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RRNMF
RICK'S REAL NEUROMUSCULAR Friends

Cover Image: *Giuliano de' Medici* by Sandro Botticelli.

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Letter from the Founding Facilitator for Volume 3, Issue 3

Dr. Richard J. Barohn, MD

We, the RRNMF NM Journal team, are glad to publish Volume 3, issue 3 of the journal. This is the third year we are privileged to publish the abstracts and proceedings of the annual Neuromuscular Study Group, which is being held in northern Italy from Sept 30 to Oct 2. We changed the organization's name from the MSG to the NMSG to reflect that we are home to not only muscle researchers but also researchers in the field of motor neuron disease and peripheral neuropathy. This year the meeting has an all-time high number of registered participants and abstracts. I am sure it will be an exciting event in a beautiful part of the world.

We also have another packed issue with many exciting publications. My good friend Josh Freeman has again allowed us to publish his wonderful pieces from his blog. We have decided to publish two of his great editorials in our What's on Your Mind forum. Another well-known family medicine physician, Dr. Don Frey, also has a blog site, and in this issue, we publish another of his pieces.

I asked another good friend, Bud (Vernon) Rowe, for more examples of his creative writing. He has provided us with another poem and a short prose piece which I am sure you will enjoy.

This issue is loaded with Clinic Stuff. Dr. Wright from the University College London Hospitals has an interesting case of recurrent rhabdomyolysis in the setting of autosomal dominant scoliosis. A transthyretin mutation case presenting as a small fiber neuropathy is from Dr. Desai and the team at Vanderbilt. An atypical limb-girdle presentation of myasthenia gravis is from Dr. Luster and the military neurology team in San Antonio.

A Case of CIDP with IgG tubulin autoantibodies comes from the Dr. Giacobbe group at the University of Pittsburgh. Dr. Zachary McKee and our distinguished Associate Editor, Dr. Yuebing Li, at the Cleveland Clinic have three lymphoma cases with engaging neuromuscular and neurologic presentations. Drs. Hans, Dimachkie, and Bhai have a very novel case of exercise-induced rhabdomyolysis due to mitochondrial pathogenesis, which required both cycle exercise testing and DNA analysis from the muscle tissue to confirm a diagnosis. And finally, Dr. Nakul Katyal was a senior neurology resident with me and Dr. Ensrud at U of Missouri when we saw a patient in the clinic with what we believe is primary lateral sclerosis and who had the ear of the lynx sign on MRI. Most cases published with this interesting MRI finding have had hereditary spastic paraparesis. There is a wide range of clinic stuff to learn from.

We already have most of the manuscripts for Vol 3, issue 4, which we plan to publish in late November or December. Please continue to send in your cases and new stuff manuscripts. Also, do not forget to send us your grants and critiques on whether or not the grant was funded. To date, only our neuromuscular group in Missouri/Kansas has taken advantage of this unique publishing opportunity.

The art on the cover is a famous painting of Giuliano de' Medici by Sandro Botticelli. It is in the National Portrait Gallery in Washing, DC (the Smithsonian). It is a wonderful painting. And it is appropriate to have this on the journal's cover of the issue when we publish the abstracts and information about the annual Neuromuscular Study Group (NMSG) meeting that is being held in Italy, just north of Milan. The Medici family were the rulers of Florence in Tuscany in the 1400s and 1500s. Giuliano de' Medici (1453-1478) was the co-leader of Florence with his brother Lorenzo until he was assassinated. Giuliano was a great patron of the arts.

Hope to see many of you in Italy for the NMSG. If you want to stream the NMSG meeting contact Liz Paulk (epaulk@kumc.edu).

- Rick

Why do we have to wait so long to see the doctor? It's all about the money...

Joshua Freeman MD

I have seen a number of articles describing the difficulty of getting doctor's appointments in the era of COVID-19. In many parts of the country, it was difficult to get a quick appointment even before the pandemic, but it has become much worse. I hear from friends in several different cities that they cannot get into their doctors' offices for weeks or, commonly, months. This is not OK for routine care; it is certainly not ok when something urgent, or relatively urgent, or even a little bit "needs to happen before I get really sick" is going on. A recent article in the *Wall Street Journal* by Devorah Goldman ('The doctor's office becomes an assembly line', December 30, 2021) describes a woman who came to her father's Brooklyn office from New Jersey because she couldn't get an appointment for 8 months!

There are Emergency Rooms, of course, but waiting (frequently for hours!) in them increases your risk of acquiring COVID infection. And, as in "regular" times, they should be for emergencies, not for care for chronic or minor acute disease. Of course, if you cannot get regular care for your chronic disease, it can become an emergency. And, as I have written before (Emergency services, COVID, and the health system: Your life could well be at risk, Jan 19, 2021), when you have an emergency, like a ruptured appendix, waiting in an ER for hours is also very dangerous, and the more "non-emergent" people waiting the more likely this is to happen. There are Urgent Care Clinics, but these have their own issues: they can only take care of a limited (and variable by location) menu of problems, most of which are those your mother used to take care of, and they may not take your insurance (if you have it). Also, the prices and profit margins are very high.

So why are the waits so long, and what can be done about it? Goldman's emphasis is the takeover of physician private practices by hospital systems and large groups; she notes that, according to the AMA, 75% of physicians owned their own practices in 1983, but by 2018 it was 46%. This is part of the problem; even if an individual physician is compassionate and caring, the big corporation they work for probably is not. Another part is the maldistribution of physician specialists. Studies of efficient and effective health care systems indicate that 40-50%+ of physicians should be in primary care, seeing people for most problems, providing continuity of care for a patient panel, and diagnosing "undifferentiated patients" (those who do not have a specific diagnosis) and caring for them or appropriately referring them. In the US, however, it is less than 30% and dropping. Quite reasonably, subspecialists want to see people with the problems that they know how to take care of; this works well when they are referred by family physicians and other primary care clinicians, and much less well when people have to self-refer, essentially having to diagnose themselves. Such direct self-referral also backs up the subspecialist practices with patients whose problems could have been well taken care of by a primary care clinician (not everyone with a heart needs a cardiologist!) making it more difficult for those with complicated or rarer conditions that need the subspecialist's care to get in. Medicare's reimbursement method figures prominently in Goldman's article; she identifies ways that it tends to give preference (i.e., pays more) to large, and especially hospital-owned, medical groups. And, of course, since COVID the demand for care has gone up, and the number of clinicians available (because of sickness and overwork) has gone down.

Many other articles claim to provide the reasons for this problem, and some even have proposed solutions, but most of them examine only one aspect of it. I am reminded of the old Indian story about the blind men and the elephant, each touching a different part of the beast and thus presuming, based on contact with the trunk, the tail, or a leg, that they knew what the whole elephant looked like. Often this is influenced by the agenda of the writer and whether (like, e.g., Goldman) they get their information mainly from groups like the AMA ("oh, for the days of physician-owned private practice!"), hospital associations ("consolidation is good!"), government agencies ("reimbursement policy is governed by competing needs"), or academics, think tanks, or nonprofits like the Commonwealth Fund, Kaiser Family Foundation, and Pew Trusts, often with their own biases. To me, it is clear what the whole elephant looks like, what is the common factor in this equation, what can be seen behind all the decisions that have led us to where we are (and continue to make it worse) and, by implication, could show us the way out: Money. Corporate profit.

We live in a profit-driven capitalist society. More than that, we have moved well beyond simple "Adam Smithian" capitalism to what Noam Chomsky identifies as "gangster capitalism". In this stage, merely making money is not sufficient – the only goal becomes to make ever more money, by any and every means possible, no matter who, or what is destroyed. This includes people, animals, plants and the earth itself -- it hurts, screws, destroys, even though neither those who control it, nor their descendants could ever spend it all. Fewer and fewer people control more and more, and it would be naïve to assume this is not the case in health care.

Virtually all the systemic bad things (as opposed to the much less common individual error) in healthcare derive

from corporate owners' efforts to make more money, and to game the system to maximize profit. While huge practice groups owned by hospitals or investors *could* operate more efficiently to improve both the quality of and access to care for patients, they don't since they are interested in squeezing every dollar of profit. Conversely, small physician-owned practices *could* do better than they do, but often, in pursuit of income, do not care for significant portions (poor, uninsured, badly insured) of the population. Explicitly for-profit (as opposed to ostensibly non-profit, but still fixated on making as much as possible) healthcare entities, whether large hospitals and hospital systems or more 'niche' services like dialysis, physical therapy, and long-term care, are the worst. There is certainly plenty of blame to go around – healthcare systems blame insurance companies for not paying them enough and insurance companies blame healthcare systems for demanding too much, but both are seeking to earn money for themselves, not to ensure all people get the highest quality health care.

Pharmaceutical companies are notoriously rapacious. For example, see Aduhelm® (FDA approves Alzheimer's drug against the recommendation of its scientific panel. Be very concerned, June 21, 2021); every (60 million!) Medicare recipient's Part B payments will now rise $11/month so some Alzheimer's patients can receive this drug that, though probably ineffective, costs a huge amount (now, graciously, reduced to only $28,200/year!). It was approved by the FDA over the recommendation of its scientific advisory panel in a move completely reminiscent of the fraudulent labeling of Oxy-Contin® described in the film "Dopesick", which I recently discussed ("Dopesick": The story of the marketing of killer opioids will really make you sick. Don't trust any of them!, Dec 7, 2021).

I have often advocated for a single-payer health insurance system, such as Medicare for All. The advantage of this would be that 1) everyone in the US is covered, and 2) everyone in the US has the SAME coverage. The second is not a minor point, as it means that the educated and powerful will make sure it works, also helping the disenfranchised and disempowered. A universal health insurance system (or something comparably effective) is necessary, but not sufficient. Medicate for All needs to be an improved and expanded Medicare, as described in the bills introduced by Sen. Bernie Sanders, Rep. Pramila Jayapal and others. (See this good analysis by Sen. Sanders on the "Vulgarity" of the US health system.) It must be *expanded* to cover not only everyone but everything (mental health, dental, vision, hearing, long-term care) and *improved* to cover them completely without co-pays, co-insurance, deductibles. This will eliminate the flaws Goldman describes in Medicare payments.

Since we already spend 2-3x as much per capita on health care as any other wealthy country, including premiums, deductibles, co-pays, government benefits, and the profits and administrative costs sucked out of the "healthcare" pool by insurers and providers, we don't even need to tax the richest a lot more to pay for it. We just need to spend it on actually providing healthcare! Not that we shouldn't make the billionaires and corporations pay at least their fair share of taxes; we can use that money to provide adequate housing, food and education to all our people – really, the biggest factors in health.

Don't get distracted by the circuses and diversions created by those with a profit-motivated dog in the fight. Profit has little place in healthcare. Obscene profit has none.

Direct Contracting Entities: Scamming Medicare and you and bad for your health!

Joshua Freeman, MD

On October 25, 2021 I wrote about 'Medicare Advantage, Direct Contracting Entities, and other scams to transfer your money to insurance companies'. In the interim, it has become clear that the impact, and even existence, of DCEs is not well known among Medicare recipients, physicians, members of Congress, and many policy analysts. Indeed, it involves a lot more than insurance companies, particularly "private equity" (a newish term for "venture capitalists" including hedge funds, that maybe sounds better). While DCEs are still an 'experimental' program by the Centers for Medicare and Medicaid Innovation (CMMI) it is significant that the Biden administration has continued this Trump-initiated policy. As, presumably, part of its experimental nature, it has not had much publicity; few Medicare recipients know about it and it is just getting known to Congress, particularly with Senate Finance Committee hearings on February 2, 2022. It is probably worth calling attention to again, even if this piece repeats some of what I wrote in October.

Medicare was established in 1965, and the first two cards were issued, by President Johnson, at the Truman Library in Independence, MO to Harry and Bess Truman, in recognition of Truman's efforts to pass national health insurance during his presidency. It meant that for the first time in American history, older adults would not suffer and die just because they could not afford medical care. It remains, along with Social Security, the most popular program in the US, in every poll, by almost everyone (except of course the rich elites, who believe the best programs are the ones that funnel money directly into their pockets, but more on that later).

Medicare has been a rousing success, but there are two problems. The real and serious problem, as seen from the point of view of Medicare recipients, or for that matter anyone who claims to be a decent non-narcissistic human being, is that it does not comprehensively cover health care costs. For starters, there are several important health conditions it does not cover, including vision, hearing, and long-term care. Also, even for the conditions (most hospitalizations and office visits) it does cover, it does not cover the entire cost. Generally, for hospitalization, it covers 80% of the Medicare-approved fee (which is always less than hospital charges, but which is in fact all the hospital can charge Medicare patients). This puts patients on the hook for the other 20%, which as anyone who has been hospitalized knows can be a lot of money.

The other problem, perceived as egregious by the small but powerful group of very wealthy investors (not regular people at all) is the same as with all effective government programs: it doesn't put money in *their* pockets. Medicare is funded by different sources; Part A is for hospitalization and comes from the Medicare tax on your paycheck. Part B is for outpatient care and is funded from general revenue funds, plus a monthly charge to Medicare recipients (a minimum of about $135 now, which can go quite a bit higher for high-income people and be waived for low income). Part D is the drug plan that each recipient is required to buy. We'll talk about Part C later.

Medicare, as a public (government) program that is in the business of paying for health care rather than generating shareholder profit operates very efficiently, with about a 2% overhead for administrative costs. As a taxpayer, I'd think this is good. But for the small number of powerful wealthy investors (for short, let's call them GNPs, for Greedy Narcissistic Pukes) it represents an opportunity; if they could control it they could reap profit from it!

So, of course, while the fact that it is not making rich people even richer is not a problem for most of us, the problem we have is the *solution* that the government has come up with in service to the GNPs. It has been regularly altering Medicare to help them make money from it. First Congress created Medicare Part C, or Medicare Advantage (MA), which, if you choose it, basically enrolls you in an HMO. You get everything paid for plus other stuff that traditional Medicare (TM) doesn't cover, like hearing and dental and maybe gym memberships. This is good for you provided you don't get sick. If you do, you don't have the choice of virtually all doctors and hospitals that you do with TM, just those "in network" (an even greater problem if you don't spend all your time in the same area, since those networks are geographic). Also, since, if you are sick, those MA programs would just as soon you left and went to TM so they don't have to pay your bills, and they have a variety of tricks to encourage you to do so. MA may be good for basically healthy seniors, unless they travel, until they're not healthy. MA plans also don't pay for long-term care – that's expensive and would cost too much; gym memberships are cheap. And they can – and do -- pocket overhead and profits of up to 15%. (The insurance term is that their "medical loss ratio" -- the amount that they have to spend on actually providing medical care – has to be 85%, while in TM with its 2% overhead, it is effectively 98%.) Medicare Part D, the required drug coverage was another gift, this time to big pharmacies and pharmacy benefit managers (PBMs) who make big profit from them.

But wait! A lot of people were and are still choosing TM, and not all of them are the high-cost really sick people that the MA plans don't want! While the insurance companies and GNPs are glad that they are in TM when they are sick and costly, there are still a lot of them who we could make money on. How can we do that? Well, let's get the Center for Medicare and Medicaid Innovation (CMMI), which is supposed to come up with innovative programs that improve quality and save the government money, to

implement an "innovation" that lets us pocket money from even those who chose TM! Cool! So they did, without even having to have Congress approve it. These are called Direct Contracting Entities (DCEs). If your primary care clinician is affiliated with a DCE, the DCE collects all your money from Medicare, and – this is a really good part – they only have a medical loss ratio requirement of 60%, so they can keep 40% if they can deny you enough care! A better deal (for them!) than even Medicare Advantage! And since most primary care physicians are now employees or part of large groups, the DCEs can just contract with the group, not with each physician. And even better, the DCEs, the majority of which are now owned by "private equity" (a particularly noxious form of GNP), can just buy the primary care groups! *Voilà!* The group is now owned by the DCE, your doctor is part of it, and you are part of it and being hosed. Your only recourse is to change your primary care doctor. Which you may not want to because you may like and trust your doctor...

Of course, the two problems I mentioned are mirror images of each other. Medicare does not pay for all your care because Congresspeople and Wise Policy Analysts say that would be bad because it would cost too much. They see it as much better to spend lots of money on further enriching the insurance companies, PBNs, DCEs, and other GNPs. Why? Because they contribute a lot of money to Congress, and because many congresspeople are heavily invested in these; often they are also GNPs, either before entering Congress or as a result of it (how they get so rich on a Congressional salary is another story).

By the way, in case I haven't been clear in what I think, these are all both bad and evil programs, taking money that should be spent on your healthcare. They are healthcare examples of the impact of "gangster capitalism", or in another term I've heard, *Götterdämmerung* capitalism, which describes our current situation where the GNPs would rather destroy the world than stop acquiring all its wealth. And if they are willing to destroy the world, how much weight do you think your health and life have? These programs are not developed by accident; they are purposely designed to take what you have (as in the cost of health insurance premiums) or have previously been recognized as social benefits (as Medicare) and transfer them to the richest people in society.

The only – maybe, hopefully -- good news is that Congress has recently started holding hearings on DCEs, recently by the Senate Finance Committee, with outstanding testimony by many experts including Dr. Susan Rogers, current president of Physicians for a National Health Program (PNHP), whose website has lots of good information on DCEs. At the end of the hearing, Sen. Elizabeth Warren (D, MA) urged the Biden administration in the strongest terms to have CMMI end this "innovative experiment" (or perhaps you prefer grift or scam). Maybe they will.

Let your Congresspeople know what you think. And everyone else.

You Say You Want To End Abortion

Donald R. Frey, MD

Originally published in Dr. Frey's blog "A Family Doctor Looks at the World."
https://afamilydoctorlooksattheworld.com/you-say-you-want-to-end-abortion/

You say you want to end abortion...?

"Tell Jake to sleep on the roof."— In 1912, Sadie Sachs was living in terrible poverty with 3 hungry children in a tiny one room apartment in New York City. Barely surviving the complications of a desperate self-induced abortion, she begged the doctor to tell her anything she could do to keep from getting pregnant again. This was all the Doctor would say – "Tell Jake to sleep on the roof." Six months later, after another attempted self-induced abortion, Ms. Sachs was dead.

"There's a high school girl with a bourgeois dream/Just like the pictures in the magazine/She found on the floor of the laundry mat/Well a woman with kids can forget all that/ If she turns up pregnant, what'll she do?/Forget the career, forget about school?/Can she live on faith, live on hope?/ High on Jesus or hooked on dope?/When it's way too late to just say no/You can't make it here anymore."—from We Can't Make It Here Anymore, on the album Childish Things, by James McMurtry, 2005.

This subject will be difficult for many of you. Few issues are more immersed in raw emotion than this one, nor have such potential to divide us into warring factions.

So if you can stay with me, I hope we can approach this from a standpoint of reason and logic, rather than hatred and demonization.

Fair warning—I'm not writing about philosophy or theology here. That's what makes this different from 99% of what's usually written about abortion.

Most people want to argue about the nature of an embryo or a fetus. Is it really alive? Is it life? Is it human life? Is it *a* human life? Does it have a heartbeat? When does it get a heartbeat? Does that make any difference?

Does it have a "soul?" When does it get a "soul?" What is a "soul" anyway, and what does it mean to have a "soul?" Is it connected to an afterlife? What kind? Does it feel? Does it think? Is it just a mass of dividing tissue? If it's not life, then what is it? When does it become "life?" When does it become *a* "life?"

Feel free to argue about that stuff with your friends and neighbors all you want. But you'll probably just make yourself nuts in the process.

I'm not going to do that. Because today, people are getting shot, clinics burned, and nurses and doctors harassed and threatened by some of the bitterest people I've ever met, all who seem to think they have the moral high ground.

What they don't seem to realize is that their hatred is accomplishing nothing. That's why any *honest* discussion of abortion needs to be based on thought and reason.

So if you're really someone who wants to end abortions, here's what you need to know.

First, let's start with some basic facts. Humans have been having sex for centuries, and it hasn't changed much.

Every bit of research shows that the age at which people begin having sex is similar across most groups, usually beginning in the mid to late teens. Kids in conservative homes, kids in Christian schools, kids who attend multiple religious services, all seem to have sex no differently from their peers. And just as often, they get pregnant. No, religion doesn't somehow magically protect you from pregnancy. And it certainly doesn't keep religious young men from getting young women pregnant, either.

In fact, teens exposed to "abstinence only" sex-education have higher pregnancy rates than those who learn about other methods of birth control.

Let's get down to brass tacks. Abortion becomes an issue only if someone gets pregnant. Someone only gets pregnant if they have sex. And people have—and will continue to have—sex, regardless of how much preaching is done.

You can't legislate away sex. And the hard truth is that you can't legislate away abortions, either.

This is what the people who demand that we overturn Roe vs. Wade refuse to acknowledge.

As a physician, I can't begin to tell you how many times I've sat in an examination room with a woman who was crying, shaking, and desperately trying to come to terms with an unplanned pregnancy. Each was different. Some were married, some weren't. Their ages varied, their lives varied, their families varied. The impact of the pregnancy on the future of each one of them was profoundly different.

Each one struggled with the physical, psychological, emotional, and spiritual aspect of what they might have to do. And in most instances, there wasn't a male in sight.

And no, not a single one of them approached it lightly. I've never had a patient who came in and said, "Gee Doc, I got up this morning and thought 'what can I do today? Go to the zoo? Clean out the garage? Hey, you know what, I think I'll just go get an abortion!'" Rather, for each woman, it was the most gut-wrenching decision they ever made, regardless of whether they ultimately had the abortion or not.

But the *last thing* any of them was concerned about was

whether or not it was "legal."

I went to a rural Missouri high school. We had 39 students in my graduating class. And in my school alone, I knew of 2 young women who had abortions. There were undoubtedly more.

This was in the 1960's—*before* Roe vs. Wade. Abortions were technically illegal, just like they were in 1912. That didn't keep them from happening—whether in 1912 New York or 1968 Missouri. According to her biographers, Frank Sinatra's mother was the "go-to" person in Hoboken, New Jersey if you were an Italian-American woman who needed an abortion.

Long before Roe vs. Wade.

If you had money, you could get a relatively safe abortion. But it would cost you. And if you didn't have money? Then you had to engage in the Russian Roulette of unsafe, risky abortions.

You might bleed to death. You might become septic, dying of dehydration, fever, and an overwhelming infection.

The conditions of the procedure were sometimes medieval. One woman from California had to drive to Mexico for an abortion. She screamed in pain as the doctor performed the procedure without any form of anesthesia or pain killer. "You must burn for your sins," he snorted.

Burn for your sins? No mention of the son-of-a-bitch who got her pregnant in the first place, burning for his sins.

Most often, a pregnant woman, especially an unmarried young woman, confronts her condition without the support of the man who impregnated her, often with rejection from her family, and all too often, with her future shattered.

And it doesn't end there. Records show that domestic violence against women actually *increases* during pregnancy. And if you already have a child you're trying to protect, getting out of a dangerous relationship while pregnant becomes even harder. Without community or family support, it may be impossible.

What if the abuser resents your pregnancy, blames you for the imposition it might place on *his* life, and if he's cruel, controlling, and paranoid enough, starts thinking that he might not even be the child's father?

We see the outcomes all of the time. The woman winds up dead. Pregnancy is a documented risk factor for both physical abuse and homicide.

All too often, it's the women who *most need* help that can't get it. Poorer states and communities often have nothing to offer women other than thoughts and prayers.

In addition, assistance with oral contraception (birth control pills), condoms, and other birth control methods is often most lacking in poorer areas where women can least afford to pay for them out of pocket.

Why? First, because state budgets often prioritize just about everything ahead of women's health, and secondly, because many self-righteous politicians seem to think that making birth control more readily available will turn women into sex-crazed creatures who'll go out and have sex faster than a bunch of rabbits in spring.

The second point is obviously ridiculous. Let's go over it again. People *already* have sex, and without contraception women will become pregnant. Contraception doesn't force anyone to have sex, but it will allow people to plan families, and *eliminate the need* for abortion.

But only if contraception is actually available. More on that in a minute. But for the moment, let's just say that anyone who claims to be "pro-life" and "anti-contraception" is as loony as someone who is "pro-health" but "anti-health care." Study after study has shown that woman who use contraception have sex no more often than women who don't. They just don't get pregnant.

And thus don't confront the issue of abortion.

Don't just take my word for it. Look at the rest of the world. The United States has *higher* rates of abortion than *any* country in western Europe. Yet in each of those countries, abortions are easier to obtain than in the U.S.

Let me say that again. European countries that make abortion more available have *fewer* abortions. The key is that they also make contraception far easier to obtain, and it works. Fewer unplanned pregnancies, and fewer abortions. And sex occurs just as often as in the U.S.

But these facts haven't stopped many hypocrites in American politics and media from acting in outrageous ways. These are people like former Georgia Congressman Bob Barr, an outspoken proponent of "pro-life family values" who repeatedly voted to block any funding for abortions. According to one of his several ex-wives, Barr not only encouraged her to get abortions, but actually drove her to the clinic for the procedures and later picked her up. He apparently didn't want to be seen in the waiting room.

And then there's Republican Congressman Dr. Scott Desjarlais of Tennessee, who might best be described as the Gynecologist from Hell. He's admitted to having sex with his patients (he got a $500 fine and a slap on the wrist). He also supported his ex-wife's decision to get two abortions, and has been caught on tape advising a patient (who was pregnant by way of the good doctor) to go out of state for an abortion. He claims he wants to now outlaw all abortions (apparently only for other people). And he keeps getting reelected.

And don't forget Rush Limbaugh. The multiply-wedded pride of Cape Girardeau, Missouri and self-proclaimed Family Values Guy famously told a Georgetown co-ed who

spoke out about the need for affordable contraception that she was a "slut" and he "wanted to see movies" of her sex life.

Who knows? He might be watching movies right now by a very warm fire.

Finally, let's not forget that abortions for the rich and famous have always been around. When a man who's rich and powerful gets a woman pregnant, he can easily hush the whole thing up with a pay-off and an abortion. And the more women he has sex with? The greater the possibility for a pregnancy—and an abortion.

To anyone who thinks that a certain ex-president, who's openly bragged about his multiple sex partners, hasn't gotten some of those women pregnant and paid for their abortions, let me say this: I've got a big bridge in New York City I'll sell you.

The four examples I've just given you are, of course, all men. And if any of them had somehow gotten pregnant themselves, do you think they would have hesitated for a minute before getting an abortion? You know the answer as well as I do.

I've known several people who worked for Planned Parenthood. They were subjected to daily abuse and scorn from protestors. Yet on several occasions, they'd see some of those same protesters in a different light—when they'd show up afterhours, tearfully describing a pregnant daughter, and asking for help in getting an abortion.

Hypocritical? Of course it was. But in each case, the parent rationalized that their situation was somehow different, that they were the exception.

A few weeks would go by, and the parent would be back outside protesting as if nothing had happened. This, my friends said, was what convinced them that their work was indeed essential.

But let's talk about legislation for a moment. In state after state, legislators are passing laws making access to abortion more and more difficult (except for the rich, of course). Texas has tried to lead the way by placing a $10,000 "bounty" on anyone who performs an abortion. I'll have a few things to say about that in a minute. But for the time being, keep in mind that the law hasn't significantly reduced the number of Texas women getting abortions, bounty or no bounty.

Currently, with a far-right Supreme Court, Roe vs. Wade may soon be declared unconstitutional and abortions will be banned across wide swaths of America (presumably, there will be exceptions made for the kinds of politicians I mentioned above).

And if this happens, there'll likely be a huge party. Anti-abortion advocates will high five and fist bump. But they will have accomplished nothing.

Abortions will continue, just like they continue in every state where attempts have been made to restrict them. Rich women (or women pregnant by rich men) will continue to get them under the table. Poor women will get them in unsafe situations, and many will die. But abortions will still occur, just like they did *before* Roe vs. Wade.

So you say you want to do whatever's necessary to end abortion? Twenty years ago, I was on a panel of speakers discussing health care in front of a large group of medical students. The subject of abortion came up. This was at a Catholic medical school, and some of the panel talked about overturning Roe vs. Wade. Finally, it was my turn. These students need to hear the truth, I thought. So I told them.

Abortions won't go away if Roe is overturned, I said bluntly. Overturning a law is easy. But ending abortion? That's much harder. Here's what it will take.

Only when contraception is universally available, and barriers to access are removed. Only when contraception is affordable to everyone, and not hidden off in a corner somewhere. Only when it's over-the-counter (like Aleve or Tylenol), as it is in many countries. Only when parents accept the reality of sex, and don't block their children's' access to contraception—for both men and women

Only when women are finally treated with respect as equals. Only when the male who caused the pregnancy has the *same accountability* as the woman. Only when *their* future, their life, their opportunities are impacted to the same degree as the woman.

Only when women aren't shamed for a pregnancy while the male gets off with a wink and a nod. Only when women aren't rejected by their families and friends. Only when social supports truly provide the assistance that a woman and her family need to have a decent life, a fair opportunity, and a healthy environment.

Only when a pregnancy doesn't mean the end of a career or an education. Only when it doesn't place a woman at risk for abuse and harm.

So if you want to end abortion, work to make these things happen. When they do—and *only* when they do—abortions will end. But not a moment before. In the meantime, all the protests you do, all of the signs you carry, all the letters you write about overturning Roe vs. Wade, will accomplish nothing.

Nothing.

I pushed the microphone away, and glanced at the other faculty members at the table. They were staring at me with their mouths open. Up to that point, whenever anyone on the panel had spoken, the students responded as students usually do—with polite applause.

But my remarks were met with stunned silence at first. Then they gave me a standing ovation.

Today, I would say the same things I told those students 20 years ago, but with one addition. That Texas Law—the one that allows a $10,000 bounty on anyone performing an abortion? I'd actually be willing to support that.

But *only if* in order to collect the bounty you'd *also* have to find the bastard that got the woman pregnant, and drop off his testicles in a mayonnaise jar at the county courthouse. I think that would be more effective in ending abortions than anything the Texas Governor and his Legislature could do.

In the meantime, people can rant and scream, picket and protest, pass restrictive laws and overturn judicial decisions, and even resort to violence. They can debate the issues of "what is life?" and "is abortion murder?" until the cows come home. But until they have the resolve to deal with the underlying issues, abortions—anywhere—will not end.

And one more small detail. The sad story that opened this piece, about the death of Sadie Sachs? Each time the Doctor who treated Ms. Sachs made a home visit, he was accompanied by his Nurse. The day Ms. Sachs died, the Nurse was so overwhelmed by the death that she spent hours walking through the streets of New York, trying to come to terms with what had happened, and wondering what she might have done to have prevented the tragedy from happening.

The Nurse's name was Margaret Sanger. She did do something. She founded an organization called Planned Parenthood.

I just thought you might want to know.

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Recurrent rhabdomyolysis and an autosomal dominant family history of scoliosis: clinical features leading to a diagnosis of metabolic myopathy

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Exertional rhabdomyolysis is typically associated with metabolic or mitochondrial myopathies; however, there are important causes such as muscular dystrophies. Herein we describe a case of recurrent exertional rhabdomyolysis in which the diagnosis of RYR1 associated disease was made on clinical presentation avoiding the need for extensive or invasive investigation.

A 29-year-old man experienced six episodes of self-limiting muscle contractures and myoglobinuria over several years. Each episode occurred 1 to 3 weeks after significant exercise or dehydration with marked alcohol consumption, though we suspect a more proximal trigger due to recall bias. The most recent episode occurred after a week of intensive road cycling in the French Alps. On returning home, his creatine kinase (CK) was found to be 30,000 U/L. Review of previous blood test revealed that his transaminases had been intermittently raised over several years. He reported no exertional symptoms during childhood or adolescence. The only family history of note was scoliosis affecting his mother and maternal aunt. Examination revealed spinal rigidity and subtle contractures of the finger flexors, hip extensors, and ankle dorsiflexors and was otherwise unremarkable including strength and lack of scoliosis.

Based on the clinical presentation of delayed onset of recurrent rhabdomyolysis and joint contractures, spinal rigidity and a family history of scoliosis, a clinical diagnosis of RYR1 associated neuromuscular disease was suspected. Muscle imaging with MRI did not show associated changes. Molecular genetic panel testing revealed a known pathogenic heterozygous sequence change in exon 39 of RYR1 (c.6488G>A;p.Arg2163His). Family testing confirmed that his mother and maternal aunt carried the same pathogenic variant in RYR1. The patient has been followed up for over 24 months since diagnosis. During this time, he has experienced further, but less frequent, episodes of rhabdomyolysis due to avoiding triggers including over exercising, alcohol, and dehydration.

It is estimated that pathogenic variants in RYR1 account for more than one third of unexplained rhabdomyolysis events [1]. Despite this, the examination findings indicative of the diagnosis are not widely known, possibly because pathogenic variants in RYR1 are associated with varied phenotypes and histopathology. Clinical phenotypes can include malignant hyperthermia syndrome (MHS), proximal muscle weakness, scoliosis, contractures, and rhabdomyolysis [2]. The histopathology on muscle biopsy is equally diverse and includes central core disease, multiminicore disease, centronuclear myopathy, core-rod myopathy, and congenital fibre-type disproportion [3]. The pathogenic variant in this case has been described in association with central core disease and MHS [2,4&5], but never with exertional rhabdomyolysis as the presenting symptom. Nine UK families were identified to carry this pathogenic variant after an index case developed MHS following general anaesthesia [3].

The key messages we wish to convey are first, the importance of careful examination for contractures in the context of recurrent rhabdomyolysis, as this can avoid the need for extensive and invasive investigation. Early contractures are associated with several inherited muscle disorders most notably collagen VI disease, Emery-Dreifuss muscular dystrophy and rarely spinal rigidity can be seen with other metabolic myopathies. Secondly, the classification of RYR1 mutations is challenging, particularly with a variant of unknown significance, and invitro contracture testing may be considered. If patients do not wish to proceed with biopsy, patients and their families should be warned about the risk of MHS.

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p.Val142Ile (p.Val122Ile) Transthyretin Mutation Presenting Exclusively As Small Fiber Neuropathy

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Introduction

Familial amyloid polyneuropathy is an autosomal dominant disorder caused by mutations in the transthyretin gene, TTR. More than 100 mutations in the *TTR* gene are known. P.Val30Met was identified first as a cause of FAP and is the most common mutation worldwide. This mutation has been described as associated with peripheral neuropathy while p.Val142Ile (C.424G>A) (also known as p.Val122Ile) is associated with cardiac amyloidosis [1, 2, 3] . In this context, we report a patient harboring p.Val142Ile mutation with exclusive small fiber neuropathy and absence of any cardiac involvement by cardiac MRI representing genotypic-phenotypic heterogenicity.

Case Presentation

A 58-year-old, African American woman presented with distal tingling and electric shock-like, piercing pain sensations for 10 years. She denied numbness and distal weakness. She had no history of diabetes mellitus, exposure to toxins or tick bite. She reported an impairment in detecting cold temperatures and dysesthesias. She denied autonomic symptoms of temperature dysregulation or intolerance and syncope, but did complain of gastrointestinal dysmotility and postural dizziness from sitting to standing position corroborated by reduced systolic blood pressures observed in the range of 90mmHg or lower in sitting position, albeit orthostatic drop in BP was not observed. The patient did not complain about visual disturbances. She was a daughter of nonconsanguineous parents with 7 siblings and has 2 children. Her family history was otherwise negative regarding any cardiac or neuromuscular disorders.

Pertinent findings on examination included normal cardiac, respiratory and gastrointestinal system exams but distal skin discoloration with loss of normal hair. No deformities involving feet were seen like hammer toes or high arch feet. On neurological examination, she demonstrated normal cranial nerves and normal muscle strength in both upper and lower extremities. Sensory testing demonstrated a symmetric, length- dependent loss to pinprick to 5 cm above ankle and up to distal IPJ in lower and upper extremity, respectively. Large fiber sensations showed normal proprioception and vibration sensations.

Extensive polyneuropathy and inflammatory etiology assessments were normal. Notably, there was no monoclonal gammopathy, diabetes mellitus (fasting and 2-hour GTT were normal), nutritional deficiencies of vitamin B12 or B6 nor hypervitaminosis of vitamin B6. Paraneoplastic antibodies were absent. ANA and RF were negative. Hepatitis and HIV testing and genetic testing of SCN9A mutation were normal. Because of significant pain symptoms, she was evaluated by a rheumatologist, and physical examination and thorough laboratory workup did not reveal any findings of autoimmunity or systemic inflammation.

Electrophysiological studies demonstrated that there was no electrodiagnostic evidence of a large fiber sensory or motor peripheral polyneuropathy but electrically mild, bilateral, compressive, median sensory mononeuropathies at or distal to the wrists affecting only sensory fibers.

Discussion

Corine Andrade [5] described 'A peculiar form of Peripheral Neuropathy: Familiar Atypical Generalized Amyloidosis with Special Involvement of The Peripheral Nerves' from Northern Portugal in 1952. This original description observed carpal tunnel syndrome as well as small fiber involvement with 'early impairment of thermal and painful sensibilities' as in our patient. The disease now has been identified worldwide due to the widespread availability of genetic testing [4]. To date, 123 amino acid substitutions, one deletion and one synonymous base substitution have been reported for the transthyretin protein and its encoding gene [6]. The ATTR-Val30Met mutation is the most common variant found in Europe and Latin America, whereas the ATTR-Val142Ile is most commonly found in the USA and West African populations [7]. It is observed that approximately 4% of black Americans carry the ATTR Val142Ile variant. This mutation is widely described in the literature as the leading cause of cardiac amyloidosis in patients with African ancestry [7] and is also seen in patients of European descent [4]. It is predominantly associated with cardiomyopathy and increased mortality from heart failure [8] with a primary expression as a hypertrophic restrictive cardiomyopathy. Delayed diagnosis and misdiagnosis are common because phenotypic heterogeneity can be compounded by a lack of family history in TTR-FAP [3]. In a study from Italy, the rate of misdiagnosis in this cohort of TTR-FAP was as high as 32% with CIDP as the most frequent diagnostic error in

about 20% of cases, followed by lumbosacral radiculopathy, lumbar central canal stenosis, paraproteinemic neuropathy, and AL amyloidosis. A study observed that such errors lead to not only an average delay in diagnosis of up to 46 months but inappropriate treatments such as immunomodulating therapy, chemotherapy, or spinal surgery in a number of cases [9].

It is observed that heterogeneity in the clinical course with similar mutations also complicates the scenario. French patients with the TTR-FAP genotypes Ile107Val, Ser77Tyr, and late-onset Val30Met show a more rapid and severe disease progression compared to Portuguese Val30Met patients, with onset of gait disorders three times faster [10]. A study has demonstrated that non-coding variants contribute to the clinical heterogeneity and thus provided novel insights into the molecular mechanisms as the basis of the genotype–phenotype correlation of TTR amyloidosis. However , the study also observed strong genotype–phenotype correlations with p.Val422Ile mutations with the cardiac phenotype as supported by previous studies [11]. Because Val142Ille has been viewed as a traditionally cardiac phenotype, minimal data exist on the breadth and presentations of patients with coexistent PN and there is no data on patients presenting with PN prior to cardiomyopathy development. Other variants typically show development of PN prior to cardiomyopathy such as in the original Portuguese cohort. However, as described our patient represents a significant variation in presentation with sole neurological and not cardiological manifestations in the form of a small fiber neuropathy.

Conclusion

Diagnostic work-up of our patient with biopsy proven small fiber neuropathy demonstrated a heterozygous pathogenic transthyretin mutation p.Val142Ile (p.Val122Ile) (C.424G>A). In patients with SFN, TTR should be considered in the differential diagnosis, despite lack of family history and absence of other organs system involvement. As the precise etiology of small fiber neuropathy (SFN) often remains elusive, TTR testing should be integrated in the SFN diagnostic algorithm to prevent delay in diagnosis and potential therapeutic options. This is important considering that our ability to recognize these disorders have improved with more recent availability of genetic testing and treatment options, other than liver and/or heart transplantation for FAP. These newer treatment modalities include TTR stabilizer drugs which appear safe and could delay the disease progression, TTR gene modifiers, e.g. silencing RNA and antisense oligonucleotide therapies as well as immunotherapies targeting the amyloid deposits [4]. One of such therapy is Patisiran, approved in the USA for the treatment of the polyneuropathy of hereditary TTR-mediated amyloidosis (hATTR). It is a double-stranded, small, interfering RNA encapsulated in a lipid nanoparticle which is delivered to hepatocytes where it binds to a genetically conserved sequence in the 3' untranslated region of mutant and wild-type transthyretin (TTR) messenger RNA, causing a reduction in serum TTR protein levels and tissue TTR protein deposits [12]. Another therapy approved in the USA for the treatment of the polyneuropathy of hereditary TTR-mediated amyloidosis (hATTR) is Inotersen, a 2'- O-methoxyethyl-modified antisense oligonucleotide, which inhibits hepatic production of transthyretin [13]. Our patient noticed improved sensory symptoms following initiation of a gene silencer therapy. As these currently available gene silencer treatments significantly decrease TTR protein levels and improve patient outcomes, it is highly important to consider TTR as an etiology even if no family history in selected cases or coexistence of cardiomyopathy are present in addition to the awareness of such genotype-phenotype variability.

Abbreviations

TTR: Transthyretin

TTR-FAP: Transthyretin-associated familial amyloidotic polyneuropathy

SFN: Small Fiber Neuropathy

CIDP: Chronic Inflammatory Demyelinating Peripheral Neuropathy

hATTR: hereditary TTR-mediated amyloidosis

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Appendix 1: ELECTRODIAGNSOTIC FINDINGS

A punch skin biopsy showed severely reduced intradermal nerve fiber density consistent with a severe, length-dependent, small fiber neuropathy. Paraffin-embedded nerve tissue processed for Congo red staining did not demonstrate endoneural deposits of amyloid.

Motor NCS

Nerve / Sites	Rec. Site	Lat	Amp	Rel Amp	SPAR	Segments	Dist.	Vel	Dur.	Area
		ms	mV	%	%		cm	m/s	ms	mVms
L MEDIAN - APB										
Wrist	APB	4.05	10.9	100		Wrist - APB	8		5.50	28.6
Ref.		4.20	4.2		50	Ref.				
Elbow	APB	8.10	9.9	91.1		Elbow - Wrist	21.5	53.1	5.55	26.8
Ref.			4.2			Ref.		49.0		
L ULNAR - ADM										
Wrist	ADM	2.75	8.8	100		Wrist - ADM	8		4.85	24.9
Ref.		4.20	5.6		50	Ref.				
B.Elbow	ADM	5.60	8.1	91.8		B.Elbow - Wrist	18.5	64.9	5.10	25.0
Ref.			5.6			Ref.		49.0		
A.Elbow	ADM	7.25	8.0	91.7		A.Elbow - B.Elbow	10.5	63.6	5.35	24.2
Ref.			5.6			Ref.		49.0		
L COMM PERONEAL - EDB										
Ankle	EDB	3.70	4.6	100		Ankle - EDB	8		5.20	13.8
Ref.		5.70	2.2		50	Ref.				
Fib Head	EDB	9.15	4.0	86.8		Fib Head - Ankle	27	49.5	5.90	12.8
Ref.			2.2			Ref.		39.0		
Knee	EDB	11.25	3.8	82.6		Knee - Fib Head	10.5	50.0	5.70	13.1
Ref.			2.2			Ref.		39.0		
L TIBIAL (KNEE) - AH										
Ankle	AH	3.95	9.0	100		Ankle - AH	8		5.10	21.8
Ref.		5.70	2.8		50	Ref.				
Knee	AH	11.35	7.1	79.2		Knee - Ankle	35	47.3	5.85	20.0
Ref.			2.8			Ref.		39.0		

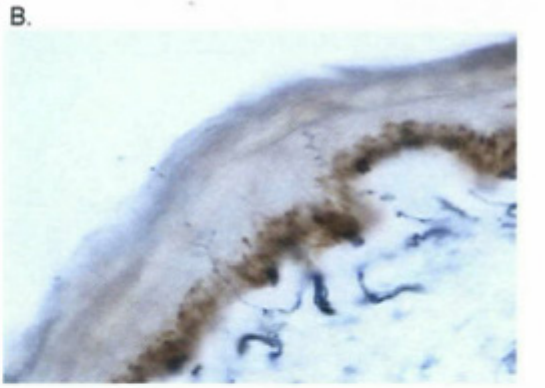
F Wave

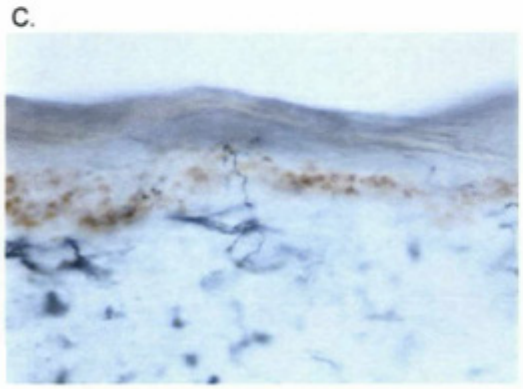
Nerve	Fmin
	ms
L COMM PERONEAL	46.70
REF	56.00
L TIBIAL (KNEE)	48.75
REF	56.00
L MEDIAN	25.30
REF	31.00
L ULNAR	25.05
REF	31.00

Sensory NCS

Nerve / Sites	Rec. Site	Onset Lat	Peak Lat	NP Amp	PP Amp	SPAR	Segments	Distance	Velocity
		ms	ms	µV	µV	%		cm	m/s
L MEDIAN - Dig II Antidr									
Wrist	Dig II	3.20	***4.10***	19.6	26.7		Wrist - Dig II	14	43.8
Ref.			3.80	10.0		50	Ref.		
L MEDIAN - Palmar Ortho									
Palm	Wrist	2.30	***3.05***	***20.2***	27.9	***35.6***	Palm - Wrist	8	34.8
Ref.			2.20	40.0		50	Ref.		
R MEDIAN - Palmar Ortho									
Palm	Wrist	1.60	***2.40***	56.7	58.4	100	Palm - Wrist	8	50.0
Ref.			2.20	40.0		50	Ref.		
L ULNAR - Dig V Antidr									
Wrist	Dig V	2.40	3.05	18.8	24.7		Wrist - Dig V	14	58.3
Ref.			3.80	10.0		50	Ref.		
L ULNAR - Palmar Ortho									
Palm	B Elbow	1.35	1.70	23.0	27.6	100	Palm - B Elbow		
Ref.			2.20	20.0			Ref.		49.0
R ULNAR - Palmar Ortho									
Palm	Wrist	1.30	1.80	21.4	24.4	93.1	Palm - Wrist	8	61.5
Ref.			2.20	20.0		50	Ref.		
L SURAL - Lat Mall Antidr									
Calf	Lat Mall	3.10	3.65	7.8	0.79		Calf - Lat Mall	14	45.2
Ref.			4.20	5.0		50	Ref.		
L SUP PERONEAL - Ankle Antidr									
Lat Leg	Ankle	1.95	2.50	7.1	11.1		Lat Leg - Ankle	10	51.3
Ref.			3.20	5.0		50	Ref.		

Appendix 2. In absence of etiology of her small fiber neuropathy, she underwent genetic testing for TTR (transthyretin) which demonstrated a p.Val142lle (C.424G>A) (also known as p.Val122lle) transthyretin mutation consistent with hereditary amyloidosis. As this mutation is predominantly associated with cardiac involvement, she underwent a cardiac evaluation with echocardiography which was normal and showed normal ejection fraction as well as cardiac MRI which did not show any amyloid infiltration. With the negative cardiac MRI, PYP scan was not performed .





Microscopic Findings

Location	Nerve Fiber Density	Normal Value
A. Right Foot	0.0/mm	>3.0/mm
B. Right Calf	2.4/mm	>4.3/mm
C. Right Lower Thigh	4.2/mm	>6.0/mm

Acute Limb-GIrdle Weakness with myasthenic features

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Keywords: Limb-Girdle, Myasthenia Gravis, Limb-Girdle Myasthenia Gravis

ABSTRACT

Myasthenia gravis is a disorder characterized by autoantibodies targeting different proteins across the neuromuscular junction. The typical presentation of myasthenia gravis involves oculobulbar weakness, classically ptosis that may or may not be symmetric. Patients may also present with a more dramatic presentation of generalized weakness or in myasthenic crisis requiring respiratory support for oxygenation. While these are the common presentations, atypical presentations sparing the eyes have been described. Here we present the case of a 63-year-old male who presented with proximal arm and leg weakness that rapidly progressed with a negative workup for central structural or inflammatory etiologies and was best explained by a likely limb girdle presentation of myasthenia based on electrophysiologic features and response to therapy. While long term follow-up was limited due to a co-morbid malignancy, the case highlights the utility of advanced electrodiagnostics in the workup of rapidly progressive weakness and the importance of considering a wide differential to identify potentially reversible etiologies.

Introduction

Myasthenia gravis (MG) is a disorder characterized by autoantibodies targeting different proteins on the neuromuscular junction. The incidence of MG ranges from 5 to 30 per million person-years with a prevalence of 10 to 20 cases per 100,000.[1-3] The most common of these autoantibodies are ones that directly target the acetylcholine receptor (AChR), which can be seen in 85% of patients with generalized MG and 50% of patients with ocular MG. Up to 40-70% of patients that are seronegative for AChR antibodies may have MuSK antibodies.[4] While autoantibodies remain the most specific diagnostic test available, single fiber electromyography is the most sensitive, being abnormal in 94% with generalized and 80% with ocular myasthenia gravis.[5,6]

The typical presentation of MG involves oculobulbar weakness, classically ptosis, that may or may not be symmetric. Patients may also present with a more dramatic presentation of generalized weakness or even in myasthenic crisis requiring non-invasive or invasive respiratory support for oxygenation. Some of the factors that may worsen or precipitate MG include surgery, pregnancy, stress, antibiotics (most notably fluoroquinolones, tetracyclines, and aminoglycosides), anesthetics, neuromuscular blocking agents, and cardiovascular medications including beta-blockers, calcium channel blockers, quinine, and quinidine.[7]

Case Report

A 63-year-old right-handed male was hospitalized for bilateral upper extremity weakness. His past medical history included benign prostatic hyperplasia, gastroesophageal reflux disease, and a recently diagnosed lung mass concerning for malignancy. The patient had a bronchoscopy 5 days prior for tissue diagnosis of the mass and described muscle pain and 'pins and needles' after the procedure, which slowly improved over 24 to 36 hours. Following resolution of the 'pins and needles' sensation in a rostral to caudal fashion, the patient started to feel weak, noting he was unable to stand or walk even short distances without some support. Over the next 24 hours, he noted improvement in the strength of his legs, but declining strength of his upper extremities, especially proximally as he found he was unable to lift his arms above his head. The patient denied any changes in bowel or bladder function and denied any muscle pain on initial evaluation. Review of systems was negative for any fevers, chills, nuchal rigidity, headache, changes in vision, weakness of his face, trouble swallowing, neck weakness, trauma, changes in his voice, or shortness of breath. He denied family history of neurologic conditions or autoimmune conditions. He reported drinking one glass of wine nightly but had never smoked himself (did have second-hand smoke from his mother as a child).

Initial exam revealed intact cognition, mental status, repetition, naming, memory, and attention. His cranial nerve exam was without any evidence of diplopia, fatigable changes in extra-ocular movements, ptosis, asymmetry of facial musculature, alterations in sensation or hearing, and intact strength of his sternocleidomastoid and trapezius bilaterally. The patient's motor exam demonstrated normal tone and bulk without any drift or fix, but significant symmetric weakness in proximal muscles, worse in his upper extremities than lower extremities, and worse in upper extremity extensors and lower extremity flexors. The most significant weakness was found in his deltoids which were

2/5 bilaterally. The patient's reflexes were intact and normal in biceps, triceps, brachioradialis, patellar, and Achilles; his plantars were down-going bilaterally. Complex motor including finger-tapping, finger-to-nose, heel-to-shin, and rapid alternating movements were intact bilaterally without any evidence for tremor. Sensation was grossly intact to pin prick and temperature with vibratory sensation diminished to 3 seconds in distal right lower extremity and 4 seconds in distal left lower extremity with normal findings at the knees bilaterally. There was no sensory level. Gait was physiologic with retained ability to walk tandem, walk on his heels, and walk on his toes.

Laboratory studies at the time of evaluation were normal with thyroid stimulating hormone of 1.930 and no evidence of infection or metabolic derangements, but a slightly elevated creatinine kinase (CK) of 390. The lung biopsy at time of initial evaluation had not been finalized.

MRI Brain and C-Spine, obtained given the possible upper motor neuron pattern of weakness, demonstrated no evidence of metastatic disease or acute diffusion restriction in the brain with mild to moderate nonspecific hyperintense white matter foci attributed to chronic microvascular changes. The MRI C-spine demonstrated no evidence of intraspinal or extradural mass and no cervical cord compression.

The patient's exam remained relatively unchanged per documentation on hospital day (HD) 2 with the exception that reflexes were unobtainable in his bilateral upper extremities by multiple physicians. As a result, clinical concern for possible Guillain-Barre Syndrome (GBS) or a variant was considered versus less likely Lambert-Eaton Myasthenic Syndrome (LEMS) due to his underlying lung mass and possibly fluctuating reflexes. Therefore, the decision was made to schedule an electromyography/nerve conduction study (EMG/NCS) to better differentiate.

EMG/NCS was completed on HD 3 at which time his exam remained unchanged but reflexes continued to have variable documentation. NCS of the right upper and lower extremity demonstrated a prolonged distal latency (6.6 ms) and normal amplitude (6.1 mV) of the right median motor study (consistent with right median neuropathy at the wrist) but otherwise normal distal latencies, amplitudes, and conduction velocities of the right ulnar and radial motor studies. Right peroneal motor study recording over extensor digitorum brevis demonstrated a normal distal latency but reduced amplitude (0.1mV) in all nerve segments. The tibial motor study demonstrated normal distal latency, amplitude, and conduction velocity. F waves were completed and normal in the right ulnar and tibial nerves, but mildly prolonged in the right median nerve (34.8 ms; normal <31 ms).

Sensory studies demonstrated normal peak latencies and amplitudes of the right superficial radial and ulnar-digit V sensory nerves with a prolonged peak latency (5.2 ms) and reduced amplitude (4 μV) of the right median-digit II sensory study. The right superficial peroneal sensory response was absent.

Given lack of diffuse demyelinating features and the only findings of a right median neuropathy at the wrist and a lower extremity sensorimotor axonal polyneuropathy, neither of which explained the patient's clinical presentation, repetitive nerve stimulation (RNS) was performed in the upper extremity (Table 1). 2Hz repetitive stimulation of the right ulnar nerve at baseline, immediately after 1 minute isometric exercise, 1 minute post exercise, and 2 minutes post exercise showed a maximal decrement of 23%, 17%, 18%, and 21% respectively. The right radial motor nerve demonstrated a maximal decrement with 2Hz RNS of 60% at baseline which improved slightly to a maximal decrement of 44% after 10 seconds of isometric exercise. The right median nerve also demonstrated a maximal decrement of 22% at baseline with 2 Hz RNS, however, no additional studies were done given the supportive findings in the radial and ulnar RNS studies. Given the above findings, normal compound motor action potential (CMAP) amplitudes (with exception of the right peroneal motor study presumed secondary to neuropathy), and lack of CMAP facilitation with 10 seconds of exercise, the repetitive nerve studies were felt to be most consistent with a postsynaptic neuromuscular junction disorder.

Needle EMG was completed on the right extensor digitorum communis and triceps brachii demonstrated reduced recruitment with very unstable MUPs with near complete exhaustion and absent MUAPs within 10-12 seconds of activation which further supported the diagnostic concern for a disorder of neuromuscular transmission.

Following completion of the EMG/NCS and initial laboratory/imaging studies, the patient's clinical presentation was felt to be inconsistent with a disorder of the upper motor neurons given reassuring brain and spinal imaging. Additionally, while the patient had a mildly elevated CPK, his lack of myopathic motor units on his EMG along with his fluctuating exam made an acute myopathy lower on the differential. While the patient did have a known pulmonary mass concerning for malignancy, his lack of autonomic features, upper greater than lower extremity weakness, normal CMAP amplitudes with lack of facilitation on his EMG, and a pattern on RNS most consistent with a post synaptic neuromuscular junction transmission disorder made the clinical picture less consistent with LEMS.

Review of the patient's chart demonstrated that the bronchoscopy completed 5 days prior to admission was prolonged (approximately 3 hours), during which the patient received 3 doses of succinylcholine for vocal cord spasms in addition to propofol, ketamine, and phenylephrine for sedation. Additionally, it was found that he had another bronchoscopy 15 days prior to admission during which he was diagnosed with pseudomonal pneumonia prompting a 10-day course of levofloxacin (no clear documentation

or prior fluroquinolone exposure prior to this). While diagnostic uncertainty remained, given his NCS/EMG findings and exposure to two medications (succinylcholine and levofloxacin) associated with potential myasthenia gravis exacerbation prior to his presentation, he was treated empirically for presumed limb-girdle onset myasthenia gravis with a course of plasmapheresis (PLEX) including 5 exchanges over 10 days. He was started on 60mg daily of prednisone following his third exchange. Serology for myasthenia gravis was pending at the time of treatment initiation. By the time the patient completed his third exchanged, he had significant recovery of his strength and reflexes. Acetylcholine receptor binding, blocking, and modulating autoantibodies and muscle specific kinase autoantibodies (MuSK) returned negative. A voltage-gated calcium channel antibody was not sent.

Following discharge from the hospital, the patient was maintained on 60mg daily of prednisone with plans for outpatient follow-up and taper. At follow up appointments 1- and 2-months post hospital discharge, it was noted he had returned to his prior activity levels and was walking up to 2-3 miles daily. He did not have any residual weakness documented and he had begun a gradual taper of his prednisone by 10mg monthly which he was tolerating up until 1 month prior to his death (at 40mg daily at that time). Unfortunately, as part of the patient's lung mass evaluation, he was ultimately diagnosed with a metastatic malignancy of unknown primary (assumed pulmonary versus prostate based on biopsy results) and passed away 3 months after his hospital admission due to his burden of metastatic disease.

Discussion

The above case highlights the importance of broadening a differential for acute onset weakness unexplained by initial structural imaging, especially in the setting of a rapidly changing neurological exam. In the above case, given the change in reflexes noted on examination as well as initial laboratory screening demonstrating a mildly elevated CK, the patient was referred for electrodiagnostic studies to evaluate for potential GBS variants and/or muscle and neuromuscular disease.

At the time of the patient's death, the leading proposed etiology for his presentation was an acute atypical limb girdle myasthenic syndrome. While MG typically presents with oculobulbar weakness, a study completed in Italy over 27 years followed a total of 508 patients with newly diagnosed MG. Of the 508 patients that were evaluated, 21 patients had a presentation that was incongruent with a typical presentation of MG including asymmetric distal upper limbs weakness, foot drop, isolated triceps brachii weakness and foot drop, post exertional axial weakness with dropped head, acute facial diplegia, limb-girdle MG, and MG with sudden lower limbs weakness and recurrent falls. The limb-girdle type presentation, like our patient, was present in 9 patients total (1.8% of the study population). These patients had a high rate (56%) of being seronegative for both AChR (22%) and MuSK (22%) autoantibodies, as was also the case in our patient.[8]

The patient's pattern on RNS was most consistent with a post-synaptic neuromuscular junction disorder, especially given the lack of significant CMAP amplitude facilitation greater than 60% with 10 seconds of isometric exercise. The finding of post-exercise facilitation of CMAP amplitude greater than 60% has been shown to have a high sensitivity of 84-96% for the diagnosis of LEMS. [9,10] While we cannot definitively rule out the possibility of LEMS based on the short term follow up available after hospitalization, the fact that the patient had such a robust response to immunotherapy despite progression of his cancer and maintenance with only prednisone would be atypical for paraneoplastic LEMS. Severe weakness in the setting of LEMS has been shown to be responsive to PLEX in the short term, however, the effect is only typically present for 6 weeks and maintenance therapy with prednisone (as in our patient) is typically only associated with mild to moderate improvement in symptoms, not the robust improvement we saw in our patient.[9]

Additional etiologies for the patients electrodiagnostic findings on RNS could include centronuclear myopathies (BIN1, DNM2, MTM1 mutations), congenital myopathies associated with RYR1 mutations, or even myotonic dystrophy type I and myotonia congenita; all of which have been shown to be associated with co-morbid dysfunction of the neuromuscular junction demonstratable on RNS studies.[11] While the patient did have a slightly elevated CK, none of the listed conditions would be expected to respond robustly to immunotherapy and the patient did not have any prior history or stigmata to suggest a long standing neuromuscular disorder at the time of presentation.

While at the time of the patient's death the best explanation for his presentation was an atypical limb-girdle presentation of myasthenia gravis, potentially provoked by recent fluroquinolone and succinylcholine exposure. We do not believe the syndrome was representative of a paraneoplastic myasthenic syndrome as this tends to present with a distinct non-limb MG presentation characterized by prominent oculobulbar and respiratory symptoms.[12] While long term clinical follow-up and response to tapering of immunotherapy would have helped provide a more definitive diagnosis in this case, we believe the atypical presentation and clinical course highlights the importance of considering disorders of neuromuscular transmission, even when a presentation may not appear to be consistent with typical clinical heuristics for the hallmark disorders.

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A Second Case of Treatment-resistant CIDP in an IgG Tubulin Autoantibody Positive Patient

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Introduction

In this case report, we describe the second case of treatment-refractory chronic immune demyelinating polyradiculoneuropathy found to have high titers of positive IgG anti-tubulin antibodies. As described previously,[1] the clinical significance of anti-tubulin antibodies found in the serum of CIDP patients is still uncertain.

IgG anti-tubulin antibodies can be found generally in low titers of human sera. It has been shown that an epitope on beta-tubulin has some sequence homology to several human viruses. However, the role of these antibodies in the pathogenesis of acquired demyelinating neuropathy remains unclear.[2] An association between anti-tubulin autoantibodies and CIDP was first hypothesized in a 1993 study by Connolly et al. when analysis of the serum of 70 patients with CIDP showed that 57% had high-titer IgG or IgM anti-tubulin reactivity compared to 3% on controls determined by ELISA.[3] However, later studies using immunoblot techniques could not replicate these results.[4,5]

In a previous report, a patient with typical CIDP had a quickly relapsing disease requiring monthly hospitalizations despite treatment with IVIG, glucocorticoids, and PLEX. She underwent extensive workup, which was only notable for positive serum IgG tubulin autoantibodies at 20,000 (ref range 2500). Subsequently, the patient remained stable off steroids and PLEX therapy for the last two years on rituximab monotherapy every six months without further hospitalizations.[1] This report is meant to support the possibility that tubulin autoantibodies are related to a rare subset of CIDP that is more resistant to typical treatment for CIDP with IVIG, PLEX, and glucocorticoids.

Case Presentation

A 57-year-old female with a history of idiopathic transverse myelitis 16 years prior, hypothyroidism, and autoimmune hemolytic anemia presented to an outside hospital with one week of muscle soreness and proximal lower extremity weakness. The patient had no preceding illness and received a second Moderna covid vaccine three months earlier. On exam, the patient had symmetric lower extremity weakness, proximal>distal, and preserved upper extremity strength. Bulbar and respiratory muscles were spared. She was areflexic. Given her remote history of transverse myelitis, which presented with lower extremity numbness, weakness, and urinary retention that improved with IV steroids, MRIs of her brain and whole spine with and without contrast were ordered and were unremarkable. Still, she was treated with IV 1g Methylprednisolone for five days for presumed central nervous system disease with improvement and was discharged home with physical therapy. She was discharged on a short steroid taper but started to worsen after completing the taper, so prednisone was restarted at 80 mg daily.

Despite this intervention, she continued to decline and presented to our hospital again a month later with a fall. The initial exam was like prior except for new proximal upper extremity weakness and decreased sensation to pinprick in bilateral feet. Medical Research Council-sum score (MRC) of six muscle groups (shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, ankle dorsiflexion) was 50. Initial workup for serum autoimmune, infectious, and metabolic etiologies of polyneuropathy was unremarkable apart from mildly elevated Gad-65 antibodies (0.16 nmol/L, ref <0.02) on the serum autoimmune panel. Lumbar puncture (LP) was performed on admission with 58 protein (ref 15-45 mg/dL), WBC 1 (ref 0-5/cu mm) and mildly increased IgG index 0.7 (ref <0.70) in the cerebrospinal fluid (CSF). CSF GAD antibodies were negative. EMG showed prolonged distal latencies, abnormal temporal dispersion with decreased conduction velocity, absent F waves, and partial motor conduction block consistent with demyelinating polyneuropathy. Given EMG findings, home prednisone 80mg daily was tapered, and 2g/kg intravenous immunoglobulin (IVIG) over five days was started. The patient worsened after being treated with IVIG. She was then treated with another five days of IV 1g Methylprednisolone with some improvement. However, she worsened again upon completion despite starting maintenance pulse therapy with prednisone 600mg weekly. Due to continued progressive weakness, plasma exchange (PLEX) was started and did not prove effective. See Table 1 for MRC scores before and after treatments.

The repeat EMG while the patient received PLEX showed a non-length-dependent demyelinating radiculoneuropathy with some ongoing denervation and active axon loss (likely secondary). Compared to the prior study, there was evidence of some interval worsening.

Also, while receiving PLEX, the patient developed cranial nerve involvement (VII, R > L V1, L V2-V3, XII). Workup included repeat Brain MRI with and without contrast and an unremarkable ophthalmology evaluation.

Table 1: Treatments with corresponding MRC Sum scores

	1	2	3	4	5
Treatment	IVIG 2g/kg	1g Solumedrol	Plex x5	1g Solumedrol	Rituximab 1000 mg/m^{2}x2
		Pulse steroids 600mg weekly started after 1st solumedrol round			
MRC pre-tx	50	41	40	12	20
MRC post-tx	41	44	38	16	44 (4 months post d/c)

MRC= Medical Research Council sum score (grades the sum of motor strength from 0 to 5 in bilateral deltoid, biceps, wrist extensor, iliopsoas, quadriceps femoris, and tibialis anterior for total score of 60 in patients with normal strength). Tx = treatment

AchR antibodies were negative. She also had involvement of respiratory muscles with NIF/VC as low as -20/1100. Given that cranial nerve involvement is less common in CIDP, there was an increased concern for CIDP mimics. Serum VEGF was negative. Further investigation for malignancy included pan-CT scans, which revealed a left renal mass concerning paraneoplastic polyradiculoneuropathy. She underwent a left radical nephrectomy which returned only to be an angiomyolipoma. Transvaginal ultrasound showed an ovarian dermoid cyst. Her physical exam reached a nadir (MRC 12). She was started on another course of IV methylprednisolone with mild improved strength and resolution of bulbar and respiratory symptoms.

Given the patient's temporary responsiveness to steroids with subsequent disease progression and lack of response to IVIG/PLEX, there was a concern for lymphoma. Her steroids were stopped to increase the sensitivity of LP for lymphoma versus an infiltrative process. LP was repeated twice. Both CSF studies had negative cytology and flow cytometry with elevated protein (57,47 mg/dL). Bone marrow biopsy without signs of lymphoma. Of note, the patient's hospital course was also complicated by worsening anemia with workup consistent with a hemolytic process such as autoimmune hemolytic anemia; however, her coombs test was negative three times.

Additional laboratory testing included anti-MAG antibodies, which were negative. The demyelinating neuropathy panel from Washington University in St. Louis returned positive for IgG B-Tubulin at 14,000 (ref range <2500). IgM tubulin, neurofascin, and contactin antibody titers were negative. CIDP was the most likely diagnosis due to peak disability occurring >2 months since the onset of symptoms. The patient was started on rituximab infusions, 1000mg, administered two weeks apart. She was discharged to inpatient rehabilitation and continued on pulse prednisone 600mg weekly with plans to taper as an outpatient. MRC on discharge was 20. She stayed at inpatient rehab for two months.

At outpatient follow-up four months after discharge, the patient reported gradual improvement in her strength with physical therapy (MRC 44). She was able to walk 10 feet after previously being paraplegic. Her repeat EMG/NCS showed improvement in upper extremity latencies and amplitudes. There was some interval worsening in lower extremity sensory amplitudes and motor conduction velocities, with mild ongoing denervation in her right gastrocnemius.

Discussion

Our patient meets the EFNS/PNS clinical and electrodiagnostic criteria for typical CIDP, based on progressive proximal and distal muscle weakness for >2 months, sensory involvement in bilateral feet, absent reflexes, distal motor latencies >50% above ULN in two nerves, motor conduction velocity >30% below LLN in two nerves, absence of F waves in two nerves, conduction block and abnormal temporal dispersion in >2 nerves.[6]

Cranial nerve involvement is atypical of CIDP; however, in a recent case series, it was shown that bilateral cranial neuropathies were seen in 11% of typical CIDP cases and were associated with more severe limb muscle weakness.[7] Respiratory insufficiency is also uncommon in CIDP; however, there are at least 20 reported cases of ventilatory failure in the literature that improved with typical treatment of CIDP,[8] and one study documented respiratory muscle weakness in 20% of patients with acute-onset CIDP.[9] Interestingly, prospective studies of CIDP patients found abnormal phrenic nerve conductions in 80-92%, which could suggest respiratory insufficiency is more common than traditionally thought and should be regularly evaluated in hospitalized patients.[10,11]

The fact that the third EMG showed worsening NCS in the lower extremities despite clinical improvement of symptoms reflects the gradual evolution of CIDP electrodiagnostically. In support of this theory is that she had improvement in the median and ulnar distal motor

latencies and compound motor action potentials.

Our patient's development of AIHA in parallel with CIDP supports prior case reports suggesting a possible association between the two autoimmune diseases.[12] Notably, a negative coombs test does not exclude a diagnosis of AIHA.[13] There have also been prior research linking polyclonal IgG tubulin autoantibodies in serum to acquired thyroid disease, which our patient has a history of.[14] Additionally, her history of transverse myelitis supports the association of CIDP with polyautoimmunity.[15]

Extensive workup for underlying autoimmune, inflammatory, neoplastic, and infectious etiologies was only notable for high-titer positive beta-tubulin antibodies. This case report suggests the role of high-titer beta-tubulin autoantibodies in refractory CIDP as previously described.[1] In both cases, patients were considered to have refractory disease based on failure to respond to or only partial response to typical immunotherapies for CIDP, including IVIG, glucocorticoids, and plasma exchange.

Based on the initial worsening of symptoms on daily steroid therapy and evidence that pulsed steroids may be effective in treating CIDP and reducing steroid-related adverse effects, we decided to treat our patient with pulsed steroids.[16]

Rituximab has been demonstrated to be more effective in treating nodal and paranodopathies that are less responsive to IVIG, glucocorticoids, and PLEX.[17] There is currently no known mechanism of action of anti-tubulin antibodies in CIDP,[2] but based on similar responses to treatment, it may be hypothesized that anti-tubulin antibodies act similarly to antibodies direct against the Node of Ranvier.

Conclusion

This case report describes the second case of a patient with treatment-refractory CIDP who was found to have a high titer of IgG tubulin autoantibodies. In both cases, patients were refractory to treatment with IVIG, glucocorticoids, and PLEX and responded to rituximab infusions, which suggests the use of rituximab treatment may improve outcomes in future cases. Increased testing for tubulin autoantibodies in CIDP is needed to determine their significance. Compared to the last case, this case is unique because of respiratory and cranial nerve involvement and existing past medical history of other autoimmune diseases.

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Unusual neurological presentations resulting in diagnosis of lymphoma in three patients

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ABSTRACT

Nervous system involvement affects up to one-third of patients with lymphoma, via a variety of mechanisms ranging from direct invasion to demyelination, paraneoplastic processes, and treatment-related complications. Nervous system involvement can manifest at any location and occur at any stage of lymphoma, often resulting in distinct and atypical patterns. Here we describe three patients, presenting each with motor predominant polyradiculoneuropathy and cranial neuropathy, transient encephalitis, and frontal gait dysfunction. Through further workup, all were diagnosed with lymphoma, with their neurological manifestations directly or indirectly related to the underlying lymphoma. Our study serves as an alert that in patients presenting with unusual neurological symptoms, lymphoma should be a consideration on the differential diagnosis.

Keywords: lymphoma, polyradiculopathy, encephalitis, frontal lobe dysfunction, PET

Introduction

A variety of neurological complications are associated with lymphoma that can variably arise at different stages of malignancy and in different locations of the nervous system.[1-8] The mechanisms underlying the nervous system involvement are diverse, including direct lymphomatous invasion of the central nervous system parenchyma or peripheral nerves, paraneoplastic/immune-mediated damage, demyelination, vascular dysfunction, therapeutic intervention related neurotoxicity, metabolic derangement, and opportunistic infection.[7,9-11] The existing diversity in the underlying mechanisms, the difference in timing of occurrence, and the heterogeneity in involved location often render the diagnosis of lymphoma difficult. In this case series, we describe three patients that highlight the variability in neurological patterns as the presentation of underlying lymphoma.

Patient 1

A 65-year-old male with a history of hypertension and nephrolithiasis presented with symptoms of bilateral hand weakness and numbness for one month, and blurred vision and slurred speech over two days. The numbness mainly involved the last two fingers of each hand and the medial forearms. There was also a 10-pound weight loss, myalgia, and arthralgia in the preceding month, and analysis of peripheral blood count revealed persistent eosinophilia. Initial rheumatological and hematological evaluations did not lead to a definitive diagnosis, and a bone barrow biopsy was unremarkable. At presentation, his cranial nerve exam showed intact eye motility, moderate weakness in the bilateral orbicularis oculi, bilateral lower facial weakness, and mild flaccid dysarthria. Muscle strength exam revealed the following (right/left, Medical Research Council Scale): shoulder abductors 5/5, elbow flexors 5/5, elbow extensors 5/5, first dorsal interossei 3/4, abductor digitorum minimi 4/5, hip flexors 5/5, knee extensors 5/5, knee flexors 5/5, dorsiflexors 5-/4, planter flexors 5/4, evertors 5/4, and invertors 5/4. Findings on tendon reflex examination were as follows: bilateral biceps reflexes were hypoactive, triceps reflexes normal, bilateral knee and right ankle jerks absent, and left ankle jerk normal. No clear sensory deficits were observed. Based on the clinical examination, it was felt that the patient may have an acute to subacute asymmetrical motor more than sensory polyneuropathy or polyradiculoneuropathy. Electrodiagnostic (EDX) study confirmed the presence of a motor predominant polyradiculoneuropathy that affect cervical, thoracic and lumbar segments. No significant demyelination was found on nerve conduction studies. Brain MRI revealed contrast enhancement of the distal canalicular segments of cranial nerves VII and VIII bilaterally (Figure 1). No significant contrast enhancement was observed on MRI of the cervical, thoracic, and lumbar spine segments. Cerebrospinal fluid (CSF) studies revealed the following: protein 95 mg/dl, glucose 60 mg/dl, and white blood cell 3 per microliter.

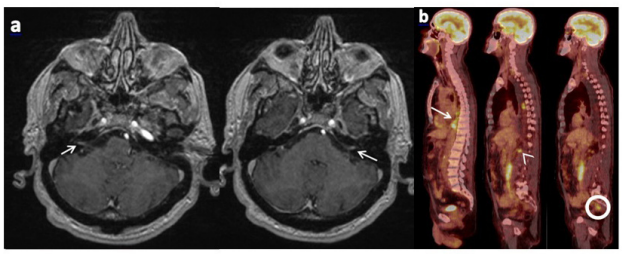

Figure 1. Image findings in patient 1. (a) MRI of the brain with contrast showed bilateral, distal enhancement of cranial nerves VII and VIII within the internal auditory canals.; (b) PET CT showed FDG avid lesions in posterior mediastinal (arrow), retroperitoneal (arrowhead), and pelvis (circle).

CT scan of chest, abdomen and pelvis showed multifocal lymphadenopathy. Whole body PET scan showed multifocal fluorodeoxyglucose (FDG) avid lesions involving the posterior mediastinum, retroperitoneum, and extra peritoneal spaces in the pelvis (Figure 1). A retroperitoneal node biopsy confirmed the diagnosis of a T-cell lymphoma. Flow cytometry analysis confirmed the presence of T cell lymphoma cells in CSF. The patient was initially treated with intravenous immunoglobulin (IVIG) which led to minimal improvement. His condition was stabilized with further chemotherapy treatment consisting of CHOP plus intrathecal methotrexate.

Patient 2

A 51-year-old-male with history of lumbar spine degeneration presented with acute headache, nausea, vomiting, confusion, and poor balance, notably without fever. Three weeks prior, he had signs of sinus congestion and nasal drainage, treated with amoxicillin and pseudoephedrine. On exam he was noted to have fluctuating level of consciousness, transient right gaze preference, and left sided neglect. CT angiogram of the cerebral vessels was normal. Brain MRI with and without contrast were unremarkable. Bedside EEG monitoring for 24 hours showed no epileptiform discharges. CSF study revealed the following: protein 98 mg/dl, glucose 52 mg/dl, and white blood cell 193 per microliter (lymphocytes 92%). Numerous studies to evaluate for infection resulted negative including human immunodeficiency virus screening. He was started on a treatment regimen of ceftriaxone, vancomycin, ampicillin, acyclovir, and dexamethasone with rapid and dramatic improvement in his condition. A repeat CSF study the day after presentation revealed the following: protein 88 mg/dl, glucose 74 mg/dl, and white blood cell 8 per microliter (lymphocyte 74%). It was felt that he likely had lymphocytic meningitis of a viral etiology, and he was discharged without further antibiotics or corticosteroid treatment.

Three days following discharge, his symptoms of headache, nausea and vomiting, neck stiffness, and gait instability returned. He was readmitted two weeks following discharge. On exam, he was found to have speech delay, deficits in attention and performing calculations, and gait ataxia. A third CSF study revealed the following: protein 86 mg/dl, glucose 45 mg/dl, and white blood cell 5 per microliter (lymphocyte 29%, monocyte 70%). CSF cytology and flow cytometry were negative. Clinical concern was raised for possible autoimmune encephalitis. Autoimmune encephalitis antibody panels via Mayo Clinic were negative in both serum and CSF. Brain PET scan did not reveal evidence of autoimmune encephalitis. PET scan of the body revealed an FDG-avid process in the lungs, brain, kidney, spleen, and bone marrow (Figure 2). Bone marrow biopsy of the right posterior superior iliac crest and biopsy of the left kidney confirmed the diagnosis of a diffuse large B cell lymphoma. He was treated with R-CHOP therapy. Six weeks following the diagnosis and treatment of lymphoma, his neuralogic examination had improved, though the wide-based gait persisted.

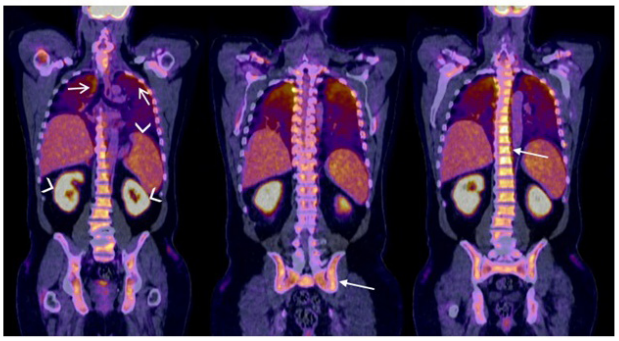

Figure 2. Image findings in patient 2. PET CT showed FDG avid lesions in bilateral lung (open-head arrows), bilateral kidney and spleen (arrowheads), and bone marrow (closed arrows).

Patient 3

A 63-year-old male presented with difficulty walking, leg heaviness, and left-sided headache. Over several years prior to presentation, his walking had gradually become slower with shorter distances traveled. His major concern was inability to pick up his legs high, stating "my brain tells me not to walk." On physical exam, muscle strength was normal. He demonstrated difficulty in raising his legs up while sitting but could do it well while lying down. A slightly wide-based gait was observed. EDX studies did not show evidence of a large fiber polyneuropathy or lumbosacral radiculopathy. Lumbar spine MRI was unremarkable. Brain MRI revealed an overlying extracranial soft tissue mass involving a large portion of the left greater than right frontoparietal, extra-skeletal calvarium with underlying marrow replacement and associated mild pachymeningeal thickening resulting in subtle signal changes in the underlying brain parenchyma on FLAIR sequence (Figure 3). Concerns for an intraosseous meningioma versus slow-growing metastasis or myelomatous lesion were raised. CSF study revealed the following: protein 32 mg/dl, glucose 58 mg/dl, and white blood cells 2 per microliter, with normal CSF cytology. Further PET scan revealed FDG avid left frontoparietal scalp/subcutaneous soft tissue thickening without significantly increased FDG activity in the underlying calvarium (Figure 3). No FDG avid lesions

were observed in the brain parenchyma or other regions of the body. A left frontal scalp biopsy confirmed the diagnosis of small B-cell lymphoma. Bone marrow biopsy was normal. Radiation treatment to the scalp was initiated.

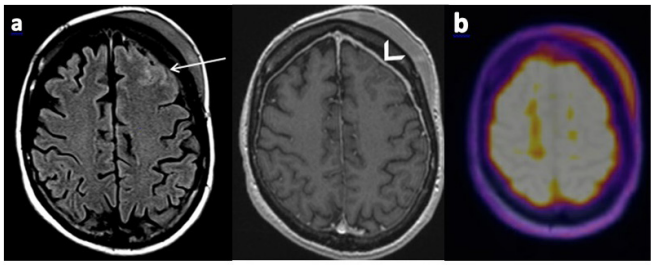

Figure 3. Image findings in patient 3. (a) MRI of the brain showed the left frontal scalp mass with underlying frontal lobe compression and FLAIR hyperintense changes (arrow) and left greater than right pachymeningeal thickening and enhancement (arrowhead) on post-contrast T1 sequence; (b) Brain PET FDG avidity in left frontal soft tissue scalp.

Discussion

Nervous system involvement in lymphoma is frequent and may affect up to one-third of patients. [4,7,9] The clinical presentation of lymphoma affecting the nervous system varies widely depending on the site of involvement. Typical central nervous system complications include intracranial or intramedullary metastases, leptomeningeal metastases, limbic encephalitis, paraneoplastic cerebellar degeneration, and primary central nervous system angiitis. Classical involvement of the peripheral nervous system includes subacute to chronic mononeuropathies, radiculopathies, plexopathies, cranial neuropathies, symmetrical axonal polyneuropathy, mononeuritis multiplex, and demyelinating polyneuropathy mimicking Guillain-Barre syndrome (GBS) or chronic inflammatory demyelinating polyneuropathy (CIDP). Given the myriad timing, location, and pathophysiological mechanisms underlying these conditions, the presentation of nervous system involvement in lymphoma may be atypical, not fitting well to any of the classical presentations of the above-mentioned diagnoses.

Our patient 1 presented with subacute motor and sensory symptoms that affected the craniobulbar region and limbs. Further workup indicated the presence of cranial neuropathy and asymmetrical, motor-predominant polyradiculoneuropathy. His EDX study did not reveal evidence of demyelination. Further treatment with IVIG did not lead to significant improvement. No nerve root enhancement was observed on spinal MRI. Therefore, it is unlikely that he suffered from acute inflammatory demyelinating polyradiculoneuropathy (AIDP, GBS) or CIDP. Flow cytometric analysis confirmed the presence of T cell lymphoma in his CSF, making leptomeningeal lymphomatosis a distinct possibility. We cannot rule out a diagnosis of neurolymphomatosis due to a lack of nerve biopsy.

Our patient 2 presented with a multitude of symptoms that were concerning for a form of encephalitis. However, his presentation lacked the typical features of limbic encephalitis. On MRI and PET scan, there was a lack of mesial temporal lobe and amygdala involvement. No clinical or electrographic seizures were observed. CSF study initially showed prominent pleocytosis, but this quickly resolved. Autoimmune antibody panel testing in the serum and CSF was normal. The patient improved quickly with a short course of corticosteroids, and subsequently with the treatment of the discovered, underlying lymphoma. This supports the neurological symptoms as being associated with the underlying lymphoma, possibly through immune-mediated mechanisms resulting in the appearance of an aseptic meningoencephalitis on initial testing and evaluation.

Our patient 3 presented with headache and a gait disorder that seemed to suggest frontal lobe dysfunction. His evaluation was remarkable for the presence of a frontal scalp lesion that affected the underlying meninges and frontal lobe. Oncologic evaluation showed histopathologic and genetic abnormalities consistent with small B-cell lymphoma. The diagnosis of lymphoma in this case was surprising; the origin of this lymphoma as being extracranial or intracranial remains unclear.

In all three patients, FDG-PET scan was invaluable in supporting or leading to a diagnosis of lymphoma. Therefore, we feel that such diagnostic scans should be considered in patients with atypical neurological presentations where lymphoma is in the differential diagnosis.

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A 36-year-old male with episodes of exercise-induced rhabdomyolysis: the importance of exercise testing and muscle biopsy for mitochondrial myopathies

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This case has been previously presented at the virtual 44th Annual Carrell-Krusen Neuromuscular Symposium in Dallas, Texas held from February 24-25, 2022.

Introduction

The differential for recurrent exercise-induced rhabdomyolysis is broad and includes, amongst many other conditions, metabolic myopathies and mitochondrial disorders. While metabolic and mitochondrial diseases can be challenging to confirm, given the episodic nature or non-specific symptoms, mitochondrial myopathies are particularly challenging because of the clinicopathologic heterogeneity. This case illustrates the importance of exercise testing and muscle biopsy in evaluating patients with suspected mitochondrial myopathies.

Mitochondria possess proteins from nuclear DNA (nDNA) and mitochondrial DNA (mtDNA), maternally inherited latter. Since some of the mitochondrial proteins are encoded by nuclear genes, inheritance for these nuclear genes follows Mendelian patterns [1,2]. Diagnosis of these conditions is complicated by the numerous genes (approximately 1500 genes encoded in both mitochondrial and nuclear DNA) that do not have clear genotype-phenotype correlates[1,3]. Variability is partly attributable to varying heteroplasmy levels between family members and even within different tissue types in a single person[1].

Mitochondrial myopathies may have systemic complications, but symptoms can be isolated to muscle and exercise intolerance. The physical exam can be normal outside of systemic symptoms (e.g., hearing or vision loss, ptosis, or ophthalmoplegia) related to mitochondrial myopathies. Laboratory findings, such as elevated creatine kinase (CK) or lactic acid values, are nonspecific and can be normal, with suspicion of a metabolic myopathy likely to arise from the appropriate clinical history[3]. Multiple testing modalities may be needed to confirm the diagnosis of mitochondrial myopathy.

Case Report

History

A 36-year-old man with a history of migraines was referred to the neuromuscular clinic for unexplained episodes of exertional rhabdomyolysis. He was lifting weights approximately three years before his visit. He then had an episode of pain, weakness, and edema in his upper arms with an elevated CK, which was diagnosed as rhabdomyolysis. Before that, he was healthy and athletic. He was a competitive athlete and was doing well in sports though he had difficulty with long-distance sports. He was able to lift heavy weights without difficulty. Since then, he has had four total episodes of rhabdomyolysis. He described cramps that were more prominent than myalgias. He had no change in his exercise tolerance with glucose intake before exercise. He had no worsening of muscle symptoms with fasting or fevers. He denied contractures or transient contractures. He also denied dyspnea, dysphagia, and diplopia. Notably, he had prominent fatigue after longer workouts. He could complete his workouts and was not limited to short bursts of exercise like lifting or sprinting; however, he could not engage in continuous, prolonged exercise.

He has a history of hypertension, a cholecystectomy, and two lumbar decompression surgeries. He has three daughters that are all healthy. One maternal nephew has ptosis. There is no sudden cardiac death in the family. He denied current tobacco, alcohol, or drug use. He had no known drug allergies. He takes lisinopril, coenzyme Q10 (CoQ10), and a multivitamin daily.

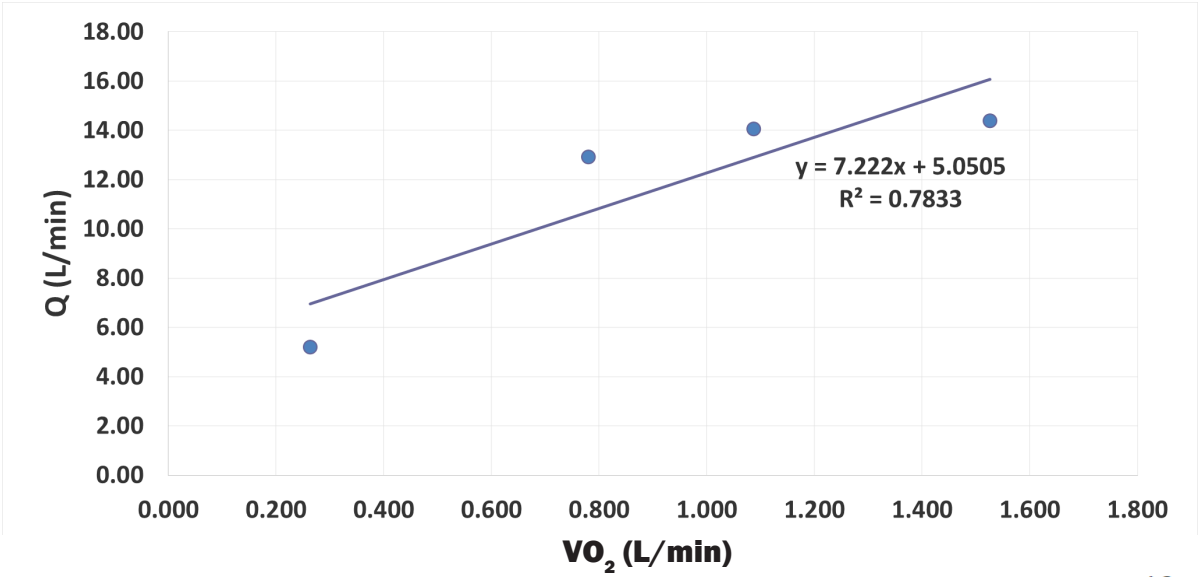
Physical

His exam was nearly normal except for his cranial nerves, where he had bilaterally limited abduction, left worse than right. He also had left non-fatigable ptosis. Otherwise, his cranial nerves, muscle strength, sensation, reflexes, coordination, and gait were normal.

Diagnostic testing

Prior laboratory workup was notable for normal baseline CK, total and free carnitine, non-fasting acylcarnitine profile, and lactic acid. Additional studies, including hemoglobin A1c, methylmalonic acid, cobalamin, antinuclear antibodies, serum protein electrophoresis

Figure 1: Aerobic exercise test



Q: cardiac output, VO_2: volume of oxygen consumption. The ratio between cardiac output and oxygen consumption ($\frac{\Delta Q}{\Delta VO_2}$) is 7.222, suggestive of a defect in oxidative phosphorylation.

with immunofixation, serum-free light chain, erythrocyte sedimentation rate, thyroid stimulating hormone, basic metabolic panel, complete blood count, and syphilis were unremarkable. He had a normal MRI of bilateral thighs with contrast, including no fatty replacement or abnormal signal. Electromyography (EMG) revealed mild chronic non-irritative proximal myopathy, and the nerve conduction study was normal. His Invitae limb-girdle muscular dystrophy and GeneDx metabolic myopathy gene testing panel did not reveal a pathogenic mutation. The patient had mtDNA gene testing via buccal swab testing that revealed a DNA polymerase gamma (*POLG*) c.2642 C>T heterozygous variant of unknown significance (VUS) and did not reveal any mutations in the mtDNA. The Provean score was -9.89, with conflicting interpretations of pathogenicity.

Given his clinical picture, there was suspicion of mitochondrial myopathy. He had an aerobic cycle exercise test with a ramp protocol. His cycle exercise test showed a peak exercise heart rate of 171 bpm, 93% of his predicted maximal heart rate. The patient's perceived exertion was of maximal effort (19/20 rated perceived exertion and 9/10 leg exertion scales), with general and leg fatigue symptoms. Peak oxygen consumption (VO_2 max) was 24.4 ml/kg/min, and the predicted VO_2 max was 26.1 ml/kg/min, below average for age and sex. Cardiac output (Q) was within normal limits at rest but was exaggerated during exercise with respect to oxygen utilization. There was a blunted peak arteriovenous oxygen difference at peak exercise (a-vO_2). Lactate was normal at rest and during exercise, with normal elevations post-exercise. The change in cardiac output relative to VO_2 was 7.22 (Figure 1).

These results suggest an oxidative defect; thus, a muscle biopsy was pursued to assess his mitochondria. Muscle biopsy mtDNA analysis revealed multiple deletions of the mitochondrial genome (13 kilobase (kb) deletion m.3264_16071del12808 and 12 kb deletion m.3578_15546del11969, the entirety of the mtDNA is 16.6 kb). Interestingly, his muscle's histochemical analysis and electron microscopy did not reveal any changes suggesting a mitochondrial myopathy.

Based on the cycle exercise testing (Figure 1) and muscle biopsy mtDNA analysis results, the diagnosis was consistent with mitochondrial myopathy. Given the multiple deletions, this is consistent with the *POLG* mutation, which was reclassified to likely pathogenic. He was given the clinical diagnosis of chronic progressive external ophthalmoplegia (CPEO).

Discussion

This case emphasizes the importance of tissue-specific testing in cases where prior blood or buccal testing is inconclusive. Additionally, exercise testing can help identify defects in oxidative phosphorylation, which can support a diagnosis of mitochondrial myopathy and help resolve unclear genetic findings. There can be reduced VO_2max, reduced peripheral oxygen extraction (a-vO_2), and hyperkinetic circulation (elevated baseline

cardiac output)[3,5]. In a study of 40 patients with primary mitochondrial disease (PMD), the capacity to increase oxygen extraction during exercise was severely attenuated in the PMD group, as indicated by a low peak systemic a-vO_2 difference compared with healthy subjects[5]. Care must be taken when interpreting exercise tests, as several factors can alter the results, including a submaximal effort.

Next-generation sequencing (NGS) of DNA can be useful[6]. Although NGS is useful when pathogenic variants are found, variants of unknown significance are common, particularly in mitochondrial myopathies[3]. Unlike mutations in nuclear-encoded genes, the proportion of mtDNA copies containing a mutation can vary widely between different cells in the same individual[1]. While serum and buccal samples are sensitive to point mutations mtDNA, there is greater sensitivity for deletions and duplications in muscle tissue, and mutations may only be present in specific tissues due to heteroplasmy (e.g., no mutations in leukocyte and buccal samples with a mutation in muscle)[6]. Thus, muscle biopsy can be used to identify mimics or perform enzyme or respiratory analysis in addition to performing mtDNA analysis.

Diagnosis of mitochondrial myopathies may require multiple testing modalities, including exercise testing, muscle pathology, enzyme or respiratory analysis, and molecular testing, as false negatives are common. Analysis of mtDNA has rapidly expanded in the last 30 years and is particularly useful in cases with high suspicion of disease, mainly when supported by exercise physiology data[6]. Data from performance on exercise testing and findings on muscle biopsy (multiple mitochondrial DNA deletions in this case) are essential for reclassifying variants of unknown significance as a pathogenic mutation.

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"Ear of the Lynx Sign" in a patient with Primary Lateral Sclerosis

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Introduction

The "Ear of the lynx sign" refers to an abnormal cone-shaped hyperintensity seen on fluid attenuated inversion recovery (FLAIR) sequence of the magnetic resonance imaging (MRI) of the brain at the tip of the frontal horn of the lateral ventricles which resembles the tufts of hair on the ears of a lynx (1, 2). This radiological sign has been reported in hereditary spastic paraplegia (HSP), including spastic paraplegia (SPG) type 11 and SPG type 15 (1,2). To our knowledge, this imaging sign has never been reported in disorders other than HSP, such as primary lateral sclerosis (PLS) and/or amyotrophic lateral sclerosis (ALS). In this case report, we discuss the first description of this radiological sign in a patient with PLS.

Case Report

A 59-year-old female presented with a history of progressively worsening bilateral lower extremity stiffness and difficulty with ambulation for over a 7-year period. Her symptoms started after a left hip replacement surgery. Prior to surgery, she was ambulatory and was able to carry out activities of daily living without any difficulties. After the hip surgery, she started using a cane for ambulation. Despite physical therapy, she was unable to progress to her previous level of ambulation. A few months later, she started developing stiffness in bilateral hips which progressively worsened thereafter and gradually progressed from bilateral hips to knees and then to ankle, over a period of 1 to 2 years in an asymmetrical pattern affecting the right lower extremity more than the left. She had a corrective hip surgery after a year which improved her left hip pain but not the stiffness. She then started having difficulty getting up from sitting position, difficulty turning and developed a shuffling gait. She eventually started requiring a walker to ambulate. 5 years later, she started having urinary incontinence. She denied any family history of similar symptoms.

Over the years, she was trialed on high doses of Sinemet for concern of parkinsonism, which did not improve her symptoms. Oral baclofen for concern of lower extremity spasticity resulted in minimal improvement. Eventually, a baclofen pump was implanted which helped with the stiffness and spasticity. Given continued symptoms, she was referred to our clinic for a second opinion.

Her physical examination revealed increased tone in bilateral lower extremities, consistent with grade 2 on modified Ashworth scale. Detailed muscle strength examination is summarized in Table 1. She had a brisk jaw jerk reflex, 3+ biceps and brachioradialis reflex bilaterally, 2+ knee and ankle reflex bilaterally and upgoing plantars bilaterally. No sensory abnormalities or lower motor neuron features including atrophy or fasciculations were noted on examination. She had reduced stride width and length and

Table 1: Detailed muscle strength examination, scored as per Medical Research Council (MRC) scale.

Muscles	Strength Right	Strength Left	Muscles	Strength Right	Strength Left
Orbicularis oculi	5	5	Hip flexion	5	5
Orbicularis oris	5	5	Hip extension	5	5
Shoulder abduction	5	5	Hip abduction	4-	4-
Elbow flexion	5	5	Hip adduction	5	5
Elbow extension	5	5	Knee flexion	4-	4-
Wrist flexion	5	5	Knee extension	4+	4+
Wrist extension	5	5	Ankle dorsiflexion	4+	4+
Finger abduction	5	5	Ankle plantarflexion	5	5
Finger extension	5	5			
Finger flexion	5	5			
Thumb abduction	5	5			

a shuffling gait.

Lab testing included zinc, copper, ceruloplasmin, vitamin D, B12, folate, vitamin E, thyroid function, antineutrophil cytoplasmic antibodies, ribosomal and centromere antibodies, glutamic acid decarboxylase 65, human immunodeficiency virus, human T-lymphotropic virus, rheumatoid factor, and serum protein electrophoresis, which were all normal. Hereditary spastic paraplegia gene panel testing was negative. Table 2 includes all the genes tested in the SPG gene panel.

DaTscan of the brain was normal. Positron emission tomography scan of the body was normal. Spinal fluid assessment showed 1 nucleated cell, mildly elevated protein to 78 mg/dL, 2 oligoclonal bands, within normal limits, and normal IgG synthesis rate and index. Paraneoplastic and autoimmune antibodies in cerebrospinal fluid and serum were negative. Very long chain fatty acids testing in serum was negative.

MRI of the brain showed T1 and FLAIR sequence cone-shaped abnormalities at the forceps minor region of genu of corpus callosum bilaterally. The signal abnormality was hypointense on T1 and hyperintense on FLAIR sequence, resembling the "Ear of the lynx sign" (Figure 1a &1 B).

MRI cervical and thoracic spine with and without contrast were normal.

Nerve conduction studies of the right upper and lower extremities were normal. Needle electromyography revealed evidence of mild to moderate, widespread reinnervation changes in the right upper and lower extremities. No fibrillation potentials or positive sharp waves were noted. A few rare fasciculation potentials were seen in the right lower extremity.

Patient was diagnosed with PLS and fulfilled the consensus diagnostic criteria (3). These consist of the following: age of symptom onset > 25 years, symptoms of progressive upper motor neuron (UMN) dysfunction for more than 2 years, signs of UMN dysfunction in upper extremity (brisk triceps and biceps reflexes), lower

Table 2: Genes tested in hereditary spastic paraplegia gene panel.

ABCD1	ERLIN1	SPAST
ALDH1A1	ERLIN2	SPG11
ALS2	FA2H	SPG21
AP4B1	FARS2	SPG7
AP4E1	GBA2	TECPR2
AP4M1	GJC2	TFG
AP4S1	HACE1	UCHL1
AP5Z1	HEXA	VAMP1
ARG1	HSPD1	WASHC5
ARL6IP1	KCNA2	ZFYVE26 (SPG15)
ATL1	KDMSC	
ATP13A2	KIDINS220	
B4GALNT1	KIF1A	
BSCL2	KIF1C	
C12ORF65	KIF5A	
CAPN1	L1CAM	
CPT1C	MAG	
CYP27A1	NIPA1	
CYP2U1	NKX6-2	
CYP7B1	NT5C2	
DDHD1	PLP1	
DDHD2	PNPLA6	
ENTPD1	RAB3GAP2	
RTN2	REEP1	
SACS	REEP2	
SLC16A2	SPART	

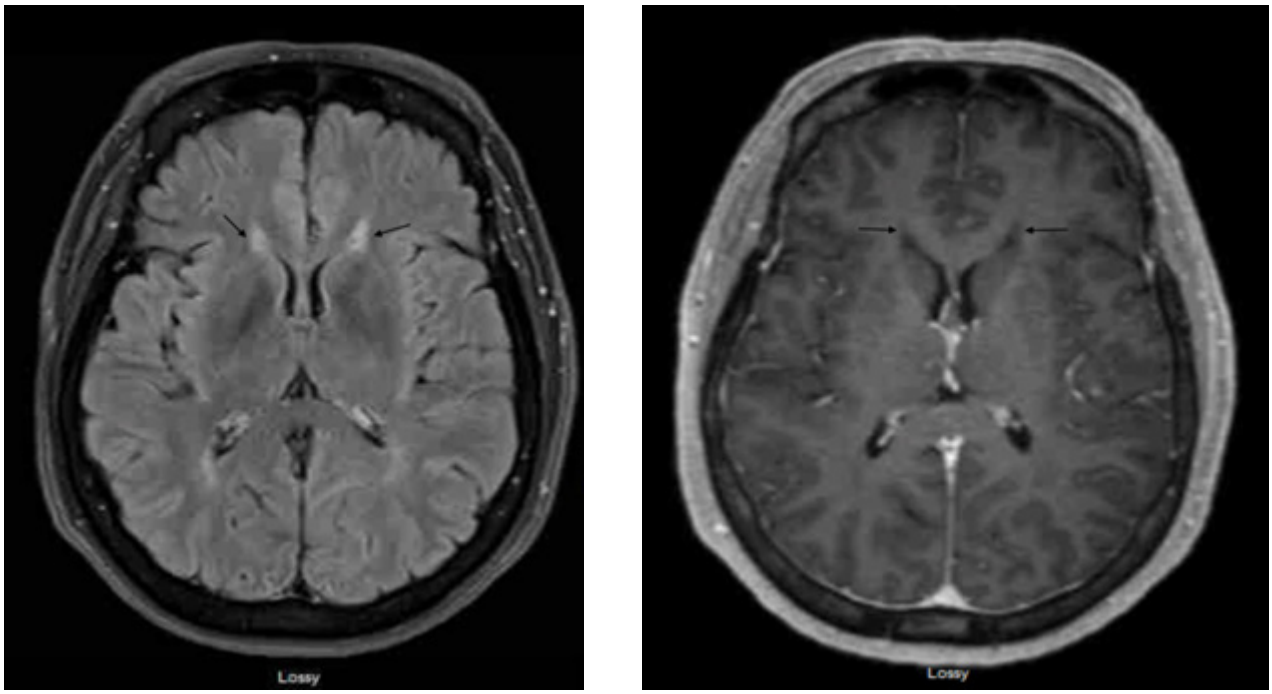

Figure 1: Axial FLAIR (A), axial T1 (B) MRI brain showing characteristic signal abnormalities involving forceps minor region of genu of corpus callosum (arrows) resembling the Ear of the Lynx sign.

extremity (spasticity of bilateral lower extremities, upgoing plantars) and bulbar (brisk jaw jerk), in absence of sensory symptoms, active LMN degeneration, and absence of UMN pathology on neuroimaging, or biofluid testing (3).

Discussion

Our case is the first documented description of the abnormal radiological sign, "Ear of the lynx sign" in a patient with PLS.

The forceps minor is a subcortical white matter tract of the anterior corpus callosum connecting lateral and medial frontal lobes bilaterally (4, 5). Bilateral involvement of the forceps minor may lead to disruption of the adjacent descending corticospinal tracts in the corona radiata which may explain the bilateral lower extremity involvement. The anterior cingulate gyrus, located in close proximity to the forceps minor, plays an important role in behavioral control of micturition (6). Involvement of this area may result in urinary incontinence (6).

Ear of the lynx sign has been previously reported with SPG type 11 and SPG type 15 (1,2,7). Masdeu et. el compared T1-weighted and T2-FLAIR MR images from 24 patients with SPG mutations (18 in SPG11, 2 in SPG15, 2 in SPG7 and 2 in SPG4), with 24 disease controls with multiple sclerosis, and 24 healthy controls matched by age and sex. They reported that the sign was present only in patients with SPG11 and SPG15 mutations (2). The radiological sign on T2-FLAIR sequence was found to have high sensitivity (94%) and high specificity (97%) for SPG type 11 and SPG type 15 (2).

A case report from Pacheco et al described this sign in a patient with Marchiafava-Bignami syndrome (8). However, they did not obtain genetic testing for HSP (4,8).

Prior studies have suggested that PLS has considerable cerebellar, medial motor cortex, and selective corpus callosum involvement with the relative sparing of the postcentral gyrus and genu of the corpus callosum (6). Focal 'knife edge' atrophy of the precentral gyrus has been identified as the only structural abnormality allowed in PLS (10). Our study adds to the limited literature of radiologic abnormalities reported with PLS. It is important to note that these imaging findings may be suggestive of PLS, but they are not pathognomonic.

In conclusion, the "Ear of the lynx" radiological sign is not limited to SPG 11 and 15 and can be seen in patients with PLS.

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The Country Doctor

Vernon Rowe, MD

"It stands beside the same old apple tree." From *The Grindstone*, by Robert Frost, a poem about the creation of art.

I was alone in the small helicopter, the rotor blades spinning above my head. They sliced the fog into spirals, like a knife peeling an apple. My throat muscles drew as tight as a noose, as cloud pushed me closer and closer to the ground. With all that training in medicine and flying, how in the hell had I got myself into a fix like this?

I held Neurology clinics at hospitals in small towns around Kansas City. Some of the patients worked family farms, in the field day and night during planting and harvest. Others worked in small factories, manufacturing moldings or battery parts. Some worked in meat processing plants. A few were lawyers or teachers or dentists. Some were third generation welfare, who would never make it over the poverty line. All in all, they were like the folks I grew up with, in a small mountain town in western North Carolina.

To get to these clinics, I flew small planes, and landed at local airports. Sometimes I had to fly the planes on instruments, racking up hard instrument hours, especially in winter. But I was instrument rated, current, and legal. And I loved to fly, suspended as I was between heaven and earth, whatever the weather.

One day, though, I made a mistake. I took off and climbed on instruments, but Center told me I was flying in the wrong direction. In my rush to avoid even worse weather, I forgot to adjust a critical instrument. It was then I realized I was legal, but not safe.

As the old saying goes: There are old pilots, and bold pilots, but there are no old bold pilots. So I turned to flying a two-seat helicopter. I resolved I was through with instrument flying. I wasn't going anywhere unless I could see the ground below, and land anywhere if the weather turned foul.

And that little helicopter was like a magic carpet. From it, flying at a few hundred feet, I could see deer foraging in the fields in the morning. I could see wind-rippled fields of wheat, that looked like waves on the surface of the ocean. At night, the jeweled lights of the city passed beneath me, like phosphorescent plankton. And best of all I could land at the helipads of most of the hospitals, and hover taxi to a parking place.

But now, now, fog and cloud were smothering me, forcing me into the ground and a grave. The weather had started off clear with unlimited visibility, CAVU as pilots like to call it. The forecast was good. But I should have known better. The little town where I was headed might as well have been in another universe. In-route fog could develop quickly, when sunlight hit the rain-drenched fields.

Carburetor heat with visible moisture and low manifold pressure—Check. A quick 180-degree turn—and I'm out of it—for a few seconds.

I'd flown that route a hundred times. I thought I knew every inch by heart. But without a good view of the ground, and without instruments, I was lost. If I could reach a highway a few miles to the west, I could follow it to my destination. So I turned west, found the highway, and began to inch along its course

Poles began to appear out of the fog. Sometimes they switched sides of the road, along with the wires they carried. Wires—a big killer of helicopters. Pilots couldn't see them until it was too late. Low visibility and a ragged ceiling would kill Kobe Bryant, many years later.

The fields on either side of the road were drowned in standing water. Landing on the highway itself was death by truck. So I crept, crept along.

Then suddenly a farmhouse appeared to my right, as if materializing out of the mist. At first I thought it was an illusion. But then a calf appeared in the yard, beside an ancient apple tree.

Ease over the power line. Keep away from the tree and the calf. Kiss the ground with the skids...and mixture, mags, master...off. The rotor blades whirling over my head slowly came to a stop.

My hands were white as death as I reached for the door latch. Stepping onto the skid, my legs gave way, and I tumbled to the ground. For an eternity of relief I lay there, gazing at the grayness above.

The house and yard were quiet as a graveyard. I somehow got up and stumbled to the door. Before I could knock, a woman with gray eyes deep set in a wizened face opened it. She wore a flour sack dress, like one of my Appalachian aunts. She offered me coffee, bitter and hot.

I called my nurse and told her what happened. She said she knew just where I was, about four miles north of town.

When I got to the clinic, patients were waiting. I said I was sorry for being late, and told them I was held up by the weather. Helen was there with her husband. He took her for rides to familiar places to remind her of who she was. *For better or for worse.* And Jim and his wife—I gave them the news of his brain tumor with his little girl playing on the office floor. *In sickness and in health.*

Those clinics died a long time ago, but their memories can come alive with me still. If I close my eyes, and conjure them up, I can still see the farmhouse and apple tree, that saved the life of a country doctor.

Thanks, David Ray

Vernon Rowe, MD

Whirling out of the dustbowl,
infused with grief from the very start,
you showed us how to treasure life
and friends and our beloveds.

And to listen to birdsong
through the A-10 fighters thundering over
the sands of your early and late life home.
And to speak for peace in the face of war.

You taught us to sing each syllable
of alternative reality before we think.

And you taught us that though we are not
always who we think we are
and perhaps never will be who we hope
to be, who we are will always be
enough.

Proceedings of the 2022 Neuromuscular Study Group Meeting

Richard J. Barohn, MD

It is a pleasure to once again publish the proceedings of the Neuromuscular Study Group (NMSG), formerly known as the Muscle Study Group (MSG) meeting that will be held in Stresa, Italy, Sept. 30-Oct 2, 2022. We have officially changed the name to NMSG to emphasize that this scientific group is home to researchers in both motor neuron and peripheral nerve disorders.

This year we are pleased to announce that we have an all-time record number of conference participants. This is our first in-person meeting since the start of the COVID pandemic. We are lucky to hold this meeting on beautiful Lake Maggiore, Italy. We want the NMSG to become the popular forum for neuromuscular researchers to gather and share ideas.

The attendance this year is over 200 and we had 141 abstracts submitted. The majority of the abstracts will be presented as posters, and some were selected for platform presentations. We have invited many international experts in neuromuscular disorders to present at this meeting.

We once again have brought back the popular neuromuscular "shark tank". This will be our fourth year hosting this event. The six presenters, who are junior researchers, will pitch their research idea to our shark judges. The shark panel this year are Aziz Shaibani, Emma Ciafaloni, Tahseen Mozaffar and Anthony Amato. The sharks will then select one of the competitors to receive a $10,000 award that they will use to conduct the research project they pitched. The winner will present at a future NMSG conference. In the spring of 2022, we hosted our first shark tank competition that was not part of the annual NMSG meeting.

Below is a table of the previous shark tank competition winners, the title of their projects and year they won the event:

Dr. Vinojini Vivekanandam (UK)	MEND (Mexiletine Versus Lamotrigine in Non-Dystrophic Myotonia)	2020 Annual Meeting
Dr. Katy Dodd (UK)	The Innate Immune System in Myasthenia Gravis	2021 Annual Meeting
Jenna Linn Lammers (USA)	The Therapeutic Play Gym Pilot Study	2021 Annual Meeting
Anza Memon (USA)	Plasma Exosomes as a Blood Biomarker for Diabetic Peripheral Polyneuropathy	2022 Spring Shark Tank

This year the NMSG is again very grateful for this year's planning committee who spent hours working to organize the program.

The 2022 planning committee is:

CHAIR
Valeria Sansone, M.D., Ph.D.
NEMO Clinical Center

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NMSG CO-CHAIR
Michael Hanna, M.D.
University College London

Thank you to the 2022 sponsors for the NMSG who made this meeting possible. The complete list of sponsors is located in the attached meeting program.

We also want to thank Liz Paulk, our NMSG administrative director, for her amazing work to pull off another successful NMSG meeting.

We are publishing the issue of the RRNMF Neuromuscular Journal (Volume 3, Issue 3) before we gather in Italy. This will allow the opportunity for all to review the program and abstract prior to the conference.

- Richard J. Barohn
Co-Chair, Neuromuscular Study Group

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Abstract #610 Shark Tank Winner/presenter

Therapeutic Play Gym: Feasibility of a caregiver-mediated exercise system for infants and young children with severe neuromuscular weakness

J. Lammers, S. Norman, J. Berthy, J. Bender

Powell Gene Therapy Center, University of Florida
Gainesville, Florida

ABSTRACT

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

Objective*:* Evaluate safety and feasibility of caregiver-mediated exercise training with a Therapeutic Play Gym (TPG).

Methods: Nine children with severe neuromuscular weakness enrolled in the study. All completed baseline and Month 3 testing with the exploratory TPG-specific FUNctional Measure (FUNM), and Caregiver Impression of Change Questionnaire (CICQ). Testing occurred in home environments or at naturally occurring episodes of care at the University of Florida.

Mid-study results: Participants collectively trained for 16,730 minutes with no TPG-related adverse events. FUNM scores (attached) minus (not attached) to TPG was p=0.0039 and change in function (while not attached to TPG) was p=0.0078. CGIC average score was p=0.0039 and Overall Physical Wellbeing p=0.0078.

Conclusion: Exercise training using the TPG device is yielding promising results in terms of functional and global improvements over 3 months.

Abstract #524 Presenter

Effect of different corticosteroid dosing regimens on clinical outcomes in boys with Duchenne muscular dystrophy (DMD): a randomized clinical trial

M. Guglieri[1], K Bushby[1], M. P. McDermott[2,3], K. A. Hart[2], R. Tawil[2], W. B. Martens[2], B. E. Herr[2], E. McColl[4], C. Speed[4,5], J. Wilkinson[4], J. Kirschner[6,7], W. M. King[8], M. Eagle[1], M. W. Brown[2], T. Willis[9], R. C. Griggs[2], and the FOR DMD Investigators of the Muscle Study Group.

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[7]Department of Neuropediatrics, University Hospital Bonn, Bonn, Germany
[8]Ohio State University, Columbus, Ohio
[9]The Robert Jones and Agnes Hunt Orthopaedic Hospital, NHS Foundation Trust, Oswestry, United Kingdom

Introduction: Corticosteroids improve muscle function in boys with DMD.

Objective: This study compares efficacy and side effects of the three most commonly prescribed corticosteroid regimens in young boys with DMD.

Methods: we completed an international randomized, double-blind, parallel-group clinical trial at 32 sites. Participants were randomized to daily prednisone, daily deflazacort or intermittent prednisone. The study enrolled 196 corticosteroid-naïve boys with DMD ages 4-7 years. Boys were assessed for three years.

Results: Daily regimen were superior to the intermittent regimen for all motor function outcomes. There were no significant differences in efficacy between daily prednisone and deflazacort. Both daily and intermittent prednisone regimen were associated with greater weight gain than deflazacort. Slowing of growth was less severe with the intermittent regimen than with the daily regimens, with daily deflazacort associated with the greatest slowing of growth.

Conclusions: This study establishes the benefit and safety of long-term daily corticosteroid treatment.

Abstract #585

BALance Training in CMT1A- BALTiC Study- A randomised controlled feasibility trial

M.M. Dudziec, L.E. Lee, C. Massey, D. Tropman, M. Skorupinska, M. Laurá, M.M. Reilly, G.M. Ramdharry
(London, UK)

Introduction: People with Charcot Marie Tooth Disease (CMT) report problems with balance. Few studies have looked at practical interventions to improve this.

Objectives: To investigate the feasibility and effect of a home-based programme of multi-sensory balance and strength training for people with CMT1A.

Methods: Outcome measures included disease severity, function, patient reported measurements and posturography, performed at baseline and 12 weeks. Fourteen participants were randomised to either 12 weeks of intervention or treatment as usual (TAU). The intervention was a home-based programme of strengthening and multi-sensory balance exercises. Final assessments repeated those carried out at baseline.

Results: Thirteen people completed the study. The intervention was well tolerated. Posturography measures demonstrated moderate to large effect sizes in favour of the intervention. Functional measures of balance and mobility showed larger effect sizes.

Conclusions: The intervention was safe and feasible with improvements in balance measures.

Abstract #587

The feasibility and effect of Ankle Foot Orthoses and in-shoe vibrating insoles on standing balance in people with inherited neuropathy- preliminary results

M.M. Dudziec, L.E. Lee, D. Tropman, M. Skorupinska, M. Laurá, M.M. Reilly, G.M. Ramdharry (London, UK)

1. Introduction: People with inherited neuropathy (IN) report problems with balance. External support to the foot and ankle are frequently prescribed, though no data currently looks at the effects of these on balance. Vibration to the foot has shown promise in diabetic neuropathy, though has not been explored in IN.

2. Objectives: To investigate the effect of (1) external support from ankle foot orthoses (AFOs) and (2) vibratory feedback to the sole of the foot on standing balance in people with IN.

3. Methods: This cross-sectional feasibility study used posturography measures to compare shoe only, AFOs and vibrating insoles. Demographic data included disease severity, strength, sensation.

4. Results: Ten people with IN participated. 50% used AFO's prescribed by a health professional. Mean CMT Examination Score was 10.2 (range 6-15). Posturography data is in preparation.

5. Conclusions: The study was safe and feasible. Effect on balance will be assessed and presented.

Abstract #507

Barriers in decision making for patients with ALS accepting a PEG feeding tube

Introduction: What are barriers and concerns regarding placement of a PEG tube feeding?

Objectives: Identify the level of knowledge about tube feedings and the sources used to obtain knowledge, barriers and concerns that ALS patients have regarding PEG tube feeding.

Methods: Two surveys were given before (when a feeding tube was felt indicated) and at a clinic visit 3 months later, to determine factors influencing their decision for or against a PEG.

Results: Patients have stress, anxiety, and fear regarding placement, which influence choosing PEG. After PEG placement, most report that the procedure and use are easier than expected and they would do it again and would recommend it to others. Several factors were identified that could reduce concerns and lead to placement.

Conclusions: Early introduction and education about PEG placement may be beneficial to improve acceptance of PEGs relieving, fears and stress for ALS patients and caregivers.

Abstract #516

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USE OF 3D PRINTER IN A REHAB LAB FOR THE CREATION OF CUSTOMIZED ASSISTIVE DEVICES WITH USERS WITH RADIATION-INDUCED BRACHIAL PLEXOPATHY TO INCREASE PARTICIPATION: CASE STUDY

F. Pilla, P.G. Ianes*, S.Casagrande**, B. Gasperini*, R. Zuccarino***

*U.O. Medicina Fisica e Riabilitazione APSS Trento - Ospedale Villa Rosa Pergine Valsugana (TN)
**Centro Clinico NeMO Trento - Ospedale Villa Rosa Pergine Valsugana (TN)

Background: Villa Rosa RehabLab, Trento Italy, aims to design 3D printed personalized Assistive Devices (AD) to facilitate and promote participation through a user-centred co-design process.; direct involvement of the user in the design process ensures a correspondence of the AD to his/her needs, aiming to empower the person in the therapeutic strategy, ensuring the AD's continuous use and avoiding stigmatization. The use of 3D printer is increasingly popular in the medical world, particularly in rehabilitation and occupational therapy for the manufacture of personalized adaptations and assistive devices. M.A. 58 y.o., diagnosed with radiation-induced brachial plexopathy since 2012, at the initial occupational therapy interview reported difficulty in cutting hard foods, reporting pain when he presses the knife with his left arm. Patient's quality of performance was observed and self-perception of performance and satisfaction scored using the Canadian Occupational Performance Measure (COPM)

Objective: Improve quality of performance and decrease pain when performing this task

Method: After ascertaining that no commercial AD was available, an AD dedicated to this function was designed by the user on paper, and afterwards the occupational therapist created a wood prototype. Once the functionality of the prototype was ascertained, the user, guided by the therapist, drew the object with desired shape and sizes using FUSION360, which was then fabricated with the 3D printer.

Result: The client's quality of performance improved using the fabricated AD, as did his COPM scores

Conclusion: The RehabLab and use of 3D printer can improve independence and participation with individuals with radiation-induced brachial plexopathy.

Abstract #520

PHASE 3 STUDY OF ORAL EDARAVONE IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS: 48-WEEK RESULTS

Angela Genge, MD, FRCP(C)*, Gary L. Pattee, MD**, Gen Sobue, MD, PhD***, Philippe Couratier, MD, PhD****, Daniel Selness, RN, BA, MBA*****, Sachin Bidani, M Pharm*****, Manabu Hirai, MS******, Takeshi Sakata, MS******, Alejandro Salah, MD, PhD, MBA, BCMAS*******, Stephen Apple, MD*******

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INTRODUCTION: Intravenous (IV) edaravone (Radicava®/Radicut) slows the rate of physical functional decline in ALS. There is interest in a non-IV formulation.

OBJECTIVES: To assess the long-term safety and tolerability of recently FDA-approved Radicava ORS® (edaravone) oral suspension in patients with ALS in a global, open-label, phase 3 study (MT-1186-A01).

METHODS: A 105-mg ORS dose was administered in treatment cycles that replicated IV edaravone dosing.

RESULTS: In the Week 48 safety analysis (n=185), the most common treatment-emergent adverse events (TEAEs) were fall (22.2%) and muscular weakness (21.1%). TEAEs considered to be related to ORS, serious TEAEs, and TEAEs leading to death were reported by 46/185, 48/185, and 12/185 patients, respectively. TEAEs leading to discontinuation included tremor (n=1) and gait disturbance (n=1), both considered ORS-related. There were no serious TEAEs, or TEAEs leading to death, related to ORS.

CONCLUSIONS: ORS was generally safe and well tolerated, with no new safety concerns identified.
Sponsorship: Mitsubishi Tanabe Pharma Development America, Inc., and Mitsubishi Tanabe Pharma America, Inc.
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Disclosure:
A. Genge has served as a consultant for Mitsubishi Tanabe Pharma, Inc.
G.L. Pattee has served as a consultant for Mitsubishi Tanabe Pharma, Inc.
G. Sobue has a served as a medical advisor for Mitsubishi Tanabe Pharma Corporation.
P. Couratier has served as a consultant for Biogen and as an editor for Elsevier.
D. Selness and S. Bidani are employees of Mitsubishi Tanabe Pharma Development America, Inc.
M. Hirai and T. Sakata are employees of Mitsubishi Tanabe Pharma Corporation.
A. Salah and S. Apple are employees of Mitsubishi Tanabe Pharma America, Inc.

Abstract #521

PHASE 3B, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP STUDY TO EVALUATE EFFICACY AND SAFETY OF INVESTIGATIONAL ORAL EDARAVONE ADMINISTERED OVER 48 WEEKS IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (MT-1186-A02)

Jeffrey Rothstein, MD, PhD[1], Shari DeSilva, MD[2], Lorne Zinman, MD, MSc, FRCPC[3], Marvin Chum, MD, FRCPC[4], Adriano Chio, MD, FAAN[5], Albert C. Ludolph, MD[6], Gen Sobue, MD, PhD[7], Manabu Doyu, MD, PhD[8], Daniel Selness, RN, BA, MBA[9], Vesna Todorovic, MD, MPhil[10], Manabu Hirai, MS[11], Takeshi Sakata, MS[11], Art Wamil, MD, PhD[9], Alejandro Salah, MD, PhD, MBA, BCMAS[12], Stephen Apple, MD[12]

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INTRODUCTION: Intravenous (IV) edaravone (Radicava®/Radicut) slows the rate of physical functional decline in ALS. There is interest in a non-IV formulation.

OBJECTIVES: Evaluate and compare long-term safety, efficacy, and tolerability of 2 dosing regimens of recently FDA-approved Radicava ORS® (edaravone) oral suspension over 48 weeks in patients with ALS in an ongoing, multicenter, phase 3b, double-blind, parallel group, randomized study (MT-1186-A02).

METHODS: Patients (n=380 expected, definite/probable ALS, FVC ≥70%, ALS duration ≤2 years) will be equally randomized into 2 groups: 1) 105-mg ORS daily x28 days, 12 cycles; 2) ORS daily x14 days, then placebo daily x14 days (Cycle 1); followed by ORS daily x10 days, then placebo daily x18 days (Cycles 2-12).
The primary objective will evaluate dosing regimen efficacy based on baseline to Week 48 ALSFRS-R score changes.

RESULTS: Ongoing.

CONCLUSIONS: Safety, efficacy, and tolerability of 2 oral edaravone dosing regimens in patients with ALS will be determined.
Sponsorship: Mitsubishi Tanabe Pharma Development America, Inc., and Mitsubishi Tanabe Pharma America, Inc.
Acknowledgements: *p*-value provided editorial support.
Disclosure:
J. Rothstein is a consultant for Expansion Therapeutics, National Institutes of Health, Department of Defense, F Prime, The ALS Association.
S. DeSilva has nothing to disclose.
L. Zinman has received honoraria for consulting with MTP, Biogen, Amylyx, and Cytokinetics.
M. Chum has nothing to disclose.
A. Chio 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.

A. C. Ludolph has served as a scientific consultant for Mitsubishi Tanabe Pharma America, Inc.
G. Sobue has served as a medical advisor for Mitsubishi Tanabe Pharma Corporation.
M. Doyu is a medical advisor for MT-1186-A02 study.
D. Selness is an employee of Mitsubishi Tanabe Pharma Development America, Inc.
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A. Salah is an employee of Mitsubishi Tanabe Pharma America, Inc.
S. Apple is an employee of Mitsubishi Tanabe Pharma America, Inc.

Abstract #522

Phase 3, Open-Label, Safety Extension Study of Investigational Oral Edaravone Administered Over 96 Weeks in Patients with AMYOTROPHIC LATERAL SCLEROSIS (MT-1186-A03)

Daniel Selness, RN, BA, MBA*, Manabu Hirai, MS**, Takeshi Sakata, MS**, Alejandro Salah, MD, PhD, MBA, BCMAS***, Stephen Apple, MD***

Mitsubishi Tanabe Pharma Development America, Inc., Jersey City, New Jersey, USA*; Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan**; Mitsubishi Tanabe Pharma America, Inc., Jersey City, New Jersey, USA***

INTRODUCTION: Intravenous (IV) edaravone **(**Radicava®/Radicut) slows the rate of physical functional decline in ALS. There is interest in a non-IV formulation.

OBJECTIVES: To assess the continued long-term safety and tolerability of Radicava ORS® (edaravone) oral suspension in patients with ALS in ongoing, multicenter, phase 3 studies.

METHODS: Study MT-1186-A03 (n=130 anticipated) is a long-term safety and tolerability extension study for MT-1186-A01. Patients who complete MT-1186-A01 and still meet the enrollment criteria will be eligible for MT-1186-A03 and will receive ORS for another 96 weeks.
Patients will continue to be administered a 105-mg ORS dose in treatment cycles that replicate IV edaravone dosing. Study MT-1186-A03 includes a primary safety analysis, and exploratory end points including ALSFRS-R score change from baseline, and time to death, tracheostomy, or permanent assisted mechanical ventilation.

RESULTS: Ongoing.

CONCLUSIONS: MT-1186-A03 will provide important information on the continued long-term safety and tolerability of ORS in patients with ALS.
Sponsorship: Mitsubishi Tanabe Pharma Development America, Inc., and Mitsubishi Tanabe Pharma America, Inc.
Acknowledgements: *p*-value communications provided editorial support.
Disclosure:
D. Selness is an employee of Mitsubishi Tanabe Pharma Development America, Inc.
M. Hirai is an employee of Mitsubishi Tanabe Pharma Corporation.
T. Sakata is an employee of Mitsubishi Tanabe Pharma Corporation.
A. Salah is an employee of Mitsubishi Tanabe Pharma America, Inc.
S. Apple is an employee of Mitsubishi Tanabe Pharma America, Inc.

Abstract #534

Evolution of Treatment induced Airway Obstruction in ALS patient on NIV

Introduction: Treatment induced Airway Obstruction (TAO) is associated to increased mortality in ALS patients, therefore early detection of this problem is relevant in clinical care. No longitudinal data on the evolution of TAO are available.

Case Report: 3 ALS patients showed TAO-associated desaturation after several months of NIV use.

Methods: A retrospective analysis of ventilator data, ABGs and sleep studies or night oximetry was performed on these patients.

Results: At NIV initiation 3/3 patients showed an AHI weekly average>10/h (respectively 15.7, 13.2, 16.3 event/h). Detection of TAO-associated desaturation occurred at planned follow-ups after respectively 15, 5 and 12 months. AHI from ventilator software was fluctuating, but AHI values >5/h were associated with T89>5 min only in 16/21 nights and with ODI>10 in 8/22 nights.

Conclusions: AHI from ventilator software may allow early detection of TAO and predict the risk of developing TAO-associated desaturations.

Abstract #539

Preliminary data from the ADAPT-NMD study: experiences of patients and clinicians using a new co-designed self-management support programme

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Introduction: As there is no cure for most neuromuscular diseases (NMDs), self-managing symptoms is essential for participation in daily activities. The Bridges Self-Management Programme was originally developed in stroke and has now been adapted for people living with neuromuscular diseases (NM Bridges), but this new version needs evaluation.

Methods: Ten NMD patients who received NM Bridges, and the six clinicians who were trained in delivering it, participated in semi-structured interviews exploring their experiences of the programme. These interviews will form part of a wider mixed methods feasibility evaluation which is currently ongoing. Reflexive thematic analysis was used to code data and identify key domains and themes.

Results: Results will be presented at the 2022 Muscle Study Group Annual Scientific Meeting.

Conclusion: Qualitative data generated from this study will form part of an evaluation of the feasibility of delivering and implementing NM Bridges within the context of a specialist neuromuscular service.

Abstract #544

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

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

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

Methods: Data will be collected from people with PMMs who have previously participated in Phase I and Phase II/III clinical trials at The National Hospital for Neurology and Neurosurgery, using a patient-administered survey.

Conclusion: We anticipate our data informing the early stages of study design to ensure recruitment and retention of patients during PMM clinical trials are maximised. This work will have potential implications for other rare disease interventional studies.

Abstract #548

Baseline Characteristics of Patients with Myasthenia Gravis Enrolled in an Expanded Access Programme (EAP) for Efgartigimod

Jan L. De Bleecker[1], Wolfgang N. Löscher[2], Christiane Schneider-Gold[3], Jan Verschuuren[4]; Céline Tard[5], Deborah Gelinas[6], Omar Rahman[6], Erin Lambert[6], Benjamin Van Hoorick[6], Jon Beauchamp[6], Renato Mantegazza[7]
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Introduction: In the phase 3 ADAPT study, efgartigimod was well-tolerated and efficacious in patients with generalised myasthenia gravis (gMG).

Objective: The EAP is for patients with gMG and ineffectively controlled symptoms (IgG ≥4g/L in previous month), who cannot enrol in a clinical trial.

Methods: Enrolment is ongoing across Europe (USA ceased following efgartigimod approval). Country-specific/individual protocols aligned to local practice apply (US protocol: NCT04777734).

Results: Enrolled patients (N=46) receive intravenous efgartigimod 10mg/kg according to fixed/flexible treatment cycles. As of 8 April 2022, most are female (56.5%), aged 45–64 years (39.1%); 69.6% are AChR-Ab+, 21.7% are seronegative and 8.7% are MuSKAb-positive. 86.9% had IgG >6g/L. 54.5% (N=44) are MGFA class III; previous/current treatments (≥30 patients) include: steroids 95.3%, pyridostigmine 72%, intravenous immunoglobulin 69.7%, and 25% had prior thymectomy, 63.6% had ≥2 comorbidities.

Conclusions: The EAP addresses an unmet need and provides insights into characteristics and management of patients with gMG.

Abstract #553

Design and Implementation of the Tofersen Early Access Program

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*Cambridge, MA, USA
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[a]at the time the abstract was developed

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Abstract:

Introduction: Tofersen (BIIB067) is an investigational drug in people with amyotrophic lateral sclerosis associated with mutations in the superoxide dismutase 1 (*SOD1*) gene (*SOD1*-ALS).

Objectives: To describe the design and implementation of the tofersen EAP.

Methods: The tofersen EAP, initially limited to persons with rapidly progressive disease, began in July-2021 when the last randomized participant received their first dose in the open-label extension (NCT03070119) of the Phase 3 VALOR (NCT02623699). In October-2021, VALOR results revealed that although the primary endpoint did not achieve statistical significance, consistent evidence suggested slowing of decline in faster-progressing participants. The EAP was then expanded to the broader *SOD1*-ALS population.

Results: As of 30-April-2022, the tofersen EAP was available in 31 countries and 115 people had been treated in 12 countries.

Conclusions: The tofersen EAP is designed to be inclusive, consistent with principles of medical ethics and prudent medical practice.

Abstract #556

One-year ENDEAVOR data (ambulatory, ≥4- to <8-year-olds): Phase 1b trial of delandistrogene moxeparvovec in Duchenne muscular dystrophy (DMD)

C. Zaidman,[1] C. Proud,[2] C. McDonald,[3] S. Mason,[4] M. Guridi,[5] S. Wang,[4] C. Reid,[6] E. Darton,[4] C. Wandel,[5] S. Lewis,[4] J. Malhotra,[4] D.A. Griffin,[4,7] R.A. Potter,[4] R. Salazar,[4*] L.R. Rodino-Klapac,[4] J.R. Mendell[7,8]
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*Presenting on behalf of the authors

Introduction: Delandistrogene moxeparvovec (SRP-9001) is an investigational gene transfer therapy being studied in DMD.

Objectives: ENDEAVOR (NCT04626674) is a two-part, open-label, Phase 1b study assessing expression/safety of commercially representative delandistrogene moxeparvovec material in four cohorts of patients with DMD.

Methods: Participants received a single intravenous dose ($1.33x10^{14}$ vg/kg, linear qPCR) of delandistrogene moxeparvovec. The primary outcome measure is change in micro-dystrophin protein expression from baseline to Week 12 (Part 1). Secondary outcome measures include safety (over 260 weeks).

Results: Data from the first 11 patients (Cohort 1; ≥4- to <8-year-old ambulatory boys) demonstrated micro-dystrophin protein expression at Week 12. We present 1-year safety and functional data and 12-week expression data from all Cohort 1 patients (n=20).

Conclusion: Data suggest that safety of commercially representative delandistrogene moxeparvovec material is consistent with clinical process material. One-year data from all Cohort 1 patients (n=20) will provide valuable information on safety/efficacy of delandistrogene moxeparvovec.

Disclosures:
CZ receives research support from and serves on an advisory board for Biogen, and was a paid consultant for Optum. CP participates on an advisory board and is a consultant for Biogen, Sarepta Therapeutics, AveXis/Novartis Gene Therapies, Genentech/Roche and Scholar Rock; serves as a speaker for Biogen; is PI of studies sponsored by AveXis/Novartis Gene Therapies, AMO, Astellas, Biogen, CSL Behring, Fibrogen, PTC, Pfizer, Sarepta Therapeutics, and Scholar Rock. CM reports grants from Capricor, Catabasis, Edgewise, Epirium Bio, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, Sarepta Therapeutics; and other from Capricor, Catabasis, PTC therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics. SM, SW, ED, SL, JM, DAG, RAP and RS are employees of Sarepta Therapeutics and may have stock options. MG, CR and CW are employees of F. Hoffmann-La Roche Ltd and have nothing to disclose. LRR-K is an employee of Sarepta Therapeutics, has received grant support from Sarepta Therapeutics and the Parent Project Muscular Dystrophy, and financial consideration from Sarepta Therapeutics and Myonexus Therapeutics. LRR-K is a co-inventor of AAVrh74.MHCK7.micro-dys technology. JRM has received study funding from Sarepta Therapeutics and has a service agreement with Sarepta Therapeutics to provide training on ongoing studies. JRM is a co-inventor of AAVrh74.MHCK7.micro-dys technology.

Abstract #557

Oro-Bulbar Involvement in patients with Spinal muscular atrophy treated with Nusinersen

Federica Trucco[1,2,3], Francesca Salmin[1], Andrea Lizio[1], Emilio Albamonte[1], Maria Chiara Frisoni[1], Luca Mauro[1], Giovanni Palazzo[1], Jessica Lops[1], Camilla Cattaneo[1], Susanna Pozzi[1], Jacopo Casiraghi[1], Alessandra Di Bari[1], Giorgia Coratti[4,5], Maria Carmela Pera[4,5], Marika Pane[4,5], Eugenio Mercuri[4,5] and VA Sansone[1]

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Introduction Nusinersen improves motor and respiratory function in spinal muscular atrophy (SMA). Less is known on oro-bulbar involvement (OBI).

Objectives To identify OBI assessments in SMA and to evaluate chewing and swallowing 1y post-nusinersen.

Methods Two-year multicentre prospective study. SMAII and III underwent tongue and facial muscle strength (Iowa Oral Performance Instrument,IOPI) and chewing and swallowing (Test of Masticating and Swallowing Solids,TOMASS) assessments.
Nusinersen-treated were compared with age-SMA-type matched naïve patients at baseline. Treated patients were followed for 1 year.

Results 63 patients were included, 42 naive(median age 32.7years), 21 treated(median age 28.5years). Baseline IOPI, TOMASS were similar in both groups.
Nusinersen treatment>1y was associated with improved chewing (SMAII) and swallowing (SMAIII). Time from disease onset to treatment was inversely correlated with chewing (r-0.4) and swallowing (r-0.6).

Conclusions TOMASS detects changes in OBI in SMA. Early and longer nusinersen treatment duration (>1year) was associated with reduced decline in oro-bulbar function.

Abstract #558

One-year ENDEAVOR data (ambulatory, ≥4- to <8-year-olds): Phase 1b trial of delandistrogene moxeparvovec in Duchenne muscular dystrophy (DMD)

C. Zaidman,[1] C. Proud,[2] C. McDonald,[3] S. Mason,[4] M. Guridi,[5] S. Wang,[4] C. Reid,[6] E. Darton,[4] C. Wandel,[5] S. Lewis,[4] J. Malhotra,[4] D.A. Griffin,[4,7] R.A. Potter,[4] R. Salazar,[4*] L.R. Rodino-Klapac,[4] J.R. Mendell[7,8]
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*Presenting on behalf of the authors

Introduction: Delandistrogene moxeparvovec (SRP-9001) is an investigational gene transfer therapy being studied in DMD.

Objectives: ENDEAVOR (NCT04626674) is a two-part, open-label, Phase 1b study assessing expression/safety of commercially representative delandistrogene moxeparvovec material in four cohorts of patients with DMD.

Methods: Participants received a single intravenous dose ($1.33x10^{14}$ vg/kg, linear qPCR) of delandistrogene moxeparvovec. The primary outcome measure is change in micro-dystrophin protein expression from baseline to Week 12 (Part 1). Secondary outcome measures include safety (over 260 weeks).

Results: Data from the first 11 patients (Cohort 1; ≥4- to <8-year-old ambulatory boys) demonstrated micro-dystrophin protein expression at Week 12. We present 1-year safety and functional data and 12-week expression data from all Cohort 1 patients (n=20).

Conclusion: Data suggest that safety of commercially representative delandistrogene moxeparvovec material is consistent with clinical process material. One-year data from all Cohort 1 patients (n=20) will provide valuable information on safety/efficacy of delandistrogene moxeparvovec.

Disclosures:
CZ receives research support from and serves on an advisory board for Biogen, and was a paid consultant for Optum. CP participates on an advisory board and is a consultant for Biogen, Sarepta Therapeutics, AveXis/Novartis Gene Therapies, Genentech/Roche and Scholar Rock; serves as a speaker for Biogen; is PI of studies sponsored by AveXis/Novartis Gene Therapies, AMO, Astellas, Biogen, CSL Behring, Fibrogen, PTC, Pfizer, Sarepta Therapeutics, and Scholar Rock. CM reports grants from Capricor, Catabasis, Edgewise, Epirium Bio, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, Sarepta Therapeutics; and other from Capricor, Catabasis, PTC therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics. SM, SW, ED, SL, JM, DAG, RAP and RS are employees of Sarepta Therapeutics and may have stock options. MG, CR and CW are employees of F. Hoffmann-La Roche Ltd and have nothing to disclose. LRR-K is an employee of Sarepta Therapeutics, has received grant support from Sarepta Therapeutics and the Parent Project Muscular Dystrophy, and financial consideration from Sarepta Therapeutics and Myonexus Therapeutics. LRR-K is a co-inventor of AAVrh74.MHCK7.micro-dys technology. JRM has received study funding from Sarepta Therapeutics and has a service agreement with Sarepta Therapeutics to provide training on ongoing studies. JRM is a co-inventor of AAVrh74.MHCK7.micro-dys technology.

Abstract #560

Phase 1/2a trial of delandistrogene moxeparvovec in patients with Duchenne muscular dystrophy (DMD): 4-year update

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*Presenting on behalf of the authors

Introduction: Delandistrogene moxeparvovec (SRP-9001) is an investigational gene transfer therapy being studied in DMD.

Objectives: Study 101 (NCT03375164) is a Phase 1/2a, single-dose, open-label study assessing safety of delandistrogene moxeparvovec in DMD.

Methods: Four ambulatory patients with DMD (4–7 years old) were given an intravenous dose ($2.0x10^{14}$ vg/kg, supercoiled qPCR; linear plasmid standard equivalent of $1.33x10^{14}$ vg/kg) of delandistrogene moxeparvovec. The primary outcome measure is safety. Efficacy outcome measures include change in the North Star Ambulatory Assessment (NSAA).

Results: Previously, delandistrogene moxeparvovec demonstrated an acceptable long-term safety profile 3 years post-treatment. No serious adverse events (AEs), study discontinuations, or AEs associated with clinically relevant complement activation were reported. All patients demonstrated clinically meaningful improvement on the NSAA (mean change [standard deviation] from baseline to Year 3: +7.5 points [3.42]). We present long-term (4-year) safety/functional data.

Conclusion: The response following treatment provides proof-of-concept for continuation of delandistrogene moxeparvovec clinical trials.

Disclosures:

JRM has received study funding from Sarepta Therapeutics and has a service agreement with Sarepta Therapeutics to provide training on ongoing studies. In addition, he is a co-inventor of AAVrh74.MHCK7.micro-dys technology. ZS has received grant support from Sarepta Therapeutics and the Parent Project Muscular Dystrophy. KJL has received an institutional grant from Sarepta Therapeutics. LPL reports receiving salary support from Sarepta Therapeutics through Nationwide Children's Hospital to support training and quality control activities for their ongoing clinical trials and licensing fees for natural history data. NFR reports receiving salary support from Sarepta Therapeutics for Clinical Evaluator training for ongoing and upcoming clinical trials. MAI has nothing to disclose. LNA reports receiving salary support from Sarepta Therapeutics through Nationwide Children's Hospital to support training and quality control activities for their ongoing clinical trials. SL, RAP, DAG, MH, LH, SM, ED and DT are employees of Sarepta Therapeutics and may have stock options. KC and RS have nothing to disclose. LRR-K is an employee of Sarepta Therapeutics, has received grant support from Sarepta Therapeutics and the Parent Project Muscular Dystrophy, as well as financial consideration from Sarepta Therapeutics and Myonexus Therapeutics (now acquired by Sarepta Therapeutics). In addition, she is a co-inventor of AAVrh74.MHCK7.micro-dys technology.

Abstract #562

Integrated analyses of data from clinical trials of delandistrogene moxeparvovec in Duchenne muscular dystrophy (DMD)

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*Presenting on behalf of the authors

Introduction: Delandistrogene moxeparvovec (SRP-9001) is an investigational gene transfer therapy being studied in DMD.
Objectives: To analyse 1-year functional data from ambulatory patients (≥4 to ≤8 years old) with DMD who received a dose ($1.33x10^{14}$ vg/kg by linear qPCR) of delandistrogene moxeparvovec in clinical studies. These data were compared with a propensity score-weighted external comparator (EC) cohort (n=103) comprised of patients with DMD from other studies.
Methods: The dataset included patients from Study 101 (Phase 1/2a; NCT03375164), Study 102 (Phase 2; NCT03769116), and ENDEAVOR (Phase 1b; NCT04626674). The primary endpoint is 1-year change from baseline in the North Star Ambulatory Assessment.
Results: Functional data from 53 patients (Study 101, n=4; Study 102, n=29; and ENDEAVOR, n=20, Cohort 1) will be compared with the EC cohort. Safety data from all cohorts (Studies 101, 102 and ENDEAVOR) will be presented.
Conclusion: These analyses will provide valuable information on safety/efficacy of delandistrogene moxeparvovec.

Disclosures:
CZ receives research support from and serves on an advisory board for Biogen, and was a paid consultant for Optum. PBS reports being a consultant/independent contractor (AveXis, Biogen, Cytokinetics, and Sarepta Therapeutics) and receiving grants/research support (AveXis, Biogen, Cytokinetics, Ionis Pharmaceuticals, Sanofi Genzyme and Sarepta Therapeutics). CP participates on an advisory board and is a consultant for Biogen, Sarepta Therapeutics, AveXis/Novartis Gene Therapies, Genentech/Roche and Scholar Rock; serves as a speaker for Biogen; is PI of studies sponsored by AveXis/Novartis Gene Therapies, AMO, Astellas, Biogen, CSL Behring, Fibrogen, PTC, Pfizer, Sarepta Therapeutics, and Scholar Rock. CM reports grants from Capricor, Catabasis, Edgewise, Epirium Bio, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, Sarepta Therapeutics; and other from Capricor, Catabasis, PTC therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics. JWD reports grants from AMO, Audentes, Avidity, Biogen, Cytokinetics, Ionis Pharmaceuticals, Novartis Gene Therapies, Roche Pharmaceuticals, Sanofi-Genzyme, Sarepta Therapeutics, Scholar Rock. JWD participates on advisory boards and is consultant for Affinia Therapeutics, AMO Pharmaceuticals, Astellas Gene Therapies, Audentes Therapeutics, Avidity Therapeutics, Biogen, Cytokinetics, Epirium Bio, Ionis Pharmaceuticals, Kate Therapeutics, Novartis, Novartis Gene Therapies, Pfizer, Roche/Genentech Pharmaceuticals, Sarepta Therapeutics, Scholar Rock, Shift Therapeutics, Vertex. JWD participated in the PepGen Scientific Advisory Board (2021). JWD was a paid advisor to the Muscular Dystrophy Association and an unpaid advisor to Myotonic Dystrophy Foundation, CureSMA, SMA Foundation, Parents Project Muscular Dystrophy, Foundation Building Strength for Nemaline Myopathy, Cure CMD and Solve FSHD. JWD holds patents licensed to Athena Diagnostics for genetic testing of myotonic dystrophy type 2 (US patent 7442782) and spinocerebellar ataxia type 5 (US patent 7527931). SM, LH, LY, ED, JR, JM, TS and RS are employees of Sarepta Therapeutics and may have stock options. MG, CR and CW are employees of F. Hoffmann-La Roche Ltd and have nothing to disclose. LRR-K is an employee of Sarepta Therapeutics, has received grant support from Sarepta Therapeutics and the Parent Project Muscular Dystrophy, and financial consideration from Sarepta Therapeutics and Myonexus Therapeutics. LRR-K is a co-inventor of AAVrh74.MHCK7.micro-dys technology. JRM has received study funding from Sarepta Therapeutics and has a service agreement with Sarepta Therapeutics to provide training on ongoing studies. JRM is a co-inventor of AAVrh74.MHCK7.micro-dys technology.

Abstract #564

Preliminary Results from MLB-01-003: An Open Label Phase 2 Study of BBP-418 in Patients with Limb-girdle Muscular Dystrophy Type 2I (LGMD2I)

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Introduction: BBP-418 (ribitol) is an oral substrate supplementation intended to saturate the FKRP enzyme driving increased glycosylation of αDG, potentially ameliorating the root cause of LGMD2I.

Objectives: The study is intended to explore the safety, tolerability and efficacy of BBP-418 in patients with LGMD2I.
Methods: Study involved three open-label ascending dose cohorts treated for 3 months with BBP-418. Thereafter, all patients received 12g BID (weight adjusted) for 3 additional months.

Results: 14 patients (aged 12-53, 8/14 homozygous for the L276I mutation) were enrolled. After 90 days, participants showed a mean +0.14 (43%) increase in αDG glycosylation. Creatine kinase (CK) decreased an average of 64% at day 180, 36% to below 400 U/L. BBP-418 was well-tolerated with no observed treatment-related serious AEs or dose-limiting toxicity. Updated data will be provided.

Conclusions: Preliminary data suggests a positive effect on αDG glycosylation and CK. A global, double-blind placebo-controlled Phase 3 study is planned.

Abstract #565

Providing a sustainable, accessible cough and secretion management service for patients with Neuromuscular Disease throughout the COVID-19 pandemic

Introduction: In 2018, we set up an interdisciplinary cough and secretion management service for patients with neuromuscular disease. The aim was to improve the quality of life for those experiencing challenges with secretion management secondary to progressive cough or swallowing difficulties.

Here we show how the service adapted to meet patient needs during the pandemic.

Method: Data was collected retrospectively from clinic appointments April 2020 - October 2021.

Results: 166 appointments were conducted via face-to-face (n=34), video call (n=63), telephone call (n=63) and text exchange (n=2). Two did not attend.

Set-up of cough augmentation was possible via video consultation when pre-assessment and couriering of equipment was in place prior to the appointment. Virtual monitoring of peak cough flow was possible via electronic records.

Conclusion: The clinic is now a hybrid face to face and virtual clinic. This ensures accessible, effective and sustainable treatment.

Abstract #568

Comparison of open- and closed-state sodium channel blockers in the treatment of myotonia

P. Walker II, J. Myers, A. Voss, M. Rich (Dayton, OH)

Introduction: Myotonia Congenita patients suffer from debilitating stiffness. A subthreshold, non-inactivating, sodium persistent inward current (NaP), plays a central role in triggering myotonia. The current treatment for MC is mexiletine, an open-state Na+ channel blocker, which is only partially effective and has significant side effects. Mu-conotoxin GIIIA (uCTX) is a potent closed-state Na+ channel blocker.

Objectives: Our objective was to (1) compare each drug's ability to reduce NaP amplitude and (2) compare the use-dependent blocking of the Na+ current needed to trigger action potentials (NaF).

Methods: We utilized current clamp and voltage clamp of single muscle fibers from a mouse model of Myotonia Congenita.

Results: uCTX was significantly better than mexiletine in treating myotonia. uCTX selectively blocked NaP and spared NaF, whereas Mexiletine caused a much greater use-dependent block of NaF.

Conclusions: Our findings suggest that state-dependent blocking of Nav1.4 is a predictor of hypoexcitability as a side effect.

Abstract #569

Comparison of change in ability to perform timed function tests (TFTs) in nonsense mutation Duchenne muscular dystrophy (nmDMD) patients receiving ataluren: Strategic Targeting of Registries and International Database of Excellence (STRIDE) Registry vs phase 3 clinical trial

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Introduction: STRIDE is an ongoing registry providing real-world data on ataluren use in nmDMD patients.
Objective: We investigated if ataluren-treated nmDMD patients in STRIDE and a phase-3 clinical trial (Study 20) performed similarly in TFTs.
Methods: TFTs were assessed over 48 weeks for STRIDE and Study 020 patients.

Results: Ataluren-treated patients from STRIDE and Study 020 experienced smaller mean increases in time (s) to perform TFTs vs Study 020 placebo-allocated patients: 1.run/walk 10m [95% CI]: STRIDE 1.3 [0.6, 2.0],n=113; ataluren 020, 2.3 [1.3, 3.3],n=109; placebo, 3.5 [2.3, 4.7],n=110; 2.climb four stairs: STRIDE, 0.4 [−0.3, 1.0],n=73; ataluren 020, 2.7 [1.6, 3.7],n=105; placebo, 4.5 [3.0, 5.9],n=103; 3.descend four stairs: STRIDE, 0.3 [−0.1, 0.8],n=59; ataluren 020, 2.2 [1.1, 3.2],n=106; placebo, 4.0 [2.4, 5.5],n=100; 4.stand from supine STRIDE, 1.7 [0.6, 2.8],n=93; ataluren 020, 3.8 [2.7, 5.0],n=101; placebo, 3.9 [2.5, 5.3],n=96.

Conclusion: Ataluren delays decline in TFT performance in nmDMD patients vs placebo.

Abstract #571

Associations Between Daily Deflazacort or Prednisone and Ages at Disease Progression Milestones Among Patients with Duchenne Muscular Dystrophy (DMD)

Craig McDonald[1], Audrey Powell[2], Nicholas Mastrandrea[2], Efthimia Leonardi[2], James Signorovitch[3], Jessica Marden[3], Molly Frean[3], Henry Lane[3], Adina Zhang[3], Ha Nguyen[3]

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INTRODUCTION: Corticosteroids are the standard of care for DMD.

OBJECTIVE: Compare ages at disease progression milestones between patients on daily prednisone and deflazacort.

METHODS: DMD patients were identified from two natural history studies. Associations between daily steroid treatment, deflazacort or prednisone, and disease progression milestones were assessed.

RESULTS: 463 patients (mean age 9.86 years; n=288 deflazacort; n=175 prednisone) were identified. Deflazacort patients experienced a delay in timed rise from floor (RFF)>=10 seconds and RFF>=5 seconds of 0.88 years (log-rank $p<0.01$) and 0.94 years ($p<0.05$), respectively. Delays in progression were also observed for inability to RFF (+1.61 years, $p<0.001$) and inability to complete 4-stair climb (+1.87 years; $p< 0.01$) for patients receiving deflazacort vs. prednisone. Median age at loss of ambulation was older for deflazacort patients (15.92 vs. 14.89 years; $p<0.001$).

CONCLUSION: Use of daily deflazacort was associated with delayed progression of multiple ambulatory milestones in patients with DMD.

Abstract #572

Associations between deflazacort vs prednisone/prednisolone and disease progression markers in subgroups of patients with Duchenne muscular dystrophy (DMD)

Craig McDonald[1], Audrey Powell[2], Nicholas Mastrandrea[2], Efthimia Leonardi[2], James Signorovitch[3], Jessica Marden[3], Henry Lane[3], Adina Zhang[3], Ha Nguyen[3]

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INTRODUCTION: Corticosteroids are the standard of care for DMD.

OBJECTIVE: Compare outcomes in DMD by steroid type stratified by baseline age, ambulatory function, and steroid duration.

METHODS: Mean changes in 6WMD and other ambulatory outcomes were compared between patients from placebo arms of 4 DMD trials receiving daily deflazacort vs. daily prednisone,

RESULTS: Of 328 patients, 231 received daily steroids (n=127 deflazacort; n=104 prednisone). Deflazacort was associated with preservation of 35.4 meters of 6MWD over 48 weeks vs prednisone ($P<0.01$). Differences between deflazacort vs. prednisone were most pronounced among boys with the following baseline characteristics: aged ≥8 years (+44.5m, $P<0.01$), rise time ≥5 seconds (+41.3m, $P<0.01$) and steroid duration >3 years (+57.5m, $P<0.01$).

CONCLUSION: Benefits of daily deflazacort vs daily prednisone for preserving ambulatory function in DMD were most evident among patients who were older, had been on steroids longer, or were at a more progressed disease stage.

Abstract #573

Associations between steroid treatment and clinical outcomes among non-ambulatory patients with Duchenne Muscular Dystrophy (DMD)

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INTRODUCTION: Corticosteroids are the standard of care for DMD.

OBJECTIVE: Compare outcomes by steroid treatment among non-ambulatory (NA) DMD patients. **METHODS:** NA DMD patients were identified from an observational study of DMD disease progression (PRO-DMD-01). Associations between steroid treatment (prednisone, deflazacort, or no steroids) were assessed.

RESULTS: 86 NA patients (mean age 13.4 years; n=40 deflazacort; n=29 prednisone; n=17 no steroids) were included. Relative to no steroids, both steroids were associated with delays in median age at FVC%-predicted<60% (+0.9 [prednisone]; +2.3 [deflazacort]; log-rank p<0.01). Median ages at LVEF<55% were numerically prolonged, but non-significant (+2.7 [prednisone]; +0.8 [deflazacort]; p=0.65). While median ages at loss of hand-to-mouth function were not consistently reached, higher proportions of steroid patients maintained function at age 15 (85%-deflazacort; 83%-prednisone; 78%-no steroids; p<0.001).

CONCLUSION: Steroid use after loss of ambulation was associated with delayed progression of important pulmonary, cardiac and functional deficits in DMD.

Abstract #576

Assessment of Nusinersen Effect in Adult SMA Patients by Different Tools

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Introduction: Clinical data of nusinersen in adults is sparse and needs alternative tools other than HFMSE.

Objectives: To show the efficacy of nusinersen by different tools in adult SMA patients.

Methods: The outcome was assessed by HFMSE, MRC-SS, ALSFRS-R and 6-MWT at five different time points.

Results: Thirty-two patients were analyzed. Twenty-three patients improved by HFMSE at least 3-points after loading doses. There was a significant HFMSE increase in type 3 at each time point, whereas type 2 patients benefited from loading doses and subsequently stay stable. Motor improvement was positively correlated with baseline scores. There was a correlation between ALSFRS-R and HFMSE scores. Even ambulatory patients who could not show a 3-points increase by HFMSE, had more than 30m improvement by 6-MWT. Overall, 78% of patients have responded to treatment according to HFMSE or 6-MWT.

Conclusions: ALSFRS-R and 6-MWT may be alternative tools to monitor nusinersen effect.

Abstract #606

Efficacy of Efgartigimod in Clinical Practice: A Southwestern United States Perspective

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INTRODUCTION: Efgartigimod alfa-fcab is the first-in-class FcRn antagonist approved for treatment of acetylcholine receptor antibody-positive generalized myasthenia gravis (AChR+ gMG). Patients receive an initial 4-infusion treatment cycle with subsequent variability in treatment cycles.

OBJECTIVE: Describe clinical response to first treatment cycle in AChR+ gMG patients across four academic centers in Southwestern United States.

METHODS: Retrospective case series. Inclusion criteria: Patients with AChR+ gMG, completed first treatment cycle, and documented Myasthenia Gravis Activities of Daily Living (MG-ADL) score pre- and post-treatment cycle. Information regarding MG history, MG treatment(s) immediately prior to efgartigimod start, MG-ADL and other MG-specific outcome measures, laboratory data and adverse events will be discussed.

RESULTS: Twenty-two patients have completed at least one treatment cycle at our centers. Data collection and analyses are pending IRB approvals at each site.

CONCLUSIONS: Our experience suggests clinical improvement trends may not mirror findings of the pivotal trial.

Abstract #608

Results from STARFiSH: The Study of Testosterone and rHGH in FSHD

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Introduction: Testosterone combined with recombinant human growth hormone (rHGH) (combination therapy) synergistically improves respiratory function, lean body mass, protein synthesis, strength, and aerobic endurance in healthy adult populations.

Objectives: To determine the safety and tolerability of daily rHGH combined with biweekly testosterone injections in ambulatory men with FSHD.

Methods: Subjects received 24-weeks of combination therapy followed by a 12-week washout period. We collected safety and pharmacokinetics data and recorded changes in body composition, functional status, and disease-burden (FSHD-HI).

Results: Nineteen participants completed the study with no participants experiencing a serious adverse event. At 24 weeks, six minute walk distance increased by 37.3 meters ($p=0.0007$), lean body mass improved by 2.2 kg ($p<0.0001$), and total disease burden (FSHD-HI) decreased by 19% ($p=0.04$).

Conclusions: Combination therapy was safe and well-tolerated and may improve function, muscle mass, and disease burden in FSHD. Placebo-controlled trials are needed to further investigate this therapeutic approach.

Abstract #612

Exon skipping: The molecular mechanism underlying KIF5A-linked ALS pathogenesis?

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Single nucleotide variants in the cargo-binding domain of KIF5A, a neuronal motor protein involved in transport along microtubules, have been linked to ALS. Specifically, the variants are clustered near exon 27 splice-site junctions. To determine potential RNA splicing defects, we performed multiplexed digital PCR to quantify KIF5A mRNAs in HEK293 cells and calculated exon 27 incorporation rates for each variant. We showed that 5' splice-site (5'ss) variants selectively result in exon 27 exclusion. We further confirmed this result in CRISPR-edited human iPSCs differentiated into motor neurons. In a mouse model of one 5'ss variant, we observed a decrease in Kif5a protein expression in addition to RNA mis-splicing, implicating disrupted transcription and translation in KIF5A-linked ALS pathogenesis. We hypothesize that 5'ss variants in KIF5A selectively disrupt consensus splice sequences where crucial ribonuclear proteins – such as U1 RNP – bind, leading to exon exclusion from RNA, altered protein, and eventually ALS.

Abstract #613

A Qualitative Patient Experience Study of Eteplirsen Treatment for Duchenne Muscular Dystrophy

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Introduction: Eteplirsen is indicated for patients with Duchenne muscular dystrophy (DMD) with exon 51 skip-amenable mutations.

Objectives: Explore changes that eteplirsen-treated patients experienced in health-related quality of life (HRQoL), physical functioning, and activities of daily living (ADLs).

Methods: Fifteen caregivers of males with DMD were interviewed.

Results: Caregivers of ambulatory children reported improvements or maintenance since eteplirsen initiation in walking (n=7/9), running (n=6/9), and using stairs (n=4/9). Half of caregivers (n=7/15) reported improvements or maintenance in fine-motor movements; 1 caregiver (non-ambulatory) reported a continued decline. Improvements or maintenance in ADLs were reported in the total sample, as well as in fatigue (n=9/15), muscle weakness (n=7/15), and pain (n=6/15). Caregivers perceived maintenance as a positive outcome (n=6/9). Improvements generally occurred within 6 months post-eteplirsen initiation.

Conclusions: Most caregivers observed improvements or maintenance in aspects of their child's HRQoL, physical functioning, or ADLs since eteplirsen initiation.

STUDY SUPPORT: This study was funded by Sarepta Therapeutics, Inc.

DISCLOSURES: This study was funded by Sarepta Therapeutics, Inc. **CM, IS, and JI** are employees of Sarepta Therapeutics, Inc., and may own stock/options in the company. **CJ, HK, and SM** are employees of and own stock in Clarivate. Clarivate provides consultancy to various pharmaceutical and biotech companies, including Sarepta. **CT-R** reports consulting fees (Avexis, Biogen, Sarepta Therapeutics, Inc.) and site investigator for clinical trials: Avexis, Biogen, Cytokinetics, Genzyme, Pfizer, PTC, Roche, Sarepta, Scholar Rock. Previously presented at the Virtual ISPOR Europe 2021, November 30–December 3, 2021, and the Academy of Managed Care & Specialty Pharmacy (AMCP) Annual Meeting, March 29–April 1, 2022; McCormick Place Convention Center; Chicago, IL.

Abstract #614

Safety, β-Sarcoglycan Expression, and Functional Outcomes From Systemic Gene Transfer of rAAVrh74.MHCK7.hSGCB in LGMD2E/R4

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Introduction: Limb-girdle muscular dystrophy type 2E/R4 (LGMD2E/R4) is caused by mutations in the β-sarcoglycan gene.

Objectives: Report results from the phase 1/2 trial (NCT03652259) evaluating SRP-9003, a self-complementary rAAVrh74.MHCK7.hSGCB construct designed to restore SGCB protein production in patients with LGMD2E/R4.

Methods: Patients received single-dose of SRP-9003 IV infusion: Cohort 1 (n=3), 1.85×10^{13} vg/kg; Cohort 2 (n=3), 7.41×10^{13} vg/kg. Endpoints included safety, SGCB protein expression, and timed function tests.

Results: We report Year 3 (Y3; Cohort 1, n=3) and Year 2 (Y2; Cohort 2, n=2) results. SRP-9003 was well tolerated; adverse events occurred early and were manageable. Immunofluorescence showed robust SGCB expression post treatment maintained to Y2 in both cohorts. Improvements at or over baseline were demonstrated in timed function tests, which were generally sustained at Y3 in Cohort 1 and Y2 in Cohort 2.

Conclusions: These data suggest sustained efficacy of SRP-9003 therapy, supporting advancement of the clinical development program.

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DISCLOSURES: LRRK, ERP, SL, DAG, ASM, SN, and **XL** are or have been employees of Sarepta Therapeutics, Inc, and may own stock in the company. **LNA** and **LPL** received fees from Sarepta Therapeutics, Inc, for licensure of the LGMD natural history data set. **JRM** received financial support from Sarepta Therapeutics, Inc, for the travel to meetings to present any products sponsored by Sarepta. **BS**, **KJL, KC, NFR,** and **MAI** have no conflicts to disclose. Product is investigational only. Previously presented at the Muscular Dystrophy Association Clinical & Scientific Conference, March 13–16, 2022, Nashville, TN, the 2022 Academy of Managed Care & Specialty Pharmacy (AMCP) Annual Meeting, March 29–April 1, 2022, Chicago, IL, and the 14th Congress of the European Paediatric Neurology Society, 28 April–2 May 2022, Glasgow, Scotland, UK.

Abstract #618

Switching from alglucosidase alfa to avalglucosidase alfa: Baseline data from the Pompe Registry

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Introduction: Avalglucosidase alfa has received marketing authorization in several countries for Pompe disease.

Objectives: To characterize Pompe Registry patients who switched to avalglucosidase alfa.

Methods: Eligible participants had ≥1 alglucosidase alfa record immediately preceding switch to avalglucosidase alfa. Demographics, treatment duration/dose, and respiratory, ambulatory, and biomarker measures are summarized at switch.

Results: Through 01 April 2022, 41 participants (1[2.4%] IOPD/40[97.6%] LOPD; 37[90.2%] USA/4[9.8%] Europe; 21[51.2%] male) switched at a mean age of 49.0 (range 7.3–83.0) years; 29 (70.7%) had ≥5 years of alglucosidase alfa. The most common dose was 14–27 mg/kg/2 weeks for both alglucosidase alfa pre-switch (72.5%) and avalglucosidase alfa post-switch (78.0%). Baseline parameters (mean±SD) were 56.2±22.39% for FVC(Upright) %predicted, 353.0±159.47 meters for 6MWD, 11.7±25.48 mmol/mol urine hexose tetrasaccharide, and 596.8±460.36 U/L serum creatine kinase.

Conclusions: Pompe Registry post-switch patient data will support future studies of avalglucosidase alfa respiratory, ambulatory, and biomarker effectiveness in the real-world setting.
Funding: Sanofi
Type of study: Industry-sponsored

Abstract #620

LONG-TERM SAFETY, TOLERABILITY, AND EFFICACY OF EFGARTIGIMOD IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS: INTERIM RESULTS OF THE ADAPT+ STUDY

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Introduction: Efgartigimod is a human IgG1 antibody Fc-fragment that reduces pathogenic IgG autoantibody levels through neonatal Fc receptor blockade. Patients completing the phase 3 ADAPT study could enroll in the ADAPT+ long-term extension study.

Objective: To evaluate long-term safety and efficacy of efgartigimod.

Methods: Efgartigimod (10 mg/kg IV) was administered in cycles of once-weekly infusions for 4 weeks, with subsequent cycles initiated based on clinical evaluation.

Results: The most common adverse events were headache, nasopharyngitis, and diarrhea, which were mostly mild/moderate and occurred at frequency similar to ADAPT. Consistent improvements in MG-ADL and QMG (mean[SE] decrease at week 3 of cycles 1-5: –5.5(0.34) and –4.7(0.44), respectively) scores were observed during each cycle, mirroring repeatable reductions in total IgG and anti-AChR autoantibody levels.

Conclusion: These analyses suggest long-term efgartigimod treatment results in consistent reductions in IgG antibody levels and repeatable improvement in function and strength, with no new safety signals identified.

DISCLOSURES

RM has received consulting fees/honoraria or support for meeting participation from Alexion Pharmaceuticals, argenx BV, Ra Pharmaceuticals, Biomarin, Catalyst, UCB, TEVA, Merck, Roche, and Biogen.

VB has received research support from CSL, Grifols, UCB, Bionevia, Shire, and Octapharma.

TV has served as a speaker for Alexion, argenx, CSL Behring, and Allergan/Abbvie. He performed consulting work for argenx, Alexion, and UCB, and participated in trials in MG sponsored by Alexion, argenx, Ra/UCB, Horizon/Viela Bio, Regeneron, Janssen/Momenta, Cartesians Therapeutics, and Sanofi.

CK served as a deputy editor for *Neurology* and as a consultant for Acceleron Pharma, Inc, Akcea Therapeutics, Alnylam Pharmaceuticals, Inc, argenx, Biogen, CSL Behring, and Sanofi Genzyme. Dr Karam has received personal compensation for speaking engagements from Akcea Therapeutics, Alnylam Pharmaceuticals, Inc, CSL Behring, and Sanofi Genzyme and research/grant support from Akcea Therapeutics and Sanofi Genzyme.

SP reports following conflicts of interest, all outside this work: receiving lecture honoraria from Pfizer, Teva Actavis, Berlin Chemie Menarini, Mylan, Worwag, Adoc, and Salveo; research grants from Kedrion and Octapharma; consultant fees from argenx and Mylan; and travel grants from Octapharma, Kedrion, Teva Actavis, Sanofi Genzyme, Pfizer, Roche, Adoc, and Berlin Chemie Menarini; and reports no other conflicts of interest outside or related to this work.

JLDB has served as a consultant for argenx, Alexion Pharmaceuticals, CSL, UCB Pharma, Alnylam, and Orion Pharma.

HM has served as a consultant for Alexion Pharmaceuticals, argenx, and UCB. He received speaker honoraria from Japan Blood Products Organization and Chugai Pharmaceutical, and received research support from the Ministry of Health, Labour and Welfare of Japan.

AM received speaker honoraria from Alexion, argenx, Grifols, and Hormosan; honoraria from Alexion, UCB, Jansen, and Vitaccess for consulting services; and financial research support from Octapharma and Alexion. He is chairperson of the medical advisory board of the German Myasthenia Gravis Society.

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MP has served as a medical advisor or consultant for CSL Behring, Momenta, Alexion Pharmaceuticals, argenx BV, Zwijnaarde, Belgium, Catalyst Pharmaceuticals, and Terumo BCT.

AG, **PU**, **BVH,** and **CT** are employees of argenx.

KU has served as a paid consultant for argenx, Ra Pharma, UCB Pharma, Janssen Pharma, Viela Bio, Chugai Pharma, and Mitsubishi Tanabe Pharma and has received speaker honoraria from argenx, Alexion Pharmaceuticals, and the Japan Blood Products Organization.

JV receives financial support from the Target to B consortium and Prinses Beatrix Spierfonds; has been involved in trials or consultancies for argenx, Alexion, and NMD Pharma; and is coinventor on patent applications based on MuSK-related research. The LUMC received royalties from IBL and funding from argenx for MG research. All reimbursements were received by the LUMC. The author is a member of the European Reference Network for Rare Neuromuscular Diseases.

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Abstract #622

Treatment of active idiopathic inflammatory myositis by inhibiting FcRn: Pre-registration report of ALKIVIA, a phase 2/3 trial with efgartigimod

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Background: Idiopathic inflammatory myositis (IIM) is a potentially IgG-mediated group of diseases that targets muscle, skin, and other organs. Efgartigimod (EFG), an engineered Fc fragment that inhibits activity of the neonatal Fc receptor, will be studied as a therapy for IIM in a Phase 2/3 randomized, double-blind, placebo-controlled ALKIVIA trial.

Objective: To evaluate the efficacy and safety of EFG PH20 subcutaneous (SC) treatment compared with placebo in IIM, in addition to standard-of-care therapy.

Methods: ALKIVIA includes two independent stages – a proof-of-concept (24-week) Phase 2 and a confirmatory (52-week) Phase 3 stage. Randomized participants will receive EFG PH20 1000 mg or placebo PH20 SC weekly, added to standard-of-care. Immune-mediated necrotizing myopathy, dermatomyositis, or polymyositis (including antisynthetase syndrome) subtypes will be included in the study.

Results: The primary endpoint is total improvement score at weeks 24 (Phase 2) and 52 (Phase 3).

Conclusion:
ALKIVIA will evaluate three IIM subtypes that are potentially IgG-mediated.

Disclosures

Rohit Aggarwal	**Consultant**: argenx
Anthony A. Amato	**Medical Advisory Boards /Consultant:** Abcuro, argenx, Ra Pharmaceuticals, Horizon Therapeutics, OnoPharma, Alexion, EMD Serono, Takeda, Johnson & Johnson (COVID-19 vaccination program) CDC.
Despoina Papadopoulou	Employee of argenx
Bas van der Woning	Employee of argenx
Paul Duncombe	Contractor to argenx
Ingrid E. Lundberg	**Consultant**: Corbus Pharmaceuticals; Research grants: AstraZeneca; **Advisory boards**: AstraZeneca, Bristol Myers Squibb, Corbus Pharmaceutical, EMD Serono Research & Development Institute, argenx, Octapharma, Kezaar, Janssen, Pfizer **Stock shares**: Roche, Novartis

Abstract #633

The potential for remote aerobic exercise monitoring in people with neuromuscular disease – an example from experience with Parkinson disease

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Purpose: Regular aerobic exercise (AE) may alter the progression of neuromuscular disease (NMD)[1]. In-home virtual platforms may facilitate AE and allow monitoring for researchers and clinicians. As an example of potential feasibility in NMD, we present our data from in-home monitoring of AE behavior in people with Parkinson Disease (PwPD).

Participants: 81 PwPD [52(64%) male, age 64.±8.4 yrs; mild to moderate PD.

Methods: Goal AE dosage was cycling >20min, 3x/week x 12-months with virtual coaching. Successful monitoring of AE behavior was defined as the recording of summary exercise data.

Results: Over 9,100 exercise sessions were recorded. Ride duration ranged from 5->60 minutes. Participants completed 92.84% of the prescribed 150 rides (mean/SD 129.26±53.36).

Conclusion: Over a 1-year period, virtual AE monitoring was successfully implemented in a chronic neurologic disease sample. These results demonstrate potential feasibility for use in long-term (>6 mo) studies of exercise effects on individuals with NMD.

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Abstract #637

Evaluating the Efficacy and Safety of Tofersen in Adults with ALS and a *SOD1* Mutation: Results from the Phase 3 VALOR Trial and Open-Label Extension

Authors: A. Chiò, T.M. Miller*, M.E. Cudkowicz**, A. Genge***, P.J. Shaw****, G. Sobue*****, T. Cochrane******, I. Nestorov******, D.L. Graham******, P.Sun******, M. McNeill*******, L. Fanning******, T.A. Ferguson******,S. Fradette,******* on behalf of The VALOR and OLE Working Group (Turin, Italy; St. Louis, MO*; Boston, MA**; Montreal, QC, Canada***; Sheffield, UK****; Aichi, Japan*****; Cambridge, MA******; Maidenhead, UK*******)

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Abstract:
Introduction: Tofersen (BIIB067) is an investigational drug for amyotrophic lateral sclerosis associated with mutations in the *SOD1* gene (*SOD1*-ALS).

Objectives: The Phase 3 trial (VALOR) and its ongoing open-label extension (OLE) evaluated efficacy and safety of tofersen.

Methods: 108 adults were randomized in VALOR 2:1 to intrathecal tofersen 100 mg or placebo; 95 subsequently enrolled in the OLE. By January-2022, all participants had opportunity for 12 months of follow-up from VALOR baseline.

Results: Tofersen produced sustained reduction of total CSF SOD1 protein and neurofilament levels. Early tofersen initiation resulted in less decline across clinical and patient-reported measures compared with delayed initiation. Preliminary data suggest a reduction in risk of death and death or permanent ventilation. Most adverse events were mild/moderate. Serious neurologic events, including myelitis, aseptic meningitis, and papilloedema, were observed.

Conclusions: Longer-term integrated data from VALOR and its OLE suggest meaningful biological and clinical disease-modifying effects of tofersen.

Abstract #655

Development and evaluation of virtual pilates group for people with channelopathies

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Background: Muscle ion channelopathies are rare conditions where weakness, paralysis and/or muscle stiffness (myotonia) can be caused either by movement or following rest after exercise. People with channelopathies may be able to move normally between episodes or when warmed up, making it difficult for others to be able to understand the challenges related to exercise and activity.

Pilates is an exercise approach that focuses on controlled, repetitive movements, supporting individuals to optimise stability and strength especially around the core muscles and pelvis. This approach has been well received at patient engagement events, as well as YouTube videos developed for people with Neuromuscular conditions.

People with a channelopathy attending a specialist clinic expressed an interest in joining Pilates groups, but had found local groups inaccessible as the pace, and set up of classes often aggravated symptoms causing pain and/or weakness.

With increased isolation and new options for remote healthcare options following Covid-19 restrictions, there was an opportunity to trial a video Pilates group for people with channelopathies.

Aims:

1. To develop and evaluate a video pilates class for people with paramyotonia congenita (PMC)
2. To develop and evaluate a video pilates class for people with Andersen Tawil syndrome (ATS)

Methods/Materials: individual pre group assessments allowed participants to identify priorities, and to select individual outcome measures or targets. Group sessions were designed around individual group members feedback, with evaluation and reflection at the end of each session which then informed the next session.

Groups consisted of six 60 minute sessions. Questionnaires were completed after the course of 6 sessions.

Results: Participants of the PMC group completed all sessions. 2 of 3 from the ATS group completed all sessions.

Conclusion: Participants participated in all sessions, increasing repetitions, difficulty of and numbers of exercises over the 6 sessions. Sessions were structured to allow individuals to exercise without developing pain or stiffness or weakness, focusing on a maximum of 2 to 4 repetitions for the PMC group.

Informal peer support and motivation were also reported to be beneficial by participants.

Results of the ATS group will be presented once analysed.

Stratification of NMD and Outcome

Abstract #593 Platform Presenter

Clinical trial readiness and validation of onsite and remote evaluation in valosin containing protein-associated multisystem proteinopathy

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Introduction/Objective: The purpose of our study was to validate functional and patient reported clinical outcome assessments (COA) in patients with valosin containing protein-associated multisystem proteinopathy (VCP-MSP), a rare multisystemic disorder. Disease onset and presentation is heterogeneous, highlighting the need for a prospective clinical trial readiness study to inform future clinical trial design.

Methods: Thirty-two subjects have enrolled to-date (mean age: 53.1 years (range: 28-73)). A battery of COA were completed both in a clinic setting and remotely in the patient's home.

Results: COA performance was correlated with disease duration and genotype but not with age at visit highlighting the variability in the relationship between genotype and phenotype in VCP-MSP. Test-retest reliability was excellent (ICC≥0.8; P<0.001). Performance of most COA was the same across remote and onsite environments.

Conclusions: Cohort level feasibility and cross-sectional performance of all COA, sensitivity to change and meaningful change on included assessments over 1-year will also be presented.

Abstract #545 Flash Presenter

Motor Outcomes to Validate Evaluations in Facioscapulohumeral muscular dystrophy (MOVE FSHD): Protocol for an observational study.

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Introduction: 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.

Objectives: Evaluate 450 FSHD participants over three years with 200 participating in an MRI and muscle biopsy sub-study to validate FSHD evaluations.

Methods: Annual visits collect FSHD history, physical examination, patient reported outcomes, strength, timed functional tasks, and respiratory parameters. Sub-study participants will have additional biomarkers collected, including whole-body MRI at Baseline and 12-month visits with muscle biopsy occurring at Baseline and (n=40) at 4-month visits.

Results: MOVE FSHD study has over 175 participants across 12 US sites who have completed their Baseline visit and has begun enrolling sub-study participants.

Conclusions: MOVE FSHD addresses barriers to clinical trials by validating motor, clinical, and patient reported outcomes, as well as potential biomarkers. The data from MOVE FSHD can also improve our understanding of FSHD and directly impact patient care.

Funding: Grants from FSHD Society, Friends of FSH Research, FSHD Canada, and Avidity Biosciences.

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Abstract #590 Flash Presenter

Towards digital monitoring of Amyotrophic Lateral Sclerosis (ALS) patients: a deep learning-based application to assess the evolution of dysarthria via the analysis of multimedia data

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INTRODUCTION: Dysarthria is among the onset symptoms of bulbar ALS and, although its evolution correlates with other bulbar signs' decline, it is still a poorly characterized condition in literature[1].

OBJECTIVE: Based on Dysarthria Robertson's Profile (DRP), this work's aim is identifying new indices for assessing dysarthria progression from multimedia data analysis acquired via a remotly-usable digital tool based on a web-application (app) for smartphones.

METHODS: The app guides bulbar-onset ALS patients in performing DRP's verbal and motor tasks while recording audio and video through the smartphone's microphone and camera. Deep-learning algorithms process the acquired data and quantify patients' performance.

RESULTS: We delivered the app to 12 patients and compared the per-task app-outcome with the respective DRP-score. As a sample of result, app-outcomes show a correspondence with clinician's DRP-scores when assessing fatigability in diadochokinesis tasks.

CONCLUSIONS: The tool may support clinicians in early identification of dysarthria's progress enabling them to timely identify changes in disease trajectory.

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Abstract #504

Muscle Structure, Function, and Gait Patterns in Distal Hereditary Motor Neuropathy and the Effect of Carbon fiber Ankle Foot Orthosis on Gait

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Introduction: Distal Hereditary Motor Neuropathy (dHMN) is an inherited neuromuscular disorder characterised by distal weakness. It is a disabling condition and eventually many patients need aids to walk. Research is needed to understand the muscle impairments that lead to altered gait patterns, and to develop interventions to correct walking gait conservatively. The preliminary data presented here focuses on relationships between intramuscular fat infiltration, muscle strength and gait. We also explored the effect of bilateral carbon fibre ankle foot orthoses (AFO) on gait of people with DHMN.

Methods:
Participants: Eight people with dHMN.
Outcome measures: Intramuscular fat measured by MRI using modified Mercuri muscle grading scale. Isokinetic and isometric ankle muscle strength measured by a Humac Norm Testing & Rehabilitation System. Spatiotemporal parameters of gait measured by 3D gait analysis.
Rehabilitation Interventions: Carbon fiber Ankle foot orthosis, bilateral.
Statistical analysis: The collected data was analysed to explore the relationship between Intramuscular fat infiltration and muscle function using Spearman test, and to investigate effect of bilateral carbon fibre ankle foot orthoses on gait using paired T-test.

Results:
- Summary of participants characteristics and study preliminary results are given in table1.
- MRI T1-weighted cross-sectional scan at the calves' level showed involvement of calves' muscles mostly at the posterior compartment (planter flexors) (table1).
- The stride length has a moderate to strong correlation with the Soleus Muscle fat infiltration; 0.601(P= 0.1153) and 0.715 (P= 0.0461) for the right and left side respectively (table2). However, the correlation with other planter flexor muscles was weak to very weak (<0.5). Correlation of stride length with planter flexors isometric torque values was higher than the isokinetic.
- The gait significantly improved with using AFO in speed (P=0.0266). Step length (P=0.0032), stride length (P=0.0031), and the stance phase duration (P=0.0395). However, this improvement was shown on the right side only and this could be due to the small sample, but we also experienced some visibility issues of the left side and the lab settings (table3).
-

Conclusions:
We present a dHMN cohort showing greater plantar flexor muscle weakness. This was associated with reduced ankle torque and stride length. Variation existed between cases, however, with differences in ankle strength and MRI findings, indicating that this is not a homogenous group of diseases. The study preliminary results suggest that carbon fibre ankle foot orthoses can compensate for calf weakness and improve gait of people with DHMN. Results also showed that 3D gait analysis is a valuable tool for research to measure gait spatiotemporal parameters.

Table1: Summary of participants characteristics and study results		R	L
Demographics	Numbers	8	
	Gender (Male/Female)	(5/3)	
	Age; mean years; range	58 (44/75)	
	Genetic diagnosis (HSPB1/unknown)	(4/4)	
	CMTES; mean (SD)	5.25(2.8)	
	Walk-12 questionnaire; mean (SD)	32(10.8)	
Manual muscle testing	DF MRC; mode; range	4- (1-5)	4+ (1-5)
	PF MRC; mode; range	4+ (1-5)	4+ (1-5)
Dynamometry	DF isokinetic mean (SD), N/m	14(8.2)	19.25(7.6)
	PF isokinetic mean (SD), N/m	22.1(23.6)	18.4(14.7)
	DF isometric 10° mean (SD), N/m	15.9(19.9)	16.7(18.6)
	DF isometric 30° mean (SD), N/m	19.5(17.8)	23.6(20)
	PF isometric 10° mean (SD), N/m	34(23.8)	32.7(15.9)
Calf MRI: Modified Mercuri's scale for Muscle grading	Anterior Tibial Muscle; mode; range	1 (0-3)	1 (0-3)
	Extensor Digitorum Longus; mode; range	2a (0-3)	1 (0-3)
	Extensor Hallucis Longus; mode; range	2a (0-3)	1 (0-3)
	Long Fibular Muscle; mode; range	1 (0-4)	2a (0-4)
	Medial Gastrocnemius; mode; range	3 (2a-4)	2b (2a-4)
	Lateral Gastrocnemius; mode; range	1(0-3)	1 (1-3)
	Soleus Muscle; mode; range	2a (2a-4)	3 (1-4)
Gait Parameters	Speed; mean (SD), m/s	1.1(0.2)	1.1(0.2)
	Stride Length; mean (SD), m	1.2(0.2)	1.3(0.2)
	Stride Time; mean (SD), s	1.1(0.06)	1.1(0.05)
	Strides/Minute; mean (SD)	53(3.3)	52.4(2.4)
	Step Length; mean (SD), m	0.6(0.1)	0.6(0.1)
	Step Time; mean (SD), s	0.6(0.03)	0.6(0.02)
	Steps/Minute; mean (SD)	106.1(6.7)	104.8(4.7)
	Percent Stance; mean (SD), %	0.62(0.01)	0.6(0.02)
Gait Parameters with AFO	Speed; mean (SD), m/s	1.2(0.2)	1.2(0.2)
	Stride Length; mean (SD), m	1.3(0.2)	1.3(0.9)
	Stride Time; mean (SD), s	1.1(0.1)	1.1(0.09)
	Strides/Minute; mean (SD)	52.7(3.6)	52.9(4)
	Step Length; mean (SD), m	0.7(0.09)	0.7(0.09)
	Step Time; mean (SD), s	0.6(0.04)	0.6(0.04)
	Steps/Minute; mean (SD)	105.4(7.2)	105.8(8)
	Percent Stance; mean (SD), %	0.6(0.03)	0.6(0.03)

Modified Mercuri's scale: stage 0= normal appearance; stage 1= early moth-eaten appearance, with scattered small areas of increased signal; stage 2a= late moth-eaten appearance, with numerous discrete areas of increased signal with beginning confluence, comprising less than 30% of the volume of the individual muscle; stage 2b=late moth-eaten appearance, with numerous discrete areas of increased signal with beginning confluence, comprising 30 – 60% of the volume of the individual muscle; stage 3= washed-out appearance, fuzzy appearance due to confluent areas of increased signal; stage 4= end stage appearance, muscle replaced increased density connective tissue and fat, with only a rim of fascia and neurovascular structures distinguishable; N; Newtons; m; meters; s, seconds; R, right; L, left; DF, Ankle Dorsiflexion; PF, Ankle plantarflexion; MRC, medical research council scale; SD, standard deviation; CMTES, CMT examination score; HSPB1, Heat-Shock 27-KD Protein 1.

Table2: Correlation coefficient of Plantarflexion parameters	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
Stride Length	0.601	0.715	0.469	0.469	-0.1	-0.17	0.5	0.386	0.476	0.548
PF isokinetic dynamometer	-0.1	0.013	-0.136	0.144	-0.601	-0.106			0.619	-0.024
PF isometric dynamometer	-0.15	0.281	-0.309	-0.086	-0.751	-0.509	0.619	-0.024		
1 0 -1	Soleus Muscle FI		Medial Gastrocnemius FI		Lateral Gastrocnemius FI		PF isokinetic dynamometer		PF isometric dynamometer	

Correlation represented by R values between 0.0 and .030 are very weak, 0.30 to 0.50 are weak, 0.50 and 0.70 are moderate, 0.70 and 0.90 are strong, and 0.90 and 1.00 are very strong. FI, fat infiltration; DF, Ankle Dorsiflexion; PF, Ankle plantarflexion.

Table3:The effect of AFO on Gait Parameters	Mean difference (±SD)		P- value		95% CI of difference	
	Right	Left	Right	Left	Right	Left
Speed, m/s	0.09154 (0.09252)	0.05463 (0.1618)	0.0266	0.3713	0.01419 to 0.1689	-0.08062 to 0.1899
Stride Length, m	0.1108 (0.07086)	0.05338 (0.1391)	0.0031	0.3138	0.05151 to 0.1700	-0.06294 to 0.1697
Stride Time, s	0.007500 (0.03872)	-0.006042 (0.05850)	0.6008	0.7787	-0.02487 to 0.03987	-0.05495 to 0.04287
Strides/Minute	-0.3397 (1.8169)	0.4825 (2.7257)	0.6133	0.6319	-1.8587 to 1.1792	-1.7962 to 2.7613
Step Length, m	0.05517 (0.03546)	0.02683 (0.06948)	0.0032	0.3108	0.02552 to 0.08481	-0.03125 to 0.08492
Step Time, s	0.003667 (0.01940)	-0.003125 (0.02927)	0.6095	0.7715	-0.01255 to 0.01989	-0.02760 to 0.02135
Steps/Minute	-0.6792 (3.6338)	0.9650 (5.4517)	0.6134	0.632	-3.7171 to 2.3588	-3.5927 to 5.5228
Percent Stance, %	-0.01825 (0.02043)	-0.02288 (0.02502)	0.0395	0.0362	-0.03533 to -0.001167	-0.04379 to -0.00198

Difference is significant when the P-Value is less than 0.05 ($p<0.05$). m; meters; s, seconds; SD, standard deviation; CI; confidence interval.

Abstract #509

vCMTES: a validated virtual evaluation for Charcot-Marie-Tooth patients

V. Prada, M. Laura*, R. Zuccarino**, M. Reilly*, M. Shy*** (Genova, IT; London, UK*, Pergine Valsugana, IT**, Iowa City, IA***)

Introduction: COVID-19 pandemic highlighted the need for reliable scales for remote evaluations of Charcot Marie Tooth (CMT) disease patients unable to travel to clinics because of their disabilities, distance, financial concerns or other reasons.

Objective: To demonstrate the validity and reliability of vCMTES

Methods: We modified the CMT Examination Score (CMTESv2) replacing the pinprick and vibration items with light touch and position sense, which can be performed by the patient on his own or with assistance remotely. We developed a standardized protocol. We then evaluated patients in person and remotely.

Results: Sixty-four patients with CMT were evaluated with CMTESv2 and vCMTES. CMTESv2 correlates strongly with the vCMTES in person and virtually. Test-retest analysis showed good results.

Conclusions: All the statistical analyses showed that the vCMTES is valid and reliable as a clinical outcome assessment for CMT. Further studies are needed to test responsiveness to change and progression in different subtypes.

Abstract #513:

Description of Motor Function Test and Parent Report of Gross Motor Abilities in Congenital Myotonic Dystrophy.

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Introduction: Congenital Myotonic Dystrophy (CDM) is a multi-systemic neuromuscular disorder with known cognitive and physical impairments. There is concern that these cognitive impairments impact individual's ability to reliability and accurately compete motor function tests (MFT).

Objective: Understand if motor performance measured by MFTs, is similar to caregiver's report of motor performance in the community.

Methods: Participants (n=29, age: 3-14 years) completed MFTs- four stair climb, 10m run, rise from floor and six-minute walk. Participants were allowed exceptions to standardized administration due to cognition and attention difficulties. Caregivers completed the gross motor domain of the Vineland Adaptive Behavior Scales (VABS) via clinical interview.

Results: The majority (93%) of participants were rated to have low to moderately- low adaptive gross motor skills by their caregivers and performed lower than age matched peers on MFTs.

Conclusions: Caregiver's rating of participants with CDM motor skills agree with performance on MFTs.

Abstract #523

Evolving the multidisciplinary approach to whole genome sequencing analysis enhances precision genetic diagnostics

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Introduction: Diagnostic whole genome sequencing (WGS) is increasingly used in NMDs, though standard analysis may overlook diagnoses.

Objectives: We aimed to improve the WGS diagnostic rate by establishing an enhanced personalised approach to analysis.

Methods: 102 patients with suspected mitochondrial disease underwent WGS. Undiagnosed cases were reviewed by a clinician and bioinformatician enabling bespoke informatic approaches, co-ordinated phenotypic validation (e.g., pathology and radiology), and functional work.

Results: A ~two-fold increase in diagnostic rate was achieved (from 16.6 % to 31.3%) with strong candidate disease-causing variants in an additional 3.9% of patients. There were management implications for all new diagnoses including two patients becoming eligible for drug trials.

Conclusions: We demonstrate a new standardised model of care that supports neuromuscular clinicians to maximise the potential benefits from genomics. This research was made possible through access to the data and findings generated by the 100,000 Genomes Project.

Abstract #527

Balance Confidence in Individuals with Charcot-Marie-Tooth

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Introduction: Balance and function impairment is common in individuals with Charcot Marie Tooth disease (CMT).

Objectives: The aim of this study was to evaluate the balance confidence, fall frequency, and perceived effect of AFOs on balance in individuals with CMT who use AFOs.

Methods: The Activities Specific Balance Confidence Scale (ABC) was distributed by email to individuals with CMT, through the Inherited Neuropathy Consortium Contact Registry.

Results: 306 individuals participated in this study. Participants reported decreased balance confidence across a range of activities. Many participants reported daily (14.1% of participants) or weekly (37.6% of participants) falls and 77.8% of participants indicated their AFOs improved their balance.

Conclusions: Results from this study will help to focus future studies to refine AFO design and prescription to better improve balance, reduce falls, and meet the needs of individuals with CMT.

Abstract #532

High Frequency Remote Data Collection is Feasible and can Provide Novel Insights into Idiopathic Inflammatory Myopathy Disease Trajectory – Implications for Clinical Trials and Personalised Patient Care

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Background: Technological advances of wearables and ubiquity of smartphones provides the opportunity for remote collection of high-frequency data from patients with chronic muscle diseases, such as the idiopathic inflammatory myopathies (IIM).

Objective: To assess feasibility/acceptability of collecting daily symptom data and continuous gait pattern data in an IIM cohort.

Methods:
Adult IIM patients were recruited to the study in 2019. Participants were asked to:

1. Complete daily patient-reported outcome measurements (PROMs) via a specially designed smartphone-based app for 91 days each (Table 1).
2. Continuously wear a single thigh-worn accelerometer sensor throughout the 91 day period (Figure 1).

Results: 21 participants submitted 22,880 individual PROMs (88% of potential total) and 42,308 hours of sensor data throughout the study (93% of potential). Individual patient data indicates ability to identify the start of a flare (Figure 2).

Discussion: Remotely collected high frequency data collection is feasible and facilitates insights into disease trajectory.

Table 1 - Question sets related to disease activity and impact, and their frequencies

Domain	Question stem	Answer scale	Answer anchors
Daily data collection			
Global activity	Considering all of the ways it affects you, how active do you feel your myositis is today?	VAS	"Not active" (0); "Very active" (100)
Pain	What is your overall level of pain today?	VAS	"No pain" (0); "Extreme pain" (100)
Pain	What is your level of pain due to myositis today?	VAS	"No pain" (0); "Extreme pain" (100)
Fatigue	How much fatigue do you feel today?	VAS	"No fatigue" (0); "Very severe fatigue" (100)
Sleep	How refreshed did you feel when you woke up for the day?	5 point Likert scale	"Not at all rested" "Slightly rested" "Somewhat rested" "Well-rested" "Very well-rested"
Sleep	How would you rate the quality of your sleep last night?	5 point Likert scale	"Very poor" "Poor" "Fair" "Good" "Very good"
Weakness	How weak do you feel today?	VAS	
Mood	How would you rate your mood today?	5 point Likert scale	"Poor" to "Excellent"
Function	Are you able to wash and dress yourself today?	Ordinal with checkbox	"Unable to do" "With some difficulty" "With much difficulty" "Without any difficulty"
Function	Are you able to walk outdoors on flat ground today?	Ordinal with checkbox	"Unable to do" "With some difficulty" "With much difficulty" "Without any difficulty"
Function	Are you able to walk up five steps today?	Ordinal with checkbox	"Unable to do" "With some difficulty" "With much difficulty" "Without any difficulty"
Weekly data collection			
Flare occurrence	Have you experienced a flare of myositis in the last seven days?	Dichotomous	Yes; no
Function	Have you been able to carry shopping bags in the last seven days?	Ordinal with checkbox	"Unable to do" "With some difficulty" "With much difficulty" "Without any difficulty"

Exercise	Have you been able to exercise in the last seven days?	Ordinal with checkbox	"Unable to do" "With some difficulty" "With much difficulty" "Without any difficulty"
Social interaction	Have you been able to socialise in the last seven days?	Ordinal with checkbox	"Unable to do" "With some difficulty" "With much difficulty" "Without any difficulty"
Function	Have you been able to reach and get down a 5 pound object (such as a bag of sugar) from just above your head in the last seven days?	Ordinal with checkbox	"Unable to do" "With some difficulty" "With much difficulty" "Without any difficulty"
Function	Have you been able to bend down to pick up clothing from the floor in the last seven days?	Ordinal with checkbox	"Unable to do" "With some difficulty" "With much difficulty" "Without any difficulty"
Employment status	Are you currently employed (working for pay)?	Dichotomous	Yes; no
Effect of myositis on employment	Has your ability to work been affected by myositis in the last seven days?	Dichotomous	Yes; no
Hours of employment missed due to myositis	During the past seven days, how many hours did you miss from work because of problems associated with your myositis?	Numerical	
Hours missed due to other reasons	During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?	Numerical	
Hours worked	During the past seven days, how many hours did you actually work?	Numerical	
Degree myositis affected work productivity	During the past seven days, how much did your myositis affect your productivity while you were working?	VAS	Myositis had no effect on work (0); Myositis completely prevented me from working (100)
Monthly data collection			
Function	Health Assessment Questionnaire. Validated questionnaire comprising 23 item assessing physical function	Overall score of 0-3	

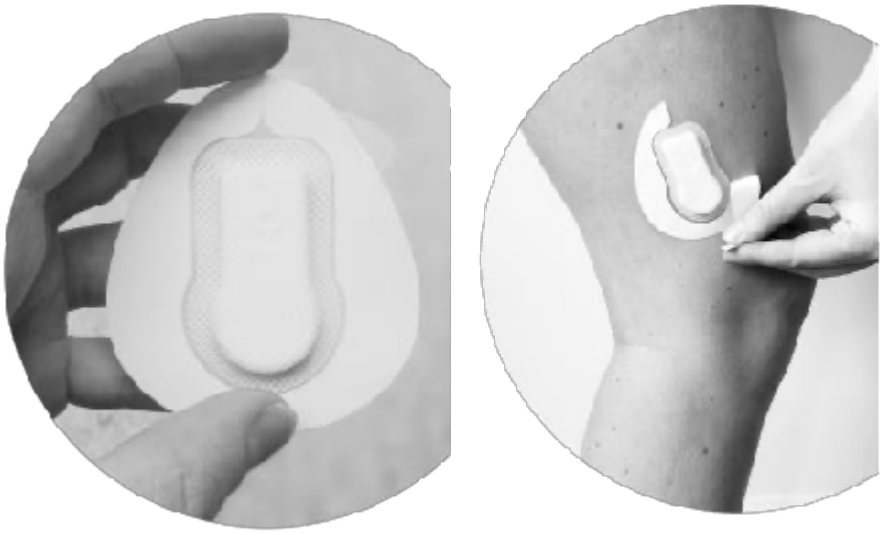

Figure 1 – Pictures of wearable sensor employed in study

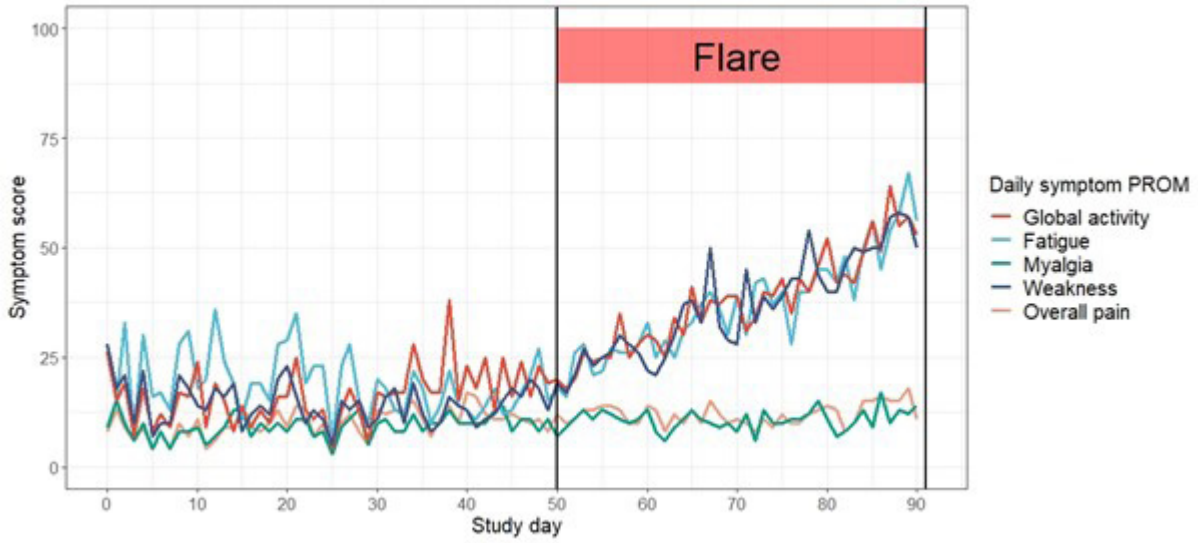

Figure 2 – Individual participant PROM data demonstrating ability to identify the start of a flare (study day 50) via increasing symptom scores (global activity, myalgia, weakness)

Abstract #533

Assessment of muscle mass measurements by dual-energy X-ray absorptiometry (DEXA) as a correlate for muscle strength and function in facioscapulohumeral muscular dystrophy (FSHD)

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Introduction: FSHD is a progressive disease of skeletal muscle. DEXA is a widely available, cost-effective, and sensitive measure of whole body and regional lean tissue mass.

Objectives: Investigate the association between lean tissue mass measurements (composed of mainly muscle) and clinical outcomes assessments (COAs) in FSHD patients.

Methods: We obtained DEXA scans and COAs (i.e., 10-meter-walk-run) in 160 patients with FSHD at the baseline visit of the ReSolve study, a prospective, longitudinal, observational multisite study (NCT03458832).

Results: There was moderate correlation between arm strength measured by quantitative muscle testing and lean tissue mass of both upper extremities (ρ = 0.46-0.49); moderate correlation between leg strength and lean tissue mass of each lower extremity (ρ = 0.61); and moderate correlation between ambulatory COAs and lean tissue mass of lower extremities (ρ = 0.44-0.61).

Conclusions: DEXA lean tissue mass may be a biomarker in FSHD clinical trials.

Abstract #535

Morphological and quantitative imaging biomarkers obtained with high-field MRI in sciatic nerves of patients with CMT1A and controls

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Introduction: There has been growing interest in developing more sensitive biomarkers to evaluate disease progression in peripheral nerve diseases such as Charcot-Marie-Tooth (CMT) disease.

Objectives: We explored combine morphological and quantitative imaging using 7T MRI in patients with CMT1A patients and healthy controls.

Methods: We used Double-Echo in Steady-State (DESS) 7T MRI sequence to assess T2 relaxation, apparent diffusion coefficient (ADC), and fat fraction (FF), in the lower right thigh of 6 patients and 6 age-matched controls. We obtained quantitative measurement from individual nerve fascicles of proximal and distal tibial and peroneal nerves.

Results: In addition to individual fascicle visualization, we get better quantitative assessment of sciatic nerve in patients and healthy controls. Nerve fascicles were significantly larger and had larger variability in diffusion and T2 measurement.

Conclusions: The study provides feasibility and further insight in the assessment of peripheral nerves as potential biomarkers.

Abstract #538

Understanding falls in FSHD

Enrico Bugiardini[1], Katy Eichinger[2], Michael G Hanna[1], Gita Ramdharry[1], Michael McDermott[2], Kiley Higgs[3], Michaela Walker[3], Leann Lewis[2], Bill Martens[2], Doris Leung[4], Sabrina Sacconi[5], Karlien Mul[6], Valeria Sansone[7], Elena Carraro[7], Leo Wang[8], Perry Shieh[9], Bakri Elsheikh[10], Samantha LoRusso[10], Russell Butterfield[11], Nicholas Johnson[12], Chiara Frisoni[7], Rabi Tawil[2], Jeffrey Statland[3] and ReSolve Investigators of the FSHD CTRN.

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Background: Patients with neuromuscular disease are at a risk of falls.

Objective: To assess prevalence and consequences of falls in a multicentre observational study in FSHD (ReSolve).

Methods: We administered a fall survey weekly for 12 weeks (Fsu) and a retrospective fall questionnaire (Fhx). Based on survey falls count, patients were classified as non-fallers, infrequent (n=1) or recurrent fallers (n>1). Patient reported outcomes (FSHD-HI and PROMIS57), manual muscle testing (MMT) and Motor Function Measurement (MFM) were compared between groups.

Results: Prevalence of falls was high (52% in Fhx, n=97; 36% in Fsu, n=132 respectively). Infrequent and recurrent fallers are weaker in proximal lower limbs and had a higher disease burden and motor impairments compared to non-fallers (FSHD-HI mean score 37.47, 41.15, 25.54 range 0-100; MFM 58.97, 53.85, 82.05, range 0-100; $p < 0.05$).

Conclusions: Prevalence of falls is high in FHSD patients. Fallers are weaker and have lower quality of life compared to non-fallers.

Abstract #541

Co-creating a multi-sensory balance programme for people living with Charcot-Marie Tooth Disease

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Introduction: People with Charcot-Marie-Tooth disease (CMT) experience poorer balance than the general population. Multi-sensory balance rehabilitation is effective in people with other conditions, and early studies have shown promising results in CMT. Co-design strategies can ensure that interventions address real-world problems and are tailored to the target group.

Methods: A series of co-creation workshops involving six people with CMT, facilitated by physiotherapists, a patient expert, and an artist/designer. Experience-based co-design methods will be used to explore priorities and preferences for a selection for balance exercises, design of a digital and paper-based resource, and a strategy for dissemination to the international CMT community.

Results: The results of this co-design project will be disseminated at the 2022 Muscle Study Group Annual Scientific Meeting.

Conclusion: Output from this project will stand alone as a tangible resource for the CMT community, but the findings will also be integrated into a larger future exercise trial.

Abstract #561

Longitudinal analysis of PUL 2.0 domains in ambulant and non-ambulant Duchenne patients: how do they change in relation to functional ability?

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Introduction: PUL is a functional scale assessing upper limb function in both ambulant and non ambulant DMD patients. As the scale is increasingly used in clinical trials, it is becoming crucial to understand if the progression in the different domains is related to the overall functional abilities.

Objectives: To establish the patterns of 24-month PUL total and domain changes in different functional groups subdivided by ambulatory status and time since loss ambulation(LOA).

Methods: Data were collected from 14 tertiary Italian centers, the PUL 2.0 was used to assess upper limb function.

Results: Two-hundred-seventy-two patients had at least one pair of assessments at 24 months, for a total of 812 paired assessments. There were different pattern of changes in the individual domains in relation to different functional abilities.

Conclusions: Patterns of changes should be considered at the time of designing clinical trials for stratification, inclusion criteria or for their interpretation.

Abstract #567

Validity of remote evaluation of the North Star Ambulatory Assessment in patients with Duchenne muscular dystrophy (DMD)

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*Presenting on behalf of the authors

Introduction: In ongoing delandistrogene moxeparvovec (investigational gene transfer therapy) studies, remote functional assessments were initiated during the COVID-19 pandemic, in accordance with FDA guidance.

Objectives: To evaluate the reliability of remote functional assessments versus in-person assessments for patients with DMD.

Methods: The reproducibility of remote North Star Ambulatory Assessment (NSAA) and timed function tests were assessed against in-person scores using pre-specified statistical analyses—including intraclass correlation coefficient (ICC), Pearson, Spearman and Bland-Altman analyses.

Results: Results from 21 patients with DMD in Studies 101/102 found strong correlations between remote and in-person NSAA scores (ICC=0.96 [95% confidence interval; CI 0.91–0.98]; Pearson=0.96 [95% CI 0.90–0.98]; Spearman=0.96 [95% CI 0.90–0.98]), with no statistical or clinical differences attained remotely versus in person.

Conclusions: Findings suggest that remote functional assessment of patients with DMD is not statistically different from in-person assessment and has comparable clinical meaningfulness, validating its use in delandistrogene moxeparvovec trials.

Disclosures: LPL reports receiving salary support from Sarepta Therapeutics through Nationwide Children's Hospital to support training and quality control activities for ongoing clinical trials and licensing fees for natural history data. LNA reports receiving salary support from Sarepta Therapeutics through Nationwide Children's Hospital to support training and quality control activities for their ongoing clinical trials. MAI reports no conflicts of interest. NFR reports receiving salary support from Sarepta Therapeutics for Clinical Evaluator training for ongoing and upcoming clinical trials. KG is an employee of Eli Lilly and was previously an employee of Sarepta Therapeutics, and may have stock options. LH, LY and SW are employees of Sarepta Therapeutics and may have stock options. JRM has received study funding from Sarepta Therapeutics and has a service agreement with Sarepta Therapeutics to provide training on ongoing studies. JRM is a co-inventor of AAVrh74.MHCK7.micro-dys technology.

Abstract #570

Motor unit compensation in adults with spinal muscular atrophy varies by functional status

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Introduction: Motor unit (MU) enlargement via collateral sprouting is a mechanism by which the MU pool can compensate for motor neuron loss. However, MU compensatory mechanisms across the functional spectrum remain unexplored.

Objective: To investigate relationships between MU characteristics and disease severity in adults with SMA.

Methods: Adults with SMA on nusinersen and healthy controls were enrolled. MUs were decomposed from multi-electrode surface recordings during a 30-second maximum contraction of the abductor digiti minimi. MU characteristics were compared by ambulatory status and correlated to Revised Upper Limb Module (RULM) score.

Results: The MU action potential amplitude and firing rates of ambulatory adults with SMA were significantly greater than non-ambulatory adults with SMA and healthy controls. Moderate to strong correlations exist between these MU characteristics and RULM score.

Conclusions: There is differential capacity for MU compensation across the functional spectrum. This has implications for expected treatment effectiveness and long-term functional outcomes.

Abstract #591

Evaluating the expression of spontaneous movements in infants with neuromuscular conditions using Prechtl's General Movements Assessment

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Introduction: Prechtl's General Movements Assessment (GMA) uses visual analysis to evaluate infants' spontaneous movements. Developed for early identification of cerebral palsy, little is understood about the expression of general movements (GMs) in infants with neuromuscular disorders (NMD).

Objective: We seek to describe GMs in infants birth to 6 months of age with NMD.

Methods: Fourteen infants have been enrolled to date (spinal muscular atrophy [SMA], N=7; Duchenne muscular dystrophy [DMD], N=3; and others, N=4). Each infant's GMs were evaluated using the GMA global categorization and detailed scoring forms.

Results: Four (29%) were evaluated as having normal movement patterns; of those, 2 were post-treatment SMA. There was a moderate correlation between other clinical outcome assessments and the GMA detailed scoring. Further exploration into the influence of disease-modifying treatments on the expression of GMs will be presented.

Conclusions: These preliminary results suggest many infants with NMD express movement abnormalities from birth.

Abstract #592

The bolus journey behind a horizontal smile. A clinical-functional evaluation of dysphagia in facioscapulohumeral muscular dystrophy (FSHD).

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Introduction: the assumption of deglutition-sparing in FSHD has been challenged, but thorough explorations are lacking.

Objectives: to detect, estimate incidence, and characterize swallowing patterns and dysfunction in FSHD.

Methods: the FSHD Evaluation Scale, the EAT10 questionnaire, and the Three-oz Water Swallow test were administered to 43 FSHD patients. Dysphagic subjects were assessed by IOPI Medical LLC, videofluoroscopy, esophageal barium transit, and double-contrast esophagography. Dysphagia severity was scored by the DOS-Scale.

Results: DOSS scores and tongue strength among the 15 mild dysphagic patients were correlated with the EAT10-assessed symptoms, disease's duration and severity. Lip dysfunction was associated with tongue asymmetric weakness, leading to altered oral management. Pharyngeal and esophageal transit impairment were also detected and often associated with Zenker diverticulus, hiatal hernia and gastroesophageal reflux.

Conclusions: a generally mild but progressive dysphagia is clinically detectable and often radiographically confirmed in FSHD, related not only to the oral bolus management but often to pharyngeal and esophageal motility disorders.

Abstract #600

Correlating Fatigue Severity Scale to objective measures of disease progression in Kennedy's Disease.

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Introduction: Kennedy's disease (KD) or X-linked spinal and bulbar muscular atrophy (SBMA) is a rare inherited adult-onset neuromuscular disorder. In our dedicated service, we undertake assessments to evaluate markers of muscle damage and muscle weakness progression. Fatigue is very common in people living with KD.

Objective/aim: To correlate mean values in Fatigue Severity Scale (FSS) to other functional and biological indicators of disease progression such as CPK and Creatinine levels, 6 minutes' walk test, adult myopathy assessment tool and patient reported functional rating scales.

Methods: Using a custom code in "R", we have run correlations between FSS and other validated measures of disease progression in 60 participants.

Results: Correlation between mean values of FSS and indicators of disease progression in SBMA were statistically significant

Conclusion: Fatigue is an important feature in KD impacting quality of life. We suggest using FFS as an outcome measure in upcoming interventional trials in KD.

Abstract #601

Descriptive Analysis Of Promis Mobility And Upper Extremity Scales In Patients With Duchenne Muscular Dystorphy (Dmd): Implications For Assessing Physical Functioning From The Patient Perspective

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INTRODUCTION: PROMIS Mobility and Upper Extremity (UE) questionnaires were administered to DMD patients and caregiver proxies attending Nationwide Children's Hospital.

OBJECTIVE: Examine psychometric properties of generic PROMIS Mobility and UE to establish suitability for assessing physical functioning in DMD and determine need for further customization.

METHODS: 170 and 279 complete records of PROMIS Mobility and UE questionnaires, respectively, filled in by caregivers of DMD patients aged 4-27 years were used to assess item performance (ceiling/floor effect), internal consistency reliability (ICR), and item correlations.

RESULTS: Item ceiling effects were observed in PROMIS Mobility, primarily in youngest ambulatory subgroup (4-7) whilst floor effects were noted in the oldest (13-17). Item ceiling effects were prevalent in PROMIS UE across all ages. ICR was excellent for both domains. Item correlations revealed some item redundancy within domains.

CONCLUSIONS: Results suggest both scales have good potential for assessing physical functioning in DMD but require further work.

Disclosures: LL, NR, LA and MI are employees of the Nationwide Children's Hospital, Columbus, OH, USA, and have provided the data for this study. CLR is an independent biostatistician who received funding from Sarepta to help with the analysis. IA and KG are employees of Sarepta.

Abstract #602

Pilot Assessment of Pain in Adults with Spinal Muscular Atrophy (PAIN in SMA)

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Introduction: There is limited data on pain in adults with spinal muscular atrophy (SMA).

Objectives: To evaluate the frequency, characteristics, severity, and therapy used for pain and explore its association with functional status.

Methods: We conducted a cross-sectional study using the Brief Pain Inventory, Fatigue Severity Scale, and SMA-specific motor function measures.

Results: We analyzed data from twenty patients (12 women and 8 men; median age 37.5). Fifteen (75%) reported pain related to SMA. Pain location varied and was frequently (55%) described as aching. The majority used NSAIDs and acetaminophen—only two used opioids. Ten patients (50%) reported significant fatigue. We found no significant association of pain with fatigue score, ambulatory status, disease duration, SMA type, SMN2 copy number, or motor function measures.

Conclusions: Our study demonstrates a high frequency of pain in adults with SMA and highlights pain as a significant issue that warrants detailed evaluation and investigation.

Abstract #603

Is Sustained Phonation Time related to Forced Vital Capacity in Individuals with Amyotrophic Lateral Sclerosis?

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Introduction: Respiratory failure is the leading cause of death in individuals with Amyotrophic Lateral Sclerosis (ALS). Sustained Phonation Time (PT) may be a potential identifier of changes in respiratory capacity.

Objectives: Examine the relationship between PT with Forced Vital Capacity (FVC).

Methods: Individuals with ALS completed three sustained phonations trials (hold an "ah"--seconds) and FVC (liters) measurements. A regression analysis was performed to determine the relationship between their best PT and their FVC.

Results: Twenty-nine individuals (10 females, age M=69.1 (SD=11.7)) (M ALSFRS=35.6 (SD=8.2)) resulted in a variance, R^2 of 0.39, (p-value, < 0.001) meaning the variation in measured PT accounted for 39% of the variation in measured FVC; suggesting a moderate relationship between PT and FVC.

Conclusions: These preliminary results suggest that PT could be a clinical tool to understand FVC and potential decline in respiratory capacity. We will be increasing our sample size to examine this possibility.

Abstract #604

Validation of the Toronto Cramp Impact Index (TCII)

Hans Katzberg, Sara Al Najjar, Meg Mendoza, Lorne Zinman, Agessandro Abrao, Hemant Shah, David Cherney, Vera Bril, Carolina Barnett Tapia.

Introduction: Although cramp frequency has been used traditionally to assess cramp severity, a more comprehensive outcome measure is needed.

Objectives: To validate a novel patient reported outcome, the 16-item Toronto Cramp Impact Index (TCII).

Methods: Cramp frequency, location, intensity, duration, as well as muscle pain, stiffness, quality of life, sleep quality and sleepiness parameters were collected on each patient. A subgroup of patients had the TCII repeated at 2 weeks to assess intra-rater reliability.

Results: Preliminary review of 86 patients with idiopathic and secondary cramps were included. Mean number of cramps/week was 10, mean severity 6.8/10 and mean duration 6.7 minutes. There was significant and moderate correlation between the TCII and all associated cramp characteristics and associated parameters. Intra-rater reliability (n=61) was moderate the total TCII score (Cohen's kappa = 0.55).

Conclusions: The TCII shows promise as a patient centred, reliable and comprehensive way to assess muscle cramps (final results expected at the MSG meeting).

Abstract #605

Associations between speech-language difficulties, speech delay, *DMD* genotype, and motor function performance in corticosteroid-naïve boys with DMD.

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We tested the hypothesis that care-giver reported neurodevelopmental symptoms and distal *DMD* mutations are prognostic of worse motor function performance in DMD. We analyzed care-giver-assessed speech-language difficulties (SLD), age at speaking in full sentences, *DMD* mutation location, six-minute walk distance (6MWD), North Star Ambulatory Assessment (NSAA) total score and timed motor function tests from 196 corticosteroid-naïve boys with DMD. Boys with reported SLD walked 25.8 fewer meters on average than those without SLD on 6MWD but did not demonstrate statistically significant results in the NSAA total score or other timed motor function tests. Boys with distal *DMD* mutations walked 20 fewer meters on 6MWD and were slower on timed-motor-function tests. The difference in mean 6MWD between those with and without SLD was independent of *DMD* mutation location, and the difference in mean 6MWD between *DMD* genotypes was independent of SLD. Distal *DMD* genotype is associated with worse baseline motor function.

Abstract #611

Wearable Sensors Detect Changes in Timed Up and Go Performance after Nerve Tumor Excision

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Background and Purpose: Individuals with neuromuscular disorders experience postural instability during turning tasks placing them at high risk for falls. Functional tests often rely on overall performance to quantify postural stability. This study sought to determine if wearable sensors could detect changes in turning task performance following nerve tumor excision.

Methods: 10 patients (50% female, age= 40.2±13.1) performed Timed Up and Go (TUG) tests pre- and post-vestibular schwannoma excision. T-tests were used to compare pre- and post-surgical TUG performance.

Results: Wearable sensors detected significant pre to post surgery differences in peak turning velocity (p=0.007) and turn duration (p=0.006). TUG total time did not differ significantly between assessments.

Conclusion: Wearable sensors used during turning tasks detected differences in TUG performance not apparent by overall task time. Similarly, quantification of turning tasks with wearable sensors in individuals with neuromuscular disorders may allow quantification of fall risk and more sensitive assessment of performance changes associated with rehabilitation.

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Abstract #615

Patient Reported Upper Extremity Function is Associated with Measures of Strength and Function in Individuals with Facioscapulohumeral Muscular Dystrophy (FSHD)

Katy Eichinger,[1] Kiley Higgs,[2] Leann Lewis,[1] Nuran Dilek,[1] Michaela Walker,[2] Valeria Sansone,[3] Doris Leung,[4] Sabrina Sacconi,[5] Karlien Mul,[6], Elena Carraro,[3] Leo Wang,[7] Perry Shieh,[8] Bakri Elsheikh,[9] Samantha LoRusso,[9] Russell Butterfield,[10] Nicholas Johnson,[11] Enrico Bugiardini,[12] Maya Hatch,[13] Jay Han,[13] Michael McDermott,[1] Tawil R,[1*] Statland J.[2*] on behalf of the ReSolve Investigators of the FSHD CTRN.

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Introduction: Measuring clinically relevant upper extremity function is challenging in FSHD studies. The Upper Extremity Functional Index (UEFI) is a patient reported outcome measure assessing the difficulty performing daily tasks such as grooming/dressing and household activities.

Objective: To examine the relationship between the UEFI and measures of strength and function in individuals with FSHD.

Methods: Individuals with FSHD participating in the ReSolve study completed the UEFI, measures of strength and measures function including donning/doffing a coat and measures of reachable workspace.

Results: Participants (n=251) were 56% male with a mean age of 50 years. Participants had a UEFI score of 54.60 (range 4-80). UEFI score was moderately correlated with donning/doffing coat (ρ=0.45; $p<0.001$), reachable workspace (ρ=0.44 (R) and 0.49 (L); $p<0.001$), and strength (ρ=0.55; $p<0.001$).

Conclusions: The UEFI is correlated with measures of strength and function, supporting the clinical relevance of using these outcome measures in future FSHD clinical trials.

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Abstract #617

Muscular activity monitoring with an artificial intelligence-based wearable sensor in facioscapulohumeral muscular dystrophy: A pilot study

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Introduction. As the field anticipates more facioscapulohumeral muscular dystrophy (FSHD) clinical trials, there is an acute need for reliable/quantitative clinical outcome measurements to monitor FSHD.

Objectives. To assess an innovative clinical outcome assessment using an artificial intelligence (A.I.)-based wearable device for tracking shoulder joint kinematics and muscle activity in FSHD subjects.

Methods. A flexible experimental wireless apparatus comprising a triaxial accelerometer and four surface electromyography sensors (over bilateral trapezius, infraspinatus, biceps, and deltoid muscle regions) was employed on 4 adult FSHD and 4 healthy control subjects.

Results. The device reliably showed range of motion (ROM) measures in all activities tested (shoulder abduction, elbow flexion, shoulder external and internal rotations) with 3 trials in each performance. There was also a significant difference between the detected ROM and muscular activity between control and FSHD subjects ($P<0.05$).

Conclusions. Our pilot data demonstrated a potential utility of an A.I.-based wearable sensor in monitoring FSHD.

Abstract #626

Construct validity of the 10-meter walk and modified time up and go tests in inclusion body myositis: an observational cross-sectional study

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Introduction: There is a lack of validated outcome measures to assess the effect of interventions in inclusion body myositis (IBM).

Objectives: Our aim was to evaluate the construct validity of the 10-meter walk (10MW) and modified time up and go (mTUG) tests in IBM.

Methods: Observational cross-sectional study. The construct validity of the 10MW (4 versions: normal and fast pace, each one measured in seconds and in steps) and mTUG was tested at baseline using Spearman correlation with other strength and disability outcome measures (MMT, QMT and IBMFRS).

Results: Among 58 patients, 69% were male, with mean (SD) age and disease duration of 66.3 (9.6) and 7.4 (4.0) years, respectively. Moderate to strong correlations between 10MW/mTUG and other outcome measures were found.

Conclusions: The 10MW and mTUG proved to be valid in IBM. Their potential to evaluate the impact of IBM and its treatment on functioning should be further evaluated.

Abstract #628

Evaluation Cognitive Function, Cerebral Structure and Functional Connectivity in Children with Congenital (CDM) and Childhood-Onset Myotonic Dystrophy Type 1 (chDM1)

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Introduction: Cognitive function (CF) is significantly impaired in children with CDM/chDM1.

Objective: Identify key cerebral structural and functional connectivity (FC) factors predictive of CF deficits in CDM/chDM1.

Methods: Thirty participants with CDM/chDM1 and controls completed neuropsychological, structural and resting state functional MRI (rsfMRI) evaluations. A 3T scanner, DPARSFA toolbox and SPM8 were used for image collection and processing. Group differences in brain structure and FC were examined. Regression analysis was used to identify relationships between neuropsychological measures and MRI/rsfMRI.

Results: Preliminary data revealed significant differences in brain structure and FC in CDM/chDM1; greater connectivity between the cingulate cortex (CC) and prefrontal brain regions (PBR) in CDM; strong associations between CF and CC-PBR connectivity in CDM.

Conclusion: Our results are consistent with previous reports of prefrontal white matter changes in DM1 and suggest that anomalous prefrontal development plays a key role in the cognitive deficits in CDM/chDM1.

Abstract #630

Application of muscle MRI in Complex Upper Extremity Neuropathies

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Introduction: Complex upper extremity neuropathies can have varied clinical presentation. Physical examination and detailed history are often not sufficient to make a conclusive diagnosis. While nerve conduction studies with electromyography (NCS/EMG) can be valuable, the yield is often limited when there is underlying confounding pathology. In such cases magnetic resonance imaging (MRI) of muscles can be helpful.

Objective: To report a series of patients in whom MRI upper extremity assisted in diagnosis.
Case Presentations: To date four cases were identified where EMG/NCS was inconclusive, and muscle MRI helped in diagnosing posterior interosseous nerve syndrome, proximal median neuropathy, multifocal motor neuropathy, and malignant infiltration of the axillary nerve bundle.

Results: This study illustrates how muscle MRI can identify certain pattern of muscle involvement and complement EMG findings in complex upper extremity neuropathy cases.

Conclusion: MRI of the upper extremities can provide complimentary information to EMG and help making a correct diagnosis.

Abstract #653

Validation of the Inclusion Body Myositis Functional Rating Scale (IBMFRS): Results from 2 studies.

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Introduction: The IBMFRS is a Clinician Reported Outcome measure that assesses a patient's ability and independence in completing 10 functional activities. There is limited information about IBMFRS psychometric properties.

Objective: Our aim was to investigate IBMFRS content validity, inter- and intra-rater reliability, responsiveness, and what constitutes a meaningful change in IBMFRS scores.

Methods: Two prospective studies provided data for both validity (content and construct) and reliability evaluation of the IBMFRS. Evaluation of responsiveness and derivation of a meaningful change threshold was also conducted.

Results: Data show that the IBMFRS is content valid based on both patient and clinician feedback with the key functional limitations captured. Additionally, the IBMFRS has strong construct validity (convergent and known-groups validity), reliability, and responsiveness. Additionally, a meaningful change threshold has been derived.

Conclusion: The IBMFRS is a valid and reliable measure for assessing the key functional impacts of IBM.

Impact and Burden of NMD

Abstract #644 Flash Presenter

Risk factors for falls and fracture in myositis: A cross-sectional study of 470 patients

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Introduction: Myositis can lead to marked weakness, predisposing patients to falls/injuries.
Objectives: We investigated risk factors for falls/fractures.
Methods: A survey was sent to members of Myositis Support and Understanding inquiring about falls and fractures. Ordinal logistic regression was performed.
Results: In a cross-sectional study of 470 participants with myositis, 80% reported having at least one fall since their initial diagnosis. 57% of participants fell at least once in the past year and 121 falls resulted in a fracture (32%). Mobility aids were used by 57% of participants. Fall risk was highest for IBM (OR 2.5, $p=0.002$) or PM (OR 2.0, $p=0.037$) compared to DM, and for those using mobility aids (OR 3.1, $p<0.001$). Only 47% of participants reported being prescribed fracture prevention. Only 52% of participants on >1 month of steroids were prescribed calcium/vitamin D.
Conclusions: Fall and fracture prevention efforts should be emphasized in myositis.

Abstract #471

Neuromuscular Manifestations Associated With COVID-19

Billie Hsieh, Ashley Smith, Xiaojin Li, Kristin Brown, Suur Biliciler, Thy Nguyen

Introduction: Both central and peripheral nervous system (PNS) manifestations of COVID-19 have been reported. A Chinese retrospective case series, on 214 hospitalized COVID-19 patients, found that 8.9% presented with peripheral nerve disease and 7% had muscular injuries. Other studies looking at the prevalence of PNS manifestations are limited and have significantly lower numbers.

Objectives: Determine neuromuscular manifestation incidence in COVID-19 patients from the longitudinal electronic health record database Optum.

Design/Methods: The COVID-19 data is sourced from more than 700 hospitals and 7000 clinics in the US. Patients with numerous neuromuscular diagnoses were identified based on ICD-10 coding. Examples include carpal tunnel syndrome, radial nerve lesion, sciatic nerve lesion, myasthenia gravis, acute transverse myelitis, Bell's palsy, and trigeminal neuralgia.

Results: We reviewed a total of 598,847 patients with positive COVID-19 PCR and/or diagnosis coding. Neuromuscular complications must have been within 45 days of diagnosis to be included. Incidence of similar neuromuscular complaints was evaluated in 3,001,153 controls without COVID-19. Critical illness neuropathy was found in 35,782 COVID-positive patients and 6,281 of those without. Retrospective study limitations include temporal relationship to COVID-19 does not necessarily indicate causality and inability to confirm the coding by record review or EMG/NCS.

Conclusions: Incidence of neuromuscular disorders is generally lower or equivalent in COVID-19 patients than in the general population, except for critical illness neuropathy and myopathy. This finding may be explained by more COVID-19 patients being in the intensive care unit and bedbound for longer periods. It is worth noting that a small case series of COVID-related critical illness neuropathy and myopathy patients showed no histopathological or clinical differences compared to non-COVID patients. To our knowledge, this report includes an analysis of neuromuscular manifestations in one of the largest cohorts of COVID-19 patients. This can assist with risk-benefit discussions regarding treatment initiation, etiology of diagnoses, and counseling for COVID-19 questions.

Abstract #510

Myalgia and fatigue as "LONG COVID" Symptoms: a 1-year follow up

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ABSTRACT

Introduction: COVID-19 is a syndrome caused by SARS-CoV-2 virus and the main manifestation is interstitial pneumonia. However, many neurological and also neuromuscular manifestations were described as associated to SARS-CoV-2 infection. Multiorgan symptoms after COVID-19 are being reported by increasing numbers of patients, lately grouped in a syndrome called "long COVID". However, the long-term health consequences of COVID-19 remain largely unclear.

Methods: We enrolled 124 patients hospitalized between March and May 2020 for SARS-COV-2. We established a 6 and 12 months follow-up. For each patient cognitive tests, scales for depression and anxiety and a specific Fatigue Severity Scale (FSS) were performed.

Results : Twenty-five patients (19.8%) died during hospitalization. Eighty-seven (70%) patiens were male and mean age was 67.3 years. During hospitalization 38.5 % of patients complain of myalgia. Patients with reported myalgia had higher CK (534 U/L vs 93 U/l, $p<0.001$) and LDH levels (363 U/L vs 303 U/L) and they needed more often oxygen therapy (78% vs 42%, $p<0.001$) and non-invasive ventilation (20% vs 5%, $p<0.001$).

At 12 months follow up 85 patient were evaluated and 42 % still complain about myalgia while 34% reported fatigue. Mean FSS value were significatively higher in patiets who complain about fatigue (40.2 vs 25.5 $p<0.001$) and muscle pain (40, 84 vs 26,80, $p<0.001$) compared to who did not.

Conclusions: During hospitalization for COVID-19 myalgia was associated with an higher level of CK and LDH , suggesting a possible direct muscle involvement. At 12 months myalgia and fatigue were commonly reported. These manifestation could be the main "long COVID" symptoms at one year follow-up.

Disclosures: no disclosures

Abstract #529

Understanding the Perseverance of the Muscular Dystrophy Community One-Year into the COVID-19 Pandemic

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Introduction: We examined the social and health impacts of the coronavirus disease 2019 (COVID-19) pandemic on people with muscular dystrophy (MD).
Objectives: Assess the impacts of the pandemic on social factors, muscle disease, and medical care.
Methods: Our "COVID-19 Impact Survey" was a de-identified, electronic survey distributed to adults with MD via international registries and advocacy group websites from February 8, 2021 to March 22, 2021.
Results: Respondents (n=1243: 49% Facioscapulohumeral Muscular Dystrophy; 43% Myotonic Dystrophy, and 8% Limb-Girdle Muscular Dystrophy) were mostly women and middle-aged (range 18-90 years). COVID-19 infections rates were low (8%); reported recovery times were short. Most reported slight worsening of their dystrophy and moderate stress levels.
Conclusions: People with MD managed their stress and overcame obstacles during the COVID-19 pandemic. COVID-19 infection rates and medical complications were similar to the general population. Previously predicted risks for MD patients may need to be reconsidered.

Abstract #530

The Worldwide Impact of the COVID-19 Pandemic on the Muscular Dystrophy Community by Geographical Region

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Introduction: We examined the social and health impacts of the coronavirus disease 2019 (COVID-19) pandemic on people with muscular dystrophy (MD) worldwide.
Objectives: Comparing impact of the pandemic by geographical region.
Methods: Our "COVID-19 Impact Survey" assessed the pandemic's effects on social factors, muscle disease, and medical care. The de-identified, electronic survey was distributed to adults with MD via international registries and advocacy group websites from February 8, 2021 to March 22, 2021.
Results: Rates of COVID-19 infections, symptoms, and recovery time were similar between geographical regions. The most common challenges due to the pandemic were different between regions: social distancing in Europe (60%), obtaining treatment in Canada (54%) and United Kingdom (48%), and stress management in the United States (41%). Individuals living in the United States reported significantly less stress than other regions.
Conclusions: We identified significant differences and similarities of impacts on people with MD between geographical regions.

Abstract #531

Long-term outcomes of mitochondrial myopathies diagnosed in adulthood

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Introduction: Little is known regarding the natural history of mitochondrial myopathies (MM) in adults.
Objectives: To describe the clinical spectrum and long-term outcomes of MM diagnosed in adulthood.
Methods: Retrospective review of adult patients diagnosed with MM at Mayo Clinic (2005-2021).
Results: We identified 94 patients (82 genetically-defined, 12 histopathologically-defined); 48 females. Median age was 31 years at symptom onset and 48 years at diagnosis. Most common presentations included chronic progressive external ophthalmoplegia (37 patients); a nonsyndromic multisystem disorder (24); MELAS (14) and isolated myopathy (13). On muscle biopsy, cytochrome-c oxidase negative fibers were the most common mitochondrial abnormality, representing on average 5.1% of fibers. Progression of muscle weakness was overall slow, with a decline of 0.05 point/year in the summated strength score. Median overall survival was 10.9 years from diagnosis and 33.5 years from symptom onset.
Conclusions: MM are characterized by slowly progressive muscle weakness and probably limited longevity.

Abstract #540

A qualitative exploration of self-management in people living with a neuromuscular condition

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Introduction: Self-management support (SMS) is now widely accepted as a fundamental component of high-quality personalised care. Qualitative data can provide valuable insights into the ways we conceptualise patients' experiences and can influence service design and delivery. However, there is a paucity of data exploring SMS in people with neuromuscular diseases (NMD).

Methods: Semi-structured interviews explored the perspectives of 28 individuals with NMD on their perspectives, preferences, and priorities for SMS. Reflexive thematic analysis was used to code data and identify key domains and themes.

Results: Three overarching themes were identified, linking into two fundamental questions: *"what keeps me going"* and *"what holds me back"*. The overarching themes were '*support systems', 'adapting to change',* and *'it's not just physical'*.

Conclusion: Qualitative data reflecting the perspectives of people with NMD on SMS is lacking. The findings from this study provide insight into the way that SMS is enacted in this population.

Abstract #543

Introduction: The International Centre for Genomic Medicine in Neuromuscular Diseases (ICGNMD) launched in 2019. It is a 5-year initiative to improve health outcomes in neuromuscular diseases (NMDs) globally and spans 14 centres in Brazil, India, Turkey, South Africa, the UK, and Zambia.

Objectives:
1. Deliver research/capacity-building in genomic medicine
2. Facilitate NMD patient access to genetic diagnoses
3. Assemble deeply phenotyped/genotyped NMD cohorts
4. Grow clinical capacity in NMDs by training a clinical academics

Methods: Participants are consented and details entered into a secure database. Cross-site meetings determine best genetic testing options, Samples are analysed locally or at UCL, London. Results are discussed at cross-site MDT meetings.

Results: After 3 years, 4,718 participants (2855 probands) have been recruited, with a balance of paediatric/adult muscle/nerve/mitochondrial disorders.

Conclusions: Genetic results are emerging at scale; these will seed international collaborations and underpin research concerning the global genetic architecture and aetiology of NMDs.

Abstract #547

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 with neuromuscular diseases (NMDs) in clinical research. The people best placed to develop the strategies for engagement are people with these demographics.

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 for a strategy and action points; Workshop 3: Agreeing the final strategy.

Results: Workshop 1 highlighted key challenges, such Knowledge, Personal Choice, Trust and Shame. Ideas were developed around Communication and will be expanded in workshop 2 to create a recruitment strategy.

Conclusion: The first step of the process has concluded. We will launch the final strategy to research colleagues to facilitate greater diversity in trial cohorts at our institution.

Abstract #577

Investigating "scarcity theory" in DMD

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Recent lived experiences have raised awareness regarding socioeconomic determinants of health. The "scarcity theory" identified by economists postulates that financial scarcity affects decision-making due to consumption of cognitive resources, leaving the individual with narrow cognitive control. We investigated the hypothesis that mothers of DMD patients from a lower socioeconomic status had lower cognitive capacity than mothers from a higher socioeconomic status. We used the psychometrically-sound NIH Toolbox Cognition Battery to obtain crystallized and fluid intelligence scores. We correlated these scores to self-reported annual income. Our results show that mothers of DMD patients who reported an annual income of less than US 50,000 scored an average of 25 points lower in fluid intelligence scores compared to mothers who reported an annual income of more than USD 150,000 (p-value of 0.02). Our preliminary findings underscore the importance of recognizing socioeconomic determinants of health in DMD.

Abstract #586

Exploring the impact of balance impairments and falls in people with Charcot Marie Tooth disease

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Introduction: Balance confidence in people Charcot Marie Tooth disease (CMT) is reduced. More exploration is needed to understand how this influences everyday activities, physical and psychological well-being.

Objectives: This qualitative work aims to gain further insight and understanding into the experience of living with balance impairments in people with CMT1A.

Methods: Participants underwent semi-structured interviews. Questions focussed on the impact of balance impairments on daily life. Interviews were transcribed and coded using thematic analysis.

Results: 13 people participated. Themes included (1) *Living with CMT*; (2) *Emotional Issues related to balance;* (3) *Physical Issues;* (4) *Strategies to avoid falls*. The ability to cope with the changing nature of the condition is important. People with CMT adapt and identify strategies which work for them, though some feel more able to do this than others

Conclusions: Clinicians can use this information when supporting patients to self-manage their condition.

Abstract #598

Longitudinal study of cognitive function in DMD: is it really stable?

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Introduction: So far cognitive abilities in DMD have been reported to be stable over time
Objectives: To evaluate the consistency of longitudinal cognitive findings in DMD boys and their relation to behavioural patterns.
Methods: Data were collected from 2010 to 2021 using the Weschler scales (cognitive), CBCL and clinical observation (behaviour). Patients were subdivided depending on IQ level, behavioural disorders, brain dystrophin involvement.
Results: Seventy patients had at least two assessments. Concordant results were found in 63% of the paired assessment. Discrepancy were mostly observed in patients with abnormal CBCL and/or attention deficits.
Conclusions: Changes in IQ may occur in DMD boys and these are more likely to be associated to behavioral or attention deficits than to the involvement of Dp140 and 71 or to IQ level.

Abstract #596

Long term follow-up of scoliosis progression in type II SMA patients.

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Introduction: Scoliosis is one of the most common and feared complications in type II SMA.
Objectives: The aim of this study is to retrospectively evaluate the onset and the progression of scoliosis in a large cohort of untreated type II patients, in relation to different variables.
Methods: Data were collected between 2007 and 2022 from 3 tertiary Italian centers. Cobb angle measurement method was standardized among centers. The model was adjusted by age, sex, Cobb, HFMSE values at baseline, and SMA function.
Results: Eighty-four SMA II patients were enrolled. The mean annual rate of increase in Cobb angle was 5.22 (95%CI: 4.22-6.23). Age and Cobb value at baseline were identified as modifiers of scoliosis progression.
Conclusions: the available data in untreated patients will be of help to determine possible differences in treated patients.

Abstract #607

Frequency of SMA cases and treatment accessibility in Zambia

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Introduction: Known to be the most common genetic cause of morbidity and mortality, SMA affects approximately 1 in 12,000 live births with a prevalence of approximately 1-2 per 100 000 persons.
Objective: Determine the proportion and accessibility of SMA treatments in Zambia.
Methods: Participants were evaluated by a neurologist prior to study entry. Diagnosis was based on available clinical data.
Results: SMA accounted for 20% of the total NMDs being seen with females slightly more affected than males. Mean age of onset was 1.7 months and mean diagnostic age 3.6 months.73% of the patients had access to physiotherapy while 27% to medical care.
Conclusion: SMA was the highest in frequency of NMDs. The current cohort of SMA has access to physiotherapy but their motor function as well as their life span could be better improved with access to the current therapeutics.

Abstract #619

Quality of Life Survey Assessing Accessibility for Patients with Spinal Muscular Atrophy

Kelsee Parry, Tate Keough, Sarah Moldt, Emily Woolsey

Introduction: While there has been disease-stopping advancement in SMA, loss of ambulation shows gaps in accessibility.
Objective: Community-wide accessibility is a barrier for persons' with SMA (pwSMA), and participants feel this is not being properly addressed.
Methods: An open-ended QOL survey was used to identify pain points with accessibility, such as the want for longer transition periods in schools, difficulty with social activities and job searches, and frustrated caregivers.
Conclusions:
Overall data suggest our patients feel some needs are met, but there is still much room for improvement. With better awareness, schools and the community could contribute to accessibility, resources, and awareness of community challenges to improve QoL for pwSMA. This especially pertains to patients approaching adulthood (majority of surveyed patients) and losing public school services.

Abstract #621

Pain impacts quality of life, psychological disorders and exercise in a large international cohort of patients with facioscapulohumeral muscular dystrophy

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Introduction: Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common forms of muscular dystrophy affecting more than 870,000 patients worldwide.

Objectives: Discover the impacts of pain, a significant cause of morbidity, in people with FSHD.

Methods: We analyzed data from a large international observational study run by the FSHD Clinical Trial Research Network which included patient reported data, motor assessments, and quality of life measurements.

Results: We included 219 patients in the analysis. 182 patients (83%) reported pain most commonly in the lower back and shoulders. We uncovered differences in pain management between the US and EU. Univariate analysis found a statistically significant association between the presence of pain and quality of life, psychological problems and resistance exercise rates.

Conclusions: Taken together, these data point to the importance of further characterizing pain in FSHD patients and to develop methods for assessing pain in FSHD clinical trials.

Abstract #639

Impact of Socioeconomic and Insurance Status on Time to Myositis Diagnosis

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Introduction: Socioeconomic factors may impact time to myositis diagnosis.

Objectives: We investigated the impact of socioeconomic and insurance status on time to diagnosis and creatine kinase (CK) normalization.

Methods: Primary outcomes, time to diagnosis and CK normalization, were analyzed using Cox regression. Secondary outcomes, including probability of MRI femur and muscle biopsy completion, were analyzed using logistic regression.

Results: 189 patients were included. Charity and Medicare/Medicaid status were associated with 4.58-fold (p=0.0009) and 4.6-fold (p=0.006) increase in probability of being diagnosed 200 days after first elevated CK, respectively. Females had a 66% decreased probability of being diagnosed after the first elevated CK within the first 40 days (p=0.0003). Median household income, race, and ethnicity showed no significant difference in time to diagnosis and CK normalization. No factors impacted the probability of MRI femur or muscle biopsy completion.

Conclusions: Differences in insurance type and sex may impact time to myositis diagnosis.

Abstract #643

Risk factors for delayed diagnosis of myositis: A cross-sectional study of 470 patients

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Introduction: Myositis can be difficult to diagnosis leading to delayed diagnosis and increased morbidity.

Objectives: We aimed to investigate the risk factors for delayed diagnosis.

Methods: A survey was sent to members of Myositis Support and Understanding inquiring about circumstances around diagnosis. Multivariate linear regression was performed.

Results: In a cross-sectional study of 470 participants with myositis, the average time to diagnosis was 28.1 months (range: 0-120 months), 33.8% of participants traveled >50 miles to a center of excellence and 64% of participants saw >2 providers before a diagnosis was made. Variables associated with longer time to diagnosis were seeing >2 providers (coefficient=32, $p<0.001$), being uninsured (coefficient=52, $p=0.003$), having inclusion body myositis (coefficient=54, $p<0.001$), or having income <$20,000/year (coefficient=42, $p=0.005$).

Conclusions: To obtain faster diagnosis, uninsured and poorer patients are likely to require social support, and those with suspected myositis, especially IBM, should be referred to myositis specialists.

Abstract #645

Risk factors for financial burden in myositis: A cross-sectional study of 470 patients

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Introduction: Myositis requires multidisciplinary care, which may increase financial burden, an unknown dimension in myositis.

Objectives: We investigated risk factors for financial burden in myositis.

Methods: A survey was sent to members of Myositis Support and Understanding to assess financial burden using two validated measures: Financial Worry Score and Financial Burden Composite Score (FBCS). Multivariate linear regression was performed.

Results: In a cross-sectional study of 470 participants with myositis, high financial worry was endorsed by 202 participants (43%) and moderate FBCS (avg±std dev. 1.8±1.9). Factors associated with high financial worry/burden were annual income <$75,000 (OR 2.4-5.1, $p<0.001$) and being on disability (OR 1.98, $p=0.023$). Medicare was the only protective factor for decreased likelihood for high financial worry/burden (OR 0.4, $p=0.008$).

Conclusions: Financial worry/FBCS in myositis are like that in cancer and orthopedic trauma. Policy changes should allow myositis patients to enroll in Medicare earlier than the 24-month waiting period.

Mechanisms of Disease and Less Common Disease

Abstract #554 Platform presenter

Neuromuscular junction transmission failure is a translationally-relevant mechanism of sarcopenia

Authors: W.D. Arnold*, C.J. Padilla*, L.A. Clark**, H Harris*, T.S. Grønnebæk***, J. Bold***, T.H.***, J. Hutchison***, B.C. Clark** (*Columbus, OH, USA; **Athens, OH, USA; .*** Aarhus, Denmark)

Introduction: Sarcopenia, loss of muscle strength and size, contributes to loss of physical function in older adults. Improving physical function in older adults is an urgent need to reduce healthcare costs and improve quality of life. Mixed data exists regarding altered form and function of the neuromuscular junction (NMJ) transmission during aging.

Objective: We aimed to investigate NMJ transmission failure as a potential mechanism of age-related weakness.

Methods: We applied stimulated single fiber electromyography as an in vivo measure of NMJ transmission that can be applied across species.

Results: We show for the first time that NMJ transmission failure is a conserved feature in aged rodent models and older adults with clinically-meaningful weakness. Severity of NMJ deficits is associated with indices of muscle strength in both rodents and humans.

Conclusions: Our findings provide direct evidence for NMJ dysfunction as a mechanism of sarcopenia and target for therapeutic development.

Abstract #563 Platform Presenter

Survival Motor Neuron Protein: Addressing Therapeutic Concerns of Sensorimotor Toxicity

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Introduction: Spinal Muscular Atrophy (SMA) is a motoneuron disease caused by homozygous loss of *SMN1*, and consequentially, low Survival Motor Neuron protein (SMN) levels. scAAV9- mediated *SMN1* gene therapy is routinely used to treat SMA patients. A recent report raised concern of sensorimotor toxicity via protein aggregation in scAAV9-SMN-treated wildtype mice, implying caution is warranted with the clinical therapy; yet, neither promoter nor dose tested matched the clinical construct.

Objective: Determine whether scAAV9-SMN therapy induces sensorimotor toxicity/SMN aggregation when utilizing the clinically-relevant construct.

Methods: Using the clinically-relevant promoter, dose, and mouse model, we assessed the toxicity potential of scAAV9-mediated SMN delivery in wildtype mice.

Results: We found no functional, behavioral, or electrophysiological evidence of toxicity, nor SMN aggregation, following scAAV9-SMN treatment.

Conclusions: Our data support that clinically-relevant scAAV9-mediated SMN delivery is not expected to cause sensorimotor toxicity and argues against the call for concern/alteration to the current clinical therapy paradigm.

Abstract #580 Platform presenter

Bridging the preclinical-clinical gap: reverse translation of muscle velocity recovery cycles allows in vivo assessment of skeletal muscle excitability in mice and humans.

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Transgenic mice with Hypokalaemic periodic paralysis have no spontaneous attacks of weakness whilst recessive Myotonia Congenita mice exhibit muscle atrophy rather than the hypertrophy seen in humans. This suggests a species' difference in muscle excitability.

Muscle Velocity Recovery Cycles (MVRCs) use post-impulse changes in conduction velocity as an indirect measure of excitability. We reverse translated MVRCs to allow mouse-human skeletal muscle excitability comparison.

Whilst human MVRCs (n=26) have two phases of increased conduction velocity known as early and late supernormality, mouse MVRCs only have one. Instead of late supernormality mice exhibit late *sub*normality (reduced velocity). Subnormality has never been seen in human MVRCs. The subnormal phase in mice was converted to supernormality by intraperitoneal injection of 30mg/kg 9-Anthracene Carboxylic Acid a ClC-1 blocker.

MVRCs are a valuable new tool to compare in vivo muscle membrane properties between species and will allow further dissection of the molecular mechanisms regulating muscle excitability.

Abstract #499 Platform presenter

Symptom Onset In Maternally *versus* Paternally Inherited Myotonic Dystrophy type 2.

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Introduction: Myotonic dystrophy type 2 (DM2) is likely underdiagnosed and there is no definitive evidence of genetic anticipation or congenital form in this muscular dystrophy.

Objective: To investigate phenotypic differences with focus on symptom onset and type of symptoms in maternally- and paternally- inherited DM2 patients.

Methods: We reviewed the chart of 70 genetically confirmed DM2 patients and collected information about phenotype and parental inheritance when available.

Results: 26 DM2 patients (from 18 families) were identified as having maternal (14 patients) or paternal inheritance (12 patients). 13 out of 14 maternally inherited DM2 patients developed symptoms by third decade of life. Within paternally inherited DM2 group; none developed symptoms before third decade of life, six developed symptoms during third decade of life or later, and six remained asymptomatic by at least third decade of life.

Conclusions: An earlier symptom onset was observed in maternally inherited DM2 patients in this cohort.

Abstract #506 Platform presenter

A comparison of in silico predictive tools to robust in vivo functional characterisation of CLCN1 genetic variants in skeletal muscle channelopathies.

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Accurate determination of the pathogenicity of missense genetic variants of uncertain significance is a huge challenge for implementing genetic data in clinical practice. In silico predictive tools are increasingly used to score variants' pathogenicity. However, their value in clinical settings is often unclear since they have usually not been validated against robust functional assays. We compare nine in silico predictive tools with detailed cell-based electrophysiology for 126 *CLCN1* variants we discovered in patients with the skeletal muscle channelopathy myotonia congenita. We found poor accuracy for most predictive tests. The highest accuracy was with Mutation Taster (84.58%) and REVEL (ROC 0.89). However, both scores have poor specificity. EVE has better specificity while maintaining good AUC and sensitivity. Combined methods based on concordance, improved performance but still lacked specificity. Tools with better specificity are urgently required. This is a wider issue and a huge challenge for effective clinical implementation of genetic data.

Abstract #517 flash presentation

Unmasking anti-HMGCR myopathy: the hurdles of a prompt recognition

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INTRODUCTION. Anti-HMGCR (3-hydroxy-3-methylglutaryl coenzyme A reductase) is an immune-mediated necrotizing myopathy induced by statin. Atypical presentations hinder recognition and prompt treatment. We present two cases with either atypical clinical or pathological features.

CASE REPORT. First patient was found with asymptomatic high CK (~10000IU/L) at age of 45. Biopsy showed minimal changes without significant inflammation. She then developed slowly progressive proximal weakness and diagnosed as limb girdle muscular dystrophy. Genetic investigations resulted negative. Twelve years later, she had severe proximal weakness and muscle MRI showed diffuse fatty infiltration and disproportionate high STIR signal. HMGCR antibodies resulted positive. Immunosuppressive therapy stopped progression with a partial improvement of symptoms.
Second patient developed slowly progressive upper and lower proximal weakness with high CK (~4000IU/L); muscle biopsy revealed a lymphocyte infiltrate with angiocentric distribution suggestive for vasculitis. Clinical reassessment prompted testing of HMGCR antibodies that resulted positive.
Anti-HMGCR myopathy can present with slowly progressive myopathy and atypical pathology.

Abstract #518 Platform Presenter

Caveolae-Associated Protein (cavin)-4 autoantibodies in immune mediated rippling muscle disease (iRMD)

Importance: iRMD is a rare autoimmune myopathy characterized by electrically silent abnormal muscle excitability and mosaic caveolin-3 sarcolemmal expression.

Objective: To identify a novel autoantibody biomarker of iRMD.

Methods: Archived sera from iRMD patients were evaluated for a common biomarker using phage immunoprecipitation sequencing (PhIP-Seq). Patients' muscle biopsies were also evaluated for putative autoantigen expression.

Results: PhIP-Seq identified peptides corresponding to different regions of the cavin-4 in iRMD sera. Eight of ten iRMD patients were positive for cavin-4 IgG by immunofluorescent cell-based-assay. Healthy and disease controls were cavin-4 IgG seronegative. Muscle biopsy was performed in 7/ 8 cavin-4 IgG seropositive patients; 6/6 muscle specimens revealed a mosaic pattern of sarcolemmal cavin-4 immunoreactivity, matching caveolin-3 expression. Three of 6 seropositive patients who received immunotherapy had resolution of symptoms; one had mild improvement and two had no change.

Conclusion: Cavin-4 IgG is a novel and specific serological autoantibody biomarker of iRMD.

Abstract #476

Skeletal Muscle Channelopathies: A UK Prevalence Study

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Introduction: Skeletal muscle channelopathies are a group of skeletal muscle disorders caused by variations in genes that encode for ion channels. The last UK prevalence study found the minimum point prevalence of skeletal muscle channelopathies to be 1.12/100,000 in 2011. Since then, there has been an implementation of Next Generation Sequencing in the National Hospital for Neurology and Neurosurgery and increased research into variants associated with skeletal muscle channelopathies.

Objectives: To provide an up-to-date and accurate minimum point prevalence of genetically defined Myotonia Congenita (MC), Sodium Channel Myopathy (SCM), Paramyotonia Congenita (PMC), Hyperkalemic Periodic Paralysis, Hypokalemic Periodic Paralysis and Anderson-Tawil Syndrome (ATS). It also looks at the different variants associated with the conditions and the mode of inheritance.

Methods/Materials: Analysis of 4241 patients on the National Channelopathy database was undertaken, looking at the variants of CLCN1, SCN4A, CACNA1 and KCNJ2.

Results: The point prevalence of all Skeletal Muscle Channelopathies is 2.04/100,000 population. The minimum point prevalence of MC is 1.13/100,000, of SCN4A variants which encode for PMC and SCM is 0.37/100,000, of periodic paralysis is 0.44/100,000 and of ATS is 0.1/100,000.

Conclusion: There has been an overall increase in point prevalence in skeletal muscle channelopathies, with the biggest increase found to be in MC. This can be attributed to an increased implementation in NGS for patients and relatives presenting to channelopathy services. Despite there being an increase in total number of variants, a small number account for a large proportion of patients with the condition.

Abstract #491

Proposal for the functional assessment of acute inflammatory neuropathy (FAAIN) in Guillain-Barré syndrome

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Introduction: Guillain Barré syndrome (GBS) functional assessment is necessary in clinical practice, research and clinical trials. Existing instruments are not sensitive to change and are not applicable to the current GBS clinical spectrum.

Objectives: To construct a functional assessment for acute inflammatory neuropathies (FAAINGBS), inclusive for current GBS spectrum.

Methods: FAAIN-GBS was made up of two subscales (extension and intensity). Its structure and interpretation were defined. It was validated using data from medical record of 167 GBS patients admitted to the Institute of Neurology and Neurosurgery.

Results: FAAIN-GBS was constructed. Internal consistency was acceptable (Cronbach 0.745). Spearman correlation between FAAIN-GBS and Hughes scale was 0.463. Sensitivity was 0.714 and specificity, 0.986. AUROC was 0.93.

Conclusion: FAAIN-GBS was constructed and a first step of validation was made, showing good internal consistency and validity. New prospective studies will be necessary to perfect this instrument that could be useful in neurological practice.

Abstract #501

Creatine Kinase (CK), Mitochondrial CK, and Macro-CK.

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Introduction: Testing for serum creatine kinase (CK) activity level is a routine practice when evaluating patients with muscle weakness. Whereas serum CK is well-known and often used in clinical practice, mitochondrial CK (Mt-CK) and macro-CKs are not.

Objectives: To understand origin, structure, function, tissue expression, and potential clinical applications of Mt-CK and macro-CKs.

Methods: We reviewed PubMed medical literature about Mt-CK and macro-CKs and their significance in health and disease.

Results: Macro-CK type 1 has been found in the serum of patients with autoimmune disorders such as myositis and in healthy subjects. Macro-CK type 2 is a Mt-CK oligomer that has been associated with malignancies. In biopsied skeletal muscle, electrodense intramitochondrial deposits of Mt-CK resembling the appearance of "parking lot" has been reported as a feature of mitochondrial cytopathies.

Conclusions: Existing data in literature suggest that Mt-CK and macro-CKs may be clinically useful when evaluating patients with neuromuscular diseases (myopathies).

Abstract #511

Dominant Cardioskeletal Titinopathies Reflect Distinct Mechanisms of Disease

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Introduction: We identified novel dominant skeletal/cardioskeletal titinopathies segregating in families with single truncating, splice-site or deletion *TTN* variants.

Objective: To investigate mechanism of disease.

Methods: Tibialis anterior biopsies were studied via Western blot, RNASeq, EM, and muscle fiber mechanic studies in 9 cases, 7 controls, and one disease control.

Results: Western blot revealed normal full-length and truncated titin in the deletion case (exons 346-362), but only normal titin in the truncating and splice-site cases. *TTN* transcript levels were reduced in the truncating and deletion cases and in the HMERF control, but normal in the splice-site cases. Skipping of exons 347-361 was observed in the deletion case. Reduction of *RBM* transcripts and differential splicing of known gene targets was observed in 3 cases with the c.44816-1G>A splice variant.

Conclusions: Dominant truncating, splice-site or deletion *variants appear* to result in distinct disease mechanisms in skeletal titinopathies, including dominant negative modes of action.

Abstract #512

Characterising the molecular consequences of LMNA-related congenital muscular dystrophy in patient myoblasts

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Mutations in LMNA, encoding lamin A/C, can cause congenital muscular dystrophy (L-CMD), but the downstream molecular mechanisms that give rise to L-CMD are not fully understood. Using quantitative western blotting and immunofluorescence microscopy, we show that myoblasts from three individuals with L-CMD have abnormal nuclear morphology and mislocalised emerin, whilst the expression levels of lamin A/C and emerin are comparable to myoblasts from health controls. Quantitative proteomics analysis revealed differential expression of 124 and 228 proteins in L-CMD myoblasts and myotubes, respectively, compared to controls. Ingenuity pathway analysis revealed enriched canonical pathways associated with the differentially expressed proteins including synaptogenesis signalling and necroptosis signalling pathways in L-CMD myoblasts, and Huntington's disease signalling, xenobiotic metabolism signalling and insulin secretion signalling pathways in L-CMD myotubes. The proteins and molecular pathways identified here shed light on the downstream molecular consequences of L-CMD and may represent targets for future development of therapies.

Abstract #514

A Novel Approach to Treating Myotonia Congenita

Introduction: Myotonia Congenita (MC) is an inherited disease affecting the skeletal muscle chloride channel. Patients with MC suffer from debilitating involuntary muscle stiffness. Myotonia can be triggered through voluntary movement or percussion. It is still unknown if the two mechanisms are distinct.

Objective: To determine the mechanism causing percussion myotonia with the goal of improving treatment for MC.

Methods: In vitro and in vivo electrophysiology experiments were performed on both genetic and pharmacologic mouse model of MC.

Results: We examined the role of transient receptor potential vanilloid 4 (TPRV4) in myotonia. Percussion myotonia was markedly suppressed in TRPV4-KO muscles and in muscles treated with selective TRPV4 channel inhibitors. Inhibition of TRPV4 did not alter intrinsic muscle excitability and it reduced the severity of myotonia by 80% in vivo.

Conclusion: These results suggest two distinct mechanisms generate myotonia and block of TRPV4 offers a new therapeutic option for MC.

Abstract #519

A stable human Schwann cell model of Charcot-Marie-Tooth disease type 1A

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Charcot-Marie-Tooth disease type 1A (CMT1A) is a hereditary condition affecting the insulating myelin sheath surrounding peripheral nerves, resulting in muscle weakness and wasting and loss of sensation. CMT1A is caused by duplication of the *PMP22* gene which leads to overexpression of peripheral myelin protein 22 in Schwann cells, leading to myelin sheath defects and axonal loss. The reduction in levels of PMP22 is therefore a promising approach for potential therapies. To study this, we have established a stably transfected, clonal, immortalized human Schwann cell line with high over-expressed levels of cytoplasmic PMP22 fusion protein. Plasma membranes were often irregular and spindly in the PMP22 transfectants but generally had a smooth appearance in control transfectant cells. Ongoing work aims to identify drugs and interaction partners in these cells which may have potential to regulate the expression levels or stability of PMP22 as an approach to therapy.

Abstract #525

Unlocking the potential of oligonucleotide therapeutic candidates for Duchenne muscular dystrophy through enhanced delivery.

Ashling Holland, Sonia Bracegirdle, Sam Ching, Jaya Goyal, Smita Gunnoo, Calum Irwin, Rachel Johnson, Jane Larkindale, Pallavi Lonkar, James McArthur, Michelle Mellion, Niels Svenstrup, Caroline Godfrey, PepGen Inc.

Introduction: PepGen's Enhanced Delivery Oligonucleotide (EDO) technology is engineered to optimize tissue penetration, cellular uptake and nuclear delivery of oligonucleotide therapeutic candidates, potentially enhancing therapeutic activity. PGN-EDO51 is designed to treat individuals with Duchenne muscular dystrophy (DMD) amenable to exon 51 skipping.

Objectives: Evaluate the potential of PGN-EDO51 in *mdx* mouse and non-human primates (NHP).

Methods: Single administration in *mdx* mice (0, 30, 60 mg/kg) and single/repeat administration in NHP (0, 10, 20, 30, 40, 60 mg/kg).

Results: PGN-EDO23 (murine analogue of PGN-EDO51), induced 90.4%, 99.7% 80.6% and 25.7% of normal dystrophin levels in the quadriceps, biceps, diaphragm, and heart of the *mdx* mouse respectively. NHPs showed broad biodistribution, with significant levels in skeletal, smooth, and cardiac muscle and central nervous system. Repeat administrations demonstrated accumulation of exon skipping. No significant toxicology was observed.

Conclusions: PGN-EDO51 was generally well tolerated through clinically relevant doses and is currently being evaluated in a Phase 1 healthy volunteer study.

Abstract #526

Unlocking the potential of oligonucleotide therapeutic candidates for myotonic dystrophy through enhanced delivery.

Ashling Holland, Sonia Bracegirdle, Sam Ching, Jaya Goyal, Smita Gunnoo, Calum Irwin, Rachel Johnson, Jane Larkindale, Pallavi Lonkar, James McArthur, Michelle Mellion, Niels Svenstrup, Caroline Godfrey, PepGen Inc.

Introduction: PepGen's Enhanced Delivery Oligonucleotide (EDO) technology is engineered to optimize tissue penetration, cellular uptake and nuclear delivery of oligonucleotide therapeutic candidates. The EDO platform achieves robust delivery of oligonucleotides to skeletal, smooth and cardiac muscle and central nervous system in non-human primates (NHPs). PGN-EDODM1 is designed to deliver a PMO into muscle cells that binds to the pathogenic CUG repeat expansion present in the *DMPK* mRNA, reducing the ability of the repeats to sequester MBNL1, thereby correcting splicing and reducing disease symptoms.

Objectives: Evaluate potential of PGN-EDODM1 to treat the underlying cause of DM1.

Methods: Single dose administration in DM1 cellular model (2,600 CTG repeats) and HSA^{LR} murine model.

Results: Dose dependent correction of mis-splicing was observed in both models. Cellular model showed reduction in toxic foci. The HSA^{LR} murine model showed sustained correction of mis-splicing and complete amelioration of myotonia. No significant toxicology was observed at clinically relevant doses.

Conclusions: These results support further development of PGN-EDODM1 as a disease-modifying treatment for DM1.

Abstract #528

Development of a diagnostic framework for vestibular causes of dizziness and unsteadiness in patients with mitochondrial disease – a Delphi consensus

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Introduction: Vestibular dysfunction is prevalent in adults with mitochondrial disease (MD) (Holmes et al. 2018). A consensus method was employed to identify statements for a diagnostic framework to facilitate identification of vestibular dysfunction in MD.

Methods: A three-round, modified electronic Delphi approach was used. Round one developed the statements from evidence-based literature. Statements were emailed to neuro-otologists of the European Academy of Neurology to obtain their level of agreement with the statements being in the framework. Consensus was defined when ≥75% of the responses were in the lower or higher tertile (Boulkedid et al., 2011).

Results: Twelve statements were emailed in round two, five reached consensus, four were removed and three were reworded. One reached consensus in round three.

Conclusion: Six questions were identified to ask patients with MD reporting dizziness and unsteadiness. These are included in a diagnostic framework being validated in an observational cohort study design.

Abstract #536

Evaluation of face mobility in spinal muscular atrophy: exploiting a face tracking approach

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Introduction: Weakness in the oro-facial district may affect several functions. Quantitative assessments and oro-facial response to current therapies are scanty in Spinal Muscular Atrophy (SMA).

Objectives: To quantitatively evaluate face mobility in SMA.

Methods: Subjects were asked to perform different tasks (eg. frown, close your eyes, smile, kiss, inflate your cheeks) while frontal face videos were acquired prior to acquisition of a neutral face expression. Face mobility index (FMI), an easy-to-interpret index based on a face tracking algorithm that exploits Facial Action Coding System, was calculated.

Results: 23 adults (33.30±13.06 years) and 13 kids (9.46±3.55 years) with SMA and 10 age-matched healthy controls were recruited. FMI detected a significant difference in the 'smile' task in children and in the 'kiss' task in adults compared to controls.

Conclusions: FMI seems to be an interesting non-invasive measure of face mobility in SMA. Follow-up data in patients on nusinersen are on-going to explore the potential effects of treatment in the facial district.

Abstract #537

Neurophysiological study of facial nerve and Motor Unit Number Index (MUNIX) of orbicularis muscle in spinal muscular atrophy (SMA)

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INTRODUCTION. Orobulbar involvement in SMA is frequent but quantitative assessment still relies on exploratory measures. MUNIX studies have shown correlation with disease severity but its application has been limited to limb muscles.

OBJECTIVES. To explore MUNIX of the orbicularis oculi and facial nerve in SMA.

METHODS. MUNIX of the orbicularis muscle and facial nerve responses (measured as compound motor action potential, CMAP), was cross-sectional recorded in SMA patients and compared to healthy controls (HCs).

RESULTS. 36 SMA (20 SMA2;16 SMA3) patients and 27 HCs (comparable in age and gender) have been recruited. In the SMA cohort median CMAP amplitude and MUNIX scores were 1.5 mV and 20.8 respectively. Mean CMAP amplitude and MUNIX scores were significantly lower in SMA patients compared to controls and correlated to functional status (SMA2 vs SMA3) and Active Maximum Mouth Opening.

CONCLUSIONS. Follow-up analysis to monitor facial muscle strength is ongoing to explore the potential benefit of nusinersen over time in facial muscles.

Abstract #546

A case of myotonic dystrophy type 1 associated with Parkinson disease

Introduction: Myotonic dystrophy type 1 (DM1) is a genetic disorder that caused muscle dystrophy and myotonia in combination with multisystemic involvement. Coexistent parkinsonism symptoms are very uncommon and since 1996 only six cases are reported.

Case Report: A 62-year-old male presented with complaints of a 6 years of worsening dysphagia and balance disorder and subsequently a bilateral foot dorsiflexion deficit. Hospitalized in March 2022 for further worsening of dysfagia and weight loss; on examination the patient showed moderate bilater bradykinesia, biliteral limb rigidity and slowing gait with reduced arm swing.

Methods and results: Electromyographic exam and DAT-Scan were carried out. EMG confirmed the diagnostic suspicion of DM1 while DAT imaging demonstrated presynaptic dopaminergic deficit in bilateral putamen. Then we started levodopa treatment without benefit.

Conclusion: These data are similar to those reported in literature; the association of DM1 and parkinsonism may not be coincidental. Poor-levodopa response is a common aspect in all DM1 reported cases.

Abstract #549

Proteomic profiling of fibroblasts differentiates patients with severe, intermediate and mild spinal muscular atrophy

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Most research characterising the molecular consequences of spinal muscular atrophy (SMA) have focused on SMA I. Here, quantitative proteomic profiling of skin fibroblasts from severe (SMA I), intermediate (SMA II), and mild (SMA III) patients, compared to controls, found limited overlap of differentially expressed proteins across each SMA type. Nevertheless, enriched canonical pathways common to all types included mTOR signalling, regulation of eIF2 and eIF4 signalling, and protein ubiquitination. BioLayout expression clustering identified proteins that discriminate or correlate with severity, from which PYGB (SMA I), RAB3B (SMA II), and IMP1 and STAT1 (SMA III) were selected and verified. Transfection of SMA II fibroblasts with an SMN-construct enhancing its expression confirmed RAB3B expression is SMN-dependent. Combined, this four-protein panel may be useful for stratifying patients in clinical trials or for therapeutic monitoring. The proteins and pathways identified pave the way for studies to optimise therapies for SMA patients of differing severities.

Abstract #550

Dysregulation of intermediate filament proteins associated with cardiac pathology in two mouse models of differing Spinal Muscular Atrophy (SMA) severity

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Using quantitative proteomics analysis, we previously detected widespread molecular defects in heart tissue from the Taiwanese mouse model of severe spinal muscular atrophy. Using the same approach, we now report significant perturbation of the heart proteome in the *Smn*$^{2B/-}$ milder SMA mouse model. In *Smn*$^{2B/-}$ hearts, 277 proteins were significantly dysregulated compared to controls with 50 similarly dysregulated in Taiwanese hearts. Bioinformatics analysis found many of the dysregulated proteins to be associated with cardiovascular development and function. Similarly, to Taiwanese mice, lamin A/C was increased in *Smn*$^{2B/-}$ hearts whilst desmin was reduced in both. Lentiviral-mediated SMN restoration restored desmin levels in *Smn*$^{2B/-}$ hearts to control levels whereas lamin A/C remained elevated. Intermediate filament proteins have key roles in cardiac function and their dysregulation may explain cardiac impairment in SMA. Cardiac pathology may need considering in long-term care of SMA patients, as current treatments may not fully rescue SMA peripheral pathology.

Abstract #551

Hypercapnic respiratory failure in a patient with rheumatoid arthritis and systemic sclerosis overlap caused by hydroxychloroquine-induced toxic myopathy

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Hydroxychloroquine (HCQ) and chloroquine (CQ) have been commonly used agents in the prevention of malaria and the treatment of a variety of systemic inflammatory disorders since the 1950s. Off-target effects due to accumulation of HCQ/CQ in lysosomes include myopathy. We describe a 51-year-old female with rheumatoid arthritis and systemic sclerosis overlap complicated by type 1 pulmonary arterial hypertension treated with a combination of methotrexate, etanercept, and hydroxychloroquine who developed acute hypercapnic respiratory failure and inability to wean from the ventilator despite aggressive pulmonary management. Diagnostic workup yielded evidence of a proximal myopathy, atrophic diaphragms, near-absent phrenic nerve responses, and non-specific chronic myopathic changes on muscle biopsy. Electron microscopy ultimately revealed evidence of abnormal autophagy with accumulation of curvilinear material associated with hydroxychloroquine drug toxicity. After discontinuation, she gradually weaned from positive pressure ventilation and regained strength. This case demonstrated the value of ultrastructural examination differentiating HCQ toxicity from overlap myositis.

Abstract #566

Detection of alpha-dystroglycan glycation in muscle biopsies using a multiplexed western blot method

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Introduction: Limb-girdle Muscular Dystrophy (LGMD) Type 2I is an autosomal recessive disease caused by partial loss of function mutations in fukutin-related protein (FKRP) leading to hypo-glycosylation of alpha dystroglycan (αDG).

Objectives: Develop a method for evaluating the extent of glycosylation of αDG in muscle biopsies from patients with LGMD2I.

Methods: A multiplex western blot (WB) was developed to assess glycosylation of αDG by detecting both total αDG and glycosylated αDG. This generates a ratio of αDG-glycan to total αDG that estimates glycosylation.

Results: Two compatible antibodies were identified. Specificity was assessed using DAG1 HEK293T knockout cell lysates. Signal linearity was evaluated using control tibialis anterior (TA). This WB method will assess muscle biopsies in participants of our LGMD2I natural history study.

Conclusions: A multiplexed WB has the potential to inform on the extent of αDG glycosylation in LGMD2I patients and to assess cellular response to a therapeutic intervention.

Abstract #574

The Tragic Couple: Adult Onset Desmin-Related Myopathy and Multiple Sclerosis

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Introduction: Mutations of *DES* gene, which encodes an intermediate filament called desmin, mostly causes myofibrillar myopathy.

Case report: We report a patient with desmin-related myopathy and multiple sclerosis (MS) simultaneously.

Methods: A 26-year-old male was admitted with progressive proximal weakness. He had no family history of myopathy. Decrease in right-sided visual acuity and mild sensory impairment were noted besides limb weakness. Brain MRI was compatible with primary demyelinating disease. High serum creatine kinase, and myopathic changes in electromyography were detected. Muscle biopsy showed myopathic features consisted of cytoarchitectural abnormalities and mild increase in connective tissue.

Results: New generation DNA sequencing revealed homozygous splice site mutation c.1289-2A>G in *DES* gene, which has been reported once before.

Conclusion: Although central nervous system involvement can be present in various muscle disorders, the co-occurrence of MS and myopathy is very rare. In our knowledge, this is the first case with desmin-related myopathy and MS.

Abstract #575

Evaluation of the Biodistribution, Efficacy, and Side-Effect Profile of Deflazacort, Prednisone/Prednisolone and Vamorolone in a Duchenne Muscular Dystrophy (DMD) Mouse Model

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Introduction: Corticosteroids are the standard of care for DMD.

Objective: Compare the biodistribution, efficacy and side-effects of deflazacort, prednisone/prednisolone, and vamorolone in adult mdx mice.

Methods: All 3 corticosteroids were evaluated using biologically equivalent doses that were compared at clinically relevant exposures.

Results: Deflazacort had a lower brain:plasma ratio(0.05) than vamorolone(0.55). D. All three corticosteroids inhibited NF-kB inflammatory cytokines associated with the beneficial effects of corticosteroids, and induced genes associated with drug side-effects.
Predinosne/prednisolone and vamorolone had a greater extent of altered gene expression in mdx mouse brain (4914 and 4730 genes) vs deflazacort (329 genes, highest dose). Mice treated with deflazacort showed greater improvement in grip strength vs prednisone/prednisolone or vamorolone (67%, 27%, and 0%, respectively). Vamorolone and prednisone/prednisolone induced greater depression than deflazacort in corticosteroid-induced depression tests in these same mice.

Conclusion: Deflazacort was most effective in increasing muscle strength, with the least potential for behavioural side-effects.

Abstract #578

Clinical Improvement Mirrored Antibody Reduction in Myasthenia Gravis

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Introduction: The relationship of anti-acetylcholine receptor (AChR) antibody levels to treatment response remains unclear in seropositive myasthenia gravis (MG) patients.

Objective: To examine whether changes in AChR antibody level (ΔAb) correlate with clinical response in subjects in the Thymectomy in Myasthenia Gravis Trial (MGTX).

Methods: Post-hoc analysis of the MGTX antibody level dataset at baseline, 12, 24, 36 months. Changes in Myasthenia Gravis Activities of Daily Living (ΔMG-ADL) and Quantitative Myasthenia Gravis (ΔQMG) scores compared to ΔAb between the thymectomy+prednisone versus prednisone only groups. Statistical methods included bivariate linear regression, Spearman correlation and Mann-Whitney test.

Results: Data from 86/126 enrolled subjects, including outliers, was analyzed. Correlation with ΔMG-ADL was statistically significant at 12 and 24 months (P 0.0397 and 0.0008 respectively). ΔQMG and ΔAb directly correlated at all 3 timepoints [P= 0.0032, P= 0.0031, P=0.0005, respectively].

Conclusion: Reductions in AChR antibody level generally correlated, in both treatment arms, with improvement in QMG and MG-ADL scores.

Abstract #581

Spectrum of multisystem proteinopathies: single center experience

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Introduction: Multisystem proteinopathies (MSPs) are genetically heterogenous disorders sharing the common pathomechanism of RNA granule function defect leading to protein aggregation.

Objectives/Methods: To study the MSP spectrum in patients evaluated at Mayo Clinic (2010-2022) by reviewing clinical and laboratory findings.

Results: Among 25 patients (22 families), *VCP*-MSP was the most common (68%) followed by *SQSTM1+TIA1*-MSP (20%). *HNRNPA1*-, *MATR3*-, and *TFG*-MSP, each accounted for single cases. Myopathy occurred in 92%: mean age-onset was 53 and phenotype was limb-girdle (12/15 *VCP*-MSP), distal or scapulo-distal (other MSPs). Rimmed vacuoles were present in 85% of muscle biopsies. Motor neuron phenotype was rare (2 *VCP*-MSP; 1 *TFG*-MSP). Frontotemporal dementia and Paget's disease of bone each occurred in 12% of patients. Within 12-year follow-up, 72% required a gait-aid 9 years (median; range 1-21) after disease-onset; 24% developed restrictive lung disease; none had cardiomyopathy.

Conclusion: Rimmed-vacuolar myopathy was the most common presentation in our MSP cohort.

Abstract #583

Characterization of Inclusion Body myositis (IBM) population, single center study

Introduction: IBM is a slowly progressive myopathy beginning in mid life with no proven treatment.

Objective: to characterize the IBM population seen in our Myositis Clinic over the years.

Methods: retrospective chart review from 1/2017 until present.

Results: Out of 32 patients with IBM, 18 were tested for the NT5c1A antibodies. 72% were positive and 28% were negative. The NT5c1A seropositive patients, dropped in average with 3.3 points IBMFRS per year. The seronegative patients progressed in average with 1.76 points on the IBMFRS per year. The seropositive patients had their disease in average for the past 16 years and 61% are ambulatory and 30 % are non-ambulatory and one died after 40 years of disease. The seronegative patients had their disease in average for the past 11.2 years and all but one are still ambulatory (80%).

Conclusions: The seropositive patients seem to decline faster and are more likely to lose ambulation than the seronegative patients.

Abstract #584

Myasthenia gravis with “frozen globes” responding to Complement inhibitors

Introduction: Ocular MG can cause ophthalmoplegia or “frozen globes”. Here we describe a case responding well to eculizumab.

Case report: 48 year old with ocular MG AchR + presents with double vision and ptosis. His worst MGFA Score IIB. He has bilateral eye ptosis left worse than right and ophthalmoplegia. He is currently on Mestinon and monthly IVIG. Prior medications include prednisone and Azathioprine. His MRI orbits was negative with no atrophy of the extraocular muscles. While his disease is ocular only, the symptoms are severe and interfere with his quality of life.

Results: With eculizumab, in 3 months his MMT cranial muscle score went from 10 to 2 and in 10 months he was asymptomatic.

Conclusion: Intrinsic complement regulators are expressed at lower levels at EOM neuromuscular junctions, which would put them at risk for the complement-mediated injury that occurs in MG. Thus complement inhibitors should be used early in ocular MG before progression to atrophy of EOM.

Abstract #588

Early assessment of infants with SMA identified through newborn screening

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Introduction: Neonatal screening for SMA is allowing the identification of patients with mutations in the SMN gene generally considered as presymptomatic.

Objectives: The aim of this study was to assess a cohort of infants identified through screening and to compare them to healthy controls. We also aimed to establish if the scores were different in patients who had already signs of SMA.

Methods: CHOP INTEND was performed in both SMA patients and healthy controls.

Results: A total of 26 (SMA) and 130 (controls) assessments were collected. Of the 26, 18 were from presymptomatic and 8 from symptomatic patients. CHOP INTEND score was different between symptomatic and presymptomatic or controls ($p<0.001$), while was not different between presymptomatic and healty controls ($p>0.05$).

Conclusions: The CHOP INTEND is able to identify symptomatic patients identified by neonatal screening.

Abstract #589

Female carriers for dystrophin gene mutation with various clinical manifestations – case series.

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Introduction: Female dystrophin (DMD) gene mutation carriers manifest various disease symptoms. Very little is known about the disease progression resulting in lack of Standards of Care (SOC).

Objectives: To review a cohort of symptomatic females with DMD mutation.

Methods: A retrospective review of patient medical notes.

Results: Thirteen females with DMD gene mutations presented with various sequela including: respiratory (31%) (one started non-invasive ventilation when ambulant), cardiomyopathy (62%), motor function decline and muscle weakness (100%), contractures (54%), falls (38.5%), lower limbs fractures (15%), bulbar involvement (31%) (in 4 ambulant patients), pain (38.5%), fatigue (31%), gastro-intestinal disturbances (15%), cognitive (23%) and psychological (31%) involvement. Four (31%) were treated with long-term corticosteroids of whom three (23%) found them beneficial.

Conclusions: Manifesting female DMD gene carriers are clinically heterogeneous, demonstrating similarities to affected males however, progression may differ. Recognising various disease presentations is critical to establishing SOC for management of this patient group.

Abstract #594

The Importance Of Segregation in the Genetic Diagnosis Of Hereditary Neuropathies

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Introduction: Confirming pathogenicity of genetic variants in Charcot-Marie-Tooth (CMT) disease is of vital importance, particularly with the emergence of potential treatments. Segregation studies involving family members play a pivotal role in this.

Objectives: To assess the impact of the segregation studies on the diagnostic rate when using family-analysis compared to proband-only analysis for patients with genetic findings.

Methods: Blood was requested from relatives of 150 patients, in whom only the proband's DNA was initially available. Segregation of candidate variants was performed where applicable. Variants were reassessed as to the likelihood of their pathogenicity.

Results: Out of a total of 59 positive genetic test results 43 (73%) were confirmed pathogenic using segregation and 16 (27%) were confirmed pathogenic through singleton studies.

Conclusions: Segregation is crucial in the genetic diagnosis of hereditary neuropathies and remain a major part of the overall assessment of genetic variants in complex hereditary neuropathy clinics.

Abstract #595

Episodic weakness in patients with mitochondrial DNA MT-ATP6 mutations: the Queen Square experience

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Introduction: Episodic muscle weakness has been described in people harbouring mitochondrial DNA (mtDNA) *MT-ATP6* mutations, mimicking periodic paralysis.

Objectives: To report the prevalence and clinical/electrophysiological features of episodic limb weakness in patients with mtDNA *MT-ATP6* mutations.

Methods: We retrospectively evaluated 19 patients with pathogenic *MT-ATP6* variants attending the Queen Square NHS England Highly Specialised Service for Rare Mitochondrial Disorders, London. Demographic, clinical, and electrophysiological data were collated.

Results: Of 19 patients, five (26.3%, two female) reported episodic lower limb weakness. The following *MT-ATP6* mutations were reported: m.9185T>C (n=3); m.8782G>A (n=1); and m.9176T>G (n=1). In all cases but one, a diagnosis of CMT2-like neuropathy was present. Long exercise testing was performed in three cases and resulted negative.

Conclusions: *MT-ATP6* mutations should be considered in patients with episodic weakness, normal long exercise testing, and negative pathogenic variants in skeletal muscle channelopathy genes.

Abstract #597

Clinical heterogeneity in IBM patients

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Introduction: IBM is the most common acquired myopathy in individuals over age 50, and currently no therapeutic treatment is available. Clinical heterogeneity may influence treatment responsiveness; however, data regarding heterogeneity in IBM is limited and often conflicting.

Objectives: We aimed to identify clinically distinct subgroups within a large IBM cohort, as well as prognostic factors for disease progression.

Methods: Clinical, histologic, radiologic, and electrophysiologic data from IBM patients enrolled in a longitudinal cohort at the Johns Hopkins Myositis Center was analyzed. Univariate, multivariate, and graphical analyses were used to identify prognostic factors.

Results: 335 IBM patients met the inclusion criteria, with an average age of 58.7 years of disease onset. Average delay of diagnosis was 5.2 years, and in 20% onset was before age 50. Initial misdiagnosis and immunosuppressant treatment were common.

Conclusion: the study demonstrated distinct clinical phenotypes, particularly among female and Black patients.

Abstract #599

New role for dystrophin in neuronal homeostasis

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Abnormal synaptic proteome function is a mediator of cognitive deficits in Duchenne Muscular Dystrophy. Neurons are highly polarized cells with multiple dendrites but a single axon, which underscores a highly regulated trafficking of cellular organelles, with the somatodendritic cargo not permitted to enter the axon. To investigate the mechanisms that regulate neuronal trafficking, we investigated the expression of ankyrin-G, the master regulator of neuronal polarity in CA1 hippocampal neurons of the mdx52 mouse model, using high resolution structural illumination microscopy, proteomics immunohistochemistry, and neuronal modeling. AIS structure and function was abnormal in mdx52 mice. The AIS was abnormal in length and diameter in mdx52 mice. Ankyrin-G colocalized with kinesin KIF5a, the anterograde protein transporter, with higher levels in older mdx52 mice compared to young mdx52 mice suggesting functional compromise of the AIS in neurons. Our data suggests that dystrophin deficiency compromises neuronal homeostasis through ankyrin-G based mechanisms.

Abstract #609

Atypical cases of Sporadic Inclusion Body Myositis

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Introduction: Sporadic inclusion body myositis (sIBM) is classically heralded by weakness in the finger flexors and quadriceps in patients aged over 50. Respiratory and tongue involvement can be seen later but it is unusual to be seen early in the disease. There have been a few reports describing facial weakness as a presenting feature.

Case Series: We describe five cases of sIBM with atypical presentations.

Methods: The patients had undergone in depth investigations including histopathology, muscle MRI and in some cases advanced neurogenetics.

Results: Facial weakness was a presenting feature in two middle-aged patients. Marked tongue involvement and respiratory dysfunction early during the disease was seen in three cases. Two patients developed symptoms in their thirties with one such patient presenting with proximal weakness.

Conclusions: Despite the classical archetype described in the literature sIBM can present in a heterogenous fashion. sIBM should be increasingly recognised as a potential differential for early facial weakness and respiratory dysfunction.

Abstract #616

Swallowing impairment in Myotonic Dystrophy type 1 (DM1): a slowly progressive event

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Introduction: Swallowing disorders in DM1 are potentially life-threatening.

Objectives: To determine the prevalence and progression of dysphagia and its correlation to neuromotor and self-assessment scales.

Methods: We retrospectively reviewed charts from 113 adults with DM1 and recorded clinical-demographic features, fiberoptic endoscopic evaluation of swallowing scores and nutritional status.

Results: At baseline 25% of patients had normal swallowing, 69% mild-moderate and 6% severe dysphagia. 4 of 113 had a PEG tube. After 2 years of follow-up (n = 65) over 80% of population was unchanged. From 2 to 4 years 50% of patients progressed from normal swallowing function to mild-to moderate dysphagia and 35% showed swallowing alterations with liquid consistency. 5 of 65 required a PEG tube (9%). BMI was unchanged.

Conclusions: Dysphagia is frequent in DM1 but progression seems to be slow. Management needs to be disease-specific and balanced between patients and caregivers perception and the potential to cause morbidity and mortality.

Abstract #625

Characterising sex differences in human skeletal muscle excitability and function.

Sinéad Smith (Honorary Research Associate at Newcastle University, Year 2 Scientist Training Programme Trainee at the Department of Neurophysiology, Royal Victoria Infirmary, Newcastle and MSc Student in Neurosensory Science at Aston University, Birmingham).
Dr Thomas Bulea Ph.D. (Tenure Track Investigator, Rehabilitation Medicine Department National Institutes of Health).
Professor Roger Whittaker (Professor of Clinical Neurophysiology at Newcastle University and Consultant at Department of Neurophysiology at the Royal Victoria Infirmary, Newcastle).
Dr Karen Suetterlin (Academic Clinical Lecturer in Neurophysiology at Newcastle University and Clinical Neurophysiology Registrar at the Royal Victoria Infirmary, Newcastle).

Introduction: Women are at greater risk of sudden cardiac death from drug-induced and genetic long QT arrhythmia. Sex differences in skeletal muscle excitability are also likely to exist as females with genetic skeletal muscle channelopathies may be asymptomatic carriers and have negative electrodiagnostic tests.

Aims: To investigate sex differences in healthy human skeletal muscle membrane properties and ionic homeostasis.

Methods: Muscle Velocity Recovery Cycles (MVRCs) and 30Hz frequency ramp EMG of Tibialis Anterior and Rectus Femoris of 70 healthy volunteers (35 males; 35 females; 18-39 years) will be used to assess excitability. Ionic homeostasis will be assessed by comparing continuous and intermittent voluntary contraction using the HandClench relaxometer. A KardiaMobile device will be used to measure QT interval and correlate with MVRC parameters.

Results: Early data will be presented at the conference.

Conclusions: We hope this study improves the techniques available for diagnosis/monitoring of diseases affecting muscle ion homeostasis.

Abstract #636

Distal Adermatoglyphia (loss of fingerprints) in a patient with sporadic Inclusion body Myositis

Breanna Tuhlei, Nakul Katyal, Praveen Attele, Erik Ensrud, Richard J. Barohn

Introduction: We discuss the first description of partial distal adermatoglyphia in a patient with IBM.

Case Report: A 68 year old male presented with distal right hand and both proximal and distal left leg weakness of 5 years duration. Examination showed right hand finger flexion strength of ⅗ in digit 2 and 3 and ⅘ in digit 1 and 4. Left hip flexion strength was 4+/5. EMG showed myopathic findings in the left psoas and flexor digitorum profundus. NT5C1A antibody was positive. Muscle biopsy showed inflammatory infiltrates with T cell predominance in the endomysium with scanty rimmed vacuoles. The patient was diagnosed with sporadic IBM.
At age 68, his fingers started turning smooth and glossy. Distal fingerprints could not be obtained on the biometric scanner. Examination showed a lack of epidermal ridge pattern on the distal palmar aspect of bilateral fingers.

Conclusion: Partial distal adermatoglyphia can be seen in patients with sporadic IBM.

Abstract #638

POLG mutation causing autosomal dominant progressive external ophthalmoplegia and distal weakness.

Introduction: POLG-related disorders comprise a group of mitochondrial diseases with overlapping phenotypes. In the subtype, autosomal dominant progressive external ophthalmoplegia, the pattern of weakness is traditionally proximal.

Case Report: A 53-year-old female presented with bilateral ptosis and distal upper extremity weakness. At age 40, she developed bilateral ptosis followed by bilateral hand weakness over five years. The patient's sister, paternal aunt and her son have ptosis. Examination revealed bilateral ptosis, symmetric bilateral weakness of finger extension (3/5), wrist extension (4/5), and finger abduction (4/5). EMG showed fibrillation potentials and diffuse chronic neurogenic changes in the upper and lower limb. Sequence analysis revealed a heterozygous mutation in the POLG gene.

Conclusion: We describe an unusual case of POLG mutation presenting as distal weakness

Abstract #641

TDP-43 loss of function in the skeletal muscle

M. Zanovello, M. Keuss, A. Merve, P. Machado, L. Greensmith, P. Fratta (London, UK)

TDP-43 is a predominantly nuclear RNA-binding protein that mislocalizes to the cytoplasm in both ALS/FTD and muscular disorders. The concomitant nuclear loss of function leads to impairment of gene expression and splicing, which can be analysed through RNA-sequencing, as successfully done in ALS/FTD brain. There is a lack of characterisation of such mechanisms in muscles. Thus, we developed an IHC-guided RNA-sequencing pipeline that can detect RNA changes in affected tissues, and we are applying it to biopsies from several muscle diseases and healthy controls.
We report on this ongoing effort, and on the importance of impaired RNA processing in muscle diseases.

Abstract #642

Implementing genome and transcriptome sequencing methods to improve the diagnosis of Mendelian myopathies

Ganesh VS, Weisburd B, DiTroia S, Aguet F, Tiao G, Rehm HL, O'Donnell-Luria A

Introduction: Fewer than half of individuals with Mendelian (i.e. monogenic) myopathies obtain a molecular diagnosis. Prior work in our group was the first to demonstrate the diagnostic utility of RNA sequencing (RNA-seq) in Mendelian myopathies.

Objectives: To improve the diagnostic yield in Mendelian myopathies using a combined platform of whole genome sequencing (WGS) and bulk RNA-seq.

Methods: We performed WGS from whole blood, annotating single nucleotide variants, indels, structural variants, short tandem repeat expansions, and mitochondrial variants. In addition we performed RNA-seq from muscle biopsies or cultured fibroblasts, applying autoencoder denoising methods (FRASER, OUTRIDER) paired with a web browser visualization tool to identify gene and splice isoform outliers in a cohort of 172 individuals with suspected Mendelian myopathies.

Results: Implementation of these methods 1) improved the diagnostic yield in our cohort by 18%, and 2) validated the transcriptional effect of variants predicted to affect splicing.

Conclusions: Low diagnostic yield in Mendelian myopathies can be mitigated by optimization of WGS and RNA-seq methods for variant identification and resolution.

Academic Registries and Patient Organizations

Abstract #542

Self-reported postural symptoms predict vestibular dysfunction and falls in patients with multi-sensory impairment

Professor D. Kaski, Dr N. Koohi, S. Holmes, E. Bennet, A. Male, Dr R D S Pitceathly, and Professor M.G. Hanna (London, UK)

Introduction: Primary mitochondrial diseases (PMDs) are a genetically heterogenous group of conditions. Ataxia, neuropathy, myopathy, and vestibular dysfunction (VD) are common manifestations. We investigated the relative contributions of sensory impairment to postural control in patients with MD, using PMDs as a clinical model of multi-sensory impairment.

Methods: 130 patients with a confirmed genetic and/or clinicopathological diagnosis of MD attending a specialist clinic in the United Kingdom were included: the presence of ataxia, peripheral neuropathy, myopathy, symptoms of dizziness and imbalance and self-reported falls were reported.

Results: 52% of patients with ataxia, and 52% of patients with confirmed VD, reported falls; compared to 38% with neuropathy and 30% with myopathy. 80% of MD patients with confirmed VD reported imbalance, 56% reported dizziness.

Conclusions: Dizziness and imbalance are useful self-reported indicators of vestibular dysfunction in patients with multisensory impairment, and highly predictive of falls.

Abstract #552

Nurse coaching for newly tracheostomized patients at the Nemo Clinical Center: a single center experience

INTRODUCTION: Nurse coaching plays a crucial role in coordinating the multidisciplinary team involved in the care of patients with Amyotrophic Lateral Sclerosis (ALS).

OBJECTIVES: To describe the holistic approach used at the NEMO Clinical Center to train caregivers of patients with ALS subjected to neotracheostomy.

MATERIALS AND METHODS: Charts from caregivers of neotracheostomized patients with ALS discharged to their homes between April 2020 and April 2022 were retrospectively reviewed.

RESULTS: 24 people with ALS (average age at tracheostomy: 62.17 years ± 8.60) and 42 caregivers were recruited. The NC coordinated the multidisciplinary team for each patient. Training consisted of at least 2 frontal lessons and 3 days or more of practical training. The average duration of the training process was 26.29 days ± 11.76.

DISCUSSION: The study highlights the importance of nurse coaching within a multidisciplinary team. The educational reports emphasize the need for training in activities of dialy living in patients with a neotracheostomy and not only in specific procedural skills (e.g. endotracheal aspiration technique) usually the only issues addressed.

Abstract #555

Updated demographics and safety data from patients with nonsense mutation Duchenne muscular dystrophy (nmDMD) receiving ataluren in the Strategic Targeting of Registries and International Database of Excellence (STRIDE) Registry

Francesco Muntoni,[1] Filippo Buccella,[2] Isabelle Desguerre,[3] Janbernd Kirschner,[4] Eugenio Mercuri,[5] Andrés Nascimento Osorio,[6] Már Tulinius,[7] Shelley Johnson,[8] Christian Werner,[9] Allan Kristensen,[8] James Li,[8] Audrey Powell,[8] Nicholas Mastrandrea,[8] Efthimia Leonardi,[8] and Panayiota Trifillis[8]

[1]University College London, Great Ormond Street Institute of Child Health, London, United Kingdom; [2]Parent Project APS, Rome, Italy; [3]Hôpital Necker – Enfants Malades, Paris, France; [4]Medical Center – University of Freiburg, Freiburg, Germany; [5]Department of Pediatric Neurology, Catholic University, Rome, Italy; [6]Hospital Sant Joan de Déu, Unidad de Patología Neuromuscular, Universidad de Barcelona, Barcelona, Spain; [7]Department of Pediatrics, Gothenburg University, Queen Silvia Children's Hospital, Gothenburg, Sweden; [8]PTC Therapeutics Inc., South Plainfield, New Jersey, USA; [9]PTC Therapeutics Germany GmbH, Frankfurt, Germany.

Introduction: STRIDE is an ongoing registry providing real-world data on ataluren use in patients with nmDMD.

Objective: To describe the demographics of the STRIDE population and the interim safety results, as of January 31, 2021.

Methods: Patients' data are collected at the consent date. Patients are followed for ≥5 years.

Results: As of January 31, 2021, 286 boys enrolled in STRIDE in 13 countries and received ≥1ataluren dose. Mean (±SD) ataluren exposure was 1352±517 days. Safety outcomes were consistent with the known safety profile of ataluren. Of the 286 boys enrolled, 269 had genetically confirmed nmDMD. Mean(±SD) age at consent date was 9.9±3.8 years. Mean(±SD) age at first symptoms and nmDMD confirmation was 2.7±1.7 years and 4.9±2.7 years, respectively. Median time between first symptoms and nmDMD confirmation was 1.4 years.

Conclusions: These data suggest ataluren's safety profile is in consistent between clinical trials and clinical practice.

Abstract #559

Comparing the change in 6-minute walk distance (6MWD) in nonsense mutation Duchenne muscular dystrophy (nmDMD) patients receiving ataluren: Strategic Targeting of Registries and International Database of Excellence (STRIDE) Registry compared with phase 3 clinical trial

Francesco Muntoni,[1] Mar Tulinius,[2] Filippo Buccella,[3] Isabelle Desguerre,[4] Janbernd Kirschner,[5] Andrés Nascimento Osorio,[6] Shelley Johnson,[7] Christian Werner,[8] Allan Kristensen,[7] James Li,[7] Audrey Powell,[7] Nicholas Mastrandrea,[7] Efthimia Leonardi,[7] Panayiota Trifillis,[7] and Eugenio Mercuri[9]

[1]University College London, Great Ormond Street Institute of Child Health, London, United Kingdom; [2]Department of Pediatrics, Gothenburg University, Queen Silvia Children's Hospital, Gothenburg, Sweden; [3]Parent Project APS, Rome, Italy; [4]Hôpital Necker – Enfants Malades, Paris, France; [5]Medical Center – University of Freiburg, Freiburg, Germany; [6]Hospital Sant Joan de Déu, Unidad de Patología Neuromuscular, Universidad de Barcelona, Barcelona, Spain; [7]PTC Therapeutics Inc., South Plainfield, New Jersey, USA; [8]PTC Therapeutics Germany GmbH, Frankfurt, Germany; [9]Department of Pediatric Neurology, Catholic University, Rome, Italy.

Introduction: STRIDE is an ongoing registry providing real-world data on ataluren use in patients with nmDMD.

Objective: We investigated if ataluren-treated nmDMD patients in real-world practice (STRIDE Registry) experienced a similar decline in 6MWD vs ataluren-treated patients in a phase 3 clinical trial (Study 020).

Methods: 6MWD for STRIDE patients (n=42) and Study 020 patients (ataluren [n=45] and placebo [n=50]) was assessed over 48 weeks.

Results: Mean (95% CI) first baseline 6MWD assessment for STRIDE patients (349.7 [341.4, 358.0] m, n=42) was comparable to that for patients in Study 020 (ataluren, 356.7 [348.9, 364.5] m, n=47; placebo, 354.5 [346.3, 362.8] m, n=52). Mean (95% CI) decline in 6MWD were: STRIDE patients (−3.5 [−20.9, 13.8] m), ataluren-treated Study 020 patients (−28.3 [−45.1, −11.5] m), placebo-allocated Study 020 patients (−75.5 [−105.7, −45.3] m).

Conclusion: In both the real-world and clinical trial setting, ataluren delays motor function decline in nmDMD patients vs placebo.

Abstract #582

Executing an Exception from Informed Consent (EFIC) Plan

J. Fong, J. Shah, B. Albala, D. Vanblitter, E. Drum, D. Gutierrez, B. Boden-Albala (Irvine, CA)

Introduction: Exception from Informed Consent (EFIC) is implemented in emergency studies and allows patients to enroll into clinical trials without the standard informed consent process.

Objectives: UC Irvine (UCI) developed and executed an EFIC plan to ensure our local community was informed and had the opportunity to provide feedback.

Methods: Community consultation and public disclosure events were implemented. Our clinical trial team worked closely with various UCI employees such as the Center for Clinical Research, Program in Public Health, PR/marketing, and medical doctors.

Results: 11 community events were completed including presentations/focus groups, social media messaging, and marketing booths. We spoke with 460 community members and received feedback from 210 members. 17 public disclosure events were completed including posting on websites/social media and mailing/newspaper/radio advertisements. Within 3 months, 1,176,323-people were reached.

Conclusion: Community members were made aware of EFIC and gained research knowledge. This plan will be implemented for future UCI clinical trials that require EFIC.

Abstract #623

Clinical Research Coordinator Shortage and an Approach for an Educational Partnership to Increase Candidates

A. Bartlett, J. Agriesti *(Columbus, OH) The Ohio State University

Prior to the "Great Resignation" that occurred during COVID-19, the medical field was exploding with clinical research studies and many sites were having a shortage of staffing to administer the trials, which has only increased after COVID. NeuroNEXT Clinical Research managers will be surveyed to understand current employment opportunities at their site, staffing educational details, length of employment, training programs, career path and the perceived impact of shortage of trained staffing on trials. An educational program at Columbus State Community College (CSCC) is being discussed for a partnership to create a clinical research associate's degree and training opportunity for hire at the medical center. Then as people work in clinical research they could potentially be earning a bachelor's degree (tuition free) while increasing the workforce and the average time employed.

NOTE: The survey is being constructed and response analysis will be complete by August. We have already had a meeting with CSCC and they are interested. Therefore, some of the background work is yet to be done, but we feel this is a timely proposal.

Abstract #627

TREAT-NMD FSHD Global Registry Network: A Collaboration of Neuromuscular and FSHD Patient Registries

B Porter1, N Bennett1, R Forbes2, E Yiu2, M Jagut3, M Cosyns3, L Mokrá4, S Voháňka4, A Mahoney5, U Werlauff5, S Thiele6, MC Walter6, T Matsumura7, H Nakamura8, S Setlere9, I Micule9, M Rodrigues10, R Roxburgh10, T Golli11, D Osredkar11, JC Deenen12, BG van Engelen12, N Bulut13, I Gürbüz13, S Mergen14, H Durmus14, H Walker15, C Marini-Bettolo16, D Allison1, C Campbell17, M Guglieri18, A Ambrosini19, R Tupler20

1 TREAT-NMD Services Ltd, Newcastle upon Tyne, UK; 2 Australian Neuromuscular Disease Registry, Royal Children's Hospital and Murdoch Children's Research Institute, Melbourne, Australia; 3 Belgian Neuromuscular Diseases Registry (BNMDR), Belgium; 4 ReaDY Registry, Czech Republic; 5 The Danish National Rehabilitation Centre for NMD, Denmark; 6 German NMD Registry, Friedrich-Baur Institute Dept. of Neurology, Ludwig-Maximilians University Munich, Germany; 7 Department of Neurology, National Hospital Organization Osaka Toneyama Medical Center, Oasaka, Japan; 8 Registry of muscular dustrophy (Remudy), National Center of Neurology and Psychiatry, Tokyo, Japan; 9 NMS datu kolekcija, Children's Clinical University Hospital, Latvian Biomedical Research and Study Centre, Latvia; 10 Punaha Io Neurogenetic Research Bank (New Zealand Neuromuscular Disease Registry), Neurology, Auckland DHB and Centre for Brain Research Neurogenetic Research Clinic, University of Auckland, Auckland, New Zealand; 11 Registry of Slovenian Children with NMD, Slovenia; 12 FSHD registratie, Radboud University Medical Center, Nijmegen, the Netherlands; 13 Turkish NMD Registry – KUKAS, Hacettepe University, Ankara, Turkey; 14 Department of Neurology, Istanbul Faculty of Medicine, Istanbul University, Turkey; 15 UK FSHD Patient Registry, John Walton Muscular Dystrophy Research Centre, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK; 16 UK FSHD Patient Registry, John Walton Muscular Dystrophy Research Centre, Translational and Clinical Research Institute, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK; 17 Department of Paediatrics, Clinical Neurological Sciences & Epidemiology, Western University, London, ON, Canada; 18 John Walton Muscular Dystrophy Research Centre, Translational and Clinical Research Institute, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK; 19. Fondazione Telethon, Milan, Italy; 20 Department of Biomedical Science, Unimore, Modena, Italy

Introduction TREAT-NMD operates a Global Registry Network (GRN) where member registries collect agreed disease-specific datasets. The FSHD GRN collects data from 21 registries.

Objective: Perform a high-level analysis of data collected by the FSHD GRN.

Method: An electronic survey requesting demographic/diagnostic data was sent to registries in 2022.

Results: Thirteen registry responses provided data on 3,372 FSHD patients (female:1,528; male:1,645; unknown:199). Most patients had FSHD1 (1,747/3163) with fewer FSHD2 (82) cases. However, 42% of patients were of unknown FSHD type. Overall, 1,463 patients received genetic confirmation of FSHD, with FSHD1 cases (1,262/1747;72%) higher than FSHD2 (32/82;39%) or unknown FSHD type (171/1334;13%).

Conclusions: TREAT-NMD FSHD GRN represents an international harmonised data resource, which can support clinical trial planning through registry enquiries. Despite most registries being clinician-reported (62%), many patients lacked genetic confirmation or a specific FSHD type diagnosis. Understanding these aspects will be important as they represent clinical trial essential criteria.

Abstract #629

Engaging Participation in Research in Fascioscapulohumeral Dystrophy (FSHD)

S. Moldt CCRC; M. McIntyre PT, DPT; K. Wong MS, CGC; R. Butterfield MD, PhD
University of Utah, Utah, Pediatric Neurology

Introduction/Objectives: Participant engagement and retention are common barriers to clinical research. With slow progression and limited treatments, patients with FSHD have reported being disengaged from the healthcare system and research. With the majority of recruitment for research taking place in clinic, we are missing a portion of the population who don't routinely seek out healthcare, hurting the generalizability of current studies.

Methods: To increase enrollment in our study of genetic modifiers in a historic Utah kindred with FSHD, we implemented a multi-faceted approach to patient/family outreach focused on minimizing participation barriers and engaging patients, including family engagement, community outreach, and education events.

Results: With expanded outreach, we enrolled 102 participants to the study including affected and unaffected individuals and obtained DNA sample, self-reported phenotype, and/or clinical evaluations.

Conclusions: We implemented multiple recruitment strategies that minimized barriers and increased participation in a population that would otherwise been lost to follow-up, improving the generalizability of studies.

Abstract #631

Prospective Analysis of Early-Onset Facioscapulohumeral Muscular Dystrophy in the United States

Natalie Katz[1], Rabi Tawil[1], Jeffrey Statland[2]
[1]Department of Neurology, University of Rochester Medical Center, Rochester, NY, USA
[2]Department of Neurology, University of Kansas Medical Center, Kansas City, KS, USA

Introduction: Early-onset FSHD (EO-FSHD) is associated with a more severe phenotype, faster disease progression, and extra-muscular manifestations. Few studies have described this population in the United States (US).

Objective: Understand how the EO-FSHD population in the US differs from adult-onset FSHD.

Methods: Prospective data from 578 genetically confirmed FSHD type 1 participants enrolled in the US FSHD National Registry will be used to determine baseline demographics, disease severity, and risk factors contributing to disease progression. EO-FSHD is defined as diagnosed before age 10.

Results: As of September 2019, 35 individuals had EO-FSHD (6%); were more likely to be female (74.3%) compared to the overall registry (47.9%); and had a higher frequency of 1-3 D4Z4 repeats (65.7% vs. 10.4%).

Conclusion: This represents the largest EO-FSHD cohort to be prospectively described. Additional data on incidence of the need for ambulatory aides and risk factors for disease progression will be presented.

Abstract #634

Creation of a Scalable Registry and Data Dashboard for Neuromuscular Immune-Related Adverse Events of Immune Checkpoint Inhibitors Using Consensus Disease Definitions

M Eskian, LB Burton, J Hillis, BK Chwalisz, M O'Hare, GS Manzano, S Shalhout, L Zubiri, D Miller, KL Reynolds, AC Guidon (Boston, MA)

Introduction: Mis-classification of neuromuscular (NM) immune-related adverse events (irAEs) from immune checkpoint inhibitors (ICIs) has limited care and research. We recently published consensus disease definitions (CDD) for neurologic irAEs.[1]

Objectives: To describe 1) development of a Redcap registry for NM irAEs based on CDD and 2) results from application of CDD to a cohort with NM irAEs,

Methods: Patients with suspected neurologic irAEs from Massachusetts General Brigham were systematically identified. Diagnoses of irNeuropathy, irNeuromuscular Junction (NMJ) disorders and irMyopathy assigned using CDD. Testing, treatments and outcomes were included. R was used for statistical analyses and data visualizations.

Results: Forty-one patients with 53 NM irAEs (23, irMyopathy; 19, irNeuropathy; 11, irNMJ Disorder) are currently included. Median age 73 [37, 91]. Most NM irAEs reached probable-definite certainty (40/53, 75.5%). Updated data will be presented.

Conclusions: Study of NM irAE phenotypes and outcomes is feasible using this rigorous, scalable registry based on CDDs.

Neuromuscular Study Group

ANNUAL SCIENTIFIC MEETING

SEPTEMBER 30 - OCTOBER 2
HOTEL REGINA PALACE
STRESA, LAKE MAGGIORE, ITALY

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Welcome

On behalf of your Neuromuscular Study Group, we would like to welcome each of you to the 23rd Annual Neuromuscular Study Group Meeting. This is an exciting time in neuromuscular research as we continue to grow and adapt.

One of those ways was to update our name to include Neuro. This year, the members along with the Executive Committee settled on the current name, Neuromuscular Study Group (NMSG).

After two years of very successful online meetings, we decided for the meeting to be held in Italy this year. We are pleased that our in-person meeting has received over 200 registrations and an unprecedented 141 abstract submissions. This year we are excited to have so much industry involvement from both Europe and the U.S. Thank you so much to our sponsors for the support. Clearly, an in person meeting in Italy was a great choice.

We held our first online Shark Tank event earlier this year. The Shark Tank session has gained momentum and we will host our 4th Shark Tank event during the meeting with 6 proposals presented. The winner will receive a $10K grant to use towards their study. Last year's winners will present at the meeting and we look forward to learning how their funded proposals have progressed.

The NMSG continues to fund a Neuromuscular Research 2-year fellowship program, so at any one time we have one Fellow in the first year, and one in the second year. Both our current Fellows will be presenting during the meeting.

As the Co-Chairs of the Neuromuscular Study Group, we would like to thank this year's planning committee for putting together an excellent agenda that covers such a broad range of topics and interests within the neuromuscular field. We also want to thank Liz Paulk, NMSG Administrative Manager, for organizing another successful and large event. The planning committee and Liz all have spent much time planning this international meeting that will appeal to our global audience and advance the field of Neuromuscular medicine.

RICHARD J. BAROHN, M.D.

Chair, Neuromuscular Study Group

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

PROF MICHAEL G. HANNA, M.D.

Co-chair, Neuromuscular Study Group

Director, University College London Institute of Neurology

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WIFI
The NMSG has a special wifi access for NMSG meeting attendees.
This network can be used in all the meeting rooms and also the hotel.

Network name: **MSG2022**
Password: **Meeting22**

GALA

For the Gala dinner on Saturday night we will be taking a very short ferry to Isola dei Pescatori on Lake Maggiore. The location of the ferry will be announced during the meeting as it is dependent on the lake level.

Because of the large number of registrees we will host dinner at two restaurants on the island very close to one another.

After dinner we will have dessert and reception and return by ferry to Stresa.

Dress for the evening is business attire.

All are welcome, guests not attending the scientific sessions may also attend for an additional $75 per person.

SPEAKERS/PRESENTERS

Please bring your presentation to Amardeep Gill, our onsite AV expert, in the Lalique general session room the morning of your session so that your slides can be loaded. Our technical staff will assist you with any audio/visual needs you may have. You will not need your own laptop as we have one available.

POSTERS

The poster exhibition is located in the Azalea Room.

Walk through poster session is
Friday, September 30th 6:30-8:00pm

Please set up your poster in the Azalea Room on Thursday evening after 8:00pm or first thing on Friday. 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 before Friday evening, start of dinner.

Agenda

THURSDAY, SEPTEMBER 29

6:00 - 7:30 p.m.	Check-In *Hotel Regina Palace Lobby* Welcome Reception *Front Terrace*

DAY 1
FRIDAY, SEPTEMBER 30

7:00 - 8:00 a.m.	Check-In *Hotel Regina Palace Lobby* Buffet Breakfast for Hotel Regina Palace Guests *Liberty*
8:00 - 8:20 a.m.	Welcome and State of the Neuromuscular Study Group **Dr. Richard Barohn and Prof Michael Hanna** *Lalique*

SESSION I: BIG THERAPEUTIC WAVES

Moderator: James Lilleker, MBChB, Ph.D.
Lalique

8:20 - 8:40 a.m.	Near term prospects for disease targeted therapies in FSHD **Jeffrey Statland, M.D.** *University of Kansas Medical Center*
8:45 - 9:05 a.m.	Duchenne Muscular Dystrophy: Learning From Our Failures — a Clinical Trialists View **Prof Laurent Servais, M.D., Ph.D.** *University of Oxford,* *MDUK Oxford Neuromuscular Centre*
9:10 - 9:30 a.m.	The Evolving Therapeutic Options for Pompe Disease **Mazen Dimachkie, M.D.** *University of Kansas Medical Center*
9:35 - 9:55 a.m.	Update on treatment in CIDP and MMN **Prof Edwardo Nobile-Orazio, M.D., Ph.D.** *Milan University,* *IRCCS Humanitas Research Institute*
10:00 - 10:15 a.m.	Refreshment / Exhibitor Break *Azalea*
10:15 - 10:35 a.m.	Therapeutic Promise in Myotonic Dystrophy Type 1 **Nick Johnson M.D., Msci, FAAN** *Virginia Commonwealth University*
10:40 - 11:00 a.m.	Muscle Dysfunction in Myotonia Congenita **Mark Rich, M.D., Ph.D.** *Wright State University*

SESSION II: N&M IMAGING

Moderator: James Lilleker,MBChB, Ph.D.
Lalique

11:05 - 11:25 a.m.	Muscle MRI as a tool for the diagnosis and follow-up of myopathies **Giorgio Tasca, M.D., Ph.D.** *Fondazione Policlinico Universitario A. Gemelli IRCCS*
11:30 - 11:50 a.m.	Contribution of nerve and muscle ultrasound in diagnosis and management of peripheral nerve diseases **Luca Padua, M.D., Ph.D.** *Fondazione Policlinico Universitario A. Gemelli IRCCS*

12:00 - 1:30 p.m.	Lunch *Liberty Lago*
12:00 - 1:30 p.m.	Neuromuscular Study Group Executive Committee Meeting *Rododendro*
1:30 - 3:00 p.m.	Coordinators/Evaluators Session Breakout **Moderators: Melissa McIntyre, DPT, Marie Wencel, CCRP, Tina Duong, PT, Ph.D., Gita Ramdharry, Ph.D.** *Margherita*
1:30 - 3:00 p.m.	Young Investigator Session Breakout **Moderators: Prof Valeria Sansone & Dr. Emma Ciafaloni** *Lalique*
3:00 - 3:15 p.m.	Refreshment / Exhibitor Break *Azalea*

SHARK TANK SESSION

Moderator: Aziz Shaibani, M.D., FACP, FAAN, FANA

Sharks: Tony Amato, M.D., Tahseen Mozaffar, M.D., Emma Ciafaloni, M.D.

Lalique

3:15 - 5:00 p.m.	Improving the Study of Falls in Muscle Disease **Kristina M. Kelly, PT, DPT, MS, EdM, NCS** *The Ohio State University*
	Quantifying Idiopathic Inflammatory Myopathy Associated Cancer Risk via Comprehensive Phenotyping of a Large UK-Wide Cohort **Alexander Oldroyd, MBChB, Ph.D., MRCP, MSc** *University of Manchester*
	Salivary Melatonin: Can this Detect Patients in Myotonic Dystrophy Type 1 (DM1) with Disrupted Sleep Wake Cycle and EDS? **Giovanni Colacicco, M.D.** *The Nemo Clinical Center in Milan Neurorehabilitation Unit University of Milan*
	Exploring the Experience of Pain for People with Facioscapulohumeral Muscular Dystrophy and the effects of Physiotherapy/Vojta Therapy **Jose Manuel Sanz Mengibar, Ph.D. Physiotherapy** *University College London Hospital*
	Predictive models in spinal muscular atrophy treated patients using machine learning **Giorgia Coratti, Ph.D.** *Fondazione Policlinico Universitario Agostino Gemelli IRCCS*
	Therapeutic Dietary Intervention Attenuates Weight Gain From Corticosteroid Use in Boys with DMD **Grace Warner Gough, MS, RDN, CD** *University of Utah*
6:30 - 8:00 p.m.	Reception and poster walk through session *Azalea*
8:00 - 9:00 p.m.	Dinner & Shark Tank Award Announcement *New Liberty*
9:00 - 11:30 p.m.	Reception *Bar Regina Palace*

DAY 2
SATURDAY, OCTOBER 1

7:00 - 8:15 a.m.	Buffet Breakfast for Hotel Regina Palace Guests
8:15 - 8:30 a.m.	Opening **Dr. Richard Barohn and Prof Michael Hanna** *Lalique*

SESSION III: MOTOR NEURON DISEASE CHALLENGES

Moderator: Dr. Senda Adjroud-Driss
Lalique

8:30 - 8:50 a.m.	Respiratory management of patients with neuromuscular disease in ALS **Lisa Wolfe, M.D.** *Northwestern University*
8:55 - 9:15 a.m.	Update on Clinical Trials for ALS **Angela Genge M.D., FRCP(c)** *Montreal Neurological Institute and Hospital*
9:20 - 9:40 a.m.	Clinical Trials Landscaping in ALS **James Berry, M.D., MPH** *Massachusetts General Hospital*
9:45 - 10:05 a.m.	Spinal muscular atrophy: hope vs hype; guide to handle patients' expectations **Prof Eugenio Mercuri, M.D., Ph.D.** *Catholic University*
10:10 - 10:30 a.m.	Refreshments/Exhibitor Break *Hotel Regina Palace Lobby*

SESSION IV: STRATIFICATION OF NM DISEASES

Moderator: Dr. Salman Bhai
Lalique

10:30- 10:50 a.m.	Seronegative Myasthenia Gravis **Vern Juel, M.D.** *Duke University School of Medicine*
10:55 - 11:15 a.m.	Early detection of peripheral neuropathy in hATTR **Chafic Karam, M.D.** *University of Pennsylvania*
11:20 - 11:40 a.m.	Updates in the therapeutic landscape of myositis **Julie Paik, M.D., MHS** *Johns Hopkins University School of Medicine*
11:45 a.m. - 12:05 p.m.	Deconvoluting phenotypic complexity in myositis: from syndromes to diseases **Iago Pinal Fernandez, M.D., Ph.D., Ph.D.** *Muscle Disease Unit, NIAMS/NIH* *Johns Hopkins Neurology Department*
12:10- 12:30 p.m.	Myositis Autoantibodies: What's new? **Lisa Christopher Stine, M.D., MPH** *Johns Hopkins University*
12:30 - 1:30 p.m.	Lunch *Liberty Lago*

SESSION V: TECHNOLOGY AND DIGITAL OUTCOMES IN NMD

Moderator: Prof Valeria Sansone
Lalique

1:30 - 1:45 p.m.	Video capture and machine learning to assess hand myotonia and other functional timed tests **Tina Duong, PT, Ph.D.** *Stanford University*

1:50 - 2:05 p.m.	Full day infant movement analysis: potential for wearable sensors to support early identification and assessment of neuromuscular diseases **Beth Smith PT, DPT, Ph.D.** *Children's Hospital Los Angeles and University of Southern California*
2:10 - 2:25 p.m.	First regulatory qualification of a digital outcome in DMD: How can SV95c change the course of clinical developments **Prof Laurent Servais, M.D., Ph.D.** *University of Oxford, MDUK Oxford Neuromuscular Centre*
2:30 – 2:45 p.m.	Technology and digital outcomes in Neuromuscular Disorders: be to tech experience at the NeMO Lab **Dr. Stefano Regondi** *NeMO Lab Milan*
2:45 - 3:00 p.m.	Break *Hotel Regina Palace Lobby*

SESSION VI: ABSTRACT PLATFORM PRESENTATIONS

Moderator: Eli Naddaf, M.D.
Lalique

3:00 - 3:15 p.m.	Effect of different corticosteroid dosing regimens on clinical outcomes in boys with Duchenne muscular dystrophy: a randomized clinical trial **Robert Griggs, M.D.** *University of Rochester*
3:15 - 3:30 p.m.	Caveolae-Associated Protein (cavin)-4 autoantibodies in immune mediated rippling muscle disease (iRMD) **Divyanshu Dubey, M.D., M.B.B.S.** *Mayo Clinic*

SPONSOR UPDATES

3:30 - 3:50 p.m.	DYNE-101 and DYNE-251: Moving from bench to clinic to deliver potentially transformative therapies in DM1 and DMD **Ashish Dugar, Ph.D. MBA** *SVP, Global Medical Affairs, Dyne Therapeutics*
3:55 - 4:15 p.m.	Update on the growing body of evidence for Duchenne muscular dystrophy therapies **Dr. Christian Werner** *Executive Director, Global Medical Affairs – Global DMD Lead, PTC Therapeutics*
4:20 - 4:40 p.m.	Our commitment to NMDs: the present and the near future **Kathryn R. Wagner, M.D., Ph.D.** *Global Head Neuromuscular, Roche*
4:45 - 5:05 p.m.	Following the Science in Rare Neurological Diseases **Cinzia Dorigo, Pharm.D.** *Alexion*

ROBERT C. GRIGGS ANNUAL NMSG KEYNOTE SPEAKER

Lalique

7:00 p.m.	Neuromuscular Diseases — lessons learnt 1980-2020 **Shree Pandya, PT, DPT** *University of Rochester*
7:45 p.m.	Meet for transportation to Isola Pescatori for evening activities
8:30 p.m.	Dinner Evening reception on Borromean Islands following dinner

DAY 3
SUNDAY, OCTOBER 2

7:00 - 8:00 a.m.	Buffet Breakfast for Hotel Regina Palace Guests
8:00 - 8:10 a.m.	Opening **Dr. Richard Barohn and Prof Michael Hanna** *Lalique*

SESSION VII: NMSG YOUNG INVESTIGATORS PROJECTS

Moderator: Karissa Gable, M.D.
Lalique

8:10 - 8:25 a.m.	Post-translational Modifications of DUX4 **Renatta Knox, M.D., Ph.D., NMSG Fellow** *Washington University School of Medicine*
8:30 - 8:45 a.m.	Neuromuscular ultrasound as a biomarker to improve clinical trial readiness in Charcot-Marie-Tooth Neuropathies **Tyler Rehbein, M.D., NMSG Fellow** *University of Rochester*
8:50 - 9:05 a.m.	2021 Shark Tank Award Update: Circulating Myeloid Profile in Myasthenia Gravis **Katy Dodd, MBChB MRCP, Ph.D. Candidate** *Manchester Centre for Clinical Neuroscience*
9:10 - 9:25 a.m.	2021 Shark Tank Grant Award Update: Therapeutic Play Gym: Feasibility of a caregiver-mediated exercise system for infants and young children with severe neuromuscular weakness **Jenna Linn Lammers, MSR/PT, CNT, PCS** *University of Florida*

ABSTRACT PLATFORM PRESENTATIONS

9:30 - 9:40 a.m.	A comparison of in silico predictive tools to robust in vivo functional characterisation of CLCN1 genetic variants in skeletal muscle channelopathies **Vino Vivekanandam, MBBS** *QS University College London*
9:45 - 9:55 a.m.	Neuromuscular junction transmission failure is a translationally-relevant mechanism of sarcopenia **W. David Arnold, M.D.** *University of Missouri*
10:00 - 10:10 a.m.	Symptom Onset In Maternally versus Paternally Inherited Myotonic Dystrophy type 2 **Paloma Gonzalez-Perez, M.D., Ph.D.** *Massachusetts General Hospital*
10:15 - 10:25 a.m.	Clinical trial readiness and validation of onsite and remote evaluation in valosin containing protein-associated multisystem proteinopathy **Megan Iammarino, DPT** *Nationwide Children's Hospital*
10:30 - 10:45 a.m.	Break *The Regina Palace Lobby*
10:45 - 10:55 a.m.	Bridging the preclinical-clinical gap: reverse translation of muscle velocity recovery cycles allows in vivo assessment of skeletal muscle excitability in mice and humans **Karen Suetterlin, MBBS, MRCP, Ph.D.** *Newcastle University*
11:00 - 11:10 a.m.	Proposal for the functional assessment of acute inflammatory neuropathy (FAAIN) in Guillain-Barré syndrome **Dra. Zurina Lestayo O´Farrill, Ph.D.**

11:15 - 11:25 a.m.	Survival Motor Neuron Protein: Addressing Therapeutic Concerns of Sensorimotor Toxicity **Maria Balch, Ph.D.** *The Ohio State University*
11:30 - 11:40 a.m.	Episodic weakness in patients with mitochondrial DNA MT-ATP6 mutations: the Queen Square experience **Chiara Pizzamiglio, M.D., Ph.D. Candidate** *QS University College London*

ABSTRACT FLASH PRESENTATIONS

11:45 - 11:55 a.m.	Risk factors for falls and fracture in myositis: A cross-sectional study of 470 patients **Salman Bhai, M.D.** *UT Southwestern*
11:57 a.m. - 12:07 p.m.	Towards digital monitoring of Amyotrophic Lateral Sclerosis (ALS) patients: a deep learning-based application to assess the evolution of dysarthria via the analysis of multimedia data **Michela Coccia, M.D.** *The Nemo Clinical Center in Ancona*
12:10 - 12:20 p.m.	Unmasking anti-HMGCR myopathy: the hurdles of a prompt recognition **Andrea Barp, M.D.** *The Nemo Clinical Center in Trento*
12:22 - 12:32 p.m.	Motor Outcomes to Validate Evaluations in Facioscapulohumeral muscular dystrophy (MOVE FSHD): Protocol for an observational study **Michaela Walker, MPH, CCRP** *University of Kansas Medical Center*
	Closing
12:35 - 1:35 p.m.	Lunch *Liberty Lago*

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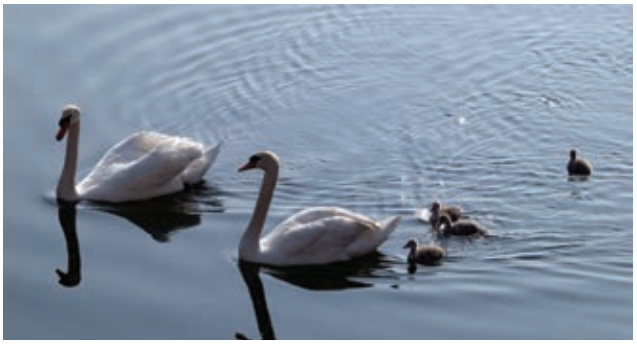

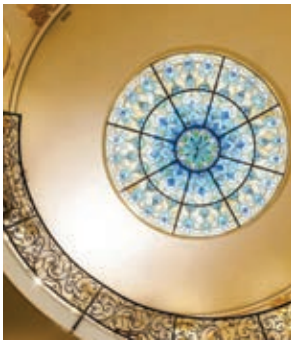

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Update on the growing body of evidence for Duchenne muscular dystrophy therapies

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