# RRNMF Neuromuscular Journal

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## FACILITATORS



**Cover Image:** "Raymond" by Jessica Wohl.

# CONTENTS

# Letter from the Founding Facilitator, Volume 2, Issue 4

Richard J. Barohn, MD

Welcome back to the RRNMF Neuromuscular Journal for Volume 2, Issue 4, which opens the fall season. This is the second fall issue where we publish the abstracts of the annual Muscle Study Group meeting. These are at the end of the issue and I have some additional comments to make about the annual MSG meeting preceding the abstracts and messages from industry sponsors of the meeting.

To begin this issue, in the "What's on your Mind?" section, Dr. Raghav Govindarajan teaches us his 25 steps to diminish diagnostic errors and he cleverly puts them under three categories: "know thy patient", "know thy test", and "know thyself." The next article is by my great friend, colleague and author of ethical topics concerning the practice of medicine, Dr. Josh Freeman. This one comes from one of his blog sites, the Medicine and Social Justice blog. In this piece, Dr. Freeman gives his views on the complicated issue of parts of the population that are resistant to getting vaccinated for COVID.

In "New Discoveries/New Stuff," Dr. Melissa Feuerborn publishes a study she began as a medical student at the University of Kansas during the research block between her first and second year of medical school. Dr. Feuerborn is now an intern in internal medicine at the University of Utah Health Science Center. She was interested in Batten's disease (neuronal ceroid lipofuscinosis) as she was involved in some preclinical research in a mentor's lab as an undergraduate. During medical school she became interested in how families with children who have Batten's disease to learn about the disease, the obstacles they face and how well disease-related organizations are doing to support their needs. Dr. Carla Keirns in the History of Medicine Department at KUMC and I helped Melissa on this project. Using the resources of our CTSA supported Frontiers Institute, we connected her with several rare disease community engagement groups. She attended a Batten's disease conference and spoke to caregivers. She used semi-structured interviews for this process and I believe she did a tremendous job in understanding the interplay between caregivers and these organizations. Also in the "New Stuff" section is an article by Drs. Al Sultani, K. Hafeez, and M. Ubaid Hafeez under the leadership of Dr. Aziz Shabani who report their results of a survey of neuromuscular physicians regarding telehealth versus standard in person patient interactions. They did this survey via the RRNMF (Rick's Real Neuromuscular Friends) website, not the journal! However, I am pleased that they are reporting their findings in the RRNMF Neuromuscular Journal. The results may or may not be surprising to you, depending on your opinion regarding telemedicine. The majority of the neuromuscular experts in the survey indicated they preferred in-person patient visits. Based on the experience I am seeing at the Missouri University Health Care (MUHC) system, I suspect this may be true of most physicians. After the near complete use of telehealth visits at the beginning of the COVID pandemic, we are now down to a 10% telehealth visit rate in most of our clinics. I think this is unfortunate and a missed opportunity to change the way medicine is practiced in the United States, and the world, but those are the facts.

In the "Clinic Stuff" section, Dr. Watson and colleagues from Sydney, Australia describe a five year old patient that had both myasthenia gravis and Grave's disease and review the literature of this association. A pediatric case is unusual.

Also in "Clinic Stuff," Drs. Isaacoff and Waheed in the Department of Neurology at the University of Vermont Medical Center present a case of an adult with a GBS-like illness who is found to have a renal cell carcinoma (presumed.. no biopsy) and serum antibodies to contactin-associated protein-like 2 (CASPR2) and leucine -rich glioma inactivated proteins (LGI1). In addition, on EMG, there was evidence for peripheral nerve hyperexcitability. The authors do an excellent job in tying these pieces together and reviewing the interesting new literature on these auto-antibodies.

Drs. Fathi and Nafissi from the Neuroscience Institute at the Tehran University of Medical Sciences report an interesting observation that myotonic dystrophy patients can have a Beevor sign. Initially described by Dr. Beevor as a sign of a thoracic myelopathy below T10, it has also been described in some muscle disorders such as facioscapulohumeral dystrophy (FSHD), GNE myopathy, inclusion body myositis and Pompe disease but only in one case previously with myotonic dystrophy type 1; here is a second case. We are so glad to have submissions from our physician colleagues in Iran.

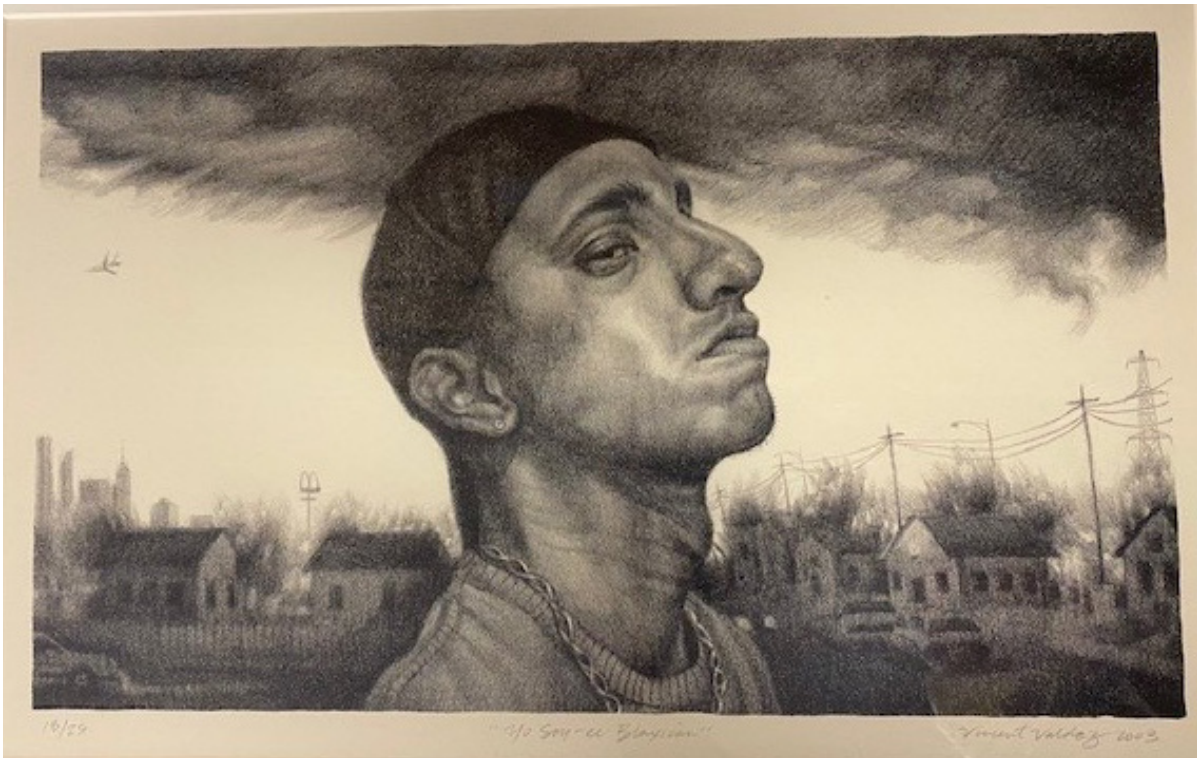
In the "Looking Back/Looking Forward at Stuff" section, Dr. Murala and her colleagues at the University of Missouri, Columbia review sleep disorders in amyotrophic lateral sclerosis (ALS). And finally, the last section has abstracts from the MSG meeting which will be held virtually on October 1-3, 2021.

In "Other Good Stuff," we are so pleased to have Dr. Michael Abraham, a neurologist at the University of Kansas Medical Center, submit another of his wonderful

poems. This one is called “Hamilton Awakening.” Keep them coming, Michael! You are a true Renaissance physician.

The cover of this issue is by a tremendous artist, Jessica Wohl. This portrait of an elderly man is called “Raymond” and I believe it was painted in the early 2000s when he was living at the Village Shalom facility in Overland Park, Kansas. I purchased it at an art auction at the Epstein Art Gallery in Village Shalom not long after she painted it to raise money for the gallery and institution. It has been one of my favorite pieces and whenever I have guests in my home they are drawn to the painting as it portrays the honorable progression into old age so well. Jessica relocated a number of years ago to Kentucky, where she continues her art work in a variety of mediums. I emailed her and got her permission to publish the photograph. I believe the man in the painting has deceased.

Lastly, a quick postscript from the amazing diptych painting we published on the cover of Vol 2, Issue 3 by Vincent Valdez. Vincent is one of the major artists in the United States and he still works out of San Antonio, Texas. He was thrilled that we used a photograph of his paintings which I had purchased almost 20 years ago. When I sent him a copy of the RRNMF Neuromuscular Journal, he corrected me on the titles I used for the diptych. The title for both pieces together is “Ah yes, the notorious place everyone speaks of.” The other title refers to the original lithograph; the blue painting is based on, “Yo Soy-ee Blaxican”. An image of that print is below:



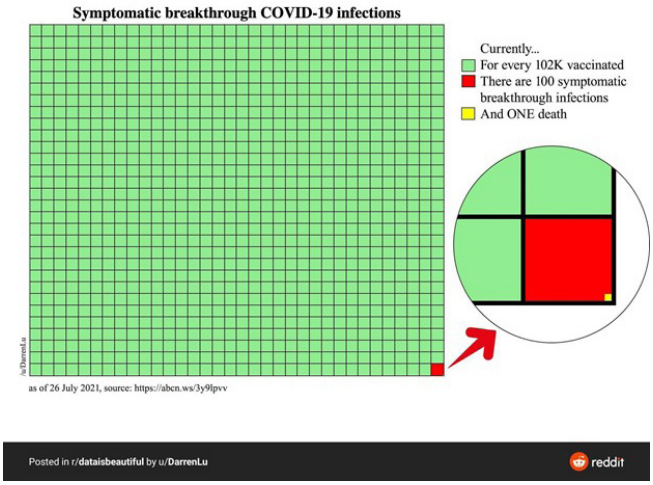
# COVID is still with us. Vaccine resistance is real, and it is dangerous

Joshua Freeman, MD

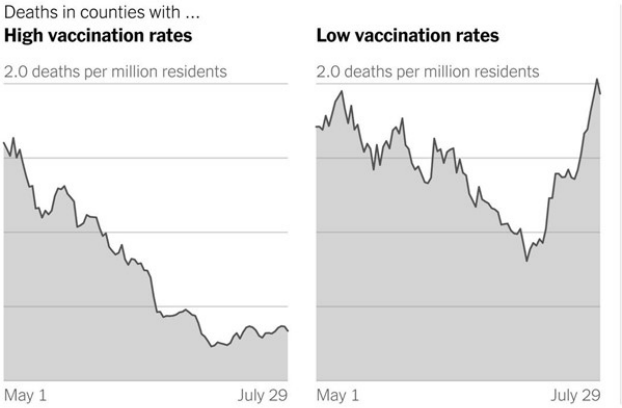
Originally published in the *Medicine and Social Justice* blog, https://medicinesocialjustice.blogspot.com/2021/08/covid-is-still-with-us-vaccine.html

That there are a lot of people who are vaccine-resistant will be news to no one at this point. I wrote about this on May 17, 2021 (COVID, Vaccine, Racism, and Masks: Changing for better or for worse?), and while many people who were initially resistant have now changed their minds and have gotten (or in many cases, are trying to get) vaccinated, there is a hard-core residual group. There are a variety of reasons that people have, and sometimes articulate, for not getting vaccinated. These include a lack of knowledge (hard, I know, given the amount of discussion) and a mindset that disbelieves those who are in power (also in some ways understandable; they do lie a lot). This is complicated for some parts of the population, particularly members of minority groups like African-Americans and Native Americans, by the fact that the US history is loaded with stories of exploitation and oppression and infection, from the passing out of measles and smallpox-infested blankets to Indians to the Tuskegee experiments that denied treatment for syphilis to Black men and many other crimes.

But at this point, there are no responsible people at all who are urging folks to not get vaccinated. Virtually all doctors, epidemiologists, and scientists have been (with some effectively evil exceptions, such as Joseph Mercola, DO (The Most Influential Spreader of Coronavirus Misinformation Online). Inversely, I mean anyone (which unfortunately includes many politicians, FoxNews personalities, and other "influencers") who is not responsible. COVID is real, it is infectious, the Delta variant is more infectious, it makes people really sick, and it kills people. A lot of people. Irrespective of whether they believe it is "real" or "dangerous" or not. Indeed, most of the people dying now (over 95%) in the US are those who have not been vaccinated. There is definite evidence that people who are vaccinated CAN get infected, and maybe even a few of them will die, but this is also definitely being overplayed by the media. Most of the media does not lie, exactly, but most people don't go beyond the headlines and a very large number have no concept of relative risk or odds (I would assume, therefore, that poker players have been vaccinated!) You can cross the street very carefully, on a green light, at a corner, looking both ways, and still be hit and killed by a car driven by a lunatic speeding around the corner. But it is pretty unlikely compared to, say, running across a busy 6-lane highway without looking. Most folks can get that kind of relative risk, and it is not really unlike the risk of being vaccinated or not. This graphic illustrates that risk:




Another way to express it, with a more traditional line graph, by county:




A recent article in the *NY Times,* "Workplace vaccine mandates reveal a divide among workers" describes another way that workers are being divided, not just by whether they are *willing* to be vaccinated, but by whether their employers are willing to mandate (and pay for) vaccination for them. Apparently, they are for white collar workers who they want back in the office (not clear why) but not necessarily for the blue collar workers, those who actually do work that cannot be 'phoned (or Zoomed) in' but requires their physical presence, those people who have often been called essential workers. Walmart, for example, '*announced mandatory inoculation for employees at its headquarters and for managers who travel domestically. For a sense of*

*scale, about 17,000 of Walmart's 1.6 million employees are expected to work in new headquarters in Bentonville, Ark.'* The argument for this seems to be that companies like Walmart need lots of workers and don't want to alienate those who don't want to be vaccinated by mandating it. But somehow it is ok for office workers. I am not sure that I understand this, but it must have something to do with pay: if you get paid a reasonable living wage you are more likely to be willing to get a mandatory vaccine, and you should anyway. It seems to me that if Walmart and other companies wish to increase the demand for their jobs, the better way to do it is: pay more!

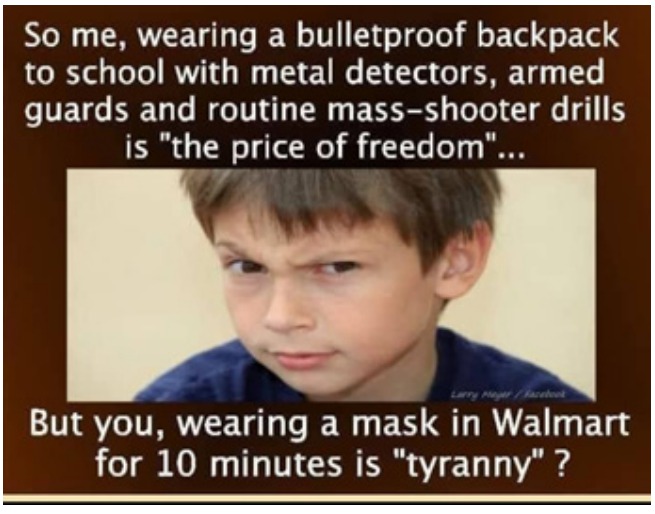
We read that 'Trump's COVID-19 testing czar warns the unvaccinated: 'You're going to get the delta variant' (The Daily Kos article's author notes that they didn't remember that #TFG *had* a testing czar. Neither did I.) Of course, a lot of people regret having not been vaccinated once they end up sick, hospitalized, and on a ventilator, like conservative radio talk show host Phil Valentine and others covered in a recent article in *Rolling Stone*. The *NY Times* also had an article titled "They Spurned the Vaccine. Now They Want You to Know They Regret It". I heard from a friend about a hospital-based health professional (not a physician) they knew who had been vaccinated but ended up on a ventilator, which was very concerning. A few weeks later, we called to follow up. Guess what? Turns out they weren't vaccinated; they and their whole family were lying. Embarrassed. Reassuring, in one sense, but also very worrying that folks are lying.

I hope that others who have reservations will take their advice and get vaccinated. It is, of course, a bit disingenuous; if they *knew* they were going to get sick and maybe die they would have gotten vaccinated. If we had *known* that the roulette wheel was going to come up black, we would never have bet on red! You can't be *sure* what will happen to you, but the important point is that you have to do it because you *might*, and at least as important, because you can infect others.

But there are many people who steadfastly believe that being vaccinated is not for them, and some who believe that it is not for anyone. They are getting sick, and will continue to get sick, and infect others, and cause others to die. They will not wear masks, and they will not wear signs. When they say that vaccine mandates, or mask mandates, are oppression, they are being, frankly, ridiculous.

The pandemic is not over. Delta is very serious. Get vaccinated. Wear a mask indoors.

I cannot resist including two other posts that make that point:

# 25 steps to diminish diagnostic errors

Raghav Govindarajan, MD
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**Know thy patient:**

1. **H and P:** obtaining a thorough history and doing a focused yet comprehensive exam is still the key and will remain so
2. **Organize:** symptoms and signs systematically as problems for clarity of thought
3. **Time out:** don't rush your thoughts, there's a reason professional sports have time outs
4. **Ask:** if you are unsure of a sign/symptom/problem or its interpretation ask around
5. **Use:** as many resources as possible to gather knowledge and facts...this is not USMLE!
6. **Identify:** patterns of symptoms and signs which can fit a diagnosis
7. **Never:** rush to fit a pattern to a particular diagnosis. If patterns don't fit keep looking
8. **Keep:** your mind open even if a patient comes to you with a known diagnosis
9. **Remember:** uncommon presentations of common conditions are generally more common than common presentations of uncommon conditions
10. **Differentiate:** between signal and noise
11. **Know:** your community/hospital system and the common conditions that come
12. **Question:** your diagnosis if new symptoms or signs come up
13. **Revisit:** your diagnosis periodically as new diagnostic tools, treatments and conditions are described
14. **Don't:** miss conditions that you can treat or which can become catastrophic if delayed

**Know thy tests:**

15. **Don't:** be afraid to order tests but know their limitations
16. **Value**: of a test depends on the pre-test probability of a particular condition. In other words your clinical suspicion
17. **Tests:** can be ordered to confirm a diagnosis, rule out a diagnosis or differentiate between identical conditions.
18. **Rarely**: tests will give you new information that you had never thought of in your H and P

**Know thyself:**

19. **Refer:** if a case beats your limitations
20. **Learn:** from each case- the ones you diagnosed and the ones you missed
21. **Observe:** how master clinicians make decisions and learn from them
22. **Humility:** takes you a long way as it's in the nature of medicine to make mistakes
23. **Update:** your knowledge periodically as medicine is a rapidly evolving science
24. **Team:** embrace the team concept and don't neglect data from allied healthcare personnel
25. **Patient:** centered care is sometimes more important than getting a diagnosis

# Building a Bridge for Batten Disease

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**Keywords:** *Batten, NCL, Rare disease, Advocacy, Caregivers*

## Introduction

Living with a rare disease creates unique physical and emotional challenges. It is estimated that nearly 30 million people live with a rare disease in the United States. It is important to realize that a rare disease is not rare for the patient because they often experience the consequences of their disease daily. Fortunately, awareness for rare diseases has grown in recent decades, resulting in advocacy groups for specific rare diseases, organizations for rare diseases in general, and increased research and drug development (1). Exploring the challenges patients experience can help improve the process of diagnosing and raising awareness for rare diseases, while improving the quality of life for individuals with a rare disease.

One of the most common neurodegenerative diseases of childhood is Neuronal Ceroid Lipofuscinosis, or Batten disease (2). It is a group of lysosomal storage disorders linked by the accumulation of an auto fluorescent pigment that leads to progressive degeneration of neuronal tissue (2). To date, fourteen Ceroid Lipofuscinosis, Neuronal genes (abbreviated CLN) have been identified that comprise the NCLs. The exact genetic mutation present determines the clinical manifestations, ultimately leading to the unfortunate outcome of a vegetative state and premature death. The presence of dementia, vision loss, epilepsy, or motor deterioration, especially when present in combination, should raise suspicion for a form of NCL (3). These symptoms can present as early as birth, such as in Congenital CLN10 disease. Neonates are typically born with microcephaly and experience seizures shortly after birth (4). The NCLs can also present as late as adulthood, such as Classic adult onset CLN4 disease. The classic juvenile form caused by a CLN3 gene mutation is thought to be the most prevalent, manifesting between ages 4 and 7 years (5).

Due to the heterogenous nature of the NCLs with multiple dysfunctional protein products, therapeutic targets must be mutation specific to restore the proper metabolic processes. Currently, the only disease modifying agent approved for NCL treatment is Cerliponase alfa, which is a recombinant human proenzyme that replenishes the defective enzyme in CLN2 disease (6). Enzyme replacement therapy and gene therapy are areas of continued exploration in ongoing research. Even though differentiating the NCLs based on the affected gene allows for target treatments to be discovered, it can turn a rare disease into an ultra-rare phenomenon. This dissection can impede the initiation of research and discovery due to a lack of utility. Fortunately, the Batten community is filled with dedicated individuals and organizations working together towards solutions and creating opportunity for growth.

While Batten disease tragically affects children, family members are also impacted by the disease. A 2016 study reported on the experiences of caregivers with children who have inherited metabolic disorders (7). They found that most caregivers established coping strategies, but worried about social challenges for the child. It is essential to recognize the strain a rare and terminal childhood illness can add to families. Fortunately, the emergence of rare disease patient organizations has been incredibly valuable in raising awareness and supporting families. There is a National Rare Disease Day on the last day of February to raise awareness for rare diseases (8). It is difficult for individuals to raise awareness about their disease alone, which can lead to feelings of isolation. Rare disease patient organizations play a vital role in building camaraderie between individuals to help increase funding and researcher interest (9). There are several Batten disease foundations around the world. Additionally, an international conference is held bi-yearly to promote collaboration between researchers working to understand and discover treatments for Batten disease. This project aims to identify areas of difficulty for families affected by Batten disease and what role rare disease organizations play in mitigating these challenges. The areas of interest mainly focus around gaining information pertaining to support and management of the disease and addressing areas of health and wellbeing that are negatively impacted by the disease. By interviewing both caregivers and disease organizations, this study endeavors to analyze the interplay between them.

## Methods

### *Participants*

Group 1: Batten Caregivers. We attended the Batten Disease Support and Research Association family meeting, which is an annual event held for families affected by

Batten disease. We had a table set up where attendees could come get information about the study and volunteer to participate. The interviews were conducted in a private conference room. Interviews were semi-structured with a set of questions relating to the diagnosis process, the impact of the disease on the family, resources available at diagnosis, resources used now, involvement in disease advocacy, and the consequences of being a rare disease. Consent was obtained and responses were audio recorded. Recordings and interview notes are stored on a secure and password-protected server. This group consists of seven interviews. Eligible participants for this group are caregivers of individuals diagnosed with Batten disease who volunteered to participate in an interview. Child characteristics provided by caregiver participants are listed in table 1.

Group 2: Disease Organization Representatives. We identified rare disease organizations involved in Batten disease. Organizations were contacted via email and asked if a representative would be willing to participate in the study. Consent was obtained and interviews were conducted over the phone and audio recorded. Recordings and interview notes are stored on a secure and password-protected server. Interviews were semi-structured with a set of questions relating to the role of their organization in the rare disease community, what it means to the interviewee individually, how other people can get involved, and the current state of the rare disease space. This group consists of five interviews. Eligible participants in this group are individuals involved in a rare disease organization. List of organizations interviewed are in table 2.

## Results

*Caregiver Interviews*

### Identifying Resources after Diagnosis

Most children in this study were diagnosed through a genetic counselor recommended by a neurologist. Gaining a diagnosis is a vital first step in getting connected to disease organizations. The lifestyle changes that caregivers make to support their child is immense. The in-home accommodations that caregivers reported included features such as a main level bedroom for the child, a supportive chair at the dinner table, and medical equipment utilization. In a child with complex medical needs, it is difficult to find a babysitter. Extended family, often grandparents, played a vital role in providing relief to the parents. Caregivers reported feeling isolated due to a lack of time for social interactions or friendships. Caregivers reported difficulty in providing adequate attention to siblings of their affected child. Caring for a child with Batten disease is multifactorial. Most caregivers reduced the hours they worked or quit working altogether to care for their child.

> "After her seventh-grade year we brought her home. She started having seizures more frequently... When she ended up that spring with seizures, we were like okay, now it's time for her to be at home. So, we brought her back home and I quit my job that spring, not this year but the spring of last year, May 2017, so that I could be a caregiver for her because we have no other option." (Caregiver)

Fortunately, once connected to the rare disease space, caregivers often found ways of coping. The information about Batten disease that was available to caregivers at the time of diagnosis was variable. Some resources that were identified early included information about the disease, support organizations such as the BDSRA, open clinical trials, and palliative care services. Some caregivers were given information about the most likely diagnoses before the genetic testing results arrived to prepare for a possible diagnosis. Being included in the BDSRA closed Facebook group was advantageous to many caregivers.

> "But then Facebook came along. It became easier to keep in touch with other parents and so that's been the biggest thing. I am a part of a couple of different groups specific to Batten, but a lot of it is just being friends and just talking to each other that way... and that's more or less just a place for us to go and vent. It doesn't even have to be about Batten disease. It can be about work or somebody at the store that irritated you or whatever." (Caregiver)

Searching the internet was practical to some caregivers in identifying local resources. When looking for more in-depth data, the amount of material available was intimidating and understanding the information was a common challenge

Table 1. Characteristics of children provided by caregiver participants (n = 7)

| Interview | Type | Gender | Current age | Symptoms onset age | Diagnosis age |
|---|---|---|---|---|---|
| A | CLN1 | M | 8 | 2.5 | 3.5 |
| B | | F | Deceased | 1 yr., 5 mo. | 2 yr., 2 mo. |
| C | | M | 21 | 5.5 | 6.5 |
| D | CLN2 | F | 4 | 3 | 3 yr., 9 mo. |
| E | Unclassified | M | 8 | 2.5 | 8 |
| F | CLN3 | F | 14 | 4.5 | 10.5 |
| G | | M | 16 | | 10 |

among caregivers. Reasonably, caregivers looked to the BDSRA to get updates about research, events, and policies related to rare diseases. Many caregivers found conferences helpful to listen and talk with researchers and other families, as one caregiver explained about the family conference.

> "It's actually sitting down and talking to somebody who actually knows what they're talking about, that's where the most help has come from. And this past couple of days has been more help than the past 5 years. It's been very beneficial." (Caregiver)

Many caregivers expressed difficulty in finding reliable information about Batten disease. It is hard to find information that applies specifically to the caregiver's child because of the variability within Batten disease. However, sharing information on the internet has allowed people to expand the knowledge base and as one caregiver stated, "not reinvent the wheel" on how to manage Batten patients. A common trend was that the sooner caregivers were able to connect with other caregivers, the better they were able to navigate managing the disease.

> "It's super overwhelming and super emotional, but it's so comforting at the same time to know that I'm not the only one going through this. Where I live, I'm the only one going through this and nobody can possibly understand. But now we've got this extended family that I know I can reach out to and be like I'm frustrated, what do we do from here." (Caregiver)

**Addressing Health and Wellbeing**

Caregivers reported that most schools are not well equipped to handle a child with a life limiting disease. There was dissatisfaction in setting appropriate educational goals, which require a balance between promoting learning yet understanding the gradual loss of abilities in the child. One caregiver reported that her daughter attended a school for the blind, which provided tactile based communication devices and more individualized ways of learning. Notably, the BDSRA provides materials to school systems in an effort to guide how they can best serve students with Batten disease.

Children with Batten disease require extensive ancillary services and durable medical equipment (DME) in variable forms and amounts depending on the stage of the disease. Unfortunately, access to these services and equipment can take months and the child's needs may have changed in the interim due to the progression of the disease. Caregivers reported that one way being connected through disease organizations can help with this problem is the ability for them to share DME they are no longer using.

The most common gap in care noted by caregivers was a lack of in-home skilled nursing aid availability. It is incredibly difficult to do everyday tasks such as grocery shop, spend time with siblings, or even get a good night of sleep while caring for a child with complex medical needs. This was especially true for the single parent caregivers who felt like every moment was spent trying to balance life. Even while at work, they would answer phone calls from the school or be thinking about what needs done at home.

> "She requires full assist care minus the lifting and the tube feeding. And yet we don't qualify for an in-home aid of any type. And it's like, wow, I mean what do you expect the families to do?" (Caregiver)

Connections with other families were crucial in finding an experienced neurologist. It was rare to identify a local neurologist who had managed a Batten disease patient in the past. Caregivers reported that a good neurologist was eager to learn about Batten disease and willing to listen to the caregiver, regardless of whether he/she had experience with Batten disease. Currently, there are three centers of excellence for Batten disease in the United States located in Boston, MA, Columbus, OH, and Rochester, NY. Several caregivers reported visiting one of these centers even if it meant traveling long distances or battling with insurance to cover the visits.

> "We were like, okay yes, it's still another two and a half hours. But we know that's a center for excellence for Battens and so we were like, let's go there." (Caregiver)

The biggest challenge reported by caregivers of a child with Batten disease was the emotional toll on the family. Caregivers reported the unbearable reality of seeing their child want to do things that they will never do while losing abilities they used to have. A caregiver revealed the terrifying reality of waking up every morning knowing this could be the last day for her child. Even though this was reported to be the most distressing aspect of caring for a child with Batten disease, having a support group through disease organizations to share these experiences with was an invaluable tool for coping.

*Disease Organization Interviews*

**Acting as Connectors**

Most Batten disease specific organizations are focused on connecting families to each other and to resources. Fortunately, Batten families are very supportive to the newly diagnosed in order to help them move forward more smoothly.

> "We sit down on the phone with them for an hour, hour and a half, whatever it takes and kind of go over the state of where everything is, what's been

> successful for us, what has not been successful. Just to try to get them on a smoother path than perhaps we had." (Noah's Hope)

The broader rare disease organizations focused heavily on providing resources to help each disease community make change for themselves and remove the burdens associated with being rare. They connect people to others who have accomplished the same or a similar endeavor. They also have resources such as how to start a 501c3 nonprofit, online courses, webinars, podcasts, drug development education, medical professional education, how to advocate in the community or on the hill, and rare disease summits.

> "We are not looking to find a cure for all 7000 rare diseases. We know that that is something that may not be achievable. But what we want to do is not only connect and empower and inspire the rare disease community, but to create a globally connected community equipped to eliminate the challenges of rare disease." (Global Genes)

Leaders in the Batten community took a tragic story and made it one of fortitude and inspiration for others. Most of the Batten organizations are founded by parents of children with Batten disease. This is similar in the general rare disease community. Those involved often had experienced a rare disease in either themselves or someone close to them. After facing the challenges firsthand, people wanted a better future for others.

> "I guess I just decided that if I was going to fight that battle and navigate that journey, then I was going to hopefully use my resources and use my education to make it better for families that came behind us." (Rare KC)

**Advocacy and Awareness**

The average person may not feel capable of making an impact, but each person can help raise awareness. Disease organization representatives made several suggestions including to reach out to affected families, spread patient stories, share on social media, attend fundraisers, contact the state representatives, educate others that rare diseases are not rare collectively, and be open to learning why it is important to care.

> "If you have a child or you personally are going through a cancer, people know it. Because typically you go through chemotherapy, you lose your hair, people know it, they understand it. The problem is with rare disease, it's really hard to define." (Rare KC)

Building a sense of camaraderie between individuals with a rare disease is a key role of disease organizations. People are connecting through Facebook, through call or text, and meeting in person at conferences. The BDSRA closed Facebook page was mentioned by most caregivers as especially helpful at the time of first receiving a diagnosis. Having a community to confide in appeared to be invaluable.

> "Tragedy brought us together, but we have become good friends and we understand one another. The highs the lows, you really do become a family." (Taylor's Tale)

The representative for Taylor's Tale expressed the importance of advocating for the day-to-day issues that are difficult for the public to understand because these issues are hidden inside the home. Everyday tasks can be challenging. Caregivers try diligently to provide the best quality of life for their child. Advocacy gives people a combined voice where they feel empowered to share the day-to-day issues.

> "My heart is in the advocacy part of this because it touches everything." (Taylor's Tale)

Bringing awareness to rare diseases is sometimes done by the media, as pointed out by the representative for the National Organization for Rare Disorders (NORD). Occasionally, a celebrity has a rare disease or has a child with a rare disease. The publicity sheds light on rare diseases while exemplifying that rare can affect anyone. For people who cannot advocate for themselves, rare disease organizations can act as their voice.

**Progressing Research**

Many organizations raise money to fund scientific research. When new advancements are made, it creates a legacy for children who have passed from Batten disease. The representative of Noah's Hope explained how he/she attends Batten conferences every year and builds a network that is useful in connecting people to difference resources. He/she knows the community and can help new scientists move forward, admitting that it is promising to see how Batten research and lysosomal storage disorder research has expanded over the years.

> "Every time we see a child that's on ERT (enzyme replacement therapy) now, we can't help but smile knowing that Noah and Laine played a part in making that happen, in changing those children's lives." (Noah's Hope)

In recent years, there has been a large push to involve more patients in the drug development process. Global Genes holds a symposium every year to educate advocates on how to get research moving and find therapies. Rare KC is constantly discussing the topic of research by educating patients in the local community. Topics that are covered include the importance of participation, how to get involved, science terminology, and making connections with researchers. Basic science is important, but many

organizations are focused on promoting translational science. Taylor's Tale is focused on funding research that can treat patients living with the disease today.

**Moving Forward**

Predicting a future for the rare disease community is incredibly optimistic. The representative for Global Genes described the rare disease community as becoming increasingly educated. They connect with other people much faster and create change more efficiently. The NORD representative envisions the future as bright, and a lot of people are working hard to make that true. There is hope that as the new generation replaces the old, they will keep pushing the message of rare disease advocates.

> "I think there is a lot of work to do. And that can sometimes feel daunting, but the passion and the drive of the people in this space is so incredible!" (NORD)

Of course, there is still work that needs done for individuals living with a rare disease. Noah's Hope and Taylor's Tale representatives illustrated hurdles the Batten community must work to overcome. The difficulties depend on the stage of the disease. Physically, it is devastating to lose vision, speech, and the ability to move around. Yet importantly, families affected by Batten disease must come to terms with the fact that their future is going to be different than they expected. Even though it is not a desirable destination, many people are working to make it as beautiful of a place as possible.

Notably, the representative for Global Genes shared some insight about ultra-rare disease patients. They may not ever meet someone with their disease and it is more difficult to start research projects. Fortunately, with rare disease organizations individuals are armed with resources to initiate the projects. Therefore, it only takes one person to start making progress for an ultra-rare disease.

> "A lot of times these parents that are caring for a chronically ill child, not only do they have to take care of that child, but they are out there raising money and developing registries and finding researchers and learning scientific knowledge that they thought they would never need to learn." (Global Genes)

One of the main areas reported as needing improvement focused on research. Participants described how researchers have made incredible progress with the few funds that are provided for rare diseases. Moreover, industry is playing an increasing role in getting drugs approved for rare diseases. Yet, the rarer forms of Batten are at a roadblock due to a difficulty in partnering with industry.

**Discussion**

By interviewing both caregivers and disease organizations, the study was able to analyze the interplay between them. The semi-structured interviews allowed caregivers to elaborate on their experiences and talk about points that they felt were significant. Additionally, the disease organization representatives were able to share personal experiences about their involvement in the organization. Moreover, they could describe their role as a leader in the community and goals for the future.

A key finding from the caregivers in the study was that not having a diagnosis can lead to much distress in caregivers. However, once the diagnosis is made, many families are finding other affected families through social media. The disease organizations are key in providing information about how to be involved in the future of Batten disease. Despite the progress, challenges remain present with regards to education, in-home aid, timely medical equipment, and receiving expert disease management care. Yet through connections with others and support through disease organizations, many of the challenges can be mitigated.

Some key findings from the disease organization representatives in the study were the roles they embodied by acting as connectors for families. The resources they offer are centered around eliminating challenges for families, creating support groups, advocating, and educating. They identify specific problems and work towards solutions, giving a voice to many people who cannot stand alone. The organizations play an active role in progressing research by bringing awareness to specific diseases, funding projects, and encouraging patient participation.

One noteworthy point of bias in the study was that the caregivers were all attendees of the BDSRA family conference. Therefore, they may be more involved in disease organizations than the Batten disease community at large. Additionally, the attendees of the conference had the resources and flexibility to travel. This may represent a group that faces different challenges than people who were not able to attend. It would be beneficial to interview caregivers who are less involved in disease organizations. Another limitation was the small sample size. Each caregiver has a unique story about finding a diagnosis and managing the disease. Added interviews may reveal challenges that were not expressed by caregivers in this study. Despite the mentioned limitations, the study provided valuable information about caregiver experiences and the role of disease organizations.

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**References**

1. Griggs R, Batshaw M, Dunkle M, et al. Clinical research for rare disease: Opportunities, challenges, and solutions. *Molecular Genetics and Metabolism*. 2009 Jan;96(1):20-6. DOI:10.1016/j.ymgme.2008.10.003

2. Nita D, Mole S, Minassian B. Neuronal ceroid lipofuscinoses. *Epileptic Disorders*. 2016 Sep 1;18(S2):73-88. DOI:10.11684/epd.2016.0844

3. Schulza A, Kohlschüttera A, Minkb J, Simonatic A, Williamsd R. NCL diseases — clinical perspectives. *Biochim Biophys Acta*. 2013 Nov;1832(11):1801–1806. DOI:10.1016/j.bbadis.2013.04.008

4. Barohn R, Dowd D, Kagan-Hallet K. Congenital Ceroid-Lipofuscinosis. *Pediatric Neurology*. Jan-Feb 1992;8(1):54-9. DOI:10.1016/0887-8994(92)90054-3

5. Freund K, Sarraf D, Mieler W, Yannuzzi L. The Retinal Atlas. Elsevier Inc. 2017;3:233-278.

6. Kohlschütter A, Schulz A, Bartsch U, Storch S. Current and Emerging Treatment Strategies for Neuronal Ceroid Lipofuscinoses. *CNS Drugs*. 2019 Apr;33(4):315-325. DOI:10.1007/s40263-019-00620-8

7. Siddiq S, Wilson B, Graham I. Experiences of caregivers of children with inherited metabolic diseases: a qualitative study. *Orphanet Journal of Rare Diseases*. 2016 Dec 7;11(1):168. DOI:10.1186/s13023-016-0548-2

8. Rarediseaseday.org [Internet]. Eurordis Rare Diseases Europe. c2020. Available from: https://www.rarediseaseday.org/article/what-is-rare-disease-day

9. Pinto D, Martin D, Chenhall R. The involvement of patient organisations in rare disease research: a mixed methods study in Australia. *Orphanet Journal of Rare Diseases*. 2016 Jan 12;11:2. DOI:10.1186/s13023-016-0382-6

# Physicians Preferences of Virtual Versus In-Person Visits in Neuromuscular Clinical Practice

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**Keywords:** *Telemedicine, Neuromuscular, Physician, Teleneurology*

## Introduction

The use of telemedicine in clinical practice is becoming popular and many practices have adopted some form of telemedicine or plan to do so in the future[1]. The COVID-19 pandemic compelled the medical community to utilize telemedicine and policies were rapidly changed to continue patient care during the pandemic[2]. While the role of telemedicine is well established in certain fields of medicine, its role in other disciplines like neuromuscular medicine is not as clear. There have been small scale studies that assessed satisfaction for subgroups of patients like ALS[3]. However, data on physician perspectives is almost non-existent. A recent survey of neuromuscular patients on their preference of virtual vs in-person visits showed an inclination towards in-person visits (in press). However, the opinion of neuromuscular physicians on telemedicine is essential for understanding the future direction of tele-neurology. We designed this survey to answer the question of physician preference and the factors influencing their decision.

## Method

### *Study Design and Data Collection*

We called for participants using the forum provided by Rick's Real NeuroMuscular Friends (RRNMFs), an online group of about 2000 neuromuscular disorders physicians. 94 physicians were interested. We used an online form (Microsoft Forms) composed of eleven questions to survey the interested 94 neuromuscular specialists from the USA and Canada during September 2020 (the questionnaire and consent template uploaded in supplementary materials). The survey was conducted unanimously, and surveyed physicians consented to participate in the study while their personal information was kept discrete. We conducted a descriptive analysis of the data.

The primary outcome, neuromuscular physician visit preference, was assessed by the survey item "When you see a new patient, what type of visit do you prefer?". Responses were categorized as 'Physical (face-to-face)', 'Virtual (through the phone or video-audio system)', or 'No preference'. The second question was "When you see a follow-up patient, what type of visit do you prefer?" Responses were categorized as 'Physical (face-to-face)', 'Virtual (through the phone or video-audio system)', or 'No preference'. Each question had 3 categories of responses.

## Results

62.77% (n=59) were males, 32.98% (n=31) were females and 4 participants declined to declare their gender. 59.57% (n=56) were younger than 50 years old, 37.23% (n=35) were older than 50 years old while three declined to answer. Regarding the type of practice, 53.19% (n=50) worked in an academic-based practice while 18.09% worked in a group practice, 15.96% worked in hospitals, 5.32% in large HMO, and 6.38% in solo-based practices (table 1).

Table 1. Numbers and percentages of participants of the study divided according to their type of practice.

| Practice type | Percentage of total | Number of participants |
|---|---|---|
| Academic based | 53.19% | 50 |
| Group practice | 18.09% | 17 |
| Hospital based | 15.96% | 15 |
| Large HMOs | 5.32% | 5 |
| Solo practice | 6.38% | 6 |
| Declined to answer | 1.06% | 1 |
| **Grand Total** | **100.00%** | **94** |

When seeing new patients, 90.43% (n=85) of the participants preferred physical visits, 4.26% (n=4) preferred virtual visits while the rest had no preference or declined to answer. In response to their preference in seeing follow-up patients, 44.68% (n=42) preferred physical visits, 28.72% (n=27) preferred virtual visits while 25.53% (n=24) had no preference. Moreover, 45.74% (n=43) of the participants said that practicing telemedicine did not influence the number of procedures like EMG and biopsies, while 38.30% (n=36) thought it would decrease them, and 13.83% (n=13) thought it would increase them. The majority thought that telemedicine reduces revenue 58.51% (n=55), while 27.66% (n=26) declared no effect on revenue, and 12.77% (n=12) thought it would increase revenue. When participants were asked about the quality of service, 57.45% (n=54) answered in the negative, 24.47% (n=23) said telemedicine did not affect the quality of service, while 17.02% (n=16) thought that the quality of service would improve. 44.68% (n=42) somewhat agreed that quality time spent with patients would be reduced, 18.09% (n=17) strongly agreed with the previous statement, while 36.17% (n=34) disagreed. Most surveyed physicians agreed that telemedicine was time-efficient: 57.45% (n=54) somewhat

agreed, and 26.60% (n=25) strongly agreed, while 14.89% (n=14) disagreed. 52.13% (n=49) somewhat agreed that telemedicine improved patient compliance, 18.09% (n=17) strongly agreed, while 28.72% (n=27) disagreed. 62.77% (n=59) declared that telemedicine would be a long-term solution in clinical practice, 31.91% (n=30) thought telemedicine was effective only during the pandemic, while 4.26% (n=4) said it was not efficient in both cases. 58.51% (n=55) revealed that telemedicine did not affect workload, while 26.60% (n=25) thought it increased workload and 13.83% (n=13) thought telemedicine decreased workload. Finally, 75.53% (n=71) preferred to reveal a new diagnosis during a physical visit, and none 0.00% during a virtual visit, while 23.40% (n=22) had no preference.

## Discussion

Our study showed that the majority of the surveyed neuromuscular disorders physicians preferred in-person visits for new patients. Even for follow-up visits, there was a high inclination towards in-person visits (44%), but almost

Table 2. Physician preference of the study type and revealing a new diagnosis.

| Percentage of total (n) | New patient preference | | Follow up patient preference | | Revealing new diagnosis | |
|---|---|---|---|---|---|---|
| No preference | 3.19% | (3) | 25.53% | (24) | 23.40% | (22) |
| Physical visits | 90.43% | (85) | 44.68% | (42) | 75.53% | (71) |
| Virtual visits | 4.26% | (4) | 28.72% | (27) | 00.00% | (0) |
| total | | (92) | | (93) | | (93) |

Table 3. Subjects opinion on the number of procedures, revenue, service quality, and workload

| Percentage of total (n) | Influence of telemedicine on number of procedures | | Influence of telemedicine on revenue | | Influence of telemedicine on the quality of services | | Influence of telemedicine on workload | |
|---|---|---|---|---|---|---|---|---|
| Increase in numbers / Revenue /quality | 38.30% | (36) | 58.51% | (55) | 17.02% | (16) | 13.83% | (13) |
| Decrease in numbers / Revenue /quality | 13.83% | (13) | 12.77% | (12) | 24.47% | (23) | 26.60% | (25) |
| No effect | 45.74% | (43) | 27.66% | (26) | 57.45% | (54) | 58.51% | (55) |
| Total | | (92) | | (93) | | (93) | | (93) |

Table 4. Subjects opinion on the effect of telemedicine on the reduction of quality time with patients, time-efficiency, and improving patient's compliance

| Percentage of total (n) | telemedicine will reduce the quality time with patients | | telemedicine is time-efficient | | telemedicine will improve patient's compliance | |
|---|---|---|---|---|---|---|
| Strongly agree | 18.09% | (17) | 26.60% | (25) | 18.09% | (17) |
| Somewhat agree | 44.68% | (42) | 57.45% | (54) | 52.13% | (49) |
| Disagree | 36.17% | (17) | 14.89% | (25) | 28.72% | (27) |
| Total | | (93) | | (93) | | (93) |

half the physicians either preferred virtual visits (28%) or did not have a preference (25%). The results are not surprising but differ from other surveys which have shown higher satisfaction rates and a tendency towards choosing telemedicine in future[4]. The data on physician preference is very limited and almost non-existent in the field of neuromuscular medicine. The comparative studies have key design differences. The studies done before the COVID-19 pandemic had compared the satisfaction and feasibility of telemedicine in selected patient populations with set models[4,5]. Since the start of the pandemic, physicians were forced to use telemedicine for all types of patients to provide care in the era of social distancing and we entered this practice unprepared. Hence, we faced multiple challenges including policies regarding reimbursement, lack of trained staff, and equipment[1]. It affected everyone differently and our data provides how neuromuscular physicians feel about telemedicine use in the future.

Adoption of telemedicine in routine clinical practice faces multiple challenges and giving this option to patients comes at a cost. Despite the new regulations of telemedicine reimbursement matching that of in-office visits, 97% of private practices reported negative financial outcomes during the pandemic[6]. Our survey showed similar results as the majority (58%) of physicians said that telemedicine decreases revenue. This is an important factor that will influence the implementation of telemedicine in the future.

The fact that physicians preferred in-person visits for new patients, and none chose virtual visits to reveal a new diagnosis reveals that physicians are not mere diagnosticians. The first interaction with the patient is not only meant to make the best judgment about the diagnosis and exam but is also the first step to building a relationship. Preferences of this study are justified by the fact that in the neuromuscular specialty, a detailed neurological examination is needed which is not feasible virtually, and neurophysiology is often used as an extension of the physical examination. Most neuromuscular conditions are chronic and require long-term care. To build rapport with the patient, gestures, face-to-face interaction, assessing personality, and patient expectation is best done in person. This is compromised in telecommunication. With the advancement in technology and more preparation to facilitate virtual interaction, the opinion is subject to change.

Despite physicians choosing in-person visits, the majority agree that telemedicine will be a long-term solution and does not affect the quality of service. This indicates that in physician's opinion, there may be a role of telemedicine although in a selected patient population. One main limitation of our survey is that we do not have data on the challenges and limitations faced by each practice and if it influenced the decision of choosing visit type. Since the COVID-19 pandemic affected each practice differently, the barriers faced by one practice and hence the translation to workload and quality of care might be different. It will be helpful to know the individual challenges to come up with a solution.

Table 5. Telemedicine efficiency during COVID-19 pandemic versus a long-term solution

| Percentage of total (n) | | |
|---|---|---|
| During the pandemic only | 31.91% | (30) |
| Long term solution | 62.77% | (59) |
| Not efficient at all | 4.26% | (4) |
| Total | | (93) |

In conclusion, despite the preference of telemedicine in many specialties of healthcare practices, neuromuscular physicians still prefer face to face visits especially in seeing new patients emphasizing the distinct nature and peculiarities of neuromuscular disease specialty. While preferences for new patients and breaking new diagnoses clearly favored physical visits, such preference only marginally favored follow-up visits. While most of the participants agreed that telemedicine improved patient's compliance and it was a time efficient solution, they still had doubts about the economic factors, quality of service, and time spent with patients. The COVID-19 pandemic imposed difficult questions in clinical practice, and while healthcare facilities and physicians showed flexibility in dealing with the new norms[7], the prospect of the sudden change might take clinicians out of their comfort zone. Neuromuscular specialists preferred seeing new patients and revealing new diagnoses to patients in physical visits, but they also considered telemedicine a long-term method that would continue to increase in the post-pandemic future[8]. There was a crucial need to stimulate neuromuscular practices into adopting telemedicine by addressing their concerns and boosting the positive factors like continuing the current insurance policies and patient privacy flexibility.

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**References**

1. George BP, Scoglio NJ, Reminick JI, et al. Telemedicine in Leading US Neurology Departments. *The Neurohospitalist*. 2012;2(4):123-128. doi:10.1177/1941874412450716

2. Klein BC, Busis NA. COVID-19 is catalyzing the adoption of teleneurology. *Neurology*. 2020;94(21):903-904. doi:10.1212/WNL.0000000000009494

3. Van De Rijn M, Paganoni S, Levine-Weinberg M, et al. Experience with telemedicine in a multi-disciplinary ALS clinic. *Amyotroph Lateral Scler Front Degener*. 2018;19(1-2):143-148. doi:10.1080/21678421.2017.1392577

4. Donelan K, Barreto EA, Sossong S, et al. Patient and clinician experiences with telehealth for patient follow-up care. *Am J Manag Care*. 2019;25(1):40-44.

5. Mammen JR, Elson MJ, Java JJ, et al. Patient and Physician Perceptions of Virtual Visits for Parkinson's Disease: A Qualitative Study. *Telemed E-Health*. 2018;24(4):255-267. doi:10.1089/tmj.2017.0119

6. Bajowala SS, Milosch J, Bansal C. Telemedicine Pays: Billing and Coding Update. *Curr Allergy Asthma Rep*. 2020;20(10):60. doi:10.1007/s11882-020-00956-y

7. Garcia-Huidobro D, Rivera S, Valderrama Chang S, Bravo P, Capurro D. System-Wide Accelerated Implementation of Telemedicine in Response to COVID-19: Mixed Methods Evaluation. *J Med Internet Res*. 2020;22(10):e22146. doi:10.2196/22146

8. Kichloo A, Albosta M, Dettloff K, et al. Telemedicine, the current COVID-19 pandemic and the future: a narrative review and perspectives moving forward in the USA. *Fam Med Community Health*. 2020;8(3):e000530. doi:10.1136/fmch-2020-000530

Appendix 1. Questionnaire distributed to participants.

# Preferences of virtual versus in-person visits in neuromuscular clinical practice

In supplementation to our study "Patient's preferences of virtual versus in-person visits in neuromuscular clinical practice" we would appreciate your participation in this survey to examine the physician's preferences of telemedicine in neuromuscular clinical practice. Your personal information will be strictly confidential.

* Required

* This form will record your name, please fill your name.

1. Do you agree to participate in this survey? *

   *Personal information will be strictly confidential.*

   ◯ Yes

   ◯ No

2. Initials

   *For the purpose of reference please write your initials.*

3. Age

   *For demographic data*

8/24/2020

4. Gender

*For demographic data*

- ◯ Male
- ◯ Female
- ◯ Other
- ◯ Prefer not to say

5. Type of practice

*What type is your institute or practice?*

- ◯ Solo practice
- ◯ Group practice
- ◯ Large HMOs
- ◯ Hospital based
- ◯ Academic based

6. When you see a new patient, do you prefer...?

- ◯ Virtual visits
- ◯ Physical visits
- ◯ No preference

7. When you see a follow-up patient, do you prefer...?

- ◯ Virtual visits
- ◯ Physical visits
- ◯ No preference

8/24/2020

8. Do you feel that practicing telemedicine will influence number of procedures such as EMG, biopsy, etc...?

- ◯ Increases number
- ◯ Decreases number
- ◯ No effect

9. In your opinion, what is the effect of telemedicine on revenue?

- ◯ Increases revenue
- ◯ Decreases revenue
- ◯ No effect

10. In your opinion, what is the effect of telemedicine on the quality of services?

- ◯ Improves quality
- ◯ Reduces quality
- ◯ No effect

11. How do you feel about this statement "telemedicine will reduce the quality time the health care professional spends with the patient"?

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Disagree

8/24/2020

12. How do you feel about this statement "telemedicine is time-efficient"?

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Disagree

13. Do you think telemedicine is efficient during COVID-19 pandemic only or as a long term solution?

- ◯ During the pandemic only
- ◯ Long term solution
- ◯ Not efficient at all

14. How do you prefer revealing a new diagnosis?

- ◯ Virtually
- ◯ Physically (in person)
- ◯ No preference

15. Do you feel telemedicine will improve patient's compliance?

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Disagree

16. How has telemedicine affected your workload?

- ◯ Increased workload
- ◯ Decreased workload
- ◯ No effect

# Co-existent Ocular Myasthenia Gravis and Graves' Disease in a 5-Year-Old

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## ABSTRACT

Myasthenia gravis and Graves' disease are known to co-exist in adults, yet there have only been a small number of paediatric cases reported. We report a 5-year-old female who was diagnosed with ocular myasthenia gravis after presenting with unilateral ptosis and subsequently found also to have Graves' disease. She was treated successfully with pyridostigmine, corticosteroids and carbimazole without symptom recurrence or progression to generalised myasthenia gravis. The aetiology of the coexistence is not fully understood, nor is the relationship between the two disorders' presentation and treatment. We discuss the variation in the clinical presentation of myasthenia gravis with age, ethnicity and association with autoimmune thyroid disease; as well as potential HLA-related genetic susceptibility and the varying approaches to the treatment of the co-existent disorders.

**Keywords:** *Myasthenia gravis, Graves disease, thyroid disease, autoimmunity, paediatrics*

## Introduction

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction leading to fatigable muscle weakness. Graves' disease is an autoimmune thyroid disease and the leading cause of hyperthyroidism in children. The association between MG and Graves' disease is well reported in adults, however, there have only been a small number of reported cases (1,2) in children. We report the case of a 5-year-old female diagnosed with coexistent ocular myasthenia gravis (OMG) and Graves' disease.

## Case

A previously well 5-year-old girl of East Asian background presented with a two-week history of isolated left-sided ptosis, noted to be worse in the evenings. Her medical history was significant for extreme prematurity at 26 weeks but her development was appropriate for age. Her only medications were vitamin supplements. There was no known family history of autoimmune disease.

She had had a mild upper respiratory illness 2 weeks preceding presentation and was otherwise well. On examination, there was left-sided ptosis with ocular muscle fatigability. The rest of her neurological examination was normal; in particular, there were no other features of Horner's syndrome or third cranial nerve palsy. A diagnosis of probable OMG was made. Full blood count, electrolytes, liver function tests, C reactive protein and erythrocyte sedimentation rate were normal. Acetylcholine receptor (AChR) antibodies were positive at 0.45nmol/L (normal range (NR) <0.25nmol/L, equivocal 0.25-0.4nmol/L, positive >0.4nmol/L), consistent with the diagnosis of MG. Muscle-specific kinase (MuSK) antibodies were negative. Brain MRI was normal other than small areas of gliosis in keeping with prematurity, and chest MRI to exclude thymoma was normal. Ocular single fibre electromyography (EMG) was not tolerated so not performed. EMG with repetitive stimulation in the right abductor digiti minimi and right tibialis anterior was normal, supporting the diagnosis of isolated OMG only. Oral pyridostigmine (up to 30mg four times per day) was commenced.

The ptosis and extraocular muscle weakness initially completely resolved with pyridostigmine therapy, however, after one month the unilateral ptosis returned with new divergent strabismus and diplopia on left lateral gaze. Examination showed limitation of left eye adduction and left-sided ptosis with fatigability that improved after 2 minutes of ice pack application. The remainder of her neurological examination was normal. She commenced oral corticosteroids (titrated up gradually to 1mg/kg daily) with good response. During recovery, her ptosis alternated between eyes. Her symptoms completely resolved following 6 weeks of corticosteroid therapy.

Screening thyroid function tests (TFTs), taken after her diagnosis of OMG, demonstrated biochemical hyperthyroidism with suppressed thyroid-stimulating hormone (TSH) <0.004mIU/L (NR 0.4-4) and mildly elevated free T4 of 26.9 pmol/L (NR 10-20). She had no symptoms of hyperthyroidism. An endocrinology review was arranged. On examination, she was flushed with warm, sweaty peripheries and brisk reflexes. There was no evidence of goitre, thyroid thrill or bruit, and no proptosis or eyelid retraction.

Further testing revealed a significantly elevated thyrotropin receptor antibody (TRAb) of 14.2 IU/L (NR < 2.1), positive anti-thyroglobulin of 20.1 IU/mL (NR <4.1) and negative anti-thyroid peroxidase. She was diagnosed with Graves' disease and commenced on Neo-Mercazole (carbimazole). Thyroid ultrasound showed increased

vascularity, a non-specific finding commonly seen in Graves' disease, and no thyroid nodules. Coeliac serology, anti-GAD, anti-IA2 and anti-insulin antibodies were all negative; and morning cortisol, adrenocorticotropic hormone and parathyroid hormone were normal.

She tolerated all medications well. Thyroid function tests normalised with biochemical euthyroidism after 5 months and TRAb returned to the normal range after 1 year. Steroids were slowly weaned and she remained symptom-free. The pyridostigmine was also weaned without complication. At 2 years since diagnosis, symptoms have not recurred nor progressed to generalised MG.

**Discussion**

There is a well-known association in adults between autoimmune thyroid disease (including Graves' disease) and MG, particularly OMG (1,3-5). There have only been a small number of reported cases in children, including a 10-year-old boy and a 7-year-old girl (1,2). This case of a 5-year-old is the youngest case we have found_in the literature to date.

Juvenile myasthenia gravis (JMG) is an autoimmune disorder featuring fatigable skeletal muscle weakness caused by the development of autoantibodies against the AChR or related molecules, with decreased AChR activity and subsequent disruption of neuromuscular junction function (6,7). OMG refers to cases with isolated ocular muscle involvement (extraocular muscles, levator palpebrae and orbicularis oculi) and no progression to generalised myasthenia within 2 years. (6-9).

OMG may present with ptosis, strabismus or diplopia, and is more common in children than adults (6,10,11). Children with OMG have lower rates of AChR antibody positivity (41-54%) than those with generalised JMG, (72-82%) (6,7,10). OMG may progress to generalised JMG, however this is less common in children, with rates of progression ranging from 8-33% in children (6,10,12) compared to 50-70% in adults (10,12). Childhood-onset OMG has a higher rate of disease resolution than in adults; even without complete resolution, most children respond to medical management with first-line agent pyridostigmine or in combination with corticosteroids (8,10,12).

Clinical presentation of MG varies between populations. Higher rates of isolated OMG occur in children of Asian descent (up to 71-93% of East Asian children (10,11)) and paediatric onset of MG is also more common in East Asian populations (11,13). Zhang et al reported onset of MG before age 15 in 50% of 391 patients from mainland China, with a majority (75%) of these childhood cases being isolated OMG (11). This compares to paediatric cases representing 10-15% of MG in Caucasian and African-American populations (8). Correlations exist between several human leukocyte antigen (HLA) genes and MG, suggesting genetic susceptibility (11,14,15). In East Asian populations, the HLA-DRB1*09 allele (which is rare in Caucasians) has demonstrated association with MG, in particular early-onset disease and OMG (14,15). Other implicated genes include HLA-B*08 and HLA-DR3 (3,4,15). Antibody positivity rates also vary between populations, with high reported rates of AChR antibody positivity (>60%) in mainland China (11).

Graves' disease, the commonest cause of hyperthyroidism in children (incidence 1-14/100,000), is an autoimmune disorder in which TRAbs cause thyroid gland stimulation and excess thyroid hormone secretion (16-18). Graves' ophthalmopathy can occur due to cross-reactivity of TRAbs with a TSH receptor-like protein in extraocular muscles and retroorbital tissue, leading to inflammation of intraorbital contents with perioribital oedema, proptosis, eyelid retraction and impaired extraocular muscle movements (18,19). While extraocular muscle movements can be affected in both diseases, proptosis and lid retraction differ from the ptosis and fatiguability seen in MG (6,7). Graves' ophthalmopathy is less common and generally less severe in children than adults (18,19).

Graves' disease occurs in 6% of patients with MG (4) (vs. 0.5% of males and 3% of females in the general population (20)) but there are few reports of this co-existence in children (1,2). The underlying pathogenesis is not fully understood. HLA-DQ3 and HLA-DR3 have been suggested to convey genetic susceptibility to the co-existent disorders, and antibody positivity and response to steroid treatment support autoimmune pathogenesis (3,21). Those affected by MG with associated autoimmune thyroid disease may have a milder clinical course than those without thyroid involvement, characterised by isolated ocular involvement with less frequent generalisation, lower frequency of thymus involvement and lower AChR antibody positivity (3,8).

Childhood-onset OMG typically responds well to treatment and is less likely to progress to generalised disease than in adults (8,10,12,22). Treatment of OMG co-existent with Graves' disease is less predictable and approaches vary. Several authors report improvement of MG symptoms with lowering of thyroid hormones; the child in our case commenced carbimazole despite only a mildly elevated T4 because of literature suggesting aggressive treatment may improve the ocular prognosis (21,23). However, others report a "see-saw" phenomenon of worsening of myasthenic symptoms with treatment of thyrotoxicosis (24). Ratnakorn and Vejjajiva (5) found high-dose prednisolone successfully induced remission in hyperthyroidism and MG, in adults,

without the need for anti-thyroid drugs, however, there are no reports of this approach in children. In our case there was an initial improvement with pyridostigmine, however, symptoms progressed and prednisolone was commenced about one week prior to the introduction of carbimazole to treat hyperthyroidism. This led to rapid resolution of symptoms. Following symptom resolution, steroids were weaned successfully without rebound worsening of thyroid disease. The role of thymectomy is well established in adult patients and results in lower MG relapse rates in those with MG and hyperthyroidism (5). Thymectomy is not routinely indicated in pre-pubertal children with OMG and was not considered in this case but could be considered in refractory cases (13,25).

In conclusion, we report the case of a 5-year-old girl with OMG and Graves' disease who experienced incomplete response to pyridostigmine, with remission induced following the introduction of prednisolone and treatment with carbimazole. Even in young children, this association should be investigated. Early introduction of steroids should be considered in affected children, to induce remission, treat associated thyroid disease and prevent potential see-saw phenomenon with antithyroid medications.

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**References**

1. Koves IH, Cameron FJ, Kornberg AJ. Ocular Myasthenia Gravis and Graves Disease in a 10-year-old Child. Journal of Child Neurology. 2009;24(5):615-617. doi: 10.1177/0883073808324777

2. Chu HY, Shu SG, Mak SC, Chi CS. Graves' disease associated with myasthenia gravis: report of one case. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi. 1992;33(6):457-61.

3. Marinó M, Ricciardi R, Pinchera A, Barbesino G, Manetti L, Chiovato L et al. Mild Clinical Expression of Myasthenia Gravis Associated with Autoimmune Thyroid Diseases. Journal of Clinical Endocrinology and Metabolism. 1997;82(2):438-443. doi: 10.1210/jcem.82.2.3749

4. Song R, Yao Q, Wang B, Li Q, Jia X, Zhang J. Thyroid disorders in patients with myasthenia gravis: A systematic review and meta-analysis. Autoimmunity Reviews. 2019;18(10):102368. doi: 10.1016/j.autrev.2019.102368

5. Ratnakorn D, Vejjajiva A. Long-term follow-up of myasthenia gravis patients with hyperthyroidism. Acta Neurologica Scandinavica. 2002;106(2):93-98. doi: 10.1034/j.1600-0404.2002.01191.x

6. Peragallo J. Pediatric Myasthenia Gravis. Seminars in Pediatric Neurology. 2017;24(2):116-121. doi: 10.1016/j.spen.2017.04.003

7. Mansukhani SA, Bothun ED, Diehl NN, Mohney BG. Incidence and Ocular Features of Pediatric Myasthenias. American Journal of Ophthalmology. 2019;200:242-249. doi: 10.1016/j.ajo.2019.01.004

8. Fisher K, Shah V. Pediatric Ocular Myasthenia Gravis. Current Treatment Options in Neurology. 2019;21(10):46. doi: 10.1007/s11940-019-0593-y

9. Luchanok U, Kaminski HJ. Ocular myasthenia: diagnostic and treatment recommendations and the evidence base. Current Opinion in Neurology. 2008;21(1):8-15. doi: 10.1097/WCO.0b013e3282f4098e

10. Vanikieti K, Lowwongngam K, Padungkiatsagul T, Visudtibhan A, Poonyathalang A. Juvenile Ocular Myasthenia Gravis: Presentation and Outcome of a Large Cohort. Pediatric Neurology. 2018;87:36-41. doi: 10.1016/j.pediatrneurol.2018.06.007

11. Zhang X, Yang M, Xu J, Zhang M, Lang B, Wang W et al. Clinical and serological study of myasthenia gravis in HuBei Province, China. Journal of Neurology, Neurosurgery & Psychiatry. 2007;78:386-390. doi: 10.1136/jnnp.2006.100545

12. Ortiz S, Borchert M. Long-term Outcomes of Pediatric Ocular Myasthenia Gravis. Ophthalmology. 2008;115(7):1245-1248. doi: 10.1016/j.ophtha.2007.10.022

13. Gilhus NE. Myasthenia Gravis. New England Journal of Medicine. 2016;375:2570-2581. doi: 10.1056/NEJMra1602678

14. Xie YC, Qu Y, Sun L, Li HF, Zhang H, Shi HJ et al. Association between HLA-DRB1 and myasthenia gravis in a northern Han Chinese population. Journal of Clinical Neuroscience. 2011;18(11):1524-1527. doi: 10.1016/j.jocn.2011.05.002

15. Zhong H, Zhao C, Luo S. HLA in myasthenia gravis: From superficial correlation to underlying mechanism. Autoimmunity Reviews. 2019;18(9):102349. doi: 10.1016/j.autrev.2019.102349

16. Léger J, Oliver I, Rodrigues D, Lambert A, Coutant R. Graves' disease in children. Annales d'Endocrinologie. 2018;79(6):647-655. doi: 10.1016/j.ando.2018.08.001

17. Leger J, Carel JC. Diagnosis and management of hyperthyroidism from prenatal life to adolescence. Best

Practice & Research Clinical Endocrinology & Metabolism 2018:32(4):373-386. doi: 10.1016/j.beem.2018.03.014

18. Srinivasan S, Misra M. Hyperthyroidism in Children. Pediatrics in Review. 2015;36(6):239-248. doi: 10.1542/pir.36-6-239

19. Penta L, Muzi G, Cofini M, Leonardi A, Lanciotti L, Esposito S. Corticosteroids in Moderate-to-Severe Graves' Ophthalmopathy: Oral or Intravenous Therapy? International Journal of Environmental Research and Public Health. 2019;16(1):155. doi: 10.3390/ijerph16010155

20. Smith TJ, Hegedüs L. Graves' disease. New England Journal of Medicine. 2016;375(16):1552–65. doi: 10.1056/NEJMra1510030

21. Sekiguchi Y, Hara Y, Takahashi M, Hirata Y. Reverse 'see-saw' relationship between Graves' disease and myasthenia gravis; clinical and immunological studies. Journal of Medical and Dental Sciences. 2005;52(1):43-50.

22. Xu L, Castro D, Reisch JS, Iannaccone ST. Response to treatment in pediatric ocular myasthenia gravis. Muscle & Nerve. 2020;61(2):226–230. doi: 10.1002/mus.26745

23. Ali AS, Akavaram NR. Neuromuscular disorders in thyrotoxicosis. American Family Physician. 1980;22(3):97-102.

24. Mallikarjuna SK, Velayutham SS, Sowmini PR, Jeyaraj MK, Arunan S. See-Saw Relationship and its Reversal after Immunotherapy in a Case of Graves' Disease with Coexisting Myasthenia Gravis. Journal of Neurosciences in Rural Practice. 2019;10(1):136-138. doi: 10.4103/jnrp.jnrp_150_18

25. Lee HN, Kang HC, Lee JS, Kim HD, Shin HY, Kim SM et al. Juvenile Myasthenia Gravis in Korea: Subgroup Analysis According to Sex and Onset Age. Journal of Child Neurology. 2016;31(14):1561-1568. doi: 10.1177/0883073816666206

# Paraneoplastic Acute Axonal Polyneuropathy Associated with CASPR2 and LGI1 Antibodies

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## Introduction

Autoantibodies to voltage-gated potassium channel (VGKC) and its associated proteins including leucine-rich glioma-inactivated 1(LGI1) and contactin-associated protein-like 2 (CASPR2) have been implicated in numerous disorders of the central and peripheral nervous systems and observed in patients with cancer.[1] While LGI1 antibodies are associated with limbic encephalitis and faciobrachial dystonic seizures, antibodies against CASPR2 result in a broad spectrum of clinical syndromes, most notably Morvan's syndrome and neuromyotonia.[1] Additionally, one study noted a 44% prevalence of underlying cancer (one-third being thymoma) in patients with both antibodies.[1]

GBS associated with CASPR2 antibodies has been reported in two pediatric cases, one with concomitant LGI1 antibody positivity.[2] We report a case of an adult patient with acute axonal sensorimotor polyneuropathy who ultimately was found to have CASPR2 and LGI1 antibodies, as well as radiographic findings suspicious for renal cell carcinoma.

## Case Presentation

A 67-year-old man without preceding illness presented with a two-week history of intractable lumbar radicular pain with associated progressive, bilateral upper and lower extremity dysesthesias and weakness, requiring assistance with ambulation and feeding. His review of systems was otherwise non-contributory including an absence of constitutional symptoms. Except for a five-day history of constipation presumed secondary to narcotics recently prescribed for his new neuropathic pain, autonomic symptoms were absent. His examination was significant for normal bulk, diminished tone, and diffuse fasciculations. Upper extremity strength by Medical Research Council scale was 3/5 in bilateral shoulder abduction, elbow flexion, and elbow extension; 2/5 in bilateral wrist flexion, wrist extension, finger extension, finger abduction, and thumb abduction; and 1/5 in bilateral grip strength. Lower extremity strength was 3/5 in bilateral hip flexion, hip abduction, and knee flexion; 2/5 in bilateral knee extension, ankle dorsiflexion, ankle plantarflexion, and great toe extension. Finally, generalized areflexia was noted, as well as length-dependent hypoesthesia to all modalities with normalization around the level of the thighs and elbows.

### *Results*

The cerebrospinal fluid analysis revealed five nucleated cells and an elevated protein (126 mg/dL; reference range: <60 mg/dL), confirming cytoalbuminologic dissociation. CSF IgG synthesis rate was increased (12.52 mg/24 h; reference range: ≤8 mg/24 h), while CSF IgG index, oligoclonal bands, and an infectious workup were normal or negative.

Electrodiagnostic studies showed findings suggestive of acute axonal sensorimotor polyneuropathy suggested by reduced compound motor action potential amplitudes (CMAPs) and multiple non-recordable sensory responses (albeit with normal superficial radial sensory conduction) (Table 1). Needle EMG was significant for reduced motor unit potential recruitment and the presence of fibrillations/positive sharp waves without motor unit remodeling (Table 2). Peripheral nerve hyperexcitability (PNH) was supported by the presence of diffuse simple fasciculations and the appearance of afterdischarges in multiple CMAPs, which obscure the F-waves (Figure 1). Additional findings included conduction slowing in the common entrapment sites including the right median and ulnar neuropathies at the wrist and elbow, respectively.

Overall, the clinical presentation of ascending numbness, proximal and distal weakness, generalized areflexia, and severe neuropathic pain, accompanied by cytoalbuminologic dissociation and the electrodiagnostic findings led us to the initial diagnosis of acute motor and sensory axonal neuropathy variant of GBS, though PNH findings were atypical.

MR scan of the entire spine was unremarkable except for an incidental finding of a left upper pole renal mass. This finding was confirmed on MR scan of the abdomen with contrast, which showed a mass 4.2 cm in greatest dimension most consistent with renal cell carcinoma (RCC), clear cell subtype (Figure 2A, 2B). Features supportive of clear cell subtype included contrast enhancement and a central area of high signal intensity on T2-weighted images with nonenhancement after contrast administration (Figure 2A, 2B).[3] This prompted a serum paraneoplastic panel (Mayo Clinic, Rochester, Minnesota, USA), which revealed positive CASPR2 and LGI1 antibodies. The remaining diagnostic studies including a complete metabolic panel and whole-body CT scans were either normal or negative, except for moderate hyponatremia.

Table 1. Nerve conduction study results.

| **MOTOR** | | | | |
|---|---|---|---|---|
| **Nerve** | **Onset Latency (msec)** | **Amplitude (mV-motor)** | **Conduction velocity (m/sec)** | **F-wave latency (msec)** |
| Right median (abductor pollicis brevis) | 11.09 (wrist) (normal <4.2) | 1.6 (wrist) 1.2 (elbow) (normal >5.0) | 43 (normal >51) | No response |
| Right ulnar (abductor digiti minimi) | 3.59 (wrist) (normal <4.0) | 6.3 (wrist) 5.2 (below elbow) 5.0 (above elbow) (normal >5.0) | 56 (below elbow) 33 (above elbow) (normal >51) | No response |
| Right peroneal (extensor digitorum brevis) | 5.05 (ankle) (normal <5.5) | 3.8 (ankle) 2.7 (fib head) 2.3 (pop fossa) (normal >2.5) | 41 (fib head ) 42 (pop fossa) (normal >40) | 64.1 (normal <56.0) |
| Right tibial (abductor hallucis) | 5.52 (ankle) (normal <5.6) | 1.2 (ankle) 0.5 (pop fossa) (normal >2.5) | 43 (pop fossa) (normal >40) | No response |
| **SENSORY** | | | | |
| **Nerve** | **Peak Latency (msec)** | **Amplitude (µV-sensory)** | **Conduction velocity (msec)** | |
| Right median, ulnar, sural, superficial peroneal | No response | No response | No response | |
| Right radial | 2.14 (normal <2.5) | 19.9 (normal >15) | 60 | |

Table 2. Electromyography results.

| **Muscle** | **Fibrillations** | **Positive Sharp Waves** | **Fasciculations** | **Polyphasia** | **Amplitude** | **Duration** | **Recruitment** |
|---|---|---|---|---|---|---|---|
| Right tibialis anterior | 1+ | None | 1+ | Normal | Normal | Normal | Reduced |
| Right gastrocnemius | None | None | 1+ | Normal | Normal | Normal | Reduced |
| Right vastus lateralis | 1+ | 1+ | None | Normal | Normal | Normal | Reduced |
| Right tensor fasciae latae | 1+ | None | None | Normal | Normal | Normal | Reduced |
| Right biceps brachii | None | None | None | Normal | Normal | Normal | Normal |
| Right deltoid | 1+ | 1+ | 1+ | Normal | Normal | Normal | Reduced |
| Right triceps brachii | 1+ | 1+ | 2+ | Normal | Normal | Normal | Reduced |
| Right first dorsal interosseous | 1+ | None | 1+ | Normal | Normal | Normal | Reduced |

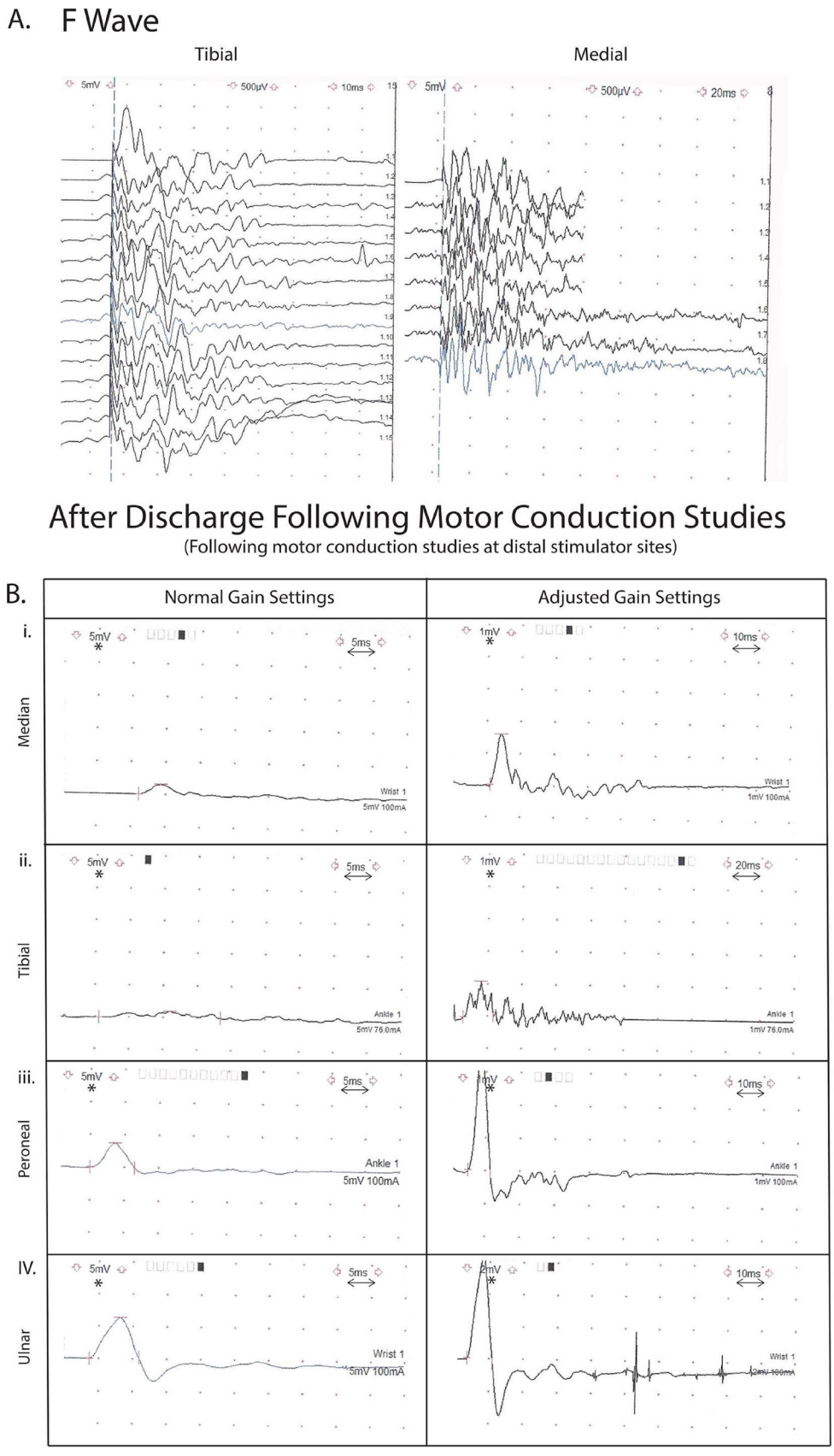


Figure 1. F-wave responses obscured by the prolonged afterdischarges (A). Prolonged afterdischarges on motor conduction studies were better visualized following adjustment of gain settings; * sensitivity , ↔ sweep speed (B).

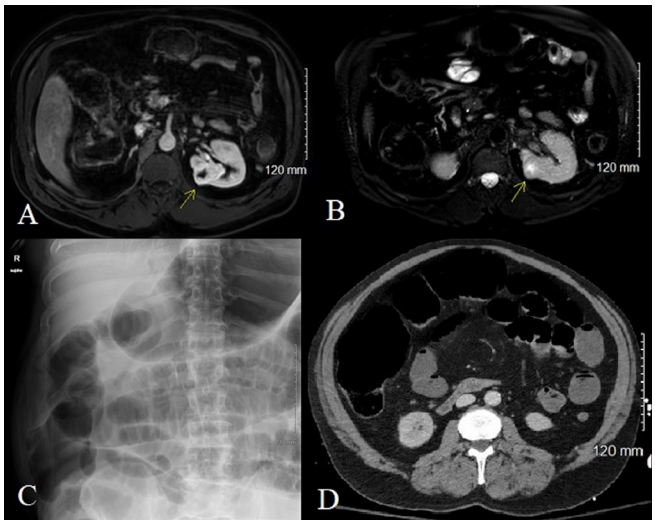


Figure 2. MR scan of abdomen, axial plane, demonstrating a 4.2 x 2.4 x 2.8 cm left upper pole exophytic contrast-enhancing renal mass (A) with central T2 hyperintensity (B) concerning for renal cell neoplasm, possibly clear cell subtype. Abdominal X-ray demonstrating distended stomach and air-filled loops of small and large bowel (C), CT scan of abdomen demonstrating diffusely distended colon (D).

*Course*

By hospital day three following a third of five planned total doses of intravenous immunoglobulin (IVIg) therapy at a daily dose of 0.4 g/kg, the patient had an objective improvement in strength and return of some upper extremity reflexes. Upper extremity strength was 4/5 in bilateral shoulder abduction, elbow flexion, and elbow extension; 3/5 in finger abduction; and 3/5 in bilateral grip strength. Lower extremity strength was 3/5 in bilateral hip flexion, knee flexion, and knee extension; and 2/5 in bilateral ankle dorsiflexion and ankle plantarflexion.

The patient's constipation remained refractory to conservative measures including laxatives, suppositories, and cessation of opioids. Unfortunately, on hospital day seven, the patient developed unremitting vomiting due to paralytic ileus (Figure 2C, 2D). Clinical deterioration with the development of abdominal compartment syndrome (intra-abdominal pressure of 38 mmHg) subsequently led to hemodynamic compromise and multiorgan failure, as evidenced by elevated troponin, liver function tests, and anuric renal failure. Despite continued aggressive supportive care and assistance from critical care and surgical consultants, the patient progressed into pulseless electrical activity and expired shortly thereafter. The family declined an autopsy.

## Discussion

This patient's presentation of progressive limb weakness, ascending numbness, generalized areflexia, and severe neuropathic pain, coupled with a CSF cytoalbuminologic dissociation and the electrodiagnostic findings, is consistent with an acute axonal sensorimotor polyneuropathy. Additionally, the findings of a presumed RCC, elevated CSF IgG synthesis rate, and the presence of CASPR2 and LGI1 antibodies were highly suspicious for an underlying paraneoplastic basis of his polyneuropathy. Our report highlights multiple evolving concepts related to the diagnostic and prognostic value of CASPR2 and LGI1 antibodies as potential biomarkers of autoimmune neuropathies.

*Pathogenesis and IVIg Responsiveness*

Rare presentations of GBS associated with nodal and paranodal antibodies, including our patient's, have shown IVIg responsiveness.[2,4,5] In contrast, chronic inflammatory demyelinating polyneuropathy (CIDP) associated with nodal and paranodal antibodies including CASPR2 responds poorly to IVIg but responds to rituximab and plasmapheresis. CIDP usually is associated with IgG4 subtypes while GBS patients have IgG1 or IgG3 subtypes.[4,5] The difference in therapeutic response could therefore be explained based on Ig isotype.

Potential mechanisms for IgG1/3-mediated diseases, which are responsive to IVIg, include clustering and internalization of receptors followed by lysosomal degradation, complement-mediated membrane receptor disruption, and direct blockade of receptors.[4,5] In contrast, IgG4 acts only by disrupting the function of the target or the interaction between the target and partner protein without the ability to fix complement or crosslink antibodies (Figure 3D). IgG4 titers decline sharply with rituximab, supporting its effectiveness in IgG4-mediated disorders such as CIDP associated with nodal and paranodal antibodies.[4]

The lack of access to paranodal antibody IgG subtyping (IgG1/3 vs IgG4) and titers at our reference laboratory as well as the inability to observe our patient's longitudinal course **and pursue autopsy**, prevent us from drawing final conclusions regarding his therapeutic response to IVIg. However, when available, testing for IgG subclasses may be useful in patients with autoantibodies against paranodal proteins and their significance should be addressed in prospective studies.

*Peripheral Nerve Hyperexcitability*

In addition to findings suggestive of acute axonal sensorimotor polyneuropathy, the patient's electrodiagnostic testing also **suggested** PNH, as evidenced by diffuse generalized fasciculations and afterdischarges. These findings **may be** explained by the effect of antibodies to the VGKC complex, including CASPR2 and LGI1, which

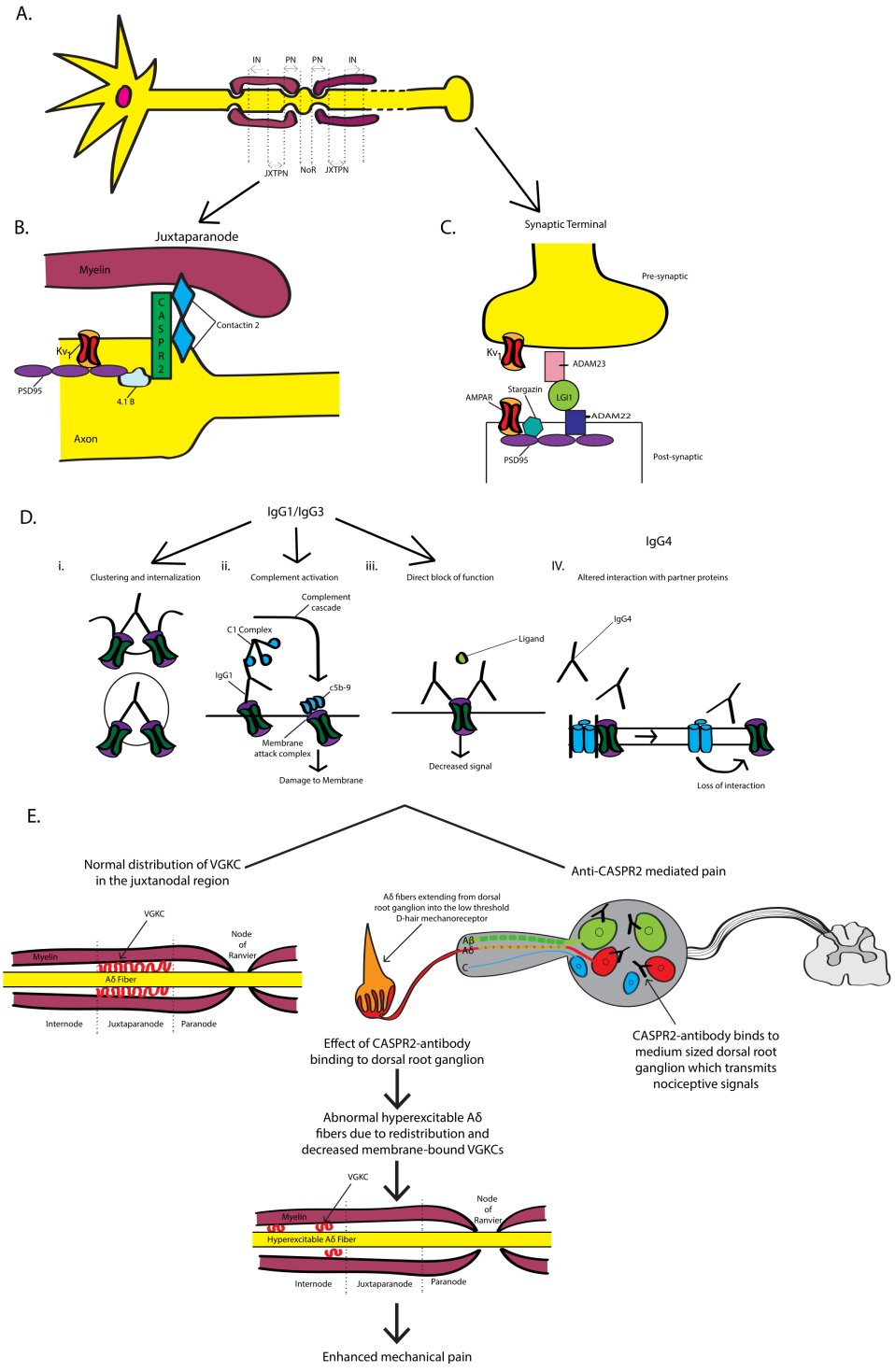


Figure 3: Schematic representation of CASPR2 and LGI1 localization at the juxta-paranode and synaptic cleft and their association with the voltage-gated potassium channel (A, B, and C). CASPR2 is a transmembrane protein which through its interaction with contactin-2 and other proteins, is responsible for the clustering of potassium channels (Kv1.1 and Kv1.2) at the juxta-paranodal region of the myelinated axons (A). Thus, CASPR2 maintains the axo-glial junction and through collaboration with Kv1 receptors, plays a prominent role in nerve repolarization. CASPR2 also prevents repetitive firing and hyperexcitability by maintaining internodal resting potential (B). LGI1 forms a trans-synaptic protein complex with pre-synaptic ADAM23, which is essential for localization of Kv1.1 and Kv1.2 subunits of VGKC, and post-synaptic ADAM22, which interacts with the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR). These interactions account for fast excitatory synaptic transmission (C).[1,4] Main pathogenic mechanisms of IgG1 and IgG3 antibodies vs IgG4 antibody (D).[4] The suggested mechanism of action of CASPR2 antibody-mediated pain (E).[10]

prevent the repolarization and termination of the neuronal action potential via a decrease in the number of functioning VGKCs and impaired voltage-gated outward potassium current (Figure 3A-3C).[1,4,5] The impulse generator in previous cases of PNH has been demonstrated to be either from the terminal arborizations of motor nerves, proximal portions of the motor nerve, or even the motoneuron, thus **potentially** explaining the presence of diffuse fasciculations in our case.[6]

Afterdischarges are defined as repetitive late potentials following initial compound muscle action potential after a stimulus. Due to the higher gain settings (100-200 μV/division), afterdischarges may be initially noted during F wave recording, however prolonged afterdischarges might obscure the appearance of F waves, as in our case (Figure 1A). As such, following the adjustment of gain settings, afterdischarges can be better visualized during motor nerve conduction studies (NCS) (Figure 1B). In one study, the sensitivity of motor NCS in spotting PNH was superior to clinical symptoms and needle EMG.[7]

In our case, with the exception of diffuse fasciculations and afterdischarges, no overt neuromyotonia or central nervous system involvement was identified to confirm previously described CASPR2/LGI1-associated Morvan's syndrome. This could be explained partly by the degree of PNH. During states of relatively low PNH, abnormal spontaneous discharges such as neuromyotonia might not be evident on resting needle EMG. However, induction of membrane hyperexcitability following electrical stimulation for motor NCS facilitates the sustained appearance of afterdischarges.[7] Moreover, a patient presenting with a syndrome consistent with GBS who developed LGI1-positive Morvan's syndrome late in their disease course has previously been described in the literature.[8] Unfortunately, our patient died soon after initial responsiveness to IVIg, which precluded the ability to observe his final clinical course.

### *Severe Neuropathic Pain*

Our case also **was consistent with** a previous finding of severe CASPR2 antibody-associated neuropathic pain. This phenomenon is mediated by the binding of CASPR2 antibodies to the soma of medium-sized dorsal root ganglion neurons resulting in decreased membrane-bound VGKC clustering, as well as their redistribution along internal segments, leading to lower thresholds for mechanical pain and hyperexcitable Aδ fibers (Figure 3E).[9] Additional evidence for a functional rather than structural effect of antibody mediated pain was provided by rapid relief of pain after treatment as well as a normal intraepidermal nerve fiber density in previously described cases of painful inflammatory neuropathy with autoantibodies against another paranodal target, contactin-associated protein 1.[10]

### *Dysautonomia*

The dysautonomia observed in GBS may manifest in the bowel as ileus. Additionally, features of dysautonomia independent of GBS have been described in 84% of patients with both CASPR2 and LGI1 antibodies.[1] Previous studies have demonstrated the presence of VGKCs in enteric neurons at every level of the gut. These findings provide pathological relevance to the severity of gastrointestinal neuromuscular dysmotility with anti-VGKC antibodies found in our case.[11] Gastrointestinal dysautonomia in our patient was evidenced by paralytic ileus, with abdominal imaging showing distended small and large bowel without obvious obstruction (Figure 2C, 2D). Persistent ileus ultimately contributed to the development of rising intrabdominal pressures and fatal abdominal compartment syndrome.[12]

Abdominal compartment syndrome is characterized by sustained intra-abdominal pressure in excess of 20 mmHg (most often measured indirectly via an intravesical catheter at end expiration in the supine position) in combination with new-onset organ dysfunction.[12] Common risk factors include intra-abdominal masses, bowel obstruction, aggressive fluid resuscitation, intraperitoneal bleeding, and third-space fluid shifts from conditions that increase capillary permeability. Abdominal compartment syndrome has been described in cases of severe ileus, similar to our patient.[12] An additional contributor to our patient's fulminant ileus was use of opioid pain medications, however ileus persisted even after these were discontinued, suggesting dysautonomia was at least in part contributing. Our case highlights the importance of recognizing the potentially fatal complication of abdominal compartment syndrome arising from dysautonomia. In similar clinical scenarios, early utilization of intravesical pressure measurement and consultation with critical care and surgical consultants may be useful.

### *Paraneoplastic Basis*

Lastly, the radiographic finding suspicious for RCC was of unproven clinical significance. **Although anywhere from 10-40% of patients with RCC are noted to have paraneoplastic syndromes, they are most often endocrine or neuroendocrine in nature. In one review of paraneoplastic syndromes associated with RCC including almost 300 journal articles, paraneoplastic syndromes with neurologic manifestations were only identified in 22 cases. Among these, a spectrum of neurological paraneoplastic syndromes were reported and include motor neuron disease, demyelinating polyneuropathies, and myopathies.[13] Identification**

**of paraneoplastic antibodies has been limited in these cases with the exception of a single case of GAD antibody positive paraneoplastic stiff person syndrome in a patient with RCC.[14] It therefore remains unknown whether or not the neurologic syndromes observed in these patients were immune-mediated or whether the antibodies simply have not yet been identified.** Although CASPR2 and LGI1 antibodies are not considered typical paraneoplastic antibodies, they have been described infrequently in solid organ tumors, and are posited to have mediated GBS in this patient with suspected RCC.[15] Screening for underlying malignancy in patients presenting with otherwise unexplained GBS may, therefore, be fruitful.

In summary, **recognizing its limitations,** the present case adds to a growing body of literature describing CASPR2/LGI1 as a biologically plausible autoimmune target in the pathogenesis of a GBS-like syndrome, but with multiple unique features including PNH, severe neuropathic pain, dysautonomia, IVIg responsiveness, and a possible association with RCC.

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**References**

1. Binks SNM, Klein CJ, Waters P, Pittock SJ, Irani SR. LGI1, CASPR2 and related antibodies: a molecular evolution of the phenotypes. *J Neurol Neurosurg Psychiatry* 2018;89(5):526-534. https://dx.doi.org/10.1136%2Fjnnp-2017-315720.

2. Rosch RE, Bamford A, Hacohen Y, Wraige E, Vincent A, Mewasingh L, et al. Guillain-Barré syndrome associated with CASPR2 antibodies: two paediatric cases. *J Peripher Nerv Syst* 2014;19(3):246-249. https://doi.org/10.1111/jns.12089.

3. Vendrami CL, Villavicencio CP, DeJulio TJ, Chatterjee A, Casalino DD, Horowitz JM, et al. Differentiation of solid renal tumors with multiparametric MR imaging. *Radiographics* 2017;37(7):2026-2042. https://doi.org/10.1148/rg.2017170039.

4. Vural A, Doppler K, Meinl E. Autoantibodies against the node of Ranvier in seropositive chronic inflammatory demyelinating polyneuropathy: diagnostic, pathogenic, and therapeutic relevance. *Front Immunol* 2018;9:1029. https://doi.org/10.3389/fimmu.2018.01029.

5. Giannoccaro MP, Wright SK, Vincent A. In vivo mechanisms of antibody-mediated neurological disorders: animal models and potential implications. *Front Neurol* 2020;10:1394. https://doi.org/10.3389/fneur.2019.01394.

6. Newsom-Davis J, Buckley C, Clover L, Hart I, Maddison P, Tüzüm E, et al. Autoimmune disorders of neuronal potassium channels. *Ann N Y Acad Sci* 2003;998:202-210. https://doi.org/10.1196/annals.1254.022.

7. Niu J, Guan H, Cui L, Guan Y, Liu M. Afterdischarges following M waves in patients with voltage-gated potassium channels antibodies. *Clin Neurophysiol Pract* 2017;2:72-75. https://doi.org/10.1016/j.cnp.2017.02.002.

8. Lotan I, Djaldetti R, Hellman MA, Benninger F. Atypical case of Morvan's syndrome. *J Clin Neurosci* 2016;25:132-134. https://doi.org/10.1016/j.jocn.2015.06.025.

9. Dawes JM, Weir GA, Middleton SJ, Patel R, Chisholm KI, Pettingill P, et al. Immune or genetic-mediated disruption of CASPR2 causes pain hypersensitivity due to enhanced primary afferent excitability. *Neuron* 2018;97(4):806–822. https://doi.org/10.1016/j.neuron.2018.01.033.

10. Doppler K, Appeltshauser L, Villmann C, Martin C, Peles E, Krämer HH, et al. Auto-antibodies to contactin-associated protein 1 (Caspr) in two patients with painful inflammatory neuropathy. *Brain* 2016;139(10):2617-2630. https://doi.org/10.1093/brain/aww189.

11. Hubball AW, Lang B, Souza MAN, Curran OD, Martin JE, Knowles CH. Voltage-gated potassium channel (K(v) 1) autoantibodies in patients with chagasic gut dysmotility and distribution of K(v) 1 channels in human enteric neuromusculature (autoantibodies in GI dysmotility). *Neurogastroenterol Motil* 2012;24(8):719-728. https://doi.org/10.1111/j.1365-2982.2012.01924.x

12. Van Noord BA, Roffey P, Thangathurai D. Abdominal compartment syndrome following opioid-induced postoperative ileus. *J Clin Anesth* 2013;25:146-149. https://doi.org/10.1016/j.jclinane.2012.07.004.

13. Yang I, Jaros J, Bega D. Paraneoplastic peripheral nervous system manifestations of renal cell carcinoma: A case report and review of the literature. *Case Rep Neurol* 2017;9(1): 22-30. https://doi.org/10.1159/000458435.

14. McHugh JC, Murray B, Renganathan R, Connolly S, Lynch T. GAD antibody positive paraneoplastic stiff person syndrome in a patient with renal cell carcinoma. *Mov Disord* 2007;22(9):1343-1346. https://doi.org/10.1002/mds.21374.

15. Tüzün E, Kinay D, Hacohen Y, Aysal F, Vincent A. Guillain-Barré-like syndrome associated with lung adenocarcinoma and CASPR2 antibodies. *Muscle Nerve* 2013;48(5):836-837. https://doi.org/10.1002/mus.23851.

# Beevor's Sign in Myotonic Dystrophy Type 1: Do we need to check in every neuromuscular patient?

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**Keywords:** *Beevor's sign, Myotonic dystrophy type 1, facioscapulohumeral dystrophy*

## Introduction

Beevor's sign, named after British neurologist Charles Edward Beevor (1854-1908), is characterized by upward deviation of the umbilicus upon attempted sitting from supine position, as a result of weakness of the rectus abdominis muscles (1–3). While commonly attributed to patients with spinal cord or root lesions between T10 and T12, in the first description of this finding, Dr Beevor also mentioned two cases in which the umbilicus deviated downwards due to weakness of the upper rectus abdominis muscles in the setting of an underlying myopathy in one of them (2). There are studies which have mentioned the association of Beevor's sign and facioscapulohumeral dystrophy (FSHD) with a sensitivity of 95% and specificity of 97% (4–6). In addition to FSHD and spinal cord and root lesions (7), several other disorders have been reported to be associated with Beevor's sign including myotonic dystrophy type 1 (5), late-onset Pompe's disease (5,8), GNE myopathy (9), sporadic inclusion body myositis (10), tubular aggregate myopathy (4), and amyotrophic lateral sclerosis (3,11). Here, we report a patient with myotonic dystrophy type 1 who showed a positive Beevor's sign when examined thoroughly.

## Case Report

A 30-year-old man presented with a 10-year history of difficulty in extending his fingers when trying to open a bottle cap. He noticed progressive weakness in the upper extremities followed which progressed to involve the lower limbs as well. He denied any respiratory, bulbar, or ocular complaints. No consanguinity was noted on family history. Past medical history was negative for any systemic disorders. He was not on any medications.

The patient's neurological examination revealed normal mental status. Cranial nerve examination was notable for bifacial weakness, bi-temporal wasting and atrophy, and neck flexor muscles weakness, graded 4/5. There was no winging of the scapula. Manual muscle examination showed bilateral $5^-/5$ weakness of deltoid, biceps, and triceps, wrist extension weakness of 4/5, First dorsal interosseous weakness of $5^-/5$, and flexor pollicis longus weakness of $4^-/5$. In the lower limbs, iliopsoas force was normal but bilateral quadriceps, tibialis anterior, and plantar flexion were weak with grades of 4/5, 3/5, and 4/5, respectively. There was percussion myotonia in extensor digitorum communis and abductor pollicis brevis muscles. Axial muscle examination showed a typical Beevor's sign (Figure 1).

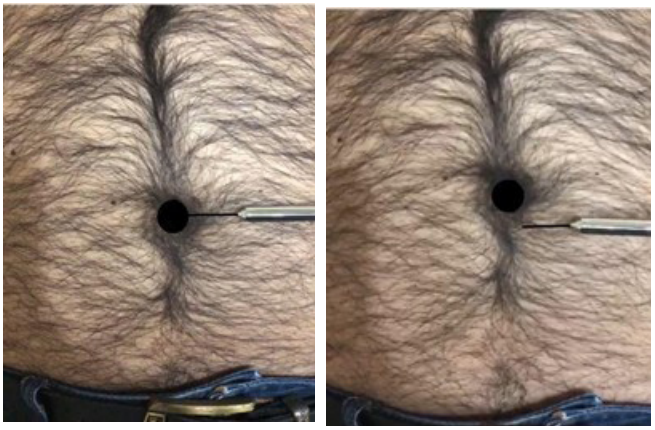

Figure 1. Part A (left): the patient is in the supine position with the handle of reflex hammer at the level of the umbilicus. Part B (right): the patient is asked to try to sit up with arms flexed and crossed over the chest and the umbilicus has moved upward from the fixed level of the handle of the reflex hammer (positive Beevor's sign).

Given the above constellation of signs and symptoms, electromyography was performed. We noted typical myotonic discharges in the first dorsal interosseous, biceps, tibialis anterior, and medial gastrocnemius muscles. The patient also underwent cardiology consultation with echocardiography. He was noted to have a normal ejection fraction without any structural or electrophysiologic abnormalities. Genetic testing was ordered to evaluate for CTG trinucleotide repeat expansion study in the DMPK gene. This test revealed pathologic CTG repeat expansion, confirming a diagnosis of myotonic dystrophy type 1. The patient has signed a consent for this case report.

## Discussion

Beevor's sign, after being initially observed in patients with spinal cord lesions, has been since reported in different neuromuscular disorders (table 1). Among all myopathies,

FSHD is most commonly associated with Beevor's sign. Although in two studies, Beevor's sign has been reported with high sensitivity for FSHD (4) (6), in another study with both typical and atypical phenotypes of genetically proven FSHD patients despite the high specificity of 97%, the overall sensitivity in combined group of typical and atypical FSHD patients for this sign was 54% which could be explained by a significant numbers of the atypical cases of FSHD in this study (5). The sensitivity for typical cases was 85% and for atypical group was 27% (5). In addition, investigating Beevor's sign in a wide range of 65 neuromuscular patients with myopathies other than FSHD revealed that only 2 (1 with myotonic dystrophy type 1 and 1 with Pompe's disease) showed positive Beevor's sign, however only 2 patients with myotonic dystrophy type 1 and 2 patients with Pompe's disease were included in the cohort (5).

In another study with 17 genetically confirmed cases of GNE myopathy, the investigators reported positive Beevor's sign in 15 cases (88.2%) proposing this sign as a clinical indicator for GNE myopathy (9). Although the researchers did not observe Beevor's sign in 10 Miyoshi myopathy and 5 myotonic dystrophy patients, the type of myotonic dystrophy was not specified (9). Sporadic inclusion body myositis also has been reported to be associated with positive Beevor's sign after developing abdominal wall muscle weakness and abdominal protrusion (10). Looking at our case of positive Beevor's sign in a patient with myotonic dystrophy type 1 in addition to the presence of this sign in a wide range of neuromuscular disorders persuades us to propose the investigation of Beevor's sign as part of the routine neuromuscular examination. Looking for this old clinical sign in patients with a broader spectrum of neuromuscular disorders may help clarify the true sensitivity and specificity of Beevor's sign for distinct diagnosis.

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**References**

1. McCarter SJ, Burkholder DB, Klaas JP, Boes CJ. Charles E. Beevor's lasting contributions to neurology. Neurology. 2018;90(11):513–7. DOI: 10.1212/WNL.0000000000005127

2. Tashiro K. Charles Edward Beevor (1854-1908). J Neurol. 2001;248(7):635–6. DOI: 10.1007/s004150170149

3. Pearce JM. Beevor's sign [Internet]. Vol. 53, European neurology. 2005. p. 208–9. Available from: http://dx.doi.org/10.1159/000086731

4. Shahrizaila N, Wills AJ. Significance of Beevor's sign in facioscapulohumeral dystrophy and other neuromuscular diseases. J Neurol Neurosurg Psychiatry. 2005;76(6):869–70. DOI: 10.1136/jnnp.2004.052019

5. Eger K, Jordan B, Habermann S, Zierz S. Beevor's sign in facioscapulohumeral muscular dystrophy: an old sign with new implications [Internet]. Vol. 257, Journal of

Table 1. Summary of studies investigating Beevor's sign in different neuromuscular disorders

| Author-year | The disorders which investigated for Beevor's sign | Beevor's sign positivity |
|---|---|---|
| Awerbuch et al – 1990 (6) | 30 FSHD patients and 40 other neuromuscular disorders | In 27/30 FSHD but 0/40 of the other neuromuscular disorders |
| Shahrizaila et al – 2005 (4) | 20 FSHD, 28 with other neuromuscular disorders, and 20 neurological patients without muscle disease | In 19/20 FSHD, in 2/28 with other neuromuscular disorders, and 0/20 with neurological controls |
| Leon-Sarmiento et al – 2007 (7) | A case of spinal cord infarction presenting with Beevor's sign | NA |
| Eger et al – 2010 (5) | 28 patients with FSHD and 65 patients with other neuromuscular diseases | In 15/28 FSHD patients but 2/65 in other neuromuscular patients. |
| Sugie et al – 2015 (10) | A case of sporadic inclusion body myositis presenting with Beevor's sign | NA |
| Matteo Garibaldi et al – 2016 (8) | A case of late onset Pompe disease presenting with Beevor's sign | NA |
| Preethish-Kumar et al – 2016 (9) | 17 GNE myopathy patients | In 15/17 GNE patients |

NA: not applicable

Neurology. 2010. p. 436–8. Available from: http://dx.doi.org/10.1007/s00415-009-5342-9

6. Awerbuch GI, Nigro MA, Wishnow R. Beevor's Sign and Facioscapulohumeral Dystrophy. Arch Neurol. 1990;47(11):1208–9. doi: 10.1001/archneur.1990.00530110066018.

7. Leon-Sarmiento FE, Bayona EA, Bayona-Prieto J. A sudden beevor's sign. Clinical Medicine and Research. 2007;5(2):121–2. DOI: 10.3121/cmr.2007.746

8. Garibaldi M, Diaz-Manera J, Gallardo E, Antonini G. Teaching Video Neuro Images: The Beevor sign in late-onset Pompe disease. Neurology. 2016;86(24):e250–1. DOI: 10.1212/WNL.0000000000002772

9. Preethish-Kumar V, Pogoryelova O, Polavarapu K, Gayathri N, Seena V, Hudson J, et al. Beevor's sign: a potential clinical marker for GNE myopathy. Eur J Neurol. 2016;23(8):e46–8. DOI: 10.1111/ene.13041

10. Sugie K, Kumazawa A, Ueno S. Sporadic inclusion body myositis presenting with beevor's sign. Intern Med. 2015;54(21):2793–4. doi: 10.2169/internalmedicine.54.5002.

11. Desai JD. Beevor's sign. Ann Indian Acad Neurol. 2012;15(2):94–5.

# Sleep disorders in Amyotrophic Lateral Sclerosis

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**Keywords:** *Amyotrophic lateral sclerosis, ALS, sleep, sleep-disordered breathing, sleep quality of life*

## ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder affecting both the central and peripheral nervous system. The median survival rate for ALS patients after symptom onset is 2.5 to 3.5 years and after diagnosis of ALS is about 1.5 to 2.5 years. Patients with ALS can have a wide spectrum of sleep disorders including but not limited to insomnia, sleep related breathing disorders, parasomnias, obstructive sleep apnea (OSA) and nocturnal hypoventilation (NH). Sleep-related breathing disorders substantially increase both morbidity and mortality in ALS patients. In this review, we have discussed the ALS motor symptoms, sleep-related breathing disorders, behavioral abnormalities and sleep disturbing factors which impair the health-related quality of life.

## Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder which affects both central and peripheral nervous system and often leads to loss of both upper and lower motor neurons (1-3). Symptoms of upper motor neuron involvement include spastic paresis, increased muscle tone and pseudobulbar palsy when corticobulbar tract is involved. Involvement of lower motor neurons leads to atrophy, fasciculations and muscle weakness. Eventually, all skeletal muscles along with extraocular and sphincter externi muscles may get involved in the later stage of the disease. (2, 4).

Spinal-onset ALS subtype results from gradual loss of anterior horn cells which supply the muscles of the trunk and limbs. Bulbar-onset ALS subtype results in dysphagia and dysarthria during the course of the disease (3, 5). The lifetime risk for ALS for men is about 1:300 and about 1:400 for women. (6, 7). Prevalence rate of ALS is about 5-8/100,000 with peak age of onset being 50-70 years. (1, 8, 9).

The median survival rate for ALS patients is about 2.5 to 3.5 years after symptom onset and 1.5 to 2.5 years after diagnosis of ALS (1, 10, 11). Although there is extensive literature available highlighting the genetic role in familial subtypes and molecular pathology of ALS, there is no definite therapy developed till this date. (12).

Riluzole and edaravone are the only two Food and Drug Administration (FDA) approved drugs for management of ALS patients. These medications have disease modifying effects rather than halting the progression of the disease (13, 14). The muscle weakness in ALS eventually leads to swallow dysfunction, dysarthria, chronic hypercapnic respiratory failure and tetraplegia. Chronic respiratory failure and respiratory infections are the most common cause of premature death in ALS patients (1, 2).

ALS not only affects the activities of daily living but also the health-related quality of life for both the patients and caregivers. The impairment of sleep quality in ALS patients significantly affects the physical and mental well-being of the patients (1, 15-17). A holistic multidisciplinary approach is warranted to address disease manifestations (18).

## Methods

### *Search Strategy and Selection Criteria*

We searched Medline, Google Scholar, and PubMed using keywords; "Amyotrophic Lateral Sclerosis", "Sleep disorders", "Breathing disorder", Motor disorders". Search was limited to English language manuscript only. We identified 60 research literature describing sleep related complications of ALS. In this review, we have described the sleep-related breathing disorders, behavioral abnormalities and sleep disturbing factors which impair the health-related quality of life of ALS patients.

### *Insomnia*

Insomnia is a frequently encountered sleep disorder in ALS patients (19). Sleep disruptions in ALS are caused by various factors which are discussed in table 1 (20).

Sleep is usually non-restorative which impacts both the daytime performance and motor symptoms. Breathing disorder along with muscle cramps, pain and restless leg syndrome (RLS) significantly impair the ability to fall asleep or maintain sleep in patients with ALS. Immobilization impairs the sleep quality. Insomnia might not only be due to the physical symptoms but also because of depression (existential fear) (2, 19, 21, 22).

Figure 1 describes factors disrupting sleep in patients with ALS.

### *Sleep and Motor Symptoms of ALS*

Motor symptoms of ALS including muscle cramps, fasciculations, RLS and immobilization impairs the sleep

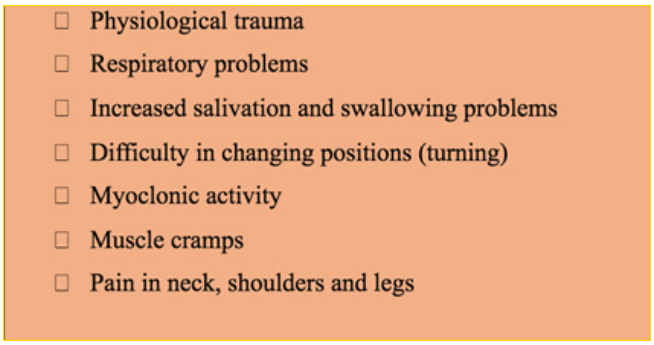


Figure 1. Most common sleep disrupting factors in amyotrophic lateral sclerosis (ALS) (20)

quality. Swallowing impairment along with sialorrhea and aspiration increases the risk of recurrent choking (1). Muscle fasciculations are caused by lower motor neuron degeneration and may cause sleep disturbance in ALS patients (23).

Muscle cramps commonly affect lower limbs and are often worse at night. Cramps have a prevalence of 45-92% (24, 25). Muscle cramps are often due to spontaneous discharges with higher frequency (> 300 Hz), than essential for voluntary contraction. Though stretching relieves the cramps, it may not be feasible in patients with ALS secondary to substantial leg weakness (2, 26). Management includes symptomatic treatment with adequate fluid intake, correction of electrolyte imbalance and discontinuation of any contributing medications (statins). In a randomized control trial, Mexiletine 150 mg twice daily was reported to be helpful in relieving muscle cramps in patients with ALS (1, 27). Baclofen and other compounds such as Vitamin-E, memantine and L-threonine have not shown any beneficial effects for management of cramps in ALS patients (28). Quinidine has been reported to decrease cramp intensity and frequency, however, given broad side effect profile (cinchonism, thrombocytopenia and myocardial toxicity), extended usage should be considered cautiously (2, 29).

Worsening motor functions can lead to immobilization (difficulty in changing positions) which often causes pain, nocturnal discomfort, risk for skin lesions and increases dependency on caregivers. Although there is sparse literature on effects of immobilization, it is still considered one of the factors that impairs sleep quality in patients with ALS (16, 30).

Diagnostic criteria of RLS includes; an urge to move the legs (unpleasant or painful sensation in legs), onset of symptoms and their exacerbation at rest or during inactivity, worsening of symptoms at night or evening and relief by stretching or walking, and none of other medical or behavioral conditions to explain the symptoms. Prevalence of RLS is about 10% in the general population, and women are affected more frequently than men (2, 31). The prevalence of RLS in ALS patients is about 14.6% - 25% (32). Small fiber neuropathy and mild sensory neuropathy have been reported in ALS which contributes to the development of RLS like symptoms in these patients (1, 33). Management strategies include iron supplementation (in iron deficiency), dopaminergic agents, α2δ ligands and opioids (for chronic pain) (34).

Periodic limb movements (PLM) in sleep are seldom investigated in ALS patients. Studies on PLM prevalence and its impact on sleep are limited. In ALS patients, PLM is caused by the spinal cord disinhibition through the degeneration of the descending central pathways (35, 36). PLM index is often elevated in many of ALS patients but is not associated with the arousals from the sleep (37).

### *Nocturnal Pain in ALS*

Pain and sleep quality are interrelated as pain disrupts sleep and disrupted sleep often enhances the occurrence and worsens pain (38). Nocturnal pain in ALS patients arises from immobilization and difficulty to change position in bed. Spasticity or intermittent muscle cramps contribute to pain. Muscle atrophy also increases the pressure load on both bones and joints. ALS patients may suffer from neuropathic pain, often due to small fiber neuropathy which is seen in almost 75% of the ALS patient population. Other ALS patients may suffer from diffuse pain, without any triggers, non-neuropathic, possibly due to central sensitization of the nociceptive pathways (1, 33).

Nocturnal pain is rarely examined in clinical studies. Nociceptive pain treatment should include preventive strategy, non-steroidal anti-inflammatory agents. Opioids should be reserved for refractory pain. Cannabis is often prescribed to ALS patients for its anxiolytic, sedating and appetite-enhancing actions. α2δ ligands and antidepressants should be considered for neuropathic pain. Central muscle relaxants can be used for spasticity. ALS patients often report pain, which disrupts sleep, hence, chronic pain should be addressed appropriately through symptomatic therapy to improve the quality of life (1, 39).

### *Sleep-related Breathing Disorders in ALS*

Sleep-related breathing disorders in ALS patients includes obstructive sleep apnea (OSA) and nocturnal hypoventilation (NH). Signs and symptoms of the respiratory system involvement in ALS are described below in table 2. OSA is more prevalent in males and often presents with non-bulbar or spinal onset of symptoms. In bulbar-onset ALS, atrophy of tongue hinders pharyngeal collapse and hence OSA is seen less often than in spinal-onset ALS. Shorter survival rates are seen in ALS patients with OSA

before initiation of ventilator therapy (40). Respiratory muscle weakness may contribute to disease progression (37, 41-42).

Sleep-related hypoventilation is caused by phrenic nerve degeneration and diaphragmatic weakness which leads to a rise in carbon dioxide during rapid eye movement (REM) sleep (44). As the disease progresses, hypercapnia can be seen in non-REM sleep. ALS patients with chronic hypercapnic respiratory failure may have diurnal hypercapnia. Clinical features suggesting hypercapnia includes; morning headache, daytime sleepiness, sleep disruption and dyspnea at rest or exertion, during sleep. In late stages of the disease, patients may adopt sitting positions to avoid orthopnea because of diaphragm weakness. Multiple factors including hypopneas, apneas and diminished gas exchange contribute to decrease in sleep efficiency, reduction of REM sleep, increased arousals from sleep and frequent changes in sleep stages (1, 37, 45, 46).

Nocturnal hypoventilation can be detected by pulse oximetry and transcutaneous capnometry. (1, 45, 47). Transcutaneous capnometry is superior to pulse oximeters in identifying nocturnal hypercapnia and is widely used in diagnosing nocturnal hypoventilation, and introduction of non-invasive ventilation. Factors that predict disease progression and survival are respiratory muscle strength measurements including; maximum inspiratory pressure (MIP), forced vital capacity (FVC), and sniff nasal inspiratory pressure (SNIP). SNIP plays an important role in predicting nocturnal hypoventilation and NIV initiation; FVC and MIP are also monitored regularly in neuromuscular patients for NIV initiation (1, 48, 49).

A study by Ackrivo et. al describing prognosticating factors for development of respiratory insufficiency in patients with ALS, reported longer diagnostic delay, advanced age at diagnosis, bulbar onset of symptoms, lower FVC, low body mass index and low dyspnea subscore or ALS functional rating scale (ALSFRS-R) were associated with development of respiratory failure (50). Another study reported nocturnal oxygen desaturations were associated with development of respiratory failure and worse prognosis (51).

Multiple retrospective studies and randomized trials have validated that early initiation of NIV increases the survival rate in ALS patients (1, 11, 52-55). Long-term usage of NIV enhances both the sleep quality and quality of life, though ventilator dependency increases over time in such patients (1, 56,57).

Treatment adherence is achieved through ideal mask fitting and selection (oronasal masks for mouth leaks),

| Symptoms | Signs |
|---|---|
| Orthopnea<br>Dyspnea with exertion<br>Dyspnea<br>Paroxysmal nocturnal dyspnea<br>Poor sleep<br>Morning headache<br>Daytime somnolence<br>Cognitive change and dysfunction<br>Softer speech<br>Poor cough<br>Difficulty swallowing | Tachypnea<br>Paradoxic abdominal movement<br>Weight loss<br>Use of accessory repsiratory muscles<br>Pooling of secretions<br>Increased work of breathing at rest<br>Decreased chest movement |

Figure 2. Most commonly reported signs and symptoms of respiratory system involvement in ALS (40, 41).

appropriate titration of respiratory settings, and education of both patients and caregivers. Bulbar-onset ALS with upper motor neuron dysfunction has shown reduced respiratory drive and intermittent glottis closure making NIV ineffective (58, 59).

Volume support ventilation may be helpful with gas exchange and symptom relief. However, it may enhance patient-ventilator dyssynchrony. This can present as flow dyssynchrony, auto-triggering or ineffective triggering. Management strategies include clearance of secretions by manual assisted coughing or mechanical cough assistance (1, 63). A follow up Polysomnography and capnometry should be considered for patients with ALS (1, 60-62). [1]

Figure 2 describes signs and symptoms of respiratory system involvement in ALS.

*Sleep-related Behavioral Abnormalities*

Sleep-related behavioral abnormalities or parasomnias are movements, behaviors, emotions and/ or perceptions which arise on falling asleep, during sleep or waking up. Parasomnias are defined by partial arousals from either REM or NREM sleep (64). There is no strong evidence that NREM parasomnias like confusional arousals or pavor nocturnus and sleepwalking occur in ALS patients. REM behavioral disorder (RBD), is distinguished by either persistent phasic or tonic muscle activation in REM sleep, which is detectable by electromyogram (EMG) and is called REM sleep without atonia (65).

Patients often act out RBD like dream-enacting vocalizations and movements which might cause falls, injuries and aggressive actions on bed partners. RBD are more commonly associated with neurodegenerative disorders like dementia with Lewy bodies, Parkinson's disease, multisystem atrophy and synucleinopathies. Management of RBD in ALS patients primarily involves injury preventive strategies and reduction in the number of RBD events in sleep. Pharmacological interventions

including melatonin (3-12 mg) or clonazepam (0.25-2 mg) at bedtime may be beneficial, however, the supporting data is sparse (1, 64-68).

Further clinical studies are required to better understand the pathophysiological and clinical role of REM sleep regulatory pathway neurodegeneration in patients with ALS, RBD or REM sleep without atonia (1, 36).

## Conclusion

Sleep disturbances are a frequent cause of increased morbidity in ALS patients. Notable contributory factors including immobilization, sleep-disordered breathing, RLS, muscle cramps, nutritional issues, loss of communication and gradual motor function impairment are associated with increased disease burden on both patients and caregivers. Sleep-related breathing disorders substantially increase both morbidity and mortality in ALS patients. Clinicians should take a thorough history of not only sleep disrupting symptoms but also of depression, fear, despair and grief and these should be addressed accordingly. Future studies are required to undermine the relation between the sleep symptoms and neuronal structural changes in ALS. Further research is warranted to distinguish the effect of sleep on disease progression, prognosis and quality of life (1, 2, 22, 41, 69).

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## References

1. Boentert M. Sleep and Sleep Disruption in Amyotrophic Lateral Sclerosis. Curr Neurol Neurosci Rep. 2020;20(7):25-.

2. Boentert MJN, sleep so. Sleep disturbances in patients with amyotrophic lateral sclerosis: current perspectives. 2019;11:97.

3. Hardiman O, Al-Chalabi A, Chio AJAlsNRDP. Corr eM, Logroscino G, Robberecht w, Shaw PJ, Simmons Z, van den Berg LH. 2017;3.

4. Carvalho M, Schwartz M, Swash MJM, Medicine NOJotAAoE. Involvement of the external anal sphincter in amyotrophick lateral sclerosis. 1995;18(8):848-53.

5. Grad LI, Rouleau GA, Ravits J, Cashman NRJCSHpim. Clinical spectrum of amyotrophic lateral sclerosis (ALS). 2017;7(8):a024117.

6. Alonso A, Logroscino G, Jick SS, Hernán MAJEjon. Incidence and lifetime risk of motor neuron disease in the United Kingdom: a population-based study. 2009;16(6):745-51.

7. Chiò A, Mora G, Calvo A, Mazzini L, Bottacchi E, Mutani RJN. Epidemiology of ALS in Italy: a 10-year prospective population-based study. 2009;72(8):725-31.

8. Kab S, Moisan F, Preux PM, Marin B, Elbaz A. Nationwide incidence of motor neuron disease using the French health insurance information system database. Amyotrophic lateral sclerosis & frontotemporal degeneration. 2017;18(5-6):426-33.

9. Nakken O, Lindstrøm JC, Tysnes O-B, Holmøy T. Assessing amyotrophic lateral sclerosis prevalence in Norway from 2009 to 2015 from compulsory nationwide health registers. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2018;19(3-4):303-10.

10. Calvo A, Moglia C, Lunetta C, Marinou K, Ticozzi N, Ferrante GD, et al. Factors predicting survival in ALS: a multicenter Italian study. 2017;264(1):54-63.

11. Zoccolella S, Beghi E, Palagano G, Fraddosio A, Guerra V, Samarelli V, et al. Analysis of survival and prognostic factors in amyotrophic lateral sclerosis: a population based study. 2008;79(1):33-7.

12. Foster LA, Salajegheh MKJTAjom. Motor neuron disease: pathophysiology, diagnosis, and management. 2019;132(1):32-7.

13. Group II RS, Lacomblez L, Bensimon G, Meininger V, Leigh P, Guillet PJTL. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. 1996;347(9013):1425-31.

14. Takei K, Takahashi F, Liu S, Tsuda K, Palumbo J. Post-hoc analysis of randomised, placebo-controlled, double-blind study (MCI186-19) of edaravone (MCI-186) in amyotrophic lateral sclerosis. Amyotrophic lateral sclerosis & frontotemporal degeneration. 2017;18(sup1):49-54.

15. Burke T, Galvin M, Pinto-Grau M, Lonergan K, Madden C, Mays I, et al. Caregivers of patients with amyotrophic lateral sclerosis: investigating quality of life, caregiver burden, service engagement, and patient survival. 2017;264(5):898-904.

16. Diaz-Abad M, Buczyner JR, Venza BR, Scharf SM, Kwan JY, Lubinski B, et al. Poor sleep quality in patients with amyotrophic lateral sclerosis at the time of diagnosis. 2018;20(2):60-8.

17. Lo Coco D, La Bella VJEjon. Fatigue, sleep, and nocturnal complaints in patients with amyotrophic lateral sclerosis. 2012;19(5):760-3.

18. Diagnosis ETFo, Sclerosis: MoAL, Andersen PM, Abrahams S, Borasio GD, de Carvalho M, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)–revised report of an EFNS task force. 2012;19(3):360-75.

19. Panda S, Gourie-Devi M, Sharma AJNI. Sleep disorders in amyotrophic lateral sclerosis: A questionnaire-

based study from India. 2018;66(3):700.

20. Hetta J, Jansson I. Sleep in patients with amyotrophic lateral sclerosis. Journal of neurology. 1997;244(4 Suppl 1):S7-9.

21. Günther R, Richter N, Sauerbier A, Chaudhuri KR, Martinez-Martin P, Storch A, et al. Non-motor symptoms in patients suffering from motor neuron diseases. 2016;7:117.

22. Skapinakis P, Rai D, Anagnostopoulos F, Harrison S, Araya R, Lewis GJPM. Sleep disturbances and depressive symptoms: an investigation of their longitudinal association in a representative sample of the UK general population. 2013;43(2):329-39.

23. Montagna P, Liguori R, Zucconi M, Lugaresi A, Cirignotta F, Lugaresi E. Fasciculations during wakefulness and sleep. Acta neurologica Scandinavica. 1987;76(2):152-4.

24. Lo Coco D, Mattaliano P, Spataro R, Mattaliano A, La Bella V. Sleep-wake disturbances in patients with amyotrophic lateral sclerosis. Journal of neurology, neurosurgery, and psychiatry. 2011;82(8):839-42.

25. Stephens HE, Joyce NC, Oskarsson BJALS, Degeneration F. National study of muscle cramps in ALS in the USA. 2017;18(1-2):32-6.

26. Caress JB, Ciarlone SL, Sullivan EA, Griffin LP, Cartwright MSJM, nerve. Natural history of muscle cramps in amyotrophic lateral sclerosis. 2016;53(4):513-7.

27. Oskarsson B, Moore D, Mozaffar T, Ravits J, Wiedau-Pazos M, Parziale N, et al. Mexiletine for muscle cramps in amyotrophic lateral sclerosis: A randomized, double-blind crossover trial. 2018;58(1):42-8.

28. Baldinger R, Katzberg HD, Weber M. Treatment for cramps in amyotrophic lateral sclerosis/motor neuron disease. The Cochrane database of systematic reviews. 2012(4):Cd004157.

29. Hogan DBJC. Quinine: not a safe drug for treating nocturnal leg cramps. 2015;187(4):237-8.

30. Hayashi T, Narita Y, Okugawa N, Hamaguchi E, Shibahara M, Kuzuhara SJALS. Pressure ulcers in ALS patients on admission at a university hospital in Japan. 2007;8(5):310-3.

31. Högl B, Kiechl S, Willeit J, Saletu M, Frauscher B, Seppi K, et al. Restless legs syndrome: a community-based study of prevalence, severity, and risk factors. 2005;64(11):1920-4.

32. Lo Coco D, Piccoli F, La Bella V. Restless legs syndrome in patients with amyotrophic lateral sclerosis. Movement disorders : official journal of the Movement Disorder Society. 2010;25(15):2658-61.

33. Dalla Bella E, Lombardi R, Porretta-Serapiglia C, Ciano C, Gellera C, Pensato V, et al. Amyotrophic lateral sclerosis causes small fiber pathology. 2016;23(2):416-20.

34. Garcia-Borreguero D, Silber MH, Winkelman JW, Högl B, Bainbridge J, Buchfuhrer M, et al. Guidelines for the first-line treatment of restless legs syndrome/Willis–Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. 2016;21:1-11.

35. Bara-Jimenez W, Aksu M, Graham B, Sato S, Hallett MJN. Periodic limb movements in sleep: state-dependent excitability of the spinal flexor reflex. 2000;54(8):1609-16.

36. Lo Coco D, Puligheddu M, Mattaliano P, Congiu P, Borghero G, Fantini ML, et al. REM sleep behavior disorder and periodic leg movements during sleep in ALS. Acta neurologica Scandinavica. 2017;135(2):219-24.

37. Boentert M, Glatz C, Helmle C, Okegwo A, Young PJJoN, Neurosurgery, Psychiatry. Prevalence of sleep apnoea and capnographic detection of nocturnal hypoventilation in amyotrophic lateral sclerosis. 2018;89(4):418-24.

38. Cheatle MD, Foster S, Pinkett A, Lesneski M, Qu D, Dhingra L. Assessing and Managing Sleep Disturbance in Patients with Chronic Pain. Anesthesiology clinics. 2016;34(2):379-93.

39. Ganzini L, Silveira MJ, Johnston WSJJop, management s. Predictors and correlates of interest in assisted suicide in the final month of life among ALS patients in Oregon and Washington. 2002;24(3):312-7.

40. Dorst J, Ludolph AC. Non-invasive ventilation in amyotrophic lateral sclerosis. *Ther Adv Neurol Disord*. 2019;12:1756286419857040. Published 2019 Jun 21. doi:10.1177/1756286419857040

41. Ahmed RM, Newcombe RE, Piper AJ, Lewis SJ, Yee BJ, Kiernan MC, et al. Sleep disorders and respiratory function in amyotrophic lateral sclerosis. 2016;26:33-42.

42. Braun AT, Caballero-Eraso C, Lechtzin NJCicm. Amyotrophic lateral sclerosis and the respiratory system. 2018;39(2):391-400.

43. Quaranta VN, Carratu P, Damiani MF, Dragonieri S, Capozzolo A, Cassano A, et al. The prognostic role of obstructive sleep apnea at the onset of amyotrophic lateral sclerosis. 2017;17(1):14-21.

44. Berger KI, Rapoport DM, Ayappa I, Goldring RMJSMC. Pathophysiology of hypoventilation during sleep. 2014;9(3):289-300.

45. Boentert M, Brenscheidt I, Glatz C, Young PJJon. Effects of non-invasive ventilation on objective sleep and nocturnal respiration in patients with amyotrophic lateral sclerosis. 2015;262(9):2073-82.

46. Vrijsen B, Buyse B, Belge C, Robberecht W, Van Damme P, Decramer M, et al. Noninvasive ventilation improves sleep in amyotrophic lateral sclerosis: a

prospective polysomnographic study. 2015;11(5):559-66.

47. Ogna A, Salva M-AQ, Prigent H, Mroue G, Vaugier I, Annane D, et al. Nocturnal hypoventilation in neuromuscular disease: prevalence according to different definitions issued from the literature. 2016;20(2):575-81.

48. Carratù P, Cassano A, Gadaleta F, Tedone M, Dongiovanni S, Fanfulla F, et al. Association between low sniff nasal-inspiratory pressure (SNIP) and sleep disordered breathing in amyotrophic lateral sclerosis: preliminary results. 2011;12(6):458-63.

49. Tilanus T, Groothuis J, TenBroek-Pastoor J, Feuth T, Heijdra Y, Slenders J, et al. The predictive value of respiratory function tests for non-invasive ventilation in amyotrophic lateral sclerosis. 2017;18(1):144.

50. Ackrivo J, Hansen-Flaschen J, Wileyto EP, Schwab RJ, Elman L, Kawut SMJERJ. Development of a prognostic model of respiratory insufficiency or death in amyotrophic lateral sclerosis. 2019;53(4).

51. Bote SM, Martinez NP, Amarilla CE, Ugalde PF, Gonzalez-Bermejo J, Collado NF, et al. Overnight pulse oximetry to determine prognostic factors in subjects with amyotrophic lateral sclerosis. 2020.

52. Bertella E, Banfi P, Paneroni M, Grilli S, Bianchi L, Volpato E, et al. Early initiation of night-time NIV in an outpatient setting: a randomized non-inferiority study in ALS patients. 2017;53(6):892-9.

53. Burkhardt C, Neuwirth C, Sommacal A, Andersen PM, Weber MJPO. Is survival improved by the use of NIV and PEG in amyotrophic lateral sclerosis (ALS)? A post-mortem study of 80 ALS patients. 2017;12(5):e0177555.

54. Elamin EM, Wilson CS, Sriaroon C, Crudup B, Pothen S, Kang YC, et al. Effects of early introduction of non-invasive positive pressure ventilation based on forced vital capacity rate of change: Variation across amyotrophic lateral sclerosis clinical phenotypes. 2019;73(1):e13257.

55. Sivori M, Rodriguez GE, Pascansky D, Saenz C, Sica REJM-BA-. Outcome of sporadic amyotrophic lateral sclerosis treated with non-invasive ventilation and riluzole. 2007;67(4):326.

56. Vandoorne E, Vrijsen B, Belge C, Testelmans D, Buyse BJACB. Noninvasive ventilation in amyotrophic lateral sclerosis: effects on sleep quality and quality of life. 2016;71(6):389-94.

57. Vitacca M, Montini A, Lunetta C, Banfi P, Bertella E, De Mattia E, et al. Impact of an early respiratory care programme with non-invasive ventilation adaptation in patients with amyotrophic lateral sclerosis. 2018;25(3):556-e33.

58. Sancho J, Burés E, Ferrer S, Ferrando A, Bañuls P, Servera EJEor. Unstable control of breathing can lead to ineffective noninvasive ventilation in amyotrophic lateral sclerosis. 2019;5(3).

59. Teschler H, Stampa J, Ragette R, Konietzko N, Berthon-Jones MJERJ. Effect of mouth leak on effectiveness of nasal bilevel ventilatory assistance and sleep architecture. 1999;14(6):1251-7.

60. Georges M, Attali V, Golmard JL, Morélot-Panzini C, Crevier-Buchman L, Collet J-M, et al. Reduced survival in patients with ALS with upper airway obstructive events on non-invasive ventilation. 2016;87(10):1045-50.

61. Ogna A, Nardi J, Prigent H, Quera Salva M-A, Chaffaut C, Lamothe L, et al. Prognostic value of initial assessment of residual hypoventilation using nocturnal capnography in mechanically ventilated neuromuscular patients: a 5-Year follow-up study. 2016;3:40.

62. Sancho J, Servera E, Morelot-Panzini C, Salachas F, Similowski T, Gonzalez-Bermejo JJALS, et al. Non-invasive ventilation effectiveness and the effect of ventilatory mode on survival in ALS patients. 2014;15(1-2):55-61.

63. Vitacca M, Paneroni M, Trainini D, Bianchi L, Assoni G, Saleri M, et al. At home and on demand mechanical cough assistance program for patients with amyotrophic lateral sclerosis. 2010;89(5):401-6.

64. American Academy of Sleep Medicine %J Westchester IAAoSM. International Classification of Sleep Disorders—Third Edition (ICSD-3) Online Version. 2014.

65. Luppi PH, Clément O, Sapin E, Gervasoni D, Peyron C, Léger L, et al. The neuronal network responsible for paradoxical sleep and its dysfunctions causing narcolepsy and rapid eye movement (REM) behavior disorder. Sleep medicine reviews. 2011;15(3):153-63.

66. Boeve B, Silber M, Ferman T, Lin S-C, Benarroch E, Schmeichel A, et al. Clinicopathologic Correlations in 172 Cases of REM Sleep Behavior Disorder±a Coexisting Neurologic Disorder (PL01. 003). AAN Enterprises; 2013.

67. Iranzo A, Fernández-Arcos A, Tolosa E, Serradell M, Molinuevo JL, Valldeoriola F, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. 2014;9(2):e89741.

68. Jung Y, Louis EKSJCtoin. Treatment of REM sleep behavior disorder. 2016;18(11):50.

69. Congiu P, Mariani S, Milioli G, Parrino L, Tamburrino L, Borghero G, et al. Sleep cardiac dysautonomia and EEG oscillations in amyotrophic lateral sclerosis. 2019;42(11):zsz164.

# Hamilton Awakening

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What's that in the future? Someone call my name? Did someone call my name? Hello?
Out of the depths I hear I heard there's a stir, good sir good Samaritan.
Calling out to me calling out to us. Did they remember? Did they realize?
I tried I tried, while down there to finalize.
The plans the paragraphs, the pettiness of political puffed up partisan pompousness.
I ran, I supported, I saw the future. The possibility of a future a time a place where we are all kings and queens.
I learned how to live, and not die, and my wings, they were energized.
Where did the pulse come, from where did the fire gets its spark?
Deep, deep, deep in the Caribbean, when I was dropped as a drop in the middle of the delving depths.
There was one, there was deux, trois, quatre, cinq, six, et sept?
I wrote, I wrote, I could not stop. The mind of the words, had to come out.
Words were said, words were sung, prose and poetry.

One last dance, one last waltz, as words I said, stung through walls.
People gathered around, people made their plans, it quickly got cold, my friend...his thoughts.
My numbers added up, but not enough to hide the hidden hatred of harlequins.
I rallied, I riled...I reminisced, ruminated, and remembered how I rose from the reckless bottoms.
I learned how to live, and not die, but death caught me.
Caught me when I tried to avoid delivering its message across the sea.
Did I know that the bullet would strike from the west.
Kissing me below the chest, sending me to my final rest?
Down, down, down to the Caribbean.
The echo in my heart, the beats were trembling down.

# Message from the Muscle Study Group Chair

Richard J. Barohn, MD

Once again, this year the Muscle Study Group (MSG) meeting will be virtual and will be held October 1- 3. We initially had planned to do this year in-person in Georgetown, but the hotel/convention center on the Georgetown University campus was not ready to take routine guests and meetings as they are still in Covid-19 mode. We looked at other in-person options but for this year it seems virtual was the best option. Last year our virtual meeting was fantastic and I am sure this year's will be as well. I know it is heresy to claim to like virtual better than in-person meetings, but I do! The biggest downside is for the junior investigators and students. They need face to face time to meet others in the field and that is the biggest part that is missing with virtual meetings.

Nevertheless, we have an outstanding meeting planned, and in this issue of the RRNMF Neuromuscular Journal we are publishing the abstracts, agenda, and announcements from our sponsors ahead of the meeting. We received abstracts from many investigators and universities, some in which the first authors were students or junior faculty, and others with very senior faculty taking the lead. I am very excited about the breadth of new information that will be transmitted at this meeting.

In addition, we offered to all our sponsors that they could also submit abstracts and many of them did. I think this is an essential unique aspect to the MSG meetings which we particularly have been promoting in recent years. We want our industry sponsors to interact very closely with our investigators and clinicians at our university campuses. For clinical translational science to advance we both need each other very much. We want to maximize the ways we can interact together in true scientific forums. While the MSG is growing, it is still intimate enough that these interactions can be very productive and meaningful. The most advanced, cutting-edge therapies often begin at the university level in pre-clinical laboratories, then move to industry to get them into clinical trials, which is where the clinical scientists are needed to give industry input on trial design, patient recruitment and so much more. And, of course, the industry trials are then done at our sites. So the interaction and partnership are essential, but it is better to have the conversation all along the spectrum and the MSG is such a forum. We have invited many of the industry presenters to also submit full length papers to the RRNMF Neuromuscular Journal and we hope to see some of these come out in the next one or two journal issues after peer review.

Also, we encourage all the academic groups presenting information to put their presentations into a full article format and submit it to the RRNMF Neuromuscular Journal in the near future. I am pleased to tell you all that earlier this year after the successful use of this journal for last year's meeting, the Executive Committee of the MSG approved my resolution to have the RRNMF Neuromuscular Journal as the official journal of our organization.

Once again, rather than having typical (or atypical) virtual "poster" sessions (which I think is difficult to pull off virtually), we are asking each presenter to give a "FLASH !" 5 minute presentation with 5 minutes of question and answer. This went well last year and I like the speed of this presentation format. This also allows us to get more presentations into the program. So FLASH speakers: please be very fast! And not many slides— five or six maximum! As usual, at each MSG meeting we have asked leaders in the field to give talks on their area of specialization.

We have many outstanding speakers. These talks are twenty minutes each. Each year we select the Robert C. Griggs Annual Meeting Lecture and we are very pleased to have Professor Gordon Smith, Chairman of Neurology at Virginia Commonwealth University to give this keynote address. Dr. Smith will have about fifty minutes to do the keynote address with ten more minutes for question and answer. Last year we inaugurated the "Shark Tank" session in which several MSG members "pitched" their research idea to a panel of neuromuscular judges. The winner receives a $10,000 grant to do the project they pitched. We have three worthy competitors again this year. We will hear from our MSG funded research fellows about the fascinating work they are doing or will do during their two-year fellowships which are jointly sponsored with the AAN/American Brain Foundation. This year two of our fellows will be presenting their work: Paloma Gonzalez-Perez, M.D. (Massachusetts General Hospital) and Renatta Knox, M.D. (Nationwide Children's Hospital). To support all that the MSG does during the meeting and throughout the year we are very happy to have so many industry sponsors who are eager to be part of this exciting event. This year we have given these sponsors space to place information about their company in the program and thus in this issue of the RRNMF Neuromuscular Journal. So please join us for the 2021 MSG meeting October 1-3. If you have not registered, it is not too late. You can register at: Musclestudygroup.org/events/2021-muscle-study-group-annual-scientific-meeting/.

I would like to thank, as always, Professor Michael Hanna, the Co-Chair of the MSG and the Director of the University College London Institute of Neurology for his steady support over the years. This year our Program Planning Committee again did an amazing job choosing and asking our speakers to be part of the program and they expertly arranged all the details of the three-day agenda.

2021 program planning committee:

Chafic Karam, MD (University of Pennsylvania Health System) – Chair

James Lilleker, MBChB, PhD (University of Manchester) – Co-Chair

Senda Ajroud-Driss, MD (Northwestern University)

Laurie Gutmann, MD (Indiana University)

Melissa McIntyre, DPT (University of Utah)

Colin Quinn, MD (University of Pennsylvania Health System)

Tracey Willis, MBChB, MMedSci, MD (Chester University, UK)

Amelia Wilson, DPT (University of Utah Health Science Center)

2021 Shark Tank Panel:

James Lilleker, MBChB, PhD

Dave Arnold, MD

Tracey Willis, MBChB, MMedSci, MD

Gita Ramdharry, DPT

The Executive Committee for the MSG which approves the planning committees and plan all that the MSG does is:

Myself and Mike Hanna, MD as Chair and Co-Chair

Robert C. Griggs, MD (Chair Emeritus)

William David, MD (Massachusetts General Hospital)

Michael Hehir, MD (University of Vermont Medical Center)

Valeria Sansone, MD (NEMO Clinical Center)

Melissa McIntyre, DPT (University of Utah Health Science Center)

Michael McDermott, PhD (Statistician - University of Rochester Medical Center)

Rabi Tawil, MD (Director, MSG Coordination Center, University of Rochester Medical Center)

Mazen Dimachkie, MD (Treasurer - University of Kansas Medical Center)

Thank you all.

Finally, the meeting this year, and every year, cannot happen without the extraordinary administrative work of Liz Paulk who serves as our MSG Administrative Director. Liz is a hands-on, detail-oriented individual who makes sure this meeting will be a positive event for all of us. She is one of the most optimistic, competent, and fun individuals I know and I am so glad we have her helping us to advance the agenda of the MSG: to be the premier neuromuscular clinical and translational research organization. THANK YOU, Liz!!

Rick

# Duchenne Muscular Dystrophy Profiles from Real World Registry Data

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## ABSTRACT

**Introduction**: Understanding real world (RW) profiles from neuromuscular databases are helpful for optimizing clinical care and planning research studies. The Canadian Neuromuscular Disease Registry (CNDR) has respiratory data from a population of Duchenne Muscular Dystrophy (DMD) boys.

**Objective:** To describe the respiratory profiles from a national DMD RW dataset.

**Methods**: Descriptive statistics summarized the respiratory profiles from all CNDR DMD cases. This registry enrolls from 36 centres and collects data directly from clinic.

**Results**: There were 414 subjects enrolled. The age range was from 2 to 39 years old. The mean FVC was 63.2% predicted and the trajectory will be modelled. The proportion of boys with non-invasive ventilation was 18.84% (78/414) and invasive ventilation was 1.69% (7/414).

**Conclusions**: The data from this large cohort are valuable for understanding patterns of clinical care and planning for clinical research. The CNDR is an important infrastructure tool for NM research.

# Loss Of TDP-43 Function And Rimmed Vacuoles Persist After T Cell Depletion In A Xenograft Model Of Inclusion Body Myositis

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*Baltimore, MD*

## ABSTRACT

**Introduction:** We generated a novel xenograft model by transplanting muscle from patients with inclusion body myositis (IBM) into the hindlimb of immunodeficient mice. IBM xenografts display robust regeneration of myofibers derived from resident satellite cells of the muscle biopsy. Myofibers in IBM xenografts are invaded by human, oligoclonal CD8+ T cells and exhibit MHC-1 upregulation, rimmed vacuoles, abnormal protein aggregates, and nuclear clearance of TDP-43.

**Objective:** To determine the role of T cells in the pathogenesis of IBM.

**Methods:** Depletion of human T cells within IBM xenografts was performed by intraperitoneal injection of mice with anti-CD3 antibody (OKT3).

**Results:** OKT3 administration rapidly depleted endomysial T cells and normalized MHC-1 expression in IBM xenografts but did not affect TDP-43 pathology, p62-positive aggregates, or rimmed vacuoles .

**Conclusions:** Myofiber degeneration in a xenograft model of IBM does not require T cells, potentially explaining why immunosuppressive therapy has been ineffective for patients.

# Protocol for a hybrid II study exploring the feasibility of delivering, evaluating, and implementing a self-management programme for people with neuromuscular diseases at a specialist neuromuscular centre (ADAPT-NMD)

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**Introduction:**
Self-management support programmes (SMSPs) are underexplored in neuromuscular diseases (NMDs). 'Neuromuscular Bridges' is a new co-designed SMSP for this population that requires evaluation. Implementation of SMSPs is complex with potential barriers at multiple levels. This study will explore the feasibility of delivering/evaluating Neuromuscular Bridges and the feasibility of several implementation strategies.

**Methods:**
The hybrid II, mixed-methods design is underpinned by Normalisation Process Theory. Feasibility of delivery/evaluation will be tested using a single-arm pre-post design, and explore acceptability, demand, performance of outcome measures, recruitment/ retention. Implementation strategies were selected from a refined taxonomy.

**Results:**
Feasibility of implementation strategies will be explored through qualitative interviews and administrative data. Impact on fidelity, acceptability, appropriateness, and adoption will be evaluated.

**Conclusion:**
There is a lack of evidence on SMSPs for NMDs. This study will provide feasibility data on a new co-designed SMSP and enhance understandings of requirements for its delivery and implementation.

# Establishing clinical trial readiness for valosin containing protein-associated multisystem proteinopathy: baseline results from a 1-year prospective study

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## ABSTRACT

**Introduction:** Valosin containing protein-associated multisystem proteinopathy (VCP MSP), also IBMPFTD, is a rare disorder of multisystemic involvement resulting in progressive weakness, cardiac, respiratory, and/or bulbar dysfunction. Presentation is heterogeneous, highlighting the need for a prospective natural history study.

**Objective:** To quantify functional disease progression and to inform clinical trial design for patients with VCP MSP.

**Methods:** 22 subjects (mean age: 52.3 years (range: 35-66)) with genetically-confirmed VCP MSP completed 82 visits to date, including 2-day remote and onsite baseline visits.

**Results:** A battery of functional and patient-reported measures were completed at each visit. Test-retest reliability was excellent within and between visit types (ICC >0.8; $p<0.001$). Cohort level feasibility and performance of all outcomes will be presented.

**Conclusions:** Performance of most functional outcomes was the same across remote and onsite environments. Continued efforts are needed to identify outcome measures that are most sensitive to change over time in individuals with VCP MSP.

# COVID-19 related outcomes in primary mitochondrial diseases: an international study

Chiara Pizzamiglio[1], Pedro M. Machado[1], Grainne S. Gorman[2], Robert McFarland[2], Michael G. Hanna[1], Robert D.S. Pitceathly[1], for the MitoCOVID-19 Study Group

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## ABSTRACT

**Introduction:** Patients with primary mitochondrial diseases (PMDs) are considered at high risk of complications of Coronavirus 2019 disease (COVID-19). However, little is known about how COVID-19 affects this group.

**Objectives:** The aim of our study was to: (1) identify risk factors associated with hospitalisation; and (2) determine outcomes of COVID-19 in PMDs.

**Methods:** Inclusion criteria: (1) clinicopathological and/or genetically confirmed PMDs; (2) COVID-19 infection with compatible symptoms and/or positive PCR-based testing. The primary outcome was COVID-19-related hospitalisation.

**Results:** Seventy-nine subjects with PMDs from ten countries were included; 25 subjects (31.6%) were hospitalised; 48 (60.8%) recovered fully; 28 (35.4%) resolved with sequelae; and three (3.8%) died. Differences in hospitalisation status were observed for: (1) NMDAS score ($p=0.003$); (2) modified Rankin scale ($p=0.001$); (3) lung disease ($p<0.001$) and neurological involvement ($p=0.003$); (4) four or more comorbidities ($p=0.002$).

**Conclusion:** Our study confirms the PMD patients most vulnerable to COVID-19 related hospitalisation, thus helping stratify risk and appropriate management.

# Self-management in neuromuscular diseases: preliminary findings from a qualitative exploration of the patient perspective

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## ABSTRACT

**Introduction:** Self-management support (SMS) is a key policy focus for many long-term conditions but is under-researched in neuromuscular diseases (NMDs). This study uses qualitative methods to explore the perspectives and priorities for SMS of people with NMDs, identifying the outcomes that matter most to them.

**Methods:** Twenty-one individuals with a range of NMDs participated in semi-structured interviews exploring various topics related to self-management. Thematic analysis was used to code data and identify key domains and themes.

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

**Conclusion:** Gaining a deeper understanding of the way that self-management support is enacted in this population is vital, and the data generated so far provides a first insight into the priorities, common values, and shared experiences of participants.

# Prospective clinical trial readiness in LGMDR9 FKRP-related muscular dystrophy: a GRASP consortium study

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## ABSTRACT

**Introduction:** The GRASP consortium is an international platform trial established to achieve clinical trial readiness across subtypes of limb girdle muscular dystrophy (LGMD).

**Objective:** To quantify disease progression and inform clinical trial design in LGMDR9/2i.

**Methods:** Subjects with genetically-confirmed LGMDR9 were enrolled in a longitudinal cohort study. A battery of assessments were completed at in-person or remote visits (as necessary due to COVID-19 pandemic).

**Results:** 57 subjects completed 151 visits. The average age at enrollment was 35.6 years (range: 10-64 years). Test-retest reliability at baseline was excellent for all outcomes (ICCs 0.96; $p<0.001$). Preliminary results for functional assessments will be presented; initial longitudinal results suggest stability over 6 months regardless of other covariates. Remote outcomes were not significantly different from those completed onsite.

**Conclusions:** Live video-based remote assessments may be a valid way to measure motor function in some circumstances. Recruitment efforts are ongoing and additional data will be presented.

# Adapting MRI as a clinical outcome measure for a facioscapulohumeral muscular dystrophy trial of prednisone and tacrolimus

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## ABSTRACT

**Introduction**: Facioscapulohumeral muscular dystrophy (FSHD) is a patchy and slowly progressive disease of skeletal muscle. MRI short tau inversion recovery (STIR) sequences of patient muscles often show increased hyperintensity that is hypothesized to be associated with inflammation. This is supported by the presence of inflammatory changes on biopsies of STIR-positive muscles. We hypothesized that the STIR positivity would normalize with targeted immunosuppressive therapy.

**Case presentation:** 45-year-old male with FSHD type 1 was treated with 12 weeks of immunosuppressive therapy, tacrolimus and prednisone. Tacrolimus was treated to a goal serum trough of > 5 ng/ml and prednisone was tapered every month. Quantitative strength exam, functional outcome measures, and muscle MRI were performed at baseline, week 6, and week 12. The patient reported subjective worsening as reflected in quantitative strength exam. The MRI STIR signal was slightly increased from 0.02 to 0.03 of total muscle; while the T1 fat fraction was stable. Functional outcome measures also were stable.

**Conclusions:** Immunosuppressive therapy in refractive autoimmune myopathy in other contexts has been shown to reverse STIR signal hyperintensity, however this treatment did not reverse STIR signal in this patient with FSHD. In fact, STIR signal slightly increased throughout the treatment period. This is the first study of using MRI STIR and T1 fat fraction to follow treatment effect in FSHD. We find that STIR might not be a dynamic marker for suppressing inflammation in FSHD.

# Racial Disparities in Skin Tone Representation of Dermatomyositis Rashes

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## ABSTRACT

**Background:** Health disparities in medicine are due to multifactorial causes, one of which is disproportionate racial representation in educational materials, such as in dermatomyositis (DM) rashes.

**Objective:** This study reviews skin tone representation in DM rash images in educational materials.

**Methods:** DM images were analyzed from textbooks and online image databases. Authors graded skin tone on the Massey and Martin Skin Color Scale (MMSCS) from 1 (very light) to 10 (very dark), with median scores categorized as: MMSCS 1-2, 3-4, 5-7, 8-10.

**Results:** 561 images were analyzed from 93 textbooks (59-dermatology, 11-neurology, 10- neuromuscular, 7-rheumatology, 6-internal medicine) and 3 online databases (UpToDate, VisualDx, DermNet NZ). Image representation for MMSCS: 1-2 73.1%, 3-4 13.4%, 5-7 11.8%, 8-10 1.8%.

**Conclusion:** Patients with lighter skin tones were represented in a higher number of dermatomyositis related educational materials. Our findings add to current research implicating that darker skin tones are underrepresented in dermatology, specifically DM.

# Longitudinal dysphagia assessment in patients with cystinosis using MBSImP

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## ABSTRACT

**Introduction:** Nephropathic cystinosis is a lysosomal storage disorder with known myopathic features, including dysphagia. Improved analysis of swallowing kinematics in patients with cystinosis is needed for adequate characterization of dysphagia and guidance towards potential treatment targets.

**Objectives:** To better characterize swallowing impairments over time utilizing advanced applied MBS-ImP analysis.

**Methods:** We retrospectively evaluated 59 video fluoroscopic swallowing studies of patients with nephropathic cystinosis with various levels of oral and pharyngeal stage dysphagia with time points spanning over the course of two years.

**Results:** We demonstrated oral stage involvement related to lingual strength and control that impacts bolus hold, transport, and clearance. There were changes in function across the two-year time span that may guide additional investigations into the myopathic process impacting swallow safety and function.

**Conclusions:** This study provides better insight to dysphagia in this patient population and paves the path for future studies of treatment targets.

# CMT-COVID Survey

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## ABSTRACT

**Introduction:** Coronavirus disease 2019 (COVID-19) is a pandemic caused by the (SARS-CoV-2).

**Objectives:** Our study evaluated the impact of the COVID-19 on patients with CMT.

**Methods:** A simple online questionnaire for CMT patients diagnosed with COVID-19 was developed to investigate how much the COVID-19 impacted the community of CMT patients and its consequences on the progression of CMT. The survey was distributed electronically with the support of the patient associations in Italy and US.

**Results:** 152 individuals completed the survey. Approximately 59% of completers were female, and the average age was 49.96 (SD 12.65, range 22-76 years). 13.8% of the respondents had a COVID diagnosis and 2% (n= 3) of them were health workers. Symptoms of COVID-19 were typically mild and none went to the ICU.

**Discussion:** These results do not show a clear increased risk of COVID in people with CMT.

# Case Series of Myasthenia Gravis (MG) Patients Prescribed Subcutaneous Immunoglobulin (SCIg) Therapy and Monitored by Patient Reported Outcome Measures (PROMs) by a Specialty Infusion Pharmacy Using SoleMetrics

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## ABSTRACT

**Introduction:** The documented use of SCIg in MG patients treated and monitored by PROMs through a Specialty Pharmacy is limited.

**Objective:** We present a case series of 7 MG patients receiving and monitored for SCIg therapy through a Specialty Infusion Pharmacy.

**Design/Methods:** Retrospective analysis from a proprietary clinical outcomes program, SoleMetrics, was conducted in patients with MG. Review included patient history, dispensing records, adverse reactions, MG symptoms, MGQOL-15 and MG-ADL scores, pain disclosure (related and unrelated to MG), fatigue (mfSS), ataxia, sensory perception, weakness, and an internal QOL (Soleo Wellness).

**Results:** Case report summaries, along with mean number of PROMs/patient and corresponding mean values will be discussed and illustrated in the poster presentation.

**Conclusions:** SoleMetrics allows the frequent collection of information by trained clinicians not readily available to treating physicians between routine office visits and SCIg self-administration. By reviewing SoleMetrics data, physicians may be able to optimize therapy and clinical outcomes in patients with MG.

The documented use of SCIg in MG patients treated and monitored by PROMs through a Specialty Pharmacy is limited. We present a case series of 7 MG patients receiving and monitored for SCIg therapy through a Specialty Infusion Pharmacy. Retrospective analysis from a proprietary clinical outcomes program, SoleMetrics, was conducted in patients with MG. Review included patient history, dispensing records, adverse reactions, MG symptoms, MGQOL-15 and MG-ADL scores, pain disclosure (related and unrelated to MG), fatigue (mfSS), ataxia, sensory perception, weakness, and an internal QOL (Soleo Wellness). Case report summaries, along with mean number of PROMs/patient and corresponding mean values will be discussed and illustrated in the poster presentation. SoleMetrics allows the frequent collection of information by trained clinicians not readily available to treating physicians between routine office visits and SCIg self-administration. By reviewing SoleMetrics data, physicians may be able to optimize therapy and clinical outcomes in patients with MG.

# Flow Cytometry and Sorting of Single Antibody Secreting Cells from Frozen Muscle Tissue

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## ABSTRACT

**Background**: Idiopathic inflammatory myopathies are rare muscle disorders. Their study is impeded by protocols requiring fresh tissue.

**Objectives**: Obtain intact antibody secreting cells from clinical myositis samples.

**Methods**: We tested tissue processing, freezing, and storage methods. Paired 1 $cm^3$ tonsil samples were collected in media [HT or saline (NS)], frozen [CS or isopentane (IP)], and digested. Single $CD_{13}8+$ cells were isolated by flow cytometry from dermatomyositis (DM) and inclusion body myositis (IBM) samples. PCR confirmed expression of immunoglobulin chains (Ig), $PRDM_1$, and BCL6.

**Results**: We recovered similar proportions of $CD_{19}+$ and downstream $CD_{27}$+IgD-, $CD_{13}8+$, and $CD_38+$ cell subsets by flow cytometry from tonsil. IP freezing was non-inferior to CS. Digestion of 3 DM and 3 IBM biopsies showed similar proportions of sorted live cells with expression of $PDRM_1$, BCL6 and Ig.

**Conclusions**: Our approach establishes the feasibility of obtaining live antibody secting cells from stored samples of frozen muscle tissue.

# Effect of Distal Hereditary Motor Neuropathy on muscle structure, function, and gait patterns: Two case reports

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## ABSTRACT

**Introduction**: Distal Hereditary Motor Neuropathy (dHMN) is an inherited neuromuscular disorder characterised by distal muscle weakness. Here we investigate the relationship between muscle impairments and gait patterns in two individuals.

**Methods**: Two cases of dHMN (cases A and B) and matched healthy controls were compared. We measured lower limb strength using isokinetic dynamometry and 3D gait analysis. MRI scans were interpreted for the dHMN participants only.

**Results**: Case A was a 47-year-old male with no genetic diagnosis. lsokinetic dynamometry showed lower torque values for case A compared to the matched control: eccentric plantar flexion was 28.65% and concentric dorsiflexion 68.67% of control values. Ankle power generation during stance phase was 35.92% of matched control values, with reduced stride length (88.48%) and increased knee power generation in swing phase (146.26%).

Case B was a 37-year-old male with BSCL2 mutation. lsokinetic dynamometry showed lower torque values for case B compared to the matched control: eccentric plantar flexion was 68.42% but concentric dorsiflexion was stronger at 153.18% of healthy control values. Ankle power generation during stance phase of gait was 59.57% of matched control values, with reduced stride length (73.39%) and he also had increased knee power generation in swing phase (274.59%). MRI scans demonstrated differing patterns of involvement between the cases, with case A showing symmetrical posterior compartment involvement, and case B showing asymmetrical, predominantly lateral compartment involvement. Thighs had normal appearance in both cases.

**Conclusion:** We present two dHMN cases showing greater plantarflexor muscle weakness than matched healthy controls. This was associated with reduced ankle power generation in stance but increased knee power generation in swing that may be a compensatory strategy to progress the swing leg. Variation existed between the cases, however, with differences in dorsiflexion strength and MRI findings, indicating that this is not a homogenous group of diseases.

# Monotherapy with Eculizumab in refractory acetylcholine receptor positive generalized myasthenia gravis

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## ABSTRACT

**Objective:** To report 2 cases of treatment refractory acetylcholine receptor antibody positive generalized myasthenia gravis (gMG) controlled with eculizumab monotherapy.

**Background:** Eculizumab is a terminal complement inhibitor recently shown to be effective in acetylcholine receptor antibody positive gMG. The sustained efficacy and the good tolerability of eculizumab are of particular benefit to those who have refractory disease requiring multiple concomitant immunotherapies. However, clinical data is currently lacking as to how much benefit eculizumab can provide in reducing the burden of concomitant immunotherapies and how to smoothly transition to eculizumab from different conventional therapies.

**Results:** We report two patients with treatment-refractory acetylcholine receptor antibody positive gMG on multiple immunotherapies, who were successfully transitioned to eculizumab. Clinical outcome measures improved and remained stable for 12 months on eculizumab monotherapy.

**Conclusion:** This case series demonstrates the efficacy of eculizumab in gMG and provides timelines of successful transition from polytherapy to eculizumab monotherapy.

# Collaboration between patient advocacy and academia drives clinical trial readiness in valosin containing protein associated multisystem proteinopathy

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[3]*Cure VCP Disease, Americus GA, USA*

## ABSTRACT

**Introduction:** Valosin-containing protein associated multisystem proteinopathy (VCP-associated MSP) is a rare inherited disorder resulting in a varied phenotype

**Objective:** To efficiently design and conduct a clinical trial readiness study in VCP-associated MSP

**Methods:** Collaborative trial design including patient advocacy and outcome measure researchers

**Results:** IRB approval was obtained March 2021; within 2 months, 18 patients had enrolled and completed baseline visits. Baseline phase completion of the full 24-patient cohort occurred within 4 months of approval. Cure VCP Disease led recruitment efforts, coordinated equipment kits for remote visits, and provided travel support as needed to reduce study burden for patients. Researchers reduced the number of in-person visits, included flexible visit windows to maximize ease of participation while ensuring essential data points were obtained.

**Conclusions:** Collaboration between researchers and patient advocacy resulted in effective study design, maximized enrollment, and reduced testing burden while ensuring efficient recruitment and study start up.

# Three-year safety and functional outcomes of a Phase 1/2a trial of SRP-9001 in patients withDuchenne muscular dystrophy (DMD)

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## ABSTRACT

**Introduction:** We designed an investigational gene transfer therapy (rAAVrh74.MHCK7.micro-dystrophin [SRP-9001]) to achieve targeted skeletal and cardiac muscle expression of a shortened functional dystrophin protein.

**Objectives:** This Phase 1/2a trial (NCT03375164) evaluated the safety of SRP-9001 in patients with Duchenne muscular dystrophy (DMD).

**Methods:** Four patients with DMD were enrolled in this single-dose, open-label, Phase 1/2a study. Eligible participants were ambulatory boys (4-7 years old) with a confirmed *DMD* gene mutation, creatine kinase (CK) elevation (>1,000 U/L), ≤80% predicted 100-Meter Timed Test (100m), negative for AAVrh74 antibodies and stable steroid dosing (≤ 3 months). Patients were given a single intravenous dose of $1.33x10^{14}$ vg/kg (linear qPCR) of SRP-9001 and prednisone (1 mg/kg/day) was initiated 1 day before gene delivery, tapering after 30 days. The primary outcome measure was safety. The secondary outcome measures included micro-dystrophin expression quantified by immunofluorescence and western blot in pre- and post-muscle biopsies. Efficacy outcome measures included decrease in CK, the North Star Ambulatory Assessment (NSAA; 10-Meter Timed Test and Time to Rise included) and timed function tests (100m and 4-Stair Climb).

**Results:** Here we report the long-term (3-year) functional data from the four patients treated with SRP-9001. Treatment-related adverse events (AEs) were mild to moderate and transient; all resolved in the first 90 days post-infusion. No serious AEs occurred. Robust expression of micro-dystrophin and correct localization to the sarcolemma were associated with vector genome copies, CK reduction, and rescue of β-sarcoglycan, a dystrophin-associated protein complex component at the Week 12 biopsy. All four patients demonstrated a clinically meaningful improvement in the NSAA as early as Day 90, with a mean change from baseline to Year 3 of +7.5 (3.42 SD). Overall, patients generally maintained muscle strength (Time to Rise and 4-Stair Climb) from baseline to Year 3. Patients also generally showed improvement in ambulation ability from baseline to Year 3 (100m Walk Test). According to a natural history study, these patients would have been expected to decline.

**Conclusions:** Three-year data from Study 101 reinforce that SRP-9001 is well tolerated, with no new safety signals, and data are consistent with safety data from the wider SRP-9001 clinical trial program. Compared with baseline, long-term functional assessment measured by the NSAA demonstrated overall improvements in motor abilities that were maintained over 3 years, demonstrating a durable response. These data provide proof-of-concept support for the continuation of clinical trials assessing SRP-9001.

**Disclosures:** Jerry R. Mendell has received study funding from Sarepta Therapeutics, Inc, for the current publication and has a service agreement with Sarepta Therapeutics, Inc to provide training on ongoing studies. In addition, he is a co-inventor of AAVrh74.MHCK7.micro-dys technology, which is exclusively licensed to Sarepta Therapeutics, Inc. Zarife Sahenk has received grant support from Sarepta Therapeutics, Inc, and the Parent Project Muscular Dystrophy. Kelly J. Lehman has received an institutional grant from Sarepta Therapeutics, Inc. Carrie Nease has received grant support (research) from Sarepta Therapeutics, Inc.

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Jordan Vaiea is an employee of Nationwide Children's Hospital.
Sarah Lewis is an employee of Sarepta Therapeutics, Inc, and may have stock options. Rachael A. Potter is an employee of Sarepta Therapeutics, Inc, and may have stock options. Danielle A. Griffin is an employee of Sarepta Therapeutics, Inc, and may have stock options. Eric R. Pozsgai is an employee of Sarepta Therapeutics, Inc, and may have stock options.
Larry Hu is an employee of Sarepta Therapeutics, Inc, and may have stock options. Kathryn Giblin is an employee of Sarepta Therapeutics, Inc, and may, have stock options.
Louise R. Rodino-Klapac is an employee of Sarepta Therapeutics, Inc, has received grant support from Sarepta Therapeutics, Inc, and the Parent Project Muscular Dystrophy, as well as financial consideration from Sarepta Therapeutics, Inc, and Myonexus Therapeutics (now acquired by Sarepta Therapeutics, Inc). In addition, she is a co-inventor of AAVrh74. MHCK7.micro-dys technology, which is exclusively licensed to Sarepta Therapeutics, Inc.
Megan A. lammarino, Kathleen Church, Richard Shell and Mark Hogan report no conflicts of interest .

# Study Designs for Clinical Trials Assessing the Pharmacokinetics and Bioequivalence of an Investigational Oral Formulation of Edaravone (MT-1186) in Patients With Amyotrophic Lateral Sclerosis

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## ABSTRACT

**Introduction:** Edaravone is an intravenous (IV) treatment for amyotrophic lateral sclerosis (ALS). As IV administration can burden patients, orally administered treatments are needed.

**Objectives:** To assess the pharmacokinetics (PK) and bioequivalence of an investigational oral suspension formulation of edaravone (MT-1186).

**Methods:** Three phase 1, open-label clinical studies were conducted in healthy subjects or in patients with ALS with or without percutaneous endoscopic gastrostomy (PEG). Study J03 was a single-dose crossover bioequivalence study with 42 healthy subjects who received 105 mg of MT-1186 and IV edaravone (60 mg/60 minutes). Assessments included PK parameters, metabolic profiles, and elimination pathways for each formulation. The 24-hour PK of a single dose of MT-1186 was also assessed in 9 patients with ALS (Study J04) and in 6 patients with ALS who had PEG tubes (Study J05).

**Discussion:** These studies should provide important bioequivalence and PK data for the development of MT-1186 for patients with ALS.

**Acknowledgements:** *p*-value communications provided editorial support.

# Study Design for a Clinical Trial Assessing the Bioavailability of an Investigational Oral Formulation of Edaravone (MT-1186) in Subjects With a Nasogastric Tube

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## ABSTRACT

**Introduction:** Edaravone is an intravenous treatment for amyotrophic lateral sclerosis (ALS). As intravenous administration can burden patients, orally administered treatments are needed.

**Objectives:** To assess the bioavailability and pharmacokinetics (PK) of an investigational oral suspension formulation of edaravone (MT-1186) when administered with a nasogastric feeding tube.

**Methods:** Study Z-101 is a phase 1, randomized, open-label, crossover-design, single-dose study. The primary objective of the study is to investigate the comparative bioavailability of MT-1186 administered orally and via a nasogastric tube in healthy adult subjects. Secondary objectives include assessing the safety, tolerability, and PK. A total of 36 subjects will be randomized to 2 groups of 18 subjects. Subjects will receive a single dose of MT-1186 and PK will be assessed over 48 hours, followed by crossover to the other form of administration.

**Discussion:** This study should provide important data for the development of MT-1186 for patients with ALS.

**Acknowledgements:** *p*-value communications provided editorial support.

# Evaluating longitudinal treatment effects of deflazacort via the North Star Ambulatory Assessment in patients with nonsense mutation Duchenne muscular dystrophy

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## ABSTRACT

**Background:** ACT DMD was a 48-week, randomized, double-blind, placebo-controlled, phase 3 trial of ataluren (40 mg/kg/day).

**Objective:** To evaluate the longitudinal treatment effects of deflazacort and prednisone/prednisolone in patients with nmDMD.

**Approach:** We measured the cumulative numbers of failures to perform items of the NSAA over 48 weeks for patients in the placebo arm of ACT DMD treated with deflazacort or prednisone/prednisolone. Curves showing the mean cumulative number of failures across all 17 items over 48 weeks were constructed for both deflazacort and prednisone/prednisolone groups.

**Results:** Over the entire study, the curve showing the mean cumulative numbers of failures over time for patients who received prednisone/prednisolone was persistently steeper than that for those who received deflazacort. The ratio of the two curves was 72%, which significantly favoured deflazacort ($p$=0.028).

**Conclusion:** These results demonstrate a longitudinal, cumulative treatment benefit of deflazacort, vs prednisone/prednisolone in patients with nmDMD over time.

# Updated demographics and safety data from patients with nonsense mutation Duchenne muscular dystrophy receiving ataluren in the Strategic Targeting of Registries and International Database of Excellence (STRIDE) Registry

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## ABSTRACT

**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 ≤ Atlaluren 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.

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**FB** has received consultancy fees from PTC Therapeutics, Santhera Pharmaceuticals, Sarepta Therapeutics and Pfizer.
**ID** has received consultancy fees from AveXis , Biogen, BioMarin and PTC Therapeutics.
**JK** has acted as a consultant for AveXis, Biogen, Ionis Pharmaceuticals, PTC Therapeutics and Roche, and has received research support for taking part in clinical research from Biogen, BioMarin, GlaxoSmithKline, Ionis Pharmaceuticals, Novartis, PTC Therapeutics, Roche, Santhera Pharmaceuticals and Trophos.
**EM** has acted as an advisory board member for AveXis, Biogen, BioMarin, Bristol-Myers Squibb, Ionis Pharmaceuticals, Italfarmaco, Prosensa, PTC Therapeutics, Roche, Santhera Pharmaceuticals, Sarepta Therapeutics and Summit Therapeutics.
**ANO** has received speaker and consultancy fees from Biogen, PTC Therapeutics and SareptaTherapeutics, and is an investigator on clinical trials sponsored by Biogen, F. Hoffmann-La Roche, Italfarmaco, Sarepta Therapeutics and TAMDMD.

**MT** has received lecture fees from Biogen and PTC Therapeutics, and has acted as a consultant on DMD clinical trials for BioMarin, Catabasis Pharmaceuticals, PTC Therapeutics,ReveraGen BioPharma and Sarepta Therapeutics, and as an advisory board member for AveXis, Biogen, Sarepta Therapeutics and PTC Therapeutics.
**SJ, CW, AK, JJ, JL, PT** and **CLS** are employees of PTC Therapeutics. Medical writing and editorial support were funded by PTC Therapeutics Ltd.

# Associations between deflazacort versus prednisone/prednisolone and markers of disease progression in clinically important subgroups of patients with Duchenne muscular dystrophy

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## ABSTRACT

**Introduction:** The standard of care for Duchenne muscular dystrophy includes steroids.

**Objective:** We compared clinical outcomes by steroid type within subgroups defined by age, ambulatory function, and steroid duration.

**Methods:** Placebo arms from three clinical trials with assessments of 48-week change were studied (NCT0l 826487, NCT0l 865084, NCT00592553). Mean changes in six-minute walk distance (6MWD) and other outcomes (NSAA, timed function tests) were compared between patients receiving daily deflazacort vs. daily prednisone, adjusting for baseline prognostic factors.

**Results:** A total of n=l99 patients were available across the placebo arms (n=l09 deflazacort; n=90 prednisone). Deflazacort was associated with preservation of 33.0 meters of 6 MWD compared to prednisone (P=0.001). This difference was most pronounced among boys with the following baseline characteristics: aged 8 years (+43. lm), rise time ≥5 seconds (+42.9m) or steroid duration >3 years (+56.0m).

**Conclusion:** These results add to the evidence for the cumulative benefit of deflazacort versus prednisone.

# Age at loss of ambulation (LoA) in patients with DMD from the Strategic Targeting of Registries and International Database of Excellence (STRIDE) Registry and the Cooperative International Neuromuscular Research Group Natural History Study (CINRGNHS): a matched cohort analysis

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## ABSTRACT

**Introduction:** STRIDE is an ongoing, multicenter, observational registry providing data on ataluren use in nmDMD patients in routine clinical practice.

**Objective:** We examined whether nmDMD patients receiving ataluren plus standard of care (SoC) in the STRIDE Registry experienced delayed age at LOA versus those in the CINRG NHS receiving SoC alone.

**Methods:** Propensity score matching identified comparable STRIDE and CINRG patient cohorts (January 31, 2021, N=241) using established predictors of disease progression: Kaplan-Meier analyses estimated age at LOA.

**Results:** The mean ages (±SD) at first symptoms (STRIDE vs CINRG; N=241 per cohort) were 2.7±1.7 and 2.8±1.5 years, respectively. Most patients received deflazacort or other corticosteroids. LOA (STRIDE vs CINRG) occurred in 24.9% versus 52.7% of patients. Median ages (95%CI) at LOA (STRIDE vs CINRG) were 17.9 (14.4, NE) and 12.5 (11.6, 13.5) years, respectively. Treatment with ataluren and SoC delayed age at LOA versus SoC alone ($p<0.0001$)

**Conclusions:** These data show ataluren and SoC slow disease progression in nmDMD patients.

**Disclosure of conflicts of interest: EM** has acted as an advisory board member for AveXis, Biogen, BioMarin, Bristol-Myers Squibb, Ionis Pharmaceuticals, Italfarmaco, Prosensa, PTC Therapeutics, Roche, Santhera Pharmaceuticals, Sarepta Therapeutics and Summit Therapeutics.
**FM** has received consulting fees from AveXis, Biogen, Dyne Therapeutics, Capricor, Catabasis, Novartis, Pfizer, PTC Therapeutics, Roche, Santhera Pharmaceuticals, Sarepta Therapeutics and Wave Therapeutics, and is supported by the National Institute of Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London.
**FB** has received consultancy fees from PTC Therapeutics, Santhera Pharmaceuticals, SareptaTherapeutics and Pfizer.
**ID** has received consultancy fees from AveXis, Biogen, BioMarin and PTC Therapeutics.
**JK** has acted as a consultant for AveXis, Biogen, Ionis Pharmaceuticals, PTC Therapeutics andRoche, and has received research support for taking part in clinical research from Biogen, BioMarin, GlaxoSmithKline, Ionis Pharmaceuticals, Novartis, PTC Therapeutics, Roche, Santhera Pharmaceuticals and Trophos.
**ANO** has received speaker and consultancy fees from Biogen, PTC Therapeutics and SareptaTherapeutics, and is an investigator on clinical trials sponsored by Biogen, F. Hoffmann-La Roche, Italfarmaco, Sarepta Therapeutics and TAMDMD.
**MT** has received lecture fees from Biogen and PTC Therapeutics, and has acted as a consultant on DMD clinical trials for BioMarin, Catabasis Pharmaceuticals, PTC Therapeutics,ReveraGen BioPharma and Sarepta Therapeutics, and as an advisory board member for AveXis, Biogen, Sarepta Therapeutics and PTC Therapeutics.
**SJ, CW, AK, JJ, JL, PT** and **CLS** are employees of PTC Therapeutics.
**CMM** has acted as a consultant on clinical trials of DMD for Astellas, Capricor, Catabasis, Edgewise Therapeutics, Epirium Bio (formerly Cardero Therapeutics), FibroGen, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals and Sarepta Therapeutics. He has received research support for clinical trials from Capricor, Catabasis, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals and Sarepta Therapeutics.
Medical writing and editorial support were funded by PTC Therapeutics Ltd.

# Ataluren delays loss of ambulation (LoA) and decline in pulmonary function in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD) compared with a matched cohort of patients receiving SoC alone in the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS)

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## ABSTRACT

**Introduction:** Ataluren targets underlying cause of nmDMD, enabling the formation of a full-length dystrophin.

**Objective:** To evaluate whether nmDMD patients receiving ataluren + standard of care (SoC) experienced a delay in LoA and a slower decline in pulmonary function versus SoC alone in CINRGDNHS.

**Methods:** Propensity score matching identified Study 019 and CINRGDNHS patients with comparable indicators of disease severity. Kaplan-Meier analyses estimated the age at LoA anddecline in FVC to <60%- or <50%-predicted or <1 L.

**Results:** Age at LoA was delayed by ~2.5 years in nmDMD patients receiving ataluren compared with CINRGDNHS patients. In non-ambulatory patients, ataluren was associated with a delay in decline to predicted FVC <60% by ~2.5 years and FVC <50% by ~1 year.

**Conclusions:** Ataluren + SoC delays LoA and may delay pulmonary function decline in nmDMD patients compared with SoC alone, although longer follow-up will be required.

# Pulmonary function in patients with Duchenne muscular dystrophy from the Strategic Targeting of Registries and International Database of Excellence (STRIDE) Registry and the Cooperative International Neuromuscular Research Group Natural History Study (CINRG NHS): a matched cohort analysis

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## ABSTRACT

**Introduction:** STRIDE is an ongoing, multicenter, observational registry providing data on ataluren use in nmDMD patients in routine clinical practice.

**Objective:** We investigated if nmDMD patients receiving ataluren plus standard of care (SoC) in the STRIDE Registry experienced a lesser decline in pulmonary function versus Soc alone in the CINRG

**Methods:** Propensity score matching identified comparable STRIDE and CINRG patient cohorts (N=241, 31 January 2021) with established predictors of disease progression; Kaplan-Meier analyses estimated ages at % predicted FVC <60% and <30%.

**Results:** Mean ages(±SD) at first symptoms (STRIDE vs CINRG; N=241 each) were 2.7±1.7 and 2.8±1.5 years, respectively. Median ages(95%CI) at% predicted FVC <60% (STRIDE vs CINRG) were 17.6(16.2,nonestimable) and 15.8(15.1, 16.5) years, respectively. Median ages(95% Cl) at% predicted FVC <30% were nonestimable for STRIDE and 26.4 (20.6, 29.4) years for CINRG ($p$=0.0085).

**Conclusions:** These data suggest that ataluren treatment plus SoC slows disease progressionin nmDMD patients.

**Disclosure of conflicts of interest: MT** has received lecture fees from Biogen and PTC Therapeutics, and has acted as a consultant on DMD clinical trials for BioMarin, Catabasis Pharmaceuticals, PTC Therapeutics,ReveraGen BioPharma and Sarepta Therapeutics, and as an advisory board member for AveXis, Biogen, Sarepta Therapeutics and PTC Therapeutics.
**FB** has received consultancy fees from PTC Therapeutics, Santhera Pharmaceuticals, SareptaTherapeutics and Pfizer.
**ID** has received consultancy fees fromAveXis, Biogen, BioMarin and PTC Therapeutics.
**JK** has acted as a consultant for AveXis, Biogen, Ionis Pharmaceuticals, PTC Therapeutics andRoche, and has received research support for taking part in clinical research from Biogen, BioMarin, GlaxoSmithKline, Ionis Pharmaceuticals, Novartis, PTC Therapeutics, Roche, Santhera Pharmaceuticals and Trophos.

**EM** has acted as an advisory board member for AveXis, Biogen, BioMarin , Bristol-Myers Squibb, lonis Pharmaceuticals, ltalfarmaco, Prosensa, PTC Therapeutics , Roche, Santhera Pharmaceuticals, Sarepta Therapeutics and Summit Therapeutics.
**FM** has received consulting fees from AveXis, Biogen , Dyne Therapeutics, Capricor, Catabasis, Novartis, Pfizer, PTC Therapeutics, Roche, Santhera Pharmaceuticals, Sarepta Therapeutics and Wave Therapeutics, and is supported by the National Institute of Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London.
**ANO** has received speaker and consultancy fees from Biogen, PTC Therapeutics and SareptaTherapeutics, and is an investigator on clinical trials sponsored by Biogen, F. Hoffmann-La Roche, ltalfarmaco, Sarepta Therapeutics and TAMDMD.
**SJ, CW, AK, JJ, JL, PT** and **CLS** are employees of PTC Therapeutics.
**CMM** has acted as a consultant on clinical trials of DMD for Astellas, Capricor, Catabasis, Edgewise Therapeutics , Epirium Bio (formerly Cardero Therapeutics), FibroGen, ltalfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals and Sarepta Therapeutics. He has received research support for clinical trials from Capricor, Catabasis, ltalfarmaco, Pfizer, PTCTherapeutics, Santhera Pharmaceuticals and Sarepta Therapeutics.
Medical writing and editorial support were funded by PTC Therapeutics Ltd.

# EFGARTIGIMOD TREATMENT OF PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS DEMONSTRATES IMPROVEMENTS REGARDLESS OF CONCOMITANT IMMUNOSUPPRESSIVE THERAPY OR REFRACTORY VS NON-REFRACTORY STATUS

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## ABSTRACT

**Introduction:** Efgartigimod, a human IgG1 antibody FC-fragment, demonstrated clinical improvement in patients with generalized myasthenia gravis (gMG) by blocking FcRn and decreasing IgG, including pathogenic IgG.

**Objective:** To assess the efficacy of efgartigimod across subgroups, including concomitant therapies and refractory *vs.* non-refractory status.

**Methods:** The phase 3 ADAPT study randomized patients with gMG to receive cycles of four weekly infusions of 10 mg/kg efgartigimod or placebo; subsequent treatment cycles initiated according to clinical response. MG-ADL responder status ( 2-point improvement for 4 consecutive weeks) was assessed across acetylcholinesterase inhibitors (AChE-i), steroids and non-steroidal immunosuppressive (NSIST) use, and refractory vs non-refractory status.

**Results:** Consistent and statistically significant improvements in MG-ADL responder status were observed in AChR+ patients (n=129) regardless of concomitant NSISTs, steroids, or AChE-i use, and in refractory and non-refractory subgroups.

**Conclusions:** Efgartigimod demonstrated consistent improvements regardless of refractory and non-refractory status or concomitant background therapies.

**Disclosures: JFH** has received research support from Alexion Pharmaceuticals, argenx BVBA, the Centers for Disease Control and Prevention (Atlanta, GA, USA), the Muscular Dystrophy Association, the NationalInstitutes of Health (including the National Institute of Neurological Disorders and Stroke and the National Institute of Arthritis and Musculoskeletal and Skin Diseases), Ra Pharmaceuticals, Takeda Pharmaceuticals, Consulting fees/honoraria from Alexion Pharmaceuticals, argenx BVBA, lmmunovant, Ra Pharmaceuticals (now UCB Biosciences), Regeneron Pharmaceuticals, Sanofi and Viela Bio Inc. and non-financial support from Alexion Pharmaceuticals, argenx BVBA, Ra Pharmaceuticals (now UCB Biosciences) and Toleranzia.
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**VB** has received research support from CSL, Grifols, UCB, Bionevia, Shire, and Octapharma.
**EB, PU, and LL** are argenx employees.
**HM** has served as a consultant for Alexion Pharmaceuticals, argenx BVBA and Ra Pharmaceuticals,and has received speaker honoraria from the Japan Blood Products Organization and research support from the Ministry of Health, Labour and Welfare, Japan.

**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.

# Safety, β-Sarcoglycan Expression, and Functional Outcomes From Systemic Gene Transfer of rAAVrh74.MHCK7.hSGCB in LGMD 2E/R4

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## ABSTRACT

**Introduction:** Limb-girdle muscular dystrophy type 2E/R4 (LGMD 2E/R4) is caused by mutations in the β-sarcoglycan gene (*SGCB*), resulting in loss of SGCB protein and other components of the dystrophin associated protein complex (DAPC). LGMD 2E/R4 manifests as progressive hip/shoulder muscle weakness and elevated creatine kinase (CK). rAAVrh74. MHCK7.hSGCB (SRP-9003) is an investigational gene transfer therapy for the expression of a codon-optimized, full-length, human SGCB transgene driven by MHCK7, a promoter optimized for skeletal and cardiac muscle expression.

**Objectives:** To evaluate the safety and efficacy of SRP-9003 in the first-in-human, phase 1/2 genetransfer therapy trial in patients with LGMD 2E/R4 (NCT03652259).

**Methods:** Six patients aged 4-15 years with *SGCB* mutation (both alleles) received a single SRP-9003 IV infusion: Cohort 1 (n=3), $1.85x10^{13}$ vg/kg dose; Cohort 2 (n=3), $7.41x\ 10^{13}$ vg/kg dose. Prednisone 1 mg/kg/day began 1 day before treatment, tapering after 30-60 days. Endpoints included safety (primary), SGCB expression (secondary), CK level, and functional assessments (North Star Assessment of Limb-girdle Muscular Dystrophies [NSAD], 100-meter timed test (100m, 10m, 4-stair climb, time to rise).

**Results:** We report Year 2 (Y2; Cohort 1) and Year 1 (Yl; Cohort 2) results. As of January 2021, SRP-9003 was well tolerated with no new safety signals since the previous data cut (July 2020). Adverse events occurred early and were manageable, and included vomiting, dehydration, and elevated liver enzymes, which all resolved. There were no other laboratory abnormalities suggestive of safety concerns, including no decreases in platelets outside the normal range and no clinical complement activation.
Western blot showed robust SGCB expression in muscle biopsies from individual patients at Day 60, and a dose-response in protein expression was observed. SGCB expression was maintained to Y2 (Cohort 1). Immunofluorescence also showed robust SGCB expression post treatment, leading to increased a-, δ- and y-sarcoglycan expression, demonstrating DAPC reconstitution at Day 60 (Cohort 1 and Cohort 2) and at Y2 (Cohort 1). CK decreased by 77% in Cohort 1 (Y2) and 74% in Cohort 2 (Yl) post treatment. SRP- 9003-treated patients showed functional improvements, maintained at Y2 in Cohort 1 (NSAD, +5.7 points; time to rise, -0.6 s; 4-stair climb, -0.3 s; 100m, -2.8 s; 10m, -0.2 s) and Yl in Cohort 2 (NSAD, +4 points; time to rise, -1.1 s; 4-stair climb, -0.4 s; 100m, -7.9 s; 10m, -0.6 s). Post hoc analysis showed improved NSAD outcomes versus untreated natural history cohort (9.2-point difference at Y2; 95% Cl, 3.2-15.1).

**Conclusions:** These data suggest long-term efficacy of SRP-9003 therapy, supporting advancement ofthe clinical development program.

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**Disclosures: LRR-K, ERP, SL, DAG, ASM, EK, SN, and XL** are or have been employees of Sarepta Therapeutics, Inc, and may own stock in the company. **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. **KJL, KC, NFR, and MAI** have no conflicts to disclose. Product is investigational only.

# Part A (Dose-Finding Phase) Results From a Phase 2 Multiple Ascending-Dose Study of SRP-5051, a Peptide-Conjugated PMO, in Patients With DMD Amenable to Exon 51 Skipping

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## ABSTRACT

**Introduction:** Peptide-conjugated phosphorodiamidate morpholino oligomers (PPMOs) are a next generation chemistry platform in which a cell-penetrating peptide is conjugated to the PMO backbone, with the goal of increasing tissue penetration, exon skipping, and dystrophin production with less frequent dosing. SRP-5051 is an investigational PPMO designed to skip *DMD* exon 51.

**Objectives:** To report results from part A dose-finding phase of MOMENTUM (NCT04004065), a phase 2 trial of SRP-5051.

**Methods:** Patients amenable to exon 51 skipping (aged 7-21 years) received ascending doses of SRP- 5051 (4, 10, 20, or 30 mg/kg) intravenously every 4 weeks. Primary endpoint was safety; other endpoints included exon skipping, dystrophin protein, and pharmacokinetics of each dose.

**Results:** Eighteen patients were enrolled. At week 12, exon skipping for the 20- and 30-mg/kg cohorts was 2.57% and 10.79%, respectively (versus 0.26% and 1.62% at baseline), and mean dystrophin protein was 3.06% and 6.55% of normal (versus 0.17% and 0.92% at baseline); all patients in these cohorts experienced an increase in exon skipping and dystrophin production. Immunofluorescence results from the 30-mg/kg cohort showed correct localization of dystrophin to the sarcolemma. Overall, 17/18 (94.4%) patients experienced a treatment-emergent adverse event (TEAE); the majority were mild to moderate in severity. Ten (55.6%) patients experienced treatment related TEAEs of hypomagnesemia (including 2 serious cases) prior to the implementation of magnesium monitoring and supplementation; most cases were mild to moderate, asymptomatic, and resolved with supplementation. No other safety concerns were identified.

**Conclusions:** MOMENTUM Part A results show SRP-5051 increases exon skipping and dystrophin production and that the majority of TEAEs were mild to moderate in severity. All participants from Part A will be invited to enroll in Part B of MOMENTUM.

**Funding:** This study was funded by Sarepta Therapeutics, Inc.

**Disclosures: CC** is a site investigator for Acceleron, AMO, Biogen, Biomarin, Cytokinetics, GSK, Pfizer, PTC Therapeutics, Roche, Sarepta, and Wave, and has received research support from Biogen, Genzyme, PTC Therapeutics, and Valerian for investigator-initiated grants. He has received fees for advisory functions from AMO, Biogen, Roche, and PTC Therapeutics, and is a data safety monitoringboard member for Catabasis and Solid. **MvdR, EP, XN, JT, NS, JM, and IS** are or have been employees of Sarepta Therapeutics, Inc, and may own stock in the company. **KM** has received research support as a site Pl from Catabasis, ltalfarmaco, Reata, Retrotope, Santhera, and Sarepta. She also has research support from CDC (U0l D0001248) and FARA and NIH (5 U54 NS053672, U24 NS-10718). **HP** has received grants from the CDC foundation and research support as a site Pl from Catabasis, ltalfarmaco, Pfizer, Santhera, and Sar epta. Products are investigational only.

# Safety, Tolerability, and Pharmacokinetics of Eteplirsen in Patients 6-48 Months Old With Duchenne Muscular Dystrophy Amenable to Exon 51 Skipping

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## ABSTRACT

**Introduction:** Eteplirsen is indicated for treatment of exon 51 skip-amenable patients with Duchenne muscular dystrophy (DMD). Previous studies in patients >4 years of age indicate eteplirsen is well tolerated and attenuates pulmonary and ambulatory declines compared with matched natural history cohorts.

**Objectives:** To evaluate safety, tolerability, and pharmacokinetics of eteplirsen in patients aged 6-48 months, the youngest population in a clinical trial to date of exon 51 skip-amenable patients with DMD (Study 4658-102, NCT03218995).

**Methods:** In this open-label, multicenter, dose-escalation study, all patients (Cohort 1: aged 24-48 months, n=9; Cohort 2: aged 6 to <24 months, n=6) received ascending doses (2, 4, 10, 20, 30 mg/kg) of once-weekly eteplirsen intravenously over 10 weeks, continuing at 30 mg/kg up to 96 weeks. Endpoints included incidence of adverse events and clinically significant laboratory abnormalities (primary) and pharmacokinetics (secondary).

**Results:** All patients completed the study (N=15). Average time since diagnosis was 10.5 months, and most (13/15, 86.7%) were not taking corticosteroids. Eteplirsen was well tolerated with no treatment related discontinuations, deaths, or evidence of renal toxicity. Most treatment-emergent adverse events were mild, and the most common were consistent with those commonly seen in pediatric populations (pyrexia, nasopharyngitis, vomiting, cough, diarrhea). Eteplirsen pharmacokinetics were consistent between both cohorts and aligned with expectations based on clinical experience in the older population.

**Conclusions:** These data contribute to the growing body of evidence supporting eteplirsen use at the approved 30-mg/kg dose by demonstrating its safety, tolerability, and predictable pharmacokinetic profile in patients as young as 6 months.

**Funding:** This study was funded by Sarepta Therapeutics, Inc.

**Disclosures: EM** has received consultant fees from Sarepta Therapeutics, Inc. **AMS** has no conflicts todisclose. **LS** has participated on advisory boards for Sarepta Therapeutics, Inc. **ND** has participated on advisory boards for Sarepta Therapeutics, Inc. **HS, LE, WZ, and SU** are employees of Sarepta Therapeutics, Inc, and may own stock/options in the company. **FM** has received consultant fees and speaker honoraria from Sarepta Therapeutics, Inc.

# ENDEAVOR: Evaluating the safety and expression of the gene transfer therapy SRP-9001 in Duchenne muscular dystrophy (DMD)

C. Zaidman[1], C. Proud[2], C. McDonald[3], K. Giblin[4], L. Collins[4], S. Wang[4], S. Upadhyay [4], S. Lewis[4], J. Malhotra[4], D. A. Griffin [4], R. A. Potter[4], M. Guridi[5] L. R. Rodino-Klapac[4], J. R. Mendell [6,7]

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## ABSTRACT

**Introduction:** rAAVrh74.MHCK7.micro-dystrophin (SRP-9001), an investigational gene transfer therapy, is being developed to achieve targeted skeletal and cardiac muscle expression of a shortened functional micro-dystrophin protein. Initial findings from ongoing Phase 1 and 2 trials in which patients received SRP-9001 clinical process material reported micro-dystrophin expression following gene transfer and suggest the potential for SRP-9001 therapy to provide clinical benefit to people with Duchenne muscular dystrophy (DMD).

**Objectives:** The aim of ENDEAVOR (Study 103; NCT04626674), an open-label, Phase 1b study, is to assess expression and safety of commercially representative SRP-9001 process material in patients with DMD.

**Methods:** Trial participants were given a single intravenous dose of $1.33x10^{14}$ vg/kg (linear qPCR) of SRP-9001 commercially representative material. The follow-up period consists of two parts: Part 1, from post infusion through Week 12; and Part 2, post-Week 12 through Week 260. The primary outcome measure is the change from baseline to Week 12 (Part 1) in micro-dystrophin protein expression as measured by western blot (WB). Secondary outcome measures include evaluation of micro-dystrophin expression at Week 12 by immunofluorescence (IF) and safety of SRP-9001 (incidence of adverse events [AEs] or clinically significant abnormalities in vital signs, including electrocardiograms and echocardiograms, up to Week 260). This interim analysis presents results for the first 11 patients enrolled (cut-off date May 2021).

**Results:** Treatment with SRP-9001 resulted in robust levels of micro-dystrophin protein expression by WB (change from baseline 55.4% of normal, SD=43.4). Expression was localized to the sarcolemma, as shown by IF (change from baseline in PDPF 57.7%, SD=22.2; change from baseline in IF intensity 75.9% of normal, SD=46.4) at Week 12. Micro-dystrophin expression was also associated with vector genome copies (change from baseline 3.9 vcgs, SD=2.4), confirming successful delivery of SRP-9001 to target cells. Safety of the commercially representative SRP-9001 material was consistent with previous experience with SRP-9001. No new safety signals were identified. Seventy-nine treatment-emergent AEs (TEAEs) occurred. As seen in previous studies, vomiting was the most common TEAE (64% of patients). No clinically relevant complement activation was observed. Two patients experienced three treatment-related serious AEs: one patient had increased transaminases that required corticosteroid treatment; one patient experienced both nausea and vomiting that required intravenous treatment. No deaths were observed.

**Conclusions:** Study 103, the first clinical study using commercially representative SRP-9001 material, provides preliminary evidence that the commercially representative material demonstrates safety and expression consistent with previous studies. The safety profile was consistent with prior studies, with no new safety signals identified.

**Disclosures:** Craig Zaidman receives research support from Biogen, serves on an advisory board for Biogen Inc, and was a paid consultant for Optum.
Crystal Proud participates on advisory boards and is a consultant for Biogen, Sarepta, AveXis/Novartis Gene Therapies, Genentech/Roche and Scholar Rock. She serves as a speaker for Biogen. She is a Principal investigator of studies sponsored by AveXis/Novartis Gene Therapies, AMO, Astellas, Biogen, CSL Behring, FibroGen, PTC, Pfizer, Sarepta and Scholar Rock.

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Kathryn Giblin is an employee of Sarepta Therapeutics, Inc and may have stock options. Larisa Collins is an employee of Sarepta Therapeutics, Inc and may have stock options. Shufang Wang is an employee of Sarepta Therapeutics, Inc and may have stock option. Sameer Upadhyay is an employee of Sarepta Therapeutics, Inc and may have stock options.Sarah Lewis is an employee of Sarepta Therapeutics, Inc and may have stock options.
Jyoti Malhotra is an employee of Sarepta Therapeutics, Inc and may have stock options. Danielle A. Griffin is an employee of Sarepta Therapeutics, Inc and may have stock options.Rachael A. Potter is an employee of Sarepta Therapeutics, Inc and may have stock options.Maitea Guridi reports no conflicts of interest.
Louise R. Rodino-Klapac is an employee of Sarepta Therapeutics, Inc, has received grant support from Sarepta Therapeutics, Inc and the Parent Project Muscular Dystrophy, as well as financial consideration from Sarepta Therapeutics, Inc and Myonexus Therapeutics (now acquired by Sarepta Therapeutics). In addition, she is a co-inventor of AAVrh74.MHCK7. micro-dys technology, which is exclusively licensed toSarepta Therapeutics, Inc.
Jerry R. Mendell has received study funding from Sarepta Therapeutics, Inc for the current publication and has a service agreement with Sarepta Therapeutics, Inc, to provide training on ongoing studies. In addition, he is a co-inventor of AAVrh74.MHCK7.micro-dys technology, which is exclusively licensed to Sarepta Therapeutics, Inc.

# A Phase 2 clinical trial evaluating the safety and efficacy of SRP-9001 for treating patients with Duchenne muscular dystrophy (DMD)

J. R. Mendell[1,2] P. B. Shieh[3] Z. Sahenk[1,2] K. J. Lehman1, L. P. Lowes[1,2] N. F. Reash1, M.A. lammarino1, L. N. Alfano[1,2], B. Powers [1], J. D. Woods[3], C. L. Skura [3], H. C. Mao [3] L.A. Stau dt[3], R. A. Potter[4], D. A. Griffin [4], S. Lewis[4], L. Hu4, S. Upadhyay [4] T. Singh[4], L. R. Rodino-Klapac[4]

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## ABSTRACT

**Introduction:** rAAVrh74.MHCK7.micro-dystrophin (SRP-9001), an investigational gene transfer therapy, is being developed to achieve targeted skeletal and cardiac muscle expression of a shortened functional micro dystrophin protein. We tested the safety and efficacy of SRP-9001 in a three-part, multicenter, Phase 2 clinical trial (Study 102; NCT03769116). Part 1 is a 48-week, randomized, double-blind, placebo controlled period. Part 2 is a 48-week period in which Part 1 placebo-treated patients receive SRP-9001 (blinded crossover). Part 3 is an open-label follow-up period (up to 212 weeks).

**Objectives:** We evaluated the safety and efficacy of SRP-9001 in a double-blind, placebo-controlled trial.

**Methods:** Participants (ambulatory boys 4-7 years old, confirmed *DMD* mutation, stable steroid dosing) received SRP-9001 (n=20) or placebo (n=21). The target dose was $2.0x10^{14}$ vg/kg (supercoiled qPCR, linear plasmid standard equivalent of $1.33x10^{14}$ vg/kg). Randomization was stratified by age (4-5 and 6-7 yearsold). Primary endpoints were change in micro-dystrophin expression (western blot; baseline to Week 12) and change in North Star Ambulatory Assessment (NSAA; baseline to Week 48). Safety endpoints included treatment-emergent adverse events (AEs) and serious AEs.

**Results:** In Part 1, the primary biological endpoint (change in micro-dystrophin expression) was met. At Week 48, NSAA change from baseline was not statistically different between groups. Pre-specified subgroup analysis of 4- to 5-year olds showed a statistically significant difference in NSAA change between SRP- 9001 and placebo groups (+2.5, P=0.0172). Baseline NSAA score of the 4- to 5-year olds was balanced across arms but was significantly imbalanced in the 6- to 7-year olds. We observed no clinically relevant complement activation. Treatment-related AEs were transient and manageable . Four patients had treatment-related serious AEs, which resolved.

**Conclusions:** Data suggest a biological effect of SRP-9001 that may be clinically relevant in people with DMD. Results reinforce a favorable benefit-risk profile.

**Disclosures:** Perry B. Shieh reports being a consultant/independent contractor for AveXis/Novartis Gene Therapies, Biogen Inc, Cytokinetics, and Sarepta Therapeutics, Inc, and receiving grants/research support from AveXis/Novartis Gene Therapies, Biogen Inc, Cytokinetics, lonis Pharmaceuticals, Inc, Sanofi Genzyme, and Sarepta Therapeutics, Inc.
Linda P. Lowes reports receiving salary support from Sarepta Therapeutics, Inc through Nationwide Children's Hospital to support training and quality control activities for their ongoing clinical trials and licensing fees for natural history data.
Natalie F. Reash reports receiving salary support from Sarepta Therapeutics, Inc, for Clinical Evaluatortraining for ongoing and upcoming clinical trials.
Lindsay N. Alfano reports receiving salary support from Sarepta Therapeutics, Inc, through Nationwide Children's Hospital to support training and quality control activities for their ongoing clinical trials.
Rachael A. Potter is an employee of Sarepta Therapeutics, Inc, and may have stock options. Danielle A. Griffin is an employee of Sarepta Therapeutics, Inc, and may have stock options. Sarah Lewis is an employee of Sarepta Therapeutics, Inc, and may have stock options.
Larry Hu is an employee of Sarepta Therapeutics, Inc, and may have stock options.

Sameer Upadhyay is an employee of Sarepta Therapeutics, Inc, and may have stock options.Teji Singh is an employee of Sarepta Therapeutics, Inc, and may have stock options.
Louise R. Rodino-Klapac is an employee of Sarepta Therapeutics, Inc, has received grant support from Sarepta Therapeutics, Inc and the Parent Project Muscular Dystrophy, as well as financial consideration from Sarepta Therapeutics, Inc and Myonexus Therapeutics (now acquired by Sarepta Therapeutics). In addition, she is a co-inventor of AAVrh74. MHCK7.micro-dys technology, which is exclusively licensed to Sarepta Therapeutics, Inc.
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Megan A. lammarino, Brenna Powers, Jeremy D. Woods, Christy L. Skura, Howard C. Mao, and Loretta A. Staudt report no conflicts of interest.

# The impact of the coronavirus 2019 (COVID-19) pandemic on enrollment of patients with chronic demyelinating polyneuropathy (CIDP) in subcutaneous immunoglobulin (SCIg) self administration training

E. Murphy, L. Barrett, C. Vanname*, C. Jackson*, J. Barber, P. Patel, A. Katz

*CSL Behring LLC, King of Prussia, PA*
*Specialty Pharmacy Nursing Network [SPNN] Inc, Sarasota, FL*

## ABSTRACT

**Introduction:** SCIg is an FDA approved treatment for adult patients with CIDP. Patients can participate in self-administration training by Specialty Pharmacy Nurse Network (SPNN).

**Objective:** To assess the impact of the COVID-19 pandemic on enrollment of patients with CIDP in SCIg self-administration training.

**Methods:** This was a retrospective study utilizing SPNN data of patients with CIDP enrolled in 1-7 training sessions between 5/2018-1/2020 ('2018/19') and 1/2020-1/2021 ('2020').

**Results:** Overall, 120 patients were referred to SPNN for SCIg training in 2020, compared with 310 in 2018/19. Training discontinuation rates were slightly lower in 2020 compared with 2018/19 (4% vs. 10%, respectively). The majority of patients (84%) continued with in-person training during 2020 (9% virtual and 7% mix of both). Most successfully-trained patients (75%) required 3-4 sessions irrespective of year trained.

**Conclusion:** Enrollment during the COVID-19 pandemic (2020) was lower compared with 2018/19, and discontinuation rates were slightly lower.

**Funding:** CSL Behring sponsored this analysis

# Risk of CIDP relapse by body mass index (BMI): a sub-analysis from the PATH and open label extension (OLE) studies

Jaclyn Barber, Palak Patel, Michaela Praus*, John-Philip Lawo*, Orel! Mielke*, and Arie Katz

*(CSL Behring LLC, King of Prussia, USA; CSL Behring GmbH, Marburg, Germany*)*

## ABSTRACT

**Introduction:** Subcutaneous immunoglobulin (SCIg) is an FDA approved maintenance treatment for adult patients with chronic inflammatory demyelinating polyneuropathy (CIDP).

**Objective:** To evaluate CIDP relapse rates vs body mass index (BMI) in PATH and its open label extension (OLE).

**Methods:** PATH was a randomized, double-blind study investigating 0.2 and 0.4 g/kg weekly SCIg versus placebo, followed by an OLE. This sub-analysis stratified data by BMI: lean (<25 kg/ $m^2$), overweight (≥25-<30 kg/ $m^2$), and obese (≥30 kg/ $m^2$).

**Results:** In PATH, relapse rates were lower with SCIg than with placebo across all BMI ranges. In both PATH and its OLE, the relapse risk was lower with 0.4 g/kg than with 0.2 g/kg. In the OLE, no difference was observed in overall relapse rate (no. of relapses/weeks on treatment) between lean,overweight, and obese patients (0.013, 0.013, and 0.016, respectively).

**Conclusion:** SCIg was effective as a CIDP maintenance therapy across a range of patient BMIs.

**Funding:** CSL Behring sponsored this study and conducted the analysis

# FORCE™ platform delivers exon skipping PMO, leads to durable increases in dystrophin protein in *mdx* mice and is well tolerated in NHPs

Cody A. Desjardins, Reshmii Venkatesan, Emma O'Donnell, John Hall, Ryan Russo, Sean Spring, Kim Tang, John W. Davis II, Tim Weeden, Oxana Beskrovnaya

*Waltham, MA*

## ABSTRACT

Duchenne muscular dystrophy (DMD) is the most common X-linked muscular dystrophy. We developed the FORCE™ platform, which consists of a Fab targeting TfR1, Val-Cit linker, and an exon skipping phosphorodiamidate morpholino oligomer (PMO), to deliver a potentially transformative therapy for patients with DMD.

Approved PMO therapies are limited by poor muscle delivery. We therefore evaluated the potential of FORCE to improve exon skipping and dystrophin expression in mdx model of DMD.

Multiple ascending doses were administered via a single IV dose of FORCE to *mdx* mice. Muscle PMO concentration, exon skipping, and dystrophin protein were measured at multiple timepoints. Tolerability was assessed in nonhuman primates (NHP).

A substantial long-lasting, dose-dependent increase in dystrophin was achieved in *mdx* mice. Our lead candidate was well-tolerated with no dose-limiting toxicities in NHP.

Together our data support the ability of the FORCE platform to deliver exon skipping therapy to patients with DMD.

# Development of a standard of care for patients with valosin-containing protein associated multisystem proteinopathy

M.K. Korb[1], A. Peck [2] K.I. Ber ger[3], M.K. James[4], N. Ghoshal [5], E. Healzer [6] C. Henchcliffe[1], S. Khan [7], P.P. M ammen[7] S. Patel Weihl[5 14], G. Pfe ff er[9], S.H. Ralston [10], B. Roy[11] , B. Seeley[12], A. Swenson[13], T. Mozaffar[1], C. Weihl[5, 14], V. Kimonis[1], L.N. Alfano[15]

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*[15]The Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus OH, USA*

## ABSTRACT

Valosin-containing protein (VCP) associated multisystem proteinopathy (MSP) is a rare inherited disorder that may result in varying phenotypes including inclusion body myopathy, Paget's disease of bone, and frontotemporal dementia. An international consortium was convened by the patient advocacy organization, Cure VCP Disease, in April 2021 to develop a standard of care for this under diagnosed disease. To achieve this goal, working groups collaborated to generate best evidence recommendations in 10 key areas: genetics and diagnosis, myopathy, frontotemporal dementia, Paget's disease of bone, ALS and CMT, parkinsonism, cardiomyopathy, supportive therapies, pulmonology, nutrition and supplements, and mental health. Timely referral to a specialty neuromuscular center and multidisciplinary team follow up are essential for screening and management of secondary complications. The goal of our consortium was to expedite the time to accurate diagnosis, initiate appropriate therapies for optimal management, and elevate the recommended best practices guidelines for VCP MSP care.

# MUSCLE STUDY GROUP

## Annual Scientific Meeting

OCTOBER 1-3, 2021

Muscle Study Group

# WELCOME!

Welcome! On behalf of your Muscle Study Group, we would like to welcome each of you to the 2021 Muscle Study Group Annual Meeting. It is an exciting time in neuromuscular research as we continue to grow and adapt.

We once again are conducting our meeting virtually given the recent surge of COVID over the summer. We were also shown by our meeting last year a ZOOM conference is an effective way to communicate at a distance. Again, we have set up the meeting for three morning sessions, as all day sessions contribute to ZFS (ZOOM FATIGUE SYNDROME), and our European colleagues need to sleep at some point!

We are excited this year to have more industry involvement than we have ever had. The Shark Tank session was such a success last year we are bringing it back with the opportunity of a $10K grant to the winner!

We also have been encouraging residents to register and have been successful. We want to encourage and stimulate residents to pursue NM Fellowships as this group is our successors to the next generation.

The MSG continues to fund a Neuromuscular Research 2-year fellowship program so at any one time we have a 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 Muscle 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. They have spent much time planning an in-person meeting and then changing course to secure a virtual meeting. Keep a lookout on the MSG website for the 2022 meeting information as next year we are hoping to meet in person in northern Italy.

Best wishes,

Richard J. Barohn, M.D.
*Executive Vice Chancellor for Health Affairs,*
*University of Missouri*
*Co-chair, Muscle Study Group*

Prof Michael G. Hanna, M.D.
*Director, University College London Institute of Neurology*
*Co-chair, Muscle Study Group*

## *2021 Planning Committee*

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*University of Pennsylvania Health System*

James Lilleker, MBChB, Ph.D. // Co-Chair
*The University of Manchester*

Senda Ajroud-Driss, M.D.
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*University of Pennsylvania Health System*

Tracey Willis, MBChB, MMedSci, M.D.
*Chester University, UK*

Amelia Wilson, DPT
*University of Utah Health*

# AGENDA //
# Friday, October 1

James Lilleker, MBChB, Ph.D.; Senda Ajroud-Driss, M.D. // *Moderators*

**8:00 - 8:05 A.M.** **OPENING** Richard J. Barohn, M.D., Prof Michael G. Hanna, M.D.

**8:05 - 9:05 A.M.** **ROBERT C. GRIGGS, M.D. ANNUAL MSG LECTURE: IDIOPATHIC DOES NOT MEAN CRYPTOGENIC: THERAPEUTIC DEVELOPMENT FOR METABOLIC NEUROPATHY**
Gordon Smith, M.D. // *Virginia Commonwealth University*

**9:10 - 9:25 A.M.** **IBM INTERNATIONAL GENETICS CONSORTIUM STUDY UPDATE**
Prof Michael G. Hanna, M.D.

## SESSION 1: INFLAMMATORY MYOPATHIES

**9:25 - 9:45 A.M.** **AUTOANTIBODIES IN MYOSITIS** Prof Neil McHugh, MBChB, M.D. // *University of Bath*

**9:50 - 10:10 A.M.** **INTERVENTIONAL STUDIES IN MYOSITIS (IVIG, TOC, RITUX)**
Rohit Aggarwal, M.D. // *University of Pittsburgh*

**10:15 - 10:35 A.M.** **RAPAMYCIN STUDY** Prof Olivier Benveniste, M.D., Ph.D. // *AP-HP*

**10:37 - 10:50 A.M.** **BREAK** Sponsored by CSL Behring

# MUSCLE STUDY GROUP

## SESSION 2: FLASH PRESENTATIONS

**10:50 - 11:00 A.M.** **MOLECULAR BIOMARKERS IN MYOTONIC MUSCULAR DYSTROPHY TYPE 2**
Paloma Gonzalez-Perez, M.D., Ph.D. // *MSG Fellow, Massachusetts General Hospital*

**11:02 - 11:12 A.M.** **CD8 POSITRON EMISSION TOMOGRAPHY (PET/CT) IMAGING WITH 89ZR-DF-IAB22M2C IN PATIENTS WITH INCLUSION BODY MYOSITIS**
Colin Quinn, M.D. // *University of Pennsylvania*

**11:14 - 11:24 A.M.** **10 PS MNEMONIC FOR DX OF IIM** Amir Sabouri, M.D. // *Kaiser Permanente*

**11:26 - 11:36 A.M.** **INFLAMMATORY MYOPATHIES PRESENTING WITH AXIAL WEAKNESS**
Elie Naddaf, M.D. // *Mayo Clinic*

**11:38 - 11:58 A.M.** **OPTIMIZING CIDP CARE WITH SCIG: PATH OLE AND BEYOND**
Mazen Dimachkie, M.D. // *CSL Behring Update*

**12:03 - 12:23 P.M.** **THE ROLES OF AUTOANTIBODIES IN IMMUNE CHECKPOINT INHIBITOR THERAPY: FROM BIOMARKERS TO MEDIATORS OF NEUROLOGICAL SYNDROMES**
Karin Hoang Woodman, M.D. // *Argenx Update*

**12:28 - 12:48 P.M.** **FORCE™ PLATFORM DELIVERS EXON SKIPPING PMO, LEADS TO DURABLE INCREASES IN DYSTROPHIN PROTEIN IN *MDX* MICE AND IS WELL TOLERATED IN NHPS**
Oxana Beskrovnaya, Ph.D. // *Dyne Therapeutics Update*

**12:50 P.M.** **CLOSING** Richard J. Barohn, M.D., Prof Michael G. Hanna, M.D.

**12:50-1:30 P.M.** **MINGLING TIME (OPTIONAL)**
Zoom Rooms: Cigar Mingling Room | CSL Behring Room
Dyne Therapeutics Room | Argenx Room

*All times US Central Time*

# AGENDA //
# Saturday, October 2

Chafic Karam, M.D.; Amelia Wilson, DPT // *Moderators*

**8:00 - 8:08 A.M.** OPENING Richard J. Barohn, M.D., Prof Michael G. Hanna, M.D.

**8:09 - 9:19 A.M.** ARIMOCLOMOL IN IBM TRIAL UPDATE
Mazen Dimachkie, M.D. // *University of Kansas Medical Center*

## SESSION 3: INFLAMMATORY NEUROPATHIES AND OUTCOME MEASURES

**8:20 - 8:40 A.M.** EXPANDING THE SPECTRUM OF CHRONIC IMMUNE SENSORY POLYRADICULOPATHY: THE CISP-PLUS SYNDROME James Dyck, M.D. // *Mayo Clinic*

**8:45 - 9:05 A.M.** BIOMARKERS IN CIDP/GBS Karissa Gable, M.D. // *Duke University Medical Center*

**9:05 - 9:25 A.M.** 2021 EAN/PNS CIDP GUIDELINES: A FOCUSED REVIEW OF THE NEW DIAGNOSTIC AND TREATMENT GUIDELINES Jeff Allen, M.D. // *University of Minnesota*

**9:30 - 9:50 A.M.** OUTCOME MEASURES Gita Ramdharry, DPT // *University College London*

**9:55 - 10:10 A.M.** BREAK Sponsored by PTC Pharma

## SESSION 4: FLASH PRESENTATIONS

**10:10 - 10:25 A.M.** POST-TRANSLATIONAL MODIFICATIONS OF DUX4
Renatta Knox, M.D. // *MSG Fellow, Nationwide Children's Hospital*

**10:27 - 10:37 A.M.** LOSS OF TDP-43 FUNCTION AND RIMMED VACUOLES PERSIST AFTER T CELL DEPLETION IN A XENOGRAFT MODEL OF INCLUSION BODY MYOSITIS
Chiseko Ikenaga, M.D., Ph.D. // *Johns Hopkins University*

**10:39 - 10:49 A.M.** PROTOCOL FOR A HYBRID II STUDY EXPLORING THE FEASIBILITY OF DELIVERING, EVALUATING, AND IMPLEMENTING A SELF-MANAGEMENT PROGRAMME FOR PEOPLE WITH NEUROMUSCULAR DISEASES AT A SPECIALIST NEUROMUSCULAR CENTRE (ADAPT-NMD)
Louie Lee, BSc (HONS) // *University College London*

**10:51 - 11:01 A.M.** ESTABLISHING CLINICAL TRIAL READINESS FOR VALOSIN CONTAINING PROTEIN-ASSOCIATED MULTISYSTEM PROTEINOPATHY: BASELINE RESULTS FROM A 1-YEAR PROSPECTIVE STUDY Megan A. Iammarino, PT, DPT // *Nationwide Children's Hospital*

**11:03 - 11:13 A.M.** COVID-19 RELATED OUTCOMES IN PRIMARY MITOCHONDRIAL DISEASES: AN INTERNATIONAL STUDY Chiara Pizzamiglio, M.D. // *University College London*

**11:15 - 11:25 A.M.** SELF-MANAGEMENT IN NEUROMUSCULAR DISEASES: PRELIMINARY FINDINGS FROM A QUALITATIVE EXPLORATION OF THE PATIENT PERSPECTIVE
Louie Lee, BSc (HONS) // *University College London*

**11:27 - 11:37 A.M.** PROSPECTIVE CLINICAL TRIAL READINESS IN LGMDR9 FKRP-RELATED MUSCULAR DYSTROPHY: A GRASP CONSORTIUM STUDY Megan A. Iammarino, PT, DPT // *Nationwide Children's Hospital*

**11:37 - 11:45 A.M.** BREAK Sponsored by Argenx

**11:45 A.M. - 12:05 P.M.** DEFLAZACORT EVIDENCE FOR ITS ROLE IN SLOWING DMD DISEASE
Richard A. Able, Jr., Ph.D. // *PTC Therapeutics Inc. Update*

**12:10 - 12:30 P.M.** EXPLORE THE SCIENCE FOR AN APPROVED SPINAL MUSCULAR ATROPHY TREATMENT
Elizabeth Kichula, M.D., Ph.D. // *Genentech Update*

**12:35 - 12:37 P.M.** SAREPTA THERAPEUTICS SPONSOR INTRODUCTION Dr. Gilmore O'Neill

**12:40 P.M.** CLOSING Richard J. Barohn, M.D., Prof Michael G. Hanna, M.D.

**12:40 - 1:30 P.M.** MINGLING TIME (OPTIONAL)
Zoom Rooms: Cigar Mingling Room | Genentech Room
PTC Therapeutics Room

# MUSCLE STUDY GROUP

*All times US Central Time*

# AGENDA //
# Sunday, October 3

James Lilleker, MBChB, Ph.D.; Laurie Gutmann, M.D.; Melissa McIntyre, DPT // *Moderators*

# MUSCLE STUDY GROUP

**8:00 - 8:05 A.M.** OPENING Richard J. Barohn, M.D., Prof Michael G. Hanna, M.D.

**8:05 - 8:15 A.M.** NIH SIBM NATURAL HISTORY STUDY TRIAL UPDATE
Tahseen Mozaffar, M.D. // *University of California, Irvine*

**8:17 - 8:27 A.M.** DUCHENNE MUSCULAR DYSTROPHY RESPIRATORY PROFILES FROM REAL WORLD REGISTRY DATA
Mona Hnaini, M.D. // *Pediatric Neuromuscular Fellow, London Health Science Centre Western University*

## SESSION 5: SHARK TANK

**8:20 - 9:45 A.M.** SHARK TANK SESSIONS James Lilleker, MBChB, Ph.D. // *Moderator*
W. David Arnold, M.D., Prof Tracey Willis, MBChB, MMedSci, M.D., Gita Ramdharry, DPT // *Shark Panel*

THE INNATE IMMUNE SYSTEM IN MYASTHENIA GRAVIS
Katherine Dodd, MBChB MRCP, Ph.D. Student //
*University of Manchester, UK*

THE THERAPEUTIC PLAY GYM PILOT STUDY
Jenna Linn Lammers, MSR/PT,CNT, PCS //
*University of Florida*

IDENTIFICATION OF NOVEL BIOMARKERS FOR INCLUSION BODY MYOSITIS USING SINGLE-NUCLEI RNA SEQUENCING OF MUSCLE BIOPSIES
Chiseko Ikenaga, M.D., Ph.D. //
*Johns Hopkins University School of Medicine*

**9:45 - 10:00 A.M.** BREAK Sponsored by Genentech

## SESSION 6: GENETICS

**10:00 - 10:20 A.M.** VUS Tanya Bardkjian, MS, LCGC // *University of Pennsylvania*

**10:25 - 10:45 A.M.** RESOLUTION OF GENETIC VARIANTS OF UNCERTAIN SIGNIFICANCE USING MUSCLE BIOPSIES
Karra Jones, M.D., Ph.D. // *University of Iowa*

**10:50 - 11:10 A.M.** GENETIC TESTING IN NEUROMUSCULAR DISORDERS Shawna Feely, MS, LGC // *University of Iowa*

**11:10 - 11:15 A.M.** ANNOUNCEMENT OF SHARK TANK AWARD

## SESSION 7: FLASH PRESENTATIONS

**11:15 - 11:25 A.M.** 2020 SHARK TANK AWARD WINNER PRESENTATION:
MEND (MEXILETINE VERSUS LAMOTRIGINE IN NON-DYSTROPHIC MYOTONIA)
Dr. Vinojini Vivekanandam, MBBS // *University College London Institute of Neurology*

**11:27 - 11:37 A.M.** ADAPTING MRI AS A CLINICAL OUTCOME MEASURE FOR A FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY TRIAL OF PREDNISONE AND TACROLIMUS
Leo Wang, M.D., Ph.D. // *University of Washington*

**11:38 - 11:48 A.M.** RACIAL DISPARITIES IN SKIN TONE REPRESENTATION OF DERMATOMYOSITIS RASHES
Salman Bhai, M.D. // *University of Texas Southwestern*

**11:49 - 11:59 A.M.** LONGITUDINAL DYSPHAGIA ASSESSMENT IN PATIENTS WITH CYSTINOSIS USING MBSIMP
Stacey Sullivan, MS, CCC, SLP // *Mass General Hospital*

**12:00 - 12:10 P.M.** CMT-COVID SURVEY Riccardo Zuccarino, M.D. // *NEMO*

**12:11 - 12:21 P.M.** CASE SERIES OF MYASTHENIA GRAVIS (MG) PATIENTS PRESCRIBED SUBCUTANEOUS IMMUNOGLOBULIN (SCIG) THERAPY AND MONITORED BY PATIENT REPORTED OUTCOME MEASURES (PROMS) BY A SPECIALTY INFUSION PHARMACY USING SOLEMETRICS
Timothy Walton, MHS, CCRP // *Soleo Health*

**12:22 - 12:32 P.M.** FLOW CYTOMETRY AND SORTING OF SINGLE ANTIBODY SECRETING CELLS FROM FROZEN MUSCLE TISSUE Vladimir Liarski, M.D. // *University of Chicago Medicine*

**12:33 - 12:43 P.M.** EFFECT OF DISTAL HEREDITARY MOTOR NEUROPATHY ON MUSCLE STRUCTURE, FUNCTION, AND GAIT PATTERNS: TWO CASE REPORTS
Aljwhara Alangary, PT, Ph.D. Student // *University College London*

**12:44 - 12:54 P.M.** MONOTHERAPY WITH ECULIZUMAB IN REFRACTORY ACETYLCHOLINE RECEPTOR POSITIVE GENERALIZED MYASTHENIA GRAVIS
Xiaoyang Li, MBBS, M.D. // *University of North Carolina at Chapel Hill*

**12:55 P.M.** CLOSING Richard J. Barohn, M.D., Prof Michael G. Hanna, M.D.

**1:00 - 1:30 P.M.** AFTER HOURS OPEN MINGLING (all welcome to attend)

*All times US Central Time*

# MEETING SUPPORT //
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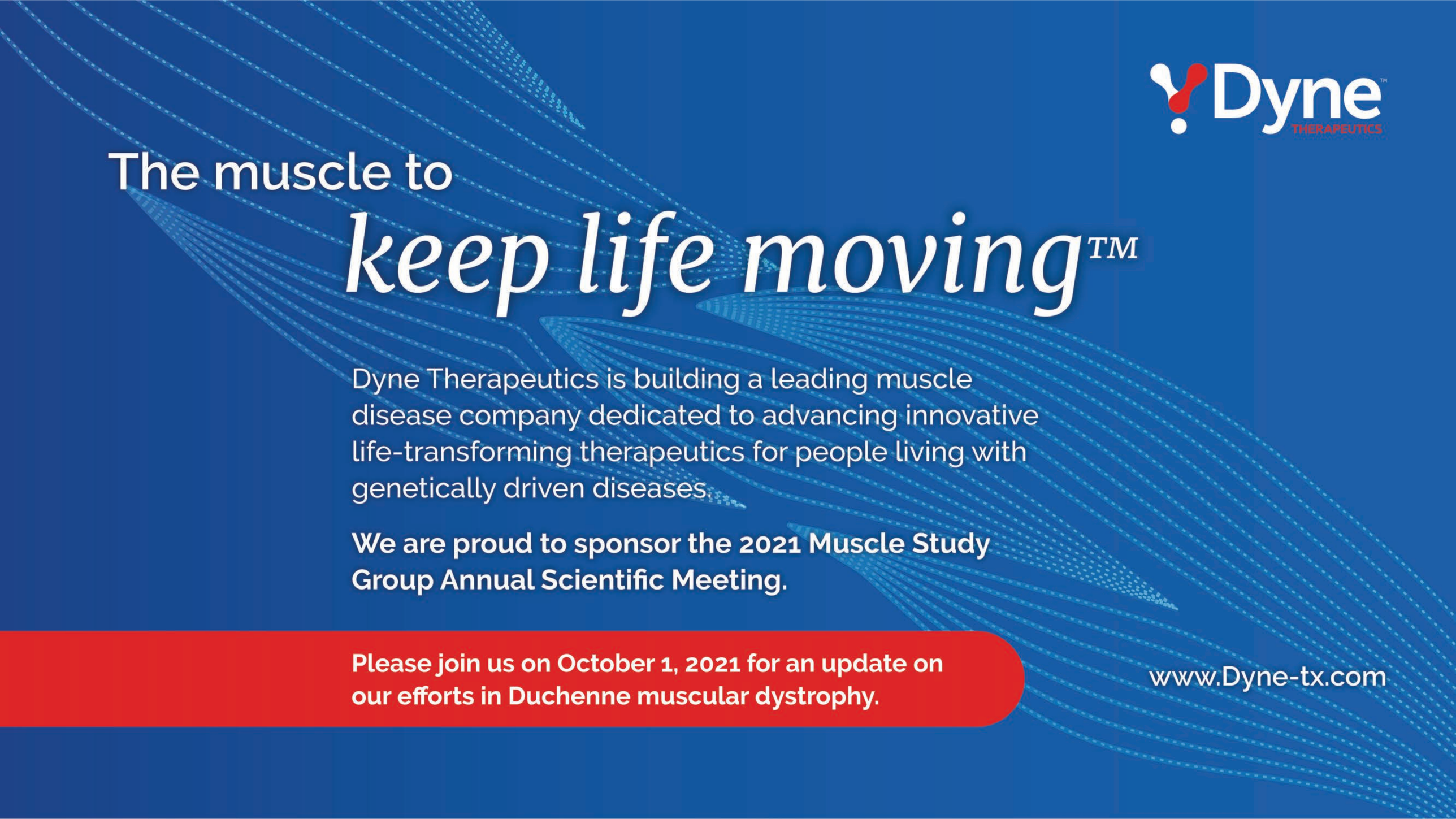
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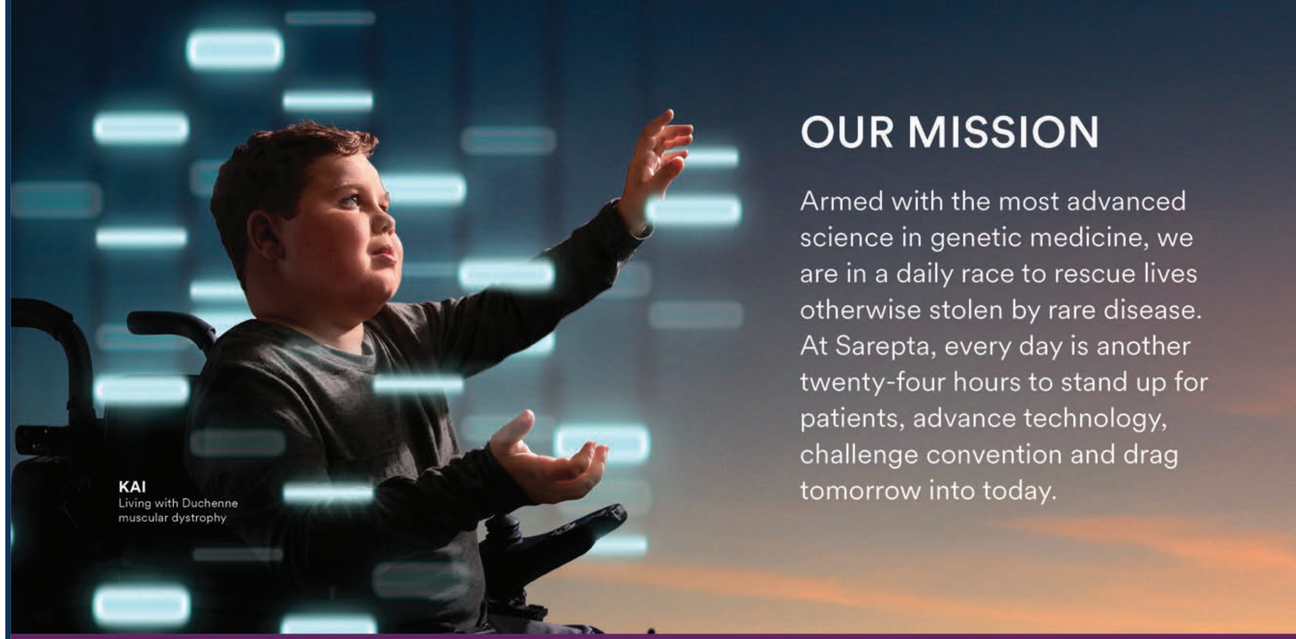


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# 2022 MSG MEETING //

## September 30-October 2

Regina Palace, Stresa, Lake Magiorre, Italy

***Our goals are to be the premier neuromuscular clinical and translational research organization and to create an environment to establish the next generation of researchers with your active involvement in the MSG we can accomplish these goals.***

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Please join us for our virtual ***Neuromuscular Review Course***. This two-part webinar will be offered on four different Saturday's. These courses offer comprehensive updates in the general diagnostic and lab approaches to neuromuscular disorders, and the presentation and management of specific neuromuscular diseases. There will be ample time for discussion and Q&A.

Morning Session - ***Diagnosis and Treatment of Neuropathies***
Afternoon Session - ***Diagnosis and Treatment of Peripheral Nervous System Motor Disorders***

Faculty
**Mazen Dimachkie, MD** – Course Director, University of Kansas Medical Center
**Richard Barohn, MD** – University of Missouri Health System
**Jonathan Katz, MD** – Forbes Norris ALS/MDA Center
**Todd Levine, MD** – Medical Director of Neurology, Honor Health

We hope that you, your colleagues and your trainees can join us. CME credit will be provided by the University of Kansas Medical Center.

To learn more, see the agendas or register – click on any of the links below. Registration fee is $25.00 per session or $40.00 for both sessions (*if attending on the same day*). ***The agenda times will be targeted toward specific time zones, but you are welcome to participate on any of the dates*** (please adjust the times to your time zone accordingly).

Saturday, September 25 – Eastern Time Zone www.eeds.com/live/672129

Saturday, November 06 – Central Time Zone www.eeds.com/live/400947

Saturday, November 20 – Pacific Time Zone www.eeds.com/live/187300

Saturday, December 18 – Pacific Time Zone www.eeds.com/live/352183