRQoL in IBM.[16] The FDA regulatory division accepted the IBMFRS as a clinically relevant primary endpoint for this study in 2016 as part of our Type C meeting correspondence.[11] Our study's key secondary efficacy endpoints will provide evaluations of participants' specific functional abilities, strength, and HRQoL. The selected outcome measures are generally accepted based

on the known impact of IBM on muscle strength, function, and HRQoL over time. Finally, we recently investigated the IBMFRS and demonstrated its content validity, inter-rater and intra-rater reliability, and equivalence between in-person and phone administration.[22]

An exploratory sub-study was planned to assess the value of quantitative MRI assessments as outcome measures in IBM.[13,23] This is to characterize muscle changes using a subset of patients participating in the main study, the primary endpoint being the change from baseline to Month 20 in thigh muscle MRI fat fraction. MRI can non-invasively monitor muscle properties in IBM with high responsiveness and has shown validity by correlation with conventional functional measures.[13,24] These data suggest that MRI biomarkers might be valuable in clinical trials, particularly for treatments in the mid stages of clinical development (e.g., proof-of-concept studies). The characterization of muscle changes using MRI in this sub-study will provide insight into the pathophysiology of IBM and the influence of arimoclomol relative to placebo on these changes.

This study is noteworthy as an example of a successful collaboration between industry and academia and serves as a useful model for future trials.[11] The collaboration, including a Scientific Steering Committee comprising members of the MSG and Orphazyme A/S, harnessed our complementary strengths to overcome numerous challenges in conducting an international study in a rare disease. The cost and complexity of clinical research can be a significant barrier and both partners worked together to secure adequate funding from commercial and academic sources. A clear program of research defined at the outset provided decision-making clarity. However, central to our success to date has been a partnership based on respect and trust with regular and honest communication in a collegial atmosphere. Industry-academia collaborations conducted in this way can be mutually beneficial in achieving our ultimate shared goal of bringing new medicines to the clinic, particularly in rare disease.

In conclusion, this study was planned to generate important data on the efficacy, safety, and tolerability of arimoclomol for people with IBM, a group with no treatment options to change disease trajectory at present. The trial outcome for this novel therapeutic strategy may also have implications for our understanding of IBM pathophysiology.

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Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure of conflicts of interest

P.M.M. has received consulting fees and funding support from Orphazyme A/S, paid to his academic institution (University College London), for the oversight and conduct of this study.

R.J.B. has received funding from the FDA Office Orphan Products Development grant for his role in this study.

M.P.M. has no relevant conflicts of interest to declare.

C.S. and T.B. are employees of Orphazyme A/S.

M.G.H. receives research funding from the Medical Research Council UK and has previously acted a consultant for Novartis and for Orphazyme A/S.

M.M.D. is a consultant for Orphazyme A/S and received funding support, paid to his academic institution (University of Kansas Medical Center, Research Institute), from Orphazyme A/S for the oversight and conduct of this study.

Abbreviations

AE: Adverse event
Base: Baseline
CGI-C/CGI-S: Clinical Global Impression of Change/ Severity
cN1A Ab: Cytosolic 5′-nucleotidase 1A antibody
C-SSRS: Columbia Suicide Severity Rating Scale
FDA: Federal Drug Association
FET: Force Evaluation and Testing
HAQ-DI: Health Assessment Questionnaire – Disability Index;
HIV: Human immunodeficiency virus
HRQoL: Health-related quality of life
HSF-1: Heat shock factor-1
HSPs: Heat shock proteins
IBM: Inclusion body myositis
IBMFRS: Inclusion body myositis functional rating scale
ICH: International Council for Harmonization guidelines
IRB: Institutional Review Board
IVIg: Intravenous immunoglobulin
MMT: Manual muscle testing

MRI: Magnetic resonance imaging
MSG: Muscle Study Group
mTUG: Modified Timed Up and Go test
MVICT: Maximum voluntary isometric contraction testing
6MWT: Six-minute walk test
OLE: Open label extension
PGI-C/PGI-S: Patient Global Impression of Change/Severity
Pop PK: Population pharmacokinetics
QoL: Quality of life
SAE: Serious adverse event
Sc: Screening
SF-36: 36-item Short Form Health Survey
t.i.d: Three times daily
UCL: University College London
UK: United Kingdom
ULN: Upper limit of normal
US: United States of America

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Appendix 1. Arimoclomol in IBM Investigators of the Muscle Study Group

Investigator name	**Investigator center**
Anthony A. Amato	Brigham & Women's Hospital, Boston, MA, USA
Richard J. Barohn	University of Missouri, Columbia, MO, USA
Emma Ciafaloni	University of Rochester Medical Center, Rochester, NY, USA
Mazen M. Dimachkie	University of Kansas Medical Center, Department of Neurology, Kansas City, KS, USA
Miriam Freimer	The Ohio State Wexner Medical Center, Columbus, OH, USA
Summer B. Gibson	University of Utah School of Medicine, Salt Lake City, UT, USA
Michael G. Hanna	University College London, Queen Square Institute of Neurology, London, UK
Sarah M. Jones	University of Virginia, Charlottesville, VA, USA
Todd D. Levine	HonorHealth, Phoenix, AZ, USA
Thomas E. Lloyd	Johns Hopkins University, Baltimore, MD, USA
Pedro M. Machado	University College London, Queen Square Institute of Neurology, London, UK
Tahseen Mozaffar	University of California, Irvine, Orange, CA, USA
Aziz I. Shaibani	Nerve & Muscle Center of Texas, Houston, TX, USA
Matthew Wicklund	University of Colorado – Denver, Denver, CO, USA

Appendix 2. IBM Functional Rating Scale [15]

Item	Score
1. Swallowing	4 - Normal 3 - Early eating problems – occasional choking 2 - Dietary Consistency changes 1 - Frequent choking 0 - Needs tube feeding
2. Handwriting (dominant hand prior to IBM onset)	4 - Normal 3 - Slow or sloppy; all words are legible 2 - Not all words are legible 1 - Able to grip pen but unable to write 0 - Unable to grip pen
3. Cutting food and handling utensils	4 - Normal 3 - Somewhat slow and clumsy, but no help needed 2 - Can cut most foods, although clumsy and slow; some help needed 1 - Food must be cut by someone but can still feed slowly 0 - Needs to be fed
4. Fine motor tasks (opening doors, using keys, picking up small objects)	4 - Independent 3 - Slow or clumsy in completing task 2 - Independent but requires modified techniques or assistive devices 1 - Frequently requires assistance from caregiver 0 - Unable
5. Dressing	4 - Normal 3 - Independent but with increased effort or decreased efficiency 2 - Independent but requires assistive devices or modified techniques (Velcro snaps, shirts without buttons, etc.) 1 - Requires assistance from caregiver for some clothing items 0 - Total dependence
6. Hygiene (bathing and toileting)	4 - Normal 3 - Independent but with increased effort or decreased activity 2 - Independent but requires use of assistive devices (shower chair, raised toilet seat, etc.) 1 - Requires occasional assistance from caregiver 0 - Completely dependent
7. Turning in bed and adjusting covers	4 - Normal 3 - Somewhat slow and clumsy but no help needed 2 - Can turn alone or adjust sheets but with great difficulty 1 - Can initiate but not turn or adjust sheets alone 0 - Unable or requires total assistance
8. Sit to stand	4 - Independent (without use of arms) 3 - Performs with substitute motions (leaning forward, rocking) but without use of arms) 2 - Requires use of arms 1 - Requires assistance from device/person 0 - Unable to stand
9. Walking	4 - Normal 3 - Slow or mild unsteadiness 2 - Intermittent use of assistive device (ankle foot orthosis, cane, walker) 1 - Dependent on assistive device 0 - Wheelchair dependent
10. Climbing stairs	4 - Normal 3 - Slow with hesitation or increased effort; uses handrail intermittently 2 - Dependent on handrail 1 - Dependent on handrail and additional support (cane or person) 0 - Cannot climb stairs

Usage of Newer Immunotherapies in Myasthenic Crisis – A Review of the Literature

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ABSTRACT

Myasthenic crisis is the most severe manifestation of myasthenia gravis that requires the use of invasive or non-invasive ventilation. Treatment of myasthenic crisis includes removal of triggering factors, airway management, and supportive care. Traditionally, plasmapheresis and/or intravenous immune globulin are the most commonly administered disease modifying treatments, and both are effective in the majority of patients leading to discontinuation of mechanical or non-invasive ventilation. More recently approved therapies for myasthenia gravis, namely, complement or neonatal Fc receptor inhibitors, may serve as additional options of rescue therapies for patients with myasthenic crisis, especially those who do not respond to traditional treatment. In this review, we provide a summary of recently published case reports and case series describing the successful usage of these newly approved therapies in the setting of myasthenic crisis.

Keywords: myasthenia gravis, myasthenic crisis, eculizumab, ravulizumab, efgartigimod

Introduction

Myasthenia gravis (MG) is a rare condition of autoimmunity at the neuromuscular junction, specifically at the postsynaptic components of the neuromuscular junction, with an annual incidence of 2-15 per million but a steadily rising prevalence as treatments and outcomes of the disease improve.[1,2] Most patients with MG first present with ocular symptoms such as ptosis or diplopia.[2,3] About 75% of patients develop generalized disease within the first 2-3 years following presentation, with a predilection for bulbar, neck, and proximal limb muscles, and about 40% of patients develop respiratory muscle weakness, including exertional dyspnea and orthopnea.[3]

Myasthenic crisis (MC), the most severe form of MG, is defined as the "worsening of myasthenic weakness requiring intubation or noninvasive ventilation to avoid intubation" by one international consensus[4] and has an estimated in-hospital mortality of 4.47%.[5] The incidence of MC, which typically occurs within the first 2-3 years of diagnosis, is approximately 12-16%.[5] Impending crisis describes a rapid clinical worsening of MG that could lead to crisis in days to weeks.[4] Impending or manifest MC can be triggered by a number of etiologies, including infections, surgery, medication changes, or pregnancy.[6] Bulbar weakness or severe disease status at onset, muscle-specific kinase (MuSK) antibody positivity, presence of thymoma, and prior history of MC increase risk of MC.[7–9]

The mainstay of MG treatment involves the suppression of various steps of the immune cascade responsible for MG pathogenesis by immunomodulating medications or thymectomy. Traditional MG immunosuppressants include corticosteroids, steroid-sparing agents, intravenous immunoglobulin (IVIG), and plasmapheresis (PLEX). Corticosteroids are the first line immunosuppressant in all clinical subtypes of MG. Due to the long-term side effects associated with corticosteroid use, a non-steroidal immunosuppressant (including azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, tacrolimus) is usually initiated in MG patients requiring long-term immunosuppression. IVIG and PLEX are primarily employed in the acute setting for treatment of MG exacerbation or MC.

Despite the wide range of treatment options available for MG, the management of MC remains a clinical challenge, particularly in the subset of patients resistant to standard rescue therapies. Acute immunomodulation with PLEX or IVIG remains the main rescue therapy options for MG crisis, each leading to significant improvement in approximately 70% of MG patients. The onset of their efficacy typically occurs 3-5 days following initiation. IVIG is easily administered while PLEX should only be provided in centers with experienced teams. However, up to 10-20% of patients in MC do not respond to these treatments, requiring tracheostomy or frequent hospitalizations with repeated rescue therapy administration.[10,11] This challenge underlines the need for additional, more effective acute treatment options for MC.

As opposed to the traditional MG therapies providing broad-spectrum immunosuppression, novel MG immunotherapies target specific steps of the MG immune cascade. Five new MG drugs received United States Food and Drug Administration approval in the last six years for use in generalized MG, including eculizumab, ravulizumab, zilucoplan, efgartigimod, and rozanolixizumab.[12–18] Eculizumab, ravulizumab, and zilucoplan are complement inhibitors that lead to clinical improvement by preventing the formation of the membrane attack complex at the neuromuscular endplate, thereby maintaining the integrity of the acetylcholine receptors at the postsynaptic junction.[19] The role of complement activation in the pathogenesis of MG renders it as a favorable therapeutic target particularly in acetylcholine receptor antibody positive (AChR+) MG.[20]

Efgartigimod and rozanolixizumab are neonatal Fc receptor (FcRn) inhibitors which function by the blockage of FcRn-mediated recycling of pathogenic antibodies, leading to their increased lysosomal degradation. FcRn inhibitors are comparable to PLEX in reducing IgG levels, but with a prolonged effect and less significant complications.[21]

The efficacy of these new therapies in treating generalized MG were all demonstrated in pivotal trials (e.g., REGAIN, CHAMPION, ADAPT, RAISE, MycarinG) eventually leading to FDA approval for their use in AChR+ generalized MG.[13–18] These early trials, however, excluded patients in MC, leaving the role of these newer immunotherapies in the treatment of patients amid MC unclear. We present here a review of the current literature on the application of these newer immunotherapies in the treatment of MC.

Methods

The PubMed, Google Scholar, and Embase databases were queried for cases of MC and treatment with either eculizumab, ravulizumab, efgartigimod, zilucoplan, or rozanolixizumab up to March 28, 2024. Case reports and case series of adult patients in MC or impending MC were included. Publications were reviewed in their entirety, and patient characteristics such as demographics, prior MG treatment, and effect of immunotherapy treatment, as well as complications during the treatment course were recorded. All publications were in English except for one, which was written in Japanese.

Results

There were 8 total publications from 2018 to 2023 reporting on a total of 16 patients presenting with manifesting or impending MC treated with eculizumab (Table 1). Of these 16 patients, 9 (56.3%) were female and average age at eculizumab administration was 51.9 years (range: 22 to 79 years). A total of 15 (93.8%) patients had AChR+ MG (one patient had seronegative MG) and 6 (37.5%) patients were found to have a thymoma. Prior to MC, 7 (43.8%) patients were taking tacrolimus, 2 (12.5%) patients were taking azathioprine, and 1 (6.25%) patient was taking mycophenolate mofetil. A total of 14 (87.5%) patients received PLEX and/or immunoadsorption, 14 (87.5%) patients received IVIG, 3 (18.8%) patients received pulse intravenous steroids, 1 (6.25%) patient received intravenous pyridostigmine, and 2 (12.5%) patients received rituximab as rescue treatments. On average, patients received 2.12 rescue treatments, defined as a combination of either PLEX, IVIG, pulse steroids, IV pyridostigmine, or rituximab, prior to initiation of eculizumab.

Eculizumab was administered as an initial dose of 900 mg weekly for four weeks followed by 1200 mg every two weeks thereafter, consistent with the dosing regimen used in the REGAIN trial in all reports except for one where dosage was not defined. While there was heterogeneity in how outcomes of eculizumab treatment were reported, all patients were able to be liberated from invasive mechanical ventilation after treatment with eculizumab, although one patient remained on intermittent non-invasive ventilation through a trach collar. Time to response to eculizumab varied, with one patient reportedly being extubated the day following eculizumab treatment while other patients took anywhere from 1 to 6 weeks for weaning of mechanical ventilation. All patients experienced clinical improvement and no relapse of MC was reported. The most common complication reported was infection, including sepsis or pneumonia which occurred in 3 (18.8%) patients. There were no reports of meningococcal infection although there was 1 case reporting polymicrobial infection partially consisting of encapsulated organisms. Other complications reported during therapy included intestinal perforation, thymoma-associated multiorgan autoimmunity, and delay in immune therapy due to logistical reasons. No other complications were reported in the remaining 10 (62.5%) patients.

The number of cases reported involving the use of efgartigimod and ravulizumab in MC thus far is limited. Watanabe et. al described the use of efgartigimod in a 54-year-old female with AChR+ MG diagnosed 5 months prior who presented with neck muscle weakness and dysphagia. She continued to worsen despite 6 PLEX sessions and 2 g/kg IVIG, eventually requiring intubation due to progression of her bulbar symptoms. Subsequently, she was administered efgartigimod at 10 mg per kilogram of body weight weekly, each cycle of four weekly infusions for a total of three cycles, which led to resolution of her weakness 18 days after the first infusion and, eventually, successful extubation. Her anti-AChR antibody titers showed a consistent decline in parallel with the clinical improvement.

Konen et. al described the use of ravulizumab in a 34-year-old female with AChR+ MG with symptom onset eight months prior who presented with progressive bulbar and limb weakness. Her MG was refractory to treatments of IVIG, PLEX, and rituximab and she was in impending MC. Consequently, she was administered one dose of 3g ravulizumab infusion and achieved clinical improvement and stability over a course of two weeks, which was sustained up to 19 weeks following the first administration of ravulizumab. To date, there are no case reports on the use of rozanolixizumab or zilucoplan in MC.

Discussion

In this review, we summarized the use of eculizumab, efgartigimod, and ravulizumab for treatment of MC. As the initial pivotal trial that led to their approval as standard treatment for generalized MG did not include patients with MC, only a small number of case reports have been included. More cases describing the use of eculizumab

compared to efgartigimod and ravulizumab were found, which corresponds to its earlier approval and availability. Overall, the positive results from the described case reports suggest the potential therapeutic value of these newer immunotherapies in the setting of MC.

Complement and FcRn inhibitors may have advantages over PLEX or IVIG for acute MG treatment. Compared to PLEX or IVIG, which are nonselective immunomodulators that may act on multiple aspects of MG pathogenesis, these newer therapies act on a unique key step of antibody reduction or complement inhibition. Both PLEX and IVIG can be associated with significant side effects. Vascular access is required for PLEX administration, and its use may be contraindicated in patients with concern of infection. IVIG treatment is associated with hypercoagulability, volume overload, and worsening kidney function. In contrast, data from the phase 3 trials and open label extension studies demonstrated that efgartigimod, eculizumab, and ravulizumab are associated with mild side effects, most commonly nasopharyngitis, upper respiratory infection, or headache.[13–15] While initial studies have demonstrated the relative safety of these newer immunotherapeutic agents, complement inhibition has been well known to increase the risk of meningococcal infection, highlighting the importance of immunization or chemoprophylaxis for those unable to receive immunization two weeks prior to drug initiation in this population in addition to close monitoring for infections as the patient is undergoing the course of therapy.[22–24]

One limitation of the cases reported in literature is that several rescue therapies were tried concomitantly or consecutively before initiation of efgartigimod, eculizumab, or ravulizumab. Therefore, it is possible that the combination of multiple mechanisms of action involving the MG pathogenesis could be responsible for the demonstrated clinical improvement. Multiple patients were continued on the complement or FcRn inhibitors that were used in the acute setting after clinical stabilization with sustained clinical benefit. Neither complement inhibitors nor FcRn inhibitors can render remission as they are not capable of stopping the production of pathogenic antibodies. However, this limitation does not preclude their use in the acute setting for the goal of eliminating the need of mechanical or non-invasive ventilation. Finally, the extremely high costs of the novel MG immunotherapeutics are one of the biggest barriers to their widespread use.

Conclusion

This review summarizes the available literature on the application of eculizumab, ravulizumab, and efgartigimod in the treatment of MC and suggests that patients in MC refractory to typical rescue treatments may benefit from the use of these newer immunotherapies. As most of the complement inhibitors and FcRN therapies are relatively new (apart from eculizumab), we expect that more case reports or case series will likely be generated in the near future, further solidifying their role in the treatment of MC or impending MC.

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Table 1. Case report on the efficacy of newer immunotherapies in refractory myasthenic crisis or impending crisis. AChR (+) = Aceytylcholine Receptor Positive, MG = Myasthenia Gravis, PLEX = Plasmapheresis, IVIG = Intravenous Immunoglobulins, IA = Immunoadsorption, MGFA = Myasthenia Gravis Foundation of America Grading, MD-ADL = Myasthenia Gravis Activities of Daily Living Score, QOL = Quality of Life Score, QMG = Quantitative Myasthenia Gravis. * = Patient administered eculizumab as 900mg on day 1 then weekly for weeks 1-3 followed by 1200mg week 4, then 1200mg every other week thereafter as per REGAIN trial protocol unless otherwise specified

Reference	# of Patients	Age/ Sex	MG Features (Duration, Antibody Status, and Thymoma Status if known)	Prior MG Treatment	Rescue Treatment Trialed	Crisis or Impending crisis	MC Treatment (Medication, Dose, Frequency)	Improvement Following MG Treatment	Time Course of Initial Improv-ement	Follow Up Duration	Complications
Yeo & Pleitez, 2018	1	79F	Seronegative, no thymoma, onset 3 years ago	Methylpredniso-lone, pyridostigmine	PLEX, IVIG	Crisis, then tracheostomy	Eculizumab*	Weaning of respiratory support, then off ventilation, improved limb strength	1 Week	Hospitalized for 2 months for sepsis, discharge to community rehab ventilator dependent	Coexisting hemolytic uremic syndrome, polymicrobial sepsis after PEG tube placement requiring stopping of Eculizumab
Oyama et al., 2020	7	22F	AChR (+), onset 1 year ago	Prednisone	PLEX	Crisis	Eculizumab*	QMG score improved from 36 to 26 at 6 months. No longer needs wheelchair	Not reported	6 months	None reported
		23F	AchR (+), onset 4 years ago	Prednisone, tacrolimus, thymectomy	IVIG, IA	Crisis, then extubated prior to eculizumab usage	Eculizumab*	QMG score improved from 28 to 16	Not reported	12 months	None reported
		33F	AChR (+), onset 21 years ago	Prednisone, tacrolimus, thymectomy	IVIG	Crisis	Eculizumab*	Disappearance of ptosis, ability to use mascara and eye liner	Not reported	6 months	None reported
		40F	AChR (+), type B3, thymoma, onset 21 years ago	Prednisone, tacrolimus, thymectomy	IVIG, PLEX, IA	Crisis	Eculizumab*	Strength improved, recovered after delivery of child	Not reported	6 months	None reported
		53F	AChR (+), type B1 thymoma, onset 7 years ago	Prednisone, tacrolimus, thymectomy	IVIG. IA	Crisis	Eculizumab*	Limb strength improved	Not reported	6 months	None reported
		55M	AChR (+), type B2 thymoma, onset 5 years ago	Prednisone, tacrolimus, thymectomy	IVIG, IA, pulse dose of corticosteroid	Crisis	Eculizumab*	Strength improved and regained employment	Not reported	6 months	None reported
		67F	AChR (+), type A thymoma, onset 1 year ago	Prednisone, tacrolimus, thymectomy	IVIG, IA, PLEX	Crisis	Eculizumab*	Strength improved, speech and swallowing improved	Not reported	6 months	None reported

Yoshizumi et al., 2020	1	40M	AChR (+), thymoma, onset three years ago	Prednisone, thymectomy	Intravenous corticosteroids, IVIG, PLEX	Crisis	Eculizumab (dosage not defined)	MG-ADL improved in 3 weeks, Resumed eating 42 days after treatment, weaned from noninvasive ventilation at day 47	3 weeks	Discharged 82 days after treatment with QMG 6 and MG-ADL 4	None reported
Furuta et al., 2021	1	77F	AChR (+), type B2 thymoma, onset five years ago	Pyridostigmine, prednisone, tacrolimus, thymectomy	IA, PLEX, IVIG	Crisis then tracheostomy	Eculizumab* - 900mg x4 and 1200mg x2 then not continued on discharge	Improved strength, discharge 70 days after treatment, no recurrence at 1 year	70 days	No recurrence of coexisting autoimmune diseases	Thymoma associated multiorgan autoimmunity, polymyositis, and myocarditis
Hofstadt-van Oy et al., 2021	1	62M	AChR (+), no thymoma, onset 11 months ago	Pyridostigmine, prednisone, azathioprine, dexamethasone	IVIG, IV pyridostigmine, PLEX, rituximab	Crisis then tracheostomy	Eculizumab*	Bulbar and limb strength improved, removal of tracheostomy and nasogastric tube	1 week	Persistent return of spontaneous breathing and oral feeding at 1 month	Aspiration pneumonia, sepsis, Enterobacter cloacae bacteremia requiring pausing azathioprine therapy
Usman et al., 2021	3	24F	AChR (+), thymoma, onset 11 years ago	Prednisone, azathioprine, thymectomy	PLEX, IVIG, rituximab	Crisis then tracheostomy	Eculizumab*	Successful extubation at 1-week, minimal manifestation status at week 4, asymptomatic at week 55	1 week	Asymptomatic at 55 weeks	Steroids held at week 8 due to intestinal perforation
		77M	AChR (+), no thymoma, onset three weeks ago	Pyridostigmine, prednisone	PLEX, IVIG	Crisis	Eculizumab*	Extubated the following day, discharged 15 days later, asymptomatic at 24 weeks	Next day	Asymptomatic at 24 weeks	None reported
		56M	AChR(+), no thymoma, onset one year ago	pyridostigmine, prednisone, mycophenolate mofetil	IVIG, PLEX	Crisis then tracheostomy	Eculizumab*	Non-invasive ventilation through trach collar at week 3, improved limb strength	3 weeks	Intermittent non-invasive ventilation at 40 weeks	Eculizumab 7th and 8th doses delayed logistically due to COVID 19 pandemic
Strano et al., 2022	1	48M	AChR (+), onset 3 months ago	Pyridostigmine, prednisone	IVIG, PLEX	Crisis then tracheostomy	Eculizumab*	MG-ADL improved in 10 days, ambulated in 20 days, weaned from invasive ventilation in 10 days with successful extubation	10 days	Maintained need for non-invasive ventilation at night only at 6 months	None reported

Vinciguerra et al., 2023	1	74M	AChR (+), onset two years ago	Pyridostigmine	IVIG	Crisis	Eculizumab*	Improved limb strength, weaned off mechanical ventilation and improved to MGFA IIa at day 5	5 days	Discharged at 5 weeks	Severe pneumonia and sepsis making IVIG and PLEX infeasible for a period of timed
Konen et al., 2024	1	34F	AChR (+), no thymoma, onset 8 months ago	Prednisolone, pyridostigmine	IVIG, PLEX, rituximab, IA	Impending crisis	Ravulizumab 3 g	MGFA improved from IVb to MGFA IIa, immunotherapy reduced	14 days	Sustained improvement at 19 weeks, improved MG-ADL and QOL	None reported
Watanabe et al., 2024	1	54F	AChR (+), type B1 thymoma, onset 5 months ago	Prednisolone, tacrolimus, pyridostigmine, thymectomy	PLEX, IVIG, IA	Crisis	Efgartigimod 10mg/kg/ week, 4 infusions per cycle, 3 total cycles	Improvement of limb and neck weakness, immunotherapy reduced	18 days	Off ventilation at day 60, minimal symptomatic expression at 196 days	First cycle efgartigimod limited to three doses due to ventilator associated pneumonia

Anti-neuronal Nuclear Autoantibody Type 1 (Anti-Hu) Paraneoplastic Neurologic Syndrome Causing Jaw Dystonia

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ABSTRACT

Anti-neuronal nuclear autoantibody type 1 (ANNA-1), or anti-Hu, paraneoplastic neurologic syndrome (PNS) classically manifests with sensory neuronopathy and encephalomyelitis. We describe a rare case of anti-ANNA-1 PNS presenting with marked jaw dystonia and cognitive impairment. The patient's symptoms complicated the evaluation for an underlying malignancy and severely impacted her functional status due to malnutrition and increased disability. Symptomatic management focused on reducing the severity of jaw dystonia, which improved her overall function and allowed for treatment of her underlying malignancy.

Introduction

Anti-neuronal nuclear autoantibody type 1 (ANNA-1), or anti-Hu neurologic syndrome, classically presents with encephalomyelitis, frequently with concomitant sensory neuronopathy in the setting of small cell lung cancer (Graus et al., 1985). We present an atypical case of a woman with jaw dystonia who tested positive for ANNA-1 antibodies. While trismus and oromandibular dystonia have been described with other autoimmune syndromes including ANNA-2/anti-Ri and anti-Ma2 (Tisavipat et al., 2023; Dalmau et al., 2004), ANNA-1 is rarely associated with jaw dystonia (Malek and Damian, 2018). This report is intended to expand our understanding of the phenotypic spectrum of ANNA-1 PNS and the potential complications involved in the management thereof.

Case Report

A 62-year-old woman with history of chronic obstructive pulmonary disease and a 20 pack-year smoking history presented with one year of progressive incoordination, diplopia, difficulty opening her jaw, and 40 pounds weight loss that led to admission for failure to thrive. She also reported four weeks of numbness starting in her left hand that progressed to involve her entire left arm. She had no other constitutional symptoms of night sweats, lymphadenopathy, or fevers. There was no history of cognitive decline, personality changes, or episodes concerning for seizures. On general examination she was cachectic, without lymphadenopathy or hepatosplenomegaly. There was no medication or substance use contributing to her jaw dystonia. Her neurologic exam revealed jaw closing dystonia (Figure 1, photograph taken after obtaining written consent from the patient), *geste antagoniste* (i.e., speech facilitation when the patient touched her chin), bilateral upper extremity ataxia, diminished light touch and proprioception in a length-dependent pattern involving all four extremities, and a conjugate left gaze palsy. Deep tendon reflexes were normal and symmetric. The Scale for the Assessment and Rating of Ataxia (SARA) quantified her degree of ataxia as 7/40. Her Montreal Cognitive Assessment (MoCA) score was 23/30, consistent with mild cognitive impairment.

Figure 1. Photograph of our patient with anti-ANNA-1 paraneoplastic syndrome attempting to open her mouth as wide as possible, with limitation reflective of her jaw dystonia.

Due to the patient's smoking history, significant weight loss, and the sub-acute onset of her neurologic symptoms, a paraneoplastic syndrome was suspected. Workup commenced with routine blood work including Complete Blood Count (CBC) and Complete Metabolic Panel (CMP) which showed no significant findings. Nutritional labs showed normal levels of copper, zinc, vitamin D, thiamine, pyridoxine, folate, and cyanocobalamin. Contrasted brain MRI showed no acute pathology (Figure 2). On electromyogra-

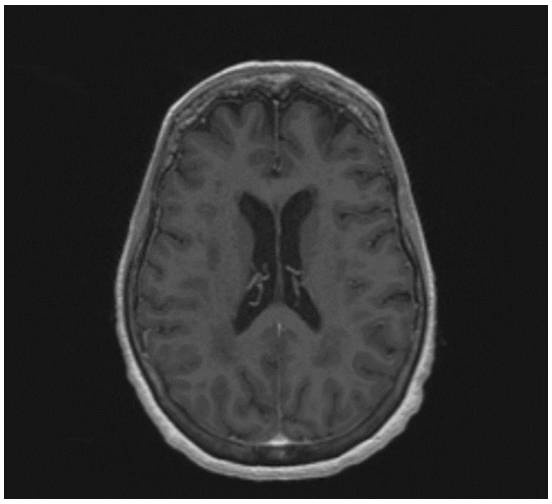

Figure 2. T1 post-contrast MRI Brain without abnormal findings or pathology.

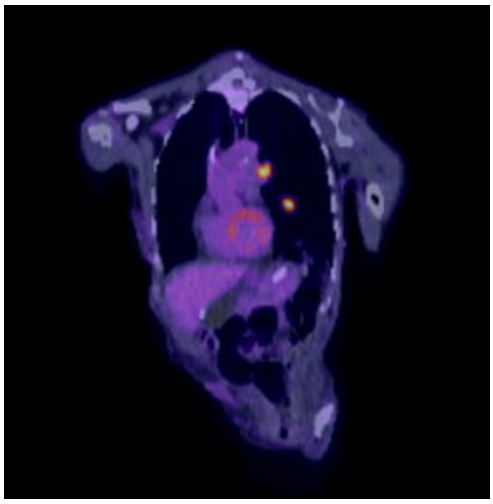

Figure 3. Whole Body Pet demonstrating FDG uptake in 2 lung nodules.

phy, sensory and motor nerve conduction studies were normal. Needle electrode examination of the upper and lower limbs, paraspinal muscles, orbicularis oris muscle and tongue were normal. Needle exam of the masseter muscle revealed a severe and persistent involuntary contraction, as can be seen in the setting of a dystonic contraction. Serology testing identified a positive serum ANNA-1 IgG with a titer of 1:3840 (Mayo Clinic Laboratories, MN USA). Her CSF studies showed normal protein and cell count and no CSF-specific oligoclonal bands (OCB), but did show a high immunoglobulin G (IgG) index of 0.77 mg/dL (reference range: 0.00-0.61). CSF was positive for ANNA-1 IgG at a titer of 1:64. ANNA-2/anti-Ri antibody. All other neural autoantibodies (Mayo Clinic Laboratories, MN USA) were negative in both serum and CSF. CT Chest revealed a left lower lobe lung nodule, which demonstrated increased fluorodeoxyglucose (FDG) uptake on a PET CT scan (Figure 3). A bronchoscopic fine-needle aspiration guided by endobronchial ultrasound was needed to confirm the diagnosis of a suspected pulmonary malignancy. This procedure was delayed due to her marked jaw dystonia. She required increasing doses of baclofen, gabapentin, clonazepam, and trihexyphenidyl, followed by botulinum toxin injections to relieve her dystonia before successfully undergoing the procedure. The biopsy pathology was consistent with small cell lung carcinoma. Given a high-risk neurologic phenotype (e.g., sensory neuronopathy), positivity of a high-risk antibody (anti-ANNA1), and identification of the most commonly associated tumor with this autoantibody, PNS was determined to be the definite diagnosis (Graus et al., 2021).

In addition to symptomatic management, she was treated with five days of IV methylprednisolone 1000 mg per day, and five cycles of plasma exchange (PLEX). Following biopsy results, her cancer was determined to be Stage 2B (T1cN1M0) SCLC. She initiated inpatient chemotherapy with cisplatin and etoposide with plans for radiation therapy with subsequent cycles. Unfortunately, her first cycle of chemotherapy was truncated due to bacteremia for which she was treated with IV antibiotics. Her jaw stiffness and pain improved with treatment, and upon discharge eight days later she was able to tolerate a full liquid diet and was trialing mechanical-soft solid foods. After discharge, the patient elected to proceed with care at a different facility.

Discussion

Anti-ANNA-1 PNS most often presents with symptoms of encephalomyelitis, but other clinical manifestations can include sensory neuronopathy, limbic encephalitis, chronic gastrointestinal pseudo-obstruction, brainstem syndromes, dysautonomia, and cerebellar ataxia (Graus et al., 2001). ANNA-1 IgG is associated with malignancy in about 85% of cases, with small cell carcinoma identified as the tumor type in around 55% of this subpopulation (Graus et al., 2001). Furthermore, the presence of a tumor at the time of PNS diagnosis is associated with a higher predicted mortality rate (Smitt et al., 2002). Our patient developed prominent sensory neuropathy followed by progressive sensory ataxia and was found to have small cell lung carcinoma, consistent with previous reports of ANNA-1 PNS. However, her prominent jaw dystonia was unusual as this has not been widely reported in association with ANNA-1.

The differential diagnosis for trismus is broad and etiologies include brainstem stroke, meningitis, tetanus, toxic exposures, and functional movement disorder (Malek and Damian, 2018). Paraneoplastic brainstem encephalitis caused by ANNA-2/anti-Ri or anti-Ma2 have been associated with jaw dystonia (Tisavipat et al., 2023; Dalmau et al., 2004). Our patient and that described by Malek and Damian (2018) are the only reports of jaw dystonia associated with ANNA-1 IgG we could find in our review of the relevant literature. Our two patients shared several interesting similarities, including the clinical finding of horizon-

tal conjugate gaze palsy. Together, our reports indicate that onco-neuronal antibodies, including ANNA-1, should be considered when a PNS is suspected in relation to subacute development of jaw dystonia.

Patients with ANNA-1 PNS may have limited benefit from immunosuppressive therapies and prognosis often depends on patient disability, performance status, and severity of disease (Graus et al., 2001). A single-center Dutch study found that anti-tumor therapy had a higher but statistically insignificant probability of successful maintenance or return of ambulatory function even after adjusting for factors indicating poorer prognosis (e.g., age at onset, level of disability at time of diagnosis) (Sillevis Smitt et al., 2002). Our patient's jaw dystonia limited her ability to receive adequate nutrition resulting in failure to thrive. She experienced significant jaw pain which negatively impacted her quality of life. Despite her relatively young age and lack of comorbidities, her limited ability to receive oral nutrition increased her overall level of disability and likely worsened her overall prognosis.

Conclusion

We report a case of jaw dystonia in the setting of ANNA-1 PNS. Jaw dystonia is an uncommon feature of PNS but has significant implications for morbidity. Although rare among the general population, this case serves as a reminder for practicing neurologists to maintain a broad differential and consider PNS in the diagnostic evaluation when progressive or atypical neurologic symptoms remain unexplained.

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Eliciting Latent Myasthenia Gravis Eye Signs Utilizing 'The Mary Walker Effect'

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Myasthenia Gravis Clinical Eye Research

ABSTRACT

Current standardized tests to induce fatigability in the Myasthenia Gravis (MG) patient do not take into consideration that, in real-world situations, the patient is using more than one muscle group at a time. In 1895, the German physician Frederick Jolly, who is famed for coining the name Myasthenia Gravis, observed that exhaustion of one group of voluntary muscles in a patient with MG induced weakness in other groups that had not been stimulated. This phenomenon was also noted by Dr. Mary Walker and was named the Walker effect in 1938. The Novel ocular motility technique described in this paper is designed to engage the extraocular muscles (EOM) simultaneously with another muscle group namely the facial muscles, specifically testing for lip weakness. This test was named The SLOW Test (Simultaneous Lip and Ocular Weakness). It was found that observable Myasthenia Gravis Eyes Signs (MGES) were quicker to elicit and more obvious when performing the SLOW Test. The SLOW Test is a method designed to confirm the presence of MG signs quickly and effectively, even when there appear to be no obvious fatigable signs with current testing regimes. The test combines 'old knowledge' by testing for the 'Mary Walker Effect' with current ophthalmic testing for MG, which increases fatigue and allows for a higher suspicion level of generalized MG as another muscle group is simultaneously tested. The development of clinical methods for identifying latent fatigable muscle weakness is critical to reducing the cases of missed MG diagnosis, testing methods such as the SLOW Test have the potential to improve patients' quality of life by enabling earlier diagnosis and initiating earlier treatment.

KEYWORDS: Myasthenia Gravis, Neuromuscular Junction (NMJ), 'The Mary Walker Effect', Ocular Motility, Ptosis, Fatigability, Functional Neurologic Disorder (FND)

Introduction

Acquired Autoimmune Myasthenia Gravis (MG), is a potentially fatal, chronic neuromuscular disease caused by impaired synaptic transmission across the neuromuscular junction resulting in fatigable weakness that can range in severity from mild ocular muscle weakness to severe respiratory failure. MG is a serious disease and can present clinically with very severe symptoms in many patients; however, patients may present clinically with less weakness than they describe in their daily lives, as the intensity of the weakness in MG is variable even within the same patient on the same day and may include periods of complete resolution.[1]

Fatigable weakness in MG can range in severity from mild ocular muscle weakness to severe respiratory failure. However, even patients who are considered to have mild eye symptoms may be suffering from troubling symptoms that are dismissed, as their clinical ocular assessment may appear normal at the time of consultation. Patients who complain of symptoms such as dizziness, blurriness, and even diplopia in the absence of clinical signs are often dismissed or diagnosed as having another condition, for example, Functional Neurologic Disorder (FND).

It has long been known that MG patients can experience symptoms even when there is no obvious discernible clinical evidence. This phenomenon, however, remains poorly understood.[2] Recent video-based eye-tracking studies were able to detect such subclinical eye movements in MG patients who had symptoms without obvious ocular misalignment.[2] These studies highlight the limitations of current methods of clinical diagnosis of MG in observing subtle eye signs.

The eye muscles are the most susceptible muscle group to an autoimmune-mediated attack on the neuromuscular junction (NMJ) and, therefore, accurate ophthalmic examination is vital to aid in an early diagnosis.[3] However, as MG patients have quite variable responses to current methods of attempting to induce muscle fatigability, diagnosis in many patients may be delayed by many months or even years.[4]

The development of clinical methods for identifying latent fatigable muscle weakness is critical to reducing the cases of missed MG diagnosis. The novel ocular motility technique described in this paper is designed to engage the extraocular muscles (EOM) simultaneously with another muscle group to identify patients with MG who present with subtle eye signs or no discernible clinical eye signs. This method was developed based on the 'Mary Walker Effect' and increases fatigue, allowing for a higher suspicion level of generalized MG as another muscle group is simultaneously tested.

Background

Ophthalmic Signs in MG

MG can be easy to diagnose when there are obvious fatigable eye signs, however, it may present with variable OM restrictions that can mimic a variety of conditions or MG patients may complain of dizziness, unsteadiness, or blurring of vision in the absence of clinical eye signs. Some MG patients have fluctuating and fleeting ocular signs and

symptoms, for example, ptosis has been known to switch from one eye to the other, lasting only a few seconds.[4] At times, ptosis may not be obvious and may appear as a narrow palpebral fissure in one eye with upper lid retraction in the contralateral eye.[5]

The key to MG clinical diagnosis is inducing objective fatigable muscle weakness, however, many clinical tests fail to induce muscle weakness within the time constraints of regular consultation. Current testing for MGES involves a variety of standard tests to disclose MGES, such as ptosis, lid retraction, restriction of ocular movement, distinct saccadic signs, and orbicularis oculi weakness. The standard procedure for testing for MGES involves sustained gaze holding in elevation and also in lateral gaze. However, the results are often fleeting and not readily replicated.

Facial weakness in MG and the patient's difficulty with smiling

MG patients with orofacial weakness may complain of stiffness of the face and weakness of the lips, which can cause variable vertical smile, or 'myasthenic snarl' associated with abnormal fatigability on exertion. This aspect of MG is important to be aware of, as such a patient may appear depressed due to the weakness causing a downturned mouth. These patients tend to have a flat, expressionless face, which can severely affect a patient's quality of life by interfering with social interactions and employment opportunities.[6] However, obvious MG mouth weakness may not always be apparent at the time of the clinical examination and disclosing such weakness when the sign is latent is not only helpful for diagnosis but also allows for a greater understanding of the patient's lived experience with MG.

MG fatigue versus fatigability

An MG patient may appear strong and not display easily observable evidence of weakness on clinical examination, however their symptoms during daily life may be significant. Current standardized tests to induce fatigability in the MG patient do not take into consideration that in real-world situations the patient is using more than one muscle group at a time.

Distinguishing between 'fatigue' and 'fatigability' is crucial in MG diagnosis. 'Fatigue' is a subjective description of excessive tiredness or exhaustion that often interferes with activities of daily living (ADL). Whereas 'Fatigability' is an objective reduction in the strength of muscle groups after a specific action. A study by Barnett, C., et al. 2014 reinforces the importance of understanding impairment in MG and the mechanism of fatigability of muscle weakness. It discusses how an inadequate clinical assessment leads to the assumption that a patient might seem stronger over their daily activities than the reality of their difficulties with ADL,[7] which leads to misdiagnosis and subsequently a poor quality of life for the undiagnosed and untreated patient.

Development of a test to disclose latent fatigable muscle weakness in MG

The development of clinical methods for identifying latent fatigable muscle weakness is critical to reducing the cases of missed MG diagnosis. This paper presents a new method of inducing fatigable eye muscle weakness in MG by incorporating the 'Mary Walker Effect' – shown when wearing out one muscle group causes fatigue in other muscle groups.

The Mary Walker Effect

In 1895, the German physician Frederick Jolly, who is famed for coining the name Myasthenia Gravis, observed that exhaustion of one group of voluntary muscles in a patient with MG induced weakness in other groups that had not been stimulated. This phenomenon was also noted by Dr. Mary Walker and was named the Walker Effect in 1938.[8,9]

Mary Walker was most notably known for discovering that physostigmine and Prostigmin temporarily restored muscle function in patients with MG.[10] This discovery formed the basis for pyridostigmine (Mestinon) being used as a primary symptomatic treatment for MG, even today. and was her famous single case study trial that is considered one of the "greatest clinical observations of the twentieth century."[11]

The clinical sign known as 'the Mary Walker effect' was introduced after another study on two approximately equally severe MG patients who had been treated with Prostigmin. The patients exercised their forearm, whilst a tourniquet was applied and inflated to 200 mm Hg, secured at the elbow. While the pressure was applied to the cuff no weakness was noted in any other muscles, however approximately one minute after the pressure was released the eyelids began to droop, and after two minutes there was widespread weakness. Subsequent studies showed that when less forearm fatigue was induced the weakness in other muscles was much less following release of the cuff.[10]

The development of the new test described in this current paper combines the old knowledge of The Mary Walker Effect with current testing methods known to elicit MEGS today. Considering the variability in signs and symptoms in all MG patients, it is expected that responses will vary, however, it is hypothesized that observable fatigability will be increased by combining current MG examination techniques with The Mary Walker Effect.

Simultaneous Lip & Ocular Weakness (SLOW)

The SLOW Test was designed based on 'the Mary Walker Effect,' eyes and lip muscle combination was demonstrated in this report as the eyes have been shown to be the most susceptible muscle group to an autoimmune-mediated attack on the NMJ[3] and orofacial muscle weakness gives a distinct myasthenic facial appearance, as

the corners of the mouth droop downwards with fatigue.[6] This combination of muscles is effective as the fatigability of the lip muscle can be easily observed by the examiner whilst simultaneously examining the eyes. The acronym SLOW (Simultaneous Lip & Ocular Weakness) was chosen as it also is a reminder of the importance of performing ocular motility testing slowly.

The SLOW Test consists of asking the patient to 'smile while showing their teeth' thereby raising their upper lip and maintaining this position whilst slowly following a target and maintaining sustained gaze holding in elevation and then in lateral gaze. This ocular motility component of the test is performed as per the standard currently used testing method for eliciting MGES. This procedure results in simultaneously fatiguing two separate muscle groups, invoking the Mary Walker Effect.

The aim of this test is not to over-fatigue the patient but to see whether there is a noticeable weakness of the lip during a 15 – 30 second sustained smile associated with observable fatigable MGES with sustained gaze holding. Weakness of the lip is observable as 'falling' of the upper lip gradually worsening to a downward-facing mouth.

Tests for MGES can be done whilst watching for lip fatigue by questioning the patient about diplopia, or observing an MGES, e.g. sustained elevation or sustained lateral gaze looking for fatigability of eyelids and/or extraocular muscles gaze restriction, ptosis, or lid retraction.

Case Presentation

The patient demonstrating this phenomenon was a 51-year-old female with seronegative, single fiber electromyography (SFEMG) and repetitive nerve stimulation (RNS) positive, Mestinon positive, generalized MG (GMG). At the time of testing, the patient's generalized MG symptoms were well controlled on a combination of Mestinon, Methotrexate, Imuran, intravenous immunoglobulin (IVIG), adequate rest periods throughout the day, sufficient nightly sleep, lifestyle factors to reduce positive and negative stress, reduction and modification of activity levels dependent on MG symptoms. During MG exacerbations her symptoms included variable eye, bulbar and other generalized symptoms of MG, including breathing difficulties.

Variable MGES for this patient were elicited in different directions of gaze while performing the Slow Test including restriction of EOMs with diplopia, upper lid retraction, Cogan's Lid Twitch, lid hoping, lower lid retraction, unilateral ptosis on lateral gaze and bilateral ptosis on upgaze. The eliciting of any known MGES faster than other test methods during the Slow Test is considered a positive Slow Test. Saccades and orbicularis weakness, weren't tested as a part of the Slow Test, however, this patient had previously displayed variable MGES for both.

MGES were even identifiable using the SLOW Test on days when she was asymptomatic and at peak Mestinon dose. This provides evidence of the high level of sensitivity and accuracy of the SLOW Test in the MG patient. The SLOW Test was performed at a variety of intervals after the Mestinon dose. It was observed that MGES could be identified at any period, however the patient's fatigue was sustained longer when tested at times when the Mestinon dose had worn off. The patient reported greater levels of fatigue when SLOW Test was performed outside of the peak Mestinon effect, which is between 3-4 hours after the 4 hourly dose was taken. This patient was tested for MGES in different directions of gaze, noting where the MGES occurred. It was found that observable MGES were quicker to elicit and more obvious when performing the SLOW Test than previous MGES testing. It was noted that the fatigable weakness associated with a positive SLOW Test remained while the patient maintained their gaze holding while simultaneously attempting to continue their raised lip position.

Discussion

The SLOW Test allows for greater reliability in the assessment of MG by more accurately representing the patient's symptoms outside of the clinical consultation. Fatigable muscle weakness in the patient was induced within 15 seconds and the MG-resulting lip and ocular signs were maintained on a sustained attempt at gaze holding combined with a sustained attempt to maintain a smile whilst showing teeth, but disappeared with a blink or movement away from the position of gaze that disclosed the MGES.

Diagnosis of MG can be quite easy when there are obvious classical signs present. However, specific testing is required to diagnose when there are only mild signs or unusual symptoms. Considering the variability in signs and symptoms in all MG patients, it is expected that responses to the SLOW Test will vary, however it is hypothesized that observable fatigability will be increased through the use of the Mary Walker Effect.

The SLOW Test is a method designed to confirm the presence of MG signs quickly and effectively, even when there appear to be no obvious fatigable signs with current testing regimes. The development of clinical methods for identifying latent fatigable muscle weakness is critical to reducing the cases of missed MG diagnosis. Testing methods such as the SLOW Test have the potential to improve patients' quality of life by enabling earlier diagnosis and initiating earlier treatment.

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Successful recovery of anti-SRP myopathy with subcutaneous methotrexate after 17 years of poor response to immunomodulation

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ABSTRACT

An 18-year-old woman presented with a year of progressive proximal limb weakness. Serum creatine kinase (CK) was elevated and electromyography suggested an irritable myopathy. Muscle biopsy revealed severe, chronic, active, necrotizing myopathy. Myositis-specific autoantibodies were initially negative; however, an immune-mediated necrotizing myopathy was suspected. She had only minimal response to variable immunomodulatory therapies over 17 years, with progression of weakness. Subsequent repeat testing confirmed positive anti-Signal Recognition Particle (SRP) autoantibodies. A thigh MRI, 17 years after symptom onset, showed extensive fatty replacement and significant muscle atrophy, suggesting a low likelihood of response to further immunosuppression. Nonetheless, motor function significantly improved after initiation of subcutaneous methotrexate (MTX). She has been stable off immunosuppressive therapy for 4.5 years. This report exemplifies that a protracted clinical course, extensive fatty replacement and atrophy on muscle MRI and normal CK levels do not preclude a late response to immunomodulatory therapy in anti-SRP myopathy.

Introduction

Anti-Signal Recognition Particle (SRP) myopathy is an immune-mediated necrotizing myopathy (IMNM) characterized by rapidly progressive proximal and symmetrical weakness that can result in severe disability and a markedly elevated serum creatine kinase (CK).[1,2] Muscle biopsy typically shows prominent muscle cell necrosis and only minimal lymphocytic infiltration.[3] Treatment usually requires long-term use of multiple immune therapies, with the prognosis being worse in those with a younger age of onset.[4] There has been growing evidence regarding the utility of muscle MRI in the management of autoimmune myopathy.[5] It has shown to be a useful tool to monitor the evolution of muscle disease over time and also to determine the optimal location for muscle biopsy to increase its diagnostic yield.

Case Report

An 18-year-old woman, who was previously healthy, except for a 5-year history of complex partial epilepsy that was managed with lamotrigine, presented with a 1-year report of progressive proximal limb muscle weakness. She was unable to dress, cut food, or stand from a chair without assistance. On examination, she had symmetric Medical Research Council (MRC) grade 3/5 weakness in deltoids, biceps, triceps, hip flexors, and knee extensors. Muscle bulk and tone were normal. Deep tendon reflexes were grade 1 at the knees and ankles, and grade 2 in the upper limbs. She had a waddling gait with hyperlordosis and bilateral circumduction. The rest of the neurological examination was normal. Serum CK was 4,384 units/L on presentation. Electrophysiologic testing was consistent with an irritable myopathy with abnormal insertional activity, fibrillation potentials, myopathic motor unit morphology, and early recruitment in the left biceps, infraspinatus, vastus medialis, tensor fasciae lata, and iliopsoas muscles. Nerve conduction studies were normal. A left quadriceps muscle biopsy revealed multiple necrotic and split fibers supportive of a severe necrotizing myopathy without evidence of invasion of non-necrotic muscle fibers (Figure 1). Minimal endomysial and perimysial inflammatory cell infiltrates were noted comprised mainly of CD68 positive macrophages. Blood vessels showed a normal pattern of staining with Eulex Europaeus (lectin) and membrane attack complex (MAC) relative to controls, but some non-necrotic muscle fibers showed MAC sarcolemmal staining. Immunohistochemical stains for dystrophin, sarcoglycanopathy, dysferlin, and merosin showed a normal pattern. Genetic testing was negative for pathogenic mutations in the FKRP, CAPN3, CAV3, and LMNA genes. Autoantibodies included negative antinuclear antibody, rheumatoid factor, anti-RNP, Smith, Jo-1; Subsequent further testing for

myositis-specific antibodies, including PL 7, PL-12, MI-2, KU, EJ, and OJ, was also unrevealing; however, an immune-mediated necrotizing myopathy was clinically suspected.

Axial T1 weighted MRI of bilateral lower extremities, obtained 4 years after symptom onset, showed evidence of diffuse fatty infiltration of bilateral thigh musculature, with abnormal high signal on inversion recovery sequences within the muscles of the anterior and posterior compartments of bilateral thighs and gastrocnemii. Diffuse enhancement was seen, most prominently in the quadriceps muscles following gadolinium administration. The patient was variously treated with regimens including corticosteroids (both daily oral prednisone [1mg/kg] and intermittent intravenous high dose methylprednisolone), intravenous immunoglobulin (IVIG), subcutaneous MTX that was only briefly used and stopped due to severe diarrhea, azathioprine, mycophenolate, extended courses of plasma exchange (PLEX), and rituximab. She had only transient and suboptimal responses to immunomodulatory therapy over 16 years, with progression of weakness and disability requiring a wheelchair, and multiple hospitalizations for exacerbations including respiratory impairment which did not require intubation. Dyspnea did subjectively improve with immunotherapy during hospitalizations.

Laboratory testing at age 30 years confirmed the presence of anti-SRP autoantibodies on a radioimmunoprecipitation assay. Anti-HMG-CoA reductase antibodies were negative. The patient, who was on prednisone and azathioprine at the time, received further intensive prolonged courses of PLEX with only a minimal response. There was also no response to another trial of rituximab.

A subsequent thigh MRI at age 33 years showed extensive fatty replacement and muscle atrophy (Figure 2). Muscle edema was noted though this was difficult to interpret due to the significant muscle atrophy. In light of the patient's MRI findings and normal CK of 125 U/l, a response to further immunosuppression was considered unlikely. Nonetheless, due to the patient's continued declining function, subcutaneous MTX (titrated to 12.5 mg weekly subcutaneously) along with weekly folinic acid 10 mg by mouth (because of prior GI intolerance of MTX) was added to her existing regimen of prednisone (45 mg by mouth daily) and azathioprine (125 mg by mouth total daily dose). Within a few months after initiation of MTX, motor function had significantly improved with recovery of independent ambulation. On examination, Medical Research Council (MRC) grade had improved to 4-5 in the biceps, knee flexors, and knee extensors. The patient weaned herself off all immunosuppressive therapy at age 35 years. She has subsequently been functionally stable off all immunosuppressive therapy for the past 4.5 years.

Discussion

This report of a patient with severe, SRP-related necrotizing myopathy is instructive, in that the patient had been relatively refractory to a multitude of immunosuppressive regimens over 17 years, with only transient or limited responses, normal CK, and a muscle MRI showing marked fatty replacement, suggesting a low likelihood of treatment responsiveness. She nonetheless showed marked functional improvement with the late initiation of subcutaneous MTX and folinic acid.

The initial clinical presentation was typical of anti-SRP myopathy with subacute severe proximal muscle weakness and significantly elevated CK levels without skin involvement. Although anti-SRP myopathy is more commonly seen after the fourth decade, younger onset including childhood or adolescence has been reported.[6-8] The presence of SRP autoantibodies is essential for diagnosis, as this form of myopathy is often clinically or pathologically indistinguishable from other types of autoimmune myopathy. For example, muscle necrosis can be observed in multiple other types of myopathy including dermatomyositis, anti-Jo1 antisynthetase syndrome, scleroderma-myositis, and various hereditary myopathies, while perivascular infiltrates can be seen in anti-SRP myopathy.[5,9] Binns et al. reported in their case series and literature review of childhood or juvenile-onset anti-SRP myopathy that the long-term functional outcomes are generally poor with severe residual weakness in 50% of 12 patients and wheelchair dependence in 40%.[6] Also, in a longitudinal cohort study of 37 adults with anti-SRP myopathy, younger age at onset was associated with more severe muscle weakness at initial and follow-up visits.[10]

Muscle MRI has been used to detect muscle edema, fatty replacement, and atrophy using both T1 weighted and short tau inversion recovery (STIR) sequences. Active muscle edema due to inflammation or myofiber necrosis appears as intramuscular hyperintensities on STIR sequences and fatty replacement is best seen for clinical purposes on T1-weighted images. In IMNM, MRI findings are characterized by a higher proportion of thigh muscles with edema, atrophy, and fatty replacement.[11,12] Thigh muscle edema on MRI was identified in each of the 12 reported patients with anti-SRP myopathy including in the vastus lateralis, rectus femoris, biceps femoris, and adductor magnus muscles.[13] Anti-SRP myopathy usually shows a more severe pattern of muscle involvement on MRI than HMG-CoA reductase antibody-related IMNM.[10] It is considered that muscle edema seen in necrotizing myopathies is likely of osmotic origin rather than inflammatory cell infiltration, given that there are typically minimal inflammatory cells in the muscle biopsy.[13] Intramuscular fat accumulation is considered an indicator of irreversible consequences of the myopathic process while muscle edema has been suggested to indicate potential reversibility with treatment in autoimmune myopathy.[5,13] A longitudinal study observed, as in our patient, that with an increasing interval between onset of disease and timing of muscle MRI, patients showed greater fatty replacement and less muscle edema.[11] Furthermore, in

the study by Zheng et al, there was a negative correlation between the degree of muscle fat accumulation and therapeutic effect.[13] The mechanism for the marked improvement seen in our patient after 17 years of disease despite marked muscle fat replacement and a low CK value is uncertain. Notwithstanding the persistence of some muscle edema, our patient's late response to treatment serves to indicate that muscle MRI findings of marked fat replacement and muscle atrophy may not be relied on alone to guide the likelihood of therapeutic response in anti-SRP myopathy but are rather a helpful adjunct in the therapeutic decision-making process.

The underlying pathogenesis of anti-SRP myopathy is unknown but is probably due to a combination of immune-mediated and environmental and genetic factors. Multiple pathways have been implicated in the pathogenesis of muscle destruction in anti-SRP myopathy, including direct pathogenic effects of anti-SRP autoantibodies, complement-dependent mechanisms, altered cytokine and chemokine milieu, and upregulation of B-cell activating factor.[14] In terms of treatment approach, our patient showed a clinically significant late improvement with the introduction of MTX. In 2017, a European NeuroMuscular Centre (ENMC) working group recommended corticosteroids and MTX as a first-line treatment regimen for anti-SRP myopathy.[4] A 16-patient retrospective case series supports the effectiveness of MTX for anti-SRP myopathy. Thirteen of these individuals received oral prednisone and MTX and showed a degree of improvement.[15] The mechanism of treatment of SRP myopathy with MTX is unknown but may relate to both anti-inflammatory and immune-modulating properties. These may include inhibition of anti-inflammatory adenosine metabolism, which leads to reduced T-cell activation, down-regulation of B cells, increased activated CD-95 T-cell sensitivity, and inhibition of the binding of pro-inflammatory beta-1 interleukin to its cell surface receptor.[16] An ENMC working group has also recommended rituximab as an alternative approach.[4] In contrast to our patient who failed to respond to 2 separate trials of rituximab, 76.5% (13/17) of patients with anti-SRP myopathy who received rituximab, showed responsiveness in one longitudinal cohort study.[14] Similarly, a literature review reported that 77.8 % (14/18) of patients with anti-SRP myopathy showed a response to rituximab.[12] Rituximab, as a B cell depleting agent, may be an effective treatment for refractory SRP myopathy due to its effects on anti-SRP autoantibodies, which play a role in both the formation of atrophic muscle fibers and muscle fiber regeneration.[14] Allenbach et al. and others have described that individuals with anti-SRP myopathy treated with IVIG, more frequently achieve remission than those not receiving IVIG therapy.[4, 17] Our patient did not show an appreciable response to IVIG. Thus, response to immunomodulatory therapy appears quite non-uniform among those with anti-SRP myopathy, possibly reflecting diversity of disease mechanisms.

Conflict of interest

Alexis Lizarraga reports no disclosures.

Yohei Harada is a salaried employee of UCB Pharma and receives stock and stock options from employment. The research presented in this publication was conducted outside of the scope of current role in the company. The views and opinions expressed in this publication are solely those of the authors and do not necessarily reflect the official policy or position of the company.

Debra Guntrum reports no disclosures for this report.

Aravindhan Veerapandiyan has worked in an advisory or consulting capacity with PTC Therapeutics, Novartis, Sarepta, Biogen, ScholarRock, Pfizer, Fibrogen, and NS Pharma, and has received grant or research support from Sarepta, Fibrogen, Novartis, Genentech, AMGEN, Impax Labs, Teva, Ely Lilly, AMO Pharma, Pfizer, and Octapharma.

Andrew L. Mammen has a patent for anti-HMGCR autoantibody testing but does not receive compensation for this.

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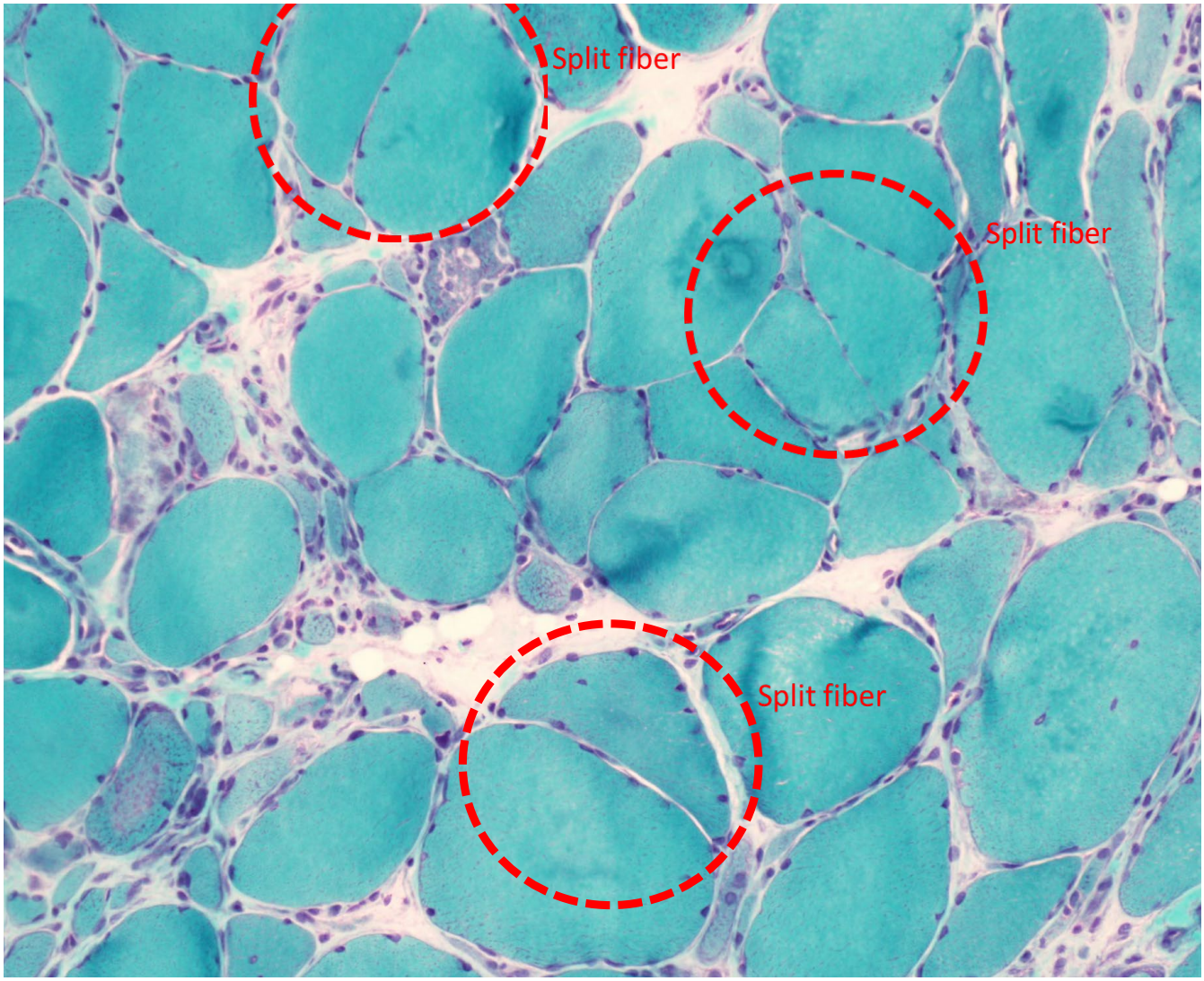

Figure 1: Left quadriceps muscle biopsy (Gomori trichrome stain):
Moderately severe, chronic, active myopathy as evidenced by increased muscle fiber size variability, split fibers, and rounded fibers with internal nuclei. Though not seen in this slide, there was minimal necrosis surrounded by macrophages There were minimal perivascular and endomysial mononuclear inflammatory cell infiltrates. No ragged-red fibers were present.

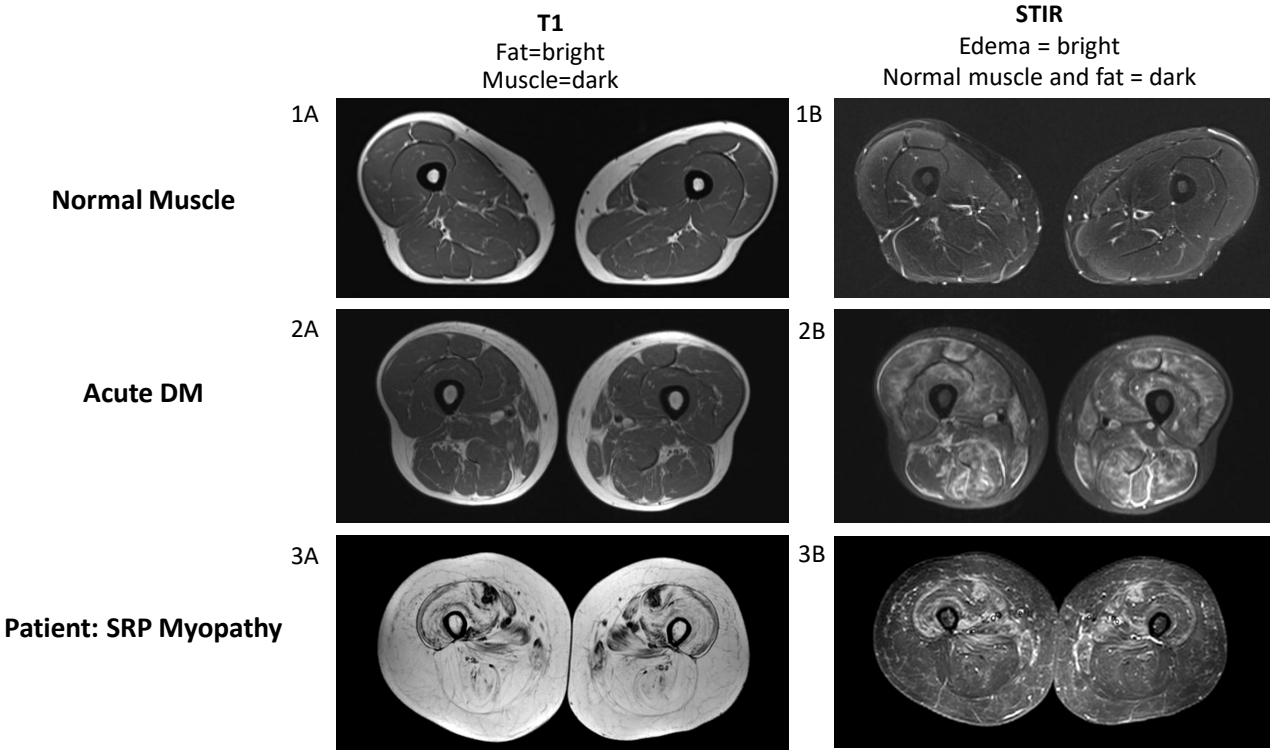

Figure 2: Muscle MRI of right and left thighs with comparison cases
(1A) Normal Axial T1 MR sequence, (1B) Normal Axial STIR MR sequence, (2A) Axial T1 MR sequence in acute dermatomyositis (DM) showing normal muscle bulk without fatty replacement, (2B) Axial STIR MR sequence in acute DM showing diffuse hyperintensity indicating muscle and fascial edema, (3A) Axial T1 MR sequence showed diffuse hyperintensity suggestive of extensive atrophy and fatty replacement of muscle, (3B) Axial STIR MR sequence demonstrated hyperintensity of the right anterior thigh muscles suggesting edema.

Pattern recognition approach to neuromuscular disorders: myopathy and neuromuscular junction

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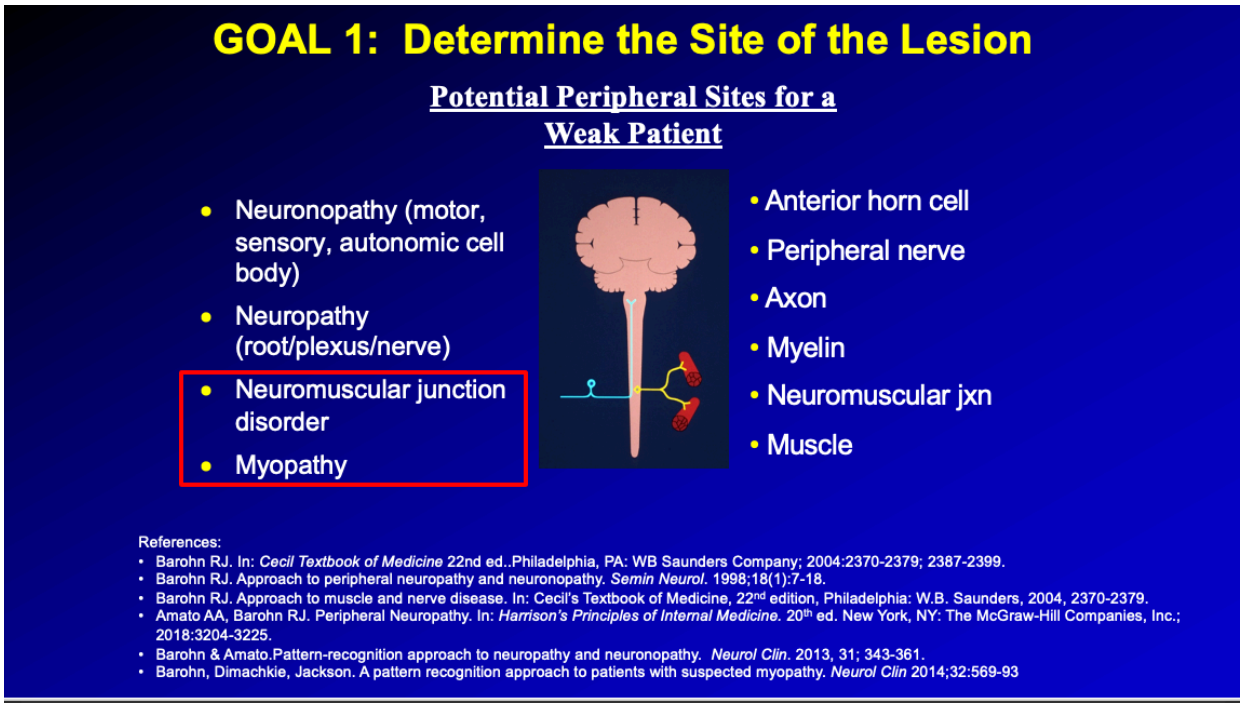
Every neurologist has three goals when they see a patient: 1. To determine the site of the lesion; 2. To determine the cause of the lesion; 3. To determine the specific therapy for the patient's problem and if not a specific therapy, what the best management is (Figure 1).

Figure 1

This discussion will concern the peripheral nervous system components that include neuromuscular junction and skeletal muscle (Figure 2).

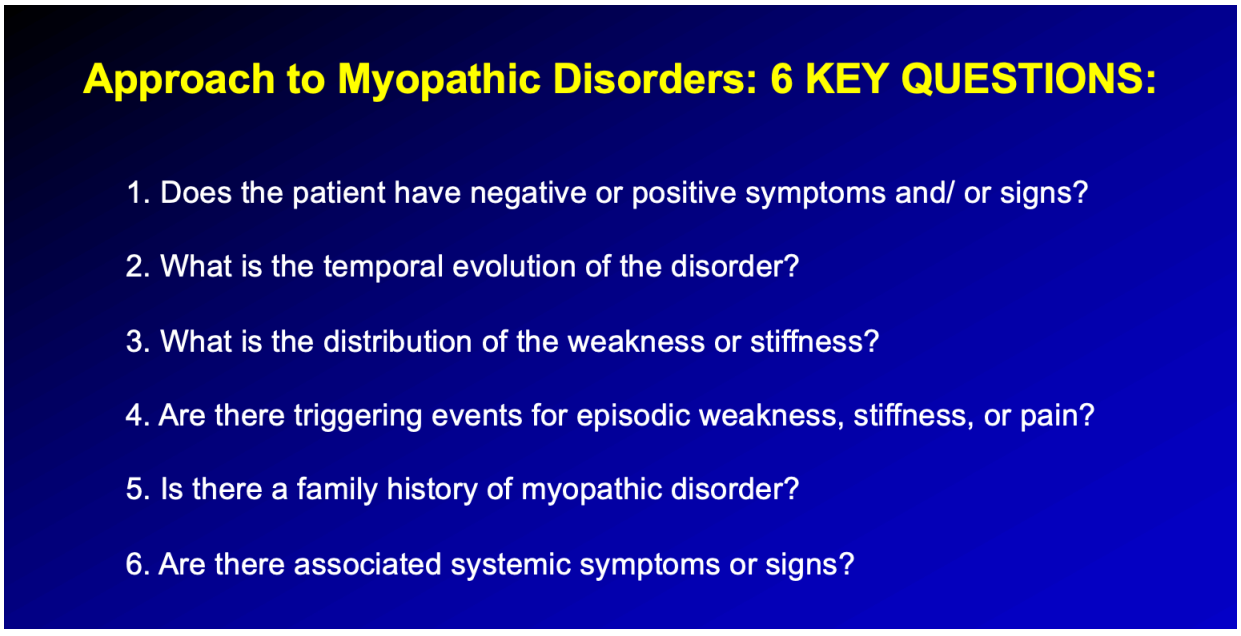
Figure 2



As is true of all areas of neurology, the pattern recognition approach will allow us to make preliminary assessments on the site of the lesion, the cause of the lesion, and what to do for the patient. This of course applies to muscle disorders.

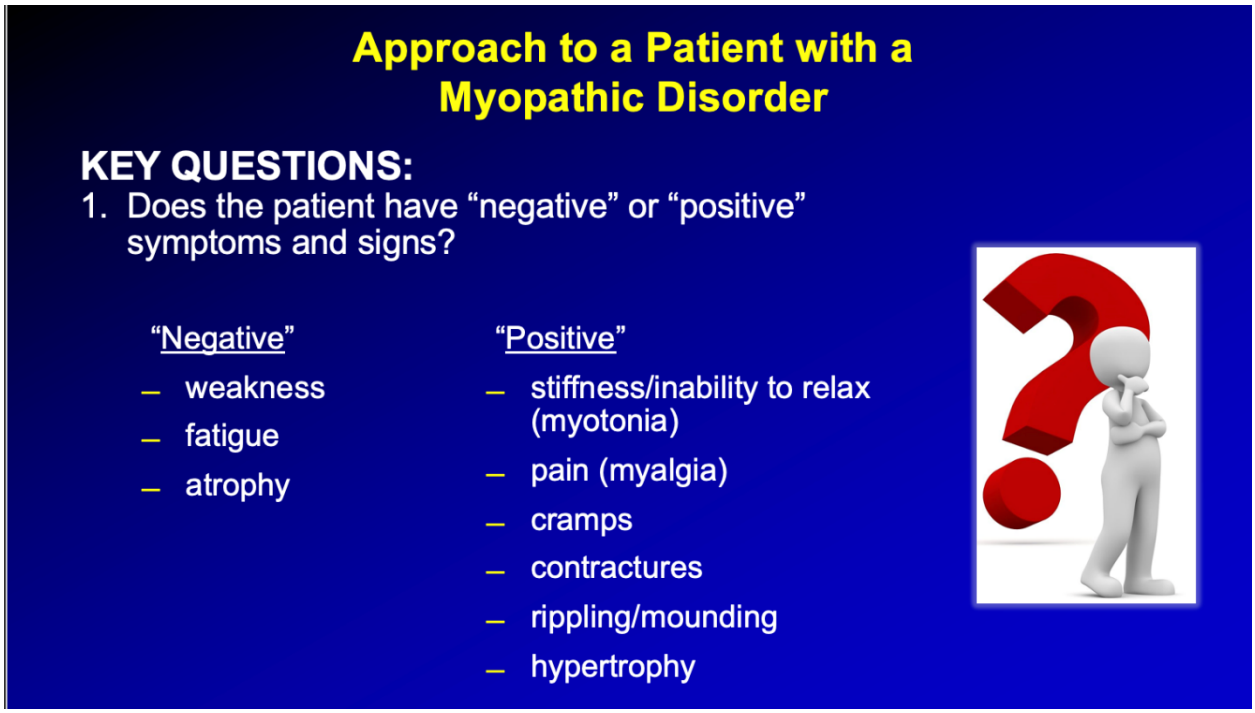
There are six key questions that you should be asking yourself when you take the history and when you do the physical exam (Figure 3). In a patient with a presumed muscle disorder as you gather the answers to these questions you will put the patient into one of the ten muscle presentation patterns. After you do this, you will be in a position to order your initial laboratory tests.

The SIX KEY QUESTIONS for muscle disorders are the following (Figure 3):



Question 1: Does the patient have negative or positive symptoms and/ or signs? (Figure 4)

Figure 4



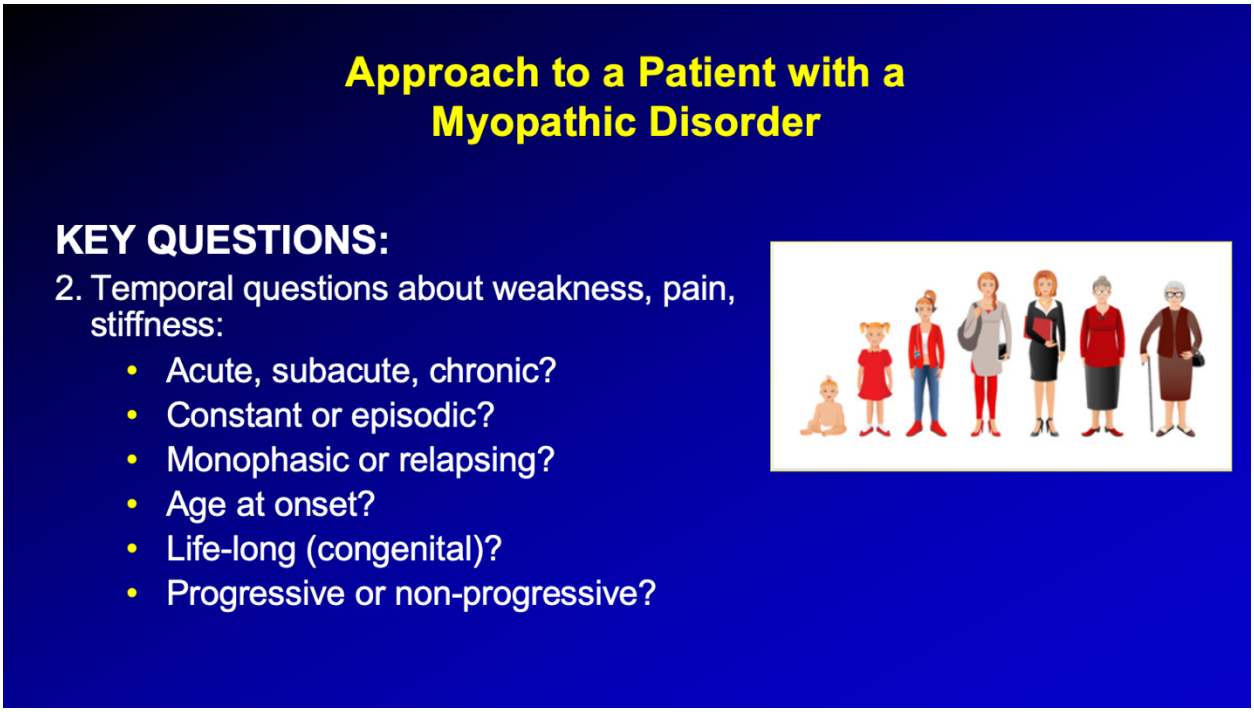
What we mean by negative symptoms/ signs is primarily **weakness**. The patient may state they are weak. On your neurologic exam, you identify that they are weak. Weakness is generally the most prominent symptom and sign of any patient with a muscle disorder. In addition, the patient may complain of fatigue, another negative symptom. However, fatigue is a symptom that is very difficult to demonstrate or quantify as a sign on the neurologic exam. One exception to this is ptosis which can be induced by having the patient maintain up gaze and observing the narrowing of the palpebral fissure. Similarly, double vision (diplopia) can often be elicited by having the patient look in a particular direction of gaze for a period of time. Speech fatigue can be demonstrated by having the patient read out loud and observing slurring of words or a nasal speech after a period of time. Eyelid fatigue, eye motility fatigue, and speech fatigue are hallmarks of neuromuscular junction weakness from disorders such as myasthenia gravis.

Muscle atrophy is a negative sign that should be documented, particularly if it is focal and combined to specific muscle groups. For example, in inclusion body myositis it is common to note atrophy of the flexor forearm muscles and the quadriceps muscles.

The main positive symptom is stiffness or inability to relax the muscles. When this symptom occurs in muscle disease, it usually is an indication of myotonia. The next step of course would be to attempt to demonstrate grip or eyelid closure myotonia or percussion myotonia on the neurologic exam. Other positive symptoms include pain and cramping. Positive signs can include mechanical or metabolic contractures, rippling or mounding of the muscles that can be induced with muscle percussion, or muscle hypertrophy or pseudohypertrophy such as enlarged calves.

Question 2: What is the temporal evolution of the disorder? (Figure 5)

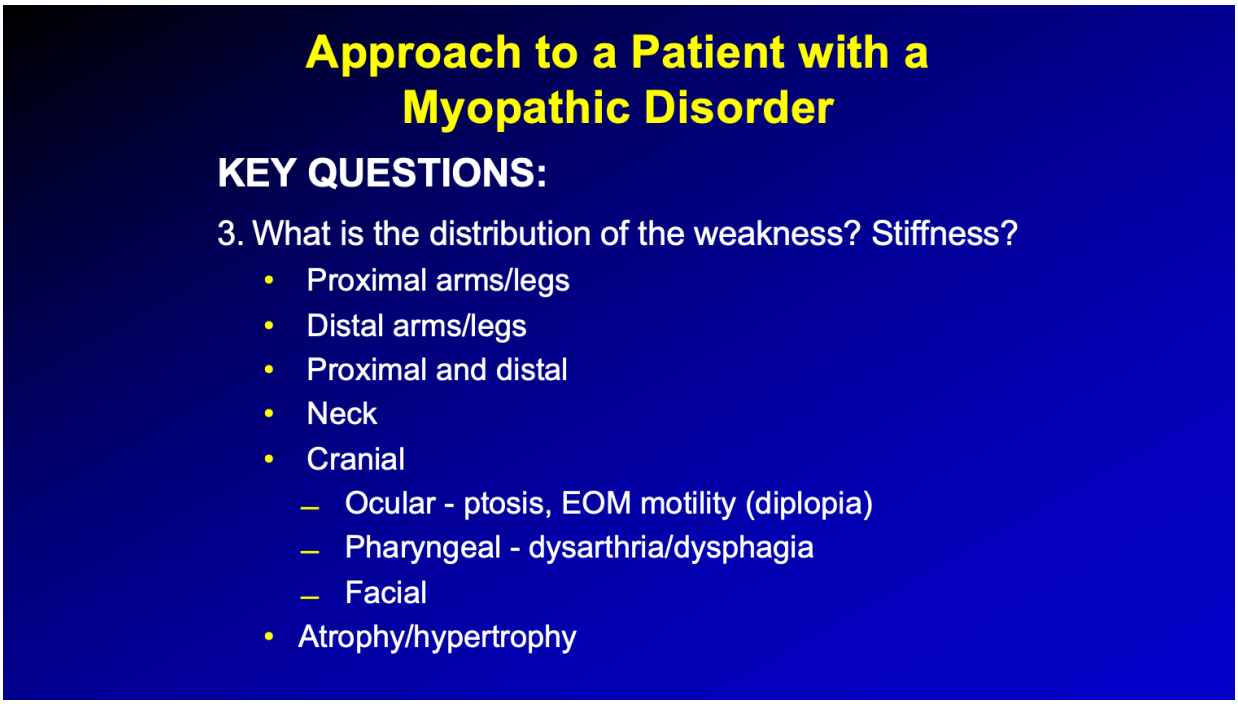
Figure 5



Is the disorder acute, less than 4 weeks? Subacute, 4-8 weeks? Or chronic, more than 8 weeks?
Is the disorder constant or episodic? In other words, do the symptoms and signs come and go?
Is the disorder monophasic or relapsing?
What is the age of onset of the patient when the disorder begins? Does it begin at birth, in the first several years of life, middle age, or late-life adult onset?
If the disorder has existed since childhood, is it congenital? In other words, was it present neonatally or in the first days and weeks of life?
Finally, is it progressive or non-progressive?
Some of the myopathic disorders such as congenital myopathies tend not to be very progressive. Other disorders such as muscular dystrophies and inflammatory myopathies are typically progressive.

Question 3: What is the distribution of the weakness or stiffness? (Figure 6)

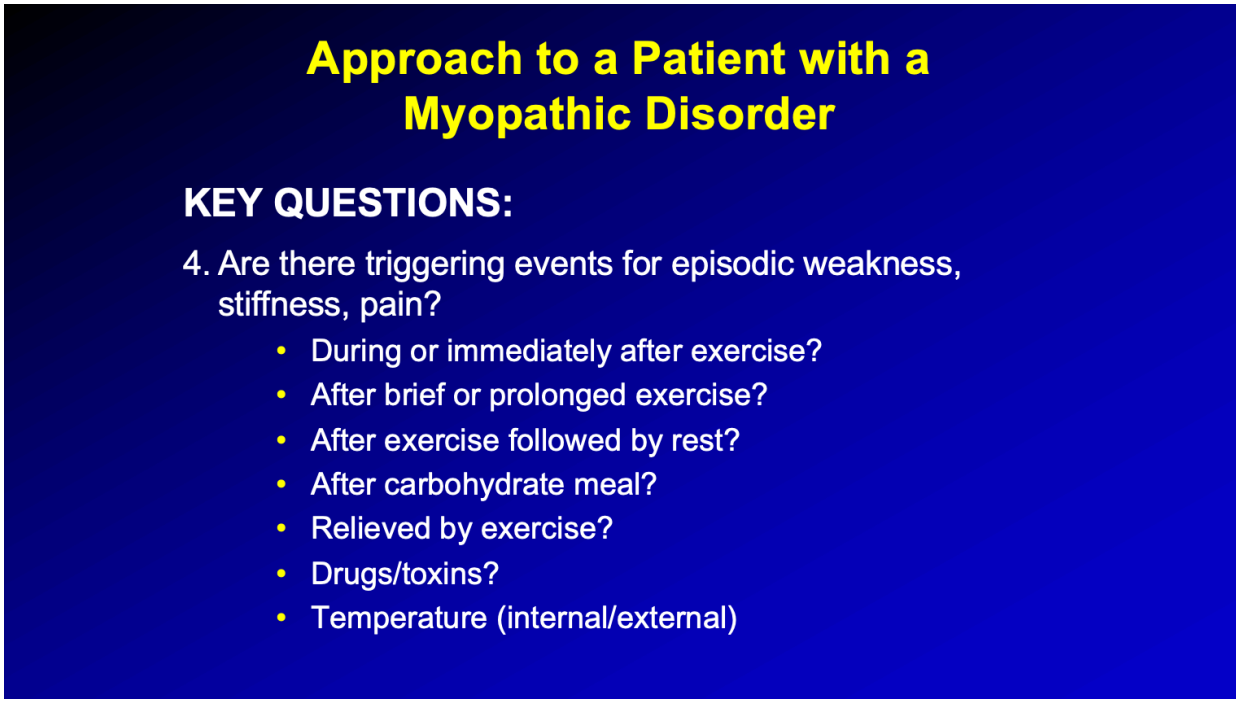
Figure 6



Based on the symptoms and signs, is the weakness primarily in the proximal arms/legs; distal arms/legs; both proximal and distal arms and legs; involve midline cervical or thoracic spine weakness; or involve cranial nerve innervated muscles?
As noted above, the positive finding of muscle stiffness usually denotes myotonia. The distribution of the myotonia can be determined based on symptoms or signs on exam. Most often it is identified in the hand muscles by demonstrating grip myotonia or percussion myotonia of the thenar muscles. But myotonia also can be elicited in the facial muscles, finger extensors, and proximal leg muscles. The distribution of atrophy or hypertrophy should also be documented.

Question 4: Are there triggering events for episodic weakness, stiffness, or pain? (Figure 7)

Figure 7



Triggering events are important in myopathy and they occur more often than in neuropathy.

Is exercise a triggering event and does the weakness occur during or after exercise?

If it is related to exercise, is it following brief exercise which occurs in metabolic glycogen disorders, or after prolonged exercise in metabolic lipid disorders and mitochondrial disorders?

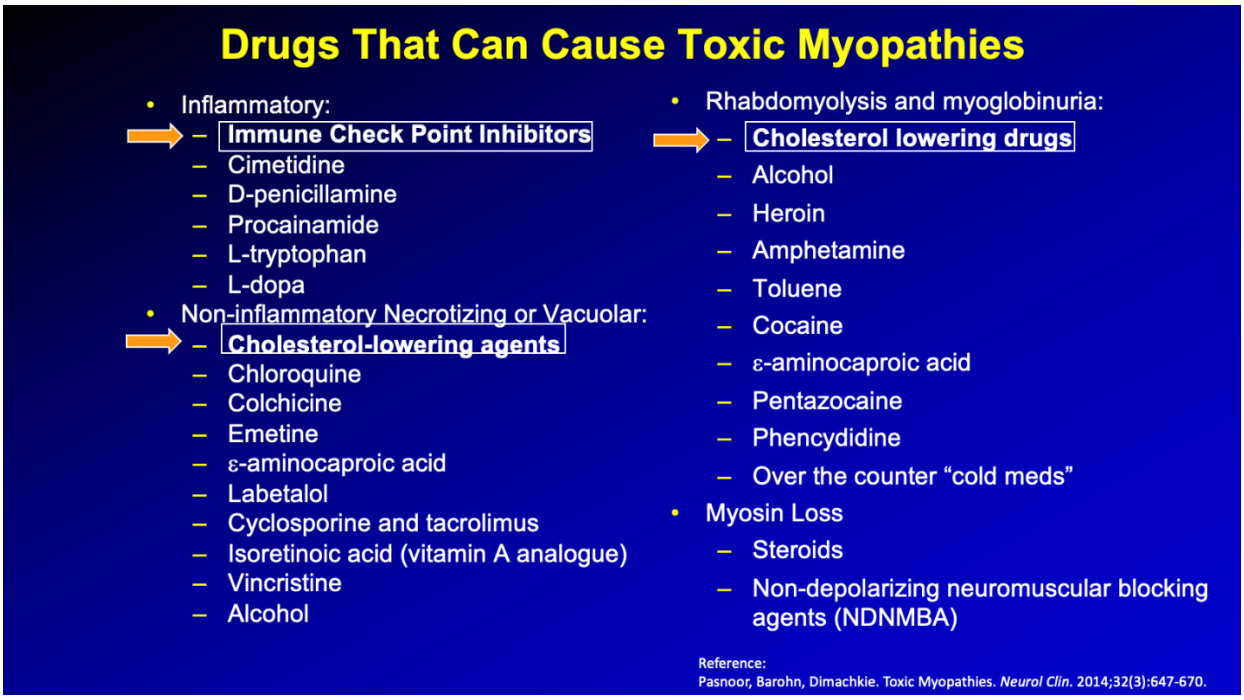
Does the weakness occur after exercise followed by rest? Does it occur after a carbohydrate meal? These are both triggers that can occur in the setting of periodic paralysis.

Are the symptoms relieved by exercise? This has to do more with stiffness. In typical myotonia, exercise makes it better or relieves the symptoms and signs of myotonia. But in paradoxical myotonia, exercise makes the symptoms and signs worse. Therefore, this is called paramyotonia.

Is a triggering event a drug or a toxin? Or was the trigger doing physical activity outside or in a very hot environment, which can occur in some instances of rhabdomyolysis, or does the patient present with an elevated body temperature which can occur in carnitine palmityl transferase (CPT) deficiency?

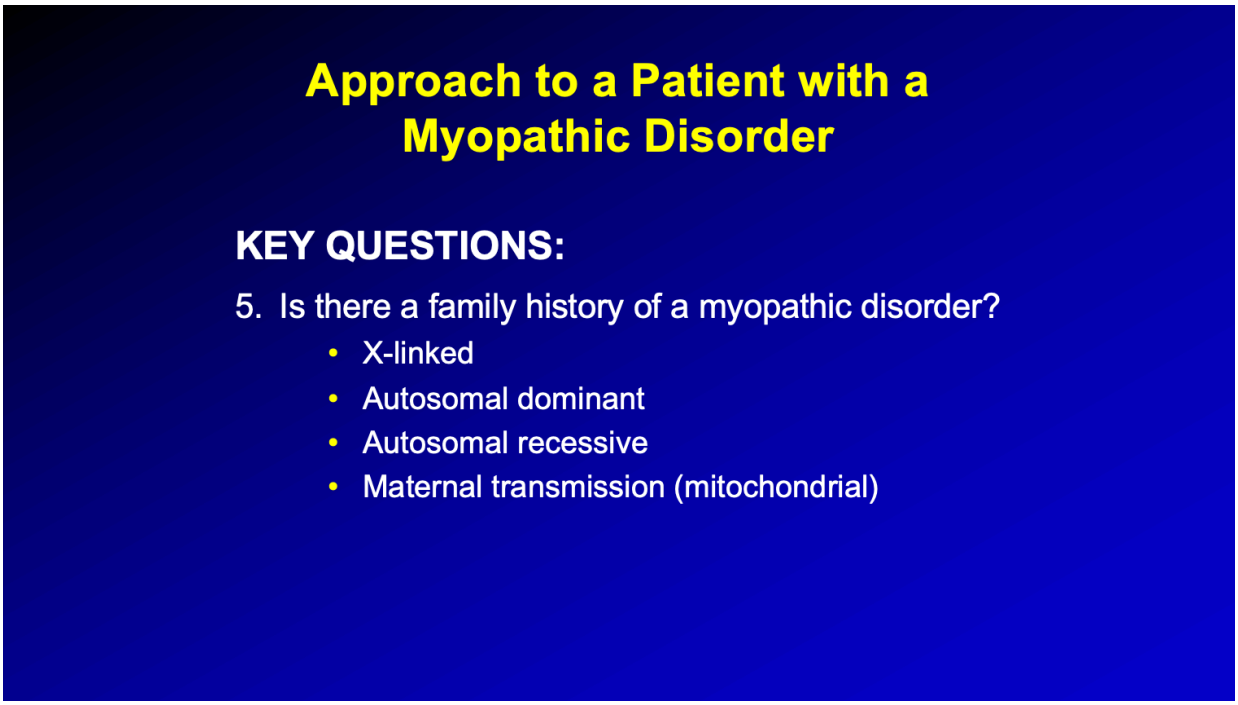
Figure 8 displays some of the drugs that can cause toxic myopathies. The list is extensive. We want to direct your attention to cholesterol-lowering drugs which are used frequently. Cholesterol-lowering drugs can produce more than one myopathic presentation. One is chronic progressive proximal weakness due to statin-associated autoimmune necrotizing myopathy (SANAM) requiring immunosuppressive and immunomodulatory therapy. In those cases, a new class of lipid-lowering drugs, the PSCK9 inhibitors, may be well tolerated. The other is a direct toxic effect leading to acute rhabdomyolysis and myoglobinuria and in milder cases of self-limited toxic necrotizing myopathy which resolves with drug cessation. A new class of agents is immune checkpoint inhibitors used for precision cancer therapy. Some patients exposed to immune checkpoint inhibitors develop weakness due to an inflammatory myopathy, myocarditis, or even a neuromuscular junction disorder as a side effect of the drug. The drugs on this list can cause several types of myopathic disorders including inflammatory myopathies, non-inflammatory necrotizing myopathies, rhabdomyolysis with myoglobinuria, or myosin (thick filament) loss myopathies as occurs in the context of critical illness.

Figure 8



Question 5: Is there a family history of myopathic disorder? (Figure 9)

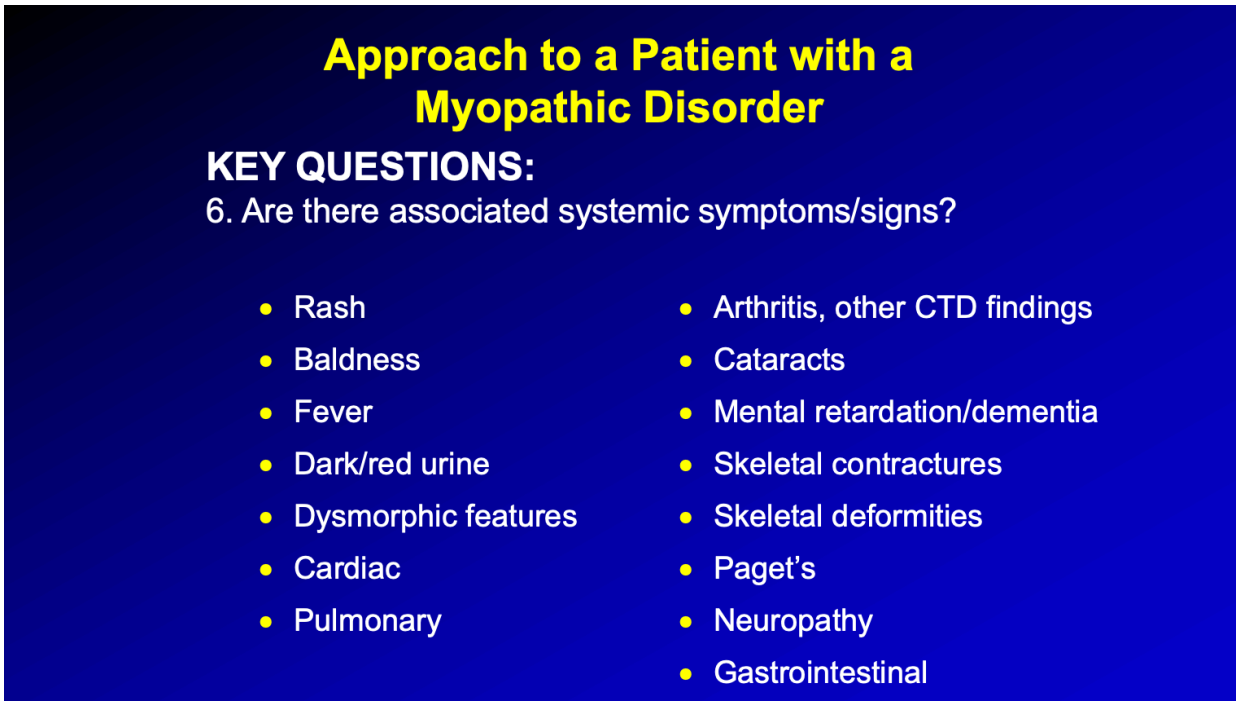
Figure 9



It is necessary to take a detailed family history in all cases of possible myopathies. Based on the family history, is there evidence of an X-linked recessive disorder where only males have the disease, and it is passed through the mother; or an autosomal dominant or autosomal recessive disorder; or maternal transmission to both men and women which is common in mitochondrial disorders?

Question 6: Are there associated systemic symptoms or signs? (Figure 10)

Figure 10



Is there a rash typical of dermatomyositis? Is there frontal baldness which can be seen in myotonic dystrophy? Does the patient have a fever concurrent with muscle symptoms which can be associated with CPT deficiency? Is there dark red urine typical of rhabdomyolysis with myoglobinuria? Does the patient have dysmorphic features of the face which can occur in a number of muscle disorders such as myotonic dystrophy, some congenital muscular dystrophies, and in rare forms of periodic paralysis such as Andersen-Tawil Syndrome? Some myopathies have mechanical muscle contractures as an early manifestation such as Emery-Dreifuss muscular dystrophy or Bethlem myopathy (a collagen-related genetic disorder). Glycogen storage myopathies can have metabolic contractures on exertion. When metabolic contractures occur during an electromyogram there is electrophysiologic silent.

Is there cardiac, pulmonary, and gastrointestinal involvement? Some myopathies have cognitive impairment or learning disabilities such as myotonic dystrophy, congenital muscular dystrophies and some cases of Duchenne muscular dystrophy. Arthritis and other signs of connective tissue disease are seen in dermatomyositis and polymyositis. Cataracts and severe cardiac conduction defects may occur in myotonic dystrophy. Paget's disease is seen in a particular form of inclusion body myopathy with Valosin-associated protein mutations.

The TEN MYOPATHIC PATTERNS (MP) are as follows:

Now we are going to go through the patterns of myopathy presentation. Based on these patterns, you will order certain laboratory tests in order to confirm the suspected diagnosis.

MP1: The limb-girdle pattern. (Figure 11)
This is by far the most common myopathic pattern. It has a broadest differential diagnostic list as evident in Figure 11. They are largely grouped as acquired disorders, most commonly autoimmune versus genetic muscle diseases. Some of this MP1 presentation overlaps with spinal muscular atrophy (SMA) or even neuromuscular junction disorders.

Figure 11

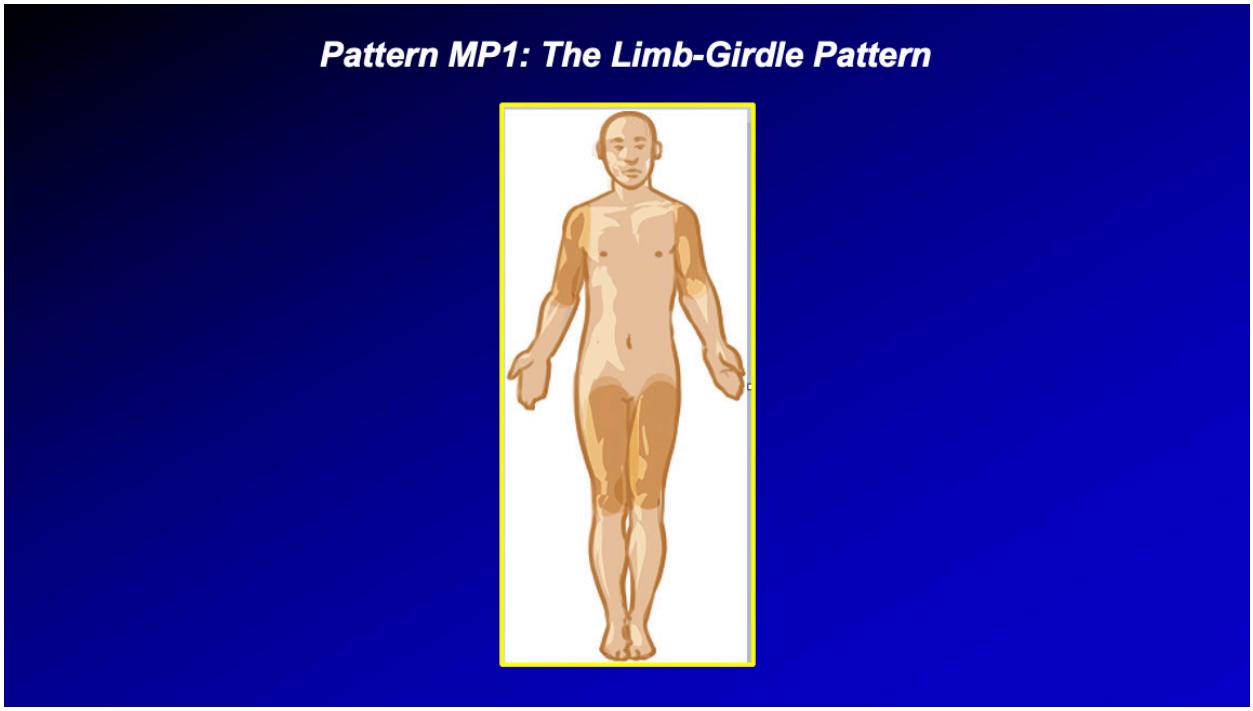
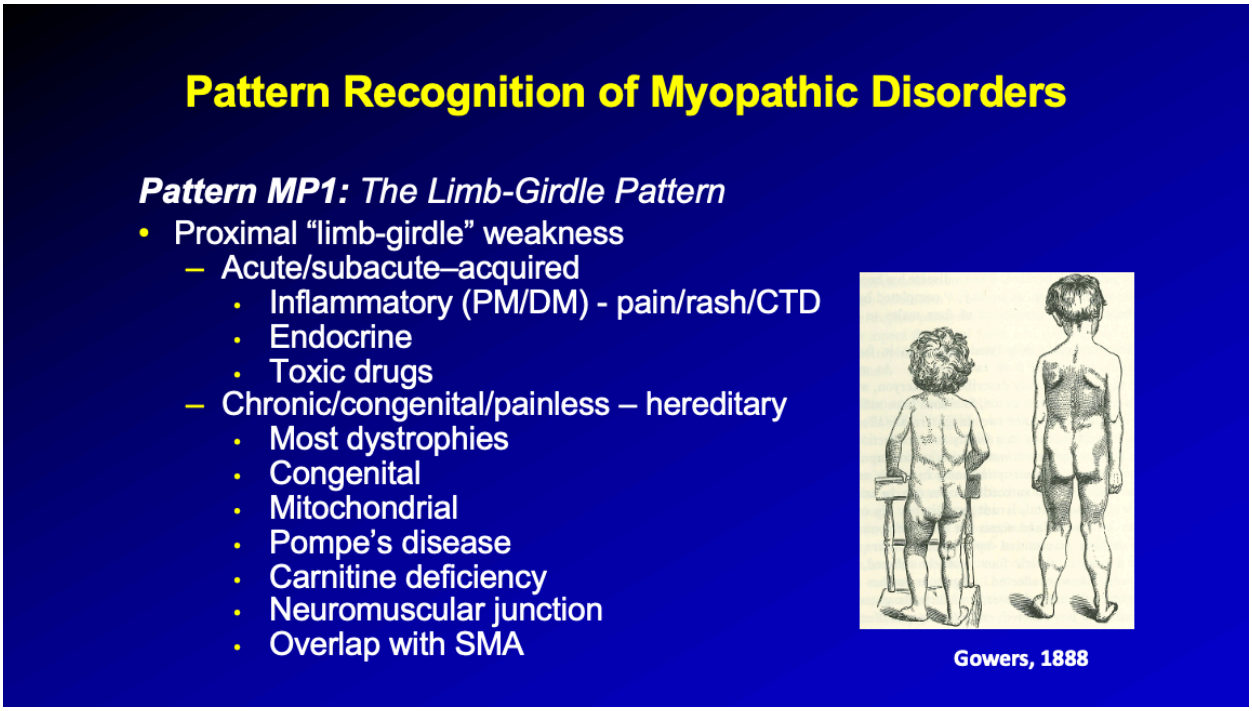


Figure 12



The drawing in Figure 12 comes from Gower's classic textbook A Manual of Diseases of the Nervous System (1888) and shows two brothers of ages 4 and 7 with what later was known as Duchenne muscular dystrophy (DMD). In the textbook, Dr. Gowers referred to the entity as "pseudo-hypertrophic muscular paralysis" because that was the term that Duchenne used in his original classic description from 1868. The drawing also shows calf hypertrophy which is typical of DMD. Figure 13 also comes from Gower's textbook and shows a young boy getting up off the floor and using his arms because he had proximal leg weakness. This observation is now known as Gower's sign. Another figure from the Gower's textbook shows a 14-year-old boy in the later stages of DMD with muscular contraction, wasting, and scoliosis.

Figure 13

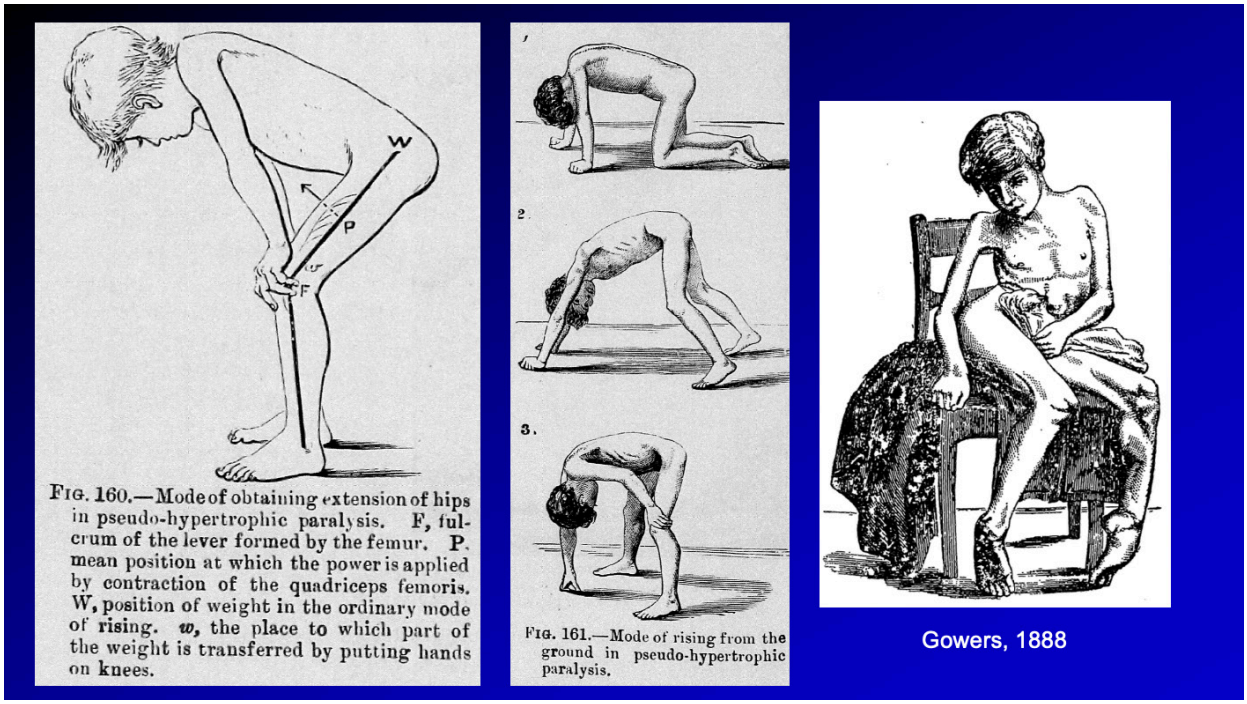


FIG. 160.—Mode of obtaining extension of hips in pseudo-hypertrophic paralysis. F, fulcrum of the lever formed by the femur. P, mean position at which the power is applied by contraction of the quadriceps femoris. W, position of weight in the ordinary mode of rising. *w*, the place to which part of the weight is transferred by putting hands on knees.

FIG. 161.—Mode of rising from the ground in pseudo-hypertrophic paralysis.

The limb-girdle pattern is the most common presentation of myopathies. A patient with an acute or subacute limb-girdle pattern is more likely to have an acquired disorder. A patient with a chronic limb-girdle pattern is more likely to have a hereditary disorder. There are often exceptions to this rule.

MP2: Distal pattern. (Figure 14)

Figure 14

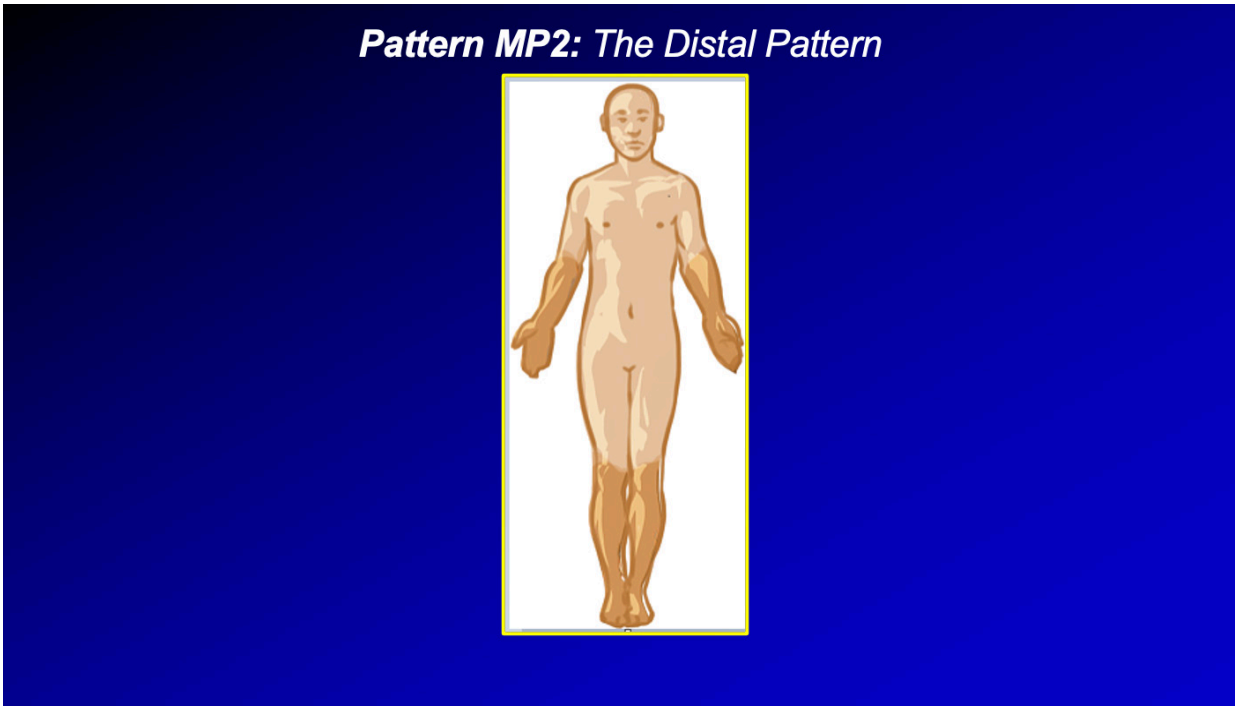
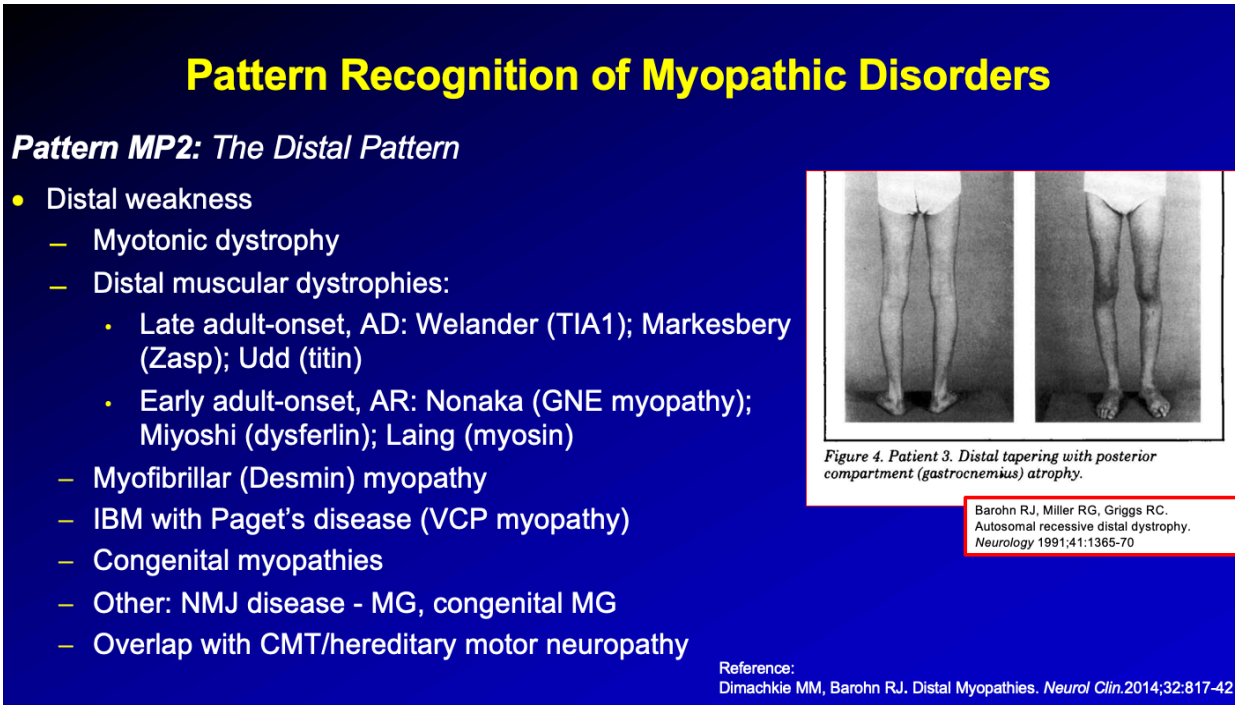


Figure 15



Myopathies with the distal pattern present with distal hand or leg weakness with relatively normal proximal muscle strength, at least initially. The most common muscle disorder that has a distal presentation is myotonic dystrophy which frequently has hand grip weakness and sometimes ankle weakness with very little proximal weakness.

Very rare disorders also come into this distal pattern group, particularly the distal muscular dystrophies. In this group, there are late adult onset distal muscular dystrophies that are autosomal dominant such as Welander (TIA1), Markesbery (Zasp), and Udd (titin) myopathies.

In addition, there are also early adult-onset distal muscular dystrophies that are autosomal recessive such as Nonaka (GNE myopathy), Miyoshi (dysferlin), and Laing (myosin) myopathies.

Other distal myopathies include myofibrillar (desmin) myopathy, hereditary inclusion body myopathy with Paget's disease also known as Valosin-associated protein myopathy. Rarely, nonprogressive congenital myopathies can have a significant distal weakness (nemaline rod, central core, centronuclear myopathy). Myasthenia gravis can have a predominant distal presentation. Usually, this involves finger extension, but ankle dorsiflexion can also be weak. Finally, some of the congenital myasthenia syndromes can have predominant distal weakness. A distal pattern of weakness can also be seen in hereditary motor neuropathy.

MP3: The proximal arm/ distal leg pattern (Scapuloperoneal) (Figure 16)

Figure 16

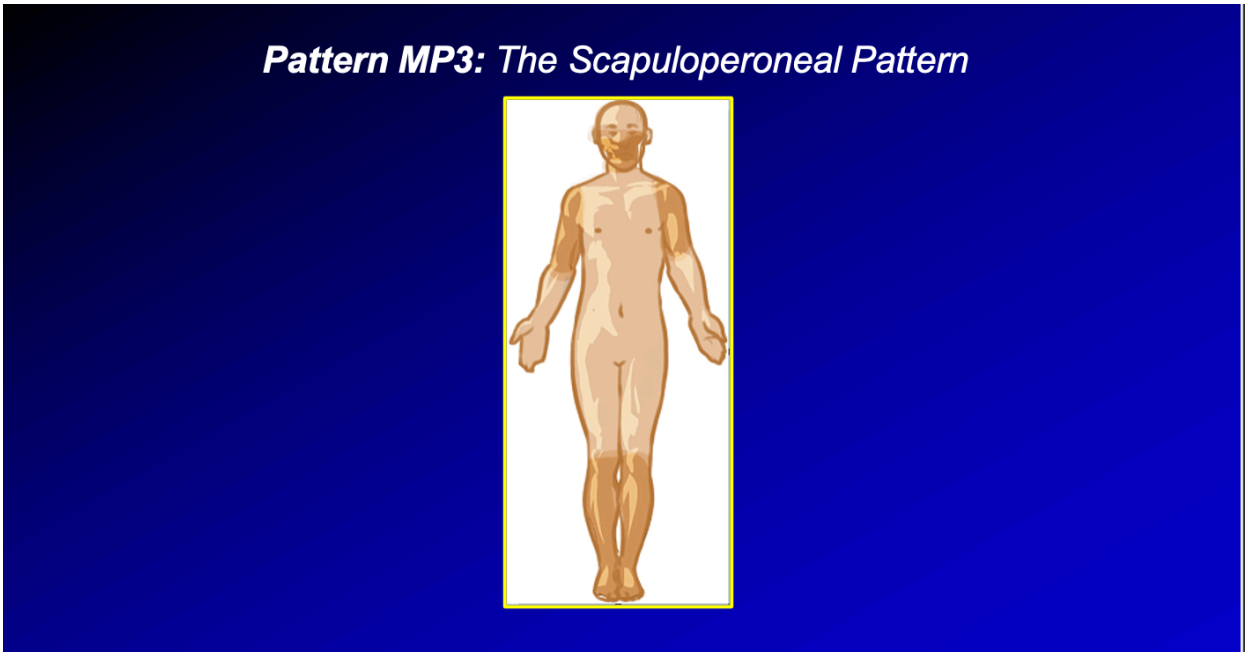
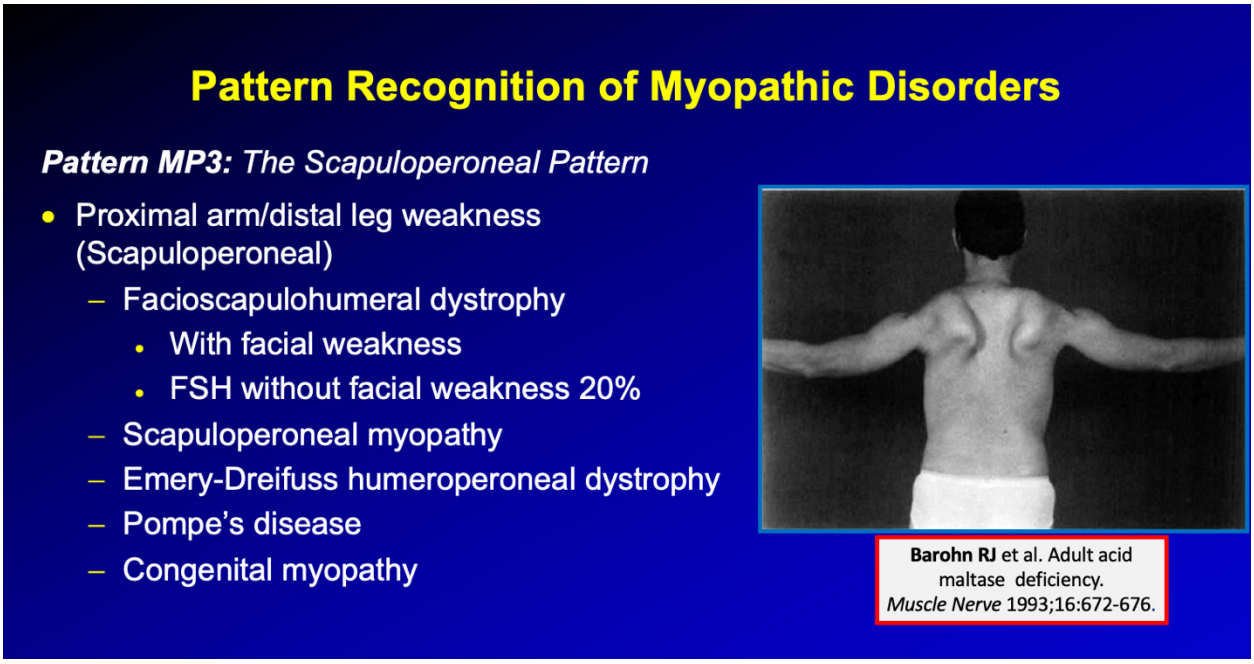


Figure 17



The MP3 pattern, also called the scapuloperoneal pattern involves scapular stabilizer muscles in the proximal arms and distal leg muscles. The distal leg involvement usually involves the tibialis anterior muscle and produces ankle dorsiflexion weakness. When facial muscles are involved, the disorder is almost always facioscapulohumeral dystrophy (FSHD). We now know through genetic capabilities that 80% of FSHD genetically positive individuals will demonstrate facial weakness, but some do not. There are other rare genetic causes of scapuloperoneal myopathy. Pompe's disease can present with a scapuloperoneal presentation, although most often it presents with an MP1 limb-girdle pattern. Emery-Dreifuss humeroperoneal dystrophy typically has a humeral peroneal pattern with prominent biceps and ankle dorsiflexion weakness, heart block, and mechanical contractures as previously noted. SANAM cases may have scapular winging in association with limb weakness.

Figure 18 shows a drawing from Gower's textbook demonstrating scapular winging due to weakness of the scapular stabilizer muscles.

Figure 18

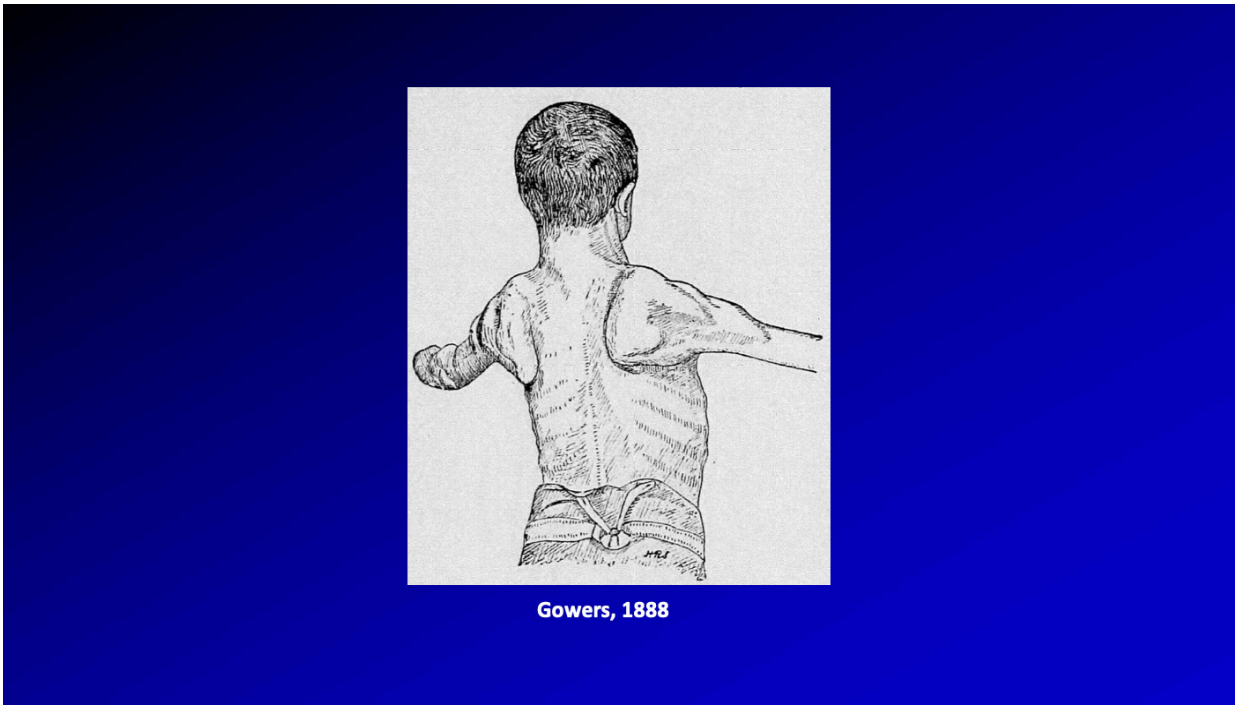


Figure 19 again comes from Gower's textbook and shows a 16 year old boy with orbicularis oculus weakness as well as weakness of the scapular stabilizer muscles and scapular winging that most likely represents a case of FSHD.

Figure 19

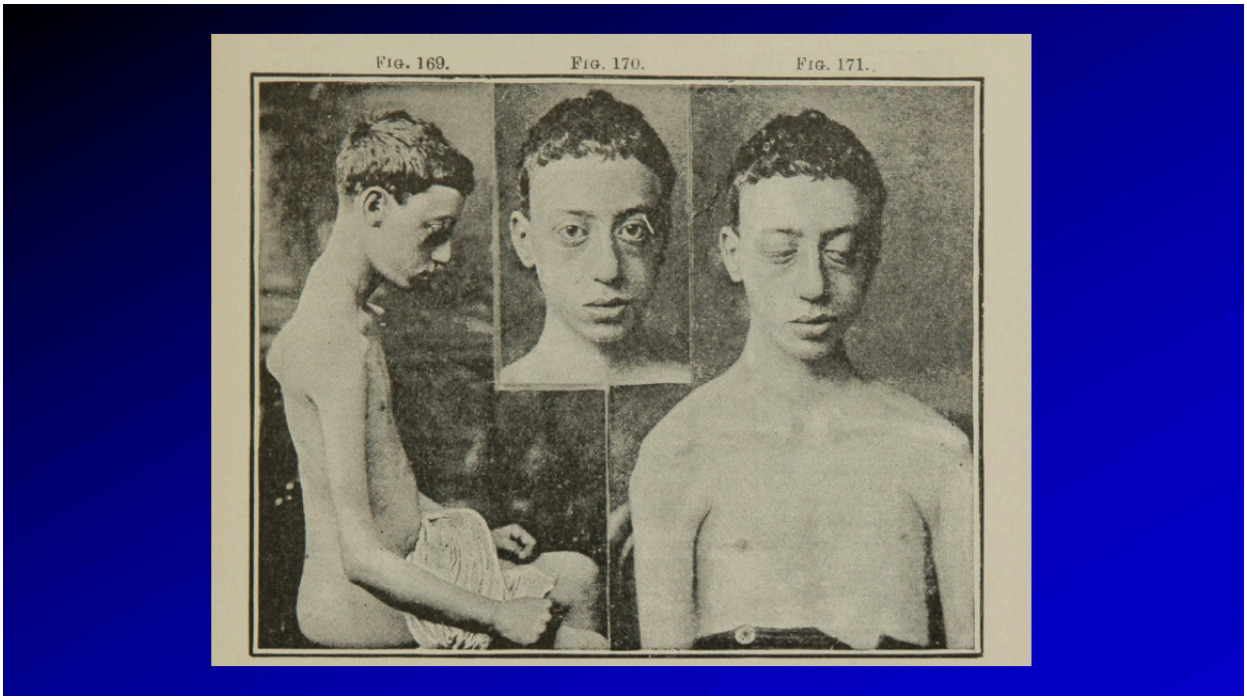
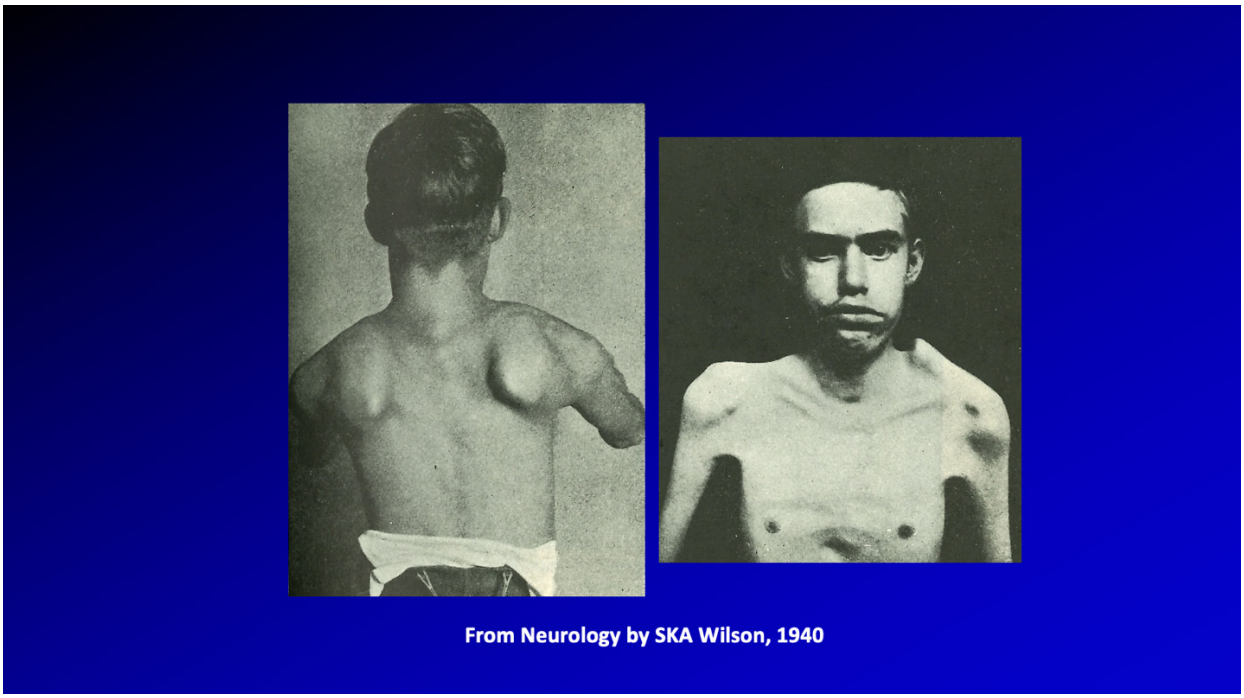


Figure 20 comes from another classic textbook called Neurology by S.A. Kinnier Wilson published in 1940 that shows a young man with FSHD who has scapular winging and facial weakness

Figure 20



MP4: The distal arm/ proximal leg pattern (The IBM Pattern) (Figure 21)

Figure 21

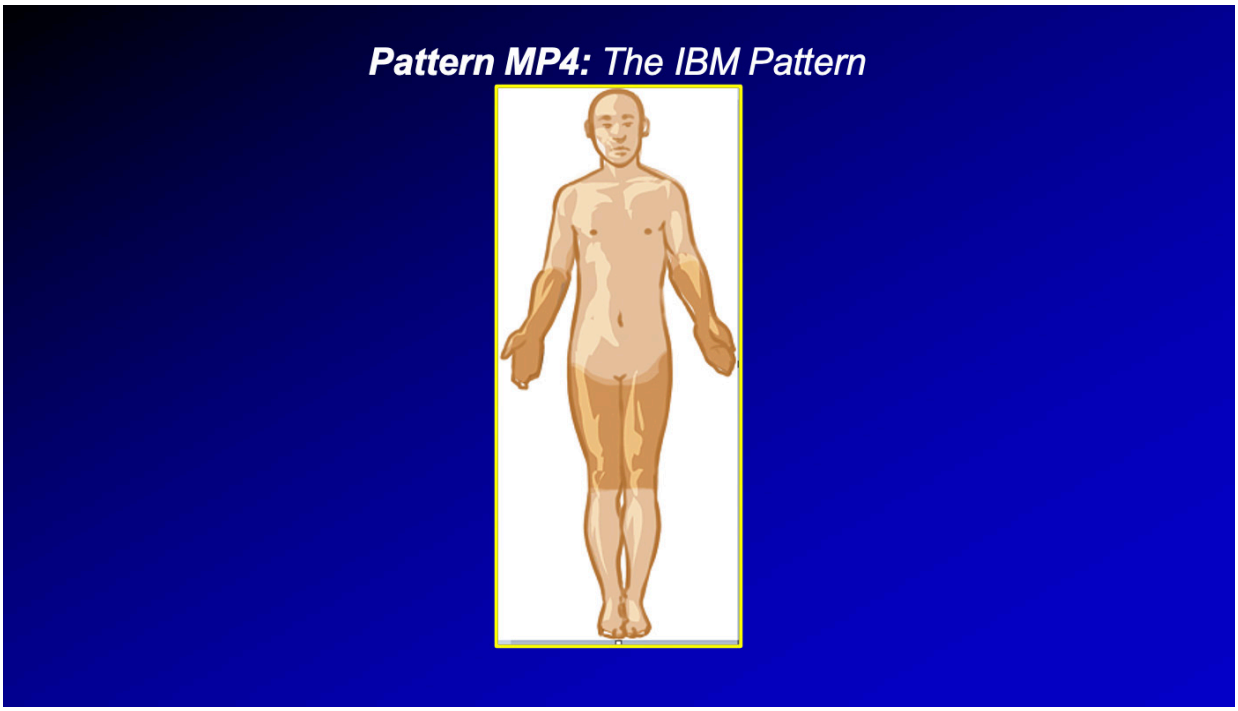
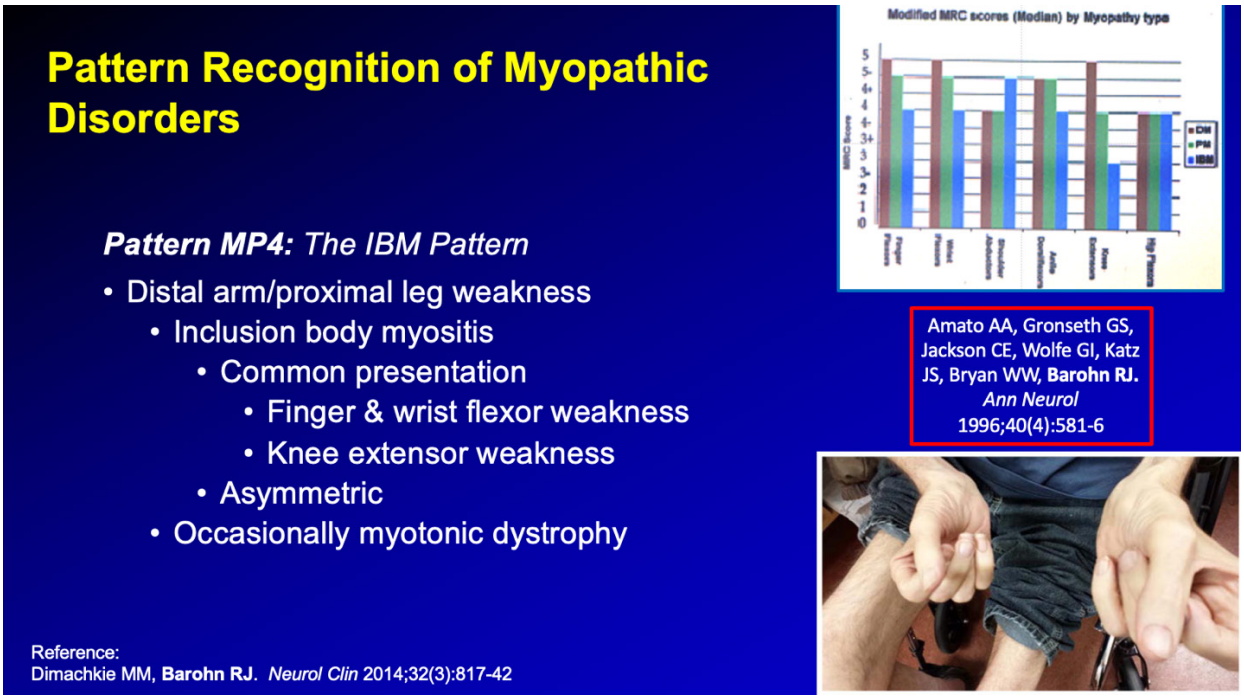


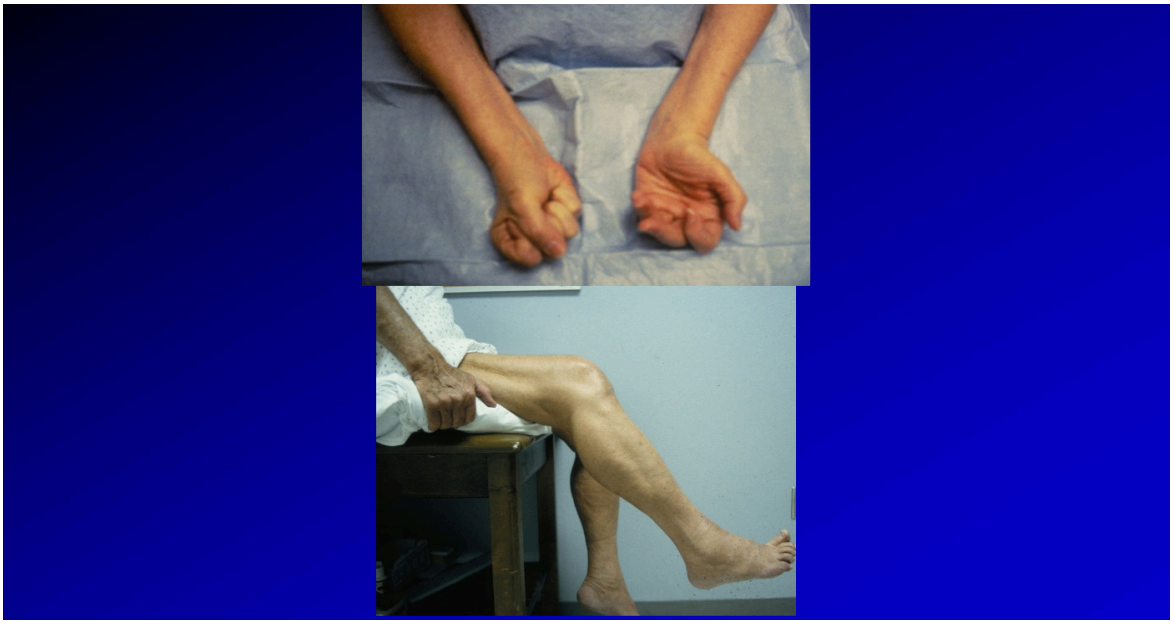
Figure 22



The MP4 pattern is the inverse of the MP3. In the MP4 the distal arm and proximal leg are predominantly involved. This is also called the IBM pattern because IBM is almost always the clinical diagnosis. These patients have prominent finger and wrist flexor weakness and knee extensor weakness. Often, the limb involvement is asymmetric with one side more affected than the other. Patients with IBM almost always have onset of weakness in the sixth decade of life or later. The only other muscle condition that can cause predominant finger flexor and knee extensor weakness is occasional cases of severe myotonic dystrophy. However, usually, there are enough other clinical features to indicate that the diagnosis is myotonic dystrophy and not IBM, for example, younger age of onset and characteristic facial appearance and balding in men and of course myotonia. Other confounders for this pattern are chronic sarcoid myopathy and rarely amyloid myopathy.

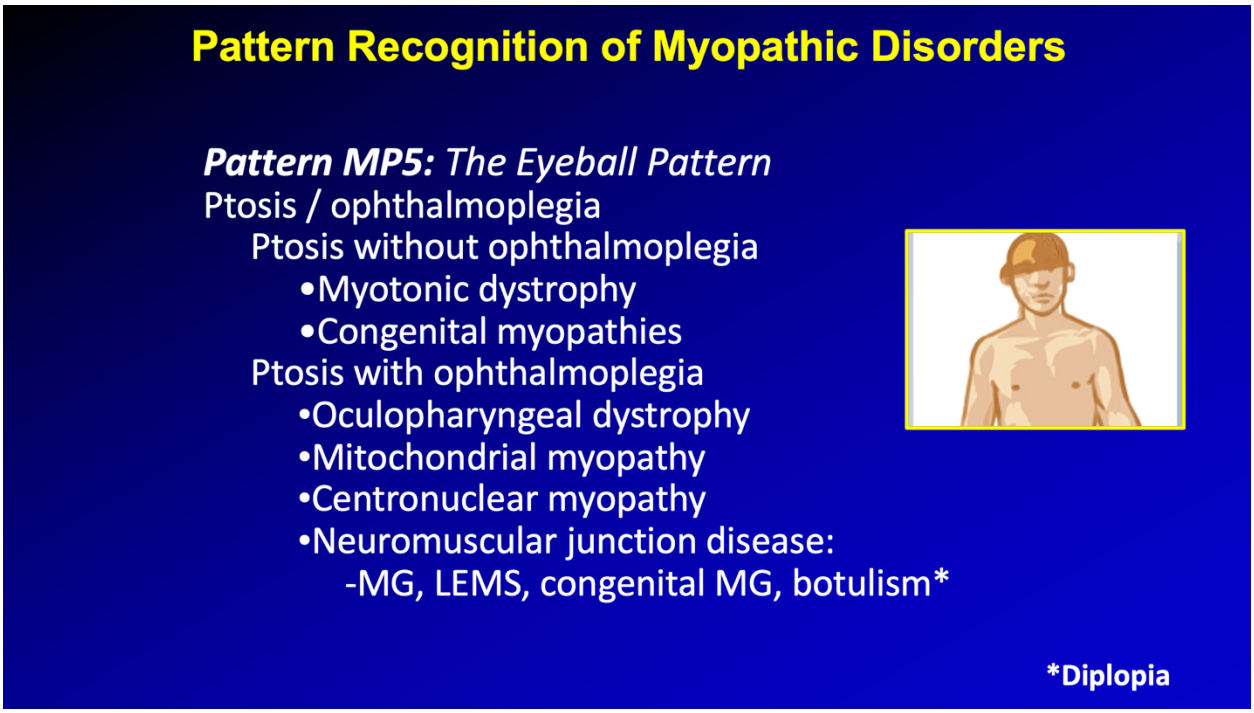
Figure 23 shows an IBM patient with distal forearm atrophy that is asymmetric, and they are having difficulty flexing their fingers.

Figure 23



MP5: The Eyeball Pattern. (Figure 24)

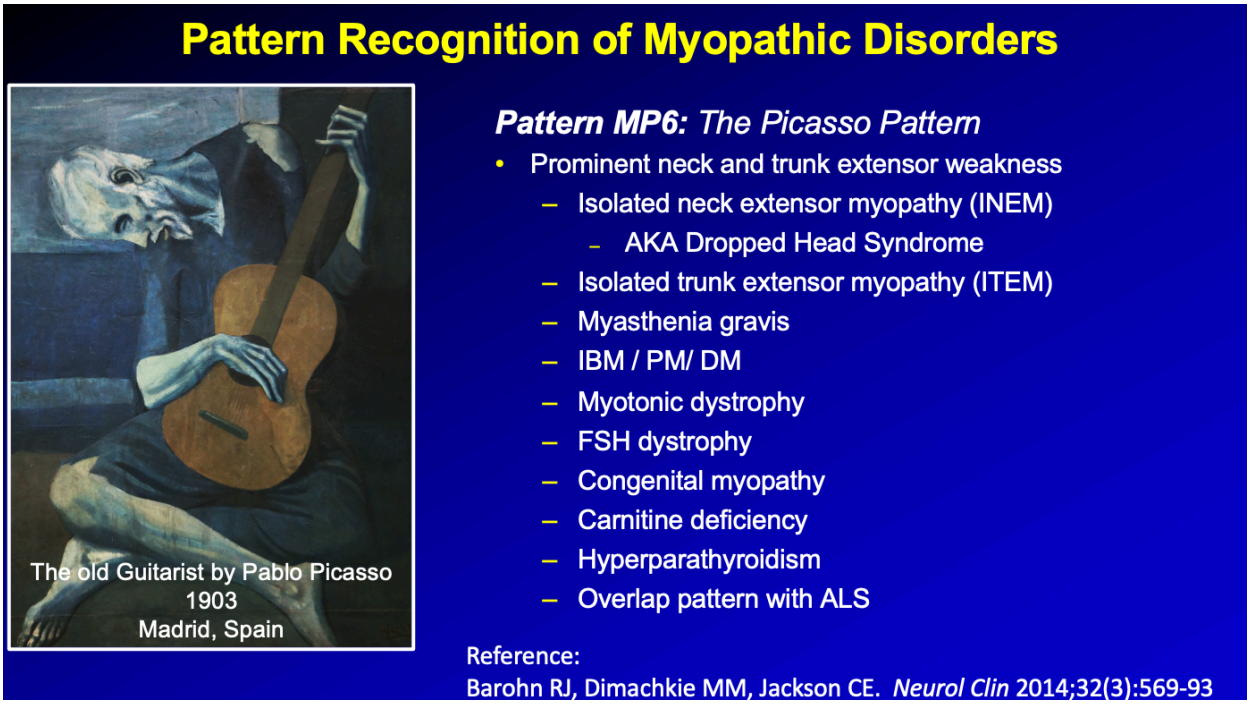
Figure 24



Ptosis without ophthalmoplegia is seen in myotonic dystrophy and congenital myopathies.
Ptosis with ophthalmoplegia is seen in oculopharyngeal dystrophy and mitochondrial myopathy.
It is also seen in X-linked centronuclear myopathies which are often male infants who are very floppy at birth, have ptosis and eye movement abnormalities. One primary difference between neuromuscular junction disorders such as myasthenia gravis versus oculopharyngeal dystrophy or mitochondrial myopathy is that neuromuscular junction disorders often have diplopia because of unequal extraocular muscle involvement. On the other hand, in oculopharyngeal muscular dystrophy (OPMD) and mitochondrial myopathy, even with very limited movement of the eyes there is usually no diplopia because all of the eye muscles are equally affected, though there are exceptions to this rule.

MP6: Neck and trunk extensor pattern (Dropped head or dropped body syndrome) (Figure 25)

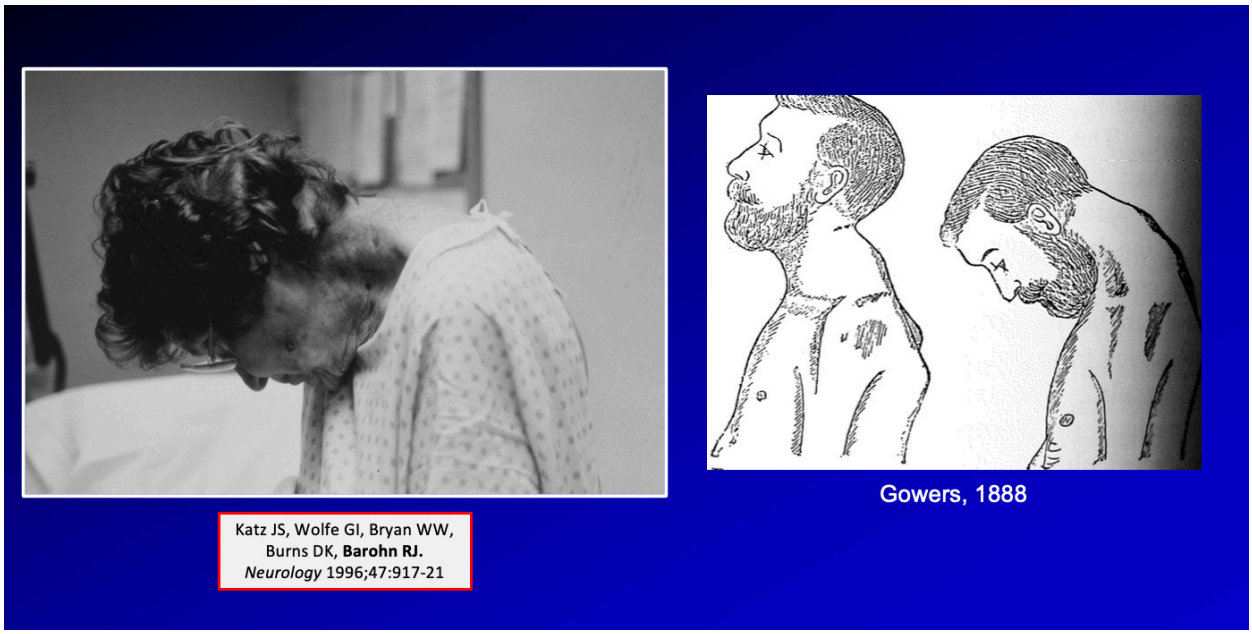
Figure 25



The MP6 pattern is demonstrated in Figure 26 which shows an elderly woman who cannot raise up her head. She has neck extension weakness due to weakness of the cervical paraspinous muscles. This is the MP6 pattern that can have either prominent neck or trunk extensor weakness, and occasionally both. The woman in Figure 26 has isolated neck extensor myopathy. We described a series of these patients in the 1990s however this pattern has been appreciated before and since then. We do not know the cause of this condition that we call isolated neck extensor myopathy (INEM). It is considered to be an idiopathic neck drop in the elderly due to weakness of the cervical paraspinous muscles. It does not respond to treatment with drugs, but it is benign in that it does not progress to other muscles or lead to death. There is a trunk form of this as well which we call isolated trunk extensor myopathy (ITEM). This is also untreatable with medications. There are a number of other muscle conditions that have been reported to be associated with neck drop such as myositis but these patients generally always begin with limb weakness, usually an MP1 pattern. Myasthenia gravis can have predominant neck extensor weakness causing a head drop. Patients often present holding their head up by placing their hand under their chin, they almost always have other features of myasthenia gravis that will lead to the diagnosis such as MP5 eyeball pattern or MP7 bulbar pattern (see below). Myasthenia gravis is of course very amenable to treatment and the head drop can usually be reversed.

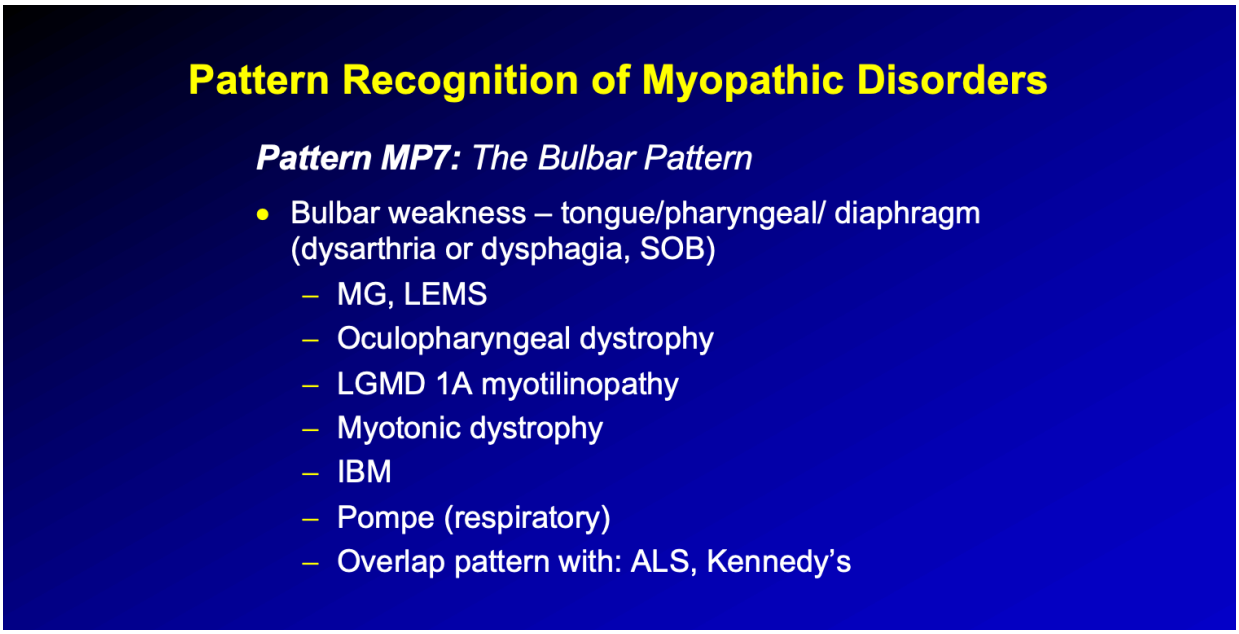
On the other hand, a neuropathic anterior horn cell condition that can cause severe head drop or trunk drop is amyotrophic lateral sclerosis (ALS). This of course is not benign and progresses resulting in death. Therefore, when a patient presents with head drop, usually the big three conditions to consider are INEM which is not treatable but benign, MG which is treatable, and ALS which is non-treatable and progressive. Figure 26 also shows another drawing in Gower's textbook of a man with head drop due to muscle weakness. We do not know the etiology of this middle-aged man's neck muscle weakness, but his probable middle age would suggest that it is not INEM but more likely another neuromuscular cause.

Figure 26



MP7: The bulbar pattern. (Figure 27)

Figure 27



Patients with the bulbar pattern have dysarthria, dysphagia, or shortness of breath due to a myopathic disorder. Myasthenia gravis patients commonly can present with a combination of these bulbar symptoms and signs. Occasionally Lambert-Eaton myasthenic syndrome (LEMS), another neuromuscular junction disorder, can as well but it more often presents with the MP1 pattern, and the bulbar symptoms are either not present or very subtle. The clinical triad of LEMS is proximal weakness, hypo or areflexia and dysautonomia .

Oculopharyngeal muscular dystrophy (OPMD) can present with both eye symptoms as well as dysarthria and dysphagia.

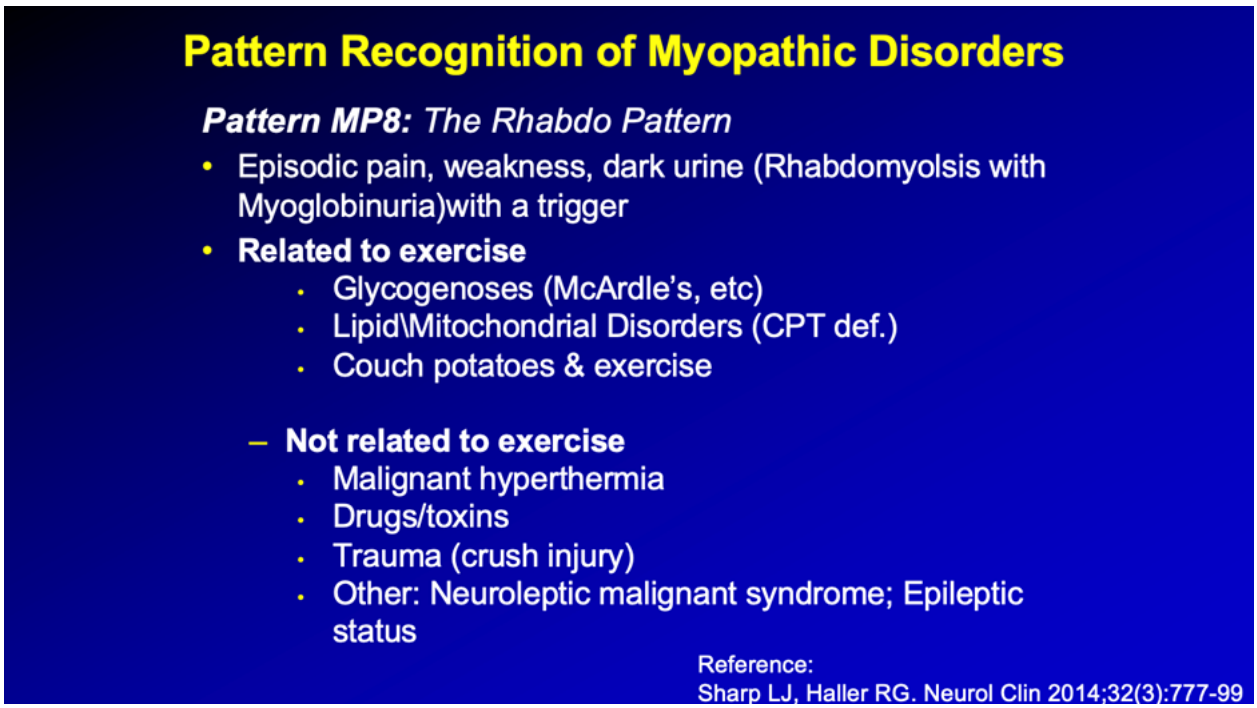
One of the limb-girdle muscular dystrophies (LGMD) with an MP1 pattern can also have prominent dysarthria-autosomal dominant myofibrillar myopathy 3 (previously LGMD 1A) due to myotilin gene defect.

Myotonic dystrophy and IBM both have prominent dysphagia.

Pompe disease is a lysosomal storage disorder that can have a significant diaphragm muscle involvement causing shortness of breath, usually in the context of MP1 or an MP3 pattern as well.

MP8: The Rhabdo pattern. (Figure 28)

Figure 28



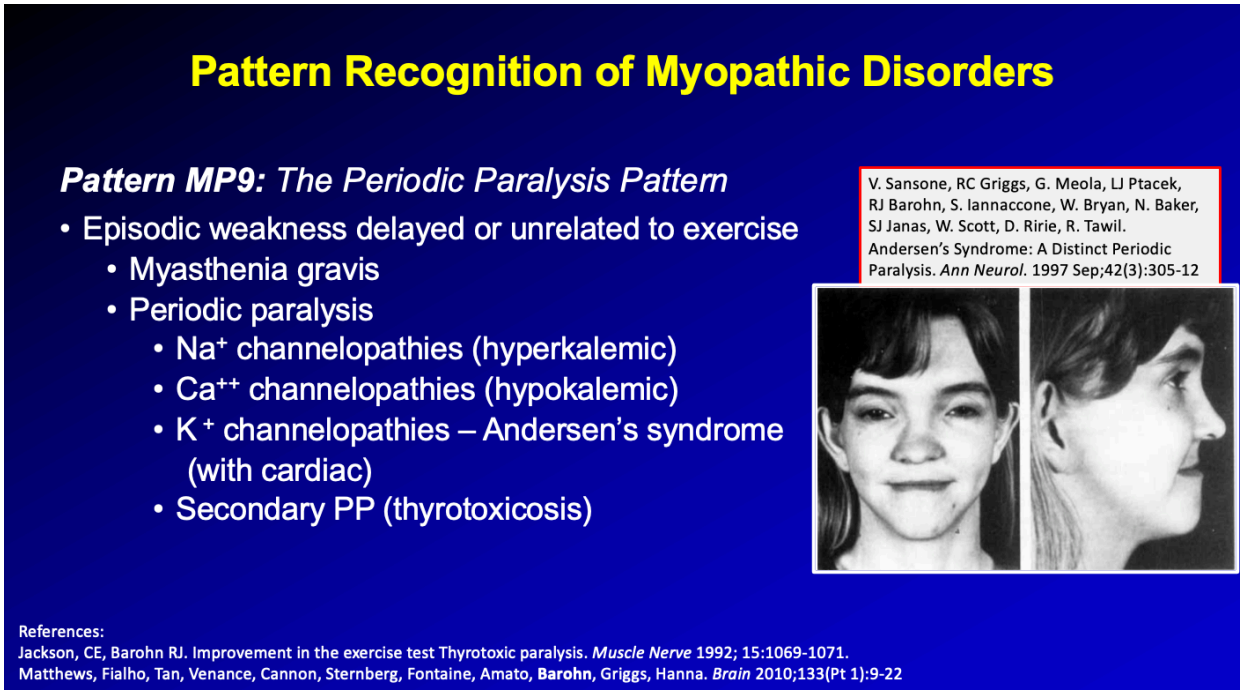
MP8 or the "rhabdo pattern", has episodic pain, weakness, and dark colored urine. There is always a trigger setting off the episode of rhabdomyolysis and myoglobinuria. When the trigger is exercise you need to consider whether it is from brief exercise, in which case there is usually an underlying glycogen disorder such as McArdle's disease. On the other hand, if the trigger is prolonged exercise, the underlying disorder is more likely to be a lipid metabolic disorder such as CPT deficiency or a mitochondrial disorder. Some of these patients who have exercise as a trigger do not have an underlying metabolic myopathy and they have simply been inactive for a prolonged period of time and are suddenly put under extraordinary conditions of exercise that can result in muscle injury. We often see the phenomenon in military recruits who are required to do intense exercise that they have never been exposed to and this can set off rhabdomyolysis and myoglobinuria. When delayed in onset by 1-2 days after exercise, this suggests delayed onset muscle soreness (DOMS).

When these patients are worked up, frequently you will not find an underlying glycolytic, lipid, or mitochondrial disorder. They have simply extended their ability to exercise beyond their capacity. We sometimes have also called this the "couch potato syndrome".

Other triggers that are not exercise-related include anesthesia-associated malignant hyperthermia, drugs/ toxins, trauma, neuroleptic malignant syndrome, and status epilepticus.

MP9: The episodic pattern. (Figure 29)

Figure 29

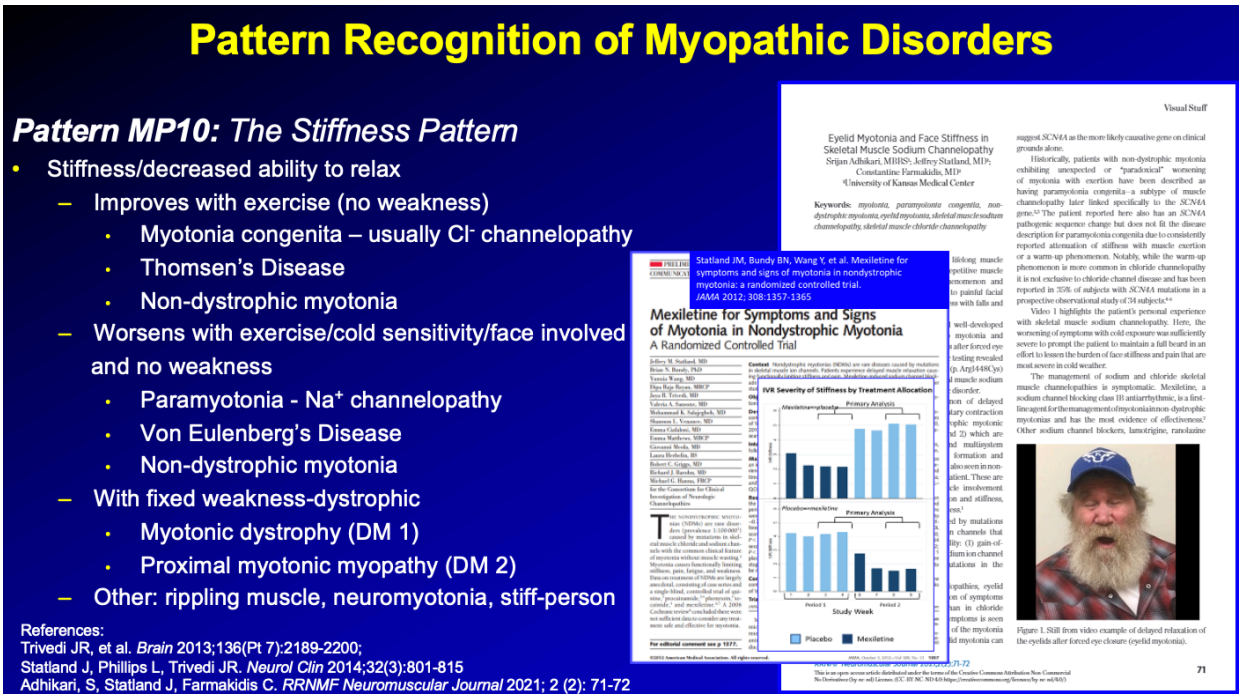


MP9 is the periodic paralysis pattern in which there is episodic weakness that is delayed or unrelated to exercise. There is no associated rhabdomyolysis or myoglobinuria, no pain, and no underlying metabolic disorder. MP9 is usually caused by muscle channelopathies. We also include neuromuscular junction disorders in this pattern because we are often taught that myasthenia gravis weakness is set off by exercise. However, for those who are experienced clinicians who take care of myasthenia gravis patients, we find that frequently you cannot get that history from the patient. Myasthenia gravis patients can have weakness unrelated to exercise nevertheless because it does occur at times, we include it in the MP9 pattern.

The main purpose of discussing the MP9 pattern is to remind you about periodic paralysis. This can be due to a sodium channelopathy that is usually hyperkalemic, a calcium channelopathy that is usually hypokalemic, or a potassium channelopathy which is the rare Andersen's syndrome. There are also secondary causes of periodic paralysis and the most common is thyrotoxicosis.

MP10: The stiffness pattern. (Figure 30)

Figure 30



Video link: https://www.youtube.com/watch?v=lyl0dPKrd2w

MP10 is the "stiffness or decreased ability to relax pattern". This is layman's terminology for myotonia. If stiffness improves with exercise and the patient is not weak, the underlying disorder is usually chloride channelopathy also known as myotonia congenita. This is one of the forms of non-dystrophic myotonia.

On the other hand, if the stiffness worsens with exercise, and is extremely cold-sensitive, particularly involving the face, and there is no weakness the underlying disorder is usually a sodium channelopathy. Sodium channelopathies are another form of non-dystrophic myotonias that are also called paramyotonia or paradoxical myotonia. The term paradoxical is used because other myotonias get better with exercise whereas paradoxical myotonia gets worse with exercise.

When there is fixed weakness with a myotonic disorder, the underlying diagnosis is usually myotonic dystrophy. Autosomal recessive chloride channelopathy present with myotonia and proximal weakness. The most common myotonic dystrophy is DM1 in which there is a significant amount of distal weakness, facial weakness, and other systemic involvement. Proximal myotonic myopathy is also known as DM2 and in these patients, the weakness is predominantly in a limb-girdle MP1 pattern but there are also varying degrees of myotonia which sometimes can be subtle. DM2 patients often also complain of myalgias.

Interestingly, no matter what type of myotonia or paramyotonia the patient may have, sodium channel-blocking drugs such as mexiletine dramatically improve myotonia symptoms and signs. The use of mexiletine for myotonic disorders is off-label and not FDA-approved .

EXCEPTIONS TO MYOPATHIC PATTERNS

There are exceptions to the pattern recognition approach of myopathic disorders. Two are noteworthy. Some dystrophinopathies present not with MP1 limb-girdle weakness but instead, present an MP8 pattern and have episodic pain and dark red urine. Patients with these dystrophinopathies usually have Becker muscular dystrophy (BMD) rather than early-onset DMD which always has an MP1 pattern.

Another exception is McArdle's disease which typically presents with the MP8 rhabdomyolysis pattern. However, we and others have noted that there are patients who present late in life with an MP1 limb-girdle pattern who have McArdle's disease and who cannot provide a good history for exercise and tolerance and rhabdomyolysis. (Figure 31).

Figure 31

Exceptions to Pattern Recognition Approach to Myopathic Disorders

1. Dystrophinopathies with episodic pain, dark/red urine (MP8, NOT MP1!)

2. Late-life McArdle's disease with fixed limb-girdle weakness; not episodic (MP1, NOT MP8!)

Figure 32

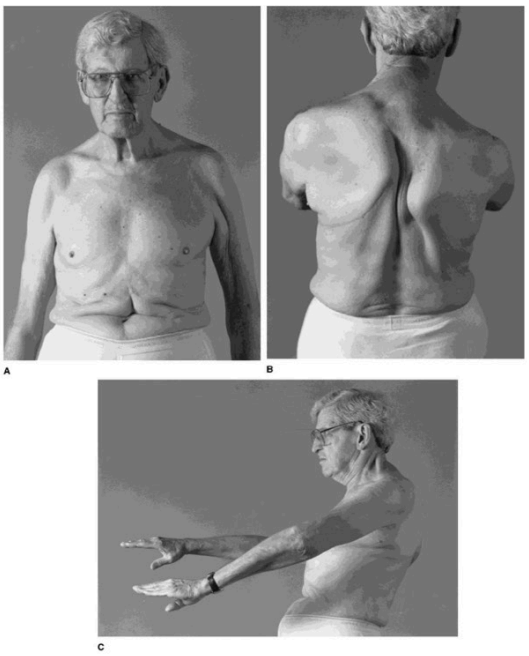


FIGURE 1. Muscle atrophy and weakness of shoulder girdle and proximal upper limb musculature. Note the prominent skin crease in the left upper arm (A) and the marked scapular winging (B). Asymmetric weakness of shoulder girdle musculature is evident, with poorer shoulder flexion on the left side (C).


CASE OF THE MONTH

ABSTRACT: McArdle's disease or myophosphorylase deficiency is one of the most common muscle glycogenoses and typically presents in childhood or adolescence with exercise intolerance, myalgia, myoglobinuria, and cramps in exercising muscle. We describe an elderly man who developed asymmetric proximal arm weakness at age 72. He had no history of exercise-induced cramps, myalgias, or myoglobinuria. Creatine kinase levels were elevated, serum lactate did not rise on ischemic exercise testing, and muscle biopsy showed a vacuolar myopathy with absent myophosphorylase activity. This unusual case demonstrates that McArdle's disease may present with fixed, asymmetric proximal weakness at an advanced age and should be considered in this clinical setting, especially when a history of poor exercise tolerance can be elicited.

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McARDLE'S DISEASE PRESENTING WITH ASYMMETRIC, LATE-ONSET ARM WEAKNESS

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McArdle's disease (glycogenosis type V) is an autosomal recessive muscle disorder due to myophosphorylase deficiency.[1] Myophosphorylase initiates the breakdown of glycogen to liberate glucose-1-phosphate.[2] The gene for myophosphorylase has been cloned, sequenced, and localized to chromosome 11q13.[3,4,5] Genetic mutations include single base substitutions causing missense or nonsense mutations and base-pair or codon deletions.[5,20–22] The R49X nonsense mutation in exon 1 accounts for the most common mutant allele in patients from North America and northern Europe.[5,20,23] McArdle's disease classically is associated with lifelong exercise intolerance. It typically presents in the first two decades of life with easy fatigability, painful muscle contractures referred to as cramps, and myoglobinuria induced by vigorous exercise.[3,5,13–15] The disease is known to present later in life in the form of symmetric, slowly progressive, limb weakness with a lesser degree of exercise intolerance. We describe a very late presentation of McArdle's disease in an elderly man who at age 73 developed asymmetric atrophy and weakness in the upper extremities.

CASE REPORT

An 83-year-old man of Swedish–Finnish heritage developed proximal left arm weakness at age 73 followed by right arm weakness at age 80. There was no pain or sensory loss, and his legs were not involved. As an adolescent, he was physically active and played sports, and later served in the U.S. Navy during World War II. After the war, he worked as a business executive until his retirement. On close questioning, he recalled experiencing fatigue and feeling short-winded after brief, vigorous exertion or when beginning lower intensity exercise such as walking briskly or serving as a golf caddy. For instance, while playing baseball, he could never run beyond second base to stretch a long hit into a triple or home run. After 10 to 15 min of moderate exertion, however, there was a second-wind phenomenon and his dyspnea would disappear. He could subsequently complete four rounds of golf in a day or walk briskly for several hours without any fatigue. There was no history of muscle cramping, myalgias, or pigmenturia. Family history was negative for neuromuscular disease.

On examination, he had marked atrophy of the supraspinatus, infraspinatus, biceps, and triceps

Abbreviations: ADP, adenosine diphosphate; AMP, adenosine monophosphate; EMG, electromyography; FSH, facioscapulohumeral; PAS, periodic acid-Schiff
Key words: late-onset; McArdle's disease; myophosphorylase; weakness
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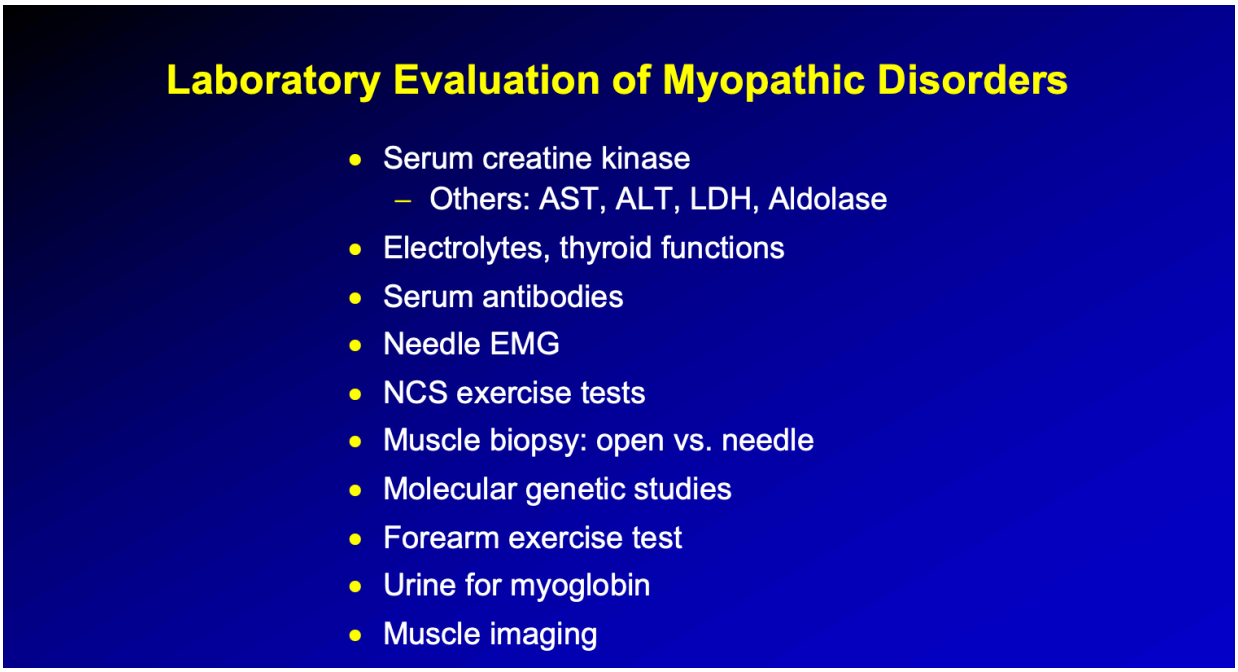
Asymmetric Weakness in McArdle's Disease MUSCLE & NERVE April 2000 641

Reference:
Wolfe al. *Muscle Nerve* 2000;23:641-645

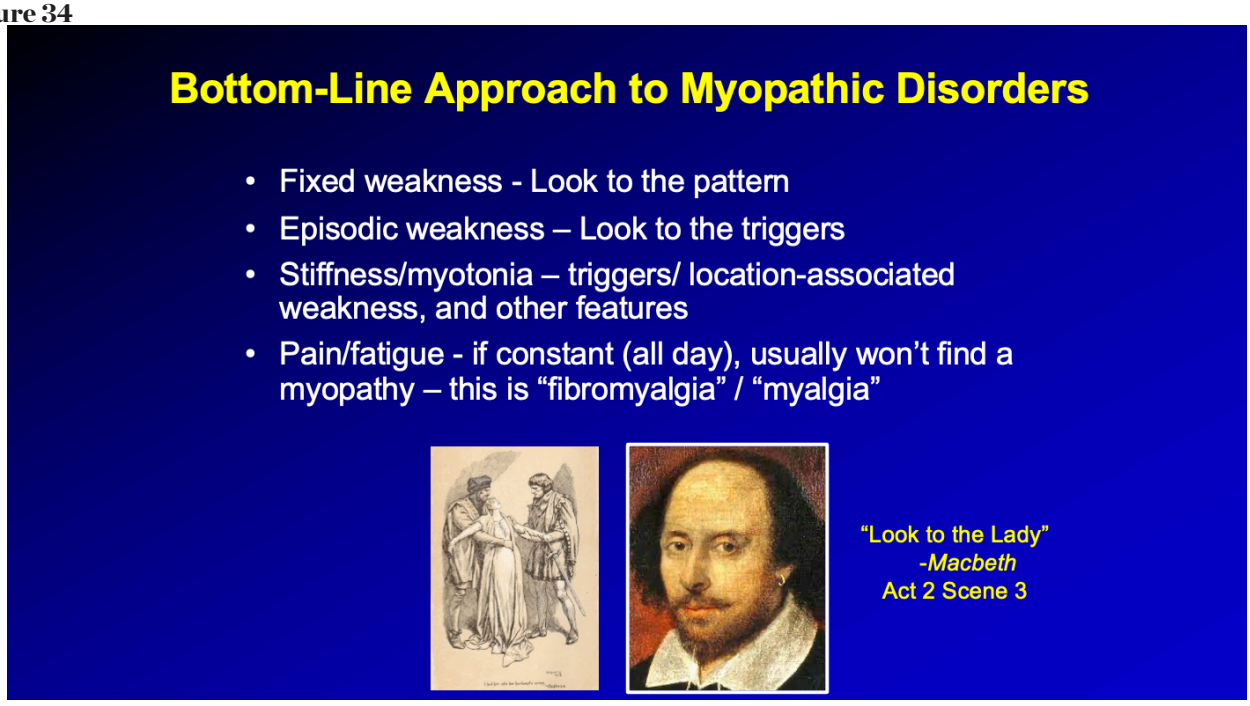
Summary
You should be using this pattern recognition approach to evaluate muscle disease before you order any laboratory or genetic tests. Once you put the patient provisionally in one of the ten patterns, then you can consider what diagnostic laboratory tests are needed (Figure 33)

Figure 33



The bottom-line approach to myopathic disorders is as follows (Figure 34):
If there is fixed weakness, look to the pattern; If there is episodic weakness, look to the trigger.
If there is stiffness or myotonia look to the trigger and location and if there is weakness.
If a patient has constant pain and fatigue, you usually will not find an underlying myopathic or neuromuscular junction disorder. The ten myopathic patterns are outlined in Figure 35.

Figure 34



Summary of Ten Clinical Myopathic Patterns
Figure 35

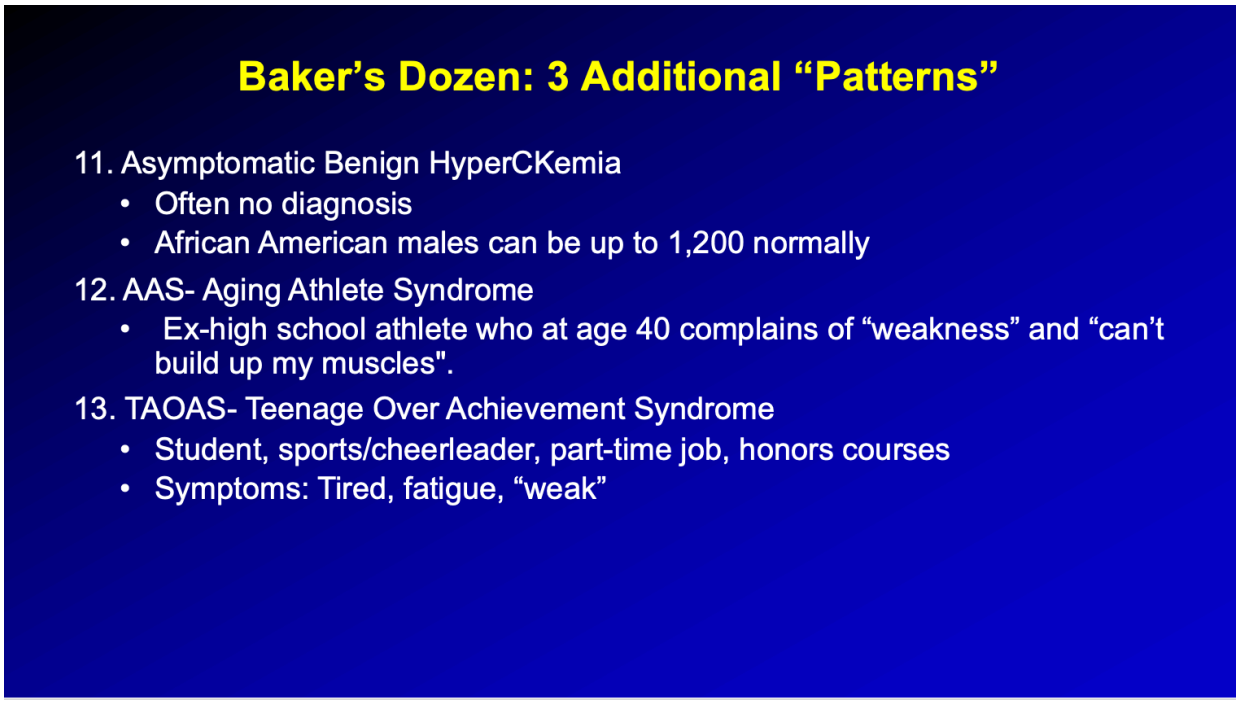
Clinical Patterns of Muscle Disorders

	Weakness						
PATTERN	Proximal	Distal	Asymmetric	Symmetric	Episodic	Trigger	**Diagnosis**
MP1 - Limb girdle	+			+			Most myopathies – hereditary and acquired
MP2 – Distal*		+		+			Distal myopathies (also neuropathies)
MP3 - Proximal arm / distal leg "scapuloperoneal"	+ Arm	+ Leg	+ (FSH)	+ (others)			FSH, Emery-Dreifuss, acid maltase, congenital scapuloperoneal
MP4 - Distal arm / proximal leg	+ Leg	+ Arm	+				IBM Myotonic dystrophy
MP5 - Ptosis / Ophthalmoplegia	+		+ (MG)	+ (others)			OPD, MG, myotonic dystrophy, mitochondria
MP6 - Neck – extensor*	+			+			INEM, MG
MP7 - Bulbar (tongue, pharyngeal, diaphragm)*	+			+			MG, LEMS, OPD (also ALS)
MP8 - Episodic weakness/ Pain/rhabdo + trigger	+			+	+	+	McArdle's, CPT, drugs, toxins
MP9 - Episodic weakness Delayed or unrelated to exercise	+			+	+	+/-	Primary periodic paralysis Channelopathies: Na^{+} Ca^{++} Secondary periodic paralysis
MP10 - Stiffness/ Inability to relax					+	+/-	Myotonic dystrophy, channelopathies, PROMM, rippling (also stiff-person, neuromyotonia)

*Overlap patterns with neuropathic disorders

Adapted from Barohn RJ, Dimachkie MM, Jackson RJ. *Neurol Clin* 2014;32(3):569-593

BONUS PATTERNS: BAKER'S DOZEN (Figure 36)
Figure 36



Asymptomatic Benign HyperCKemia
This is not truly a pattern but refers to patients that are being evaluated because they are found to have elevated creatine kinase, but they have no symptoms or signs. While some of these patients may turn out to have an underlying myopathic disorder, many do not. African Americans may have a higher creatine kinase upper limit of normal than other races, but this finding should not lead, in the absence of weakness, to a diagnosis of myopathy.

Aging Athlete Syndrome (AAS)
This refers to patients who at one point in their youth or young adult years were very athletic followed by a decade or two of relative inactivity at which point they try to "get into shape". They can present to a physician with a variety of complaints including myalgias and fatigue and also that they believe something must be wrong because they cannot reclaim the physical endurance that they had in their younger years. The best treatment here is reassuring the aging athlete.

Teenage Over Achievement Syndrome (TOAS)
This refers to teenagers who are brought in to see a physician by their concerned parents because the child is always tired, weak, and fatigued. These overachievers are often extremely bright, straight-A students, who are involved in after-school activities and also have a part-time job. No wonder they are tired and fatigued! The best treatment here is counseling the parents.

Conclusion

As in the Pattern Recognition Approach to Neuropathy lecture, we end this review by showing a quote from William James who said, "The rivalry of the patterns is the history of the world" (Figure 37). We have paraphrased William James in the following ways:

The recognition of the patterns is the key to understanding neuromuscular disease
And
The patterns are like the operating system for how we are supposed to think about neuromuscular disease (Figure 38)

Figure 37

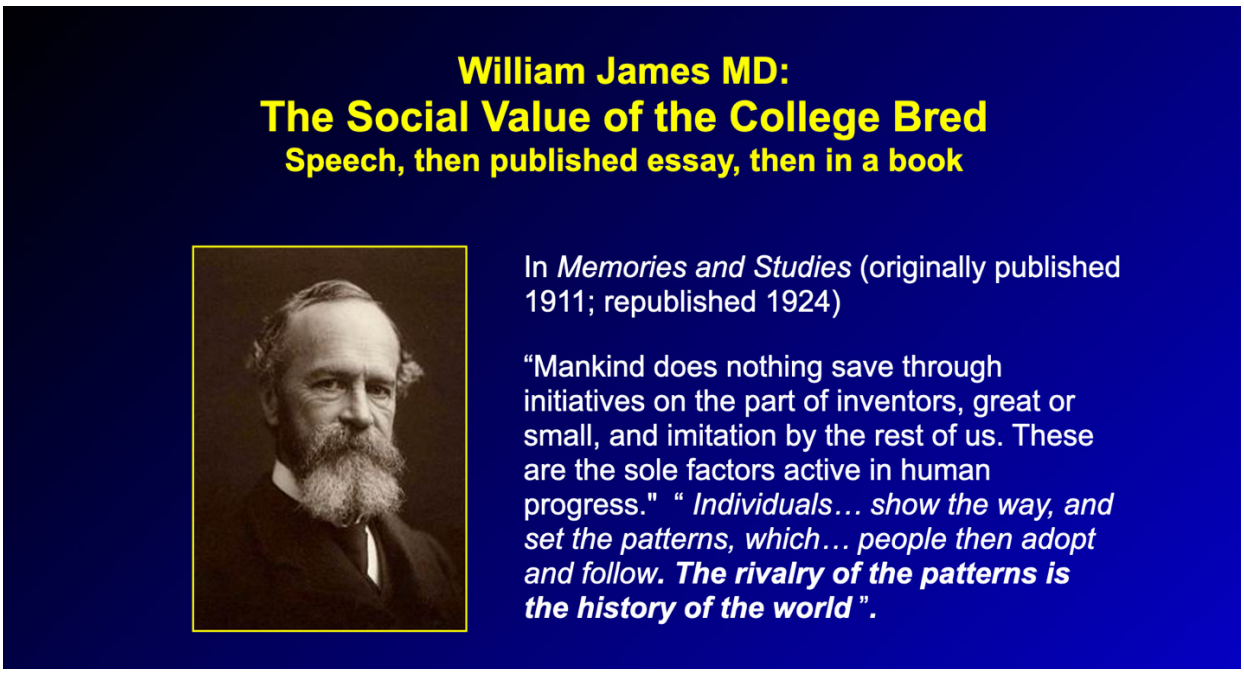


Figure 38

Figure 39

We would like to thank Amanda Sebok for her assistance in preparing the PowerPoint figures and Lauren Peck for her editorial assistance in preparing the manuscript.

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The Culmination

Michael Abraham

University of Kansas Medical Center

Last steps of the day; my body is beaten down.
My heart, it is weary, I haven't seen you in so long.
Sunset may have beat me home,
But your heart it beats in my chest.
Beeps and bells may steal me
But I will always come back to you.

Death and destruction, are all around in my waves.
Simple steps, millimeters, one slip and life is changed.
I worry, oh I worry, what has it led me to?
Missing moments, moments that should be written down.
My heart it is aching, aching to be released.

Lead me to the breakdown and let us celebrate the chorus.
Our pictures are like pictures on the movies, memories.

Rain drops keep falling, let us find a way to collect them,
And build a sea, so we can swim all the way up to the moon.

I feel the pressure it is building up, up and down.
Crashing, waves and winds, the TV, it blurs my mind.
Need to stop, gotta stop and take it in,
Live the moment before it's gone into the background.

Lead me to the breakdown and let us celebrate the chorus.
Our pictures are like pictures on the movies, memories.

Rain drops keep falling, let us find a way to collect them,
And build a sea, so we can swim all the way up to the moon.

Reaching for you in the night, seeing Your Glow in the present life.
The calm, the present, Your presence, filling me up.

Then I see your light as it floods into the darkness.
I see your light as it echoes through the night.
The stars and moon, they cheer you on.
The sun, it is jealous, that it has fallen asleep.
You hold my hand as if I wore a cape
And I close my eyes and revel for awhile.

Dr. Barohn's remarks for Dr. Griggs's Festschrift celebration, July 19, 2024, Rochester NY

Richard J. Barohn, MD

One of the greatest gifts you can receive when starting an academic career is the gift of having a good mentor. I was fortunate to have several great mentors. At Ohio State University, Jerry Mendell was my primary mentor along with John Kissel and Zarife Sahenk. But who I call my long-distance mentor from the beginning was—and continues to be—Berch Griggs. Jerry introduced me to Berch at the outset of my fellowship, and he—as many of us have experienced—became an ever-present figure in my academic career.

My first interactions with Berch were at the American Academy of Neurology annual meetings in the 1980s. I particularly remember the early years of the neuromuscular after-dinner seminar that Berch, Jerry, and Bob Miller led. As I recall, because of my junior rank and just having finished the Mendell gauntlet fellowship, Berch frequently called on me to figure out a case as my baptism by fire. I think I was much smarter then, and my goal was to not disappoint my mentors with a wrong answer.

Let me tell you about five gifts that I have received from Berch:

The first involved that early AAN experience, when I presented a case of a Miyoshi distal myopathy. We were just starting to talk about this phenotype in the United States, a decade before the molecular genetics were discovered. Berch and Bob said they both had cases, and it was HIGHLY suggested by Berch that I write up all our cases for publication, which I dutifully did—and quickly! Berch sent me not only clinical information, but also old-fashioned black and white photographs of his patient who made it into the paper. The paper was published in Neurology. I originally had the title "Miyoshi myopathy—a series of U.S. cases." Bob Miller, who became another long-distance mentor, advised me that we should not call diseases by a person's name any longer, and we should use the more descriptive term, "autosomal recessive distal muscular dystrophy." I went along with Bob's advice, and Berch weighed in, although I don't recall how—I guess you probably agreed with Bob. But I still think we should've called it Myoshi myopathy. At any rate, this was an amazing opportunity for a 30-year-old, freshly trained neuromuscular neurologist still in the Air Force to get a chance to write a paper with superstars in the field from the east and west coasts.

The second gift came a few years later, when I believe Berch was the president of the American Academy of Neurology. He brought to our attention that the neuromuscular neurologists did not have a formal section in the academy. He wanted that to be corrected. He asked me to begin the process of starting a neuromuscular section, which I dutifully did—and quickly! Petitions were signed, and the section was launched. I served as the inaugural chair of the section. I believe the neuromuscular section has played a key role in shaping the field of neuromuscular disease.

The third gift also involved the AAN, also while Berch was in a leadership position at the academy. He placed me on the annual meeting subcommittee which planned that next year's AAN meeting. This was really the first time I was able to meet neurologists outside the field of neuromuscular disease, and the first time I interacted with AAN leadership.

The fourth gift came years later when Berch asked me to be his wingman, otherwise known as co-PI on the big NIH Consortium for the Investigation of Neurologic Channelopathies (CINCH" project. This was really a career-changing experience and allowed me to work with academic neurologists not only across the U.S. and Canada, but also across Europe. I was able to establish close relationships with colleagues in England (Mike Hanna and Mary Reilly) and Italy (Valeria Sansone and Giovanni Meola). He had me attend the twice a year rare disease consortium meeting. This allowed me to meet with successful academics in medicine that were not neurologists. And it was my first real contact with insiders at the NIH in other institutes that extended beyond neurology. This helped me greatly in my later mission to get a Clinical Translational Science Award (CTSA) grant.

Then, to leverage the CINCH natural history infrastructure study, Berch HIGHLY advised me to submit an RO1 application to the FDA Orphan Products Division to study mexiletine for non-dystrophic myotonia. I dutifully did—and quickly! We got this funded on the first submission. The study, as you know, showed that mexiletine worked dramatically in these rare disorders. Not only did we get this paper published in JAMA, but even more importantly, I believe it has had a major impact on how patients with non-dystrophic myotonia are cared for.

A fifth of Berch's huge gifts to me was to encourage me to take on leadership roles within the Muscle Study Group, which he began in the late 1990s. I dutifully did this as well. Berch asked me to be his co-chair while he was the chair of the organization. Subsequently, for more than 10 years, Mike Hanna and I have been the co-leaders of this amazing organization of academic neuromuscular neurologists and industry partners. Assembling old and new members of the group, which we now call the Neuromuscular Study Group or NMSG, is the highlight of my year and truly has become one of the highlights of my career.

In addition to always giving sound advice, after working with Berch for a while, you begin to ask yourself whenever you are about to make big decision: "What would Berch do?" And, like many of us, I can honestly say that I am sure I would have had a very different, less-fulfilling and less-successful career path without the guidance and friendship of Berch.

Let me ask for a show of hands. How many in the room have had Berch help them with a manuscript? How many have had Berch's help on a grant? How many of you have had Berch give you career advice? How many of you have had Berch give you advice on how to run an organization? By my statistical analysis, I think most everyone in this room has raised their hand, with a P value of less than 0.01. I am thrilled to be here to be part of honoring Berch at this point in his career, which I know is far from over. I consider this a pause... for a celebration of all that you have achieved.

Berch, being here at this event means a great deal to me. I am so glad that I can be part of this celebration and honor your contributions to the field of neurology, but also the immense impact you have had on the careers of so many.

Dr. Griggs gave a wonderful address to the audience at the Festschrift. I want to tell you about the lists he gave us as words of advice. He called the words of advice "Hanging Ten" and had a picture of a surfer "hanging ten." I don't think Dr. Griggs is a surfer, but he was making the analogy of how to be top of your game. He showed a slide titled "Conclusion: "Hanging Ten" with ten points:

1) Pick a [rare] disease - 20,000 possibilities (if you go rare);
2) Hang out your shingle - a specialty clinic for patients;
3) Find collaborators;
4) Identify international collaborators;
5) Organize a meeting of current and future experts;
6) Work with/start on advocacy organizations(s);
7) Include non-clinician basic scientist(s);
8) Engage mentee(s);
9) Write a review/position paper;
10) Funding?

Then Dr. Griggs gave another ten suggestions for funding, with a slide titled "Conclusion: 'Hanging Ten': Funding." The ten funding suggestions were: 1) Advocacy organization; 2) Pharma support: Pharma-initiated, investigator-initiated clinical trials; 3) Federal: NIH, FDA (for credibility); 4) Intellectual property: Patent the treatment before publishing; 5) Philanthropy - do generous things; 6) Data use agreements - Rochester's strength (Kim Hart); 7) NY State funding - "members items", "special initiatives"; 8) Collaborate with others for grant support; 9) NIH R-13 grant to support meetings; and 10) practice income - only for expenses of seeing patients. I thought these words of advice were outstanding and I wanted to share them with the readers of the RRNMF NM J. I asked Dr. Griggs if I could have his permission to share them and he agreed.

Welcome to the Neuromuscular Study Group 25th Annual Scientific Meeting

Richard J. Barohn, MD
Chair, Neuromuscular Study Group
Executive Vice Chancellor for Health Affairs &
Hugh E. and Sarah D. Stephenson Dean,
School of Medicine, University of Missouri

Michael G. Hanna, MD
Co-chair, Neuromuscular Study Group
Director, University College London Institute of Neurology

As we gather for this landmark occasion, we celebrate 25 years of remarkable achievements, groundbreaking research, and invaluable collaboration in the field of neuromuscular science. This milestone event marks a quarter-century of our collective efforts to advance understanding, treatment, and care for neuromuscular disorders.

Our journey has been extraordinary, and the success of past meetings, especially the record-breaking gathering in Orlando last year, is a testament to the strength and dedication of our community. With over 245 attendees and 141 submitted abstracts, last year's event was a vibrant exchange of ideas and innovations, reinforcing our commitment to driving progress in the field.

This year's meeting, chaired by Dr. Michael Hehir, promises to build on that legacy with an exciting and diverse program. We are honored to bring together leading experts, researchers, and practitioners from around the globe to explore the latest scientific discoveries and technological advancements shaping the future of neuromuscular research.

Key highlights of this year's conference include:

Shark Tank Session: Now in its 6th event, this session will feature four innovative proposals, with the winner receiving a $10,000 grant to support their study. Last year's winner will also present updates on their funded proposals, offering insights into the progress and impact of their research.

Neuromuscular Research 2-Year Fellowship Program: We are proud to continue our partnership with the American Brain Foundation to fund this vital program. Our current fellow Natalie Katz, M.D., will present her research.

Young Investigator Session: Thanks to the hard work of this year's planning committee, this session will provide an engaging and supportive environment for emerging researchers, coordinators and evaluators to mentor and connect with established leaders in the field.

We are delighted to welcome increased industry involvement from both Europe and the U.S., with many new sponsors joining us this year. We extend our sincere gratitude to our sponsors for their support and encourage attendees to visit their tables and explore their abstracts in the poster session. All accepted abstracts are published in the current issue of the RRNMF Neuromuscular Journal, the official Journal of the NMSG.

As co-chairs of the Neuromuscular Study Group, we express our deepest appreciation to Dr. Michael Hehir and the entire planning committee for their dedication and hard work in organizing this exceptional meeting. We also thank each presenter and participant for their invaluable contributions, which make our conference a success.

Thank you for being a part of this historic anniversary meeting. We look forward to a productive and inspiring conference that will shape the future of neuromuscular science for the next 25 years and beyond.

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Clinical Research and Patient Management

#868 Coproducing care quality standards in Facioscapulohumeral muscular dystrophy (FSHD) in partnership with people with FSHD, carers and healthcare professionals: a qualitative focus group study

E. Leone, A. Pandyan*, A. Rogers, R. Kulshrestha**, J. Hill, F. Philp***
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Introduction: Facioscapulohumeral muscular dystrophy (FSHD) is a genetic disorder causing progressive muscle weakness resulting in permanent disability, which demands lifelong management. Care standards are required to ensure equitable care and measure improvement in FSHD services, but these are currently lacking, leading to disparities and a lack of focus for quality improvement initiatives.

Objectives: To collaboratively develop care quality standards for FSHD, using qualitative focus groups with people with FSHD, caregivers, and healthcare professionals.

Methods: A two-stage process was used, comprising of 1) eight online focus groups with separate groups of people with FSHD, caregivers, and clinicians and 2) two online focus groups bringing together people with FSHD, carers and clinicians to refine initial findings and co-produce FSHD care standards. Focus group transcripts were analysed using thematic analysis. Preliminary findings for agreed standards are reported here.

Results: Findings of preliminary analysis, which included 27 people with FSHD, four caregivers, and 20 clinicians from different professional backgrounds, identified the following 11 care quality domains: diagnosis support and care planning; information, education and support for patients and carers; access to a multidisciplinary team with FSHD understanding; named healthcare professional; care modality and frequency; access to services and referral; coordinated care; communication among healthcare professionals and with patients; clinical assessment; conservative management; self-management and lifestyle advice.

Conclusions: These findings offer a preliminary framework for the development of FSHD care standards aimed at enhancing care delivery, standardising practices, mitigating regional discrepancies and health inequalities, and optimising FSHD patient health outcomes.

#869 Increasing incidence and prevalence of myasthenia gravis in the elderly United States population: An analysis of the Centers for Medicare and Medicaid claims database from 2006-2019

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Introduction: Epidemiological studies suggest increasing incidence and prevalence of myasthenia gravis (MG) among the elderly population.

Objective: We aimed to provide an estimation of MG incidence and prevalence and their trend among the Medicare Fee-For-Service (FFS)-covered elderly US population.

Methods: We used Medicare claims data(2006 - 2019). Study-eligible beneficiaries were age 65 years and older, had at least one month of FFS A/B coverage, and were without health maintenance organization coverage. Study-eligible beneficiaries were aggregated into 2-year periods from 2006-2007 through 2018-2019. MG cases were ascertained using a previously validated algorithm of two MG claims within each 2-year period, from two outpatient office visits or a combination of one inpatient and one outpatient claims, separated by at least 28 days. Incident cases were determined among MG prevalent cases if the initial MG claim occurred in that period after a full calendar year of coverage. Trends of prevalence and incidence over time were examined with Poisson regression.
Results: The period prevalence of MG increased from 81 to 119 per 100,000 FFS A/B population from 2006-2007 to 2018-2019($p<.001$). Increasing trends of prevalence were observed in all sex (male/female), age (65-69/70-74/75-79/80+), race (White/Black/Asian/Hispanic/Other), and census region (Northeast/Midwest/South/West) subgroups. The incidence of MG increased from 12.2 to 13.3 per 100,000 PY from 2008-2009 to 2018-2019($p<0.05$). Increasing trends of incidence were significant in females($p=0.0018$, age 80 years and older($p=0.0017$), White non-Hispanic race($p<.001$), Midwest($p<.001$) and South($p=0.025$) census region subgroups.

Summary/Conclusions: Increasing trends in MG prevalence and incidence in the elderly US population are confirmed in this 14-year period.

#899 Motor unit magnetic resonance imaging to assess muscle twitch dynamics in mitochondrial disease after an exercise programme.

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Introduction: Primary mitochondrial myopathies (PMMs) lead to muscle fatigue and weakness. Currently trials in PMM focus on assessment of the oxidative capacity of muscle using biopsy. Muscle twitch dynamics are overlooked in PMM and can provide useful information about muscle function.

Objectives: We used a novel technique called motor unit MRI (MUMRI) to measure tibialis anterior muscle twitch dynamics in PMM participants before and after a 12-week exercise programme.

Methods: The lower left leg of each participant was scanned on a 3T Philips MRI scanner. Serial diffusion weighted images were acquired time locked to an electrical stimulus delivered to the common peroneal nerve. The stimulus was varied in time relative to the acquisition, allowing the whole muscle twitch to be captured. Voxel-wise twitch profiles were used to make measurements of rise time (T_{rise}), contraction time ($T_{contract}$) and half relaxation time ($T_{half\text{-}relax}$) in the tibialis anterior in 10 controls and 9 PMM participants. PMM participants scanned twice, before and after a 12-week exercise program.

Results: $T_{contract}$ of the tibialis anterior was significantly longer in PMM participants post exercise, T_{rise} and $T_{half\text{-}relax}$ did not change. Participants with the highest adherence to exercise demonstrated the largest increases in $T_{contract}$.

Conclusions: MUMRI detected slower muscle contraction times in primary mitochondrial myopathies post resistance exercise programme. This may evidence increased numbers of type-I fibres post-exercise. MUMRI also allows for spatial variations in muscle twitch dynamics to be observed. MUMRI could be used to measure changes in muscle twitch dynamics in neuromuscular diseases.

#909 Treatment effects on ambulation loss in Spinal Muscular Atrophy Type III: insights from the italian ISMAC registry

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Introduction: Spinal Muscular Atrophy (SMA) type III patients, while initially ambulatory, may eventually experience gait impairments, fatigue, and the risk of ambulation loss (LOA).

Objective: This study aims to investigate the variability of LOA and its correlation with treatments in a nationwide cohort of SMA Type III cases.

Methods: Retrospective data from 28 Italian centers were analyzed. The cohort included 429 individuals with Type III SMA. Initial analysis involved examining individual variables such as sex, SMN2 copy number, and SMA III subtype independently of treatment effects. Subsequently, treatment effects were incorporated.

Results: Initial analysis revealed that individuals with higher SMN2 copy numbers had a lower risk of LOA, with a 57% lower risk for those with 4+ copies compared to 2 copies. Similarly, SMA IIIB individuals had a 78% lower risk of LOA compared to SMA IIIA. The second phase of analysis revealed that treatment status significantly influenced LOA risk, with treated individuals experiencing a 96% lower risk of LOA compared to untreated individuals. Subgroup analyses by SMA subtype and SMN2 copy number further revealed substantial associations. Treated SMA IIIA individuals had a 91% lower risk of LOA compared to untreated counterparts, while treated SMA IIIB individuals had an 88% lower risk. Moreover, higher SMN2

copy numbers were associated with a reduced risk of LOA among treated individuals. Those with 3SMN2 copies had an 85% lower risk, and those with 4+SMN2 copies had a 93% lower risk compared to untreated counterparts.

Conclusions: These findings highlight the potential advantages of treatment in delaying ambulation loss.

#923 Sciatic Neuropathy with Clinico-radiological Pattern Consistent with Intraneural Perineurioma: An Underrecognized Cause of Progressive Mononeuropathy.

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Background: Intraneural perineurioma is a rare and highly underdiagnosed condition. We present a case of chronic right sciatic neuropathy in a young woman with clinical and radiological pattern consistent with this condition.

Case report: A 19-year-old female presented with slow progressive right foot weakness, right posterior thigh pain and gait difficulties of over seven-year duration. She denied any preceding inciting events. Examination showed right foot (dorsiflexion>>plantarflexion) and knee flexion weakness with absent right ankle reflex. EMG study showed findings consistent with chronic right sciatic neuropathy with ongoing active denervation in tibialis anterior and peroneus longus muscles, interestingly sparing the short head of biceps femoris.

MRI of pelvis and right thigh showed increased signal changes on T2-weighted images and thickening in the right sciatic nerve, more pronounced proximally without evidence of external compression. MRI leg showed denervation of the peroneal longus, brevis, tibialis anterior, tibialis posterior and popliteus muscles but with normal appearance of peroneal and tibial nerves. MRI lumbar spine was normal.

Careful review of MRI neurogram showed radiological pattern of T1 hypointensity, T2 hyperintensity with post contrast enhancement of sciatic nerve, a pattern consistent with
Intraneural perineurioma.

Patient was diagnosed with intraneural perineurioma based on the Perineurioma Diagnostic Criteria meeting clinical and radiological features consistent with this condition.

Conclusions: In patients presenting with slow progressive mononeuropathy, intraneural perineurioma should be considered in differentials and a careful review of imaging studies must be conducted with close attention to T1, T2 and post contrast sequences. The use of Perineurioma diagnostic criteria may obviate the need for tissue biopsy in this condition.

#930 The Myasthenia Gravis Patient Registry: Characteristics, Insights, and Learnings After a Decade (2013-23)

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Introduction: The Myasthenia Gravis Foundation of America (MGFA) Patient Registry was initiated to assess disease progression, management, for clinical trial recruitment, and as an educational platform. The registry is funded by the MGFA and previously the Coordinating Center located at the University of Alabama at Birmingham. In 2022, the next iteration of the registry, the MGFA Global MG Patient Registry (MGFAPR), was developed in partnership with Alira Health.

Objectives: To report the baseline demographics and disease characteristics of the MGFAPR, including insights/learnings from a patient-reported registry.

Methods: The MGFAPR is an online longitudinal registry with information collected at enrollment and then at 6-month intervals. Subjects are ≥18 years at enrollment, with self-reported MG. Descriptive analyses were conducted on key clinical features/variables. Enrolled subjects are contacted biannually to provide updates.

Results: 3556 subjects (95% Non-Hispanic; 87% White; 61% female) were enrolled from July 2013 through June 2023. The mean age at enrollment was 55.8 years and at diagnosis was 49.4 years. Of the 1814 reporting serostatus: 62.8% AChR antibody-positive, 5.2% MuSK antibody-positive, 0.4% LRP4 antibody-positive, and 31.6% seronegative. Enrollment and follow-up remain ongoing.

Conclusions: The MGFAPR represents the largest existing MG-specific registry which has captured data on over thirty-five hundred individuals. The advantages of this registry include the volume of the data collected, the completeness of the dataset, and the unique perspective into the MG impact with patient-reported outcomes and healthcare resource utilization. While there are limitations, unique insights and learnings over the past decade support its ongoing utility and value.

#931 Quantitative Sonographic Assessment Of Relaxed And Contracted Muscle Thickness Predicts Survival In Als

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Introduction: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease. Sonographic evaluation of muscles has been shown in the past to hold diagnostic and predictive potential. As such, we aimed to explore the ability of quantitative sonographic assessment of muscle thickness to predict mortality in ALS patients compared with manual muscle testing (MMT) and ALS functional rating scale (ALSFRS).

Methods: We prospectively recruited ALS patients attending the neuromuscular clinic at Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, from December 2018 to November 2019. All patients underwent routine clinical assessment and quantitative sonographic assessment of muscle thickness in 8 relaxed and 4 contracted limb muscles. We calculated the average monthly decline rate of MMT and ALSFRS scores from disease onset, and measured relaxed and contracted muscle thickness. To explore mortality prediction, we determined AUC and optimal cutoff points, as well as hazard ratio (HR) for 1 to 3-year mortality using COX regression analysis, including covariates (age, sex, BMI, diagnostic delay, and site of disease onset).

Results: 86 ALS patients, mean age 62 (±13), 44% females, were included. Significant increased 1-year mortality was associated only with a lower contracted muscle thickness (HR-8.1), while significant increased 3-year mortality was associated with a greater decline in MMT (HR-3.31), and ALSFRS (HR-2.12), and with lower relaxed (HR-2.65), and contracted (HR-4.85) muscle thickness.

Conclusion: Lower limb muscle thickness, especially at contracted state, is associated with significantly increased mortality in ALS and has the potential to serve as an additional biomarker in clinic and research.

#934 An Exploration of Barriers and Factors Associated with Physical Activity and Exercise Behaviors in Adults with Myotonic Dystrophy

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Introduction: Exercise studies in myotonic dystrophy (DM) have shown positive strength changes and functional improvements. However, long-term adoption of physical activity and exercise (PA/E) behaviors has been challenging.

Objective: To examine barriers and factors associated with PA/E behaviors in adults with DM using the Transtheoretical Model to identify strategies for promoting health behavior change.

Methods: National Registry members aged 18+ were surveyed. Questionnaires covered sociodemographic and clinical profile, PA/E barriers, stages of change (SOC), self-efficacy (SE), and processes of change (POC). SOC was dichotomized into inactive and active groups and compared using independent t-tests. A logistic regression model examined effects of symptoms, barriers, SE, cognitive and behavioral POC on SOC.

Results: 98 individuals (62% female) with DM (61% DM-type 1) participated. Common barriers were lack of energy (47.9%) and lack of motivation (45.9%). Inactive participants reported more symptoms (mean difference (MD)=1.418; 95%CI [0.226, 2.609]; p=0.020) and barriers (MD=2.141; 95%CI [1.404, 2.878]; p<0.001), had lower self-efficacy (MD=-3.494; 95%CI [-4.723, -2.264]; p<0.001), and used fewer cognitive POC (MD=-6.941; 95%CI [-10.824, -3.058]; p<0.001) and behavioral POC (MD=-11.784; 95%CI [-16.103, -7.466]; p<0.001). The model explained 47.8% of SOC variability, with significant effects from barriers (adjusted odds ratio (AOR)=0.666; 95%CI [0.480, 0.925]; p=0.015) and behavioral POC (AOR=1.097; 95%CI [1.025, 1.175]; p=0.008).

Conclusions: Survey findings offer insights into barriers and factors associated with PA/E behavior in adults with DM. Developing interventions that address barriers and facilitate effective use of processes may be useful in promoting adoption of PA/E behaviors in adults with DM.

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#935 ADAPT-NMD: a hybrid II study exploring the feasibility of delivering, evaluating, and implementing a self-management programme for people with neuromuscular disorders at a specialist neuromuscular centre

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Improving self-management support is an international priority for long-term conditions but research exploring its application in neuromuscular disorders (NMDs) is lacking. NM Bridges is a new self-management intervention for NMDs. The aim of this study was to explore the feasibility of delivering, implementing, and evaluating NM Bridges at a UK specialist centre.

A multiphase mixed-methods approach was employed. Qualitative data were collected from 28 individuals with NMDs to explore their experiences of self-management support. These findings, alongside stakeholder engagement activities, were used to inform the design of ADAPT-NMD, a hybrid II feasibility study of NM Bridges. A single-arm pre-post design was used to capture quantitative data from 33 patients and 6 clinicians and was enriched by a qualitative exploration of their experiences. The study was underpinned by Normalisation Process Theory, which was used to inform the study's design, implementation processes, and analysis.

Results indicate that delivering and implementing NM Bridges is feasible. At 3 months post-baseline, a positive effect was observed on patient-reported outcomes. Quantitative implementation instruments demonstrated positive responses from clinicians delivering the intervention. Triangulation of qualitative and quantitative data indicates that NM Bridges is acceptable, appropriate, and practicable.

Comprehensively developed and evaluated support programmes for people with NMDs are needed. This research has provided feasibility data on a new programme and enhanced understandings of requirements for delivering, evaluating, and implementing it at a specialist centre. Insights from this work can be used to support the delivery of a future evaluation of effectiveness in a definitive trial.

#936 Adapting to life with a neuromuscular disorder: a qualitative exploration of patient perspectives on self-management support

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Self-management support is a cornerstone of routine care for chronic conditions such as diabetes and hypertension, and there is increasing international interest in adapting it for neurological patient populations. Despite this, support for people with neuromuscular disorders (NMD) remains under-researched. This study aimed to explore the self-management priorities of people living with NMDs using qualitative methods.

Participants included 10 women and 18 men, aged 18 to 75, from diverse socio-economic and ethnic backgrounds, with a wide range of NMDs. In-depth semi-structured interviews explored self-management topics, and an inductive, reflexive thematic analysis was employed to code data and identify key domains and themes.

Three overarching themes were identified, addressing the questions: "what keeps me going" and "what holds me back." Firstly, participants used innovative problem-solving approaches to adapt to rare, progressive diseases, involving repeated 'biographical disruptions' and 'biographical reconstructions,' leading to a new model of 'adapting to life with NMD.' Secondly, the psychological burden of NMD was highlighted, compounded by uncertainty, progression, and disease rarity. Finally, a paradox emerged, challenging individualistic views of self-management and revealing it as a combination of personal traits, social capital, and available resources.

This study provides an in-depth, humanistic, and textured account of self-management support for people with NMD. Understanding how support is enacted is essential for ensuring future care is personalised and appropriate. These findings offer clinicians insights into the social context of their patients' lives, addressing a knowledge gap and informing the design, delivery, and evaluation of future self-management support for this population.

#937 Results From a Remote Longitudinal Study of Disease Burden in Friedreich's Ataxia

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Introduction: In order to better understand disease progression in FA, optimize state-of-the-art patient and caregiver-reported outcome measures, and identify factors that are associated with a faster or slower progression of disease, longitudinal studies are needed.

Objective: To conduct a remote longitudinal study with caregivers and patients with FA.

Methods: In prior work, we developed and validated disease-specific patient and caregiver-reported outcome measures (the FA-HI and FACR-HI) for patients with FA. We are currently conducting an 18-month longitudinal study where participants are remotely completing the FA-HI, FACR-HI, PedsQL, SF-36, survey preference questionnaires, and global impression of change forms.

Results: 202 caregivers and individuals with FA completed an initial cross-sectional study to validate the content of the FA-HI and FACR-HI. Beta testing and test-retest reliability were completed by 30 and 38 caregivers and individuals with FA, respectively. Forty-seven caregivers and individuals with FA were enrolled in our longitudinal study. Participants indicated a preference for the FA-HI and FACR-HI as a measure of the most important symptoms of FA. To date, 35 participants have completed their 12-month assessment.

Conclusions: The FA-HI and FACR-HI are novel and valid outcome measures capable of measuring changes in disease burden over time. Ongoing research is assessing FA disease progression and will determine the relative responsiveness of the FA-HI and FACR-HI in the context of a clinical trial.

#940 From Nerve to Brain: Toward a Mechanistic Understanding of Spinal Cord Stimulation in Human Subjects

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Introduction: Spinal cord stimulators (SCS) are commonly used to treat refractory neuropathic pain, although mechanisms underlying pain reduction remain unclear. Improved understanding of SCS and the development of biomarkers are critical for improving device design and optimizing patient selection.

Objective: our hypothesis is that SCS devices reduce pain by modulating the excitability of peripheral sensory nerve fibers that project within the spinal dorsal columns, and this effect can be leveraged for biomarker development.

Methods: this is a multicenter prospective study in two patient cohorts, namely patients who currently have stably implanted spinal cord simulators (Aim 1) and patients who are planning to undergo spinal cord implantation (Aim 2). We will apply specialized tests of peripheral nerve excitability, threshold tracking nerve conduction studies (TTNS), to detect changes in the excitability exerted on these neurons by SCS. We will also perform secondary measurements to determine other potential mechanisms of SCS in the peripheral and central nervous systems.

Results: the objective of Aim 1 is to establish the relationship between pain metric changes, effected by toggling SCS stimulation, and excitability measurements by TTNS. The objective of Aim 2 is to determine whether changes in peripheral nerve excitability are predictors for response to SCS. TTNS will be performed at baseline and at 3- and 6-months post-implantation

Conclusion: successful completion of this study will yield new mechanisms by which SCS reduces pain, relevant biomarkers, and further development of promising outcomes for broad pain research.

#941 Profiling Age-Related Loss of Motor Function: Loss of Corticospinal Excitability, A Major Contributor to Weakness?

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Introduction: Aging significantly impacts physical function, leading to loss of independence and increased risks of mortality and morbidity. Effective muscle contraction requires coordinated function of the central nervous system (CNS), peripheral nervous system (PNS), and skeletal muscle. Failures in these systems contribute to a declined physical function. While sarcopenia has traditionally been viewed as muscle-specific, emerging evidence indicates significant neurological contributions.

Objectives: Our aim was to investigate the pathophysiological mechanisms underlying motor dysfunction in aging by evaluating the CNS, PNS, and skeletal muscle in the C57BL/6 mouse model.

Methods: We assessed motor function (grip strength, rotarod, weighted cart pull test), corticospinal excitability (cMEP), motor unit number estimation (MUNE), muscle excitability (CMAP), and muscle contractility. We included 32 old mice (24-26 months) and 19 young controls (3-4 months).

Results: our data showed a 30% reduction in grip strength, 23% reduction in coordination (rotarod test), and 29% reduction in cart pull power in old mice ($p<0.0001$ for all assessments). Electrophysiological assessments revealed a 32% decline in cMEP, 33% decrease in MUNE ($p<0.0001$ for both), and 18% reduction in CMAP ($p=0.0001$). Muscle contractility decreased by 29% ($p<0.0001$). MEP had the strongest association with motor function, correlating with grip strength and cart pulling ($r=0.64$, $p<0.0001$; $r=0.49$, $p=0.005$).

Conclusions: These comprehensive evaluations demonstrated significant declines in muscle strength, coordination, and power, along with CNS, PNS, and muscle system deterioration in aged mice. The strong correlation between cMEP and motor function suggests that targeting corticospinal excitability may help counteract age-related physical declines and sarcopenia.

#942 Neuromuscular dysfunction, an early pathophysiological feature preceding cognitive decline in Alzheimer's Disease?

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Introduction: Cognitive decline is a recognized hallmark of Alzheimer's disease (AD), yet emerging evidence highlights early indications of motor dysfunction. The correlation between motor dysfunction and cognitive decline in AD, and the underlying mechanisms, remain unclear. Notably, loss of mobility and frequent falls significantly contributes to morbidity and mortality in AD patients.

Objectives: We investigated the temporal interplay between motor and cognitive functions using 5XFAD mouse model (n=18), versus wildtype controls (n=20).

Methods: Starting at 2 months of age, asymptomatic mice underwent a longitudinal study, repeated bimonthly until 12 months of age, including muscle excitability (CMAP), corticospinal excitability (Motor Evoked Potential, MEP), grip strength, motor power (weighted cart pull test), and cognitive assessments (Novel Object Recognition (NOR)).

Results: At the 6-month, 5XFAD mice displayed a 14% decline in grip strength ($p=0.0952$) and a 12% reduction in muscle power ($p=0.039$) compared to controls. NOR test showed no changes over 6 months. At 2 months, 5XFAD mice displayed a 57% increase in MEP amplitude compared to controls ($p=0.0018$). However, this increase was not sustained at 4 and 6 months. While CMAP amplitude in the gastrocnemius remained unchanged, the intrinsic foot muscle exhibited a 36% reduction at 6 months ($p=0.0257$), suggesting length dependent muscle excitability loss.

Conclusions: Our longitudinal study showed that corticospinal excitability alterations preceded neuromuscular dysfunction. There is an early motor function decline and neuromuscular excitability prior to cognitive dysfunction in AD. Our study highlights early motor dysfunction in AD aiming to inform therapeutic approaches by elucidating the motor-cognitive decline relationship.

#943 Pregnancy and post-natal outcomes in skeletal muscle channelopathies

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Introduction: Pregnancy in women with a skeletal muscle channelopathy is often challenging. There is little prospective, systematic data on pregnancy outcomes or postnatal complications.

Objectives: To prospectively assess symptom severity during pregnancy, and to compare rates of miscarriage, mode of delivery, post-natal complications in patients with Myotonia Congenita (MC) and Paramyotonia Congenita (PMC).

Methods: Data was collected prospectively in the muscle channelopathy outpatient clinics using a questionnaire developed at The National Hospital for Neurology and Neurosurgery.

Results: 16 participants (25 pregnancies) with genetically confirmed MC (10) and PMC (6) completed the survey. Participants reported 12 miscarriages (10 MC; 2 PMC) - including miscarriage of a twin, a second trimester miscarriage at 24 weeks and one termination. 15 (60%) pregnancies to 7 mothers with MC stated their muscle symptoms worsened during pregnancy compared with 5 pregnancies (38%) to 4 mothers with PMC. 3 mothers with MC (28% of the pregnancies) and 3 mothers with PMC (23% pregnancies) reported their muscle symptoms improved immediately or few days to 1 week after labour. One mother with MC who had 5 pregnancies reported her symptoms worsened after childbirth. There were a total of 6 caesarean sections (MC 2 and PMC 4). Analysis is ongoing and further details and complications will be presented.

Conclusions: Two thirds of pregnancies had worsening myotonia/muscle symptoms during pregnancy and a significant portion underwent caesarean section. Post-partum, symptoms may improve or worsen. This data provides valuable information and guidance for counselling, family planning and management in pregnancy.

#944 Refractory myasthenia gravis characterised by widespread innate and adaptive immune system changes

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Introduction: Despite recent advances in therapeutics for Myasthenia Gravis (MG), mechanisms driving treatment resistance, and biomarkers to predict refractory disease are lacking.

Objectives: We aimed to examine the immune profile in patients with MG of differing treatment requirements.

Methods: Flow cytometry was used to determine cell frequencies and expression of surface markers on peripheral blood mononuclear cells (PBMCs) from 58 individuals with acetylcholine-receptor antibody positive MG of differing treatment requirements and 20 controls.

Results: In MG the B cell compartment contains a higher proportion of highly differentiated CD27+ memory B cells, particularly in refractory disease and in those with early-onset MG. B cells in MG also display a pro-inflammatory phenotype, producing more IL-6 and TNF-α upon stimulation compared to control.

Refractory patients demonstrate reduced regulatory T cell (Treg) frequencies, which correlate negatively with disease severity and quality of life scores. Dendritic cell frequencies are also reduced in refractory cases, whereas monocytes are expanded.
Circulating levels of complement proteins C3, C5 and clusterin are highest in refractory cases. Additionally, there is higher expression of complement receptors on lymphocytes in MG, which correlate with the expression of the immune checkpoints PD-1 and CTLA-4 on T cells.
Following rituximab, Treg frequencies increase, but persistent circulating plasmablasts are identified.

Conclusion: Refractory MG is characterised by widespread immune changes that favour autoreactivity. Further work is required to determine if these findings could be utilised as biomarkers to predict refractory disease at baseline, and whether targeting these changes, such as promoting Treg expansion, would help treat MG resistant to current therapies.

#946 Mismatch between Neuromuscular Specialists and Myasthenia Gravis Patients in the US Medicare Population

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Introduction: There is a mismatch between clinical need and access to neurologists across the US. Myasthenia gravis (MG) incidence and prevalence are increasing, particularly in US patients older than 65 years. Neurologists currently comprise about 2% of US physicians; neuromuscular physicians make up about 4% of neurologists.

Objectives: Compare the prevalent number of MG patients over age 65 years to the number of board-certified neuromuscular physicians (BCNMD) by state, Census regions, and Census divisions.

Methods: Utilizing Medicare Fee-For-Service, Parts A and B coverage (FFS/AB) claims data, MG cases were ascertained using a validated algorithm; MG prevalence was calculated by state, Census region, and Census division.
Number of BCNMD per state was determined using verifyCERT, through the American Board of Psychiatry and Neurology and the American Board of Physical Medicine and Rehabilitation. Physicians were included if they held unexpired certification.

Results: BCNMD increased from 585 in 2012-13 to 806 in 2018-19. Six states had no BCNMD at both timepoints. National ratio of MG cases per BCNMD improved from 49.5 in 2012-13 to 44.3 in 2018-19. In 2018-19 ratios varied from 29.8 (Northeast region) to 63.7 (South region). South region and divisions had largest case burdens at both timepoints. Ratios improved in all regions, by the largest margin in Northeast. The ratio worsened in one division, the East central south division (up 8.9 cases per physician).

Conclusions: While the number of BCNMD have increased nationally, supply and demand are not evenly distributed. US ratio of MG cases per BCNMD is variable.

#957 Utility of the vagus nerve ultrasound in patients with autonomic dysfunction.

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Introduction: Vagus nerve (VN) holds considerable importance in the autonomic nervous system and autonomic testing is frequently ordered for patients with vague neurological symptoms suggestive of autonomic dysfunction (AD). However, there is a lack in literature regarding sonographic appearance of the VN in patients with AD.

Objective: Determine the ultrasonographic cross-sectional area (CSA) reference value of the VN in patients with AD and evaluate its potential as an alternative diagnostic method to autonomic testing.

Methods: In this prospective study, 40 patients with autonomic symptoms (20 with positive and 20 with negative tilt table test results) and 20 age-matched asymptomatic controls will be enrolled. Data includes demographic information, clinical symptoms, tilt table test result and ultrasonographic VN CSA.

Results:12 subjects (7 patients and 5 controls) have been enrolled. Median age and body mass index of patients were 38.85 years (range 21-73) and 29.8 (21-47.2) and for controls were 51.4 years (range: 25-61) and 26 (range: 19.4-36.4). No significant difference in mean right/left CSA between patients (2.2/1.99 mm^2) and controls (1.72/1.77 mm^2) were observed. The tilt table was abnormal in 4 (57%) patients: three with postural orthostatic tachycardia syndrome (POTS) and one with orthostatic intolerance. The average VN CSA of patients with abnormal autonomic testing was not statistically different from controls. However, the average VN CSA were smaller in POTS patients compared to symptomatic patients with other test result (1.65 vs.2.24 mm2, p-value 0.01).

Conclusions: Enrollment and data collection are ongoing. VN ultrasound measurement may have value for diagnosis of AD, especially in patients who are unable to tolerate tilt tables test or for whom discontinuation of medications, which could affect the interpretation of conventional testing, is not safe.

#960 Extension Range of Motion Discriminates Between Hypomobile and Non-Hypomobile Joints of the Lower Limb in Spinal Muscular Atrophy

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Introduction: Contractures are common in spinal muscular atrophy (SMA) and negatively impact function. Joint hypermobility (JH) also has been observed in the lower limbs. We hypothesize that range of motion (ROM) arcs in the sagittal plane provide more meaningful depictions of functional ROM in SMA.

Objectives: The objective was to assess lower limb ROM arcs in the sagittal plane and to evaluate the contribution of hip and knee extension and ankle dorsiflexion to the arcs.

Methods: Flexion and extension at the hip(n=119), knee(n=119), and ankle(n=105) were measured to determine the arc. Arcs were categorized as hypomobile, normal, or hypermobile based on joint-specific normative values. Extension ROM and total arc associations were evaluated at the respective joints.

Results: Hip arcs (HA) were mostly hypomobile (70%;n=83). Knee (KA) and ankle (AA) arcs were similarly distributed, and frequently normal (KA=37%,n=44; AA=44%,n=46). In 34 individuals(32%), all arcs were classified as normal or hypermobile. Hip extension, knee extension and ankle dorsiflexion were associated with the HA(r=.91, p<.001, n=119), KA(r=.88, p<.001, n=119), and AA(r=.79, p<.001, n=105), respectively. Hip extension discriminated between classifications of hypomobile, normal and hypermobile (p<.001), but not between normal and hypermobile (p=.874). Knee extension and ankle dorsiflexion discriminated between all arc classifications (p<.001).

Conclusions: The arc in the sagittal plane integrates flexion and extension ROM. In SMA, extension ROM influences the arc and discriminates between hypomobile and non-hypomobile classifications. Future work should examine the trajectory of ROM, and potential modifiers including age, functional status, and treatment status.

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#963 Dry Beriberi and Wernicke's Encephalopathy due to Thiamine Deficiency with albuminocytological dissociation mimicking Guillain-Barré syndrome: A diagnostic conundrum

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Introduction: Dry Beriberi (DB) is well known to mimic Guillain-Barre Syndrome (GBS).

Objectives: To report a case of thiamine deficiency with albuminocytological dissociation mimicking GBS.

Methods: Case report

Results: A 51-year-old woman developed vomiting and diarrhea. She was later diagnosed with cholelithiasis and underwent cholecystectomy. One week after surgery, she developed acute ascending weakness and numbness that progressed over a week, resulting in hospitalization. Examination notable for proximal> distal and lower >upper extremity weakness with areflexia. Lumbar Puncture with Cerebrospinal fluid testing showed albuminocytological dissociation with protein of 112 mg/dl and 2 WBCs. Thiamine level was drawn on admission. MRI brain showed subtle bilateral medial thalami and peri-aqueductal T2 hyperintensities. Patient received IVIG 2 gm/Kg over 5 days for concern of GBS. However, her weakness worsened. She developed confusion and then respiratory distress requiring intubation. Thiamine level resulted after 5 days was notably low (33 nmol/L). The patient was started on IV thiamine 100 mg daily. Repeat MRI brain showed improvement in hyperintensities. EMG study 3 weeks after admission showed severe sensorimotor polyneuropathy with axonal loss features. In the setting of thiamine deficiency with corroborating imaging evidence, her symptoms were suggestive of DB and Wernicke's encephalopathy. She eventually required tracheostomy and PEG tube placement and was discharged to a rehab facility.

Conclusion
A high index of suspicion for thiamine deficiency in presentations of progressive neuropathy is required. Preemptive administration of high-dose intravenous thiamine following B1 level should be considered, as delay in treatment may result in symptom worsening.

#966 Muscle Weakness Patterns in Inclusion Body Myositis

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Introduction: Inclusion body myositis (IBM) is a progressive and debilitating muscle disease, causing both proximal and distal muscle weakness. Characteristically, these weaknesses are most prominent in knee extension and finger flexion.

Objectives: We conducted a single-site, retrospective chart review of patients diagnosed with IBM to study weakness patterns for 16 muscle groups over time. Our aim was to discover which muscle groups are most affected by IBM.

Methods: We conducted a search of the University of Kansas Health System (UKHS) database to extract patients with a diagnosis of IBM and who had been seen in the clinic for 5+ years. Muscle strength scores for the 16 muscle groups were collected at 2 timepoints approximately 5 years apart.

Results: The dataset of 57 patients found that knee extension, finger flexion, and ankle dorsiflexion were the muscle groups predominately affected by IBM, all declining more than 3 muscle strength scores on average. Hip flexion and finger extension declined more than 2 scores on average. Wrist extension, elbow extension, wrist flexion, elbow flexion, ankle plantar flexion, and hip adduction declined more than 1 score on average. Knee flexion, shoulder abduction, hip abduction, neck flexion, and neck extension, all declined less than 1 score on average.

Conclusions: This limited sample size found that ankle dorsiflexion declines similarly to finger flexion and knee extension, while hip flexion and finger extension are the next muscle groups mostly affected. A larger sample size is needed before drawing conclusions.

#967 Preliminary Results of a Patient-Centric Scale For Sialorrhea in ALS Patients

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Introduction: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative motor neuron disorder causing progressive weakness. Management of ALS is primarily symptomatic. Evidence based treatment decisions for sialorrhea are limited by the lack of patient-centric, quality of life (QOL) based scales to enable clinical trials.

Objectives: Develop a preliminary scale to assess the impact of sialorrhea on QOL of ALS patients and obtain preliminary data to develop a Rasch-based scale to be used in comparative clinical trials for sialorrhea therapies.

Methods: Using interviews with ALS specialists, a 14-item instrument was generated to evaluate the significance of sialorrhea in ALS QOL. Administered as an anonymous, online Google Form over 2 weeks, the form was posted in well-known patient forums and as QR code-enabled flyers in a large ALS clinic. Respondents rated items on a 5-pt Likert Scale: 0 (little significance) to 4 (great significance). Raw scores are presented without statistical analysis.

Results: Of 36 respondents, 11 were excluded (not ALS, did not have sialorrhea). Of the remaining 25 respondents, 13 (52%) were male and 14 (56%) had ALS for more than 2 years. Fear of choking (Mean Significance 2.44), drooling embarrassment (Mean Significance 2.4), and eating/drinking difficulties (Mean Significance: 1.92) most significantly impacted QOL. Psychologically focused aspects of sialorrhea impacted QOL more than the physical aspects.

Conclusions: We identified the sialorrhea-related factors influencing ALS patients' QOL. This study supports development of a patient-centric sialorrhea scale that could be used to enable sialorrhea clinical trials.

#968 Comparing IBMFRS and sIFA as progression indicators in Inclusion Body Myositis patients from the INSPIRE IBM trial

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Objective: To assess and contrast the efficacy of IBM Functional Rating Scale (IBMFRS) and the sIBM physical functioning assessment (sIFA) in determining disease progression among participants diagnosed with Inclusion Body Myositis (IBM) enrolled in the INSPIRE IBM trial.

Introduction: Inclusion body myositis (IBM) is a common muscular disorder in individuals over the age of 40 years, characterized by atrophy and progressive muscle weakness. Patient-reported outcomes such as the IBMFRS or the sIFA questionnaire provide insights into the disease's impact on symptoms, functional limitations, and quality of life. Determining which questionnaire better correlates with disease progression requires further investigation.

Methods: The INSPIRE-IBM is a natural history study involving 150 IBM patients across 13 US sites. Evaluations are conducted biannually over two years. Patients complete IBMFRS, sIFA, EAT-10, Sydney Swallow Questionnaire, PROMIS, along with manual muscle testing and pulmonary functions tests. This abstract analyzes correlations between IBMFRS and sIFA with the other assessments using regression analysis to identify the stronger correlator with disease progression.

Results: Preliminary analysis, involving 87 patients who completed three time points, revealed a strong correlation between IBMFRS and sIFA (R^2=0.7, p=3.21E-96). Both outcomes show moderate correlation with PFTs with no significant difference in strength of correlation (R^2 between 0.5-0.7). IBMFRS and sIFA exhibit similar correlation with MMTs (R2=0.43, p=0.93).

Conclusion: While both scales are useful for monitoring overall physical decline in IBM, each scale may be more sensitive to specific functional impairments such as breathing, physical functioning, or swallowing. As the study is ongoing, additional time points per patient will be included in the final analysis.

#969 Co-designing a Strategy to Engage People with Neuromuscular Diseases from Racially Minoritized Backgrounds in Research

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Introduction: There is evidence of poor representation people from racially minoritized backgrounds and neuromuscular diseases (NMDs) in clinical research. The people best placed to develop the strategies for engagement are people with this lived experience.

Objectives: We used public engagement workshops to co-design a recruitment strategy in partnership with people living with NMDs from racially minoritized backgrounds.

Methods: We invited people to three workshops using video conferencing. Workshop 1: Exchange of experiences and ideas; Workshop 2: Bringing ideas together as a strategy with action points; Workshop 3: Agreeing the final strategy.

Results: Strategy plans were agreed in the following areas:

1. Setting up a Patient Public Involvement group for a specific study or programme
2. Access to information on research
3. Accessible and attractive information
4. Cultural sensitivity and diversity in the research team
5. Incentives for participation in research
6. Involving family members in decisions on research
7. Communicating research outcomes

Conclusions: Co-design methods gives more authentic engagement and understanding of challenges to diverse recruitment. We will launch the strategy to research colleagues to facilitate greater diversity in trial cohorts at our institution.

#970 *"It's about having the right people rather than the right system"* – The current state of cough and secretion management care in the UK for people with Amyotrophic Lateral Sclerosis (ALS)

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Introduction: Saliva, secretion, and cough problems are common in people with ALS (pwALS). These impact quality of life and ability to implement respiratory interventions such as Non-invasive ventilation (NIV) and cough augmentation and cause a risk of chest infections.

Objectives: This study is phase one of a larger project which will use evidence-based co-production to develop a tool to support cough and secretion management in ALS. The main aims of this phase were to investigate:
1. How healthcare professionals (HCPs) support pwALS to manage cough and secretion issues
2. Barriers and facilitators to management of cough and secretion problems in ALS

Methods: A structured cross-sectional online UK wide survey was completed, supplemented by four focus groups with UK HCPs. Reflexive thematic analysis was used, and data mapped to the theoretical domains framework (TDF) and COM-B behaviour frameworks to identify behaviour change interventions that could be used during development of the tool.
Results: 113 HCPs completed the survey, and 23 HCPs participated in focus groups. The following themes were identified as key barriers and facilitators to care:

- Access to equipment and specialist care
- Roles and responsibilities of each team member
- Relationships and expectations between ALS services, professional groups and pwALS/their caregivers

Themes were commonly linked with knowledge, skills, environmental context, physical opportunity and physical capability domains of the TDF and COM-B.

Conclusion: The management of cough and secretion issues in ALS in the UK remains variable. Increasing knowledge and skills of HCPs should be a core component of development of care in this area.

#974 Foot Ulceration in Patients with Charcot-Marie-Tooth Disease and Related Disorders

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Introduction: Foot ulceration frequently occurs in patients with Charcot-Marie-Tooth (CMT) disease and related disorders, primarily due to sensory deficits and structural foot abnormalities. The combination of peripheral neuropathy, muscle imbalance, and altered foot mechanics leads to pressure points and skin breakdown, resulting in ulcers and increased morbidity.

Objectives: To evaluate the prevalence of foot ulceration in patients with CMT and related disorders at our centre and identify the incidence across different genetic subtypes and associated risk factors.

Methods: We conducted a retrospective review of our clinical database and patient records from our inherited neuropathy clinics.

Results: Among 1982 patients with CMT and related disorders, 101 (5%) reported having ulcers. Of these, 70 (69%) were male, and 32 (31%) were female, with an average age of 48 (range 16-75). The average CMT Examination Score (CMTES) was 15.45 (± 5.49), (range 3-30). Of the patients with ulcers, 52 (51%) had hereditary sensory neuropathy (HSN), with 73% (38/52) having HSN due to SPTLC1 and SPTLC2 variants. Additionally, 48 (48%) were diagnosed with CMT, with 68% (33/48) having CMT1A due to the PMP22 duplication. Foot deformities were present in 58% (59/101) of patients with ulcers, with pes cavus being the most common (70%, 41/59). A significant number of patients (95%, 96/101) reported reduced sensation.

Conclusions: Preventative measures such as patient education, orthotic interventions, and footwear modifications are essential to reduce ulcer risk and complications. In addition, regular foot care management through podiatry services is an integral part of the multidisciplinary approach to CMT and related disorders.

#975 Comorbidities and adverse events in FSHD: experience from the Resolve cohort

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Introduction: Facioscapulohumeral muscular dystrophy (FSHD) is the third most common muscular dystrophy. The treatment landscape is expanding with many ongoing clinical trials. However, there is a scarcity of information on associated comorbidities in people with FSHD.

Objectives: To evaluate comorbidities, concomitant medications, and adverse events in one of the largest cohorts of FSHD with inclusion criteria resembling those of clinical trials (Resolve study).

Methods: Comorbidities were collected using a self-reported questionnaire. Medications were grouped by indication. Adverse events were recorded during the two-year follow-up of the study.

Results: 235 patients were recruited into the Resolve study. Of those 56% were male and 44% female, with mean (SD) age of 50.3 (14) years. The most common associated comorbidities self-reported by participants were pulmonary (19%), cardiovascular (14%), hearing problems (20 %) and vision problems (19%). Nine patients required a breathing machine. The most frequent medications taken were supplements (39%), analgesics (29%) and cardiovascular drugs (22%). 61 (26%) participants experienced at least one Adverse Event during the study, the most common being falls (41%, n=25), blood draw-related issues such as bruising (25%, n=15), musculoskeletal symptoms (41%, n=25) and injuries (23%, n=14).

Conclusions: Patients with FSHD primarily have cardiorespiratory comorbidities. From the Resolve data, there is a high use of supplements and analgesics among people with FHSD who could potentially be recruited into clinical trials. Adverse events were mostly musculoskeletal, and falls were commonly reported during the two years study period.

#976 Progression and Mortality of Respiratory Phenotypes in ALS

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Introduction: ALS is a motor neuron disease leading to death from progressive respiratory dysfunction in most patients.

Objective: To elucidate disease progression and mortality based on respiratory phenotypes in ALS.

Methods: We included 293 ALS patients with complete datasets followed at our center between 2009 and 2019. Respiratory measures included initial FVC and 3-month FVC decline slopes, along with changes in ALSFRS-R score as a measure for disease progression. Kaplan-Meier estimate and Cox regression were used for survival analysis. Phenotypes were defined from dichotomized (above and below median) initial FVC and their 3-month slope decline: (I) initial high, slow decline (IHSD), (II) initial high, fast decline (IHFD), (III) initial low, slow decline (ILSD), and (IV) initial low, fast decline (ILFD). Phenotypes were compared for demographic, disease-related, and survival characteristics.

Results: Initial FVC above the median (>86%) was associated with 33 months survival, while below the median was 15 months ($p < .0001$). The highest initial FVC quartile had an almost 3-fold survival advantage over the lowest quartile (37 months vs. 13 months, $p < .0001$). Median survival was 32 months for patients with a 3-month FVC decline slope ≥ median, compared to 14 months for those below median ($p < .0001$). Median survival was different in most respiratory phenotypes, ranging from 41 months in IHSD to 12 months in ILFD – all comparisons were significant ($p < .0001$) except for ILSD vs. IHFD.

Conclusions: Using respiratory phenotypes for randomization may provide more homogenous populations and reduce sample size in clinical trials.

#990 Fitness and function, not fatigability is associated with muscle quality in ambulant SMA

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Introduction: Spinal muscular atrophy(SMA) is a genetic disorder resulting in denervation leading to atrophy and disrupted muscle architecture. Muscle ultrasound(MUS), a non-invasive modality, is used in neuromuscular disorders. Poor muscle quality corresponds with strength and function, but the association to fatigability, fitness and function in SMA is unknown.

Objectives: Characterize muscle quality using MUS and explore associations with fatigability, fitness, and function in treated ambulant SMA.

Methods: Data was collected as part of an ongoing observational study. MUS was used to evaluate the vastus lateralis(VL), semimembranosus(SM), and medial gastrocnemius(MG). Mean echogenicity was determined using Gray Scale Analysis; greater scores represent poorer quality. Cardiopulmonary exercise tolerance testing(VO_{2peak}), six-minute walk test(6MWT), 10-meter walk/run test(10MWRT), 30-second sit-to-stand(30STS), and measured fitness and function. Fatigability was calculated from the 6MWT.

Results: Sixteen participants(44% male) mean age of 20.7 years(range 8-33) were evaluated. Mean echogenicity was different across all groups(p=0.031) and greatest in the VL(111.37±23.38). VL and MG echogenicity were different(p=0.049). VL echogenicity correlated with 10MWRT(r=.726, p=.001), and inversely correlated with 6MWT distance(r=-.678, p=.004), 30STS(r=-.603, p=.017), and VO_{2peak}(r=-.653, p=.006). SM and MG echogenicity was inversely correlated with 30STS(r=-.721, p=.002 and r=-.561, p=.030). Echogenicity was not correlated with fatigability.

Conclusions: Muscle quality is associated with fitness and function, not fatigability, in treated ambulant individuals with SMA. Several putative factors are implicated in fatigability, including dysfunction at the neuromuscular junction and in cellular metabolism, none of which are captured with MUS._ Known patterns of muscle involvement in SMA may explain the range in associations with fitness and function.

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#993 Comorbidities in seropositive and seronegative myasthenia gravis: a single-center experience

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Introduction: Up to 20% of Myasthenia Gravis (MG) patients remain refractory to standard treatment. Even after achieving minimal manifestation status, quality of life (QoL) may still be reduced. Medical comorbidities may influence MG disease course and treatment. Some studies suggest a higher prevalence of comorbidities in seropositive MG compared to the general population, however information about comorbidities in seronegative MG is even more limited.

Objectives: This is single center, observational, retrospective cohort study evaluating comorbidities and clinical outcomes in seropositive and seronegative MG. The purpose of this study was to increase knowledge on the epidemiology, treatment outcomes and QoL in both seropositive and seronegative MG.

Methods: MG patients evaluated at University of Rochester Neuromuscular clinic were included for analysis. Demographic information and comorbidities were obtained via chart review, including vascular disease, psychiatric disorders, systemic autoimmune, and non-autoimmune comorbidities.

Results: There were 59 patients total: 32 AchR Ab (+), 5 MuSK Ab (+), 1 LRP4 Ab (+) and 21 seronegative generalized MG patients. Overall, patients with seronegative MG had a higher prevalence of comorbidities compared to AchR Ab (+) MG patients and higher MG-ADL scores. Older patients were more likely to have vascular morbidities and higher MG-ADL scores.

Conclusions: MG patients have a high rate of comorbidities. The most common comorbidity was vascular disease. A high prevalence of psychiatric comorbidities was found in the seronegative MG population. Further multicenter study is needed to clarify clinical outcomes and to use this data to inform tailored treatment approaches in MG patients with comorbidities.

#999 A Study of the Common Factors that Influence Fatigue in Myasthenia Gravis

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Introduction: Myasthenia gravis (MG) is an autoimmune disorder causing fatigable muscle weakness. Fatigue is driven by the central or peripheral nervous systems ("central fatigue" and "peripheral fatigue") and influenced by many factors.

Objective: To characterize fatigue in MG patients at a single center and identify non-myasthenic contributors.

Methods: MG patients with symptomatic fatigue were enrolled. Baseline demographic information and disease characteristics were obtained. Fatigue was evaluated with the Neuro-Quality of Life (QOL) Fatigue and Fatigue Severity Scale (FSS), sleepiness with the Pittsburgh Sleep Quality Index (PSQI), depression and anxiety with the Neuro-QOL Depression and Anxiety scales. Laboratory testing included hemoglobin/hematocrit (anemia), B12/methylmalonic acid, vitamin D, and thyroid stimulating hormone. Spearman correlations and multiple linear regression models assessed associations between fatigue, sleep quality, and metabolic causes.

Results: 46 participants enrolled, 73.9% female, 80.4% AChR+. Vitamin D levels were negatively associated with Neuro-QOL Fatigue score ($r= -0.3$, $p= 0.046$) and Neuro-QOL Depression ($r= -0.41$, $p=0.006$). Vitamin B12 levels were negatively associated with Neuro-QOL-Fatigue score ($r= -0.25$, $p=0.10$). In multiple regression modeling, disease severity (MG-ADL) was associated with worse fatigue (Neuro-QOL-Fatigue $p<0.001$, FSS $p=0.021$). B12 deficiency was associated with much higher fatigue scores: Neuro-QOL-Fatigue is 6 points higher in the B12 deficient group ($p=0.33$), and FSS scores was 14.4 points higher in the B12 deficient group ($p=0.041$). Depression correlated with fatigue (Neuro-QOL-Fatigue $p=0.021$).

Summary: MG disease severity, depression, vitamin D and B12 deficiency are associated with worse fatigue in MG. These variables should be assessed in patients with clinically significant symptomatic fatigue.

#1003 Neck flexor weakness predicts degree of respiratory impairment in DM1

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Introduction: Neck flexor weakness at diagnosis may predict respiratory impairment in neuromuscular disorders. Weakness of flexor muscles occurs early in DM1 but respiratory symptoms may not be prominent, potentially delaying respiratory assessments and interventions.

Objectives: To investigate the effect of neck muscles' weakness on forced vital capacity.

Methods: Patients with genetically confirmed DM1 were enrolled as part of an observational longitudinal study within the DMCRN. Manual muscle testing (MMT) and sitting Forced Vital Capacity (FVC) % of predict were collected. The modified MRC 0-3 scale was used to classify weakness muscles' severity.

Results: Eighty-one DM1 patients (mean age: 42.65yrs ± 11.81, male/female ratio: 0.69, 63% with MIRS > 3) were cross-sectionally considered. The majority of patients reported slight to severe weakness in neck flexors and extensors muscles (89% and 57%, respectively). The weakness the neck muscles, the significantly lower the FVC % for both neck flexors and extensors, separately. Moreover, based on FVC% cut-off values and considering both neck flexors and extensors, neck flexors strength resulted to independently predict both restrictive syndrome (FVC<80%) and chronic respiratory failure (FVC<50%). In detail, considering the MMT 0-5 scale, a score < 3 for neck flexors emerged as the optimal cut-off in distinguish restricted from non-restricted patients (AUC: 0.78, sensitivity: 91% in screening restricted patients), whereas a score < 2 indicated a diagnosis of chronic respiratory failure (AUC: 0.82; sensitivity: 89% in screening chronic respiratory failure).

Conclusions: Neck flexor weakness can independently detect respiratory failure. This may have diagnostic and management implications, and suggests that rehabilitation protocols targeting neck posture may potentially improve respiratory function and patients care.

#1010 Safety and Tolerability of Whole-body Electrical Muscle Stimulation Exercise in Adults with Myasthenia Gravis: A Preliminary Analysis

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Introduction: Patients with Myasthenia Gravis (MG) experience fatigable muscle weakness that impacts daily activities. Exercise can improve physical function in MG but may be difficult to tolerate. Improved approaches are needed to fully realize benefits of exercise for this population.

Objectives: To assess safety and tolerability of whole-body electrical muscle stimulation (WB-EMS) exercise in adults with myasthenia gravis.

Methods: Enrolled participants complete supervised WB-EMS Exercise sessions (10-12 exercises performed in 20 minutes, 2x/week for 4 weeks, stimulation levels are customized). Vital signs and numeric pain rating scale (NPRS) are obtained before and immediately after each session. Rate of perceived exertion (RPE-10) is assessed after each exercise. Participants rate tolerability for each session on a Likert scale of 0-9 (0=very tolerable, 9=very intolerable). Participants report worst pain/soreness between sessions via NPRS. Adverse events (AEs) are discussed at each visit. Descriptive statistics are calculated.

Results: Two participants have finished the study, attending 100% of scheduled visits and completing 93.8% (15/16). One visit was terminated due to dysautonomia; this was the only AE (Grade 2, unlikely related). Vital signs responded appropriately to exercise at 15/16 sessions. NPRS showed clinically insignificant changes in 15/16 sessions. RPE-10 was at mild/moderate intensity 91.1% of the time. Average RPE-10, tolerability, and worst pain/soreness between sessions were 3.11, 3.91, and 3.06, respectively.

Conclusions: Preliminary analysis suggests that WB-EMS Exercise is safe and tolerable for adults with MG. It may be a reasonable alternative for exercise participation. Recruitment and data collection are ongoing. Updated results will be presented.

#1011 More than speed: AI-Sole derived kinetic gait parameters capture disease severity in Duchenne muscular dystrophy

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Introduction: Wearable-derived, maximal velocity (MV) is used to determine treatment response in Duchenne muscular dystrophy (DMD). In addition to spatiotemporal parameters, instrumented insoles measure kinetic parameters, including center of pressure (COP), not captured by other wearable sensors.

Objectives: Evaluate spatiotemporal and kinetic parameters using instrumented insoles (AI-Sole) and determine the association to strength in DMD.

Methods: Ambulatory individuals with DMD (n=11) and controls (n=13), mean age 18.5 years (range 5.2-41.9), were included. DMD subgroups were defined by six-minute walk test distance <350 (severe; n=6) or ≥350 meters (mild; n=5). MV was determined as the 95th percentile of stride velocity collected during six-minute walk test. COP anteroposterior and mediolateral projections (AP/ML-COP), the COP cyclogram area symmetry index (ASI), and the anteroposterior and mediolateral projections of the cyclogram intersection point (IP-AP/ML), were collected with AI-Sole. Knee extension (KE) and ankle plantarflexion (APF) strength were assessed using handheld dynamometry. Mann-Whitney U tests examined group differences. Associations were assessed using Spearman's rho.

Results: DMD and controls were different on all parameters (p<.01) except ML-COP (p=0.150). AP-COP discriminated between mild and severe DMD (p=0.028). MV correlated with IP-AP (r_s=-0.818, p=0.004), and KE (r_s=0.850, p=0.004). AP-COP was associated with IP-ML (r_s=-0.636, p=0.048), ASI (r_s=-0.648, p=0.043), KE (r_s=0.950, p<0.001) and APF strength (r_s=0.700, p=0.036).

Conclusions: Kinetic parameters are associated with strength and are sensitive to disease severity in DMD. Future studies are needed to determine the usefulness of AP-COP as a biomarker. AI-Sole allows for ubiquitous gait analysis of both speed-related and COP trajectories.

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#1016 Assessing Quality of Life and Body Image in Myasthenia Gravis Patients: A Novel Approach Using the Individualized Neuromuscular Quality of Life Questionnaire (INQoL)

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Introduction: Many different generic and disease-specific quality of life (QoL) measures have been used to gain insight into the perspective of patients with myasthenia gravis (MG). However, the use of the Individualized Neuromuscular Quality of Life Questionnaire (INQoL) and the impact of body image has not previously been studied in patients with MG.

Objectives: To investigate the use of the INQoL and the impact of body image in MG patients.

Methods: Various QoL measures, including the INQoL, were completed by 258 patients with MG and compared to each other using a correlation matrix. In addition, linear regression models were built to determine predictors of QoL and to investigate factors associated with body image in MG patients when using the INQoL.

Results: Of the different QoL measures, the INQoL correlated the strongest with the 15-Item Myasthenia Gravis Quality of Life Scale (MG-QoL15; $r = 0.80$, $p<0.05$). Modeling also showed that when using the INQoL, QoL was significantly influenced by disease severity ($p = 0.0054$), fatigue ($p = 0.0019$), age ($p = 0.0471$), and retirement status ($p = 0.0450$). Lastly, when using the INQoL body image was significantly influenced by fatigue ($p = 0.0189$) and the presence of ptosis ($p = 0.0298$).

Conclusions: Our findings introduce the use of the INQoL and body image in MG patients. This may help us better understand the perspective of MG patients as they consider different aspects not captured by other QoL measures.

#1017 Dropped Head Syndrome: A Rare Presentation of Mitochondrial Disease

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Introduction: Dropped head syndrome results from neck extensor muscle weakness and has a broad differential diagnosis, including neuromuscular and non-neuromuscular causes.

Case Presentation: A 77-year-old female with restless leg syndrome, hyperlipidemia, and lumbar degenerative disc disease presented with progressive neck weakness and head tilting over two to three years. Family history was non-contributory. Physical examination revealed a forward-bent neck tilted laterally and anteriorly to the right shoulder. The cranial nerve examination was normal. Neck flexion strength was normal (MRC grade 5), while neck extension was weak (MRC grade 3+). Muscle strength and tone were normal in limb muscles, without atrophy or fasciculations. Serum CK, aldolase, and myasthenia gravis panel were normal. Cervical MRI revealed a broad-based posterior disc osteophyte complex without myelopathy or significant spinal canal or neural foraminal stenosis. Electrodiagnostic evaluation revealed a myopathic process with abnormal spontaneous activity only in the left C7 paraspinal muscle. Soft tissue MRI of the neck showed bilateral atrophy of the erector spinae musculature with fatty infiltration. Muscle biopsy was consistent with myopathy with ragged red fibers, indicating a mitochondrial disorder.

Conclusion: This case reports a rare presentation of a mitochondrial disorder as a cause of dropped head syndrome. Differentiation of this condition from isolated neck extensor myopathy is essential, as further work-up is needed to rule out the involvement of other organs and provide appropriate surveillance for patients with mitochondrial myopathy. Muscle biopsy is key in patients without a full clinical picture and positive family history.

#1019 Can Clinical Assessment of Gross Motor Capacities and Strength Explain Environmental Mobility in people living with FSHD?

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Introduction: "Capacity" is what a person can do in a standardized context, while "performance" in their environment. In FSHD, muscle strength cannot individually explain the relation between clinical findings and overall daily performance.

Objectives: to understand which tests could predict patient reported functionality, as well as their underlaying "Body Structure and Function" and "Environmental" factors.

Methods: Data collected from 1259 contacts from 314 patients was used to perform correlation analysis of the following variables: FSHD-COM, muscle strength, Motor Function Measure, FSHD-HI and PROMIS57. Only significant rho≥ 0.60 were selected.

Results: Strong correlations were found between environmental performance, motor behaviour metrics, and muscle strength, maintained in patients not using assisted devices. With assisted devices, strength correlations were lost. Locomotor Control variables only correlated among themselves and one motor behaviour metric.

Conclusions: Environmental performance is explained by motor behaviour metrics and overall lower limb muscle strength but this last can be masked using assisted devices.

#1020 Oral Steroid therapy for management of pain in brachial plexopathy

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Introduction/Background: Oral steroids may be an effective treatment for pain in brachial plexopathy.

Objective: To present two cases of brachial plexopathy, treated with oral steroid therapy during early and late phase of the disease.

Method: Case report

Results:
Case 1
A 61-year-old woman presented with acute onset right lateral neck pain and arm weakness which started 2 days after onset of pain. Examination showed weakness in right upper trunk-innervated muscles. EMG study **14 days** after symptom onset showed subacute, right brachial plexopathy affecting the upper trunk. The patient was then started on oral steroid therapy with 60 mg daily for one week, followed by taper of 10 mg daily over the next week and had complete resolution of her pain within a week.

Case 2:
A 58-year-old man with poorly controlled type 2 diabetes presented with right upper extremity pain and weakness. Symptoms started with painful, vesicular rash along the right C5-C6 dermatome. 3 weeks later, he developed weakness in right arm. He received acyclovir but not steroids. The rash resolved but the pain and weakness continued to progress. Examination showed right proximal and distal upper extremity weakness, supra and infraspinatus and deltoid atrophy. EMG study **two months after** symptoms onset showed active denervation in upper trunk innervated muscles, C5-7 paraspinals along with right anterior interosseous neuropathy. MRI brachial plexus showed hyperintensities involving C5, 6 nerve roots, lateral, posterior and medial cords. He was diagnosed with radiculo-plexopathy. Given persistent severe neuropathic pain, patient was started on oral Prednisone 60mg daily for one-week followed by taper of 10mg daily over the next week **six months** after symptom onset that resulted in improvement of pain.

Summary/Conclusion:
Oral steroids are a reasonable consideration for management of pain in early and late phase of brachial plexopathy.

#1021 Clinical Disparities in CMT1A Among Black Compared to White Individuals

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Introduction: Charcot-Marie-Tooth disease type 1A (CMT1A) is an inherited demyelinating sensorimotor polyneuropathy that affects 1:5000 individuals worldwide. To our knowledge, no studies have attempted to determine differences in clinical care or biomarkers of CMT1A among different race groups.

Objectives: To identify potential clinical or phenotypic differences among black and white individuals with CMT1A.

Methods: Five first-generation diagnosed Black individuals with CMT1A were matched with 5 first-generation diagnosed White individuals with CMT1A. CMT neuropathy score, NCS, median and ulnar nerve ultrasound, pain intensity scale and medication review was performed in all.

Results: The mean age at enrollment was 45.6 +/- 14.0 years for Black individuals and 46.2 +/-9.1 years for White individuals (p=0.938). The average age of diagnosis for White individuals was 24.6+/-11.5 years and was 39.6 =/-8.6 year (p=0.0212) for Black individuals. Black individuals rated there daily pain as 5 / 10 (range 4-9) where as white individuals rated there pain as 2 / 10 (range 0-4) ($p < 0.01$) . All 5/5 black individuals required daily neuropathic pain medications (3/ 5 requiring two or more) whereas 2/5 white individuals required daily neuropathic pain medication (0/5 requiring two or more)

Summary/Conclusions: Here, we demonstrate that among individuals with CMT1A there is a significant difference among Black and White individuals in the mean age of diagnosis, pain intensity and pain control medications. This is despite no differences in CMT age at symptom onset, neuropathy score, ultrasound or NCS . This study highlights the need for improved recognition and management strategies of inherited peripheral nerve disease among the Black community.

#1023 Prevalence of Peripheral Neuropathy in Patients with V122I Hereditary Transthyretin Amyloidosis

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Introduction: V122I hereditary transthyretin amyloidosis (hATTR or ATTRv) is a predominantly cardiac disorder. However, a review of the literature shows prevalence of polyneuropathy ranging from 10% to over 60% which may significantly affect morbidity and choice of therapy.

Objective: We retrospectively studied the prevalence of polyneuropathy in a cohort of patients with V122I ATTRv seen at the Penn Amyloidosis Center of the University of Pennsylvania.

Methods: We reviewed charts of ATTRv patients seen between 2016 and 2024 at the Penn Amyloidosis Center. Patient demographics, characteristics, type of variant, cause of neuropathy, laboratory testing, and organ involvement were noted. Neuropathy diagnosis and its connection to amyloid were classified as possible, probable, or definite.

Results : The charts of 222 patients were reviewed. The three most common TTR variants were V122I (124 or 55.7%), T60A (44 or 19.8%), and V30M (24 or 10.8%). Seventy-one of the V122I patients had a complete neurological evaluation and were selected for analysis. The average age was 63.3 years, and 32 (45%) were women. Twenty of the 71 V122I patients had evidence of polyneuropathy (13 definite, 2 probable, 5 possible). Of those, 8 were found to have causes other than amyloidosis (mainly diabetes). No patient had isolated amyloid neuropathy without cardiomyopathy.

Conclusions: In our cohort, the prevalence of peripheral neuropathy in V122I hATTR is 28.2%. When adjusting for amyloidosis as the most likely cause, the prevalence drops to 16.9%, which is lower than what has been reported in recent publications. Diabetes is an important confounding etiology of polyneuropathy in V122I hATTR patients.

#1024 Addressing ab ingestis risk in Myotonic Dystrophy Type 1: a critical interplay between swallowing and cough efficacy

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Introduction: Dysphagia is a common symptom in DM1, and together with low cough efficacy can result in high mortality rates due to pulmonary complications. However, research is still scanty in this field, and the interplay between dysphagia and cough still needs to be addressed properly.

Objectives: The aim of our study was to investigate the connection between swallowing function and cough efficacy in adult DM1 patients.

Methods: Swallowing function and cough were evaluated using fiberoptic endoscopic evaluation (FEES) and spirometry.

Results: Among 86 patients (median age: 46.66 years [38.57-52.96]), median Dysphagia Outcome Severity Scale (DOSS): 5 [4-6], median peak cough flow (PCF): 310 l/min ([271-374]) 16 (18.6%) had normal swallowing function (DOSS 7-6), 69 (80.23%) had mild-moderate dysphagia (DOSS 5-3), 1 (1.17%) had severe dysphagia (DOSS 2-1); 63 (73.26%) had normal cough (PCF>270 l/min), 23 (26.74%) had cough impairment (PCF <270 l/min). Airway penetration was detected in 44 patients (51.16%); among these, it went completely unperceived in 36 (81.82%) patients, leading to non-activation of cough reflex. It was interesting to notice that cough reflex was absent even in patients with functional voluntary cough, who were the majority (n=29 (80.56%)).

Conclusions: Despite cough efficacy, most of our patients experienced airway penetration because of lack of perception of bolus stagnation and no cough reflex activation. This suggests the need for education of patients and caregivers about oral feeding and secretion management, in order to reduce risk of ab ingestis and disease burden that even patients with mild dysphagia can run.

Disclosures: There are no financial conflicts of interest to disclose

#1026 Characteristics of Electrodiagnostic Studies in Inclusion Body Myositis and Other Inflammatory Myopathies: A Comparative Study.

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Introduction: Inclusion body myositis (IBM) is the most common acquired myopathy in patients over the age of 50 years. The diagnosis of IBM can be challenging and is often delayed. Many patients are initially diagnosed with other forms of inflammatory myopathy, often leading to treatment with immunosuppressant agents which are not beneficial, and which may be deleterious for patients with IBM. Electromyography and nerve conduction studies (EMG/NCS) are a common tool utilized in the initial diagnosis of muscle disease. EMG abnormalities have been well-described in IBM, however few studies have compared these abnormalities with those seen in other forms of inflammatory myopathy.

Objective: Our study aimed to determine whether EMG/NCS characteristics may help distinguish IBM from other forms of inflammatory myopathy.

Methods: We utilized The Johns Hopkins Bayview Medical Center (JHBMC) Myositis Research Registry to identify patients with IBM (130), dermatomyositis (79), or other inflammatory myopathies (35) who had undergone EMG/NCS at The Johns Hopkins Hospital or JHBMC. EMG/NCS data was retrospectively reviewed, and characteristics were compared between the three groups.

Results: The combination of abnormal spontaneous activity with both myopathic and neurogenic motor unit action potentials (MUAPs) was seen more commonly in IBM compared to dermatomyositis or other forms of inflammatory myopathy. In the upper extremities, myopathic MUAPs were also more common in IBM. Sural sensory nerve action amplitude and peroneal compound muscle action potential were significantly lower in the IBM group.

Conclusions: EMG/NCS abnormalities in IBM are distinct from those seen in other forms of inflammatory myopathy.

#1029 Assessment of Falls in a Cohort of Adult Patients with SMA

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Introduction: Fatigue and gait speed are established determinants of fall risk in patients with neurological disorders. However, data on adults with spinal muscular atrophy (SMA) is limited.
Objective: The aim of this study was to investigate falls and associated risk factors in adults with SMA.
Methods: A retrospective chart review of ambulatory adults with genetically confirmed 5q- SMA included analysis of - age, sex, age of onset, SMN2 copy number, body mass index (BMI), and 6MWT distance and speed at minutes 1, 2, and 6.
Results: Thirteen ambulatory patients with SMA, including nine fallers (F_{all}) and four non-fallers (NF_{all}), with a mean age of 32.15 ± 9.11, were included in the analysis. In the F_{all} cohort, the median speed at 1, 2, and 6 minutes (obtained at visit preceding fall) were 0.87m/s, 0.83m/s, and 0.63m/s, respectively. In the NF_{all} cohort, the slowest median recorded speed at 1, 2 and 6 minutes across the study period were 1.18m/s, 1.11m/s, and 1.09m/s respectively. There was no significant statistical correlation between 6- minute gait speed and falls ($p=0.1649$). We found a three-fold greater decline in speed between the first and last minute of the 6MWT in the F_{all} (14.67%) compared to the NF_{all} (5.16%), although this was not statistically significant ($p=0.3092$).
Conclusions: Gait speed did not prove to be statistically significant predictor of falls in adults with SMA. Significant fatigue demonstrated by the substantial decrease in gait speed across the 6MWT underscores the necessity of considering factors beyond gait speed alone.

#1030 Analysis of Pulmonary Function Tests in Inclusion Body Myositis Relative to Antibody Status

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Introduction: IBM is a progressive myopathy found in individuals over age 50, characterized by asymmetric weakness. A 2016 study in 25 Californian IBM patients with 72% seropositivity showed subjects that are seropositive for NT5c1A antibody demonstrate lower FVC precent predicted, indicating severe respiratory involvement.
INSPIRE-IBM is a natural history study of 150 IBM patients across thirteen US sites. This study aims to explore differences in pulmonary function relative to serological biomarkers and document pulmonary functions over a two-year period.

Objectives: To evaluate the relationship between pulmonary function tests, including sitting and supine forced vital capacity (FVC), maximal inspiratory pressure (MIP), and maximal Expiratory Pressure (MEP), and seropositivity in IBM subjects.

Methods: An analysis was performed using seated and supine FVC, MIP, and MEP, and NT5c1A antibody status of the INSPIRE-IBM trial. Serum was isolated at baseline from blood draws for the NT5c1A antibody. A two-sample t-test was between seropositive and seronegative patients and compared to PFT results. Bonferroni correction for 4 simultaneous tests with significance levels at 0.05 was performed.

Results: There is a significant correlation between seropositivity and FVC precent predicted. The median seated FVC values in seropositive and seronegative patients were 73.6% and 88.2, respectively ($p = 0.005$). The median supine FVC values in seropositive and seronegative patients were 71.6% and 84.4%, respectively ($p = 0.003$). Median MIP and MEP values exhibited a decreasing trend in seropositive patients but were not significant.

Conclusions: The above findings corroborate the findings of the 2016 study and indicate that seropositive IBM patients may have more severe respiratory involvement.

#1032 Investigating the Influence of Dyspnea and Respiratory Function on Sleep Quality in Patients with Sporadic Inclusion Body Myositis in the INSPIRE-IBM Trial

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Objective: To investigate how measures of chronic dyspnea and wakeful respiratory function influence sleep quality in patients with inclusion body myositis (IBM).

Introduction: IBM is one of four common idiopathic inflammatory myopathies (IIM), primarily affecting men over the age of 50 years old and is characterized by chronic muscle inflammation and gradual, asymmetric distal and/or proximal muscle weakness. Although respiratory muscles are often unaffected at disease onset, respiratory complications have been reported as one of the leading causes of mortality in IBM. Some of this could be from a tendency to aspirate, with resultant pneumonia. Pulmonary function tests are a reliable, objective assessment to quantify respiratory muscle involvement; however, there is limited data on how the two measures relate to sleep quality and sleep disordered breathing in IBM patients. Previous studies have reported sleep disordered breathing to occur asymptomatically, increasing the need to assess the potential relationship between respiratory function and sleep quality in IBM.

Methods: The INSPIRE-IBM natural history study enrolled 150 participants with clinically defined IBM ages 40 years and older. Several demographic, clinical and functional data were collected, along with blood collection for PBMC, RNA, Serum, and DNA. Patients additionally completed pulmonary function tests for forced vital capacity (FVC erect and supine as well as direct diaphragmatic strength measures (Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP)) to assess respiratory function, and two self-reported questionnaires to evaluate dyspnea (NIHPROMIS dyspnea) and sleep disturbances (NIHPROMIS sleep).

Results/Conclusion: The baseline data from 150 participants will be analyzed to investigate how respiratory function may influence sleep quality.

#1035 Remote monitoring to improve adherence to physical exercise: pilot experience at the NeMO site

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Type of research: Pilot prospective longitudinal observational study.

Background: Despite recommendations to implement physical exercise adherence in Myotonic Dystrophy is low. Passive and avoidant behaviours, often characterize these patients and may exacerbate disease-related fatiguability and weakness, ultimately increasing the risk for vascular risk factors.

Objectives: The aims of this study were to verify whether remote monitoring could improve adherence to physical exercise programs in a cohort of adult DM1.

Methods: 15 patients were recruited to participate in a physical exercise program at their homes with no supervision while 15 were included in a weekly remote monitoring program for 6 months. Specific physical exercise protocols were provided. A 3, 6 and 12 month visit was planned for all. Routine neuromotor function tests were compared between the 2 groups.

Results: Preliminary data from 15 patients (9 patients in the remote control group and 6 in the group with no supervision) showed that 9 of 9 patients adhered to the program at 3 months, while of the 6 with no supervision, only 1 was still available at follow-up. Patients in the remote control group reported very good perception and this was supported by the improvement in the neuromofor functional scales. Recruitment is ongoing and follow-up continues with visits planned in the next 3, 6 and 12 months.

Conclusions: Remote monitoring may have an added value for patients with DM1 and improve adherence to care recommendations. In the era of therapeutic interventions standards of care should be implemented to maximise the action of potential pharmacological

#1036 Clinical Research is full of red tape: the organizational model at the NeMO site allows to survive the challenges.

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Introductions: Clinical research requires an efficient management to ensure studies' success and patients' safety. Logistical and organizational procedures support Principal Investigators (PIs) and Clinical Study Coordinators (CSC). Yet, lack of research personnel, increasing number of RCTs, growing complexity of regulatory requirements while maintaining the need to provide diagnostic and management protocols for new diagnosis and follow-ups are critical and potentially limiting factors to allow research to advance, ensure quality and guarantee patient safety.

Objectives: To describe the organization and management of the Clinical Research Center (CRC) in Milan to conduct an increasing number of RCTs and observational studies while providing clinical care to patients.

Methods: The CRC was restructured by creating: (i) a regulatory and start-up team; (ii) a clinical operations team; (iii) a regulatory and administrative team; (iv) 3 paired research teams with dedicated staff for phase 1 trials and for observational study; (v) a quality assurance referral.

Results: The number of RCTs trials rose from 17 in 2022 to 23 in 2024 and 30 expected in 2025. The number of observational studies rose from 18 in 2022 to 20 in 2024 and 24 expected in 2025. Quality control was maintained (≤ 28 minor deviations/year; no major deviations).

Conclusions: This model proves to be efficient and safe and allows PIs to delegate logistical/organizational and administrative tasks to specialized figures and increase their care time with patients. Coordination among the different roles and areas within the CRC is essential for successful implementation. Continuous training across staff is crucial.

#1037 An analysis of Mortality Rates and Causes of Death in an Oxford Cohort of Adult Myasthenia Gravis Patients

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Introduction: Myasthenia Gravis (MG) is an antibody-mediated disease of the neuromuscular junction. Mortality rates and causes of death in MG have not been fully elucidated.
Objectives: To determine mortality risk and leading causes of mortality in a large British MG-cohort.
Methods: A single-centre, retrospective mortality analysis was conducted in a cohort of 744 adult patients with MG who were actively followed-up at the Oxford University Hospitals, UK, over an 11-year period (1 January 2012 to 31 December 2022). Standardised mortality ratio (SMR) was calculated using mortality data for the general population from the 2019 England & Wales Death Registry.
Results: The overall SMR for the cohort was 1.20 (95% CI: 0.95-1.45) with mean age at death of 76.8 years. Eighty-eight (11.8%) of those patients died during the study period. The primary cause of mortality was malignancy (37%), followed by cardiovascular-related causes (24%), infection (20%) and others (19%). Early mortality (< 65 years) was associated with thymoma, female sex and younger age at MG-onset. No deaths due to myasthenic crisis were recorded.
Conclusion: The Oxford MG cohort mortality rates are slightly higher than those of general UK population. Malignancy is the leading primary cause of death. Higher rates of malignancy-related mortality could be driven by thymoma in patients deceased before 65 years of age. Early death in females with early-onset MG raises concerns about significant adverse-effects associated with long-term corticosteroid and immunosuppression. Possible contribution of long-term azathioprine treatment to malignancy risk in MG cohorts should be further investigated.

#1038 Concordance Between Patient and Physician Perspectives on Treatment Satisfaction and Clinical Status in Myasthenia Gravis

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Introduction/Background: A variety of treatments, including newly FDA-approved medications, are available for managing Myasthenia Gravis (MG). This study aims to investigate the alignment between physicians' and patients' perspectives on MG patients' satisfaction with their current treatment and clinical status.

Objective: To compare the perspectives of MG patients and physicians regarding patients' overall satisfaction with their current MG treatment and clinical status.

Methods: Patients and physicians will complete a questionnaire evaluating the patients' satisfaction with their current MG treatment and their overall clinical status. The responses from both groups will be analyzed and compared.

Results/Conclusions: The results and conclusions will be presented at the conference.

#1039 Depression in IBM patients: Results from the INSPIRE-IBM Study

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Introduction. Inclusion body myositis is an idiopathic inflammatory myopathy with no approved treatments. Natural progression of IBM includes gradual worsening of muscle weakness, fatigue, increased risk of falls, dysphagia, and respiratory failure. Prevalence of mental health issues, especially depression, in IBM is not well characterized. The COVAD-2-e-survey cross sectional study with 382 IBM participants and 1582 IIM participants found that having IBM was a determinant of lower Global Physical Health scores and that Global Mental Health scores were significantly lower in patients with IIM compared to those without autoimmune diseases. Lower PROMIS Physical Function scores were associated with lower Global Mental Health scores in IIM patients.

Objectives. To investigate the effects of mobility, physical function, and pain on patient-reported depression in IBM patients.

Methods. This cross-sectional analysis will use baseline data from INSPIRE-IBM, a prospective NIH-funded observational study in 150 IBM participants. Correlations between the PROMIS Depression scale and a multitude of variables, including IBMFRS, sIFA, PROMIS Physical Function scale, Mobility/Assistive Device Assessment, Falls Questionnaire, TUG, PROMIS Pain Intensity scale, and PROMIS Pain Interference scale will be investigated, through univariate and multivariate linear regression models.

Results/Conclusion. IBMFRS and PROMIS Physical Function Scores have weak, negative correlations to depression with R2 values of 0.083 and 0.088, respectively. The sIFA and PROMIS Pain Intensity scores have weak, positive correlations to depression with R2 values of 0.088 and R2 =0.098, respectively. Results are being rerun with further consideration and will be presented in September 2024.

Genetic and Molecular Studies

#929 Evaluating Neuromuscular Junction Transmission in Rodent Models Using Stimulated Single Fiber Electromyography (SFEMG)

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Introduction: Transmission at the neuromuscular junction (NMJ) is essential for proper motor function as it serves as the final link between the nervous system and muscles. Single fiber electromyography (SFEMG) is a highly sensitive clinical technique used to evaluate NMJ transmission by measuring the action potentials of individual muscle fibers during voluntary muscle contractions or nerve stimulations. Despite being a well-established and sensitive method in clinical practice, SFEMG has been underutilized in preclinical research.

Objectives: We aimed to outline an approach for performing and analyzing SFEMG recordings in preclinical rodent models.

Methods: To demonstrate increased jitter and blocking in the context of NMJ transmission failure, stimulated SFEMG was performed on five individual NMJs of an adult Sprague Dawley rat after endotracheal intubation, both with and without intravenous administration of a 0.05 mg/kg bolus of non-depolarizing neuromuscular blocking agent rocuronium.

Results: During rocuronium administration, SFEMG showed increased variability of transmission (jitter) compared to the healthy condition (untreated: 12.9 μs, 95% CI [7.2-16.9 μs] versus rocuronium: 40.7 μs, 95% CI [34.7-70.7 μs], $p = 0.0079$). The percentage of stimulations with NMJ blocking from each synapse on SFEMG also increased compared to the healthy condition (untreated: 0%, 95% CI [0-0%] versus rocuronium: 31%, 95% CI [14.0-59.0%], $p = 0.0079$).

Conclusions: Utilizing SFEMG parameters preclinically as sensitive, objective, and translational biomarkers for NMJ transmission failure in contexts such as health, aging, and neuromuscular diseases can greatly enhance and speed up the process of translating experimental findings into clinical applications.

#932 Clinical, neurophysiological, and pathological characterization of myopathy and dysphagia in adults with nephropathic cystinosis

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Introduction: Myopathy and dysphagia are relatively common in adults with nephropathic cystinosis, a rare lysosomal storage disorder. To better characterize swallowing impairment and muscle function we prospectively evaluated patients with nephropathic cystinosis.

Methods: 8 patients were prospectively evaluated using video fluoroscopic swallow studies, motor unit potential analysis and upper and lower extremity strength and function assessment. 3 Patients had muscle biopsy for satellite cell isolation.

Results: Both oral and pharyngeal stages of swallowing are affected. There was improvement in oral stage dysphagia and patient resported quality of life in follow up studies. We evaluated sensitivity of responsiveness of strength outcomes. Satellite cells were isolated and characterized in three muscle biopsy samples.

Conclusion: Dysphagia is a complex in patients with nephropathic cystinosis affecting both oral and pharyngeal phases of swallowing. Interventions targeting oral phase of swallowing may potentially improve function and quality of life.

#933 5HT2c agonism: A novel strategy for ameliorating age-related neural hypoexcitability and weakness

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Introduction: Weakness is the primary characteristic of sarcopenia, which is well known to be a major contributor to physical limitations, frailty, and premature death. Growing evidence supports neural hypoexcitability as a critical contributor to age-related weakness. Persistent inward currents (PICs) play a vital role in repetitive motor neuron firing, which are mediated by the 5HT2c receptor.

Objective: We hypothesize 5HT2c agonism can ameliorate age-related neural hypoexcitability and weakness.

Methods and Results: We began by evaluating the effect of a single dose of lorcaserin, a highly selective 5HT2c agonist, on neural excitability in aged mice. We performed *in vivo* electrophysiological assessments by stimulating the spinal cord and measuring electrical activity in the gastrocnemius muscle. A single dose of lorcaserin (1.5 mg/kg) increased motor evoked potential following cervical spinal cord stimulation (cMEP), repetitive cMEP amplitude, and H reflex amplitude across a train of repetitive nerve stimulation, suggesting acute lorcaserin treatment increases neural excitability and activation. Next, we assessed muscle force in the gastrocnemius in response to spinal cord stimulation. Mean force output was significantly increased in lorcaserin treated mice. Finally, a single dose of lorcaserin significantly improved motor coordination (rotarod) and motor power performance (weighted cart pull) in aged mice.

Conclusions: Overall, our data suggests that 5HT2c agonism is a promising therapeutic approach for treating age-related neural hypoexcitability and weakness. Importantly, 5HT2c agonism may be an effective strategy for treating weakness and physical frailty in older adults, greatly improving quality of life and healthspan.

#938 The spectrum of peripheral and autonomic neuropathies in patients with wtATTR amyloidosis and response to Patisiran therapy

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Introduction: Transthyretin-related amyloidosis (ATTR) is a group of disorders characterized by accumulation and tissue deposition of abnormal mutant or wild-type transthyretin protein. Wild-type transthyretin amyloid (wtATTR) is associated with the development of cardiac dysfunction such as cardiomyopathy.

wtATTR is not conventionally known to cause neurologic sequelae beyond an association with Carpal Tunnel Syndrome.[1,2] However, given the clinical experience at our center, we have found these patients may have further neurologic and/or autonomic dysfunction. This idea has been previously supported in the literature.[3,4,5] Our study will examine the extent and progression of peripheral neuropathy, including autonomic and non-autonomic involvement, of wild-type TTR amyloidosis. To date, there is no approved therapy for wtATTR patients with polyneuropathy.

The aim of this pilot study is to evaluate the efficacy and safety of patisiran in a wtATTR population with polyneuropathy. This may inform the validity of conducting additional clinical trials in this population, where there is currently an unmet need for treatment of polyneuropathy.

Objectives:

- To evaluate the efficacy and safety of patisiran in patients with wtATTR amyloidosis and symptomatic polyneuropathy by evaluating the effect on neurologic impairment and quality of life.
- Evaluate the burden of peripheral Neuropathy and autonomic dysfunction for 24 months.

Methods: This is a single center pilot study designed to evaluate the efficacy and safety of patisiran in adult patients with wtATTR amyloidosis and symptomatic polyneuropathy as assessed with Neuropathy Impairment Score (NIS). 10 patients with wtATTR amyloidosis and diagnosis of symptomatic polyneuropathy were followed over 24-month treatment period with patisiran IV infusion once every 21 days. During the 24-month treatment period study patients underwent assessments for efficacy and/or safety with key efficacy assessments Including NIS, Vital signs, polyneuropathy disability (PND) score, Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) score, Timed 10-meter walk, Composite Autonomic Symptom Score (COMPASS) 31, EuroQoL 5 Dimensions 5 Levels (EQ-5D-5), EMG to evaluate peripheral Neuropathies pattern and progression, Comprehensive Autonomic Nervous System testing includes Heart Rate Variability in deep breathing and tilt table, Optional exploratory nerve and muscle biopsy during visit one only to identify amyloid deposits in skeletal muscle and peripheral nerve, Lab. Safety assessment, Cardiac MRI or Cardiac Echo with Strain or PYP, NT pro-BNP, Neurofilament light chain (NFL), and 6-minute walk test is performed before the first dose and proceeding as outlined in the protocol.

Results: Primary endpoints will measure changes in neurological impairment, quality of life, and autonomic symptoms from baseline to month 24 during and after the patisiran infusion. Secondary endpoints will explore additional changes in quality of life over the study period.

Conclusions: The findings from this study will provide crucial insights into the efficacy and safety of patisiran in managing wtATTR amyloidosis with symptomatic polyneuropathy. Understanding the impact on neurological impairment, quality of life, and autonomic dysfunction will contribute valuable information for clinicians and researchers working in the field.

#939 C5b-9 Upregulation in Patients with Sporadic Inclusion Body Myositis

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Background And Objectives: Sporadic inclusion body myositis (sIBM) is an idiopathic inflammatory myopathy characterized by progressive skeletal muscle weakness. Diagnosis is typically made based on clinical criteria with or without pathologic findings on muscle biopsy. Muscle biopsy pathology in sIBM reveals focal invasion of muscle fibers, rimmed vacuoles, and congophilic inclusions. The exact pathogenesis of the disease is unknown, but the role of autoantibodies to cytosolic 5'-nucleotidase 1A (NT5c1A) supports the role of an adaptive immune response. A recent case report described C5b-9 staining in the skeletal muscle of patients with newly diagnosed sIBM, suggesting a complement-mediated component in pathogenesis. The purpose of our study was to gain an understanding of the prevalence of C5b-9 upregulation in patients with sIBM.

Methods: A retrospective chart review was performed of sIBM patients who underwent muscle biopsy from 2016-2024 at our neuromuscular center. Our inclusion criteria included patients diagnosed with sIBM based on the Griggs-Barohn 1995 and ENMC 2013 criteria, age between 45 and 75 years, and available muscle biopsy reports that included C5b-9 staining results. Biopsy results were assessed for the presence of vacuoles, cytochrome-oxidase (COX) negative fibers, succinate-dehydrogenase (SDH) positive fibers, inflammation (endomysial, perimysial and perivascular), focal invasion, C5b-9 upregulation, and MHC-class I upregulation. The phenotypic correlation was assessed based on C5b-9 upregulation on biopsy and NT5c1A serology.

Results: Muscle biopsy results from 32 patients confirmed the diagnosis of inclusion body myositis, with 24 patients meeting the inclusion criteria. Of 24 biopsies, 21 samples had C5b-9 upregulation. NT5c1A serology was positive in 11 patients, negative in 8 patients, and not done for five patients.

Conclusions: Through these results, a correlation can be seen between C5b-9 upregulation and sIBM. No correlation was noted between the presence of C5b-9 upregulation and the presence of NT5c1A antibodies. Limitations in our study included C5b-9 not being assessed for all 32 patients with biopsy-proven sIBM, not assessing the rate of progression, and not performing Nt5c1A serological testing for every patient. The results of our study support the role of the complement pathway in the pathogenesis of sIBM.

#954 Differential loss of cortical, spinal, and neuromuscular excitability in a TDP-43^{Q331K} model of amyotrophic lateral sclerosis.

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Introduction: Amyotrophic lateral sclerosis (ALS) is a fatal disorder affecting upper and lower motor neurons. Prior work in TDP-43^{Q331K} models suggest spinal excitability and neuromuscular synaptic transmission deficits. However, it remains unclear how excitability is differentially impacted along the corticospinal and neuromuscular axis.

Objective: Detailed characterization of motor function and cortical, spinal, and neuromuscular excitability in TDP-43^{Q331K} mice.

Methods:TDP-43^{Q331K} and wildtype mice (n = 20 males, 2.9-3.2 months; n=20, 2.4-3.3 months) underwent a comprehensive battery of in vivo assessments of motor function, corticospinal and neuromuscular electrophysiology, and muscle contractility recorded from the gastrocnemius muscle.

Results: Male TDP-43^{Q331K} mice (vs wildtype controls) showed significantly reduced motor function (rotarod), corticospinal hypoexcitability measured via motor-evoked potentials (cranial MEP > cervical MEP reduction), reduced motor unit number, neuromuscular hypoexcitability (reduced compound muscle action potential and increased decrement upon repetitive sciatic nerve stimulation), and loss of tibial nerve-evoked muscle contractile torque production (twitch and tetanic).

Conclusions:TDP-43^{Q331K} mice show diffuse upper and lower motor neuron and neuromuscular deficits consistent with clinical phenotypes of patients with ALS. Interestingly, reduction of MEP was greater following cranial versus cervical stimulation suggesting differential impact on upper motor neurons and possible compensatory lower motor neuron excitability modulation (despite significant loss of MUNE, cMEP was less overtly reduced). Work is ongoing to better understand the onset and progression of these deficits and to investigate phenotypes in both males and females.

#955 Can TDP-43 loss of function trigger an autoimmune response in sIBM?

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Introduction: Sporadic inclusion body myositis (sIBM) features both neurodegenerative and autoimmune aspects, although their interplay in the disease pathogenesis is still debated. Muscle cells of people affected by sIBM display TDP-43 cytoplasmic aggregation, accompanied by nuclear depletion. One significant consequence of TDP-43 nuclear loss is the derepression of cryptic exons, that can result in the inclusion of novel cryptic peptides. However, it is not known whether these peptides can elicit an autoimmune response.

Objectives: This study aims to verify the presence of novel cryptic peptides in sIBM patients and assess their ability to provoke a T-cell mediated immune response, potentially contributing to the disease pathogenesis.

Methods: RNA-sequencing was used to identify the inclusion of novel cryptic peptides in sIBM patient samples, with structural predictions facilitated by AlphaFold. This was further validated using immunohistochemistry and proteomics.

Results: RNA-sequencing and proteomics analysis confirmed the presence of cryptic peptides in sIBM samples. Moreover, immunohistochemical analysis showed HDGFL2 cryptic peptide accumulation in affected muscle tissue, especially in areas with immune infiltrates.

Conclusions: The findings crucial events linked to TDP-43 mislocalization, that can potentially drive immune dysregulation in sIBM. Future experiments include T-cell receptor sequencing and imaging to specifically detect the activation of T-cells by TDP-43 cryptic peptides, potentially improving our understanding of the autoimmune dynamics in sIBM pathogenesis and develop novel therapeutic strategies.

#988 Muscle DNA Whole Genome Sequencing identifies mtDNA deletion signatures with diagnostic implications for genetic and acquired myopathies

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Introduction: Mitochondria-related muscle dysfunction is reported in aging, inclusion body myositis (IBM), genetic myopathies and mitochondrial myopathies. Histological changes (including COX negative fibres and ragged red fibres) and molecular changes (depletion in mtDNA copy number and accumulation of mtDNA deletions) are seen across these conditions and may result in diagnostic uncertainty, particularly in atypical clinical presentations. In recent years a number of research groups have suggested that certain mitochondrial disorders, IBM and aging may have discriminatory hall marks in the patterns of mtDNA deletions observed. However, studies to date may be biased by the use of PCR enrichment and are limited by the small numbers of samples and genes studied.

Objectives: To identify discriminating factors between primary, acquired, and age-related mtDNA deletions.

Methods: We extracted genomic DNA from fresh frozen muscle samples and undertook PCR free whole genome sequencing. Mitochondrial DNA reads were extracted and studied using the MitoSALT bioinformatic tool. We compared results with clinical gold standard sequencing (NGS on long range PCR-enriched mitochondrial DNA).

Results: We observe a pronounced exaggeration of large deletions with PCR-enriched samples. In addition, we demonstrate discrete differences in deletion patterns between age-related, non-mitochondrial and mitochondrial myopathies including number of deletions seen, deletion break points, degree of mtDNA ablation.

Conclusions: Mitochondrial DNA deletion signatures may offer a new diagnostic tool for undiagnosed myopathies and evidence for upgrading of variants of uncertain significance. Age related mitochondrial dysfunction can be discriminated from true primary muscle disease by whole genome sequencing and deletional analysis.

#991 Blood lactate as a potential biomarker for exercise intolerance in SMA

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Introduction: Spinal muscular atrophy (SMA) is a genetic disorder resulting in muscle weakness. Individuals with SMA experience fatigability, which may be related to altered energy metabolism. The utility for blood lactate (BL) as a biomarker for exercise intolerance in SMA is unexplored.

Objective(s): To evaluate the association of BL with aerobic capacity and function in ambulatory SMA.

Methods: Thirteen participants, mean age of 19.8 years (range 8-33; 47% male) were evaluated. Finger pinprick BL measurements were taken at rest and post-exercise. Peak variables collected during a cardiopulmonary exercise tolerance test (CPET) included percent predicted aerobic capacity (VO_{2peak}%), workload (W_{peak}), respiratory exchange ratio (RER_{peak}), and heart rate (HR_{peak}). Predicted $VO2_{peak}$ (%) was determined using the FRIEND equation. The six-minute walk test (6MWT) measured function and fatigability. Associations were analyzed using Spearman correlation coefficients.

Results: Elevated resting lactate was observed in 76.9% of participants (n=10, mean=2.85 mmol/L, range=1.3-4.6). Post-test BL was correlated with VO_{2peak}% (r=0.803, p<0.001), RER_{peak} (r=0.639, p=0.019), W_{peak} (r=0.589, p=0.034), and 6MWT (r=0.598, p=0.031), but not fatigability (r=-0.154, p=0.615). Change in blood lactate (ΔBL) from rest to post-exercise was correlated with VO_{2peak}% (r =0.687, p=0.010) and RER_{peak} (r=0.536, p=0.059), but not fatigability (r=0.033, p=0.915). There was a moderate association between ΔBL and 6MWT (r=0.462, p=0.112).

Conclusions: BL measurements were associated with CPET variables and function. Elevated resting lactate supports metabolic impairments reported in SMA muscle. Further studies require task-specific assessment to evaluate associations with fatigability. BL may serve as a valuable biomarker in understanding exercise intolerance in SMA.

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#1009 The effect of Nav1.4 Ile582Val gain-of-function mutation on mouse skeletal muscle excitability is sex specific.

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Introduction: Periodic Paralysis (PP) is caused by ion channel mutation and characterised by episodic flaccid-paralysis. Sex differences in PP penetrance are well-established and recapitulated in PP mouse models but are so far unexplained i.e. All Draggen' (I582V) PP male mice exhibit hind-limb dragging episodes whilst only 50% of females do.

Objective: Determine if the effect of I582V Nav1.4 mutation on skeletal muscle excitability is sex specific.

Methods: Muscle Velocity Recovery Cycles provide an indirect measure of skeletal muscle excitability and ion channel function in vivo. We reverse translated and performed MVRCs under isoflurane anaesthesia on WT male TA(n=25,19±3weeks); WT female TA (n=27,17±4weeks), I582V male (n=15, 18±3weeks), I582V female (n=16, 21±4weeks) litter mates.

Results: WT male TA showed significantly greater supernormality (post-impulse increase in conduction velocity) in response to 5 conditioning stimuli than WT female TA. In I582V female TA, supernormality to 1(p=0.007) and 5 conditioning stimuli(p=0.002) was increased relative to WT female but there was no significant change in Muscle Relative Refractory Period (MRRP). In contrast, I582V male TA supernormality was reduced(p=0.01) and MRRP increased(p=0.003,) relative to both I582V female TA and WT male TA suggesting relative depolarisation of the membrane.

Conclusions: Muscle Velocity Recovery Cycles (MVRCs) enable in vivo examination of ion channel function. The effect of Nav1.4 gain-of-function mutation on skeletal muscle excitability is different in male and female mice. Sex differences in MVRC profile map to the observed sex difference in Periodic Paralysis phenotype indicating MVRCs detect endophenotype in skeletal muscle channelopathies.

#1014 Proteolysis of TDP-43 and tau in inclusion body myositis

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Introduction: CD8+ T-cells infiltrate IBM muscle and as a result granzyme A, B, K and H expression is upregulated. Aggregates of proteins including TDP-43 and tau have been found in IBM. In vitro work shows that granzyme A cleaves tau to create aggregate-prone fragments.

Objectives: To determine if granzymes cleaved tau and TDP-43 into smaller, more aggregate prone fragments which accumulate in IBM muscle.

Methods:

1. Look for fragments of TDP-43 and tau that are upregulated in IBM muscle on immunoblotting and then determine cleavage site with mass spectrometry.
2. Incubate recombinant TDP-43 and tau with granzymes to look for novel cleavage, and then determine cleavage sites.

Results: Granzyme A, B, K and M cleaved tau. Granzyme K cleaved TDP-43 into ~35kDa and ~25kDa N- and C-terminal fragments.
I did not find any fragments of TDP-43 that were upregulated in IBM, although 35kDa and 25kDa TDP-43 N-terminal fragments were upregulated in the "other IIM" control group. Combined ~36kDa/38kDa tau N-terminal fragments were upregulated in IBM muscle, as was a 27kDa tau C-terminal fragment.
During the optimisation immunoblots some TDP-43 fragments were either very intense or almost invisible in homogenate from one IBM muscle biopsy when processed using different methods.

Conclusion: It is possible that upregulated tau fragments in IBM and other IIMs are from granzyme cleavage but there are other more plausible proteases such lysosomal proteases or the proteasome/immunoproteasome.
The fragmentation and variable expression of TDP-43 fragments in IBM muscle resembles that in ALS brain and may reflect similar mechanisms.

#1015 Physiological Mechanisms of Neuromuscular Decline in a Mouse Model of Immobility

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Introduction: Immobilization syndrome follows inactivity (e.g.,hospitalization), presenting muscle wasting and weakness similar to that in aging (i.e.,sarcopenia). Little is understood about effects of immobilization, remobilization, and age on neuromuscular decline and recovery. This work will inform how immobility alters neuromuscular electrophysiology and consider combined insults of immobilization and sarcopenia.

Objective: Characterize neuromuscular decline following hindlimb immobilization (HLI), potential mechanisms, and physiological effects of age and remobilization on recovery.

Methods: Grip-strength, contractility, compound muscle action potential (CMAP), repetitive nerve stimulation response (RNS), motor unit (MU) electrophysiology, and body mass were assessed in mice (11-months, N=27, Control vs. HLI) before and after HLI (right hindlimb cast, 9days). Neuromuscular junction (NMJ) transmission, lumbar cord, and muscle weights were analyzed. Additional mice (Young/6months vs. Aged/20-months, N=16) had HLI plus 7days remobilization.

Results: Compared to Control, HLI reduced strength, contractility, MUs, and motoneuron excitability without altering NMJ transmission. Fat mass decreased; isolated muscle weights and lumbar motoneuron size/counts were not different. Remobilization recovered strength and CMAP, but only Young recovered RNS. Remobilization did not improve contractility in Young, and neither HLI nor remobilization altered RNS or contractility in Aged.

Conclusions: To our knowledge, no studies have evaluated immobilization, remobilization, and age. HLI impaired strength, MU function, and muscle output without overt atrophy or NMJ defect, implicating another source of excitation is altered, perhaps with compensatory changes in central pathways. Remobilization did not improve physiology, and Aged mice showed deficits pre-HLI. Future study includes evolution of neuronal deficits and atrophy and age-related differences in recovery.

#1018 Investigating the impact of age-related changes on lean mass and its association with muscle strength in preclinical aging model

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Introduction: Sarcopenia, the pathological age-related loss of muscle mass and strength, significantly impairs physical function and quality of life in older adults. Sarcopenia is a multifactorial syndrome with muscle and neural related factors contributing to pathophysiology. Lean mass is a critical determinant of muscle strength, with grip strength serving as a key indicator of overall muscular health and function.

Objective: Investigate the longitudinal impact of aging on measures of strength and lean mass in wildtype male and female C57BL/6J mice.

Methods: 43 mice (n=21 females, n=22 males) underwent repeated testing started at 12-13 months through approximately 22 months with Echo-MRI for lean body mass % assessment and grip testing.

Results: There was no significant loss of mean lean body mass % (mixed effects analyses, p=0.2 females, p=0.4 males). Change of lean body mass % was calculated between baseline and month 22 showing a mean loss of 7% across all females and a 3% gain across all males ($p<0.01$) (maximum loss in females 34%, 9% in males). Change of lean mass from baseline to 22 months to grip strength showed an inverse correlation (greater lean loss = less grip strength)(Pearson $r= -0.7554$, $p<0.0001$ females, and Pearson $r= -0.5254$, $p=0.0174$ males).

Conclusions: Similar to prior studies, our ongoing studies suggest that loss of lean mass is a late change in aging mice. Loss of lean mass in heterogeneous between mice and is more prominent in females. Our longitudinal studies are ongoing to investigate lean mass change at later ages.

#1025 Discrepancy of SMN2 Copy Number between Amniocentesis and Post-natal Genetic Testing: A Case Report

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Introduction: Spinal muscular atrophy (SMA) is an autosomal recessive disorder characterized by progressive muscle weakness and atrophy most commonly due to homozygous loss of the *SMN1* gene. Phenotypic severity is inversely proportional to copy number of the highly homologous *SMN2* gene. *SMN2* copy number is determined using various methodologies. We present a case of an infant diagnosed prenatally with SMA with discrepant *SMN2* copy number between amniocentesis and post-natal confirmatory genetic testing.

Case Report: This infant was diagnosed prenatally with SMA via amniocentesis after parental carrier testing was positive. Fetal testing via amniocentesis using digital droplet PCR (ddPCR) demonstrated homozygous deletion of *SMN1* and 3 copies of *SMN2*. Newborn screening and confirmatory genetic testing using quantitative PCR (qPCR) and ddPCR was completed confirming homozygous *SMN1* deletion with 2 copies of *SMN2*. Amniocentesis data was reanalyzed, and per the performing lab, data was consistent with reported presence of 3 copies of SMN2. Initial neurologic exam at 6 days of life was notable for axial hypotonia and reduced reflexes consistent with SMA type 1. Thus, decision was made to initiate risdiplam while awaiting onasemnogene abeparvovec.

Conclusions: Discrepancy between reported *SMN2* copy number can occur, particularly when testing is performed using different methodologies. *SMN2* copy number is clinically relevant for treatment decisions and may alter family counseling regarding prognosis and therapeutic options during the prenatal and newborn period. Thus, clinicians should be aware of the risk of discrepancy when counseling and provide disease-targeted therapy as early as possible to preserve motor neurons.

#1027 Genetic and Clinical Risk Factors for Status Epilepticus in a Large Cohort of Adult Patients with Primary Mitochondrial Disease

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Introduction: A growing body of evidence has highlighted the negative impact of status epilepticus (SE) on the clinical trajectory of patients with primary mitochondrial disease (PMD).

Objectives: In this retrospective cohort study, we investigated the genetic and clinical risk factors for status epilepticus (SE) in adult patients with genetically confirmed PMD.

Methods: The study was conducted at the NHS Highly Specialised Service (HSS) for rare mitochondrial disorders in London. Demographic, clinical, and laboratory data were collected retrospectively and analysed to identify possible risk factors of SE.

Results: Of the 550 adult patients followed up in the HSS, 61 had a diagnosis of epilepsy. Of these, 18 (29.51%) had convulsive or nonconvulsive SE and 5 (8.2%) had epilepsia partialis continua. Of the cases analysed, 83.6% had a mitochondrial DNA variant, while 16.3% had a nuclear DNA pathogenic variant. A significant association between the type of mitochondrial syndrome and SE was observed ($p= 0.007$). MELAS, MERRF, and non-classical syndrome were associated with an increased risk of having SE (p values= 0.014, 0.001, and 0.006). Having m.3243A>G mutation was found to be associated with the risk of having SE ($p=0.028$). Patients who had been seizure-free within the past year were found to be less likely to have experienced SE ($p= 0.04$). A significant association has been observed between the number of seizure types and the incidence of status epilepticus ($p < 0.001$).

Conclusions: SE in adults with PMD is highly heterogeneous and with poor prognosis. Our study identifies genetic and clinical risk factors for SE in PMD, thus enabling risk stratification and informed management decisions for this vulnerable population.

#1033 Digital and Palmar Nerve Enlargement in Idiopathic Axonal Neuropathies and axonal CMT variants

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Introduction: Charcot-Marie-Tooth (CMT) is an inherited peripheral nerve disease that affects 1 in 2,500. The most common form of CMT, CMT1A has been characterized as having nerve cross sectional enlargement on ultrasound. However, little information is available about nerve cross sectional area axonal variants of CMT or idiopathic axonal neuropathies.

Objectives: To characterize cross sectional area enlargement among axonal, demyelinating and mixed variants of CMT in the distal small nerves of the hand and forearm.

Methods: Among 54 individuals with CMT, 15 with CMT1A, 10 with HNPP, 12 with CMT2 variants and 12 idiopathic axonal neuropathies (IAPN) were compared to 50 controls. Cross sectional area was measured in the median nerve a digit 2, in the palm, wrist and forearm where the ulnar was imaged at digit 5 using a 22mHz transducer. This data was compared with clinical history, electrodiagnostic and CMT neuropathy score .

Results: Among patients with IAPN compared to controls we found significant cross sectional enlargement in the median (2.30; 1.69, $p<0.0001$) and mildly in the ulnar digital nerve (1.75mm2; 1.48mm2, $p=0.044$). In CMT2 variants no significant enlargement was found in any nerves compared to controls. However, we did identify a significantly reduced median palmar branch to forearm ratio in CMT2 patients compared to controls (0.45; 0.35; $p=0.0164$).

Conclusions: This study identifies novel regions of cross sectional area nerve enlargement in the sensory only digital nerves of the hand idiopathic axonal neuropathies. Additionally we show that mixed median palmar to mixed median forearm ratio is reduced in CMT2 variants.

#1034 Spatial Analysis of T-Cell Development and Tolerance in the Human Thymus at Single-Cell Resolution

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Myasthenia gravis (MG) is an autoimmune neuromuscular disease involving autoreactive T-cells. The thymus, crucial for T-cell development and central tolerance, is known to be associated with the pathogenesis of MG. While previous studies have investigated the microenvironments in healthy and diseased human thymi, spatial analysis of cellular interactions that account for the heterogeneous cell populations present has been missing. Therefore, we aimed to spatially characterise the *in-situ* cellular organisation and interactions contributing to normal T-cell development and tolerance at single-cell resolution. We optimized CODEX multiplexed imaging for human thymic tissue, creating a tailored panel of 28 antibodies. Due to the cell-dense and complex shaped stromal cells in the thymus, we developed a customized, unsupervised image analysis pipeline for cell-type segmentation and identification. Quantitative methods were also developed to study regionally varying tissue compositions and cell interactions from multiple samples. From the analysis of over 5 million cells across 9 sections (3 samples), 56 unique cell types and states were identified. Detailed descriptions were provided for the spatial characteristics of T-cells at various developmental stages, haematopoietic antigen-presenting cells, and epithelial and non-epithelial stroma. Previously unrecognized niches in the thymus were revealed, offering new insights into the migration patterns of developing T-cells. Quantitative findings exhibited low inter-sample heterogeneity. In conclusion, our study established a consistent methodology for in-depth, high-throughput spatial analysis of thymic tissue. This approach is being used to examine abnormalities in diseased thymus samples, including those with thymic tumours, to advance the understanding of MG pathogenesis.

#1040 Investigating Motor and Bulbar Severity in NT5c1A Seropositive and Seronegative IBM Participants in the INSPIRE-IBM Trial

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Objectives: To reinvestigate in a larger cohort, the differences in functional severity between seropositive and seronegative IBM patients for antibodies to NT5c1A.

Introduction: Anti-NT5c1A antibodies, directed against cytosolic 5'-nucleotidase that is abundant in skeletal muscle, were identified as the first serological biomarker for IBM. Prior research suggested that NT5c1A seropositivity prognosticated a more severe motor phenotype, with more severe motor weakness and bulbar involvement. Subsequent studies produced conflicting data, either confirming previous observations or not showing any relationship. The debate remains whether serological status may provide insight into functional severity and disease behavior.

Methods: INSPIRE-IBM is a prospective NIH-funded observational study including patients ages 40 years or older with clinically defined IBM fulfilled by the ENMC 2011 criteria, and disease onset within the past 10 years of the Baseline visit. Serology for NT5c1A was collected at Baseline. Functional assessments to evaluate disease severity included Manual Muscle Testing (MMT), Timed get up-and-go (TUG), Sydney Swallow Questionnaire (SSQ), and EAT-10.

Results: Serological status was available for 140 out of 150 participants with IBM who were enrolled. Sixty-nine of the 140 IBM patients (49%) were seropositive for NT5c1A antibodies at Baseline. Patients were divided into two groups (Group A with disease duration between 0-5 years and Group B with disease duration between 6-10 years). Seropositive group A showed significantly greater difficulty swallowing (EAT-10 and SSQ) than seronegative group A. Seropositive group B showed a trend towards more difficulty swallowing (EAT-10 and SSQ) and motor function weakness (MMT) compared to the seronegative group but did not reach statistical significance.

Conclusion: Seropositive IBM patients appear to have more swallowing difficulties than seronegative patients, and this difference appears early on in the disease course.

#1041 Investigating Highly Differentiated Cytotoxic T cells and Functional Severity in Participants with Inclusion Body Myositis in the INSPIRE-IBM Trial

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Objective: To explore the potential relationship between immunosenescent lymphocytes and functional severity in patients with inclusion body myositis (IBM).

Background: Inclusion body myositis is an enigmatic autoimmune and slowly progressive acquired myopathy. Evidence suggesting an autoimmune origin include the destruction of myofibers by large numbers of clonally expanded cytotoxic CD8+ T cells, predominately recognized in seminal studies by Arahata and Engel. Subsequently, the killer cell lectin-like receptor G1 (KLRG1) was identified as a T-cell surface receptor typical of highly differentiated CD8+ T-cell TEM and TEMRA populations; however, the refractory nature to corticosteroids has raised skepticism to its autoimmune basis. A plausible hypothesis for its refractoriness is the inability of immunosuppressive therapies to address the progressive transformation of lymphocytes to a senescent immunophenotype, as corticosteroids have been shown to be ineffective at substantially reducing T-cell infiltrates. Previous research suggests there is greater T cell differentiation with longer disease severity, though there is a paucity of information surrounding how muscle-invading T cells may influence disease behavior.

Method: INSPIRE-IBM is a longitudinal multicenter study including patients ages 40 years or older with clinically defined IBM fulfilled by the ENMC 2011 criteria. 8mL of blood was collected at the Baseline visit from 60 participants to analyze immunosenescent lymphocytes through the staining of peripheral blood mononuclear cells (PBMCs) and flow cytometry analysis, including CD8+, KRLG1+, TEMRAs, and Tregs. Functional assessments to evaluate disease severity included Manual Muscle Testing (MMT), Timed get up-and-go (TUG), Sydney Swallow Questionnaire (SSQ), and EAT-10.

Results: Results from Baseline data will be analyzed by July 2024.

Therapeutic Interventions and Outcome Measures

#855 The DMD-HI & DMDCR-HI: Development, Validation, and Translation of Regulatory-Grade Patient and Caregiver-Reported Outcome Measures for Duchenne Muscular Dystrophy

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Introduction: Sensitive, multifactorial outcome measures are needed to measure the symptoms most relevant to patients and facilitate therapeutic advancement in Duchenne muscular dystrophy (DMD).

Objectives: To develop, translate, and fully validate DMD-specific regulatory-grade outcome measures: the Duchenne Muscular Dystrophy-Health Index (DMD-HI) and the Duchenne Muscular Dystrophy Caregiver Reported-Health Index (DMDCR-HI) to support therapeutic trails and drug labeling claims involving ambulatory and non-ambulatory DMD patients.

Methods: We conducted qualitative interviews and two cross-sectional studies with patients and caregivers to identify the most impactful symptoms in DMD. Based upon their high relevance and potential responsiveness to therapeutic intervention, symptom questions were selected for the DMD-HI and DMDCR-HI. We subsequently conducted factor analysis, beta testing, test-retest reliability, known groups analysis. Lastly, we conducted interviews with patients with DMD and caregivers in the UK to translate and culturally validate the DMD-HI and DMDCR-HI for use in UK populations.

Results: Thirty-seven individuals participated in qualitative interviews and 200 participants completed the cross-sectional surveys. Validation testing confirmed that the DMD-HI and DMDCR-HI are reliable and capable of distinguishing between patients with different levels of DMD disease burden across 16 subscales. Twenty-eight patients with DMD and caregivers in the UK participated in the cultural validation of the DMD-HI and DMDCR-HI.

Conclusions: The development, validation, and UK translation of the DMD-HI and DMDCR-HI provide researchers and clinicians with a valid and reliable mechanism to measure relevant changes in DMD disease burden over time and in response to therapeutic intervention.

#859 The Myotonic Dystrophy Type 2 Health Index (MD2HI): Development and Validation of a Patient-Reported Outcome Measure to Support Drug-Labeling Claims and Patient Monitoring

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Introduction: As therapeutic advancement progresses in myotonic dystrophy type 2 (DM2), there is a need for patient-reported outcome (PRO) measures that reliably detect clinically-relevant changes in DM2 health. According to the Food and Drug Administration (FDA), PROs are an effective mechanism to support drug-labeling claims. This study describes the development and validation of the Myotonic Dystrophy Type 2 Health Index (MD2HI).

Objectives: To develop and validate a multifactorial PRO in DM2; the MD2HI.

Methods: We conducted qualitative interviews with individuals with DM2 to ascertain the most important symptoms to this population. Then, we conducted a national cross-sectional study with participants with DM2 to determine the prevalence and impact of symptoms previously identified in the qualitative interviews. Subsequently, beta testing and test-rest analysis were performed to assess the clarity, relevance and reliability of the instrument. Lastly, factor analysis and known groups validity assessment was performed to optimize the MD2HI.

Results: The MD2HI was validated by a cross-sectional study of 74 individuals with DM2. During beta testing, participants reported an appreciation for the format, wording and relevance of the instrument. Test-retest analysis and known groups validity demonstrated that the MD2HI is reliable (intraclass correlation coefficient = 0.97) and has the ability to differentiate between subgroups of participants with differing levels of disease severity.

Conclusions: The MD2HI is a disease-specific, regulatory-grade PRO that was validated using extensive patient-reported input. This instrument is fully validated and is available for use to support drug-labeling claims, therapeutic trials and patient monitoring.

#947 Development and Validation of a Patient-Reported Outcome Measure for use in Inclusion Body Myositis Therapeutic Trials and FDA Drug-labeling claims: The IBM-HI

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Introduction: In order to optimize clinical trial infrastructure and facilitate therapeutic development in inclusion body myositis (IBM), clinically-relevant patient reported outcome measures are needed that are fully validated, responsive, and compliant with regulatory standards.

Objectives: To develop and validate the Inclusion Body Myositis-Health Index (IBM-HI), a highly sensitive, multifactorial, and disease-specific PRO for use in clinical trials and drug-labeling claims in IBM.

Methods: We conducted semi-structured qualitative interviews of participants with IBM to ascertain the symptoms that contribute to their disease burden. We then administered a national cross-sectional study to determine the impact and prevalence of symptoms identified during the qualitative interviews. Using this information, we developed the first version of the IBM-HI. Finally, we optimized the IBM-HI using beta-testing, factor-analysis, known groups analysis, and test-retest reliability testing.

Results: 569 individuals participated in our IBM cross-sectional study. The IBM-HI was beta tested with 15 participants and reliability testing was completed with 21 participants. The final version of the IBM-HI and its subscales was found to be highly relevant to participants, comprehensive, reliable and capable of differentiating between patients with a higher vs. lower level of disease burden.

Conclusions: The IBM-HI is a valid and regulatory compliant instrument that consists of 13 symptomatic subscales. The instrument is capable of measuring clinically-relevant changes in multifactorial disease burden and is ideally suited for use in future therapeutic studies.

#950 Combined personalized home-based aerobic exercise and coaching to improve physical fitness in neuromuscular diseases - a multicenter, single-blind, randomized controlled trial

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Introduction: The quality of evidence for improving physical fitness of people with neuromuscular diseases (NMD) by means of aerobic exercise is low, due to most studies being uncontrolled, underpowered, or lacking intention-to-treat analyses.

Objectives: To evaluate the effects of combined personalized home-based aerobic exercise and coaching on the physical fitness of people with NMD compared to usual care.

Methods: In a multicenter, assessor-blinded, 2-armed randomized controlled trial, participants with various types of NMD were randomized (ratio 1:1) to a 6-month intervention or usual care. Assessments were done at baseline, post-intervention, and at 6 and 12 months post-intervention. The primary endpoint was peak oxygen uptake (VO2peak) directly post-intervention. Secondary endpoints included daily activity, quality of life, physical functioning and creatine kinase. We conducted a intention-to-treat linear mixed model analyses, with baseline values as a covariate.

Results: Ninety-one participants were randomized to the intervention (n=44) or usual care group (n=47). The mean group difference in VO2peak was 2.2 ml/min/kg (95% CI: 0.2-4.1) directly post-intervention, and 1.7 ml/min/kg (95% CI: 0.1-3.4) over time, in favor of the intervention group. There were no significant between group differences in secondary endpoints, and respectively 25 and 22 adverse events were reported in the intervention and usual care group.

Conclusions: Combined personalized home-based aerobic exercise and coaching was safe and improved physical fitness in deconditioned people with NMD, but without evidence of improved daily activity, quality of life and physical functioning. This home-based approach has good potential for a wider implementation.

#961 Tapering of Corticosteroids in Patients With Generalized Myasthenia Gravis Treated with Efgartigimod: A Case Series

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Introduction: Corticosteroids are a mainstay of treatment of generalized myasthenia gravis (gMG), but there is limited information on how novel therapies impact corticosteroid use in patients with gMG. Corticosteroids are associated with multiple adverse events that have a major impact on patient quality of life. Here, we describe 5 patients with anti-acetylcholine receptor autoantibody seropositive (AChR-Ab+) gMG receiving efgartigimod, a human IgG1 antibody Fc-fragment, and prednisone concurrently.

Objectives: To describe a series of cases in which patients presenting with gMG were able to taper their dose of corticosteroids after treatment with efgartigimod.

Methods: A retrospective chart review of patients with gMG seen between 2021 and 2023 was conducted to examine corticosteroid use after treatment with efgartigimod.

Results: Five patients (aged 68-86 years) with AChR-Ab+ gMG were treated with efgartigimod for ≥4 cycles (range, 4 to 12) and prednisone. At baseline, Myasthenia Gravis Foundation of America (MGFA) class ranged from IIA to IIIB. Before efgartigimod infusion, MG-ADL scores ranged from 4 to 10. After infusion, MG-ADL scores for 4 of 5 patients improved to 0, with the greatest change seen in a patient who improved from 10 to 0. Myasthenia Gravis Composite (MGC) scores improved from 8-18 to 0-5 before and after efgartigimod infusions, respectively. Before efgartigimod, all 5 patients were receiving prednisone (10-30 mg/day), and all were tapered by ≥50% (0-10 mg/day) following efgartigimod.

Conclusions: Efgartigimod treatment improved patient MG-ADL and MGC scores and allowed for tapering of the dose and/or dosing frequency of corticosteroids.

#989 Patient Reported Outcomes measures: preliminary experience using the Goal Attainment Scale (GAS) in SMA

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Introduction: Neuromotor scales in SMA may detect functional improvement in predefined tasks but may not capture what matters most to patients.

Objectives: To explore the reliability and validity of a revised version of the GAS in patients living with SMA (rGAS_SMA).

Methods: A revised version of the original GAS scale (rGAS_SMA) was administrated to adult SMA patients. Patients chose a maximum of three SMART goals rating importance and difficulty in attaining each specific goal. Goal attainment was then explored on follow-up (-2 /-1 worsening , 0 no variations, +1/+2 improvement over time).

Results: Fifthy-eight SMA patients (mean age 18.48 [8.12-32.88], 27 non-sitters, 25 sitters and 6 walkers) were recruited. A total of 149 SMART goals were collected and classified in 10 macro domains, mostly related to mobility, upper limb strength and ADL. The rGAS_SMA proved to be reliable (78% of patients choose the same SMART goals after two-week) and demostrated an external validity with a concordance (partial or full) with commonly used neuromotor assessments (95% with HFMSE and RULM, and 88% with 6MWT). Most SMART goals addressed activities were already included in the commonly used neuromotor scales, although 30% instead referred tasks which were relevant to patients but were not captured by the scales. Physiotherapists and psychologists supervised results.

Conclusions: rGAS_SMA is a reliable and valid tool to define what matters to each individual patient. This may prove useful to tailor treatment expectations, to better define “responders” and monitor treatment response. It also highlights the potential need to implement the existing neuromotor scales and add clinical meaningfulness to the assessments done.

#994 Safety and Tolerability Study of Clenbuterol in facioscapulohumeral muscular dystrophy

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FSHD IRC 2024 muscular dystrophy.

Facioscapulohumeral muscular dystrophy (FSHD) is a progressive muscular dystrophy with no currently approved FDA treatments. The muscle disease is due to a de-repression of the DUX4 gene contained in the D4Z4 repeat. Clenbuterol has been found to be a potent inhibitor of DUX4 activity in FSHD patient derived muscle cells and has anabolic effects on the muscle. We hypothesize that clenbuterol can slow disease progression and improve performance. As part of a P50 AR065139 (NIH Wellstone Study), this project will be a dose-finding/safety study to find the optimal dose that is safe, well tolerated, decreases DUX4 activity, and increased contractile muscle volume. We propose a prospective 6-month non-randomized open label study at three sites (Kansas City, Rochester, Seattle) with three sequential cohorts of 10 participants each who are clinically affected and their FSHD genetically confirmed. The cohorts will be ascending doses of clenbuterol at 20 mcg, 40 mcg, and 60 mcg, taken orally twice daily. The primary endpoints include safety/tolerability; while the secondary endpoints include changes in MRI, molecular candidate, and functional biomarkers. The goal is to determine the maximum tolerable dose of Clenbuterol in FSHD, potential side effects and preliminary signs of efficacy. We aim to start recruiting at the end of summer 2024.

#995 Trial of Oxaloacetate in ALS, TOALS

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Introduction: Mitochondrial dysfunction constitutes an important therapeutic target in patients with amyotrophic lateral sclerosis (ALS). Oxaloacetate (OAA) is a good candidate therapeutic agent as it crosses the blood brain barrier, accesses motor neurons, and activates mitochondrial bioenergetics. ALS mouse-model studies showed increased hanging time of OAA treated animals compared to untreated (H. Nishimune). OAA was safe, well tolerated, and engaged brain metabolism in patients with Alzheimer disease (R. Swerdlow), another important therapeutic target for ALS.

Objectives: The primary objective of this trial is to determine safety and the maximal tolerated dose of OAA in patients with ALS. The secondary objectives are to evaluate the pharmacokinetic profile of OAA in ALS patients and to determine OAA target engagement, including a panel of mitochondrial biomarkers, platelet TDP-43 levels and MR spectroscopy of brain glutathione.

Methods: We conducted a phase 1B prospective 3+3 dose escalating clinical trial. Dose limiting toxicity (DLT) was defined as any serious adverse event (SAE) related to OAA requiring hospitalization, or any adverse event (AE) related to OAA that required stopping the medication.

Results: We enrolled 19 subjects, 1 screen failed and 1 patient withdrew due to a DLT. OAA was well tolerated up to a dose of 2500mg BID. PK data are being analyzed. For the small sample analyzed, target engagement did not show a clear signal.

Conclusion: A future randomized placebo control trial would be a reasonable next step to evaluate efficacy and target engagement.

#996 Deep immunoprofiling in inclusion body myositis and trajectory analysis of cytotoxic T cells development

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Introduction: Inclusion body myositis (IBM) is the most common idiopathic inflammatory myopathy (IIM) above age 50. IBM typically presents with asymmetric muscle weakness, predominantly involving quadriceps and long finger flexors.

Objectives: Highly differentiated cytotoxic T cells play an important role in IBM pathogenesis; however, what drives such differentiation is unclear. Similarly, the role of abundant plasma cells in muscle tissue in IBM remains unknown.

Methods: We are using gene expression profiling along with B cell repertoire (BCR) and T cell repertoire (TCR) analyses of peripheral blood mononuclear cells at a single cell level in IBM patients compared to healthy controls, along with spatial transcriptomic analysis of muscle tissue.

Results: We included five patients with IBM, three men, and two women in this preliminary analysis. Four healthy controls were recruited. We observed major differences in gene expression in the transitional and memory B cells and plasmablasts in IBM patients. As expected CD8 T cells in IBM showed higher expression of cytotoxic markers. Gene enrichment analysis reflected differences in immunoglobulin production, leucocyte migration, and T-cell differentiation pathways. Trajectory inference suggested a distinct developmental trajectory of cytotoxic T cells in IBM patients, possibly mediated by DUSP1 and TAVR6. Spatial transcriptomics analysis confirmed a localized immunoglobulin signature in IBM.

Conclusions: These findings implicate a potential role for both B cells and abnormally differentiated cytotoxic T cells in the pathophysiology of IBM and shed light on the potential drivers of abnormal differentiation of cytotoxic T cells in IBM.

#998 Motor Outcomes to Validate Evaluations in Facioscapulohumeral muscular dystrophy (MOVE FSHD): Interim Baseline Data and Potential Predictors for FSHD

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Objective: 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.

Design/Methods: The MOVE FSHD study will evaluate 450 FSHD participants over 24-months with 200 participating in a MRI and muscle biopsy sub-study to validate FSHD evaluations and biomarkers. Visits collect FSHD history, physical examination, patient reported outcomes, strength, timed functional tests (TFTs), and spirometry. Sub-study participants have additional biomarkers collected, including reachable workspace at each visit, whole-body MRI at Baseline and 12-months, and an optional muscle biopsy occurring at Baseline and (n=40) at 4-months.

Results: The MOVE FSHD study has enrolled 315 participants across 14 international sites. More than 150 12-month visits and 75 24-month visits have been completed, 37 are enrolled in the MOVE+ sub-study, ~20 participants are non-ambulatory and ~20 enrolled are <18. MOVE FSHD participants span the full clinical severity scale with more than a third of participants having mild to moderate weakness in their lower extremities. TFTs, such as the 10-meter walk run (10mwr) and Timed Up and Go (TUG), correlate well with disease severity (>0.6), change from Baseline in 12-24-months and may predict a shift in other TFTs. The current abilities patient reported outcome also has a strong correlation to disease severity and strength (>.7) and a moderate correlation to function (>.5).

Conclusions: The MOVE FSHD study can improve our understanding of FSHD, impact patient care, refine inclusion criteria for trials, and identify outcomes and biomarkers for FSHD.

Funders: Grants from FSHD Society, Friends of FSH Research, FSHD Canada, Avidity Biosciences, Dyne Therapeutics, and Hoffman-La Roche.

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.

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. The MOVE FSHD study will evaluate 450 FSHD participants over 24-months with 200 participating in a MRI and muscle biopsy sub-study to validate FSHD evaluations and biomarkers. Visits collect FSHD history, physical examination, patient reported outcomes, strength, timed functional tests (TFTs), and spirometry. Sub-study participants have additional biomarkers collected, including reachable workspace at each visit, whole-body MRI at Baseline and 12-months, and an optional muscle biopsy occurring at Baseline and (n=40) at 4-months. The MOVE FSHD study has enrolled 305 participants across 14 international sites. More than 150 12-month visits and 75 24-month visits have been completed, 25 are enrolled in the MOVE+ sub-study, ~20 participants are non-ambulatory and ~20 enrolled are <18. MOVE FSHD participants span the full clinical severity scale with more than a third of participants having mild to moderate weakness in their lower extremities. TFTs, such as the 10-meter walk run (10mwr) and Timed Up and Go (TUG), correlate well with disease severity (>0.6), change from Baseline in 12-24-months and may predict a shift in other TFTs. The current abilities patient reported outcome also has a strong correlation to disease severity and strength (>.7) and a moderate correlation to function tasks, such as 10mwr (>.5). The MOVE FSHD study can improve our understanding of FSHD, impact patient care, refine inclusion criteria for trials, and identify outcomes and biomarkers for FSHD.

#1022 Outcome Measures to Quantify Longitudinal Changes in Motor Function in FSHD

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Introduction. Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common muscular dystrophies, yet natural history studies and recent clinical trials have highlighted challenges in measuring disease progression.

Objectives. To conduct a longitudinal pilot study assessing whether novel non-invasive measures of upper and lower extremity function may correlate with FSHD clinical severity and provide reliable biomarkers for FSHD therapeutic trials.

Methods. We are correlating structural changes detected by muscle MRI and ultrasound (MUS) with scores of clinical severity, including manual motor function, Ricci/Lamperti scales, the FSHD Rasch-built overall disability scale (RODS), ACTIVE-WorkSpace Volume (WSV), and OpenCap 3D kinematics. Adult subjects (10 FSHD, 5 unaffected controls) are being evaluated at baseline, 6 mo, and 12 mo with MUS of 7 muscles bilaterally (biceps brachii, deltoid, trapezius, rectus abdominus, rectus femoris, vastus lateralis, and tibialis anterior).

Results. Early analyses demonstrate linear regression of qualitative blinded Heckmatt MUS scoring of trapezius and vastus lateralis muscles (n=8 subjects so far) with positive correlations to the Ricci scale ($r = 0.788$ and 0.821, respectively) and to the Lamperti scale ($r = 0.714$ and 0.645, respectively). We used OpenCap during a Sit-to-Stand-5x protocol, and initial results (n=3) show correlation between the maximum angle of lumbar bending and the Ricci scale ($r > 0.90$), RODS ($r > 0.90$), and the 100-m time ($r > 0.90$).

Conclusions. Additional OpenCap maneuvers, including Timed-Up-and-Go (TUG) and tests of stance and balance are being assessed. Ongoing developments may allow analyses of specific motor patterns relevant to future FSHD clinical trials.

#1028 Long-term tolerability and effectiveness of nusinersen in ambulatory and non-ambulatory adults with 5q-SMA

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Introduction: For adults with 5q-SMA, nusinersen appears safe and stabilizes or improves motor function in the short-term (<24 months). There is limited long-term data.

Objective: To study the long-term (>24 months) effects and tolerance of nusinersen in adults with 5q-SMA, both ambulatory and non-ambulatory.

Methods: We conducted a retrospective observational study of 5q- SMA patients, age >18 years, and receiving nusinersen for >24 months. Outcomes included: 6-minute walk test (6MWT), Hammersmith Functional Motor Scale - Expanded (HFMSE), revised upper limb module (RULM), pulmonary function test results, and medication-related adverse effects. Data were collected at baseline and post-treatment initiation at months 2, 6, 12, 24, 36, 48, and 60.

Results: Thirty-two individuals with SMA (17 female) were included. Nineteen were non-ambulatory (mean age 38.3+/- 12.1 years) and 13 were ambulatory (mean age 32.9+/-9.5 years). Average treatment duration was 53.3 months (range 24-60). Among ambulatory participants, significant improvement in 6MWT was observed at 6 months, but this improvement was not maintained by 60 months. In ambulatory participants, HFMSE scores improved from baseline at 12 months but returned to baseline levels at 24-60 months. In non-ambulatory participants, RULM, CHOP and FVC remained stable. Headaches and post-injection site pain were common adverse effects. No serious adverse events were reported.

Conclusions: Long-term nusinersen treatment is safe in adults with SMA. Ambulatory and non-ambulatory participants showed relative clinical stability in motor and pulmonary function over 5-6 years. These findings suggest that nusinersen provides relative improvement compared to the natural disease progression through 6 years of treatment.

#1031 Safety And Effect Of Risdiplam Treatment In Adults With Spinal Muscular Atrophy

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Introduction: Risdiplam is an orally administered medication for children and adults with 5q-spinal muscular atrophy (SMA). It has been shown to be safe, well tolerated, and improve or stabilize motor function in individuals with SMA. However, limited published data is available regarding efficacy and safety in adults.

Objectives: The aim of this study was to assess the effectiveness, safety, and tolerability of risdiplam in adults with SMA.

Methods: We conducted a retrospective chart review on adult patients with genetically confirmed 5q-SMA who had received treatment with risdiplam for a minimum of six months. Assessments were performed at baseline, 6, 12, and 24 months. In addition to baseline demographic data, clinical outcomes included the Revised Upper Limb Module (RULM) and the Children's Hospital of Philadelphia Adult Test of Neuromuscular Disorders (CHOP-ATEND) for non-ambulatory and the six-minute walk test, RULM, and Hammersmith Functional Motor Scale-Expanded for ambulatory patients. Forced vital capacity and self-reported adverse effects were recorded.

Results: Nineteen patients (mean age 41.58), 15 non-ambulatory, 4 ambulatory, met inclusion criteria. CHOP ATEND scores increased in the non-ambulatory group at 24 months (+2.28; p=0.031). All other outcome measures showed stability. The most common self-reported adverse effects included gastrointestinal issues. Serious adverse events included pneumonia, fractures, and appendicitis.

Conclusions: Risdiplam was well-tolerated up to 24 months in adults with SMA. Treatment resulted in improvement or stabilization of motor and respiratory function in non-ambulatory and ambulatory patients. Larger sample sizes and longer-term follow-up are needed to understand longer-term effects of risdiplam in adults with 5q-SMA.

Industry or Pharmaceutical Sponsored Clinical Trials and Studies

#918 Preliminary Analysis of Treatment Patterns in Patients With Amyotrophic Lateral Sclerosis Using Electronic Health Records

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Introduction: There are 3 US Food and Drug Administration (FDA)-approved active pharmaceutical agents for patients with amyotrophic lateral sclerosis (pALS). Riluzole was FDA approved in 1995. Intravenous and oral edaravone were FDA approved in 2017 and 2022, respectively. Sodium phenylbutyrate and taurursodiol (PB-TURSO) was FDA approved for use in pALS in September 2022, but discontinued in 2024 due to negative phase 3 trial results. Tofersen was FDA approved for pALS with superoxide dismutase 1 mutation in April 2023.

Objectives: To describe preliminary real-world data (RWD) on demographics, clinical characteristics, and treatment patterns of pALS in this US-based, electronic health record (EHR) analysis.

Methods: This retrospective, observational cohort study investigated pALS obtained from Optum EHRs from August 1, 2015, through September 30, 2023. Edaravone treatment may have been intravenous and/or oral. The index date was the date of treatment initiation.

Results: Patients were grouped based on use of ALS treatments (n=5147) vs untreated (n=7180). Treated patients were divided based on use of riluzole (n=4352), edaravone (n=82), PB-TURSO (n=13), riluzole+edaravone (n=587), edaravone+PB-TURSO (n=5), riluzole+PB-TURSO (n=39), or riluzole+edaravone+PB-TURSO (n=69). Patients were predominantly male (56.1%-57.0%), White (81.3%-83.2%), and covered by commercial insurance (43.5%-44.7%), with a mean age of 63.8 to 64.2 years. Pre-index disease progression milestones were noted, including use of canes/walkers/wheelchairs, artificial nutrition, non-invasive ventilation, invasive ventilation, hospitalization, and gastrostomy tube placement.

CONCLUSIONS: Additional results are expected for these preliminary analyses of RWD that may help clinicians and payers better understand the demographics, clinical characteristics, and treatment patterns of pALS, including edaravone-treated patients.

Sponsorship: Sponsored by Mitsubishi Tanabe Pharma America, Inc.

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Disclosure:
MC, PDS and SA are employees of Mitsubishi Tanabe Pharma America, Inc.
JZ and YL are employees of Princeton Pharmatech, which has received consultancy fees from Mitsubishi Tanabe Pharma America, Inc.

#920 Characterization of deflazacort use in young Duchenne muscular dystrophy patients: an analysis of data from the PTC Cares database

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Introduction: Deflazacort is indicated for US patients with Duchenne muscular dystrophy (DMD) aged ≥2 years and is recommended as first-line therapy. Evidence demonstrates early and uninterrupted deflazacort use translates to clinically meaningful benefits. Evidence gaps remain in patients aged <5 years.

Objectives: To characterize deflazacort use in US patients with DMD aged 2 to <5 years.

Methods: PTC Cares collects and maintains an internal database of deflazacort-treated patients in the US. De-identified data were analyzed for patient characteristics, prescription patterns by region (Northeast, West, Midwest, Southeast) and discontinuations.

Results: From February 2017 to October 2023, 277 patients aged 2 to <5 years at deflazacort referral were identified; 218 were actively receiving deflazacort (active) at time of analysis. Mean (standard error of mean [SEM]) age at referral for active patients was 4.1 (0.03) years. For active patients with known ambulatory status at time of analysis, 93% were ambulatory, 3% non-ambulatory, and 4% combination ambulatory/non-ambulatory. Referral rates of active patients aged 2 to <5 years as a proportion of all active patients were highest in Midwest (9%) and lowest in Northeast (6%). Of patients aged 2 to <5 years not receiving deflazacort at time of analysis (inactive), 23 discontinued deflazacort. Mean (SEM) age of discontinuation and time from deflazacort referral to discontinuation was 6.1 (0.78) years and 2.2 (0.64) years, respectively.

Conclusions: These data provide insights into characteristics of young patients receiving deflazacort in the US and identify discrepancies in referral rates between regions. Further analyses will be presented in the poster.

Disclosures
JB, AK, ED and GI are employees of PTC Therapeutics.

#921 Minimal symptom expression in generalized myasthenia gravis: A post hoc analysis of MycarinG and open-label studies

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Presenting author: John Vissing

Introduction: High rates of Myasthenia Gravis Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis response were observed with rozanolixizumab across MycarinG (NCT03971422) and its open-label extension (OLE) studies in adults with generalized myasthenia gravis (MG). Attaining minimal symptom expression (MSE; MG-score: 0 or 1) is indicative of therapeutic efficacy and a treatment goal in MG.

Objective: To assess the long-term efficacy of rozanolixizumab via a post hoc analysis of MSE rates.

Methods: In MycarinG, patients received once-weekly placebo, rozanolixizumab 7mg/kg or 10mg/kg for 6 weeks. Patients could subsequently enroll in OLEs MG0004 (NCT04124965) then MG0007 (NCT04650854), or MG0007 directly. MG0004 comprised once-weekly rozanolixizumab 7mg/kg or 10mg/kg for ≤52 weeks. In MG0007, after an initial 6-week cycle (rozanolixizumab 7mg/kg or 10mg/kg), cycles were administered on symptom worsening. Data were pooled across MycarinG, MG0004 (first 6 weeks) and MG0007 (data cut-off: 08 July 2022) for patients with ≥2 symptom-driven cycles. The proportion of patients achieving MSE at any time in each cycle was analyzed. Post hoc analysis of MSE rate was conducted based on achievement of MSE in Cycle 1.

Results: At data cut-off, 127 patients had ≥2 symptom-driven cycles. MSE rates were 27.6% (35/127), 26.8% (34/127) and 25.5% (25/98) in Cycle 1, 2 and 3, respectively. For patients who achieved MSE in Cycle 1 and had further cycles, MSE rate was high over subsequent cycles (Cycle 2: 77.1% [27/35]; Cycle 3: 81.8% [18/22]).

Conclusion: The majority of patients achieving MSE in Cycle 1 continued to achieve MSE in subsequent rozanolixizumab treatment cycles.

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Robert M. Pascuzzi is Professor Emeritus of Neurology at Indiana University and receives compensation for his professional work from Indiana University Health. He has no financial relationship with any pharmaceutical company and receives no compensation from any pharmaceutical company (present or past). Robert M. Pascuzzi speaks at educational seminars on a broad variety of general neurology topics for primary care physicians through the organization Medical Education Resources (an educational organization with no links or ties to any pharmaceutical or healthcare business company). Therefore, Robert M. Pascuzzi has no conflicts of interest related to this research, manuscript, presentation, or publication.
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Sabrina Sacconi has nothing to disclose.
John Vissing has been a consultant on advisory boards for Sanofi Genzyme, Sarepta Therapeutics, Viela Bio (now Horizon Therapeutics), Novartis, Fulcrum Therapeutics, Stealth Biotherapeutics, Roche, Biogen, Lupin, Genethon, Amicus Therapeutics, Regeneron Pharmaceuticals, UCB Pharma, Arvinas, ML Biopharma and Horizon Therapeutics. He has received research, travel support, and/or speaker honoraria from Sanofi Genzyme, argenx, Alexion Pharmaceuticals, Biogen, Lupin, Stealth Biotherapeutics, Edgewise Therapeutics, Fulcrum Therapeutics and UCB Pharma. He is a Principal Investigator in clinical trials for Sanofi Genzyme, Roche, Horizon Therapeutics, argenx, Novartis, Alexion Pharmaceuticals, Stealth Biotherapeutics, UCB Pharma, Genethon, ML Biopharma, Reneo Pharma, Pharnext, Janssen Pharmaceuticals, Khondrion, Regeneron and Dynacure.
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#922 Long-term zilucoplan in generalized myasthenia gravis: 96-week follow-up interim analysis of RAISE-XT

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Presenting author: James F. Howard Jr

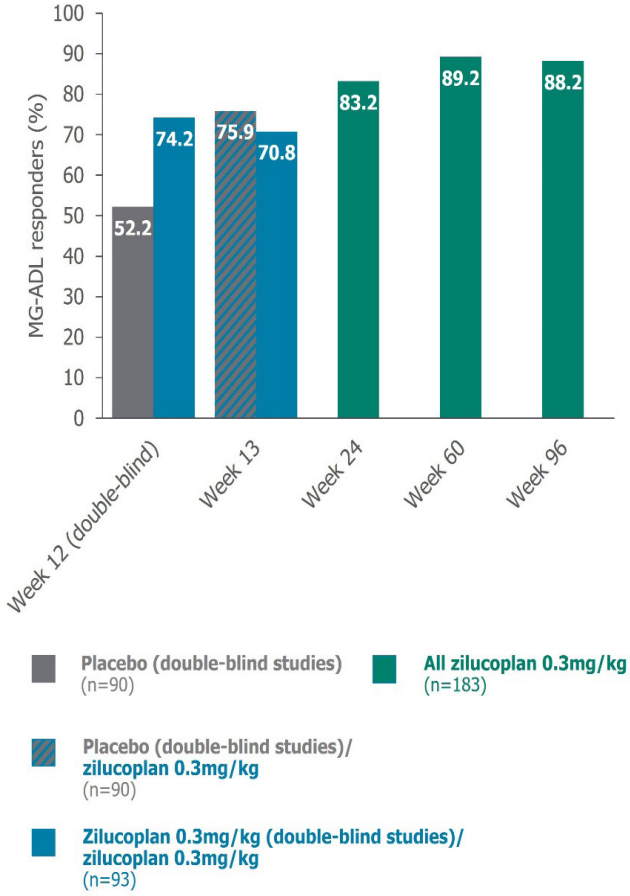
Introduction: Long-term data from RAISE-XT (NCT04225871), an ongoing, Phase 3, open-label extension study, will enhance understanding of the safety and efficacy of the macrocyclic peptide complement component 5 inhibitor, zilucoplan, in patients with acetylcholine receptor autoantibody-positive generalized myasthenia gravis (gMG).
Objective: To assess responder rates for Myasthenia Gravis Activities of Daily Living (MG-ADL), Quantitative Myasthenia Gravis (QMG) and minimal symptom expression (MSE) up to 96 weeks.

Methods: RAISE-XT enrolled adults with gMG who completed a qualifying, double-blind study (NCT03315130/NCT04115293). Patients self-administered daily subcutaneous injections of zilucoplan 0.3mg/kg. Primary outcome: incidence of treatment-emergent adverse events (TEAEs). Exploratory outcomes included responder rates for MG-ADL, QMG and MSE (reduction of ≥3 points, ≥5 points, or an MG-ADL score 0 or 1, respectively, without rescue therapy).

Results: Overall, 200 patients had enrolled at data cut-off (11 May 2023); median (range) exposure was 1.8 (0.11—5.1) years. Of 183 who received zilucoplan 0.3mg/kg or placebo in the qualifying study, 93 continued zilucoplan 0.3mg/kg; 90 switched from placebo to zilucoplan 0.3mg/kg. At RAISE-XT baseline (double-blind study Week 12), MG-ADL, QMG and MSE responder rates were 74.2%, 59.8% and 19.4% for zilucoplan (n=93) and 52.2%, 37.1% and 7.8% for placebo (n=90), respectively. At Week 96, pooled zilucoplan (n=183) MG-ADL, QMG and MSE responder rates had improved to 88.2% (Figure), 80.3% and 48.2%. TEAEs occurred in 191/200 (95.5%) patients; 71/200 (35.5%) patients experienced a serious TEAE (Table).

Conclusion: In this interim analysis, zilucoplan demonstrated a favorable safety profile and improved MG-ADL, QMG and MSE responder rates, sustained up to 96 weeks of treatment.

Figure. MG-ADL responder rates through to Week 96



mITT population (data for 17 patients who received zilucoplan 0.1mg/kg in the Phase 2 study are not shown).

MG-ADL, Myasthenia Gravis Activities of Daily Living; mITT, modified intent-to-treat.

Table. Overview of TEAEs

	All zilucoplan (N=200)
Any TEAE, n (%)	191 (95.5)
Serious TEAE, n (%)	71 (35.5)
TEAE resulting in permanent withdrawal from IMP,* n (%)	19 (9.5)
Treatment-related TEAE, n (%)	70 (35.0)
Severe TEAE, n (%)	64 (32.0)
TEAE leading to death, n (%)	4 (2.0)

Safety set, includes all patients who entered RAISE-XT.

*Includes the four deaths, which were: two cardiac arrests in patients with major cardiovascular risk factors, and one head injury. For one participant, the cause of death was unknown: a non-serious and severe TEAE of pneumonia reported two days prior to death, but it is not known whether the cause of death was related to pneumonia. None of the deaths were considered treatment-related (as determined by the investigator).

IMP, investigational medicinal product; TEAE, treatment-emergent adverse event.

Disclosures

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#925 Phase 3, Open-Label, Safety Extension Study of Oral Edaravone Administered Over 96 Weeks in Patients with ALS (MT-1186-A03)

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Introduction: Radicava (intravenous [IV] edaravone) and Radicava ORS (oral suspension edaravone) were approved by the US Food and Drug Administration (FDA) for the treatment of amyotrophic lateral sclerosis (ALS) in 2017 and 2022, respectively, and studies have demonstrated these approved formulations have similar pharmacokinetics. Study MT-1186-A01 indicated that oral edaravone was well-tolerated over 48 weeks, with no new safety concerns identified.

Objectives: To evaluate the safety of oral edaravone in patients with ALS over 96 weeks.

Methods: Study MT-1186-A03 (NCT04577404) was a phase 3, open-label, multi-center, extension study that evaluated the long-term safety of oral edaravone over an additional 96 weeks in patients who have completed the initial 48 weeks of Study MT-1186-A01. Participants received oral edaravone (105-mg dose) according to the FDA-approved dosing for IV edaravone. Patients had definite, probable, probable-laboratory-supported, or possible ALS; baseline forced vital capacity ≥70%; and baseline disease duration ≤3 years.

Results: In study MT-1186-A03, oral edaravone was well tolerated with no new safety concerns. The most common treatment-emergent adverse events (TEAEs) were fall, muscular weakness, dyspnea, constipation, and dysphagia. These TEAEs were consistent with the safety profile for edaravone from previous clinical trials.

Conclusions: Oral edaravone showed no new safety concerns and was well-tolerated during the 96-week study period.

Sponsorship: This study was sponsored by Mitsubishi Tanabe Pharma America, Inc.

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GL has served as a consultant for Mitsubishi Tanabe Pharma, Inc.

GS has served as a medical advisor for Mitsubishi Tanabe Pharma Corporation.

MA has served as medical advisor for Mitsubishi Tanabe Pharma Corporation.

HY has served as medical advisor for Mitsubishi Tanabe Pharma Corporation.

PC has served as a consultant for Biogen and as an editor for Elsevier.

CL has served as a scientific consultant for Mitsubishi Tanabe Pharma Europe, Cytokinetics, Neuraltus, and Italfarmaco.

SP has served as a scientific consultant for Cytokinetics, Biogen, and Roche, and received speaker's honoraria from Biogen, Roche, and Italfarmaco.

DS is an employee of Mitsubishi Tanabe Pharma America, Inc.

VT is an employee of Mitsubishi Tanabe Pharma Europe Ltd.

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AK is an employee of Mitsubishi Tanabe Pharma America, Inc.

CEJ serves on the Data and Safety Monitoring Board for Mitsubishi Tanabe Pharma America, Inc., and Anelixis.

#927 Ataluren delays clinically meaningful milestones of decline in 6MWD in patients with nmDMD from Study 041, a phase 3, placebo-controlled trial

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Introduction: Persistent 10% or 5% worsening and 30m decline in 6-minute walk distance (6MWD) are clinically meaningful milestones of disease progression in patients with Duchenne muscular dystrophy (DMD).

Objectives: To assess the effects of ataluren in delaying clinically meaningful milestones in nonsense mutation DMD (nmDMD).

Methods: Study 041 (NCT03179631) is an international, phase 3, randomized, double-blind, placebo-controlled 72-week ataluren trial followed by a 72-week open-label period. Eligible boys with genetically confirmed nmDMD, aged ≥5 years and with 6MWD ≥150m were randomized 1:1 to receive ataluren/placebo. The intention-to-treat population comprised boys who received ≥1 dose of study treatment. Predefined subgroups included patients with baseline 6MWD 300–400m, and patients with baseline 6MWD ≥300m and stand from supine ≥5s (primary analysis subgroup). Decline in 6MWD over 72 weeks was assessed in these populations.

Results: In the intention-to-treat population (ataluren, n=183; placebo, n=176), ataluren significantly reduced the risk of persistent 10% and 5% worsening in 6MWD by 31% (p=0.0078) and 30% (p=0.0082), respectively, and 30m decline by 31% (p=0.0067), vs placebo. In the 6MWD 300–400m subgroup, ataluren significantly reduced the risk of persistent 10% and 5% worsening in 6MWD by 47% (p=0.0011) and 42% (p=0.0029), respectively, and 30m decline by 47% (p=0.0009), vs placebo. In the primary analysis subgroup, there was a reduced risk of 10% persistent worsening in 6MWD for patients treated with ataluren compared with placebo, this did not reach statistical significance (p=0.0659).

Conclusions: These results indicate that ataluren delays clinically meaningful milestones of nmDMD progression that predict ambulatory decline.

Disclosures:
SW, SG and KH have no conflicts of interest.
HK has acted as a consultant on clinical trials for DMD for Kaneka, Takeda and Taiho Pharmaceuticals; and has received research support for clinical trials from Nippon Shinyaku, Pfizer, PTC Therapeutics, Sarepta Therapeutics and Taiho Pharmaceutical.
REE-C has acted as a principal investigator of clinical trials for PTC Therapeutics.
AK-P has received advisory board fees from Pfizer, PTC Therapeutics, Roche and Sarepta Therapeutics; has received lecture fees and travel support from PTC Therapeutics and Roche; and has acted as a principal investigator for DMD clinical trials sponsored by GSK (formerly GlaxoSmithKline), Pfizer, PTC Therapeutics and Sarepta Therapeutics.
J-HS has acted as a principal investigator on DMD clinical trials sponsored by Nippon Shinyaku, Pfizer, PTC Therapeutics and Sarepta Therapeutics.
VP, CC, CW, ED and PW are employees of PTC Therapeutics.
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#928 Ataluren slows the decline of muscle function in patients with nmDMD: a meta-analysis of three randomized, double-blind, placebo-controlled trials

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Elaine Dong,[8] Paula Williams[8] and Christian Werner,[9] on behalf of the Study 007, 020 and 041 investigators

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Introduction: Study 041 (NCT03179631) is an international, phase 3, randomized, double-blind, placebo-controlled 72-week trial of ataluren in patients with nonsense mutation DMD (nmDMD) followed by a 72-week open-label period.

Objectives: To report ataluren muscle function efficacy results from a meta-analysis of the Study 041 placebo-controlled phase and two randomized, double-blind, placebo-controlled, 48-week ataluren trials (Study 007 [phase 2b; NCT00592553] and ACT DMD [phase 3; NCT01826487]).

Methods: In all three studies, eligible boys had genetically confirmed nmDMD. The meta-analysis used a weighted random-effects model and included intention-to-treat populations from each study. Endpoints included 48-week changes in 6-minute walk distance (6MWD), timed function tests (TFTs) and North Star Ambulatory Assessment (NSAA) total and linear scores (Study 041 and ACT DMD only); change in 6MWD was also assessed in a subgroup of patients with baseline 6MWD 300–400m.

Results: The meta-analysis included 354 ataluren-treated patients and 347 placebo-treated patients. Differences in change from baseline to week 48 in 6MWD, TFTs and NSAA scores between ataluren- and placebo-treated patients were statistically significant, favoring ataluren (least-squares mean difference; 6MWD: 15.8m, p=0.0032; 10m walk/run: −1.1s, p=0.0026; climb four stairs: −1.3s, p=0.0025; descend four stairs: −1.3s, p=0.0021; NSAA total score: 1.1, p=0.0010; NSAA linear score: 2.6, p=0.0036). In the 6MWD 300–400m subgroup, ataluren significantly slowed 6MWD decline by 33.7m versus placebo (p<0.0001).

Conclusions: In this meta-analysis of a large, heterogeneous population from the intention-to-treat populations of Study 041, Study 007 and ACT DMD, ataluren slowed decline in muscle function across multiple clinically meaningful endpoints versus placebo.

Disclosures:
PK, YT and KH declare no conflicts of interest.
Y-JJ has acted as a principal investigator of clinical trials for Biogen, Novartis, NS Pharma, Pfizer, PTC Therapeutics, Roche and Sarepta Therapeutics.
JS has received grant funding from the Friends of FSH Research, FSHD Canada, FSHD Society, MDA and NIH; and is a consultant or has served on advisory boards for Avidity Biosciences, Dyne Therapeutics, Fulcrum Therapeutics, ML Bio Solutions, Roche and Sarepta Therapeutics.
ML has acted as a principal investigator of clinical trials for NS Pharma, Pfizer, PTC Therapeutics and Sarepta Therapeutics; and has consulted on advisory boards for Biogen, Roche and Sarepta Therapeutics.
AC has acted as a principal investigator of clinical trials for Biogen, NS Pharma, Pfizer, PTC Therapeutics and Sarepta Therapeutics; and has received fees for participation in advisory boards from Biogen, Novartis and Roche.
VP, CC, ED, PW and **CW** are employees of PTC Therapeutics.
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#948 2023 interim analysis of EVOLVE: A long-term observational phase 4 study evaluating eteplirsen, golodirsen, or casimersen in routine clinical practice

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Introduction: Eteplirsen, golodirsen, and casimersen are phosphorodiamidate morpholino oligomers (PMOs) approved for patients with Duchenne muscular dystrophy (DMD) with pathogenic variants amenable to 51, 53, and 45 exon skipping, respectively.

Objectives: To describe treatment patterns, safety, and functional assessments in PMO-treated patients with DMD from the ongoing real-world, phase 4, multicenter, observational EVOLVE study.

Methods: This interim analysis includes treatment-emergent serious adverse events (TESAEs; all PMOs) and loss of ambulation (LOA; eteplirsen, fully enrolled).

Results: As of October 2023, 161 patients were enrolled (mean [SD] age [years]: eteplirsen [n=126], 14.0 [5.5]; golodirsen [n=23], 13.3 [4.2]; casimersen [n=12], 16.1 [7.2]). Mean (SD) duration of treatment (years) was 6.4 (1.9) for eteplirsen, 2.6 (0.9) for golodirsen, and 1.9 (0.5) for casimersen. PMOs showed favorable safety profiles and were well tolerated; no TESAEs were treatment related. Of 126 eteplirsen-treated patients, 48 (38.1%) were ambulatory at eteplirsen initiation and through follow-up, 41 (32.5%) were nonambulatory at treatment initiation, and 37 (29.4%) lost ambulation after eteplirsen initiation. Of the 85 patients who were ambulatory at treatment initiation and included in the Kaplan-Meier analysis, the median age at LOA for eteplirsen-treated patients was 15.4 years. Persistence on eteplirsen in EVOLVE remained high, with 120 (95.2%) patients continuing therapy and 34 (91.9%) of the 37 patients who lost ambulation after eteplirsen initiation remaining on eteplirsen.
Conclusions: These data support the safety of PMOs observed in clinical trials. Eteplirsen-treated patients show age at LOA consistent with prior clinical trial post hoc results and persistence on therapy.

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#949 ClC-1 inhibition improves skeletal muscle function in rat models and patients with myasthenia gravis

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ClC-1 is a Cl- ion channel specifically expressed in skeletal muscle cells. The channel stabilizes the resting membrane potential and dampens muscle fiber excitability and is involved in regulating muscle fiber excitability during intense exercise. While neuromuscular transmission is reliable in healthy individuals, transmission failure causes weakness and fatigue in a range of neuromuscular diseases including Myasthenia Gravis (MG).

In the present study we investigated the effect of ClC-1 inhibition in pre-clinical models of neuromuscular dysfunctions. Two animal models were used; a pharmacological model induced in healthy rats and an actively immunized MG rat model. Our results show that pharmacological inhibition of ClC-1 restores synaptic transmission and skeletal muscle function leading to marked improvements in muscle strength in both the rat models.

Specifically, we found that compound muscle actions potentials and stimulated muscle force were markedly improved when animals received the ClC-1 inhibitor NMD670, and that this translated to improved running performance and grip strength.

The results encouraged further development of NMD670.

In a 3-way, cross-over design in 12 patients with MG, each patient was administered a single dose of either placebo, 400 mg NMD670 or 1200 mg NMD670. The study showed that NMD670 improved Quantitative Myasthenia Gravis (QMG) scale in patients with mild symptoms by 2 points, compared to placebo, in 42 to 50 % of the patients in both doses. Individual functional tests comprising the QMG scale, such as hand grip strength, ptosis, and dysarthria also showed improvement in patients receiving NMD670 compared to placebo treatment.

These findings suggest ClC-1 inhibition as a potential novel approach to enhancing neuromuscular transmission, leading to improved muscle function and restored mobility in MG and potentially other NMJ disorders.

#951 Treatment Patterns and Survival Benefit of Edaravone–Treated People With Amyotrophic Lateral Sclerosis in the ALS/MND Natural History Consortium

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Introduction: Riluzole, intravenous (IV) edaravone, and oral edaravone were US Food and Drug Administration (FDA)-approved for people with amyotrophic lateral sclerosis (PALS) in 1995, 2017, and 2022, respectively. The ALS/Motor Neuron Disease (MND) Natural History Consortium (NHC) is a registry that captures longitudinal clinical information from PALS.

Objectives: Obtain real-world evidence on treatment patterns, clinical outcomes, and survival of edaravone–treated PALS in the ALS/MND NHC database.

Methods: The index date for this ALS/MND NHC database analysis of PALS was the first ALS treatment dose date. Patients receiving edaravone±riluzole were propensity score matched 1:1 to those receiving riluzole only. Survival between groups was estimated using the Kaplan-Meier model. Restricted mean survival time (RMST) differences were adjusted for potential confounding.

Results: Patients receiving edaravone±riluzole (n=176) were matched to those receiving riluzole only (n=176) on sex, age, body mass index, race; and pre-index non-invasive ventilation, artificial nutrition, and disease duration; baseline mean±SD ALS Functional Rating Scale-Revised score (39.5±4.8 and 39.3±4.8, respectively) and forced vital capacity %–predicted (79.3%±23.5% and 79.4%±21.4%, respectively). Matched variables had a standardized mean difference ≤0.1. After baseline covariate adjustment, RMST analyses over 50 months suggested a survival benefit for patients receiving edaravone±riluzole (30.5 months) vs riluzole only (27.2 months), which is an RMST difference between groups of 3.2 months (P<0.03).

Conclusions: This ongoing study of edaravone–treated PALS in the ALS/MND NHC database suggests an additional survival benefit of 3.2 months with edaravone±riluzole vs riluzole only. These data may help inform choices made by clinicians and payers.

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KP, MC, and SA are employees of Mitsubishi Tanabe Pharma America, Inc.

KGG has received speaking and consulting honoraria from Alexion Pharmaceuticals, UCB, and argenx.

NO participated in the Avanir visiting expert program.

CL has served as a scientific consultant for Mitsubishi Tanabe Pharma Europe, Cytokinetics, Neuraltus, and Italfarmaco.

THP has served as a medical advisor for Mitsubishi Tanabe Pharma America, Inc., and is an employee of Temple University which has received research funding from Mitsubishi Tanabe Pharma America, Inc. She has also served on the medical advisory board for Amylyx, Novartis, Biogen, Sanofi,and Cytokinetics.

JW is an employee of the University of Florida which has received research funding from Mitsubishi Tanabe Pharma America, Inc.

DW has served as a consultant for Mitsubishi Tanabe Pharma America, Inc., Amylyx, and Biogen.

#952 Preliminary Analysis of Treatment Combinations in Patients With Amyotrophic Lateral Sclerosis Enrolled in an US-Based Administrative Claims Database

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Introduction: Patients with amyotrophic lateral sclerosis (ALS) have limited US Food and Drug Administration (FDA)-approved treatment options. Riluzole was the first FDA approved treatment for ALS in 1995. In 2017 and 2022, Radicava® (edaravone) IV and ORS were FDA-approved, respectively. Tofersen was FDA-approved for patients with ALS with a superoxide dismutase 1 mutation in 2023. Sodium phenylbutyrate and taurursodiol (PB-TURSO) was FDA-approved in 2022, but voluntarily discontinued in 2024.

Objectives: To describe preliminary data on demographics, characteristics, and treatment combinations in patients with ALS in this real-world, observational, US-based administrative claims analysis.

Methods: Patients with ALS continuously enrolled in Optum's de-identified Clinformatics® Data Mart (CDM) from August 1, 2017, through September 30, 2023, were included and grouped based on ALS treatment combination. The index date was the date of ALS diagnosis.

Results: Patients were grouped based on use of riluzole only (n=2193) vs other FDA-approved treatment(s) (n=967) including Radicava®, PB-TURSO, riluzole+ Radicava®, Radicava®+PB-TURSO, riluzole+PB-TURSO, or riluzole+ Radicava®+PB-TURSO. Patients were predominantly male (53.5%-53.6%), White (72.2%-74.4%) and covered by Medicare (68.6%-77.8%). Mean (SD) age was 67.6 (10.3) for the riluzole-only group vs 64.0 (10.4) for the other treatment(s) group. Pre-index disease progression milestones were assessed, including use of canes/walkers/wheelchairs, artificial nutrition, non-invasive ventilation, invasive ventilation, hospitalization, and gastrostomy tube placement.

Conclusions: Additional results are expected for these preliminary analyses of real-world data that may help clinicians and payers better understand the demographics, clinical characteristics, and current treatment combinations in patients with ALS, including those treated with Radicava®.

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Disclosures:

JCN has no disclosures to report.

MC and PDS are employees of Mitsubishi Tanabe Pharma America, Inc.

JZ and YL are employees of Princeton Pharmatech, which has received consultancy fees from Mitsubishi Tanabe Pharma America, Inc.

#956 Development of a Goal Area Inventory for Limb Girdle Muscular Dystrophy to Facilitate Potential Implementation of a Personalized Endpoint

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Introduction: Limb-girdle muscular dystrophy (LGMD) sarcoglycanopathy subtypes are ultra-rare genetic conditions that present with heterogeneity in age of onset, disease progression, and level of physical disability, giving rise to challenges in the assessment of meaningful change in drug development. Personalized endpoints such as Goal Attainment Scaling (GAS) may help assess within-patient meaningful change across a spectrum of ages and baseline health states.

Objectives: We aimed to develop a goal inventory for LGMD based on patient and clinician input to support potential implementation of personalized endpoints in clinical studies.

Methods: A patient-centered goal inventory was developed by reviewing relevant literature, analyzing previously collected patient/caregiver qualitative interviews [(N=23), 60.9% ambulatory, 2C/R5 (n = 4), 2D/R3 (n = 12), 2E/R4 (n = 7)], and identifying domains associated with progression of LGMD. The initial inventory was revised through a focus group with two clinicians experienced in rehabilitation and neurology and subsequent interviews with two experts in neuromuscular disorders and physiotherapy.

Results: The final goal inventory consisted of potential goal areas across the domains of upper body function, lower body function, disease manifestations, activities of daily living/independence, social/emotional concerns, and management of related disease areas.

Conclusions: This draft goal inventory provides a basis for the development of individual treatment goals, which may be beneficial for measuring progress over time using a personalized endpoint such as GAS. This may complement current functional assessments, providing a comprehensive understanding of how LGMD and its treatments impact patient experiences in clinical research.

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#958 Cyclic and Every-Other-Week Dosing of Intravenous Efgartigimod for Generalized Myasthenia Gravis: Part A of ADAPT NXT

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Introduction: Individualized cyclic dosing of efgartigimod, a human immunoglobulin G1 Fc-fragment that blocks the neonatal Fc receptor, was well tolerated and efficacious in the ADAPT/ADAPT+ phase 3 trials in generalized myasthenia gravis (gMG).

Objectives: The phase 3b ADAPT NXT study (NCT04980495) investigated the efficacy, safety, and tolerability of efgartigimod administered either every other week (Q2W) or in fixed cycle dosing regimens.

Methods: Adult participants with anti-acetylcholine receptor antibody positive gMG were randomized 3:1 to Q2W or cyclic (4 once-weekly infusions, 4 weeks between cycles) dosing of 10 mg/kg efgartigimod for a 21-week period.

Results: Sixty-nine participants were treated (cyclic, n=17; Q2W, n=52). Least squares mean (95% CI) of the change from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) total score from Week 1-21 (primary endpoint) was -5.1 (-6.5 to -3.8) in the cyclic arm and -4.6 (-5.4 to -3.8) in the Q2W arm; changes remained similar through week 21. Clinically meaningful improvements in mean (SE) MG-ADL total scores were observed as early as week 1 (-2.0 [0.4], both arms) and were maintained over time. Achievement of minimal symptom expression (MG-ADL score 0-1) was observed in 47.1% (n=8/17) and 44.2% (n=23/52) of participants in the cyclic and Q2W arms, respectively. Efgartigimod was well tolerated; COVID-19, upper respiratory tract infection, and headache were the most common treatment-emergent adverse events.

Conclusions: The results of ADAPT NXT build upon previous studies and provide additional efgartigimod dosing approaches (fixed cycles and Q2W) to maintain clinical efficacy in participants with gMG.

#962 Interim Analysis of EVOLVE: Evaluating Eteplirsen Treatment in Nonambulatory Patients in Routine Clinical Practice From a Phase 4 Observational Study

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Introduction: Progressive muscle damage in Duchenne muscular dystrophy (DMD) leads to decline in upper limb strength and function.

Objectives: To describe safety and clinical outcomes, including upper limb function, in eteplirsen-treated, nonambulatory patients with DMD from the ongoing real-world, phase 4, multicenter, observational EVOLVE study.

Methods: This interim analysis included patients who were nonambulatory at eteplirsen initiation or became nonambulatory after eteplirsen initiation. Treatment duration, safety, and Brooke upper extremity scores are described.

Results: Of 123 eteplirsen-treated patients enrolled in EVOLVE as of December 2021, 41 (33%) were nonambulatory at treatment initiation (mean age: 18.4 [range, 10.6–28.6] years; mean [SD] duration of treatment: 4.2 [1.2] years). Thirty-one (25%) patients lost ambulation after eteplirsen initiation (mean age: 14.7 [range, 7.2–23.2] years; mean [SD] duration of treatment: 6.1 [1.9] years). At the time of the analysis, most patients who either were nonambulatory at treatment initiation or lost ambulation after eteplirsen initiation (95.8%, n=69/72) persisted on eteplirsen (mean [SD] duration of treatment: 5.0 [1.8] years; mean [SD] duration of follow-up in EVOLVE: 1.1 [0.8] years). Upper limb function in patients with ≥2 Brooke scores was either maintained or improved in 14/18 (78%) patients who were nonambulatory at eteplirsen initiation and 12/15 (80%) patients who lost ambulation after eteplirsen initiation. The safety profile in nonambulatory patients was consistent with that observed in clinical trials; no treatment-related serious adverse events were observed.

Conclusions: Interim real-world data from a subgroup analysis of nonambulatory EVOLVE patients show persistence on therapy and support the safety of eteplirsen.

Sponsorship: This study is funded by Sarepta Therapeutics, Inc.

Disclosures: SG, SS, SH, IS: Employees of Sarepta Therapeutics, Inc., and may own stock/options in the company. **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, and received research support from NIH (5 U54 NS053672, U24 NS-10718), CDC (U01 DD001248), and FARA. **RS**: Received research funding from Genentech, Sarepta Therapeutics, Inc., Novartis, Fibrogen, Capricor, argenx BVBA, and Biohaven.

Prior Presentation: MDA Clinical and Scientific Congress, 2024

#964 CONNECT1-EDO51: Preliminary results from a 12-week open-label Phase 2 study to evaluate PGN-EDO51 safety and efficacy in people with Duchenne amenable to exon 51 skipping

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(PepGen Inc., Boston, MA)

Introduction: PepGen's enhanced delivery oligonucleotide (EDO) cell-penetrating peptide technology is engineered to optimize tissue delivery and nuclear uptake of therapeutic oligonucleotides. PGN-EDO51 is being evaluated for the treatment of DMD amenable to exon 51 skipping. In nonclinical studies and a Phase 1 trial in healthy male volunteers, PGN-EDO51 demonstrated nuclear delivery of the oligonucleotide resulting in high tissue concentrations and exon 51 skipping and/or dystrophin production. Collective nonclinical and clinical data support repeat administration of PGN-EDO51 once every 4 weeks in people with DMD, which may lead to production of functional dystrophin, potentially resulting in improved clinical outcomes.

PepGen's Phase 2 clinical program includes CONNECT1-EDO51, an open-label MAD study ongoing in Canada (NCT06079736) and CONNECT2-EDO51, a multinational randomized placebo-controlled MAD study. Participants completing the MAD period in either study have the opportunity to participate in a long-term extension.

Objectives: Evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics (dystrophin, exon skipping) of PGN-EDO51 following repeat dosing in people with DMD amenable to exon 51 skipping.

Methods: Participants (N=10) will receive 4 doses of PGN-EDO51 at approximately 4-week intervals over 12 weeks in ascending doses across 3 cohorts. Muscle biopsies are taken at Baseline and Week 13. Main inclusion criteria are age ≥8 years with a confirmed genetic diagnosis of DMD amenable to exon 51 skipping, and weight ≥25 kg.

Conclusion: Participants in the first cohort (n=3) have received repeat doses of 5 mg/kg PGN-EDO51. Safety and initial dystrophin results will be presented.

#965 CONNECT2-EDO51: A Phase 2 placebo-controlled study to evaluate PGN-EDO51 safety and efficacy in people with Duchenne amenable to exon 51 skipping

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(PepGen Inc., Boston, MA)

Introduction: PepGen's enhanced delivery oligonucleotide (EDO) 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. In nonclinical studies and a Phase 1 trial in healthy male volunteers, PGN-EDO51 demonstrated nuclear delivery of the oligonucleotide resulting in high tissue concentrations and exon 51 skipping and/or dystrophin production. Collective nonclinical and clinical data support repeat administration of PGN-EDO51 once every 4 weeks in people with DMD may lead to production of functional dystrophin, potentially resulting in improved clinical outcomes.

PepGen's Phase 2 clinical program includes CONNECT1-EDO51, an open-label MAD study ongoing in Canada (NCT06079736) and CONNECT2-EDO51, a multinational randomized placebo-controlled MAD study. Participants completing the MAD period in either study will have the opportunity to participate in a long-term extension.

Objectives: Evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics (dystrophin, exon skipping) of PGN-EDO51 following repeat dosing in people with DMD amenable to exon 51 skipping.

Methods: Participants will be randomized 3:1 to PGN-EDO51 or placebo in multiple ascending doses across 3 cohorts. All participants (N≈24) will receive 7 doses at approximately 4-week intervals over 24 weeks. Muscle biopsies occur at Baseline and Week 25. Main inclusion criteria are age ≥6 years with confirmed genetic diagnosis of DMD amenable to exon 51 skipping, and weight ≥25 kg.

Conclusions: CONNECT2-EDO51 is designed to support advancement of PGN-EDO51 and potential regulatory approvals. Study design will be presented.

#971 Clinical Outcomes, Disease Course, and QoL in Patients With Multifocal Motor Neuropathy: iMMersioN, Study in Progress

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Introduction: Multifocal motor neuropathy (MMN) is a rare, peripheral, immune-mediated, chronic neuropathy resulting from motor nerve conduction block due to IgM auto-antibodies, leading to axonal degeneration and progressive disabling asymmetric limb weakness with absence of sensory loss. Data on patient experience and clinical management of MMN are limited to small cohorts and retrospective analyses.

Objectives: To further understand MMN diagnosis, disease course and management, and to characterise the healthcare resource use of patients with MMN.

Methods: iMMersioN (NCT05988073), a global, prospective, longitudinal study, will enrol approximately 150 participants. No investigational medicinal product will be administered. Participants will be observed as they receive standard of care treatments. Site visits will coincide with regular MMN treatment visits and will occur approximately every 3 months, and participants will be followed for up to 24 months. In certain countries, optional blood samples may be collected from participants.

Results: The objectives of the iMMersioN study are: to characterise MMN participant profiles, assess disease management and disease course, including outcomes measures such as MMN-RODS, MMRC-10, and adjusted INCAT, estimate the economic burden and impact of MMN on quality of life, and collect data on relevant disease biomarkers such as autoantibody titers against gangliosides, components of the complement cascade, and a marker of neurological degeneration. The first participant was enrolled on 29 November 2023.

Conclusions: iMMersioN is an ongoing, global, prospective, longitudinal study to examine clinical outcomes, disease course, resource utilization and health-related quality of life in adult patients with MMN.

#972 Efficacy and Safety of Efgartigimod PH20 Subcutaneous in Chronic Inflammatory Demyelinating Polyneuropathy: Results of ADHERE/ADHERE+

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Introduction: Efgartigimod, a human immunoglobulin G (IgG)1 antibody Fc fragment, blocks the neonatal Fc receptor, decreasing IgG recycling and reducing pathogenic IgG autoantibody levels.

Objectives: To assess the efficacy and safety of efgartigimod PH20 subcutaneous (SC; coformulated with recombinant human hyaluronidase PH20) in chronic inflammatory demyelinating polyneuropathy (CIDP).

Methods: Participants with active CIDP (off treatment or on standard treatments withdrawn during run-in) enrolled in multi-stage, double-blinded, placebo-controlled ADHERE and received once weekly (QW) efgartigimod PH20 SC 1000mg (stage A). Responders were randomized (1:1) to QW efgartigimod PH20 SC 1000mg or placebo (stage B). Participants with clinical deterioration in stage B or those who completed ADHERE could enter ongoing, open-label extension ADHERE+ (QW efgartigimod PH20 SC 1000mg). Primary outcomes: confirmed evidence of clinical improvement (ECI) (stage A), relapse risk (stage B), and safety (ADHERE+) (**Fig.1**).

Results: In stage A, 214/322 (66.5%) participants demonstrated confirmed ECI. In stage B, efgartigimod significantly reduced relapse risk (HR: 0.394 [95% CI, 0.253–0.614]) vs placebo (P=0.00004); this reduction was observed regardless of prior CIDP therapy. Selected secondary outcomes are shown in **Table 1.** 99% of eligible participants entered ADHERE+. The safety profile of efgartigimod was consistent over 137.42 total patient-years of follow-up for ADHERE+. Most treatment-emergent adverse events were mild/moderate; the incidence/severity did not increase in ADHERE+ (**Table 2**).

Conclusions: ADHERE demonstrated effectiveness of efgartigimod PH20 SC in reducing relapse risk. The safety profile of efgartigimod PH20 SC was similar between ADHERE and ADHERE+, and was consistent with the previously demonstrated safety profile of efgartigimod.

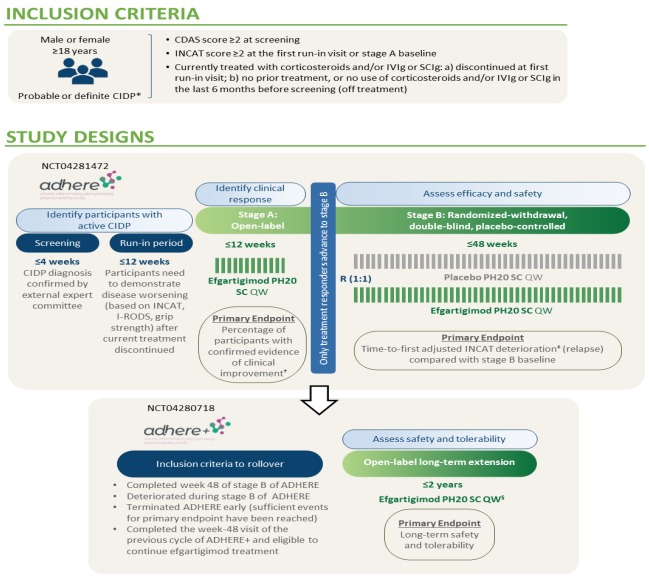

Figure 1 Study design of ADHERE and ADHERE+ trials.
CDAS, Chronic Inflammatory Demyelinating Polyneuropathy Disease Activity Status; CIDP, chronic inflammatory demyelinating polyneuropathy; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-Built Overall Disability Scale; IVIg, intravenous immunoglobulin; PH20, recombinant human hyaluronidase PH20; R, randomized; SC, subcutaneous; SCIg, subcutaneous immunoglobulin; QW, once weekly.
*According to 2010 criteria of the European Federation of Neurological Societies/Peripheral Nerve Society (Van den Bergh PYK, et al. *Eur J Neurol*. 2010;17(3):356–63), progressing or relapsing forms. †Evidence of clinical improvement was defined as a clinical improvement on the parameters that the participant worsened in during run-in (≥4-point increase in I-RODS and/or ≥8-kPa increase in mean grip strength) or clinical improvement (≥1-point decrease) in INCAT. ECI was confirmed after these criteria were met after four injections and two consecutive visits. ‡Adjusted INCAT deterioration was defined as an ≥1-point increase in aINCAT compared with stage B baseline, which was confirmed at a consecutive visit after the first 1-point increase in aINCAT or not confirmed for participants with ≥2-point increase in aINCAT compared with stage B baseline. §A subset of participants in ADHERE+ had the option of receiving efgartigimod PH20 SC once every 2 or 3 weeks.

	ADHERE		
	Open-Label Stage A	Double-Blinded Stage B	
	Efgartigimod PH20 SC (N=322)	Efgartigimod PH20 SC (N=111)	Placebo PH20 SC (N=110)
Mean (SD) change from baseline to last assessment*			
Adjusted INCAT score†	−0.9 (1.71)	0.1 (1.08)	0.9 (1.98)
I-RODS score‡	7.7 (15.48)	0.8 (12.33)	−7.0 (19.10)
Mean grip strength (dominant hand), kPa	12.3 (18.68)	2.1 (13.29)	−8.2 (20.69)
Mean grip strength (non-dominant hand), kPa	11.2 (21.12)	2.0 (17.33)	−6.9 (21.30)
I-RODS decrease of ≥4 points, n (%)	–	40 (36.0)	57 (51.8)
Hazard ratio (95% CI)	–	0.537 (0.354–0.814)	
Nominal *P* value	–	0.0034	
I-RODS increase of ≥4 points, n (%)	–	50 (45.0)	40 (36.4)
Odds ratio (95% CI)	–	1.441 (0.814–2.567)	
Nominal *P* value	–	0.2294	

Table 1 Key secondary efficacy endpoints in the ADHERE trial.

CI, confidence interval; HR, hazard ratio; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-built Overall Disability Scale; PH20, recombinant human hyaluronidase PH20; SC, subcutaneous; SD, standard deviation.

*For stage A, this was the change from stage A baseline to stage A last assessment, and for stage B, this was the change from stage B baseline to stage B last assessment. †Higher aINCAT score indicates worsening of disease. ‡Lower I-RODS score indicates worsening of disease.

	ADHERE			ADHERE+
	Open-Label Stage A	Double-Blinded Stage B		
Incidence, n (%) [event rate]*	Efgartigimod PH20 SC (N=322; PYFU= 46.9)	Efgartigimod PH20 SC (N=111; PYFU= 56.7)	Placebo PH20 SC (N=110; PYFU= 42.1)	Efgartigimod PH20 SC (N=228; PYFU= 137.4)
Any TEAE	204 (63.4) [13.4]	71 (64.0) [3.5]	62 (56.4) [5.1]	131 (57.5) [3.5]
Any SAE	21 (6.5) [0.5]	6 (5.4) [0.1]	6 (5.5) [0.2]	21 (9.2) [0.3]
Any AE of infections†	44 (13.7) [1.2]	35 (31.5) [0.8]	37 (33.6) [1.3]	73 (32.0) [0.7]
Discontinued due to TEAEs	22 (6.8) [0.5]	3 (2.7) [0.05]	1 (0.9) [0.02]	9 (3.9) [0.09]
Deaths‡	2 (0.6) [0.04]	0	1 (0.9) [0.02]	1 (0.4) [0.007]
Most common TEAEs (≥5% of participants in any group)				
Injection site erythema	33 (10.2) [1.13]	6 (5.4) [0.11]	0	7 (3.1) [0.1]
CIDP	17 (5.3) [0.41]	1 (0.9) [0.02]	1 (0.9) [0.02]	5 (2.2) [0.06]
Headache	16 (5.0) [0.6]	4 (3.6) [0.11]	2 (1.8) [0.05]	8 (3.5) [0.09]
Upper respiratory tract infection	11 (3.4) [0.26]	2 (1.8) [0.05]	11 (10.0) [0.26]	14 (6.1) [0.12]
COVID-19	7 (2.2) [0.17]	19 (17.1) [0.35]	14 (12.7) [0.33]	31 (13.6) [0.23]
Injection site bruising	4 (1.2) [0.11]	6 (5.4) [0.11]	1 (0.9) [0.02]	6 (2.6) [0.05]

Table 2 Incidence and event rates of adverse events in ADHERE and ADHERE+ trials.
AE, adverse event; CIDP, chronic inflammatory demyelinating polyneuropathy; COVID-19, coronavirus disease 2019; PH20, recombinant human hyaluronidase PH20; PYFU, patient-year(s) of follow-up; SAE, serious adverse event; SC, subcutaneous; TEAE, treatment-emergent adverse event.
*Event rates were calculated as the number of events divided by the PYFU. †Infections and infestations are grouped under System Organ Class (Medical Dictionary for Regulatory Activities v. 25.1). ‡Two deaths (cardiac arrest and deterioration of CIDP) in stage A were considered not related to efgartigimod PH20 SC by the investigator; one death (pneumonia) in the placebo arm of stage B was considered treatment related by the investigator; one death (CIDP deterioration) in ADHERE+ was considered related to efgartigimod PH20 SC by the investigator.
ADHERE+ data cut-off: 15 June 2023.

#973 Empasiprubart (ARGX-117) in Multifocal Motor Neuropathy: Initial Safety and Efficacy data of the Phase 2 ARDA Study

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Introduction: Multifocal motor neuropathy (MMN) is a rare, immune-mediated neuropathy resulting from motor nerve conduction block leading to axonal degeneration and progressive asymmetric limb weakness with absence of sensory loss. Currently, intravenous immunoglobulin (IVIg) is the only proven, efficacious therapy. Empasiprubart blocks the activation of classical and lectin complement pathways via C2 binding.
Objectives: To assess the safety, efficacy, and tolerability of empasiprubart in adults with MMN in ARDA (NCT05225675), a phase 2, multicentre, randomised, placebo-controlled, double-blinded, parallel-group study.
Methods: ARDA enrolled 52 participants with probable or definite MMN (2010 EFNS/PNS guidelines). All had proven IVIg dependency and were on a stable IVIg regimen leading to randomisation. MMN diagnosis and IVIg dependency were confirmed by committee. Enrolled participants were assigned to one of two dosing cohorts; each randomised 2:1 to empasiprubart or placebo. Key efficacy endpoints include IVIg retreatment, change in muscle strength, and disability scores.
Results: Cohort 1 randomised 27 participants. During the double-blind treatment period, empasiprubart demonstrated a 91% reduction (HR [95% CI]: 0.09 [0.02, 0.44]) in the risk for IVIg retreatment compared with placebo (**Figure 1**). Since starting therapy, 94% of empasiprubart-treated patients rated their condition improved, with 55% being much/very much improved (**Figure 2**) (Patient Global Impression of Change scale); 89% of placebo patients had no change/worsened. Empasiprubart was well tolerated overall. Most adverse events were mild or moderate. Additional results presented at the congress.

Conclusions: Early efficacy and safety signals in cohort 1 from the ongoing ARDA study support proof of concept of empasiprubart in MMN.

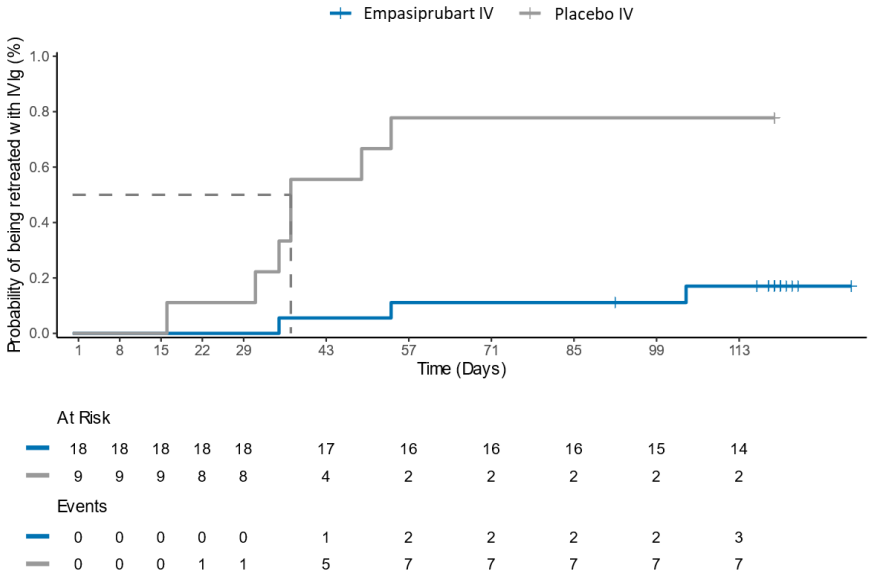

Figure 1 Time to first retreatment with IVIg during treatment period. During double blind treatment period, empasiprubart demonstrated a 91% reduction (HR [95% CI]: 0.09 [0.02; 0.44]) in the risk for IVIg retreatment compared to placebo. Time to first retreatment with IVIg is defined as the time from last IVIg administration before randomization (including unscheduled visits) up to the first IVIg retreatment during double blind trial period.

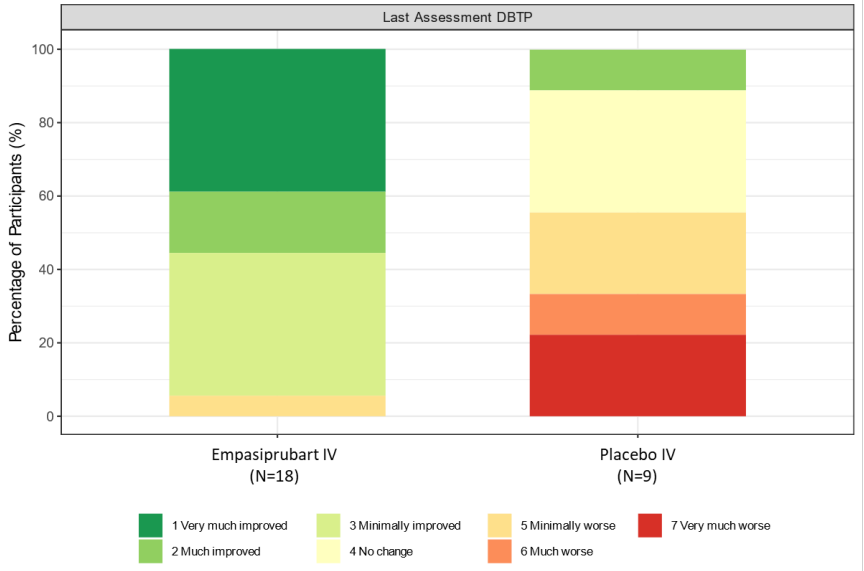

Figure 2 PGIC: Actual values at Last Assessment during treatment period. Since starting therapy, 94% (11/18) of empasiprubart-treated patients rated their condition improved, with 55% being much/very much improved (Patient Global Impression of Change scale). Conversely, 89% (8/9) of placebo patients had no change/worsened.

#977 Subcutaneous Immunoglobulin (IgPro20) Dose Adjustments for Chronic Inflammatory Demyelinating Polyneuropathy Maintenance Therapy in Clinical Practice

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Introduction: Subcutaneous immunoglobulin (SCIg), approved for maintenance therapy for chronic inflammatory demyelinating polyneuropathy (CIDP), enables consistent Ig levels and improved quality of life compared with intravenous immunoglobulin (IVIg). Optimal treatment uses the lowest effective dose tailored to patient needs. Limited data on the clinical practicalities of individualizing SCIg are available.

Objective: Here we examine CIDP cases reflecting SCIg dosing in clinical practice.

Methods: This is a retrospective, non-interventional, study of 20 patients with CIDP who were initially treated with IVIg then transitioned to maintenance SCIg (IgPro20, CSL Behring). Data were obtained from eight US centers.

Results: The approved dose for SCIg in CIDP is 0.2 or 0.4g/kg/week. Of patients with available IVIg data (n=19), 8 (40%) transitioned on a 1:1 IVIg:SCIg ratio (0.13–0.50g/kg/week SCIg). The remaining patients transitioned to lower (n=8) or higher (n=3) SCIg doses relative to prior IVIg.
Nine patients (45.0%) did not require any dose adjustments, while six (30.0%) patients had their IgPro20 dose increased at least once to maintain clinical stability. A further four patients (20%) underwent dose reductions, two of whom successfully maintained stable disease at lower doses, while two patients demonstrated signs of relapse and were returned to higher doses for disease stabilization; one returned to their baseline dose, and one underwent a series of dose adjustments and was eventually maintained on a dose slightly higher than baseline.
Conclusions: These cases demonstrate the flexibility of SCIg treatment in patients with CIDP, highlighting the importance of continued patient-physician discussions to individualize SCIg therapy and optimize clinical outcomes.

#978 Safety and efficacy of AAVrh74- and AAV9-based myotropic capsid variants in DMD^{mdx} mice and nonhuman primates

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Introduction: Targeted delivery of genetic medicines is required to optimize efficacy while minimizing potential adverse events associated with off-target gene expression.

Objectives: We evaluated the efficacy and safety of two myotropic capsid variants, rh74Myo and MyoAAV, in DMD^{mdx} mice and nonhuman primates (NHPs).

Methods: A myotropic peptide sequence was inserted into hypervariable region VIII of AAVrh74 and AAV9 for MHCK7.NHP-µDys construct delivery (rh74Myo and MyoAAV, respectively). Biodistribution and function were evaluated in DMD^{mdx} mice administered intravenous (IV) AAVrh74 (1.33×10^{14} vg/kg), rh74Myo (2×10^{13} vg/kg), or MyoAAV (2×10^{13} vg/kg). Biodistribution and safety were evaluated in NHPs (cynomolgus macaques) administered IV AAVrh74 (2×10^{14} vg/kg), rh74Myo (1×10^{14} vg/kg), or MyoAAV (5×10^{13}, $7x10^{13}$, 2×10^{14} vg/kg).

Results: At >6-fold lower dose than AAVrh74, both rh74Myo and AAV9-based-MyoAAV restored tibialis anterior muscle function (specific force and injury resistance) and produced skeletal muscle NHP-µDys expression comparable to higher-dose AAVrh74 in DMD^{mdx} mice, with a corresponding >6-fold decrease in liver biodistribution. In NHPs, skeletal muscle transgene delivery/µDys expression were enhanced with rh74Myo and MyoAAV compared with AAVrh74. No test article-related pathology or immune activation were noted with rh74Myo. Complement pathways and serum liver enzymes were elevated following MyoAAV; AAVrh74 and rh74Myo were not associated with elevated complement. A complement activation event with significantly increased serum liver enzymes and decreased platelet counts was detected with AAV9-based-MyoAAV (7×10^{13} vg/kg).

Conclusions: The myotropic capsid variant, rh74Myo, enhanced skeletal muscle transduction without increasing hepatic targeting and has a favorable safety profile similar to AAVrh74, supporting further clinical development for skeletal muscle disorders.

#979 Caregiver global impressions from the EMBARK randomized controlled trial evaluating the safety and efficacy of delandistrogene moxeparvovec

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Introduction: Duchenne muscular dystrophy (DMD) is a rare, progressive, debilitating neuromuscular disease that requires a lifetime of caretaking for most patients. Caregivers have a critical role in evaluating patients' physical functioning and/or response to treatment.

Objectives: Using a DMD-specific Caregiver Global Impression scale (CaGI-C), we evaluated the impact of delandistrogene moxeparvovec on caregivers' perceived change in patient disease status.

Methods: This post hoc analysis evaluated change from baseline to Week 52 in CaGI-C with data from the ongoing pivotal Phase 3, randomized, double-blind, placebo-controlled trial (EMBARK; NCT05096221) that is assessing delandistrogene moxeparvovec safety and efficacy in patients with DMD, aged ≥4 to <8 years. The CaGI-C gauges change in four main items: symptoms, physical ability, ability to perform daily activities, and overall health. Responses were scored from 1-7, with 1 being 'very much improved' and 7 being 'very much worse'.

Results: Multi-domain responder index analyses across all four CaGI-C items yielded a treatment difference of 1.7 (95% CI: 0.9-2.5, $p<0.0001$) favoring delandistrogene moxeparvovec. After adjusting for age, ordinal regression analysis showed an increase in the odds of being at least 'minimally improved' for delandistrogene moxeparvovec-treated patients: DMD symptoms (OR [95% CI]: 4.0 [2.0-8.0]), physical ability (OR [95% CI]: 4.9 [2.5-10.0]), activities of daily living (OR [95% CI]: 4.0 [2.0-8.0]), and overall health (OR [95% CI]: 3.8 [1.9-7.6]) (all $p\leq0.0001$).

Conclusions: These exploratory findings captured by caregiver-reported outcomes add to the totality of evidence that supports the clinical benefits of delandistrogene moxeparvovec.

Sponsorship: This trial was sponsored by Sarepta Therapeutics, Inc. and funded by Sarepta Therapeutics, Inc. and F. Hoffmann-La Roche Ltd.

Disclosures: JE, SD, KG, IA: Employees of Sarepta Therapeutics, Inc., and may hold stock/options in the company. **TC:** Employees of F. Hoffmann-La Roche Ltd. **CL:** Employee of F. Hoffmann-La Roche AG. and shareholder of F. Hoffmann-La Roche AG. **AM:** Employee of Roche Products UK and may hold shares in F. Hoffmann La Roche. **FM:** Employee of Genentech, Inc.and shareholder of F. Hoffmann La Roche AG.**CM:** Reports grants from Capricor Therapeutics, Catabasis, Edgewise Therapeutics, Epirium Bio, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, Sarepta Therapeutics; and has a consultancy/advisory role with Biomarin, Capricor Therapeutics, Catalyst, Edgewise Therapeutics, Italfarmaco, PTC Therapeutics, F. Hoffmann-La Roche Ltd, Santhera Pharmaceuticals and Sarepta Therapeutics. He has received honoraria from PTC Therapeutics and Sarepta Therapeutics.

#980 The FORCE(TM) platform resolves Pompe pathology in mice by delivering acid alpha glucosidase to muscle and central nervous system

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Introduction: Pompe is a severe neuromuscular disorder caused by deficiency of the lysosomal enzyme acid alpha glucosidase (GAA). Lack of GAA causes glycogen accumulation in tissue leading to muscle weakness, cardiomyopathy, respiratory failure, and central nervous system (CNS) manifestations. Regretfully, the standard of care (SOC), which consists of bi-weekly GAA administration, has inadequate efficacy in skeletal muscle and does not address the CNS manifestations. FORCE, a novel platform for the delivery of therapeutics via TfR1, has demonstrated clinical proof-of-concept for the treatment of DM1 and DMD. Here, we applied the FORCE platform to enhance GAA uptake into muscle and enable CNS delivery.

Objectives: To determine the impact of FORCE-GAA on glycogen accumulation, restoration of GAA activity, lysosomal size, and serum neurofilament-light chain (NF-L) levels in a mouse model of Pompe that expressing human TfR1 (hTfR1) and lacks GAA activity (hTfR1/6^{Neo}).

Methods: We engineered the FORCE platform with GAA as payload (FORCE-GAA). hTfR1/6^{Neo} mice were dosed intravenously with FORCE-GAA or GAA. Tissues were analyzed for glycogen levels, GAA activity, and lysosomal size. Serum was analyzed for NF-L levels.

Results: Infrequent intravenous injections of FORCE-GAA to hTfR1/6^{Neo} mice cleared glycogen and normalized lysosomal size in muscle and CNS after 8 weeks. FORCE-GAA reduced serum NF-L, a biomarker of axonal injury, confirming benefit in the CNS. FORCE-GAA has superior efficacy compared to GAA.

Conclusions: These data demonstrate the potential of FORCE-GAA as a novel therapy for Pompe.

#981 Impact of Vamorolone, Prednisone, and Placebo on Linear Growth in the VISION-DMD (VBP15-004) Study, as Measured by Changes in Height Over 6 Months

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Introduction: Corticosteroids are recommended as standard of care for patients with Duchenne muscular dystrophy (DMD). However, children with DMD are on average shorter than the general population by age 5 y, and daily dosing with prednisone (PRED) or deflazacort leads to further stunting of growth. In the phase 2b VISION-DMD study (NCT03439670) height percentile (adjusted by age using US CDC growth charts) was shown to decline from baseline to month 6 in patients treated with prednisone, but not in those treated with the dissociative corticosteroid vamorolone (VAM) at 6mg/kg/d.

Objective: To further study the impact of VAM or PRED vs placebo (PBO) on linear growth in the VISION-DMD study by reporting unadjusted changes in height (cm) and patient-level changes in height over 6 months.

Methods: The VISION-DMD study design has been reported previously. Boys aged 4 to <7 years were randomized to PBO, PRED 0.75mg/kg/d, VAM 2mg/kg/d, or VAM 6mg/kg/d. Height was recorded at baseline and 12-week intervals. This analysis included 118 participants in the safety population.

Results: At baseline, median height ranged from 106-111 cm across treatment groups. After 6 months of treatment, median height increases were lower in the PRED group (n=30, 2.60cm) than in the PBO (n=28, 3.55cm, P=0.03) or VAM 6mg/kg/d group (n=26, 3.50cm, P=0.009). There were no significant differences in median height increase between either VAM group and PBO (P>0.1). In the PRED group, 30.0% of children showed reductions in height z-score ≥0.2 SD after 6 months, compared with 18.5% in the VAM 2mg/kg/d group, 10.7% in the PBO group, and 0.0% in the VAM 6mg/kg/d group.

Conclusion: In patients with DMD aged 4 to <7 years, absolute height (cm) values after 6 months of treatment showed similar increases with vamorolone and placebo, while significantly less growth (ie, growth stunting) was observed with prednisone.

#982 The FORCE(TM) platform demonstrates prolonged DUX4 suppression leading to resolution of muscle pathology in an FSHD mouse model

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Introduction: FSHD is a serious muscle disease caused by aberrant *DUX4* mRNA expression in muscle. DUX4 regulates expression of downstream genes defined as the DUX4 transcriptome (D4T), thereby leading to myofiber loss and debilitating weakness. DYNE-302 consists of a fragment antigen-binding (Fab) targeting the human transferrin receptor type 1 (TfR1) and conjugated to an siRNA highly specific for *DUX4*. DYNE-302 was developed in accordance with the principles of the FORCE platform to potentially treat FSHD.

Objectives: To determine the impact of DYNE-302 on D4T in FSHD patient-derived myotubes *in vitro* and on D4T levels, myofiber morphology, and muscle function in mouse models of FSHD *in vivo*.

Methods: Patient-derived myotubes were exposed to DYNE-302 and D4T expression assessed by qRT-PCR and RNASeq. Mice constitutively expressing human TfR1 (hTfR1) and sporadically expressing tamoxifen-inducible human DUX4 in skeletal muscle (hTfR1/iFLExD) were used as an FSHD model. hTfR1/iFLExD mice subjected to a single intravenous dose of DYNE-302 were analyzed for D4T by RT-PCR and for myofiber diameter by immunofluorescence. The effect of DYNE-302 on muscle function was measured by forced treadmill run after induction of DUX4 by tamoxifen. Mice subjected to vehicle injections served as controls.

Results: DYNE-302 demonstrated inhibited D4T in myotubes *in vitro*. In hTfR1/iFLExD mice, a single intravenous dose of DYNE-302 led to robust D4T inhibition lasting up to 3 months and reduced myofiber pathology. DYNE-302 also corrected the profound functional deficit in hTfR1/iFLExD mice administered with tamoxifen.

Conclusions: Our data demonstrate the potential of DYNE-302 for the treatment of FSHD.

#983 Evaluation of Behavioral Problems in the VISION-DMD Study of Vamorolone vs Prednisone in Duchenne Muscular Dystrophy

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Introduction: Psychiatric adverse effects during systemic corticosteroid therapy are common and well documented. Typically, prednisone (PRED) is standard of care treatment for children with Duchenne muscular dystrophy (DMD).

Objective: Here we report the frequency of behavioral problems in the phase 2b VISION-DMD study (NCT03439670) using the PARS III scale, a validated index of youth psychosocial adjustment in DMD.

Methods: Male patients with DMD, ages 4 to <7 years, were randomized to placebo (PBO), PRED 0.75mg/kg/d, or vamorolone (VAM) at 2 or 6mg/kg/d. PARS III subscales assessed by parents were normalized as z-scores using historical data. Clinically relevant worsening in PARS III subscales was defined as a shift from normal baseline adjustment score (z-score <1) to an abnormal score (z-score ≥1) at week 24. Persistence of effect was evaluated over a 48-week treatment period.

Results: Frequency and rates of behavioral adverse events (BAEs) such as irritability, psychomotor hyperactivity, and aggression were recorded. Moderate or severe BAEs were more frequent in the PRED group (22.6%) than in any other arm (≤3.4% in all other groups). One patient on PRED discontinued due to a severe BAE. Clinical worsening in hostility was more frequent with PRED (26.1%) than VAM 6mg/kg/d (15.4%) or 2mg/kg/d (9.1%) or PBO (8.0%). Clinical worsening in dependency and productivity was reported in >20% of patients on PRED (24.0% and 26.9%, respectively) compared with <10% in any other group.

Conclusion: VAM 6mg/kg/d was associated with an increase in mainly mild BAEs compared with PBO, but with a lower frequency and severity of BAEs reported compared with PRED. PARS III subscales showed a reduced risk for psychosocial adjustment/functioning in hostility, dependency, and productivity with VAM compared with PRED.

#984 Interim Results from FORTITUDE, a Randomized, Phase 1/2 Trial Evaluating Del-Brax (AOC 1020) in Adults with Facioscapulohumeral Muscular Dystrophy (FSHD)

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**Presenter*

Introduction: FSHD is a rare, progressive, often asymmetric, genetic disease caused by aberrant expression of the transcription factor DUX4 in skeletal muscle, leading to a series of downstream events that result in muscle degeneration and wasting. Del-brax (AOC 1020) is an antibody-oligonucleotide conjugate (AOC) comprised of a DUX4-targeting siRNA conjugated to a humanized anti-transferrin receptor 1 (TfR1) antibody to facilitate delivery to muscle tissue. Del-brax is being investigated for the treatment of FSHD in the FORTITUDE trial (NCT05747924), a first-in-human, phase 1/2 randomized, double-blind, placebo-controlled trial in patients with FSHD.

Objective: To assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of del-brax in adults with FSHD.

Methods: The FORTITUDE study has 3 parts (A, B, and C) each with an administration of 5 doses of del-brax via infusion over 9-months plus a 3-month follow-up period. Patients in Part A receive an initial del-brax dose of 1 mg/kg increasing to 2 mg/kg for the remaining doses. Part B is a single and multiple-ascending dose design evaluating placebo, 4 mg/kg del-brax. Part C is a placebo-controlled, randomized, parallel design to further assess outcomes at selected doses.

Results: An interim 4-month analysis of del-brax of pharmacokinetic, pharmacodynamic, and safety data will be presented.

Conclusion: FSHD is a progressive, debilitating disease with no approved treatments. Interim results from the FORTITUDE study support the continued development of del-brax.

#985 PHASE 3 TRIAL DESIGNS EVALUATING RILIPRUBART, A C1S-COMPLEMENT INHIBITOR, IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

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Presenting Author: TBD

Introduction: Standard-of-care (SOC) therapies for CIDP have variable efficacy, significant side-effects, and are burdensome. Riliprubart, a first-in-class, humanized, IgG4-monoclonal antibody, selectively inhibits activated-C1s and has convenient subcutaneous route of administration. Phase 2 trial (NCT04658472) results indicated promising clinical benefits with favorable benefit-risk profile.

Objective: To present two Phase 3 trial designs which will evaluate riliprubart in 1) people with CIDP who experienced an inadequate response or failure to at least one line of treatment (SOC-refractory) and 2) responders to IVIg with residual disability.

Methods: Two global, multicenter, randomized, Phase 3 trials are planned: MOBILIZE (NCT06290128), a placebo-controlled trial targeting SOC-refractory patients; VITALIZE (NCT06290141), a double-dummy trial targeting IVIg-treated patients with residual disability. Treatment duration in both trials is 48 weeks (24-week double-blinded period [Part-A], plus 24-week open-label period [Part-B]). Participants will be randomized (1:1) to receive riliprubart or placebo (MOBILIZE; N≤140), and riliprubart plus IVIg-placebo or IVIg plus riliprubart-placebo (VITALIZE; N≤160). Sample sizes will be re-estimated based on pre-defined interim analysis during Part-A. Eligible adults with CIDP diagnosed based on 2021 EAN/PNS guidelines with INCAT score 2-9 (score 2 exclusively from legs) can be included. Primary endpoint is percentage of participants responding, defined as ≥1 point decrease from baseline in adjusted INCAT score at Week-24 (Part-A). Key secondary endpoints include change from baseline in additional disability/impairment measures (Part-A) and long-term safety (Part-B).

Results: Recruitment is ongoing for both trials.

Conclusions: Both trials will evaluate riliprubart in CIDP, including patients with refractory disease or residual disability.

Author Disclosures: ***Richard A. Lewis***: Consultant with CSL Behring, Grifols, Pfizer, Sanofi (Steering Committee), argenx, Pharnext, Roche, Johnson & Johnson, Takeda, Boehringer Ingelheim (DSMB), and Momenta. He is also part of scientific advisory boards, Alnylam and Akcea and medical advisory board - The GBS|CIDP Foundation International. ***Jeffrey Allen***: Consultant for Sanofi, Alexion, Alnylam, argenx,

Annexon, CSL Behring, Johnson & Johnson, Grifols, Takeda, Immunovant, Immunopharma, and Pfizer. ***Ingemar S.J. Merkies***: Received grants from Talecris Talents program, GBS|CIDP Foundation International and FP7 EU program, outside the submitted work. A research foundation at the University of Maastricht received honoraria on behalf of him for participation in steering committees of the Talecris Immune Globulin Intravenous for Chronic Inflammatory Demyelinating Polyneuropathy Study, Commonwealth Serum Laboratories, Behring, Octapharma, LFB, Novartis, Union Chimique Belge, Johnson & Johnson, argenx, outside the submitted work, and Octapharma during the conduct of the study. ***Pieter A. van Doorn***: Consultant with Annexon, argenx, Hansa Biopharma, Immunic, Octapharma, Roche, Sanofi, (Institutional research fund received all honoraria), and received grants from the Prinses Beatrix Spierfonds, Sanquin, and Grifols. ***Claudia Sommer***: Consultant for Alnylam, Air Liquide, Bayer, Immunic, Ipsen, LFB, Merz, Nevro, Pfizer, Roche and Takeda, and has received honoraria from Alnylam, CSL Behring, Grifols, Lilly, Merck, Novartis, Pfizer and TEVA. Erik Wallstroem, Xiaodong Luo, Miguel Alonso-Alonso, Nazem Atassi: Employees of Sanofi and may hold shares and/or stock options in the company. ***Luis Querol***: 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. He received speaker or expert testimony honoraria from CSL Behring, Novartis, Sanofi, Merck, Annexon, Alnylam, Biogen, Janssen, Lundbeck, argenx, UCB, Dianthus, LFB, Avilar Therapeutics, Octapharma and Roche. He serves at Clinical Trial Steering Committee for Sanofi and was Principal Investigator for UCB's CIDP01 trial.

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#986 Vamorolone Dose Titration in Expanded Access Programs and Its Impact on Rates of Weight Change in Duchenne Muscular Dystrophy (DMD)

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Introduction: The recommended dose of vamorolone (VAM) in children with DMD is 6mg/kg/d. Doses may be titrated to as low as 2mg/kg/day, based on tolerability. VAM is associated with a risk for weight gain, but prior studies have not investigated the impact of dose titration. In this study, patients continued treatment in expanded access programs (EAPs), allowing for up- or down-titration between 2, 4, and 6mg/kg/d as warranted.

Objective: To report experience with VAM dose titration in EAPs and the impact of down-titration on weight percentiles.

Methods: Data were collated from patients who completed studies VBP15-LTE, VBP15-004, or VBP15-006 and enrolled in 1 of 3 EAPs in the US, Canada, or Israel as of 21 July 2023. Available data were pooled to explore the effect of dose titration on weight changes. We created a down-titration analysis set (DTS; N=17) for patients with ≥3 measurements on VAM 6mg/kg/d, followed by ≥3 measurements after down-titrating to 4mg/kg/d, and an up-titration analysis set (UTS; N=16) for those with ≥3 measurements on VAM 2mg/kg/d followed by ≥3 measurements after up-titrating to 4mg/kg/d.

Results: Median duration of VAM exposure in the EAPs (N=99) was 2.1y with a maximum of 4.4y. Most patients were dosed at some point with VAM 4mg/kg/d or 6mg/kg/d, with fewer dosed at 2mg/kg/d. In the DTS, annual rate of change in weight percentiles (95% CI) decreased from 19.0 (7.5, 30.5) during treatment at 6mg/kg/d to 4.6 (−0.8, 9.9) after down-titration to 4mg/kg/d. In UTS, change in percentiles (95% CI) remained stable despite dose increase, from 12.4 during treatment at 2mg/kg/d to 10.6 after up-titration to 4mg/kg/d.

Conclusion: Dose-titration in the EAPs showed that down-titration from VAM 6mg/kg/d to 4mg/kg/d resulted in less weight gain. No evidence of increased risk for weight gain was observed in patients who up-titrated from 2mg/kg/d to 4mg/kg/d.

#987 Development of a conceptual model of the patient experience of Duchenne muscular dystrophy (DMD) through qualitative interviews

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Introduction: Conceptual models depicting the patient experience of Duchenne muscular dystrophy (DMD) are important to identify relevant outcomes for patient-focused drug development.

Objectives: To create a comprehensive conceptual model of DMD symptoms and impacts experienced across disease stages by integrating findings from primary qualitative interview studies.

Methods: Two qualitative interview studies were carried out in the US with patients and/or caregivers exploring DMD symptoms and their effect on functioning and quality of life. Qualitative data were coded using content analysis and synthesized into domains (e.g. physical function). Concepts from each study and existing published conceptual models of DMD were compared. Clinical experts and patient representatives reviewed an early draft of the conceptual model for relevance. A pooled conceptual model was developed from these sources.

Results: Study 1 included 46 patient–caregiver dyads (28 ambulatory, mean age 8.7 years; 18 nonambulatory, mean age 11.3 years). Study 2 included 15 caregivers (9 ambulatory and 6 nonambulatory, mean age 10.7 years). Progressive weakness notably limited children's mobility and lower limb function, including difficulty using stairs, running, walking, and transferring. Upper limb function limitations included difficulty lifting and carrying objects, arm weakness, and reduced fine motor skills. Consequently, daily activities and emotional well-being were substantially impaired.

Conclusions: The conceptual model provides a structured framework for understanding the patient experience across DMD disease stages and treatment histories. The conceptual model can be used to identify important concepts to patients when selecting clinical outcome assessments for DMD clinical trials.

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#992 Phase 2 Efficacy and Safety of Riliprubart, a C1s-Complement Inhibitor, in Chronic Inflammatory Demyelinating Polyneuropathy

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Presenting Author: Miguel Alonso-Alonso

Introduction: Riliprubart is a first-in-class humanized IgG4-monoclonal antibody, which selectively inhibits activated-C1s within the classical complement pathway.

Objective: To report efficacy and safety of riliprubart in CIDP.

Methods: Global, multicenter, Phase-2, open-label trial (NCT04658472) evaluating riliprubart in 3 subgroups: Standard-of-care (SOC)-Treated, SOC-Refractory, and SOC-Naïve. Participants undergo 24-week treatment (Part-A), followed by optional treatment-extension (Part-B: 52-weeks, Part-C: until end-of-study). Primary endpoint of Part-A is %-participants with relapse (SOC-Treated) or response (SOC-Refractory/Naïve), defined as ≥1-point change in adjusted INCAT disability score from baseline up to 24-weeks. Part-B evaluates safety and efficacy durability based on % relapse-free participants (SOC-Treated) or with sustained-response (SOC-Refractory/Naïve), defined as no-increase in adjusted INCAT score ≥2-points relative to 24-weeks. Exploratory endpoints include additional efficacy measures (INCAT, I-RODS, MRC-SS, grip-strength), change in total complement, and plasma NfL.

Results: As of May 2023, Part-A results from pre-specified interim-analysis show 88% (N=22/25) SOC-Treated participants improved/remained stable (44%; N=11/25 improved), and 12% relapsed (N=3/25). 50% (N=9/18) SOC-Refractory participants responded to riliprubart. Clinically meaningful improvements were seen across secondary efficacy measures. Sustained inhibition of complement activity and reduction in NfL levels were observed. TEAEs occurred in 65.1% (N=28/43) participants. Two deaths were reported in participants with significant medical comorbidities aside from CIDP.

Conclusions: Preliminary results demonstrate therapeutic potential of riliprubart in CIDP, with favorable benefit-risk profile, supporting further investigation in Phase-3.

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#997 Phase 3b Study MT-1186-A02 to Investigate the Superiority of Daily Dosing vs the FDA-approved On/Off Regimen of Oral Edaravone in Patients with ALS

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Introduction: An on/off dosing regimen of Radicava® (edaravone) IV and Radicava ORS® (edaravone) oral suspension was approved by the US Food and Drug Administration (FDA) for the treatment of amyotrophic lateral sclerosis (ALS) in 2017 and 2022, respectively. Clinical trials showed that edaravone slows the rate of physical functional decline.

Objectives: To evaluate whether investigational daily dosing displayed superior efficacy vs the approved on/off dosing regimen of Radicava ORS® in patients with ALS based on ALS Functional Rating Scale-Revised (ALSFRS-R) score changes, as well as assess safety and tolerability, over 48 weeks.

Methods: Study MT-1186-A02 (NCT04569084) was a multi-center, phase 3b, double-blind, parallel group superiority study that randomized patients to Radicava ORS® (105-mg dose) administered once daily or the same Radicava ORS® dose administered according to the FDA-approved on/off regimen. Patients had definite or probable ALS, baseline forced vital capacity ≥70%, and baseline disease duration ≤2 years.

Results: At week 48, combined assessment of function and survival (CAFS), including change in ALSFRS-R score and time to death, indicated daily dosing did not show a statistically significant difference vs the approved on/off dosing. Radicava ORS® was well tolerated and no new safety concerns were identified in either group in Study MT-1186-A02.

Conclusions: Daily Radicava ORS® did not show superiority to the FDA-approved on/off regimen in the CAFS and reinforces the appropriateness of the FDA-approved on/off regimen.

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Disclosure:

JR is a consultant for Expansion Therapeutics, National Institutes of Health, Department of Defense, F Prime, The ALS Association.

AG has served as a consultant for Mitsubishi Tanabe Pharma, Inc.

SD has nothing to disclose.

LZ has received honoraria for consulting with MTP, Biogen, Amylyx and Cytokinetics
MC has nothing to disclose.

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.

GS has served as a medical advisor for Mitsubishi Tanabe Pharma Corporation.

MD is a medical advisor for the MT-1186-A02 study

DS is an employee of Mitsubishi Tanabe Pharma America, Inc.

VT is an employee of Mitsubishi Tanabe Pharma Europe Ltd.

NS has served as a consultant for NeuroDerm and Mitsubishi Tanabe Pharma, Inc.

FT is an employee of Mitsubishi Tanabe Pharma America, Inc.

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AW is an employee of Mitsubishi Tanabe Pharma America, Inc.

SA is an employee of Mitsubishi Tanabe Pharma America, Inc.

#1000 Phase 3 Trial Investigating Impact of Intravenous Efgartigimod in Anti-Acetylcholine Receptor Antibody Negative Generalized Myasthenia Gravis

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Introduction: Approximately 15%-20% of patients with generalized myasthenia gravis (gMG) are anti-acetylcholine receptor antibody negative (AChR-Ab-). The lack of approved treatment options for the AChR-Ab- gMG population represents an unmet need in gMG treatment. Efgartigimod is a human IgG1 antibody Fc-fragment that reduces IgG levels (including pathogenic autoantibodies) through blockade of the neonatal Fc receptor. This phase 3 (NCT06298552) trial will investigate efficacy and safety of efgartigimod in participants with AChR-Ab- gMG.

Objectives: To determine efficacy and safety of 10 mg/kg IV efgartigimod compared with placebo in AChR-Ab- participants with gMG.

Methods: Adult participants with AChR-Ab- gMG who have a Myasthenia Gravis Activities of Daily Living (MG-ADL) total score of ≥5 (with >50% of the score due to nonocular symptoms) and are on a stable dose of ≥1 concomitant gMG treatment will be included. One hundred ten adjudicated participants will be randomized 1:1 to either receive 10 mg/kg IV efgartigimod or placebo. The study has 2 stages: the double-blinded placebo-controlled part A, consisting of 4 once-weekly infusions and 5 weeks of follow-up, and the open-label extension part B, consisting of varying number and frequency of cycles and weekly infusions for ≤2 years.

Results: The primary endpoint is the change in MG-ADL total score from study baseline to Day 29 in part A. Additional efficacy outcomes (QMG, MG-QoL15r, EQ-5D-5L), safety/tolerability, and pharmacokinetic/pharmacodynamic effects are also being assessed.

Conclusions: This phase 3 trial will provide important data on the efficacy and safety of efgartigimod IV in the treatment of AChR-Ab- gMG.

#1001 Plasma Proteomics and Autoantibody Screening: A Tool for Patient Stratification and Monitoring Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) Treatment Responses

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Introduction: CIDP is an inflammatory neuropathy with heterogeneous presentation. Diagnosis/patient-tailored treatment decisions are hindered by lack of quantifiable molecular markers. Aberrant immune responses and circulating autoantibodies may accompany CIDP, underlying elusive pathomechanisms.

Objectives: Investigate correlation of disease states with plasma homeostasis changes in remitting/relapsing patients receiving immunoglobulin or placebo.

Methods: We analyzed plasma samples from patients with CIDP receiving hyaluronidase-facilitated subcutaneous immunoglobulin 10% (fSCIG 10%) or placebo during ADVANCE-CIDP 1 (NCT02549170). Proteomic analysis (data-independent acquisition liquid chromatography-mass spectrometry and Olink®) compared longitudinal samples from patients experiencing remission/relapse. A novel multiplex method to detect autoantibodies against 32 CIDP-relevant antigens was developed, potentially alleviating technical hurdles associated with autoantibody detection in CIDP.

Results: For >1500 plasma proteins, concentration profiles differed significantly in patients with CIDP vs healthy controls. CIDP profiles emphasized natural killer-/B-cell-mediated immune pathway involvement. When comparing remitting and relapsing patients, differences in profiles involved in extracellular matrix homeostasis, microtubule organization, tight junction assembly, and cytokine production were noted. fSCIG 10% progressively lowered proinflammatory cytokine levels vs placebo. Autoantibody profiling uncovered a CIDP signature for evaluation in larger cohorts.

Conclusion: Plasma protein dynamics were identified in patients with CIDP vs controls, providing a base for biomarker discovery. Combining plasma proteomics and autoantibody screening may identify unbiased, quantifiable biomarkers for patient stratification and/or monitoring pharmacodynamics after high-dose immunoglobulin administration.

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- **Presenting author:** Alexander Braun
- **Author disclosures:**
    - AB, MJC-D, and LS are employees of Takeda Development Center Americas, Inc., and Takeda shareholders; AMC and IB are employees of Baxalta Innovations GmbH, a Takeda Company, and Takeda shareholders; JV is an employee of Biognosys AG; BG was an employee of Baxalta Innovations GmbH, a Takeda Company, at the time of the study.

#1002 Incidence and Outcome of Meningococcal Infection With Eculizumab or Ravulizumab in Patients With gMG or NMOSD: An Analysis of US Clinical Practice

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Presenter: Chloe Sader[1]

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This abstract was originally presented at AAN Summer 2024

Introduction: Eculizumab and ravulizumab are effective treatments for generalized myasthenia gravis (gMG) and neuromyelitis optica spectrum disorder (NMOSD). Safety mitigations, including vaccinations, are used to reduce the risk of *Neisseria meningitidis* (*Nm*) infection associated with these treatments.

Objectives: To evaluate US exposure-adjusted *Nm* infection and mortality in eculizumab- or ravulizumab-treated patients with gMG and NMOSD using postmarketing pharmacovigilance data (*Nm* case counts) and commercial data (exposure).

Methods: The US Alexion safety database was searched for eculizumab and ravulizumab (data cutoff: December 2022) across approved indications (gMG, NMOSD, paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome) using the MedDRA High Level Term "*Neisseria* infection." Only *Nm*-associated cases were included. Reporting rates were calculated cumulatively per 100 patient-years (PY).

Results: US *Nm* infection and mortality annual reporting rates in eculizumab-treated patients remained stable over 15 years across approved indications (2022: 0.13 and 0.01, respectively; exposure: 29,758.4 PY). In 2022, US postmarketing *Nm* infection reporting rates in eculizumab-treated patients with gMG and NMOSD were 0.02 (exposure: 8,042.0 PY) and 0.07 (exposure: 1,470.1 PY), respectively. At data cutoff, there were no *Nm* infections among ravulizumab-treated patients with gMG. No *Nm* fatalities were noted for eculizumab- or ravulizumab-treated patients with gMG and NMOSD.

Conclusion: *Nm* infection and mortality reporting rates for patients with gMG and NMOSD remained stable despite increasing eculizumab and ravulizumab exposure over time. These results suggest US *Nm*-related risk mitigation strategies are effective in patients receiving eculizumab or ravulizumab.

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Disclosures: SP, LJ, IAD, FY, VC, HZ, and AM are employees of, and hold stock in, Alexion, AstraZeneca Rare Disease.

#1004 Long-Term Efficacy and Safety of Ravulizumab, a Long-acting Terminal Complement Inhibitor, in Adults With Anti-Acetylcholine Receptor Antibody-Positive Generalized Myasthenia Gravis: Final Results From the Phase 3 CHAMPION MG Open-Label Extension

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Presenter: Christine Borunda[8]

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This abstract was originally presented at AAN 2024

Introduction: The randomized, placebo-controlled period (RCP) of CHAMPION MG demonstrated efficacy and favorable safety of ravulizumab in anti-acetylcholine receptor antibody-positive (AChR-Ab+) generalized myasthenia gravis (gMG).

Objectives: To evaluate long-term efficacy and safety of ravulizumab in AChR-Ab+ gMG in the open-label extension (OLE; NCT03920293).

Methods: In the OLE, patients received intravenous ravulizumab (blind induction or bridging dose at Week 26 [OLE start] for those previously receiving placebo or ravulizumab, respectively) followed by a 3000 mg–3600 mg dose according to body weight at Week 28 and every 8 weeks thereafter. Assessments included Myasthenia Gravis-Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG) total scores, and safety.

Results: Overall, 161 patients (78 ravulizumab, 83 placebo in the RCP) who received ravulizumab for ≤164 weeks in OLE were included (mean treatment duration: ~2 years). Improvements in MG-ADL total score observed in ravulizumab-treated patients in the RCP were maintained (least-squares mean [LSM] change from RCP baseline at Week 164: −4.0 [95% CI −5.3, −2.8]; $p<0.0001$). Placebo-treated patients who switched to ravulizumab in OLE showed rapid improvements in MG-ADL, which were maintained through 138 weeks (LSM change from OLE baseline at Week 164: −2.1 [95% CI −3.3, −0.9]; $p<0.0005$). QMG improvements were maintained in patients continuing ravulizumab in OLE, and scores improved from OLE baseline in placebo-treated patients switching to ravulizumab. Ravulizumab was well tolerated; no meningococcal infections were reported.

Conclusions: Ravulizumab demonstrated meaningful sustained improvements in symptoms and was well tolerated for ≤164 weeks in adults with AChR-Ab+ gMG.

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#1005 Patient Preferences for Generalized Myasthenia Gravis Treatment Profiles: Results of a Web-Based Survey

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Presenter: Emma Weiskopf[1]

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This abstract was originally presented at MDA 2024

Introduction: No studies on patient treatment preferences are available for anti-acetylcholine receptor antibody-positive (AChR-Ab+) generalized myasthenia gravis (gMG).
Objectives: To understand treatment preferences of patients with AChR-Ab+ gMG and estimate relative importance of preferred treatment attributes.

Methods: US adults with a self-reported physician diagnosis of AChR-Ab+ gMG completed a web-based survey. Two object-case, best-worst scaling (BWS) exercises were analyzed. The first BWS exercise obtained preferences for a treatment profile similar to ravulizumab compared with 4 other treatment profiles (eg, similar to eculizumab, efgartigimod intravenous and subcutaneous, and zilucoplan). The second BWS exercise obtained preferences for individual attributes used to define treatment profiles. Profile scenarios were defined by mode of administration and dosing frequency only, followed by addition of consistent disease control and meningococcal vaccination requirements. The most important gMG treatment attribute was identified.

Results: Of 153 respondents, mean age was 49 years, 77% female, and 84% were White. Mean MG-Activities of Daily Living score was 8.0 (min–max: 0–17). Respondents preferred the ravulizumab-like profile vs all other profile-based scenarios: 35% vs 10%–22% when considering mode and dosing frequency, 44% vs 3%–31% when considering addition of consistent disease control, and 39% vs 5%–29% when considering all 4 attributes. Consistent disease control was most important when choosing treatment (82%), followed by mode of administration (10%), dosing frequency (6%), and meningococcal vaccination requirements (3%).

Conclusions: Patients with gMG preferred treatments with less frequent dosing schedules and consistent disease control; consistent disease control was most important when choosing a therapy.

Funding: This study is sponsored by Alexion, AstraZeneca Rare Disease.

Acknowledgments: These data were originally presented at the 2024 Muscular Dystrophy Association (MDA) Clinical & Scientific Conference; Orlando, USA; March 3–6, 2024. The authors thank the patients and their families for their participation. Medical writing support was provided Lauren A. Hanlon, PhD, CMPP, of Red Nucleus, with funding from Alexion, AstraZeneca Rare Disease.
Disclosures: KY is an employee of Alexion, AstraZeneca Rare Disease, and holds stock options in AstraZeneca. CP, CB, and KM are employees of RTI Health Solutions, which received funding to conduct this research.

#1006 Quality of Life in Generalized Myasthenia Gravis: Results From a Global Registry of Eculizumab and Ravulizumab Treatment

Christopher A. Scheiner[1], Nan Jiang[2], Gary Cutter[2], Pushpa Narayanaswami[3], Rup Tandan[4], Lida Zeinali[5], Ema Rodrigues[5], Ashley Yegin[5], Andrew Gordon[6]
Presenter: Nada Zaki[5]

[1]University of Tennessee Medical Center, Knoxville, TN, USA; [2]University of Alabama at Birmingham, Birmingham, AL, USA; [3]Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA, USA; [4]University of Vermont Medical Center, Burlington, VT, USA; [5]Alexion, AstraZeneca Rare Disease, Boston, MA, USA; [6]Northwest Neurology, Ltd., Lake Barrington, IL, USA.

This abstract was originally presented at EAN 2024

Introduction: Complement C5 inhibitor therapies (C5ITs) eculizumab and ravulizumab are approved for anti-acetylcholine receptor antibody-positive (AChR-Ab+) generalized myasthenia gravis (gMG). The global MG SPOTLIGHT Registry enrolled patients with gMG receiving C5ITs in clinical practice to assess eculizumab and ravulizumab safety and effectiveness.
Objectives: To examine quality of life (QOL) changes after eculizumab or ravulizumab initiation using Myasthenia Gravis Quality of Life 15-revised (MG-QOL15r) scores.

Methods: Enrolled registry patients were those with MG-QOL15r assessments before and after eculizumab or ravulizumab initiation. Descriptive statistics were performed and are presented here as mean (SD). Safety was assessed by evaluating frequency and type of serious adverse events.

Results: The 47/204 (23%) enrolled registry patients with available data were 60% male (aged 46.5 [20.3] years at MG diagnosis). In eculizumab-only-treated patients (n=30), the MG-QOL15r score before eculizumab initiation, 18.2 (6.9), improved to 12.2 (8.5) after 30.9 (16.1) months of treatment. Among eculizumab-to-ravulizumab switched patients (n=10), the MG-QOL15r score of 18.2 (7.9) before treatment initiation improved to 11.2 (10.6) after 29.6 (25.4) months of eculizumab and to 8.7 (9.0) after 4.6 (3.1) months of ravulizumab. The safety profile was similar to previous analyses, including clinical trial data. Limitations include low numbers of patients with MG-QOL15r data in routine clinical practice and lack of adjustment for potential confounders.

Conclusions: These initial results show that patients transitioned from eculizumab experienced further slight QOL improvements with ravulizumab, and overall, underline clinically meaningful QOL improvements in patients with AChR-Ab+ gMG treated with eculizumab or ravulizumab in clinical practice.

Funding: This study was funded by Alexion, AstraZeneca Rare Disease.

Acknowledgments: These data were originally presented at the 10th congress of the European Academy of Neurology (EAN) 2024; Helsinki, Finland; June 29–July 2, 2024. Medical writing support was provided by Genevieve Curtis, PhD, of Red Nucleus, with funding from Alexion, AstraZeneca Rare Disease.

Author Disclosures: CAS, NJ, GC, PN, RT, and AG, or their institutions, have received compensation from research and funding organizations and/or pharmaceutical companies for speaking, consulting, and contracted research. LZ, ER, and AY are employees of Alexion, AstraZeneca Rare Disease and hold stock options in AstraZeneca.

#1007 Safety and Effectiveness of Ravulizumab in Generalized Myasthenia Gravis: Evidence From a Global Registry

Pushpa Narayanaswami[1], Samir Macwan[2], James M. Winkley[3], Andrew J. Gordon[4], Michael Pulley[5], Ericka P. Greene[6], Lida Zeinali[7], Ema Rodrigues[7], Ashley Yegin[7], James F. Howard Jr.[8]
Presenter: Cynthia Massaad[7]

[1]Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA, USA; [2]Eisenhower Health Center, Rancho Mirage, CA, USA; [3]Baptist Health Medical Group Neurology, Lexington, KY, USA; [4]Northwest Neurology, Ltd., Lake Barrington, IL, USA; [5]University of Florida College of Medicine, Jacksonville, FL, USA; [6]Houston Methodist, Houston, TX, USA; [7]Alexion, AstraZeneca Rare Disease, Boston, MA, USA; [8]The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, USA.

This abstract was originally presented at EAN 2024

Introduction: Complement C5 inhibitor therapies (C5ITs) eculizumab and ravulizumab are approved for anti-acetylcholine receptor antibody-positive (AChR-Ab+) generalized myasthenia gravis (gMG).

Objectives: The ongoing, global MG-SPOTLIGHT Registry is assessing ravulizumab safety and effectiveness in patients with gMG in routine clinical practice using the MG Activities of Daily Living (MG-ADL; includes minimum symptom expression outcome) and MG Foundation of America clinical class (MGFA-CC) assessments.

Methods: This interim analysis includes ravulizumab-treated patients with MG-ADL total scores or MGFA-CC data for ≥2 time points (before and after initiating ravulizumab). Descriptive statistics were performed and presented here as mean (SD). Safety was assessed by frequency of serious adverse events (SAEs).

Results: Of 70/204 patients (63% male; aged 60.4 [19.0] years at MG diagnosis), 17 received ravulizumab only and 53 transitioned to ravulizumab from eculizumab; ravulizumab treatment averaged 3–4 months. In ravulizumab-only patients, MG-ADL score decreased from 5.8 (3.4) to 3.4 (3.3) after ravulizumab initiation; in ravulizumab-switch patients, MG-ADL scores remained stable from 3.7 (4.2) to 3.4 (3.2) following ravulizumab initiation. In ravulizumab-only patients, the 66.7% with MGFA-CC 0–II increased to 88.9% after ravulizumab initiation; in ravulizumab-switch patients, the 92.0% with MGFA-CC 0–II remained stable at 96.0% following ravulizumab initiation. Similar patterns were observed in patients achieving MG-ADL minimum symptom expression. SAEs were similar to previous findings. Limitations included no adjustment for confounders and small sample sizes.

Conclusions: In clinical practice, ravulizumab was well tolerated and effective, with improved MG-ADL and MGFA-CC outcomes after initiating ravulizumab and sustained improvements when transitioning from eculizumab.

Funding: This study was funded by Alexion, AstraZeneca Rare Disease.

Acknowledgments: These data were originally presented at the 10th congress of the European Academy of Neurology (EAN); Helsinki, Finland; June 29–July 2, 2024.
Medical writing support was provided by Genevieve Curtis, PhD, of Red Nucleus, with funding from Alexion, AstraZeneca Rare Disease.

Author Disclosures: PN, SM, JMW, AJG, MP, EPG, and JFH Jr, or their institutions, have received compensation from research and funding organizations and/or pharmaceutical companies for speaking, consulting, and contracted research. LZ, ER, and AY are employees of Alexion, AstraZeneca Rare Disease and hold stock options in AstraZeneca.

#1008 A Quantitative Study on the Patient Journey and Experience in Patients with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Multifocal Motor Neuropathy (MMN)

Chris Blair*†, Josh Feldman**, Ade Ajibade*, Chafic Karam***, Michelle Kirby*, Megan Gower*, Faisal Riaz*, Lauren Trumbull**, Brian Chen**, Jeffrey A. Allen****

**Takeda Pharmaceuticals USA, Inc., Lexington, MA, USA; **Inspire, Arlington, VA, USA; ***University of Pennsylvania, Philadelphia, PA, USA; ****Department of Neurology, University of Minnesota, Minneapolis, MN, USA*

†*Presenting author: Chris Blair*

Introduction: MMN and CIDP are life-altering peripheral neuropathies with a substantial burden.

Objectives: To understand effects of MMN or CIDP on quality of life and evaluate patients' diagnostic/treatment journeys.

Methods: This cross-sectional mixed-methods study included US adult patients with self-reported MMN or CIDP. These quantitative findings are based on an online survey developed from qualitative patient insights.

Results: Patients with CIDP (n=173) indicated more lower body symptoms (legs/feet) vs patients with MMN (n=31) (numbness/tingling, 87% vs 32%; weakness, 80% vs 58%; pain, 56% vs 16%, respectively; all $P<0.05$). Patients with CIDP or MMN reported difficulties with performing lower body strength activities and dexterous tasks, respectively. Many patients reported caregiver involvement (ie, housework, medical appointments; CIDP:61%; MMN:52%). Patients recalled experiencing symptoms >6 months before diagnosis (CIDP:51%; MMN:90%), visiting ≥3 providers (CIDP:55%; MMN:65%), and undergoing several tests. Most patients specified neurologists as the diagnosing/treating physician (CIDP:92%; MMN:97%); approximately half were neuromuscular specialists (CIDP:54%; MMN:57%). Patients often consulted other specialists to manage symptoms, although few sought mental health support. Most patients received intravenous immunoglobulin therapy (CIDP:75%; MMN:74%), resulting in frequent disruptions to travel/work (CIDP:41%; MMN:29%) and personal life (CIDP:69%; MMN:48%). Dose adjustments were common and may have hindered patients' ability to maintain treatment schedules.

Conclusions: Patients with CIDP and MMN experience burden related to diagnosis, treatment, symptoms, and functional limitations. Most patients report care fragmented across specialty providers. This study, while limited by patient-reported CIDP/MMN diagnoses, highlig=[=[=hts the need to educate providers on these neuropathies.

Funding: Takeda Pharmaceuticals USA, Inc., Cambridge, MA, USA funded the study and writing support.

Originally accepted to the Peripheral Nerve Society (PNS) Annual Meeting, June 22-25, 2024, Montréal, Canada

- **Presenting author:** Chris Blair
- **Author disclosures:**
    - **JF**, **LT**, and **BC** are employees of Inspire; **AA**, **MK**, **MG**, **CB**, and **FR** are employees of Takeda Pharmaceuticals USA, Inc., and are Takeda shareholders; **CK** has received honoraria for consulting for Takeda, Argenx, AstraZeneca, Sanofi, UCB, Alexion, Ionis, Neuroderm, Corino, and Alnylam; has received research funding from Ionis and AstraZeneca; **JAA** is a consultant for Argenx, Alnylam, Alexion, Annexon, CSL Behring, Grifols, Takeda, Immunovant, Immupharma, and Pfizer.

#1012 Design of a Clinical Program to Assess PGN-EDODM1 for the Treatment of Myotonic Dystrophy Type 1

M. Mellion*, J. Larkindale*, B. Garg*, G. Song*, P. Lonkar*, S. Babcock*, S. Vacca,* S. Yu*, J. Shoskes*
Boston, MA

Introduction: PepGen's enhanced delivery oligonucleotide (EDO) cell-penetrating peptide technology is engineered to optimize tissue delivery and nuclear uptake of therapeutic oligonucleotides. PGN-EDODM1 is being evaluated for the treatment of myotonic dystrophy type 1 (DM1). PGN-EDODM1 binds to pathogenic CUG trinucleotide repeat expansions in *DMPK* mRNA, thereby liberating MBNL1 protein through steric blocking without degrading *DMPK* transcripts. Liberation of sequestered MBNL1 is hypothesized to restore splicing profiles of multiple downstream transcripts; a central cause of DM1 pathology. Nonclinical data demonstrate that PGN-EDODM1 reduces the number of myonuclear foci (DM1 cells), liberates MBNL1 (DM1 cells), corrects mis-splicing (DM1 cells, HSA^{LR} mouse), and normalizes myotonia (HSA^{LR} mouse).

Objectives/Methods: FREEDOM-DM1, a randomized, double-blind placebo-controlled single- ascending dose study, is underway (NCT06204809). The objective of the study is to evaluate safety and tolerability (primary) and plasma pharmacokinetics (secondary) following a single dose of PGN-EDODM1 in adults with DM1. Exploratory measurements include PGN-EDODM1 skeletal muscle concentration, pharmacodynamics (changes in splicing pattern of affected transcripts), person-reported outcome (PRO) measures, and functional assessments (including video hand opening time to assess myotonia). This study consists of three dose-ascending cohorts of participants (n=8), each randomized 3:1 PGN-EDODM1 to placebo. A muscle needle biopsy will be performed at Baseline, Week 4, and Week 16 to measure tissue drug concentrations and evaluate splicing of selected transcripts.

Conclusion: The FREEDOM clinical program is designed to support and advance clinical development of PGN-EDODM1. Study designs will be presented.

#1058 Efficacy and Safety of Targeted Immunotherapy with ANX005 in Treating Guillain-Barré Syndrome: A Phase 3 Multicenter Study

Henk-André Kroon, MD[1]; Zhahirul Islam, PhD[2]; Benjamin Hoehn, MD, PhD[1]; Eric Humphriss, MBA[1]; Ping Lin, MS[1]; Glenn Morrison, MSc, PhD[1]; Jose Navarro, MD[3]; Khan Abul Kalam Azad, MBBS, FCPS, MD, FACP[4]; Dean R. Artis, PhD[1]; Ted Yednock, PhD[1]; Quazi Deen Mohammad, MBBS, MD, FCPS[5]

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[2]Laboratory of Gut-Brain Axis, icddr,b, Dhaka, Bangladesh
[3]José R. Reyes Memorial Medical Center, Manila, Philippines
[4]Dhaka Medical College and Hospital, Dhaka, Bangladesh
[5]National Institute of Neuroscience (NINS), Dhaka, Bangladesh

Introduction: Guillain-Barré syndrome (GBS) is an autoimmune disorder where an infection triggers IgM and IgG antibodies that cross-react with gangliosides in peripheral nerve components, activating C1q and the classical complement pathway. ANX005, a monoclonal antibody against C1q, blocks the entire classical complement pathway to target complement-mediated neuroinflammation and nerve damage.

Objectives: To evaluate the efficacy and safety of ANX005 compared to placebo in patients with GBS.

Methods: This phase 3, multicenter, double-blind, placebo-controlled study (GBS-02, NCT04701164) assessed ANX005 30 mg/kg and 75 mg/kg. In total, 242 patients (aged ≥16 years) diagnosed with GBS as per NINDS criteria with onset of weakness ≤10 days before infusion and a GBS-Disability Score (GBS-DS) of 3, 4, or 5 were randomized 1:1:1 to a single IV infusion of ANX005 at 30 mg/kg or 75 mg/kg or placebo and did not receive either IVIg or plasma exchange. Stratification was by muscle strength (Medical Research Council [MRC] sum score) and time from onset of weakness to infusion. No antibiotic prophylaxis was given. The primary outcome measure was trichotomy GBS-DS at 8 weeks analyzed by proportional odds logistic regression.

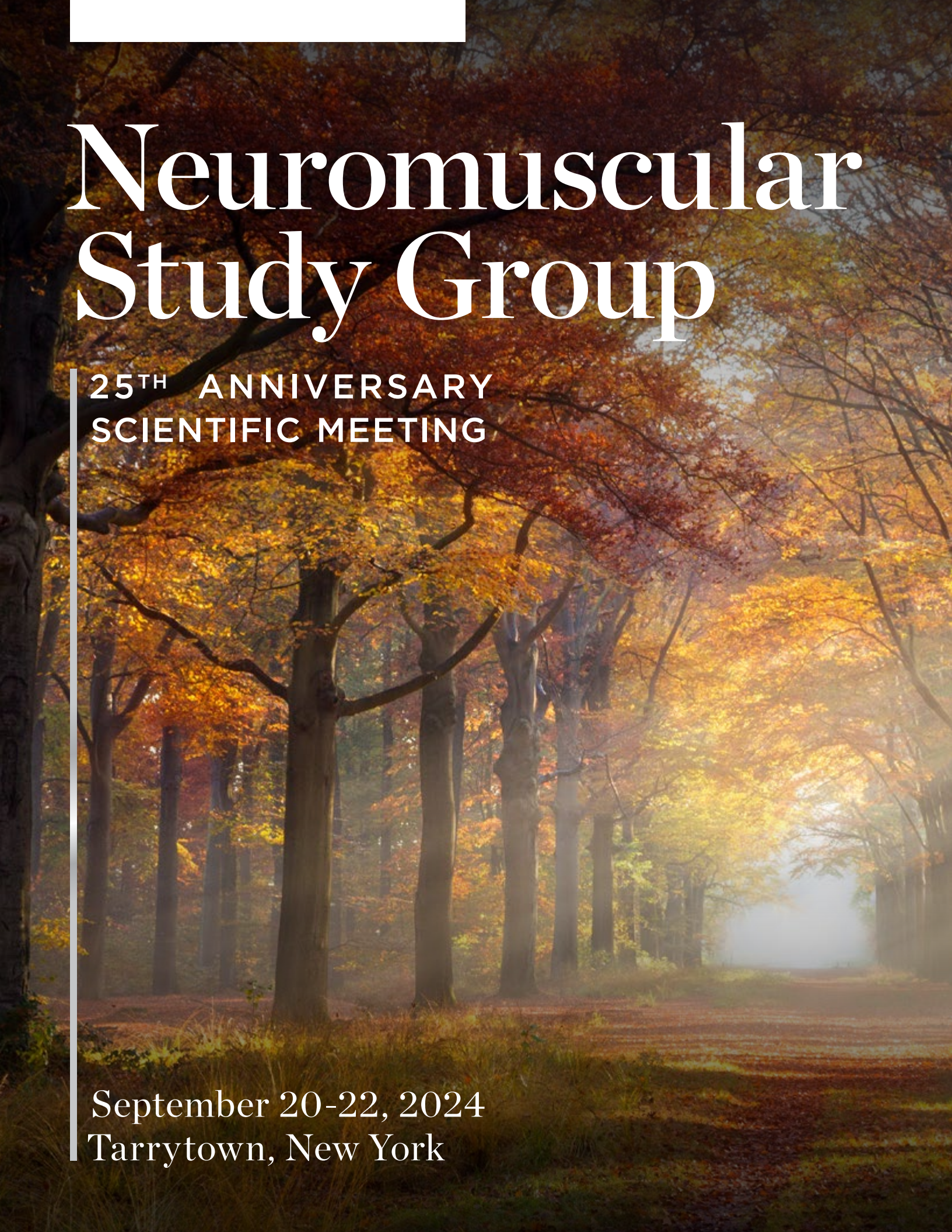
Results: ANX005 at 30 mg/kg and 75 mg/kg provided immediate inhibition of the classical complement pathway in patient serum for ~1 week and 2-3 weeks, respectively. The study met its primary endpoint by showing at least one dose (30 mg/kg) met the primary outcome measure of patients being 2.4-fold more likely to be in a better health state at Week 8 based on the GBS-DS (adjusted common odds ratio [OR], 2.4 [95% CI, 1.29-4.50; p=0.0058]). At weeks 1 and 4, the odds of being in a better health state on GBS-DS were 7.2 (95% CI, 3.07-16.96; nominal p<0.0001) and 2.5 (95% CI, 1.28-4.86; nominal p=0.0073), respectively. Assessed over 26 weeks, the common OR was 1.5 (95% CI, 1.091-2.044; p=0.0122). At the end of study, 2.5× as many patients treated with ANX005 compared to placebo were normal (GBS-DS=0; OR, 4.1; 95% CI, 1.422-12.04; p=0.0092). Compared with placebo-treated patients, ANX005-treated patients were able to walk independently a median of 31 days earlier (p=0.0211) and were off ventilator support a median of 28 days earlier (p=0.0356). ANX005 treatment resulted in an early reduction of 11.2% in serum neurofilament light chain levels, a biomarker of nerve damage, vs placebo between weeks 2-4 (p=0.03). The safety profile of ANX005 was similar to placebo, with serious adverse events (AEs) and ≥grade 3 AEs balanced across groups. Transient infusion-related reactions, for which premedication was given, occurred in 25.3% of patients. There was no impact on mortality and no difference in overall infection rates between treatment groups.

Conclusions: ANX005 30 mg/kg effectively and quickly inhibited C1q, leading to a significant and sustained improvement in patient function compared to placebo. This benefit was observed across 6 months, demonstrating a consistently better health status for patients. A single dose of ANX005 was well

tolerated, with a safety profile similar to that of placebo. As the first targeted immunotherapy to show a positive treatment effect in GBS, ANX005 has the potential to transform GBS management.

Supported by: Annexon Biosciences, Inc.

Acknowledgements: The authors would like to thank study coordinators and physicians for their contributions to this abstract and study.



Neuromuscular Study Group

25TH ANNIVERSARY SCIENTIFIC MEETING

September 20-22, 2024
Tarrytown, New York

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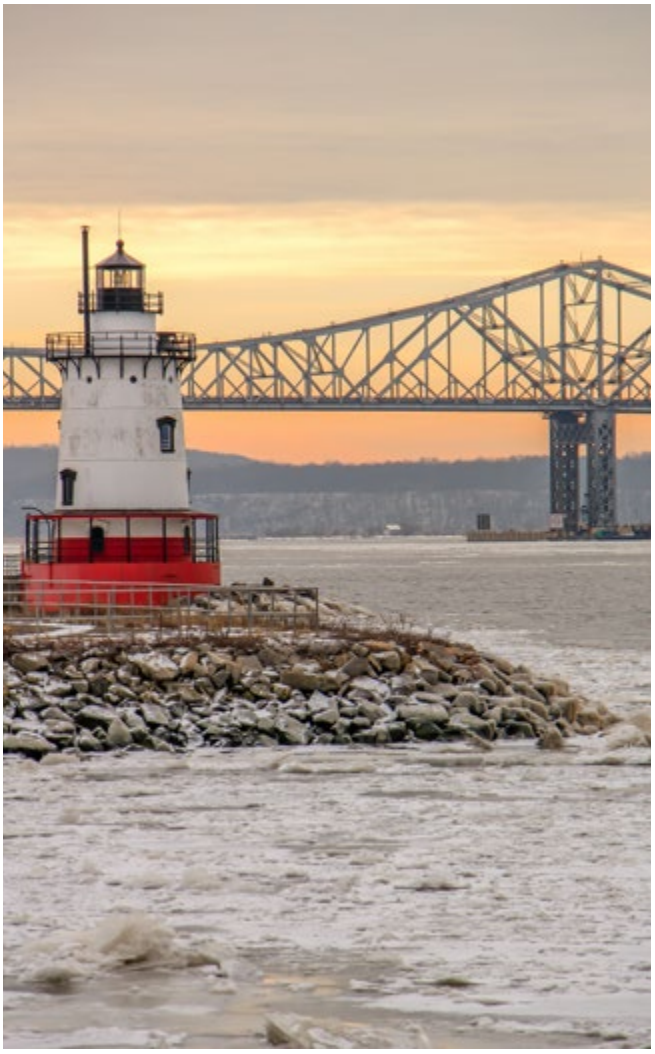
Information

WIFI

The NMSG has a unique WiFi access for meeting attendees.

This network can be used in the Duke Buildings:
Network name: **NeuromuscularStudyGroup**
Password: **25YearsOfProgress**

Hotel WiFi is also available:
Network name: **Tarrytown Wifi**
Click **Connect**



SATURDAY DINNER

Dinner on Saturday night will be outdoors on the Duke Terrace, after the conclusion of the Keynote Speaker. After dinner we will have dessert and a reception at the same location.

Dress for the evening is business attire.

SUNDAY MORNING COFFEE

7:15 - 9:15 A.M.
Please join us right outside the Mary Duke Ballroom for specialty coffees from the Espresso Guys!

Hot or Iced
Espresso, Cappuccino, Cafe Latte, Flat White, Mocha, Cortado, Cold Brew, Chai Latte, Hot Chocolate

Milk Options
Whole, Skim, Oat, Almond

Flavors
Vanilla, Hazlnut, Caramel

SPEAKERS/PRESENTERS

Our event producer, Gill, will be at the back of the Mary Duke Ballroom general session room the entire meeting. Please bring your presentation to him the morning of your session.

Our technical staff will assist you with any audio/visual needs you may have.

POSTERS

The poster exhibition is located in the Tarrytown Room in the Carriage House, located on the north side of the property.

Walk through poster session:
Friday, September 20, 5:30 - 7:30 p.m.

Please set up your poster in the Tarrytown Room 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

25TH ANNUAL NEUROMUSCULAR
STUDY GROUP SCIENTIFIC MEETING

THURSDAY, SEPTEMBER 19

6:00 – 9:00 pm
Dinner and Check In
WINTER PALACE

DAY 1: FRIDAY, SEPTEMBER 20

7:00 – 8:00 am
Buffet Breakfast
WINTER PALACE

Check In
DUKE MANSION

8:00 – 8:20 am
Welcome and State of the Neuromuscular Study Group
Dr. Richard Barohn and Prof Michael Hanna

SESSION I: GENETICS

Moderators: Karlien Mul, M.D., Ph.D., and Dr. Vino Vivekanandam

8:20 – 8:40 am
Gene Therapy for DM.D. and SMA: milestones, lessons learned and current challenges
Emma Ciafaloni, M.D., *University of Rochester*

8:45 – 9:05 am
Overview of potential genetic treatments for FSHD
Scott Harper, Ph.D., *Nationwide Children's Hospital*

9:10 – 9:30 am
Genetic Therapeutics in neuropathies/CMT
Mario Saporta, M.D., Ph.D., *University of Miami*

9:35 – 9:55 am
Genetic Therapeutics in Myotonic Dystrophy
Charles Thornton, M.D., *University of Rochester*

10:00 – 10:20 am
Neuromuscular genetic therapies COL6, HSN1
Dr. Haiyan Zhou, *University College London*

10:25 – 10:40 am
Refreshment/Exhibitor Break

SESSION II: FLASH PRESENTATIONS

Moderator: Brendan McNeish, M.D.

10:40 – 10:50 am
Refractory myasthenia gravis characterised by widespread innate and adaptive immune system changes
Katy Dodd, MBChB, MRCP,
Manchester Centre for Clinical Neurosciences

10:52 – 11:02 am
Remote monitoring to improve adherence to physical exercise: pilot experience at the NeMO site
Michela Nani, RN, *NeMo Clinical Center, Milan*

11:05 – 11:15 am
Trial of Oxaloacetate in ALS, TOALS
Katie Lillig, BS, *University of Kansas Medical Center*

11:17 – 11:27 am
Outcome Measures to Quantify Longitudinal Changes in Motor Function in FHD
Lawrence Hayward, M.D., Ph.D., *UMASS Med*

11:30 – 11:40 am
Treatment effects on ambulation loss in Spinal Muscular Atrophy Type III: insights from the Italian ISMAC registry
Giorgia Coratti, TNPEE, MsC, Ph.D.
Catholic University of Sacred Heart Fondazione Policlinico Universitario Agostino Gemelli IRCCS

11:42 – 11:52 am
The Myasthenia Gravis Patient Registry: Characteristics, Insights, and Learnings After a Decade (2013-23)
Kelly Graham Gwathmey, M.D.,
Virginia Commonwealth University

12:00 – 1:00 pm
Lunch Buffet
WINTER PALACE

NMSG Executive Committee Meeting Breakout Lunch
MUSIC ROOM

SESSION III: PLATFORM PRESENTATIONS

Moderator: Amanda C. Guidon, M.D., MPH

1:00 – 1:15 pm
Co-designing a Strategy to Engage People with Neuromuscular Diseases from Racially Minoritized Backgrounds in Research
Gita Ramdharry, Ph.D., MSc, PGCert, BSc(Hons), MCSP
University College London

1:20 – 1:35 pm
A Study of the Common Factors that Influence Fatigue in Myasthenia Gravis
Kelly Graham Gwathmey, M.D.,
Virgina Commonwealth University

1:40 – 1:55 pm
Combined personalized home-based aerobic exercise and coaching to improve physical fitness in neuromuscular diseases — a multicenter, single-blind, randomized controlled trial
Eric Voorn, Ph.D., *University of Oxford*

2:00 – 2:15 pm
An analysis of Mortality Rates and Causes of Death in an Oxford Cohort of Adult Myasthenia Gravis Patients
Dr. Pietro Zara, *Amsterdam UMC*

2:15 – 2:30 pm
Refreshment/Exhibitor Break

SESSION IV: YOUNG INVESTIGATOR/ EVALUATOR/COORDINATOR

Moderators: Dr Michael Hehir, Dr. Vino Vivekanandam, Prof Valeria Sansone, and Dr. Karen Suetterlin

2:30 – 4:30 pm
Clinical research lessons from intramural NINDS: building our field of dreams
Lauren Reoma, M.D., FAAN
Deputy Clinical Director, NINDS
Director, NINDS Clinical Trials Unit

NMSG Resources, Fellowships

Breakouts

5:30 – 7:30 pm
Abstract Poster Session
CARRIAGE HOUSE, TARRYTOWN ROOM

7:30 – 9:00 pm
Buffet Dinner
WINTER PALACE

9:00 – 11:00 pm
Reception
WEST TERRACE

DAY 2: SATURDAY, SEPTEMBER 21

7:00 – 8:00 am
Buffet Breakfast
WINTER PALACE

Meet the Experts Breakfast

8:00 – 8:15 am
Opening
Dr. Barohn and Prof Hanna
MARY DUKE BALLROOM

SESSION V: NMS AND THE BODY

Moderator: Dr. Kathy Mathews

8:20 – 8:40 am
More than Muscles: Non Motor Manifestations of Neuromuscular Disorders
Julie Parsons, M.D., *Children's Hospital Colorado*

8:45 – 9:05 am
Cognitive SMA
Valeria Sansone, M.D., Ph.D., *NeMO Milan*

9:10 – 9:30 am
Cognitive involvement/deficits in myotonic dystrophy in children and adults
Nick Johnson, M.D., *Virgina Commonwealth University*

9:35 – 9:55 am
Cardiomyopathies in the Muscular Dystrophies
Carol Wittlieb-Weber, M.D., *Children's Hospital of Philadelphia*

10:00 – 10:15 am
Refreshments/Exhibitor Break

SESSION VI: NEUROPATHY

Moderator: W. David Arnold, M.D.

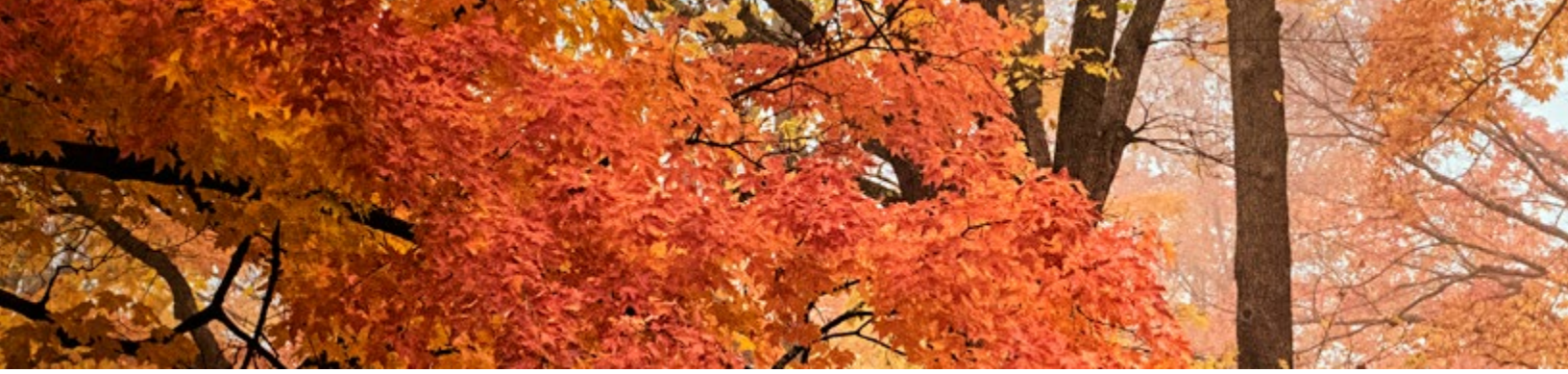
10:20 – 10:40am
Cryptic splicing: from foe to friend in tackling ALS and IBM
Pietro Fratta, M.D., Ph.D.
University College London and Francis Crick Institute

10:45 – 11:05 am
Overview and Advances in the work up and Management of Immune Mediated Peripheral Neuropathies
Karissa Gable, M.D., *Duke University School of Medicine*

11:10 – 11:30 am
Peripheral nerve imaging in CMT
Reza Seyedsadjadi, M.D., *Massachusetts General Hospital*

11:30 am – 1:00 pm
Lunch
WINTER PALACE

NMSG 2025 planning committee meeting breakout lunch
MUSIC ROOM



SESSION VII: CLINICAL TRIALS DESIGN

Moderators: Dr. Michael Hehir and Dr. Vino Vivekanandam

1:00 - 2:20 p.m.
Clinical Design Presenations

Life of Clinical Trials
Gordon Smith, M.D., FAAN
Virgina Commonwealth University

N-of-1 Trials for Personalized Medicine
Mike McDermott, Ph.D., *University of Rochester*

Greener Trials
Dr. Vino Vivekanandam, MBBS(Hons), FRACP
University College London
Queen Square Institute of Neurology

Trial Delivery and Logistics
Matt Parton, MB, BChir, FRCP, Ph.D.

Recruiting/Engaging Pediatric Participants
Kathy Mathews, M.D., *University of Iowa*

Starting a Platform Trial – helpful tips
Merit Cudkowicz, M.D., MSc
Massachusetts General Hospital, Harvard Medical School

2:05 – 2:20 pm
Panel Q&A

2:20 – 2:50 pm
Refreshments/Exhibitor Break

SESSION VIII: INDUSTRY PRESENTATIONS

Moderator: Michael Hehir, M.D.

2:50 – 3:10 pm
Rare Disease Connect in Neurology (RDCN):
An international MG community and forum providing needs-driven medical education
James F. Howard, Jr., M.D., FAAN
Director, Myasthenia Gravis Clinical Trials and Translational Research Program, The University of North Carolina at Chapel Hill

3:15 – 3:35 pm
Precision Genetic Medicines for Patients with Rare Neuromuscular Diseases
Damon Asher, Ph.D.
Senior Director, GMAL GT Team Lead, Sarepta Therapeutics

3:40 – 4:00 pm
A spotlight on the argenx pipeline: Innovation in the development of treatments for neuromuscular disease
Jeffrey Guptill M.D., MA, MHS, FAAN
Neuromuscular Franchise Lead, Clinical Development, argenx

4:05 – 4:25 pm
Exploring Corticosteroid Structure and Function in DMD
Omer Abdul Hamid, M.D.,
Nemours Children's Health | Orlando, Florida

4:30 – 4:50 pm
CHAMPION MG and Open-Label Extension Trial in Adult Patients with Generalized Myasthenia Gravis who are Anti-Acetylcholine Receptor Antibody-Positive
Gordon Smith, M.D., FAAN, *Virginia Commonwealth University*

4:55 – 5:15 pm
Efficacy and Safety of Targeted Immunotherapy with ANX005 in Treating Guillain-Barré Syndrome: A Phase 3 Multicenter Study
Henk-André Kroon, M.D., SVP
Head of Translational Medicine, Annexon Biosciences

FELLOW AND KEYNOTE PRESENTATIONS

Moderator: William David, M.D., Ph.D.

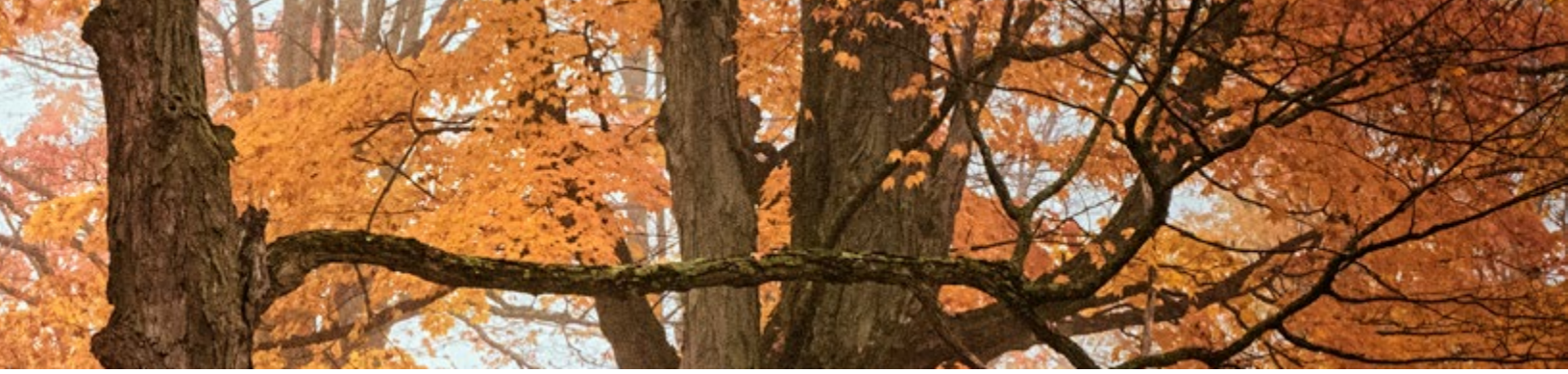
7:00 – 8:15 pm
NMSG Research Presentation: Development of Novel Imaging Biomarkers for use in Pediatric Facioscapulohumeral Muscular Dystrophy
Natalie Katz, M.D.
NMSG Fellow, Duke University

Robert C. Griggs Annual NMSG Keynote Presentation:
ALS Updates: new treatments and trial approaches
Merit Cudkowicz, M.D., MSc
Massachusetts General Hospital, Harvard Medical School

8:15 – 8:30 pm
Group Photo
OUTSIDE BIDDLE MANSION

8:30 – 9:30 pm
Outdoor Buffet Dinner
DUKE TERRACE

9:30 – 11:00 pm
Evening Reception
DUKE TERRACE



DAY 3: SUNDAY, SEPTEMBER 22

7:00 – 8:00 am
Breakfast
WINTER PALACE

7:15 - 9:15am
Specialty Coffees from the Espresso Guys
OUTSIDE THE MARY DUKE BALLROOM

8:00 – 8:10 am
Opening
Dr. Barohn and Prof Hanna
MARY DUKE BALLROOM

SESSION IX: FATIGUE FOR THE FATIGUED

Moderator: Jacqueline Montes, PT, EdD

8:10 – 8:30 am
Beyond weakness; the unyielding characteristic of fatigability in SMA
Jacqueline Montes, PT, EdD
Columbia University Irving Medical Center

8:35 – 8:55 am
Pain, fatigue and exercise in neuromuscular diseases: start low and go slow
Nicole Voet, M.D., Ph.D., *Radboud University*

9:00 – 9:15 am
2023 Shark Tank Award update — Perceived Fatigability Tracker: Improving Assessment to Enhance Spinal Muscular Atrophy (SMA) Patient Outcomes
Ralph Rodriguez-Torres, DPT, *Columbia University*

SHARK TANK SESSION

Moderator: Aziz Shaibani, M.D., FACP, FAAN, FANA

Shark Panel: Dr. James Lilleker, Senda Ajroud-Driss, M.D., Dr. Amanda Guidon, Gordon Smith, M.D.

9:20 – 11:00 am
Shark Tank Presentations

MAPP: MRI as a biomarker in Periodic Paralysis. A prospective longitudinal pilot study in periodic paralysis
Dr. Murva Asad, *University College London*

Is a mucosal trigger responsible for MuSK myasthenia gravis?
Gianvito Masi, M.D., *Yale University*

Fluctuations in Liver and Renal Function Tests in Myotonic Dystrophy Type 1 (Dml): When Should We Worry
Carola Rita Ferrari Aggradi, M.D.
NeMO Clinical Center, Neurorehabilitation Unit

Efficacy and Safety of Low Dose of anti-CD20 Therapy for New Onset Acetylcholine Receptor Antibody Positive Myasthenia Gravis in Older Adults
Pietro Zara, M.D., *Nuffield Department of Clinical Neurosciences, University of Oxford*

SESSION X: AI

Moderator: Karlien Mul, M.D., Ph.D.

11:00 – 11:20 am
AI-Enhanced Insoles for Accurate Kinematic and Kinetic Gait Monitoring in SMA and DM.D.
Damiano Zanotto, Ph.D., *Stevens Institute of Technology*

11:25 – 11:45 am
AI Tools in Muscle MRI Segmentation and Diagnosis
Jasper Morrow, Ph.D., *UCL*

11:50 am – 12:10pm
Towards Better Understanding of ALS using a Multi-Marker Discovery Approach from a Multi-Modal Database
Xing Song, Ph.D., *University of Missouri*

12:15 – 12:35am
AI methods for integrating multi-omics data and inferring gene regulatory networks
Jianlin Cheng, Ph.D., *University of Missouri*

Shark Tank Winner Announcement

Final Remarks

12:35 – 1:30pm
Lunch
WINTER PALACE

Meeting Support

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TARGETING BOTH RARE & LARGE PATIENT POPULATIONS

CANDIDATE	DESIGN	FRANCHISE/INDICATION	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	ANTICIPATED MILESTONES
FLAGSHIP PROGRAMS							
ANX005	IV mAb	Guillain-Barre Syndrome (GBS)					RWE & BLA submission 1H25
ANX007	IVT Fab	Geographic Atrophy (GA)					Initiate Phase 3 ARROW trial in 2H 2024 Archer II data 2H 2026
ANX1502	Oral small molecule	Autoimmune indications					POC 2H 2024
NEXT WAVE PROGRAMS							
ANX005	IV mAb	Huntington's Disease (HD)					Poised for late-stage phase 2b/3 development
		Amyotrophic Lateral Sclerosis (ALS)					Poised for late-stage phase 2b/3 development
ANX1502	Oral small molecule	Lupus nephritis (LN)					Evaluating options for future development

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A spotlight on the argenx pipeline:

Innovation in the development of treatments for neuromuscular disease

argenx at 2024 NMSG Annual Scientific Meeting

3:25–3:45 pm, Saturday, September 21, 2024

Mary Duke Ballroom, Tarrytown House Estates, Tarrytown, NY

We bring together our antibody engineering expertise and pioneering researchers to translate immunological breakthroughs into differentiated therapies for rare diseases.

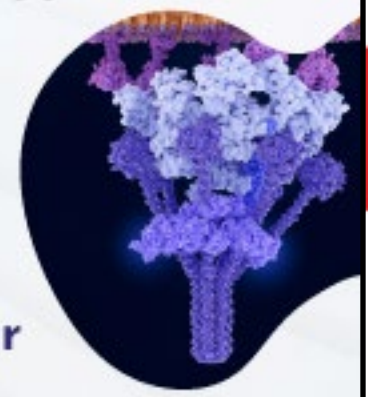
Visit the argenx medical booth to learn more

Join us at our industry-sponsored presentation showcasing the latest developments in our pipeline across a range of neuromuscular diseases, including CIDP, myositis and MMN. We will focus on their proposed mechanisms of action and ongoing clinical trials.

Jeffrey T. Guptill (Speaker)
Neuromuscular Franchise Lead, Clinical Development, argenx

CIDP, chronic inflammatory demyelinating polyneuropathy; MMN, multifocal motor neuropathy; NMSG, Neuromuscular Study Group.
This presentation is funded and organized by argenx and is intended for healthcare professionals only.
MED-US-NON-2400075 | August 2024

DIANTHUS THERAPEUTICS



Dianthus is Honored to Support the Neuromuscular Study Group

For more information or to join our clinical studies in **gMG, MMN and CIDP** as an investigator, please contact us at **clinicaltrials@dianthustx.com**

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The FDA has increased the maximum total daily dose for FIRDAPSE from 80 mg to 100 mg for adult patients and 40 mg to 50 mg for pediatric patients weighing less than 45 kg.[1]

Learn more about this dosing update and what it might mean for your patients with LEMS.

INDICATIONS AND USAGE:
FIRDAPSE is a potassium channel blocker indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults and pediatric patients 6 years of age and older.

SELECTED IMPORTANT SAFETY INFORMATION
FIRDAPSE can cause seizures. Consider discontinuation or dose-reduction of FIRDAPSE in patients who have a seizure while on treatment.

Please see full Prescribing Information.

Reference: 1. Full Prescribing Information for FIRDAPSE (amifampridine). Catalyst Pharma; 2024.

FIRDAPSE (amifampridine) Tablets 10 mg

Catalyst pharmaceuticals

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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.v5i2**

RRNMF NM JOURNAL

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SEPTEMBER 26-28, 2025

26TH NMSG ANNUAL MEETING
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and close June 1, 2025.

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