RRNMF Neuromuscular Journal

vol. 1:4 September 2020

FACILITATORS

Facilitator in Chief and Founding Facilitator

Richard J. Barohn, M.D., Executive Vice Chancellor for Health Affairs, University of Missouri and Distinguished Emeritus Professor, University of Kansas Medical Center

Associate Facilitators

Jonathan S. Katz, M.D., Director, The Forbes Norris MDA/ALS Research and Treatment Center
Todd Levine, M.D., Medical Director, HonorHealth Neuroscience Institute
Mamatha Pasnoor, M.D., Associate Professor, Dept. of Neurology, University of Kansas Medical Center
Mazen Dimachkie, M.D., Professor of Neurology & Director of Neuromuscular Division, Executive Vice Chairman & Vice Chairman for Research, Dept. of Neurology University of Kansas Medical Center
Gil Wolfe, M.D., Irvin & Rosemary Smith Professor & Chairman, Dept. of Neurology, University at Buffalo/SUNY
Dave Saperstein, M.D., Director, Center for Complex Neurology, EDS & POTS
Aziz Shaibani, M.D., FACP, FAAN, Clinical Professor of Medicine, Baylor College of Medicine, and Director, Nerve and Muscle Center of Texas
Tahseen Mozaffar, M.D., Director, UC Irvine-MDA ALS and Neuromuscular Center, Neurology School of Medicine
Erik Ensrud, M.D., Associate Professor of Orthopaedics and Rehabilitation, Oregon Health & Science University School of Medicine
John Kissel, M.D., Chair of Neurology(ret.), Ohio State University Wexner Medical Center
Laura Herbelin, EMG Technician and Research Instructor (ret), Neurology , University of Kansas Medical Center
Raghav Govindarajan, M.D., Assistant Professor of Neurology, University of Missouri School of Medicine
William Campbell, M.D., Professor Emeritus, Department of Neurology, Uniformed Services University
Yuebing Li, M.D., Staff Neurologist, Neuromuscular Center, the Cleveland Clinic Foundation

Publishing Facilitator

Marianne Reed, Digital Publishing Services, University of Kansas Libraries

CONTENTS

What's In This Issue?

Note from the founding facilitator in chief for Issue 4

Issue 4 of the RRNMF Neuromuscular Journal has lots of great "stuff". My good friend Josh Freeman, MD has an amazing blog on medicine and social justice. I asked Josh if we could begin to publish some of his very thought-provoking pieces in the journal and he agreed. The one we are publishing in Issue 4 is called "If you have a hammer...". I am sure you will enjoy these pieces and we plan to run one in each issue if possible in the "What's on Your Mind" section. Josh is a family medicine doc and I think his message is a good one for all of us super-specialists neuromuscular docs. Our hammers are our neuromuscular knowledge and EMG and biopsies and genetics. But we don't have the general overall skillset of a primary care doctor and so it's appropriate that the first encounter a patient has for a medical problem often should be a generalist. Of course, by the time a patient is referred to one of us, they have probably seen a generalist and maybe a surgeon and then a general neurologist, and then us, the neuromuscular specialists! But his point is well taken. And even among us super-specialists, we have different hammers. I remember several years ago, I was in Chile. I was asked to talk to a doctor who had chronic progressive quadriceps weakness. He wanted my opinion on whether this could be due to periodic paralysis. I told him no, it probably was due to IBM. He knew I was an IBM specialist. Then he proceeded to show me the literature he had uncovered on a chronic myopathy that occurs after years of periodic paralysis that is characterized by quadriceps weakness (without finger flexor weakness, of course). I felt embarrassed that I did not know about this condition. He was very nice in his response and said, "Well, you had a hammer and you used it." My hammer was my knowledge about IBM. So I guess the message is "Beware of the specialists with the hammer. It could be the wrong one!"

I also wrote a piece on the Covid-19 era of telehealth and my telehealth journey from the pre-Covid-19 era when I set up a telehealth ALS clinic between Kansas City and Wichita, Kansas. I was well prepared!

The "New Stuff" section contains a paper by Drs. Nicholas Olney and Richard Olney and colleagues on MUNE as a predictor for progression in ALS. As many of you know, Rick was an international leader in the field of neuromuscular disease, EMG, and ALS. And tragically he died of ALS. This is Rick's last paper and his son Nick, also a neuromuscular neurologist in Portland, Oregon submitted it. I was so glad we could publish this for many, many reasons. Of course, it is good clinical science, but it is also a testament to Rick Olney who we all admired greatly. Thank you Nick for allowing the RRNMF NM Journal to be the home for this publication.

Also in the "New Stuff" section is a paper on Isolated Bulbar ALS, also known as IBALS, by Omar Jawdat, MD and the KUMC group. Even though I am now in Columbia, Missouri at the University of Missouri I am still a part of this group! We believe you can have bulbar ALS that stays confined for at least two years as another "restricted" type of ALS, much like BAD or LAD, of which our group and my earlier group in Texas has published on. If we can understand the factors for why some patients stay restricted for so long we might be able to understand the pathogenesis of ALS to a greater degree. Dr. Stephens and the UCSF neuromuscular group also have a nice paper on how they pivoted their ALS clinic to the virtual mode in response to the Covid-19 pandemic.

In the "Clinical Stuff" section we were pleased to receive a submission by Dr. Heckman and her group in South Africa about myokymia in the setting of neuralgic amyotrophy syndrome (AKA Parsonage-Turner syndrome). Also in the "clinic stuff" category, Dr. Anai Hamasaki, our formal fellow at KUMC who is now at the University of Oklahoma has a nice case of a patient with amyloid myopathy as an IBM mimic. Dr Digala and the group at my new institution at the University of Missouri-Columbia have a case of myasthenia gravis that they believe was triggered by the shingles vaccination.

In the "Looking Back/Looking Forward Stuff" section Dr Todd Levine and colleagues have a great idea on how we can approach small fiber neuropathy in the modern era. The bottom line: Not all small fiber neuropathies are the same!

Finally, I am pleased that the Muscle Study Group (MSG) agreed to have the proceedings and abstracts from this year's virtual meeting published in the journal. We are going to get Issue 4 published just before the meeting which takes place Sept. 25-27, 2020. I believe the launch of this journal brought in a new era of how we communicate in our field. The first virtual meeting of the MSG is another example of how we have to communicate in novel formats.

Enjoy Issue 4!
Rick

"If the only tool you have is a hammer..."

Joshua Freeman, MD

Originally published in the *Medicine and Social Justice* blog, https://medicinesocialjustice.blogspot.com/2020/09/if-only-tool-you-have-is-hammer.html

"If the only tool you have is a hammer, everything looks like a nail."

This old adage has been applied in many contexts, and sometimes appropriately to the work of medical specialists, particularly those who do procedures. It is something that family physicians and other primary care doctors are only too well aware of; before referring a patient to a specialist equipped with their hammer, we like to do our best to make sure that this is the right tool for the job. Perhaps, metaphorically, the family physician has the full range of tools on their belt and can thus address most medical problems, but sometimes the complexity of the treatment that a patient needs requires someone with great expertise. Pushing the metaphor, a general contractor might think that a particular job needs a skilled electrician.

Sometimes, really a lot of the time, subspecialists are consulted for their opinion of a problem, because it is an area in which they have in-depth knowledge. This is not a bad thing at all, as long as that opinion is guided by the evidence that exists and not by the doctor having limited their knowledge to the extent that they know only one approach, or, worse yet, are guided by the potential to make money doing a procedure. This happens, but, thankfully, less often than it could. Most commonly, the issue is not lack of knowledge on the part of the specialist, or even greed, but rather a sense of what others expect of them.

If you present to a primary care doctor with chest pain that sounds like acid reflux, they'll probably prescribe treatment for acid reflux, with caution about changes in the character or frequency of the pain. If the pain sounds a little more suspicious for cardiac angina, they might refer you to a cardiologist. After examination, history and physical, the cardiologist might think it is probably acid reflux. But – and it is a big but – because they are a cardiologist there is a good chance that they will maybe do more tests, expensive and possibly invasive, because, since they are a cardiologist, missing a potential cardiac diagnosis would look worse. Plus, even if the cardiologist is not greedy (or is even on salary, not paid per procedure) the organization they work for might want them to run profitable tests.

For the society, this means a lot of extra tests are done, and this is costly. For the individual, especially if they are uninsured or poorly insured with a big deductible or co-payment, it can be particularly costly. Plus, for the individual, it can be risky – few procedures have no risk of harm, and the more extensive and invasive the greater the risk. That said, they can also be beneficial or even life-saving. The key is to do them when they are necessary, or the evidence suggests that the probability of benefit outweighs the risk of harm, and not otherwise. Of course, we ourselves, patients (or, to use the English word, people) often demand an "answer", even if the answer is not going to be clear and/or the methods for obtaining it not without risk. When I tell people that the results of their tests to rule out potentially dangerous causes of their symptoms are normal (I try to not use "negative", which sounds, unsurprisingly, negative!) they often respond "But what is it?" I have to tell them that I still don't know, but I have discovered it is not something that is really bad. That is always a good thing. Finding out that the cause of your symptoms is not cancer, for example, doesn't tell you what it is, but it is lot better than finding out that it is cancer!

Of course, this whole incentive to intervene, to do more sophisticated, high-tech, complex, invasive, and expensive tests or treatments, applies only to that segment of the population that is well-insured or rich. It is an incredible source of inequity, because a different set of decision rules is applied to different groups of people depending on their ability to pay rather than their medical need (or lack thereof). Yes, people with good coverage may get too many tests, which not only cost a lot and have some risk of harm in themselves, but also can snowball into needing to repeat tests or do more complicated ones if there is a suggestion of abnormality in the first set. [Think of the math in terms of something as "simple" as panels of laboratory tests. "Normal" is usually based on 2 standard deviations from the mean value in that lab, 95%, so 5% of normal people might have an "abnormal" test result. But if 20 tests are done – and their results are independent of each other – the probability that someone's results are "normal" on all 20 might be .95^20 or about 35%!] This can result in harm to people with money.

However, it is still more common for people without money or good insurance to suffer harms because they do not get the testing and treatment needed. And, unsurprisingly in the US, racism enters into the mix; Black

Americans are less likely to get recommended diagnostic and treatment interventions for heart disease than White, even when they are insured!

What can be done? Changing medical education to teach that interventions should be done based on the overall evidence, not evidence selected to lead in a particular direction, could hellp. This has actually improved; when I was in medical school most of the surgical literature, for example, was case series ("We did this procedure on X people, and this many got better and that many died or got worse") without control groups or controlling for how sick people were. (A famous study in my medical youth compared surgical intervention for coronary artery disease with medical treatment. Surgical was better. Of course, all the people with other diseases that made them at higher risk for surgery were allocated to the medical treatment group!)

Another very big thing would be to make sure EVERYONE is adequately insured. Not more people, but everyone. And, best, with the same insurance, so there is no gaming the system to get the folks whose insurance pays the most. If everyone has the same insurance – most simply, improved and expanded Medicare for All, there is no financial reason to do, or not do, tests or treatments on anyone (racism would, of course, not be cured by this).

Also, more primary care doctors would be great. As research presented by Etz and Stange at the recent Society of Teachers of Family Medicine (STFM) conference, and published in the *Annals of Family Medicine* has shown, currently primary care sees 50% of all physician visits (500,000,000) with only 30% of the workforce and <7% of the dollars (and, for the academic researchers, 0.2% of NIH funding). More primary care physicians, which would almost certainly result from (and probably require) a lot larger portion of the money spent on health care to be directed to primary care, would almost certainly lead to more equitable and higher quality care for everyone.

A highly-placed non-medical health care executive once asked me (a family doctor) why he would go to me with a prostate problem instead of a well-known urologist. Skipping over "how do you know it's a prostate problem?" I said "I guess it depends upon whether you want surgery or not." Oversimplistic, perhaps, since urologist might provide other options, but not entirely unrealistic. The urologist's job may be, in part, to care for prostate problems, but their training is to operate.

By the way, the executive had no follow up questions.

My Telehealth Experience pre-COVID-19 and During COVID-19

Richard J. Barohn, MD

I plunged into the telehealth world three years pre COVID out of necessity. Patients with ALS and their families from the Wichita Kansas area had difficulty driving the three and a half hours to Kansas City for our multidisciplinary specialty care clinic. Early in the disease it is not as difficult for patients to make the trip, but as the disease advances and they get progressively weaker it becomes a significant burden. Wichita is not a small city but none of the neurologist in the city would commit do to doing a multidisciplinary als clinic. They would see patients with possible ALS and refer them to Kansas City for confirmation and follow up. ALS is not a common disease. It is estimated a primary care doctor will see one als patient in their career and a general neurologists sees on average one als patient a year. On the other hand at a multidisciplanary als clinic we would see 4 or 5 new patients a week as all the patients are funneled into these clinics. ALS is such a terrifying disease to patients and families but also to providers who don't have a lot of experience with diagnosing and managing these patients. So after years of trying to convince some of the talented Wichita neurologists to take this on without success, I had the following idea. What if all new patients had to have at least once visit to the Kansas City ALS specialists to confirm the diagnosis and begin a management plan? And then all subsequent visits could be done with the patient in Wichita and me in Kansas City via zoom? I worked closely with the ALS Association chapter in the Midwest region which covers Kansas, Missouri, and Nebraska. The leadership in ALSA figured out how we could hire the health care specialists needed for a multi specialty ALS clinic in the Wichita area. These include physical therapy, occupational therapy, respiratory therapy, speech therapy, social work and a equipment vendor. All of these specialists are on site in the Kansas City ALS clinic with the neurologists when patients are seen for follow up visits. The difference in the telehealth experience was the health care providers were in Wichita but I was in Kansas City. We were able to convince a home health care company that employed most of these specialists to do home heart care visits to partner with us. The ALSA chapter provided a social worker they had on staff. The ALSA chapter also raised money from donors to pay the Wichita health care company to provide the specialists.

On Thursday mornings 4 ALS patients would come to a Wichita clinic office building we rented (again ALSA raised money for this). At 8:30 we would have a zoom huddle and go over all four patients before we saw them I also had on my team in Kansas City one of the ALS clinic nurses who was used to working with physicians that manage ALS patients Also a day or two before the scheduled visit, the ALSA social worker would call the patient and family and asked some questions about what the major issues were they wanted to talk about and gathered other clinical information. They would also obtain the ALSFRS at that time and record it so I had this to look at before the telehealth visit and I could compare it with the prior scores. They wrote this all down on a form that myself and the other health care providers had to read during the huddle. So we had a "head start." Then at 8:30 the health care providers would all go see each patient in their exam rooms. This took one and a half hours. At 10:30 I would zoom back on and I would spend about 30 minute with each patient. An iPAD would be put on a IV pole on wheels as a "head" and one of my white doctor coats would be draped over the IV pole, with a stethoscope wrapped around my neck. I was transformed into "robot ric." They wheeled me from room to room. All of the therapist would go to each patient's room as well and after some appropriate "hellos" to the patient from robot ric to break the ice I would ask a couple questions and then I would ask each therapist to report on what they discussed with the patient and we made plans for each area such as splints, walkers, wheelchairs, BIPAP, nutrition, PEG tube, communication assisted devices, medications, etc. The family was involved in the conversation on all of these issues. We would always ask questions about depression and anxiety and treat as appropriate. We would discuss "do not resuscitate" issues, power of attorney issues, and other end of life issues.

The other glitch was billing. I was able to bill a physician telehealth code. But insurers (Medicare and private insurers) still do not allow the health care providers other than physicians to bill for telehealth. This is definitely something that needs to be addressed in the health care system. In our case we could not have done this clinic withough the philanthropic support of the Midwest ALSA chapter to reimburse for the time of the providers in Wichita.

This system was amazingly well received by patients, family, and health care providers. The program achieved

the Clinic Innovation of the Year award at the annual national ALSA meeting. Patients did not miss seeing the doctor in person. They greatly appreciated the need not to drive nearly 4 hours or longer in an uncomfortable car or van. We saw patients every three months. As the patients disease progressed, they would become weaker and as they neared the end of their journey, I developed the ability even through telehealth to sensitively say "goodbye" to the patients when I felt it may be their last clinic visit, and it usually was. At the end of each clinic visit we all felt like we had done a good thing as health care providers. We always ended the experience on a satisfaction high that we had done our job well and that the patients and families benefited in many ways

Then COVID-19 hit. We did our first Wichita ALS telehealth clinic the same way in early March. But then the clinics shut down throughout our system and indeed throughout the country. And patients did not really want to come to the clinic anyway even if it was open. So we adapted.

We began home ALS telehealth. The home health care providers often went to the patients homes to do their evaluations several days before the telehealth appointment with me and the whole team. Although sometimes they just called the patient ahead of time if they could go out to the house. The ALSA home care specialists still called the patient a couple of days ahead of time and asked the preclinical questions and did the ALSFRS. Then on the day of the telehealth clinic we would all get on zoom: the patient and family, me and all the health care providers in Wichita. We still had the "huddle" with just me and the providers but moved it to 10 am. Then at 10:30 we had 30 minute slots for each patient and all the providers would interact with the patient and me one at a time to come up with a plan moving forward. It worked amazingly well. So well I don't know if I would go back to the earlier method we began with.

I was involved in the COVID-19 ALS telehealth clinic from March to May. Then I moved to University of Missouri, Columbia to become the Executive Vice Chancellor of Health Affairs. I left the ALS telehealth clinic in good hands with my neuromuscular partners at the University of Kansas Medical Center. They are modifying the Kansas telehealth operation once again and are doing the Wichita ALS telehealth visits during their large in person ALS clinic. They are using the PT, OT, ST, RT providers in the Kansas City clinic to interact with the patient This is a new way of doing things and I look forward to hearing how ALS Telehealth Version 3 in Kansas works When I arrived in Columbia all of the clinics were on full force zoom operations as all medical clinics and practices around the country were as well. They were just learning how to do telehealth. I felt like the experienced old doc giving them my three years of experience! Now I am looking for opportunities at Mizzou to utilize the skill set I have learned and to implement ALS telehealth clinics in rural Missouri with my new partner Raghav Govindrajan

I am sure that there are a number of other ways to do these telehealth clinics that work equally well. But this experience did show me how flexible and adaptable we could be in our goal to care for patients and their families. And another lesson I learned throughout the three year process was that if the physician is motivated to make this work, you can communicate with the patient and family just as effectively as you can in person. They can tell when you are an empathetic physician via telehealth. They know you as a health care provider are interested in them and want to help. And that in the end is really what our role is all about.

Changes in Motor Unit Number Estimate and Forced Vital Capacity as Predictors of ALS Progression

Nicholas T. Olney, MD[*#], Michael A. Kohn, MD, MPP,† Catherine Lomen-Hoerth, MD, PhD*, and Richard K. Olney, MD* ‡
Departments of Neurology* and Epidemiology & Biostatistics†
University of California, San Francisco, CA
Providence Brain and Spine Institute, ALS center, Portland, OR[#]
Pro
‡Deceased

ABSTRACT

Background. An independent measure of lower motor neuron function that can be monitored over time is essential in evaluating the effect of drugs or stem cell transplantation and in determining prognosis in amyotrophic lateral sclerosis (ALS). Longitudinal changes in forced vital capacity-percent of predicted (FVC%) and motor unit number estimate (MUNE) may identify patient groups with more rapid disease progression.

Objective. We attempted to define cutoff values for 3-month changes in FVC% and MUNE that identify ALS patients with rapidly progressive disease defined as survival of 30 months or less from symptom onset.

Design. Cohort study.

Subjects. We report data from 26 ALS patients, 10 patients reported previously, and 16 patients not reported previously, except for the reproducibility of their MUNE data.

Results. Of the 26 patients, 7 had rapid progression. Either a 40% decrease in statistical MUNE or a 20% decrease in FVC% over 3 months identified 6 of 7 rapid progressors (Sensitivity=86% 95% confidence interval [CI] 42.1% - 99.6%). Of the 19 patients without rapid progression, 18 met neither the FVC nor MUNE criterion (Specificity = 94.7% CI 95% 74.0% - 99.9%). In a proportional hazards model, 3-month change in both FVC and MUNE were significantly predictive of decreased survival.

Conclusion. We suggest the use of a three-month change in MUNE or FVC% as a secondary enrollment criterion in therapeutic trials or to identify a subgroup of rapid progressors that may respond differently to treatments.

Keywords: *ALS, amyotrophic lateral sclerosis, FVC, MUNE, EMG.*

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disease with loss of both upper and lower motor neurons. Patients live an average 3-5 years after symptom onset and ultimately die due to involvement of the diaphragm causing respiratory failure. Survival depends on the degree of lower motor neuron involvement, which is why stem cell trials for ALS have been targeting the spinal cord. An independent measure of lower motor neuron function that can be monitored over time is essential to evaluating the effect of drugs or stem cell transplantation and to determining prognosis. Various measurements have been used to monitor progression in ALS including forced vital capacity (FVC), compound muscle action potential (CMAP), and manual muscle testing (MMT), but these techniques do not specifically measure lower motor neuron loss. The most sensitive marker of disease progression in ALS, and the only measure of lower motor neuron loss, has been found to be motor unit number estimation (MUNE) using a variety of techniques.[1,2]

The concept of motor unit number estimation was developed in 1971 by McComas, who estimated MUNE as the ratio of the maximal CMAP divided by the average single motor unit (SMUP): MUNE = $CMAP_{max}/SMUP_{mean}$. To determine the average single motor unit, he developed the incremental stimulation technique, which is used less frequently than other techniques due to the problem of alternation in the number of axons activated at a particular stimulation current.[3] To avoid the problem of alternation, the multiple point stimulation technique was developed. Single axons are activated by moving the stimulator along different points of the nerve and stimulating just enough to activate single axons. These are then averaged together and used in the equation above to calculate MUNE.[4] Spike triggered averaging and decomposition MUNE also collects one SMUP at a time by using low levels of muscle contraction and applying decomposition algorithms to the interference pattern.[5] The amplitude is influenced by the force of contraction and this needs to be accounted and adjusted for.[6] An alternative technique, the statistical method, which does not involve moving the stimulator or collecting individual SMUPs, was developed by Daube.[7] This technique uses Poisson statistics to determine the variance at different set stimulation intensities and thus estimate the single motor units. A direct comparison of the multiple point method and the statistical method demonstrated greater reproducibility with the statistical method but systematically lower MUNE values.[8]

MUNIX is a relatively newly developed technique by Nandedkar[9] in 2003 using surface interference patterns recorded during voluntary contractions to extract the average SMUP. Preliminary results suggest it is more reproducible, at least when compared to incremental stimulation.[10]

Three studies have reported longitudinal changes in motor neurons over time using MUNE.[11, 12,13] Results show more rapid loss of motor neurons in patients with shorter survival. This loss happens even before clinical weakness, as demonstrated in SOD 1 mutation carriers.[14]

As mentioned above, we previously compared two popular MUNE methods, the multiple point stimulation method and the statistical method. In our hands the statistical method had better reproducibility than the multiple-point stimulation method.[8]

A single measurement of the FVC% has long been recognized as a strong predictor of survival in ALS patients.[15] In fact, the usual criterion for admission to hospice, denoting the expectation of less than six months to live, is the FVC% value. Vender and colleagues demonstrated that the half of their patients who had more rapid rates of change in FVC had survivals half as long.[16]

In this study, we attempted to identify specific cutoffs for 3-month decrease MUNE and FVC% to identify rapidly progressive ALS.

Methods

Subjects. The patient population for this study consisted of 26 patients with probable or definite ALS who participated in the phase 3, placebo-controlled, low-dose, brain-derived neurotrophic factor (BDNF) trial at UCSF. All 26 patients had initial and 3-month measurements of both MUNE and FVC which were technically satisfactory. Testing was performed after patients gave written and informed consent. This study was approved by the UCSF Institutional Review Board.

Electrophysiological Studies. Electrophysiological studies were performed using methods that have been described previously.[11,17] At the baseline visit, bilateral compound muscle action potentials (CMAPs) were recorded from the hypothenar muscles with stimulation of the ulnar nerve at the wrist. Subsequent electrophysiological studies were performed on the side with the larger amplitude, if this limb had signs of upper or lower motor neuron involvement clinically. If the upper limb with the larger ulnar CMAP amplitude did not have signs of upper or lower motor neuron involvement clinically, then subsequent electrophysiological studies were performed on the side with the smaller amplitude. The statistical method of MUNE was performed three times on each occasion, as we have described previously.[11,17] For longitudinal analysis, the three MUNE counts of each day were averaged.

Forced Vital Capacity. Forced vital capacity was measured with a Renaissance spirometer (Puritan Bennett, Boulder, Colorado). This spirometer calculates the forced vital capacity, percent of predicted (FVC%) based on the age and height of the patient. Three measurements were required to be within a ten percent range for acceptance. The highest of these values was used for analysis.

Statistical Analysis. The primary focus was to identify patients who had rapidly progressive ALS. Rapidly progressive disease was defined as survival from symptom onset to death of no more than 30 months. The need for ventilator support for more than 23 hours a day would have been considered equivalent to death, but this was not applicable for any of the included patients.

The rapid progressors were compared to non-rapid progressors regarding age, site of onset, 3-month percent change in MUNE and FVC%. Means were compared using t-tests with unequal variance and proportions were compared using the Fischer exact test. Both 3-month percent change in MUNE and FVC% were incorporated into a Cox proportional hazards survival model. Individual ROC curves with areas under the curve were constructed for 3-month percent change in MUNE and FVC% as tests for rapid progression. We based our choice of cut points to identify rapid progressors on visual inspection of the ROC curves. We calculated the sensitivity and specificity of a rule combining the two cut-points. We compared the Kaplan-Meier survival curves of the rule-positive to the rule-negative patients using the log-rank test. All statistical analyses were performed using STATA (Stata Corp., College Station, TX).

Results

Of the 26 patients, 7 had rapid progression as defined by survival from symptom onset of 30 months or less. The rapid progressors did not differ from the other patients regarding age or site of onset (Table 1).

The mean 3-month decrease in MUNE was almost 3 times greater among the rapid progressors than in the other patients, and the mean 3-month decrease in FVC% was more than 3.5 times greater. However, because of the small number and high variability in the rapid progression group, these differences did not reach statistical significance.

Table 1. Comparison of Rapid Progressors to Other Patients

	Survival from Symptom Onset				Total		P
	≤30 months		> 30 months				
N	7		19		26		
Mean Survival (range)	22.7	(19 - 25)	87.3	(39 - 277)	69.9	(19 - 277)	
Age (SD)	55.1	(11.6)	54.4	(10.0)	54.9	(11.0)	0.901
Males (%)							
Site of Onset							0.922
Bulbar	2	28.6%	4	21.1%	6	23.1%	
Upper Extremity	2	28.6%	6	31.6%	8	30.8%	
Lower Extremity	3	42.9%	9	47.4%	12	46.2%	
3-month % decrease							
MUNE (SD)	40.8	39.3	14.3	20.6	21.4	28.7	0.132
FVC% (SD)	22.6	22.0	6.1	6.5	10.6	14.2	0.096

In the Cox survival model, the 3-month changes in both MUNE and FVC% were statistically significant (Table 2).

A 10 percent decrease in MUNE and FVC% corresponded to an increase in mortality rate of 25% and 50% respectively.

Visual inspection of the ROC curves shows high specificity cut points at 40% for MUNE and 20% for FVC (Figure 1). A rule classifying the patient as a rapid progressor for either a 3-month decrease of 40% in MUNE or 20% in FVC correctly identified 6 of 7 rapid progressors and 18 of 19 other patients. This corresponds to a sensitivity of 86% (95% confidence interval [CI] 42.1% - 99.6%) and specificity of 94.7% (CI 95% 74.0% - 99.9%). One patient with a 3-month MUNE increase of 4% and FVC% decrease of 6% survived only 23 months and would have been a false negative by this rule. Also, a patient who had a 50% decrease in MUNE and a 7.5% decrease in FVC% survived 44 months and would have been falsely identified as a rapid progressor.

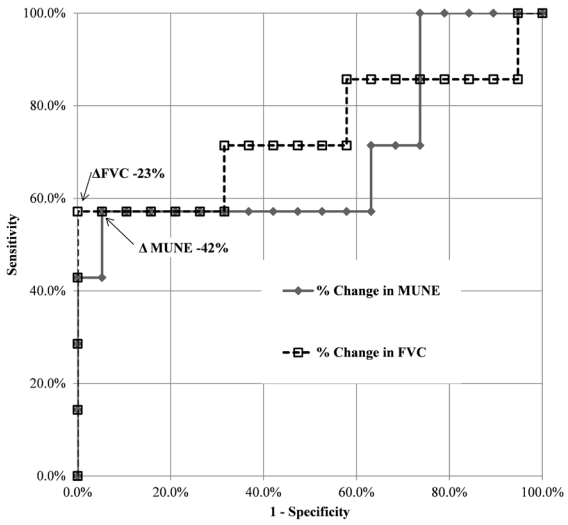


Figure 1. ROC curves for 3-month change in MUNE and FVC (percent of predicted) as tests for survival of 30 months or less. AUROC = 0.69 (MUNE) and 0.74 (FVC).

Table 2. Hazard Ratios from the Cox Proportional Hazards Model

3-month decrease	Hazard Ratio	95% Confidence Interval			Mortality Increase per 10% Decrease
MUNE	1.023	1.004	-	1.041	24.9%
FVC%	1.041	1.006	-	1.077	49.6%

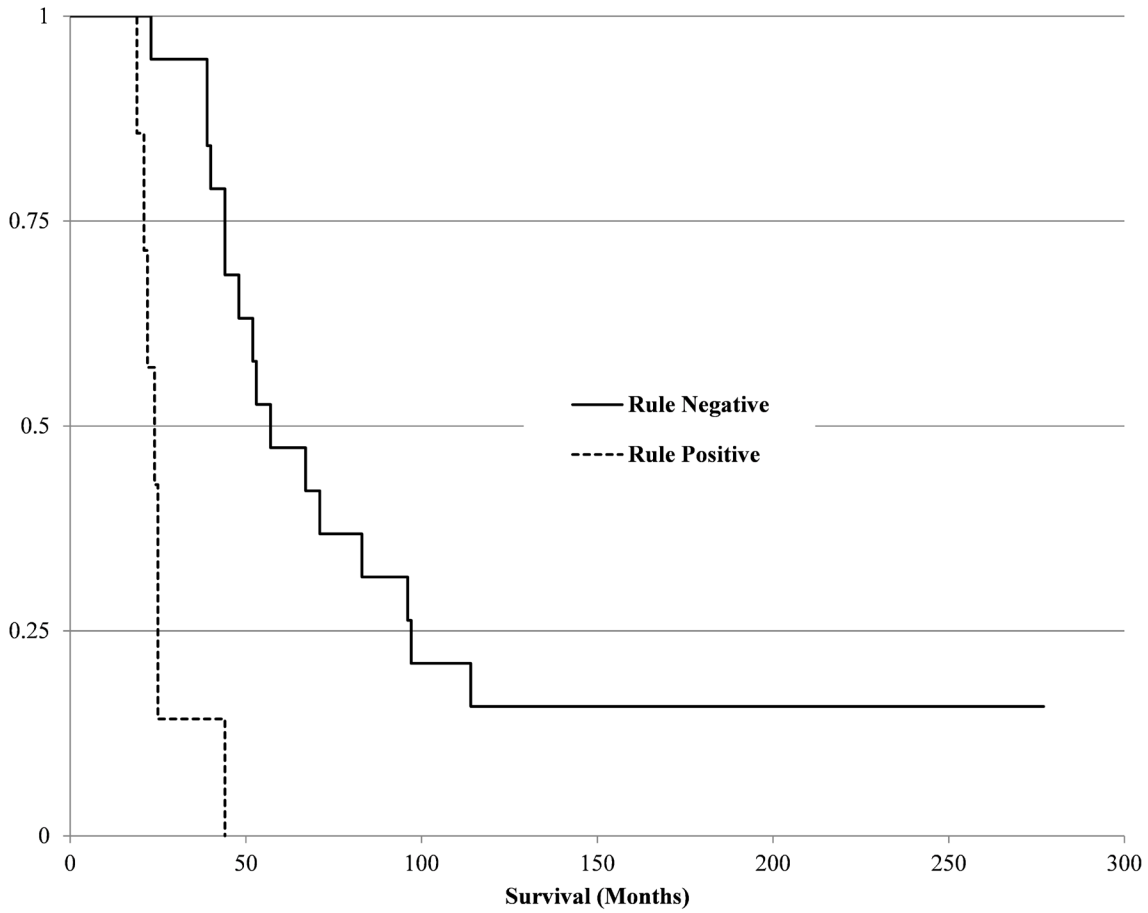


Figure 2. Kaplan-Meier survival curves for rule-negative (N=19) and rule-positive (N=7) groups. The rule is positive if the 3-month decrease is greater than 40% for MUNE or 20% for FVC (percent of predicted).

The 6 patients identified by the rule showed significantly decreased survival compared to the other patients (incidence rate ratio 4.0 [95% CI 1.6-9.7]). Figure 2 shows the Kaplan-Meier survival curves.

Discussion

We demonstrate that decreases in MUNE and FVC% over three months may separate ALS patients into two groups with markedly different survivals. The ALSFRS had not been validated at the time of this study and thus was not used, plus this study was looking at gathering physical measures to identify rapid progressors.

The number of sporadic ALS phenotypes is not known regarding potentially different etiologies or responses to treatment. Certainly, familial and sporadic ALS have different etiologies, although the pathogenic mechanisms seem to converge. In familial ALS, a single gene with a large effect is required for causation. In sporadic ALS, multiple genes possibly interacting with environmental or lifestyle factors are thought to be involved with causation. Several genetic loci have been associated with susceptibility to sporadic ALS,[18-24] but those identified by genome wide studies do not always correlate with phenotypes of ALS.[25] A favorable response to treatment may be more easy to demonstrate in a subgroup of patients with rapidly progressive ALS as identified in only 3 months if changes in MUNE or FVC% are measured and using our suggested criteria.

Our choice of a decrease of 40% in MUNE or 20% in FVC% was based on inspection of survival data in this cohort, which raises the issue of "overfitting." This classification of rapid progressors is unlikely to perform as well in other cohorts. However, our data shows a strong and independent association of both MUNE and FVC% with rapid progression and this is detectable over only 3 months of observation. Given that FVC% is far less invasive than MUNE, it would be easier for FVC% to have a more ubiquitous application looking for rapid progressors. We suggest the use of a three-month change in MUNE or FVC% as a

secondary enrollment criterion in therapeutic trials or to identify a subgroup of rapid progressors that may respond differently to treatments.

Corresponding author:
Nicholas Olney
Providence Brain and Spine Institute, ALS center
5050 NE Hoyt Street
Portland, OR, 97213

References

[1] Bromberg MB. Updating motor unit number estimation (MUNE). Clin Neurophysiol 2007;118:1-8.

[2] Shefner JM, Gooch CL. Motor unit number estimation in neurologic disease. Adv Neurol 2002;88:33-52.

[3] McComas AJ, Fawcett PR, Campbell MJ, Sica RE. Electrophysiological estimation of the number of motor units within a human muscle. J Neurol Neurosurg Psychiatry 1971;34:121-131.

[4] Kadrie HA, Yates SK, Milner-Brown HS, Brown WF. Multiple point electrical stimulation of ulnar and median nerves. J Neurol Neurosurg Psychiatry 1976;39:973-985.

[5] Boe SG, Stashuk DW, Doherty TJ. Motor unit number estimation by decomposition-enhanced spike-triggered averaging: control data, test-retest reliability, and contractile level effects. Muscle Nerve 2004;29:693-699.

[6] Boe SG, Stashuk DW, Brown WF, Doherty TJ. Decomposition-based quantitative electromyography: effect of force on motor unit potentials and motor unit number estimates. Muscle Nerve 2005;31:365-373.

[7] Daube JR. Estimating the number of motor units in a muscle. J Clin Neurophysiol 1995;12:585-594.

[8] Lomen-Hoerth C, Olney RK. Comparison of multiple point and statistical motor unit number estimation. Muscle Nerve 2000;23:1525-1533.

[9] Nandedkar SD, Nandedkar DS, Barkhaus PE, Stalberg EV. Motor unit number index (MUNIX). IEEE Trans Biomed Eng 2004;51:2209-2211.

[10] Furtula J, Johnsen B, Christensen PB, et al. MUNIX and incremental stimulation MUNE in ALS patients and control subjects. Clin Neurophysiol 2013;124:610-618.

[11] Yuen EC, Olney RK. Longitudinal study of fiber density and motor unit number estimate in patients with amyotrophic lateral sclerosis. Neurology 1997;49:573-578.

[12] Felice KJ. A longitudinal study comparing thenar motor unit number estimates to other quantitative tests in patients with amyotrophic lateral sclerosis. Muscle Nerve 1997;20:179-185.

[13] de Carvalho M, Swash M. Sensitivity of electrophysiological tests for upper and lower motor neuron dysfunction in ALS: a six-month longitudinal study. Muscle & nerve 2010;41:208-211.

[14] Aggarwal A, Nicholson G. Detection of preclinical motor neurone loss in SOD1 mutation carriers using motor unit number estimation. J Neurol Neurosurg Psychiatry 2002;73:199-201.

[15] Stambler N, Charatan M, Cedarbaum JM. Prognostic indicators of survival in ALS. ALS CNTF Treatment Study Group. Neurology 1998;50:66-72.

[16] Vender RL, Mauger D, Walsh S, Alam S, Simmons Z. Respiratory systems abnormalities and clinical milestones for patients with amyotrophic lateral sclerosis with emphasis upon survival. Amyotroph Lateral Scler 2007;8:36-41.

[17] Olney RK, Yuen EC, Engstrom JW. Statistical motor unit number estimation: reproducibility and sources of error in patients with amyotrophic lateral sclerosis. Muscle Nerve 2000;23:193-197.

[18] Cronin S, Blauw HM, Veldink JH, et al. Analysis of genome-wide copy number variation in Irish and Dutch ALS populations. Hum Mol Genet 2008;17:3392-3398.

[19] Cronin S, Greenway MJ, Prehn JH, Hardiman O. Paraoxonase promoter and intronic variants modify risk of sporadic amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2007;78:984-986.

[20] Daoud H, Valdmanis PN, Kabashi E, et al. Contribution of TARDBP mutations to sporadic amyotrophic lateral sclerosis. J Med Genet 2009;46:112-114.

[21] Dunckley T, Huentelman MJ, Craig DW, et al. Whole-genome analysis of sporadic amyotrophic lateral sclerosis. N Engl J Med 2007;357:775-788.

[22] Paubel A, Violette J, Amy M, et al. Mutations of the ANG gene in French patients with sporadic amyotrophic lateral sclerosis. Arch Neurol 2008;65:1333-1336.

[23] van Es MA, Van Vught PW, Blauw HM, et al. ITPR2 as a susceptibility gene in sporadic amyotrophic lateral sclerosis: a genome-wide association study. Lancet Neurol 2007;6:869-877.

[24] van Es MA, van Vught PW, Blauw HM, et al. Genetic variation in DPP6 is associated with susceptibility to amyotrophic lateral sclerosis. Nat Genet 2008;40:29-31.

[25] Chio A, Schymick JC, Restagno G, et al. A two-stage genome-wide association study of sporadic amyotrophic lateral sclerosis. Hum Mol Genet 2009;18:1524-1532.

Clinical Findings in Isolated Bulbar Amyotrophic Lateral Sclerosis

Omar Jawdat, MD[1], Jeffrey Statland, MD[1], Duaa Jabari, MD[1], Andrew J Heim, CCRP[1], Mazen M. Dimachkie, MD[1], and Richard J. Barohn, MD[1,2]
[1]Department of Neurology, University of Kansas Medical Center, Kansas City, KS
[2]Department of Neurology, University of Missouri, Columbia, MO

ABSTRACT

Background. Isolated bulbar amyotrophic lateral sclerosis (IBALS) is a regional variant of amyotrophic lateral sclerosis (ALS) with weakness restricted to the bulbar muscles for at least 2 years, and slower progression than generalized ALS. Bulbar-onset generalized ALS, by contrast, typically has a more rapid progression than limb-onset ALS.

Objective. To characterize patients with IBALS and compare them to patients with isolated bulbar disease at presentation who progress to generalized ALS.

Methods: We performed a retrospective chart review of patients seen in our ALS specialty clinic at the University of Kansas Medical Center between 2001-2011.

Results. Of 543 patients seen in the ALS clinic, 150 presented with bulbar symptoms at disease onset: 28 (18.7%) had bulbar signs and no evidence of extremity involvement on exam or electrodiagnostic testing at their initial visit; and 14 (9.3%) had weakness restricted to the bulbar muscles after 2 years of follow up (IBALS). IBALS patients were 57.1% male, with a mean age of symptom onset of 60.8 years (range 39-77 years). The mean disease duration was 3.1 years (range of 2-8 years), with 50% mortality at a mean follow up of 3.5 years. Minimal denervation changes were seen in at least one limb in 6 subjects (42.9%). Other clinical features included: 4 subjects (28.6%) had cognitive impairment, 4 (28.6%) had pseudo-bulbar affect, and 5 subjects (35.7%) had impaired eye movements on smooth pursuit.

Conclusions. Isolated bulbar ALS IBALS is an identifiable restricted regional ALS pattern if there is no clinical limb weakness 2 years after symptom onset. It may have a slower progression from typical ALS. The biologic factors that account for the IBALS restricted pattern are unknown.

Keywords: *Amyotrophic Lateral Sclerosis, ALS, isolated, bulbar.*

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects motor neurons in the brain and spinal cord. The median survival in typical ALS is between 2-3 years from symptom onset, and 16-19 months from diagnosis.[1, 2] Patients with bulbar onset have poorer prognoses, with shorter median survival compared to limb onset.[1-3] Several restricted regional phenotypes have been described with a slower disease course and better prognosis. These include brachial amyotrophic diplegia (BAD) and leg amyotrophic diplegia (LAD), with longer overall survival times between 3-11 years.[4-7]

Bulbar onset ALS represents a third of all ALS cases. Patients are typically older at onset, with a higher prevalence of frontotemporal dementia.[8] Despite this, the bulbar onset ALS population is very heterogeneous, with some patients having disease which stays restricted to the bulbar region for many years. A better understanding of which patients stay with restricted disease could be important for prognosis and when planning clinical trials.

Here we performed a retrospective chart review to identify and characterize ALS patients with isolated bulbar involvement after 2 years of follow up (IBALS).

Methods

We performed a retrospective chart review of all patients seen in our specialty ALS clinic at the University of Kansas Medical Center between 2001 to 2011. Patients were categorized by their initial symptom at presentation. Bulbar onset patients were further broken down into whether their disease was isolated to the bulbar region at the initial clinic visit, by the following criteria:

1) Presence of progressive bulbar symptoms (difficulty swallowing, or difficulty with speech);
2) Either bulbar upper motor neuron signs on exam (slow spastic speech, brisk jaw jerk, jaw clonus), or lower motor neuron signs (nasal speech, tongue fasciculation, atrophy);
3) An MRI of the brain without lesions that may cause bulbar dysfunction;
4) And no evidence for limb weakness on exam.

The following data was abstracted for analysis: age, gender, disease duration, survival, motor neuron signs, bulbar symptoms, extremity signs and symptoms, electromyography, use of percutaneous gastrostomy (PEG) or BiPAP.

Results

A total of 543 patients were seen in the ALS clinic between 2001-2011. Just under a third of patients presented with bulbar symptoms (150, or 27.6%), and out of these 28 (18.7%) had isolated bulbar symptoms at initial presentation. Fourteen out of 28 (50%) patients had disease confined to bulbar muscles after ≥ 2 years of follow up. The age of onset of IBALS without progression to limbs involvement was 64.1 years (39-77) with a male to female ratio of 1.3/1. Four out of 14 (28.5%) of IBALS had cognitive impairment, 5/14 (35.5%) of IBALS had impaired smooth pursuit and 4/14 (28.5%) had pseudobulbar affect. Eight patients out 14 (57%) had denervation signs on EMG at least in one limb. All 14 IBALS had dysarthria and dysphagia symptoms. Five out of 14 (35.7%) were on BiPAP and 10/14 (71.4%) had PEG tube inserted. Creatinine Kinase was normal in all patients and there was no family history of motor neuron disease in all patients with IBALS. The clinical features of these 14 patients with IBALS are presented in the Table.

Mean duration of disease among the IBALS was is 3.1 years (2-8 years) while the mean duration of the illness among isolated bulbar onset ALS with progression to limbs before 2 years was 2.2 years (1-5 years). Among the 14 patients with bulbar onset and progression to limb weakness, 50% of the progression occurred in the first year after the onset.

Seven out of 14 (50%) of IBALS were on Riluzole and eight out of 14 (57%) of bulbar onset ALS who progressed to limb involvement were on Riluzole.

Discussion

We and others have previously identified regional phenotypic variants of motor neuron disease that progress slower than typical ALS.[4-6] The arm restricted variant has been labeled brachial amyotrophic diplegia (BAD) or flail arm syndrome. The leg restricted variant is called leg amyotrophic diplegia (LAD) or flail leg syndrome. We now report a bulbar restricted phenotype isolated bulbar ALS (IBALS).

IBALS has a longer survival than typical bulbar onset ALS with a mean duration of 3 years. We termed this phenotype as isolated bulbar ALS (IBALS). We found mean age of onset of 64 years old which is slightly younger than the classic bulbar onset ALS age of onset (68 years) and slightly more male involvement (Male: female, 1.3: 1) than the classic bulbar onset (Male: female; 0.98:1). Long survival (>101 months) has been reported to occur in 10% of ALS, with spinal ALS being the predominant subgroup (92%), while bulbar onset represents 8% of the long survival subgroup.[8,9]

Table. IBALS disease characteristics. Abbreviations: A, arm; L, leg; EMG, Electromyography; abn, abnormality; Fibs/PSW, fibrillation potentials / positive sharp waves.

Patient number	Bulbar symptoms	Extremity weakness	Extremity UMN signs	Extremity LMN signs	EMG tongue (Fibs/PSW) any EMG abn	EMG A/L (Fibs/ PSW)	Disease duration in years
1.	Yes	NO	NO	NO	NO	NO	3
2.	Yes	NO	NO	Yes (A)	Yes	Yes	4
3.	Yes	NO	Yes (A,L)	Yes (A)	NO	Yes	8
4.	Yes	NO	Yes (A	NO	NO	Yes	3
5.	Yes	NO	NO	NO	NO	NO	2
6.	Yes	NO	Yes (A,L)	NO	Yes	NO	2
7.	Yes	NO	NO	NO	Yes	NO	3
8.	Yes	NO	Yes (L)	NO	NO	Yes	1
9.	Yes	NO	Yes (L)	NO	Yes	Yes	3
10.	Yes	NO	Yes (A,L)	NO	Yes	Yes	3
11.	Yes	NO	Yes (A)	NO	Yes	NO	2
12.	Yes	NO	Yes (A,L)	NO	Yes	NO	3
13.	Yes	NO	Yes (L)	NO	Yes	Yes	2
14.	Yes	NO	Yes (A,L)	NO	NO	Yes	2

Our data suggests that IBALS represent 2.5 % (14/543) of ALS.

Prior study showed that PEG tube insertion is associated with a poor prognosis (8% among long survivors),[9] however our data shows that 71% of IBALS were on PEG tubes. Similarily, 34% of IBALS were on BiPAP while prior studies showed that none of the long survivors have been on BiPAP.[9]

The somewhat arbitrary timeline for "restricted" motor neuron disease pattern is two years without clinical progression into another region. We used this 2-year time period for BAD and LAD and we used it again for IBALS. However, half of our patients had minimal EMG changes in one limb in addition. It should be emphasized that placing a patient in a restricted regional variant group such as IBALS, BAD, or LAD does not imply they do not have progressive disease that will eventually go to other regions. Instead, these restricted phenotypes imply a somewhat longer disease duration and slower progression. In addition, these restricted patterns should raise the question of what are the biologic factors that determine if a patient has a typical ALS or one of these slower phenotypes. If we can get some understanding of the factors that may be responsible for slower progression of the disease process through the nervous system, we might be able to develop more effective therapies to slow motor neuron disease progression.

Our data suggests that there might be an underlying, yet to be determined, pathological mechanism that might determine the prognosis beyond the restricted initial involvement of bulbar and respiratory muscles.

Corresponding author:
Omar Jawdat, MD
3901 Rainbow Blvd
Assistant Professor
Kansas City, KS 66160
Department of Neurology
Phone: 913-588-6970
University of Kansas Medical Center
Email: ojawdat@kumc.edu

References

[1] del Aguila, M.A., et al., Prognosis in amyotrophic lateral sclerosis: a population-based study. Neurology, 2003. 60(5): p. 813-9.

[2] Traxinger, K., et al., Prognosis and epidemiology of amyotrophic lateral sclerosis: Analysis of a clinic population, 1997-2011. Neurol Clin Pract, 2013. 3(4): p. 313-320.

[3] Turner, M.R., et al., Prognostic modelling of therapeutic interventions in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord, 2002. 3(1): p. 15-21.

[4] Katz, J.S., et al., Brachial amyotrophic diplegia: a slowly progressive motor neuron disorder. Neurology, 1999. 53(5): p. 1071-6.

[5] Dimachkie, M.M., et al., Leg amyotrophic diplegia: prevalence and pattern of weakness at US neuromuscular centers. J Clin Neuromuscul Dis, 2013. 15(1): p. 7-12.

[6] Jawdat, O., et al., Amyotrophic Lateral Sclerosis Regional Variants (Brachial Amyotrophic Diplegia, Leg Amyotrophic Diplegia, and Isolated Bulbar Amyotrophic Lateral Sclerosis). Neurol Clin, 2015. 33(4): p. 775-85.

[7] Statland, J.M., et al., Patterns of Weakness, Classification of Motor Neuron Disease, and Clinical Diagnosis of Sporadic Amyotrophic Lateral Sclerosis. Neurol Clin, 2015. 33(4): p. 735-48.

[8] Chio, A., et al., Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. J Neurol Neurosurg Psychiatry, 2011. 82(7): p. 740-6.

[9] Zoccolella, S., et al., Predictors of long survival in amyotrophic lateral sclerosis: a population-based study. J Neurol Sci, 2008. 268(1-2): p. 28-32.

Pandemic Prompted Pivoting to Virtual Multidisciplinary Care

Brian D. Stephens, MD, MS[1], Hannah C. George, MS[1], Sara Ng[1], Paul J. Sampognaro, MD[1], Laura K. Rosow, MD[1], Catherine Lomen-Hoerth, MD, PhD[1]
[1]University of California, San Francisco; Department of Neurology; San Francisco, CA, USA

Introduction

The COVID-19 pandemic has drastically changed the way that neurologists deliver care to patients and has "catalyz[ed] the adoption of teleneurology".[1] Approximately 8% of hospitalized patients diagnosed with and treated for COVID-19 have a pre-existing neurological illness.[2] Of these, patients with motor neuron disease and/or muscle disease, particularly those with bulbar or respiratory weakness, represent two of the most vulnerable groups.[3]

To provide continuity of care to these high risk individuals, the American Academy of Neurology has offered guidelines on implementing telemedicine for patients.[4] However, in a recent survey of practicing neurologists, only 29% had access to a telehealth platform , and just 17% of practices had access to teleneurology in the outpatient setting.[5] The pandemic has also led to the closure of most outpatient therapy centers, creating further difficulties in patient access to treatments.[6]

Despite these challenges, providing telehealth to patients with ALS has previously proven (at least on a smaller scale) to be feasible, provide high satisfaction, and maintain a quality of care similar to that of face-to-face visits.[7,8,9]

For these reasons, our MDA/ALS Clinic at the University of California, San Francisco (UCSF) have recently transitioned our in-person multidisciplinary clinics to a successful, virtual patient experience. Here, we outline our new clinic model, presenting detailed information about our clinics' virtual workflow and our experiences with this transition. In this way, we hope to demonstrate the feasibility of a large-scale virtual multidisciplinary clinic and assist other clinics (both local and academic) as they transition their care of patients virtually within the COVID-19 environment.

About the UCSF ALS/MDA clinic

Our multi-disciplinary team has members from 10 disciplines: respiratory therapy, physical therapy, occupational therapy, nutrition, speech language pathology, social work, research, patient care coordination, nursing, and neurology. Trainees from all disciplines often join our clinic as well. Prior to the COVID-19 pandemic, we served 20-25 patients every week, with 1-2 new patients and 3-6 follow ups every half day. As of May 26, 2020, we are serving approximately 15-20 patients every week solely through televisits. We expect this number to increase as we expand our practice beyond the California border in response to the easing of state medical licensure restrictions by the Centers for Medicare and Medicaid Services.[10]

Software

Our live video telehealth is conducted utilizing the Zoom Video Conferencing software with the waiting room feature enabled for enhanced security

Prior to the Appointment

Scheduling with Patients

Our patient care coordinator discusses the nature of the telehealth appointment and ensures that patients have access to a device with a camera and microphone such as a smart phone, tablet, or computer. If the patient is using a smart phone or tablet, we ensure that they have the appropriate software application (in our case, the Zoom application) on the device and know how to operate it.

After completing the above process, our patient care coordinator sends the patient written instructions as a reminder on how to access the meeting on the day of their appointment.

Scheduling with Providers

Each member of our team has a unique meeting identification number (ID) that has been assigned to them through the Zoom interface. Our patient care coordinator chooses one of these numbers to provide to each individual patient for use during their appointment. By assigning individual numbers, we allow patients to remain in one virtual "room" for the duration of their visit. This approximates the experience of our regular clinic, in which patients remain in one room within clinic for the duration of their visit and eliminates issues with patients having to log-in to multiple rooms to different providers. Additional benefits to the virtual environment are that patients can share their Zoom link with family not living in the home and/or other health care providers involved in their care, so they can also join the visit if desired.

To enable this workflow, all providers must grant access to the scheduler to allow them to create appointments using the meeting ID.

The scheduler then grants Host access as an "Alternate Host" to all members of our team. This allows any given team member to start the meeting independently and must be done for every patient individually.

Assessments to Assist with the Visit

One day prior to the appointment, a member of our team will call the patient to conduct functional rating scales (such as the ALS-FRS-R and CNS-LS), perform medication reconciliation, and discuss specific issues the patient would like to bring up with our team. These are documented in the medical record.

Day of the Appointment

Clinical Flow

We establish one Team Meeting Room (with a unique Zoom ID) where all members of the multi-disciplinary team can discuss patient-specific issues at the start of the day. An online Google Sheets spreadsheet is accessible by team members and lists the patients' initials (full names are not used to remain HIPAA-compliant), the Zoom IDs being used for their visit, and notes about their care. Team members (neurology, PT, etc.) are listed in the columns of the spreadsheet, and individual providers can mark their time in and out of the patient's room (Figure 1). This spreadsheet can be screen-shared via Zoom and directly annotated through the program if operating numerous screens proves challenging. A coordinator is usually present throughout clinic and helps to manage provider workflow and ensure that the spreadsheet is being updated correctly.

Patient Visit

Approximately 15-30 minutes prior to the visit, our patient care coordinator will call the patient to guide them through the process of joining the virtual room and troubleshooting issues, as necessary.

Waiting Rooms

One option is utilizing the Waiting Room feature in Zoom to ensure confidentiality. One of the team members joins the meeting first (as the Host) and will allow the appropriate patient into the room from the Waiting Room. At the conclusion of this visit, we then make the patient a "co-host," so they can remain in the room and "admit" the next provider when they arrive. If the patient's condition restricts their ability to admit the next provider, we either ensure there is a caregiver with them, or a team member will remain in the room until the next provider joins.

Breakout Rooms

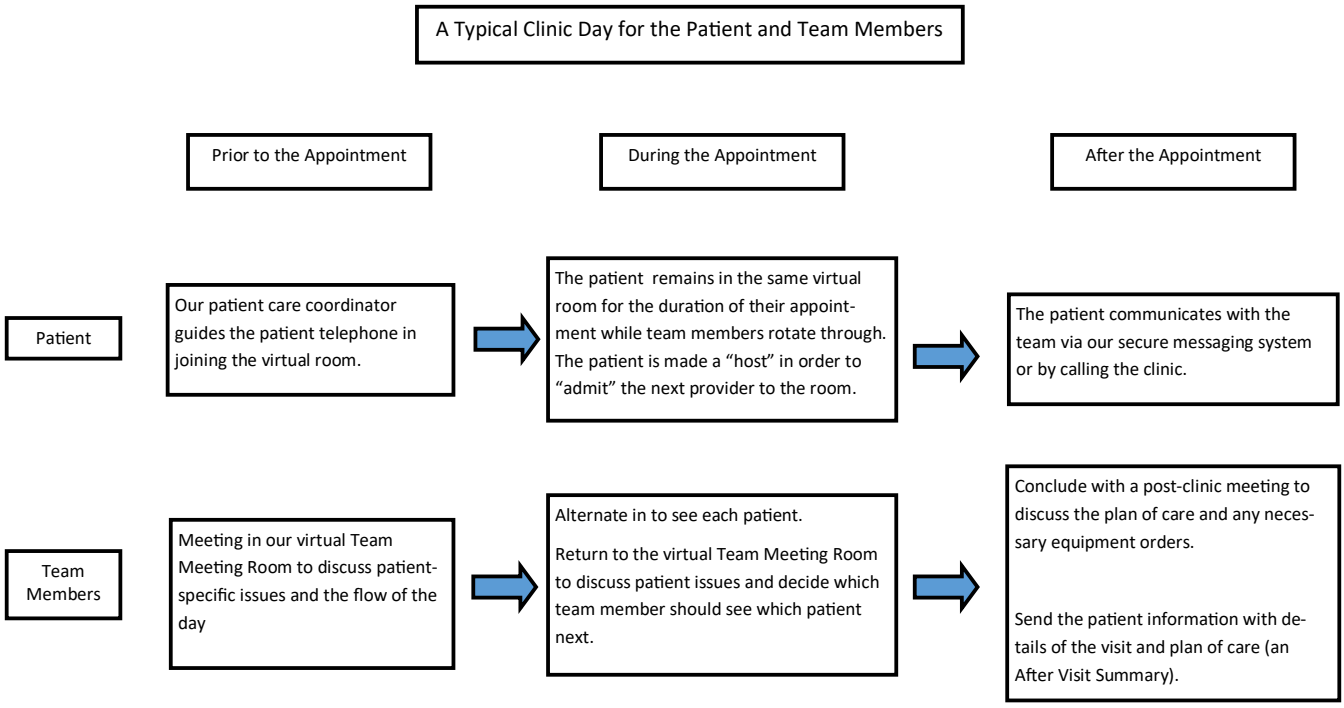
As an alternative to using multiple separate meeting IDs, Zoom now has the option of "breakout rooms," which allow multiple separate meeting spaces under one provider's Zoom ID. A coordinator still admits patients to the meeting, then "rooms" patients and caregivers/family members in separate breakout rooms, identified by patient name. Providers still congregate and discuss patients in a Team Meeting Room, then move directly into the separate patient visit rooms. Extra meeting rooms are usually created as well, which can be useful for smaller team discussions (e.g., an attending physician staffing a patient with a trainee). Patients are unable to view the different breakout rooms, thereby maintaining HIPAA compliance.

The use of breakout rooms has several potential benefits over the use of separate Zoom IDs. For one, the list of available breakout rooms includes a list of current participants in each space, thereby allowing providers to view who is in a room with a patient at any given time. Breakout rooms also allow the use of one consistent Zoom ID (e.g., that of the attending physician) over time, decreasing the likelihood of patients or providers having the wrong meeting ID. Patients and caregivers do not need to "admit" providers to their room, which can be technically challenging for some. Additionally, breakout rooms eliminate the need to log in and out of multiple meetings over the course of a single day, instead allowing providers to remain logged into

Figure 1: Example of a Virtual Clinic Spreadsheet

Appt Time	Patient	Zoom Link	RT	Dietitian	SLP	SW	PT	OT	Research	Med Student	Fellow	MD	Notes for team
			9:36	9:53		10:30	9:00	9:00		in		10:18	
9:00	XX	xxx xxx xxxx	9:47	10:08			936	936		out		10:30	
			9:06	in	9:45	9:28					10:00		
9:00	XX	xxx xxx xxxx	9:26	out	9:56	9:42							
			10:26			10:00				in			
10:00	XX	xxx xxx xxxx				10:26							

Figure 2: A Typical Clinic Day for the Patient and Team Members



one Zoom meeting for the duration of the clinic. We have recently begun using breakout rooms instead of separate meeting IDs, and providers seem to prefer this option for the many reasons listed above.

If a learner (medical student, resident, etc.) is joining us, we typically have the learner remain in the room for the majority of the visit, both for patient continuity and to manage the flow of providers entering and exiting the room.

After the Appointment

We end with a post-clinic meeting in the virtual Team Meeting Room to discuss the plan of care and any necessary equipment orders. Patients are encouraged to communicate with us via our secure messaging system (Epic's MyChart function) or by calling our clinic. Patient instructions can be entered electronically and are automatically messaged to the patient as the visit is finalized. If the patient does not have electronic access, these instructions can be printed and mailed.

Specific Care Considerations

Respiratory Care

A drawback for virtual respiratory care is that we are unable to perform pulmonary function testing with formal spirometry on those with an unknown COVID-19 status. Spirometry is an aerosolized procedure and likely will continue to be restricted as long as COVID-19 remains a significant concern even after in-person patient visits are allowed. This testing – and its trajectory over time -- typically guides recommendations regarding respiratory equipment and discussions of prognosis. While some outpatient or hospital-based laboratories have recently restarted spirometry testing patients with proof of COVID-19 negativity, in an effort to help detect neuromuscular respiratory weakness in the absence of spirometry testing, we are ordering more nocturnal oximetry in symptomatic patients to assess for nocturnal hypoventilation. Symptoms of shortness of breath or an abnormal nocturnal oximetry study now qualify patients for noninvasive positive-pressure ventilation (NPPV) due to relaxation of insurance requirements.

Physical and Occupational Therapy

While our therapists are no longer able to evaluate motor function in-person, we are now able to see patients in their home environment, where we can more readily evaluate for safety. Fortunately, due to recent insurance policy changes, we are also now able to order wheelchairs and other durable medical equipment (DME) for our patients without an in-person visit being required.

Palliative Care

Our palliative care specialists have been early adopters of telehealth, as this specialty lends itself particularly well to remote evaluation and counseling of patients.[11] Benefits of telehealth palliative care include the ability to support patients close to the end of life in a more comfortable setting, and the ability of family members/caregivers to join the visit from multiple different locations.

Clinical Trials

Clinical trials have largely been put on hold, so no new patients are being recruited at this time. For patients that were already enrolled, telehealth is utilized, and urgent/medically necessary issues are addressed in person.

Conclusion

While the COVID-19 Pandemic has changed the way we all care for our patients, comprehensive, multidisciplinary care is still possible through telehealth visits. We have continually worked to refine our process over the last three months. While every clinic must find a method that will address the challenges of its own system, we hope this outline serves as a framework for the successful adoption of telehealth multidisciplinary care.

Corresponding author:
Brian Stephens
stephensbd@gmail.com

References

[1] Klein BC, Busis NA. COVID-19 is catalyzing the adoption of teleneurology. Neurology 2020;94:903-904. doi:10.1212/WNL.0000000000009494

[2] Herman C, Mayer K, Sarwal A. Scoping review of prevalence of neurologic comorbidities in patients hospitalized for COVID-19. Neurology Apr 2020, 10.1212/WNL.0000000000009673; DOI: 10.1212/WNL.0000000000009673

[3] Association of British Neurologists. Association of British Neurologists guidance on COVID-19 for people with neurological conditions, their doctors and carers. Published March 22, 2020. Available at: https://cdn.ymaws.com/www.theabn.org/resource/ collection/6750BAE6-4CBC-4DDB-A684-116E03BFE634/ABN_Neurology_COVID-19_Guidance_22.3.20.pdf. Accessed on May 26, 2020.

[4] Telemedicine and COVID-19 Implementation Guide. American Academy of Neurology. Updated April 10, 2020. Accessed 26May2020.

[5] Sharma A, Maxwell CR, Farmer J, Greene-Chandos D, LaFaver K, Benameur K. Initial experiences of US neurologists in practice during the COVID-19 pandemic via survey. Epub ahead of print 21May2020. NEUROLOGY DOI: 10.1212/WNL.0000000000009844

[6] Lin C. Invited Commentary: Advancing telerehabilitation in the time of COVID-19. Neurology Blogs. 11May2020. https://blogs.neurology.org/covid-19-coronavirus/invited-commentary-advancing-telerehabilitation-in-the-time-of-covid-19/ . Accessed 26May2020

[7] Van De Rijn M, Paganoni S, Levine-Weinberg M, et al. Experience with telemedicine in a multi-disciplinary ALS clinic. Amyotroph Lateral Scler Frontotemporal Degener. 2018;19:143-148. https://doi.org/10.1080/21678421.2017.1392577.

[8] Geronimo A, Wright C, Morris A, Walsh S, Snyder B, Simmons Z. Incorporation of telehealth into a multidisciplinary ALS Clinic: feasibility and acceptability. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18:555-561. https://doi.org/10.1080/21678421.2017.1338298.

[9] Selkirk SM, Washington MO, McClellan F, Flynn B, Seton JM, Strozewski R. Delivering tertiary centre specialty care to ALS patients via telemedicine: a retrospective cohort analysis, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2017, 18:5-6, 324-332, DOI: 10.1080/21678421.2017.1313867

[10] Center for Connected Health Policy. Telehealth Coverage Policies in the Time of COVID-19. Available at: cchpca.org/resources/covid-19-telehealth-coverage-policies. Accessed May 27, 2020.

[11] Jess M, Timm H, Dieperink KB. Video Consultations in Palliative Care: A Systematic Integrative Review. Palliat Med. 2019 Sep;33(8):942-958. doi: 10.1177/0269216319854938.

A Proposed Taxonomy of Isolated Small Fiber Neuropathy

Todd D. Levine, MD[1], Bailey Bellaire, BS[2], Alyssa Arellano, BS[3], Richard Barohn, MD[4], Mazen Dimachkie, MD[5], Jon Katz, MD[6]
[1]Honor Health, Department of Neurology, Scottsdale, AZ
[2]CND Life Sciences, Phoenix, AZ
[3]Phoenix Neurologic Education Center, Phoenix, AZ
[4]University of Missouri, Department of Neurology, Columbia, MO
[5]Kansas University Medical Center, Department of Neurology, Kansas City, KS
[6]California Pacific Medical Center, Department of Neurology, San Francisco, CA

Introduction

The term small fiber neuropathy (SFN) is used to define a group of heterogeneous disorders that affect peripheral nerves and cause structural injury of myelinated Aδ-fibers and unmyelinated C-fibers.[1] In the somatosensory nervous system, these fibers control information about temperature, pain, and itch, and in the autonomic nervous system, they mediate thermoregulatory, cardiovascular, and gastrointestinal autonomic functions.[2] Patients can have a peripheral neuropathy with predominant small fiber symptoms such as pain, burning, and numbness, but on exam or electrophysiology one finds evidence for damage to medium and large fibers such as decreased reflexes or abnormal nerve conduction studies. These patients are considered to have mixed fiber neuropathies.[3,4] There is a second population of patients who have small fiber neuropathic symptoms but no evidence for mixed fiber involvement on exam or electrophysiology. This second group of patients is diagnosed objectively by demonstrating reduced intraepidermal nerve fiber density on skin biopsy, and these patients should be considered to have isolated small fiber neuropathy (ISFN).[1,5]

The reported prevalence of peripheral neuropathies in the United States is 2% in the general population, but in people older than 65 years the prevalence rises to about 20%. The exact frequency of SFN is unknown but has been estimated at 12 cases per 100,000.[6]

Although advances in the diagnosis of SFN have evolved over the past two decades, SFN has a poorly understood pathophysiology, and despite extensive evaluations approximately 50% of cases are idiopathic.[5,8] In a recently published series of 921 patients with biopsy-proven ISFN, immunological conditions were found in 19%, sodium channel variants were found in 16.7%, diabetes in 7.7%, Vitamin B12 deficiency in 4.7%, alcohol abuse in 3%, exposure to chemotherapy in 2.2%, and monoclonal gammopathy of unknown significance in 2.2%.[9] Other potential causes include impaired glucose tolerance, hepatitis C virus, human immunodeficiency virus (HIV), paraneoplastic syndromes, and both acquired and inherited forms of amyloid neuropathies. Familial amyloid neuropathies, familial amyloid cardiomyopathy, and leptomeningeal amyloidosis are associated with mutation of transthyretin (TTR), a transport protein that carries holo-retinol binding protein and thyroxine. Mutations of the TTR gene have been associated with the development of SFN and autonomic neuropathy.[7,10]

Diagnosis

Neuropathic pain and symptoms dominate the clinical presentation of ISFN. Symptom severity and their progression vary between patients, but typically the sensory symptoms present distally, manifesting as foot or leg pain and spread proximally to the upper limbs and trunk. Pain can be extremely severe and debilitating and is often described as burning or shooting. Other symptoms include hyperesthesia, paresthesia, numbness, restless leg syndrome, and dry eyes and mouth.

Patients with ISFN might also present with erythromelalgia and paroxysmal extreme pain disorder, which indicate small fiber sodium channel dysfunction (SFSCD).[7,11] The hallmark feature of SFSCD is normal intraepidermal nerve-fiber density (IENFD) on biopsy associated with nociceptive dysfunction. Patients with small fiber–mediated painful neuropathy (SFMPN) often have symptoms such as burning, tingling, stabbing, and numbness with normal electromyography and nerve conduction velocity.[12-14] Genetic testing for disorders of the NaV 1.7,1.8, and 1.9 can help identify these patients.

Some patients develop small fiber–mediated autonomic dysfunction (SFMAD) that is characterized by cardiovascular, gastrointestinal, urinary, pupillary, and metabolic disturbances and sweating. Cardiac symptoms include syncope, palpitations, symptomatic postural hypotension, and postural orthostatic tachycardia syndrome.

Another clinical phenotype is small fiber–mediated widespread pain (SFMWP). Patients from this group often experience muscle cramps or muscle pain and have reduced

IENFD. These patients may represent a significant percentage of patients with fibromyalgia and in some reports ISFN damage can be seen in 40-60% of these patients.[15,16]

Patients with isolated SFN (without large nerve fibers involvement) present with intact deep tendon reflexes, normal strength, normal sensory examinations, and normal motor coordination. Normal nerve conduction studies also suggest isolated SFN.

Diagnosis of SFN can be challenging and is often based on the combination of clinical signs, physical examination, and quantification of IENFD. Ancillary testing includes functional test measures such as a quantitative sensory testing (QST) and quantitative sudomotor axon reflex testing (QSART) that require special equipment and are only available in specialized centers. Nerve conduction studies can be done to establish large nerve fiber involvement but have limited diagnostic efficacy for ISFN.

Using Pathophysiology to Delineate the Underlying Pathology

The diagnosis of ISFN can be confirmed on a skin biopsy assessed for IENFD. The procedure is fast and straightforward, and it can be easily performed in the office or clinic. When performing skin biopsy for the measurement of IENFD, it is best to biopsy three separate sites, especially in cases of widespread bilateral symptoms. The preferred sites are the calf, the distal thigh, and the proximal thigh. Using these three sites the reported sensitivity and specificity of IENFD are 80% and 90% respectively.[17]

Normal IENFD varies by region of the body, and reference values ideally should be adjusted for sex, age, and site. Decreased IENFD has been correlated with clinical symptoms and abnormalities on sensory testing, for example, pain and length-dependent symptoms predict abnormal biopsy results. Furthermore, patients with an abnormal skin biopsy have a higher likelihood to respond to typical neuropathic medications than controls.[18]

Skin biopsy of upper and lower thigh and calf is very well tolerated with a very low rate of complications and can be performed in almost all patients apart from those with skin abnormalities at the biopsy site. Skin punch should be taken from upper thigh (10 cm below the greater trochanter), lower thigh (10 cm above the lateral knee) and the calf (10 cm above the lateral malleolus) for diagnostic purposes. Biopsies can also be repeated several times to monitor treatment efficacy and disease progression. Utilizing these three sites the clinician can classify patients into one of four distinct pathologic phenotypes. Several papers have shown a poor correlation between the distribution of the clinical complaints and the pathologic abnormalities.[19] For example, a patient with a proximal ganglionopathy may have their most severe symptoms initially localized distally to the feet. Only by examining three sites with a gradient from proximal to distal can one accurately classify these patients.

Pathologically defined phenotypes

Although there may sometimes be significant overlap between somatic and autonomic symptoms, we believe patients with ISFN can be classified into four clinical phenotypes: ISFN-1, ISFN-2, ISFN-3, and ISFN-4.

Non-length dependent form: ISFN-1

These patients will have abnormalities in the proximal thigh and/or distal thigh but relative preservation of the distal foot IENFD. There are no studies that evaluate to what degree the proximal sites must be abnormal compared to the distal sites, so currently we rely on normal versus abnormal, but this binary distinction may be insufficient. For example, if the proximal thigh has a 90% reduction below the lower limits of normal and the calf has a ten percent reduction below the lower limits of normal should this be considered as both abnormal or more abnormal proximally. This question requires further analysis.

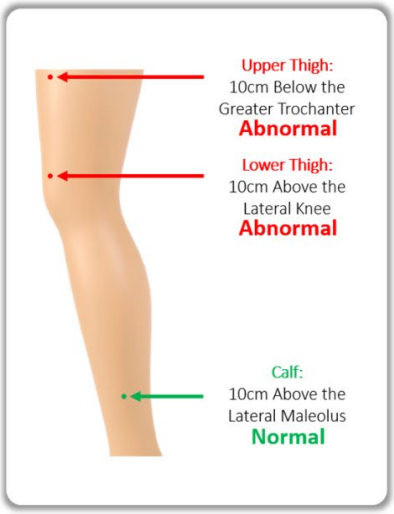
However, in cases where only the proximal sites are abnormal, studies have shown that this pathologic phenotype is distinct from other forms of SFN. This finding indicates that the disease process has begun proximally and has been shown to often represent a ganglionopathy. ISFN-1 is more common in women, often presents at a younger age and is more likely associated with diseases of acute onset that are related to immune-mediated disorders (Table 1). It is important to clinically exclude other mixed fiber conditions such as mononeuropathies (meralgia paresthetica), radiculopathies, and patchy forms of plexopathies.

Length dependent: ISFN-2

Typically, SFN presents in a length-dependent pattern in which patients present with symmetrical neuropathic pain occurring in a distal "stocking-and-glove" distribution. The skin biopsies would confirm predominant damage in the calf and/or distal thigh with relative preservation of the IENFD in the proximal thigh. This traditional pattern follows a distal-to-proximal gradient and is associated with diseases such as diabetes and impaired glucose tolerance, Vitamin B12 deficiency, lymphoproliferative disorders and Sjogren's syndrome (Table 2).

A Diagnostic Algorithm for Evaluating Small Fiber Neuropathies

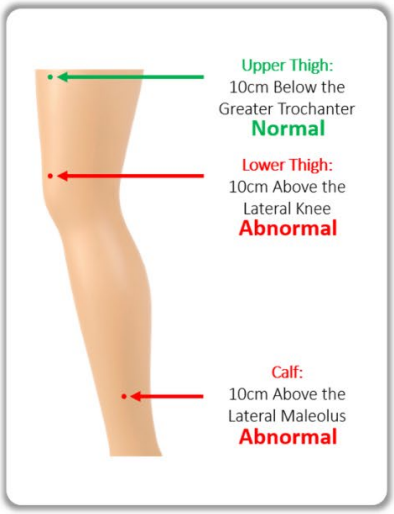
Non Length Dependent Form: ISFN-1



Disease State	Diagnostic Tests	Potential Therapies
Sjogrens Syndrome	SS-A, SS-B	IVIG, Steroids, IST [23,24]
Immune Mediated Neuronopathy	FGFR-3 antibodies	IVIG [19,25]
Immune Mediated Neuronopathy	TS-HDS antibodies	IVIG [19,25]
Immune Mediated Neuropathy	Lumbar Puncture	IVIG, steroids [19,25]
CISP	CSF Protein	IVIG, Steroids [26]
CISP	IgG Synthesis rate	IVIG, Steroids [26]

Table 1: Etiologies and potential treatments of non-length dependent small fiber neuropathies

Length Dependent: ISFN-2



Disease Association	Diagnostic Testing	Potential Treatments
Diabetes	HgbA1C	Glucose control
Diabetes	2 hour OGTT	Glucose Control
Sjogren's Syndrome	SS-A, SS-B	IVIG, Steroids, IST [23,24]
Sarcoid	ACE	IVIG, Steroids, IST [27,28]
Lymphoproliferative Disorder	Serum Immunofixation Quantitative Immunoglobulins	Heme/Onc Evaluation

Table 2: Etiologies and potential treatments of length dependent small fiber neuropathies

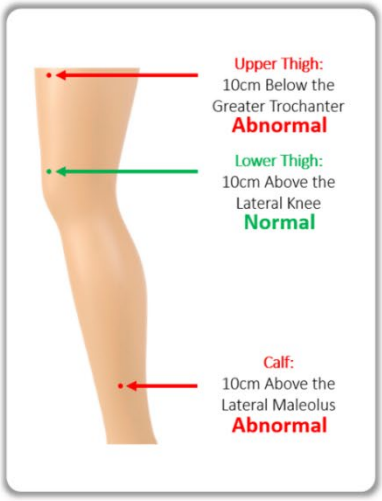
Multifocal presentation: ISFN-3

More rarely, the clinical presentation of ISFN is characterized by multifocal sensory symptoms. On the biopsy one might see the distal thigh damaged but the proximal thigh and distal calf having preserved IENFD. Multifocal SFN can present very asymmetrically, involving only a single limb, or as truncal pain, face or scalp pain. The multifocal presentation is associated with glucose dysmetabolism, cryoglobulinemia, systemic vasculitis, sarcoidosis, and HIV infection (Table 3).

Autonomic predominant: ISFN-4

Patients with ISFN-4 have significant autonomic complaints and findings. They may have abnormal autonomic

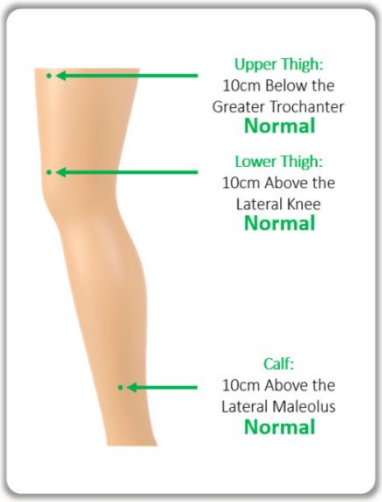
Multifocal Presentation: ISFN-3



Disease State	Diagnostic Tests	Treatment
Glucose Dysmetabolism	2 hour OGTT Fasting glucose	Glucose Control
Cryoglobulinemia	Cryoglobulins	Rituximab, IFN, Antiviral [29]
Systemic Vasculitis	ANA; ANCA	Steroids, IST [30]
Sarcoid	ACE	Steroids, IVIG, IST [28]
HIV	HIV	Retroviral Therapy

Table 3: Etiologies and potential treatments of multifocal small fiber neuropathies

Autonomic Predominant: ISFN-4



Disease State	Diagnostic Tests	Possible Therapies
Lymphoproliferative D/O	Serum Immunofixation Quantitative Immunoglobulins	Heme/Onc evaluation
Acute autonomic ganglionopathy	Anti Nicotinic Ganglionic Receptor antibodies Gad-65 antibodies	Heme/Onc evaluation
Acquired Amyloid	Serum free light chains	Heme/Onc evaluation
Inherited Amyloid	TTR Sequencing	Patiseran Inotersen

Table 4: Etiologies and potential treatments of autonomic predominant small fiber neuropathies

testing but the IENFD is normal at all three sites; yet when one examines the density of Protein Gene Product 9.5 (PGP 9.5) positive nerves in the sweat glands in the dermis there is a marked reduction. In this scenario acquired or inherited amyloidosis should be considered. Laboratory testing for inherited amyloidosis includes TTR gene mutations as well fat-pad biopsies or aspirates, rectal biopsy, and biopsies of affected organs such as heart or kidney.[20-22] Lymphoproliferative disorders and acute autonomic ganglionopathy have been described in ISFN-4 (Table 4).

Treatments options

Treatment of SFN should primarily focus on addressing the underlying cause. Skin biopsy at the proximal thigh, distal thigh, and calf can help place patients into one of the four recognized pathologic phenotypes. Utilizing the differential in Table 1-4 can help identify treatable causes in up to 50% of these ISFN patients.

There is very limited evidence for medications to treat pain associated with ISFN. Novel drugs that primarily affect sodium channels are in late stage trials. But until we

have medications approved for ISFN patients we must rely on pragmatic consensus guidelines including drugs in the treatment of other neuropathic pain syndromes (such as painful diabetic neuropathy). These agents include tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and gabapentinoids. Opioids are a second-line treatment option and should be considered in patients who have resistance to nonopioid therapy. Topical treatments such as 5% lidocaine plasters or high-dose (8%) capsaicin cream may also be used to alleviate pain.

We hope this novel algorithm to identifying the phenotypes of patients with ISFN caan lead to a more thorough understanding of the underlying causes and prompt focused research in the future.

Corresponding author:
Todd Levine, MD
pnaresearchdoc@gmail.com

References

[1] Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care 2010; 33: 2285–93.

[2] Lauria G, Lombardi R. Skin biopsy: a new tool for diagnosing peripheral neuropathy. BMJ 2007; 334: 1159–62.

[3] Wolfe GI, Baker NS, Amato AA, et al. Cryptogenic sensory polyneuropathy: clinical and electrophysiologic characteristics. Arch Neu- rol. 1999;56:540-547.

[4] Cazzato D, Lauria G. Small fibre neuropathy. Curr Opin Neurol 2017; 30: 490–9.

[5] Lauria G, Hsieh ST, Johansson O, Kennedy WR, Leger JM, Mellgren SI, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. J Periph Nerv Syst 2010c; 15: 79–92.

[6] Persson AK, Liu S, Faber CG, Merkies IS, Black JA, Waxman SG. Neuropathy-associated Nav1.7 variant I228M impairs integrity of dorsal root ganglion neuron axons. Ann Neurol 2013; 73: 140–5.

[7] Adams D, Théaudin M, Cauquil C, Algalarrondo V, Slama M. FAP neuropathy and emerging treatments. Curr Neurol Neurosci Rep. 2014;14(3):435. doi:10.1007/s11910-013-0435-3

[8] Sommer C. Nerve and skin biopsy in neuropathies. Curr Opin Neurol. 2018;31(5):534-540.

[9] de Greef BTA, Hoeijmakers JGJ, Gorissen-Brouwers CML, Geerts M, Faber CG, Merkies ISJ. Associated conditions in small fiber neuropathy - a large cohort study and review of the literature. Eur J Neurol. 2018;25(2):348-355. doi:10.1111/ene.13508

[10] Finsterer J, Iglseder S, Wanschitz J, Topakian R, Löscher WN, Grisold W. Hereditary transthyretin-related amyloidosis. Acta Neurol Scand. 2019;139(2):92-105. doi:10.1111/ane.13035

[11] Obayashi K, Ueda M, Yamashita T, et al. Long-term effects of liver transplantation on small-fiber dysfunction in Japanese transthyretin (ATTR) V30M hereditary amyloidosis with polyneuropathy (FAP). Amyloid. 2017;24(sup1):99. doi: 10.1080/13506129.2017.1286586

[12] Hoeijmakers JG, Han C, Merkies IS, et al. Small nerve fibres, small hands and small feet: a new syndrome of pain, dysautonomia and acromesomelia in a kindred with a novel NaV1.7 mutation. Brain. 2012;135(Pt 2):345-358. doi:10.1093/brain/awr349

[13] Kim MK, Yuk JW, Kim HS, Park KJ, Kim DS. Autonomic dysfunction in SCN9A-associated primary erythromelalgia. Clin Auton Res. 2013;23(2):105-107. doi:10.1007/s10286-012-0181-7

[14] Brouwer BA, Merkies IS, Gerrits MM, Waxman SG, Hoeijmakers JG, Faber CG. Painful neuropathies: the emerging role of sodium channelopathies. J Peripher Nerv Syst. 2014;19(2):53-65. doi:10.1111/jns5.12071

[15] Saperstein DS, Levine TD, Levine M, Hank N. Usefulness of skin biopsies in the evaluation and management of patients with suspected small fiber neuropathy. Int J Neurosci. 2013 Jan;123(1):38-41. doi: 10.3109/00207454.2012.723652.

[16] Oaklander AL, Herzog ZD, Downs HM, Klein MM. Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. Pain. 2013;154(11):2310-2316. doi:10.1016/j.pain.2013.06.001

[17] Saperstein DS, Levine TD, Levine M, Hank N. Usefulness of skin biopsies in the evaluation and management of patients with suspected small fiber neuropathy. Int J Neurosci. 2013 Jan;123(1):38-41. doi: 10.3109/00207454.2012.723652.

[18] De Sousa DE, Hays AP, Chin RL, Sander HW, Brannagan TH. Charac- teristics of patients with sensory neuropathy diagnosed with abnor- mal small nerve fibres on skin biopsy. J Neurol Neurosurg Psychiatry. 2006;77:983-985.

[19] Antoine JC, Boutahar N, Lassablière F, et al. Anti-fibroblast growth factor receptor 3 antibodies identify a subgroup of patients with sensory neuropathy. J Neurol

Neurosurg Psychiatry. 2015;86(12):1347-1355. doi:10.1136/jnnp-2014-309730

[20] Adams D, Suhr OB, Hund E, et al. First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. Curr Opin Neurol. 2016;29 Suppl 1(Suppl 1):S14-S26. doi:10.1097/WCO.0000000000000289

[21] Kapoor M, Rossor AM, Jaunmuktane Z, Lunn MPT, Reilly MM. Diagnosis of amyloid neuropathy. Pract Neurol. 2019;19(3):250-258. doi:10.1136/practneurol-2018-002098

[22] Sekijima Y, Ueda M, Koike H, Misawa S, Ishii T, Ando Y. Diagnosis and management of transthyretin familial amyloid polyneuropathy in Japan: red-flag symptom clusters and treatment algorithm [published correction appears in Orphanet J Rare Dis. 2019 May 21;14(1):111]. Orphanet J Rare Dis. 2018;13(1):6. Published 2018 Jan 17. doi:10.1186/s13023-017-0726-x

[23] Rist, S., Sellam, J., Hachulla, E., Sordet, C., Puéchal, X., Hatron, P.-y., Benhamou, C.-l., Sibilia, J., Mariette, X. and (2011), Experience of intravenous immunoglobulin therapy in neuropathy associated with primary Sjögren's syndrome: A national multicentric retrospective study. Arthritis Care Res, 63: 1339-1344. doi:10.1002/acr.20495

[24] Kizawa M, Mori K, Iijima M, Koike H, Hattori N, Sobue G. Intravenous immunoglobulin treatment in painful sensory neuropathy without sensory ataxia associated with Sjögren's syndrome. J Neurol Neurosurg Psychiatry. 2006;77(8):967-969. doi:10.1136/jnnp.2005.084533

[25] Levine TD. Identification of a Novel Immune Mediated Cause for Small Fiber Neuropathy, American Academy of Neurology Boston 2017

[26] Sinnreich, C. J. Klein, J. R. Daube, J. Engelstad, R. J. Spinner, P. J.B. Dyck. Chronic immune sensory polyradiculopathy: A possibly treatable sensory ataxia. Neurology. 2004;63(9) 1662-1669; DOI: 10.1212/01.WNL.0000142507.12763.58

[27] Parambil JG, Tavee JO, Zhou L, Pearson KS, Culver DA. Efficacy of intravenous immunoglobulin for small fiber neuropathy associated with sarcoidosis. Respir Med. 2011;105(1):101-105. doi:10.1016/j.rmed.2010.09.015

[28] Tavee JO, Karwa K, Ahmed Z, Thompson N, Parambil J, Culver DA. Sarcoidosis-associated small fiber neuropathy in a large cohort: Clinical aspects and response to IVIG and anti-TNF alpha treatment. Respir Med. 2017;126:135-138. doi:10.1016/j.rmed.2017.03.011

[29] Benstead TJ, Chalk CH, Parks NE. Treatment for cryoglobulinemic and non-cryoglobulinemic peripheral neuropathy associated with hepatitis C virus infection. Cochrane Database Syst Rev. 2014;(12):CD010404. Published 2014 Dec 20. doi:10.1002/14651858.CD010404.pub2

[30] Nicolle, M., Barron, J., Watson, B., Hammond, R. and Miller, T., 2001. Wartenberg's migrant sensory neuritis. Muscle & Nerve, 24(3), pp.438-443.

Neuralgic Amyotrophy Syndrome with Widespread Myokymia

Elizabeth C. Steyn, MBBCh and
Jeannine M. Heckmann, PhD
Neurology division, Department of Medicine,
University of Cape Town

Introduction

We report a patient referred to us as possible motor neurone disease due to severe atrophy of his upper limbs and widespread 'fasciculations'. However, the onset was highly suggestive of Neuralgic Amyotrophy triggered by surgery,[1] along with florid myokymic discharges in the arms, chest wall and legs. We briefly discuss the variations of the classic presentation of neuralgic amyotrophy (or brachial neuritis)[2] and consider the differential diagnosis in this case.

Case Presentation

A 38-year-old man reported developing severe shoulder pain (graded 8/10), within 3 days after undergoing drainage of an abscess in the left axilla under generalized anesthesia, and 6 months prior to attending our service. The pain was first in his left, then his right shoulder, worse at night, and non-responsive to opioid analgesia. Soon after onset, he was unable to lift his arms above his head, and experienced numbness and paresthesiae in both arms. Over the next four weeks, the pain dissipated somewhat, but he developed profound weakness proximally and distally in both arms, such that he was unable to perform activities of daily living. He also noted that his muscles started 'jumping' in his arms, chest, and legs. On presentation to our service he was noted to have flail arms although he reported minor spontaneous improvement over the preceding 2 months in certain activities such as minimal improvement in shoulder abduction, elbow, and wrist flexion related activities.

He had not experienced spasms or cramps and had no cognitive or psychiatric symptoms. There was no history of any preceding illnesses, comorbidities, toxin exposure, or drug abuse. The patient mentioned chronic abdominal discomfort, for which he used antacids daily, and unintentional weight loss which started after the onset of pain and weakness, but without bulbar dysfunction.

The examination 6 months after onset was remarkable for excessive sweating of the forehead, but normal for cranial nerves and neck muscles. Widespread continuous myokymia was noted over the chest wall, abdomen, upper limbs, and thighs (see video). He had a resting tachycardia. There was marked, left more than right, atrophy of supra- and infraspinatus, pectoral muscles, thenar muscles, and first dorsal interossei (FDI) (Figure 1). The tone was reduced in the arms with absent deep tendon reflexes, except for the left triceps. Slight asymmetrical weakness (>left) was noted: strength of shoulder abduction was medical research council (MRC) grade 2/5; elbow extension and flexion 2/5; wrist extension 3/5, flexion 4/5; finger extension 1st-3rd digits 3/5, but 4-5th digits 1/5; finger flexors 4. The rectus abdominal muscles were weak. Apart from myokymia in the legs, the muscle bulk, tone, power and deep tendon reflexes were all normal. The sensory examination showed patchy hyperesthesia and decreased vibration sensibility in the first two

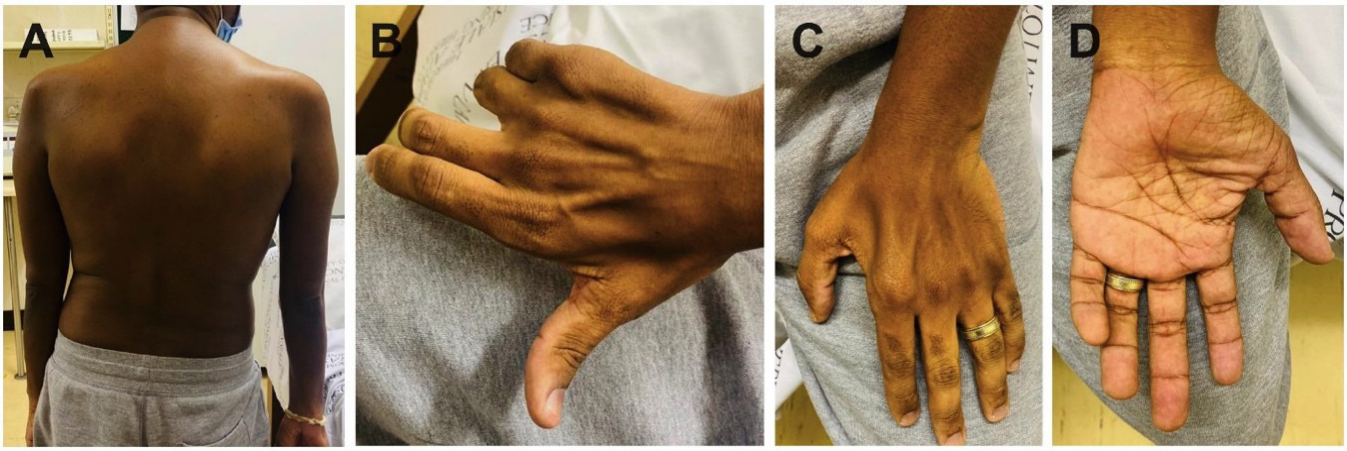


Figure 1. A. Significant wasting of the shoulder girdle including supraspinatus, infraspinatus, and deltoid muscles (> left), and mild scapular winging. B. Right hand: benediction posture with clawing of digits 4 and 5 due to weakness of the interossei and 3rd and 4th lumbricals. C, D. Left hand showing severe wasting of the first dorsal interosseus, but less atrophy of thenar and hypothenar muscles.

digits, and a glove and stocking loss to pinprick sensibility. The forced vital capacity (FVC) measured 3.4 liters sitting and supine (80% of expected).

Special investigations which had been performed 3 months after symptom onset by the first neurologist, included a normal MRI (with/without contrast) of the cervical cord and plexus, and acellular cerebrospinal fluid examination with normal chemistry. The creatine kinase was 3x the upper limit of normal, but the rest of the basic laboratory profile was normal, including erythrocyte sedimentation rate, electrolytes, urea, fasting glucose, and autoimmune antibody screen. The nerve conduction studies performed at 4 months are summarized in Table 1. Six months after onset, the anti-ganglioside antibody screen, serum protein electrophoresis, HIV- and hepatitis viral screen, and urine and blood porphyrin screens, were all negative. Repeat nerve conductions (not shown) showed reduced right ulnar compound motor amplitudes (CMAPs) with dispersion, borderline low median nerve CMAPs and normal tibial motor CMAPs, but with an absent tibial F-response. These were repeated at 8 months (Table 1) and showed similar results with mildly reduced sensory nerve amplitudes (SNAPs) in the arms but a normal sural SNAP. Electromyography (EMG) of the right deltoid, biceps, wrist extensors, FDI, quadriceps, and tibialis anterior revealed chronic neurogenic changes with fasciculations and large polyphasic motor unit action potentials with reduced recruitment, but only a small patch of fibrillation potentials in the FDI. Myokymic discharges were noted in the quadriceps. Facial muscle EMG was normal.

The onset was highly suggestive of brachial neuralgic amyotrophy. However, due to the widespread myokymia, small fiber sensory dysfunction in the legs (normal SNAPS), demyelinating features on electrophysiology (absent F-waves in the presence of CMAP >20% of the lower limit of normal), and severity of the phenotype, we started 1mg/kg prednisone 6 months after symptom onset.

After a month, the patient reported a similar trajectory of subclinical improvement to that experienced pre-prednisone. However, he had a new complaint of dyspnea and orthopnea, and recurrence of pain in the back and shoulders. The FVC was 1.9 liters (<50% of expected). The lung fields were clear on auscultation, the chest X-ray was normal, and a Covid19-PCR was negative. We administered 2g/kg of intravenous immunoglobulin (IVIG) over 3 days. Two weeks later, the patient felt the pain had improved, the orthopnea had resolved, and he was able to turn in bed independently. Objectively, the FVC had improved to 2.3 liters, and elbow extension had improved to normal strength (triceps jerk remained absent). Widespread myokymia remained visible. We elected to continue 0.5mg/kg prednisone. The patient has been referred for neurorehabilitation. At 8 months his modified Rankin remained at 3.

Discussion

We report an unusual presentation of a man with bibrachial neuralgic amyotrophy and generalized myokymia developing after surgery. After the initial severe shoulder pain subsided, he developed flail arms with severe atrophy and weakness around the shoulder girdle, distal weakness and atrophy especially prominent in the posterior interosseus branch of the radial nerve and ulnar nerve-innervated muscles, autonomic symptoms and milder sensory changes. An insidious second wave of pain and phrenic nerve dysfunction developed 7 months after the onset, with increasing truncal and respiratory muscle weakness, both of which responded partially to IVIG.

Post-operative inflammatory radiculoplexus neuropathy was described as a monophasic event separated from the 'site and time' (within 30 days) of surgery and characterized by severe pain at onset, in addition to weakness, and responsivity to immunotherapy.[3] Nerve conduction studies were characterized by variable sensorimotor axonal involvement, and nerve biopsies in the majority of their patients showed microvasculitis with epineural perivascular inflammatory cells and axonal degeneration.[3] These findings are similar to those found in the context of diabetes, viz. diabetic cervical radiculoplexus neuropathy,[4] although in diabetes the lumbosacral variant is more common.[5]

Neuralgic amyotrophy is thought to be more common than the estimated incidence of 1 per 100,000.[2] Motor symptoms predominate and atrophy is striking.[2] Although unilateral involvement occurs in most cases, ~29% have bilateral, albeit asymmetrical, plexopathy.[6] The condition was initially thought to be monophasic, but 25% may have a recurrence of painful attacks[6], which may involve the same or different regions.[2] The pathophysiological mechanism is postulated to be multifactorial such as the interactions between environmental and immune triggers (infections and/or surgery), genetic susceptibility, and biomechanical factors.[1]

Patients can also present with varied combinations of peripheral nerve involvement such as branches of the radial nerve, long thoracic nerve, and, rarely, phrenic nerve with diaphragmatic weakness and dyspnea, such as our case. Lower brachial plexus involvement with sympathetic symp-

Table 1: Clinical electrophysiology performed months after onset of symptoms.

Nerve		4 months	8 months	Reference Values
Right Median Motor[#]	DL, ms	3.9	4.2	<4.5
	CMAP, mV	5.3/4.5	3.8/2.9	>4.0
	CV, m/sec	60.2*	59.9*	>48
Left Median Motor[#]	DL, ms	3.45	3.4	<4.5
	CMAP, mV	4.6/3.5	1.1/1.1	>4.0
	CV, m/sec	62.9**	51.6**	>48
Right Ulnar Motor[#]	DL, ms	3.65	4.02	<3.6
	CMAP, mV	2.1/2.1	0.9/0.5	>6.0
	CV, m/sec	60.3**	43.3	>51
Left Ulnar Motor	DL, ms	3.1	2.8	<3.6
	CMAP, mV	3.1/2.5	2.4/2.1	>6.0
	CV, m/sec	55.7*	64.8*	>51
Right Tibial Motor[#]	DL, ms	ND	5.75	<6.0
	CMAP, mV	ND	21.2/19.4	>4.0
	CV, m/sec	ND	65.7*	>41
Left Tibial Motor	DL, ms	ND	4.55	<6.0
	CMAP, mV	ND	15.8/12.9	>4.0
	CV, m/sec	ND	56.9	>41
Left Peroneal Motor	DL, ms	ND	3.9	<5.9
	CMAP, mV	ND	5.3/5.2	>2.0
	CV, m/sec	ND	65.6	>41
Left Median Sensory	DL, ms	1.7	1.82	<2.2
	SNAP, µV	61	107[#]	>50
Right Ulnar Sensory	DL, ms	2.1	1.8	<2.1
	SNAP, µV	17.4	38.9[#]	>15
Left Ulnar Sensory	DL, ms	2.1	2.0	<2.1
	SNAP, µV	17.4	44.5	>15

DL- Distal Latency, ms- milliseconds, CV- Conduction Velocity, m/sec - meters/second-, CMAP- compound motor action potential, and the 2 values represent Distal/Proximal values. ND – Not done. The patient had a shortened examination at 6 months after symptoms (due to Covid19 lockdown); the results of the 3 nerves examined[#] (not shown) were similar to 8-month values. *absent F-waves in the presence of CMAP >20% of the lower limit of normal, **normal F-response. Right median and peroneal motor and sural sensory, not shown- all normal.

toms and lumbosacral plexopathy has also been described, even in the absence of diabetes.[2] Van Alfen and Van Engelen reported an "extended neuralgic amyotrophic syndrome" in which the phenotype extends beyond the classic upper trunk brachial plexopathy, also involving the lower trunk of the brachial plexus, individual nerves, and the lumbosacral plexus.[1] We postulate that our case has the features of this extended syndrome. However, widespread myokymia, as seen in our case, has not been reported in neuralgic amyotrophy.

Magnetic resonance imaging features of the plexus range from normal—to focal edema with T2 hyperintensity and contrast enhancement.[7] Nerve conduction studies may indicate an axonopathy with low CMAPs and normal

conduction velocities. SNAPs are usually normal. EMG may show fibrillation potentials and chronic neurogenic changes, although our patient showed very little evidence of active denervation in severely atrophic muscles. Generalized myokymia has been described in the setting of acute and chronic demyelinating polyradiculoneuropathy[8] and is thought to be due to motor axon hyperexcitability with ephaptic activation.[9] Although our patient did have some electrophysiological features of proximal conduction slowing with absent F-waves, myokymia has rarely been described in axonal disorders such as motor neuron disease.[9] It was important to exclude acute intermitted porphyria as this may present as a motor neuron disease mimic with rapidly developing severe atrophy.[10]

Corticosteroid therapy was used in a small open-label study, most frequently within 10 days of symptom onset, although the average was 30 days. Those receiving prednisone suffered more pain and greater disability compared to those not given prednisone. However , those receiving prednisone, appeared to have earlier recovery, although the degree of recovery was similar.[6] Anecdotal case reports also suggest that early treatment with IVIG followed by steroids may hasten recovery and improve outcomes.[11] Nevertheless, this is a disabling condition in most cases. Recovery of function is delayed and can take several years. Only 10% of patients report full recovery after 3 years and a further 10% remain with substantial morbidity currently.[6]

In conclusion, we describe a patient with a stuttering, extended neuralgic amyotrophy syndrome, which has resulted in flail arms, ongoing autonomic instability, and widespread myokymia after 8 months. It is uncertain whether earlier recognition and immune treatment may have altered the outcome in this case.

Corresponding author:
JM Heckmann
email: Jeanine.heckmann@uct.ac.za
Neurology E8-74, Groote Schuur Hospital, Observatory, 7925, Cape Town, South Africa.

References

[1] Van Alfen N. Clinical and pathophysiological concepts of neuralgic amyotrophy. Nat Rev Neurol 2011;7:315–22. DOI: 10.1038/nrneurol.2011.62

[2] Van Eijk JJJ, Groothuis JT, Van Alfen N. Neuralgic amyotrophy: An update on diagnosis, pathophysiology, and treatment. Muscle Nerve 2016;53:337–50. DOI: 10.1002/mus.25008

[3] Staff NP, Engelstad J, Klein CJ, Amrami KK, Spinner RJ, Dyck PJ, et al. Post-surgical inflammatory neuropathy. Brain 2010;133:2866–80. DOI: 10.1093/brain/awq252

[4] Massie R, Mauermann ML, Staff NP, Amrami KK, Mandrekar JN, Dyck PJ, et al. Diabetic cervical radiculoplexus neuropathy: A distinct syndrome expanding the spectrum of diabetic radiculoplexus neuropathies. Brain 2012;135:3074–88. DOI: 10.1093/brain/aws244

[5] Dyck PJB. Non-diabetic lumbosacral radiculoplexus neuropathy: Natural history, outcome and comparison with the diabetic variety. Brain 2001;124:1197–207. DOI: 10.1093/brain/124.6.1197

[6] Van Alfen N, Van Engelen BGM. The clinical spectrum of neuralgic amyotrophy in 246 cases. Brain 2006;129:438–50. DOI: 10.1093/brain/awh722

[7] Rehman I, Chokshi FH, Khosa F. MR imaging of the brachial plexus. Clin Neuroradiol 2014;24:207–16. DOI: 10.1007/s00062-014-0297-3

[8] Albers JW, Allen AA, Bastron JA, Daube JR. Limb myokymia. Muscle Nerve. 1981;4:494–504. DOI: 10.1002/mus.880040606

[9] Kelkar P, Kimura J. Myokymia in axonal disorders. J Clin Neuromuscul Dis. 2005;7(2):55–8. DOI: 10.1097/01.cnd.0000184804.14826.5c

[10] Albertyn CH, Sonderup M, Bryer A, Corrigall A, Meissner P, Heckmann JM. Acute intermittent porphyria presenting as progressive muscular atrophy in a young black man. South African Med J 2014;104:283–5. DOI: 10.7196/samj.7785

[11] Nakajima M, Fujioka S, Ohno H, Iwamoto K. Partial but rapid recovery from paralysis after immunomodulation during early stage of neuralgic amyotrophy. Eur Neurol 2006;55:227–9. DOI: 10.1159/000093875

Amyloid Myopathy as an Inclusion Body Myositis Mimic

Anai C. Hamasaki, MD[1], Ryan D. Jacobson, MD[3], Barbara J. Distad, MD[6], Michael D. Weiss, MD[6], Jeffrey M. Statland, MD [2], Omar Jawdat, MD [2], Melanie D. Glenn, MD[2], Laura Herbelin, BS[2], Richard J. Barohn, MD[2], Mamatha Pasnoor, MD[2], Gary W. Gallagher, MD[4], Sandra I. Camelo-Piragua, MD[5], Andrew J Heim, CCRP[2], Mazen M. Dimachkie, MD[2]

[1]Department of Neurology, The University of Oklahoma Health Sciences Center, Oklahoma City, OK
[2]Department of Neurology, The University of Kansas Medical Center, Kansas City, KS
[3]Department of Neurology, Loyola University Chicago, Chicago, IL
[4]Department of Neurology, University of Michigan, Ann Arbor, MI
[5]Department of Pathology, University of Michigan, Ann Arbor, MI
[6]Department of Neurology, University of Washington, Seattle, WA

ABSTRACT

Introduction: Amyloid myopathy is a rare presentation of systemic amyloidosis. Amyloid myopathy can be initially misdiagnosed as sporadic inclusion body myositis (IBM).

Methods: We report 4 cases of amyloid myopathy clinically mimicking inclusion body myositis and initially thought to be phenotypically IBM by neuromuscular experts.

Results: Case 1 is an 81-year-old woman who presented with distal arm and proximal leg asymmetric weakness (myopathy pattern 4). Case 2 is a 76-year-old man with primary systemic amyloidosis who presented with myopathy pattern 4 and progressive dysphagia for four years. Case 3 is an 82-year-old man with progressive myopathy pattern 4 weakness and swallowing difficulty. Case 4 is a 62-year-old man with progressive bilateral finger flexor weakness. Muscle biopsies in all 4 cases showed perivascular amyloid deposits.

Discussion: Amyloid myopathy may be clinically indistinguishable from IBM. Muscle biopsy is of critical importance in the evaluation of patients suspected to have IBM.

Keywords: *amyloid, myopathy, amyloidosis, IBM, myositis.*

Introduction

Primary systemic amyloidosis is a disease resulting from deposition of amyloid in tissues causing organ dysfunction. Kidneys, heart, peripheral nerves and liver are commonly affected organs.[1] Amyloid deposits are formed from monoclonal serum proteins in plasma cell dyscrasia[2] and may result from deposition of heavy chain, monoclonal light chains or its N-terminal fragment.[3]

Amyloid myopathy is a rare presentation of primary systemic amyloidosis. Typically, it presents with proximal muscle weakness and elevated creatine kinase level. [4,5]

Sporadic inclusion body myositis (IBM) is the most common idiopathic inflammatory myopathy (IIM) after age 50,[6] characterized by distal upper extremity and proximal lower extremity weakness, also known as myopathy pattern 4 (MP4).[7]

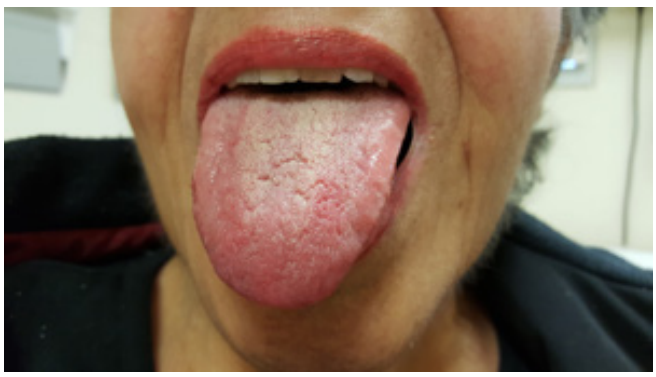
A literature search yielded two case reports of amyloid myopathy patients initially presenting with an IBM phenotype.[5,8] We present four more cases from four large academic centers.

Methods

We report four cases of amyloid myopathy clinically mimicking inclusion body myositis and initially thought to be phenotypically IBM by neuromuscular experts.

Results

Case 1: An 81-year-old female was evaluated for progressive generalized weakness and dysphagia for two years. There was no similar family history. On examination, she had tongue enlargement (Supplementary Fig. 1), MP4 with asymmetric weakness right and left respectively in knee extension 3/4, hip flexion 2/5, finger flexion 4/3 and shoulder abduction 4/4+. There was decreased pinprick below ankles, and ankle reflexes were absent. She was initially suspected to have IBM. Laboratory testing showed cre-



Supplementary Figure 1. Enlargement of the tongue of case 1.

atine kinase (CK) of 141 IU/L, IgA monoclonal protein with lambda light chain in serum and urine and elevated serum beta-2 microglobulin. Electromyography (EMG) revealed an irritative myopathy. Biceps muscle biopsy demonstrated perivascular amyloid deposits indicative of amyloid myopathy (Figure 1). There was no evidence of heart involvement by transthoracic echocardiogram. She was treated with chemotherapy (cyclophosphamide, bortezomib and dexamethasone) along with physical therapy without response and ultimately required nursing home care. She developed postural hypotension due to associated autonomic neuropathy.

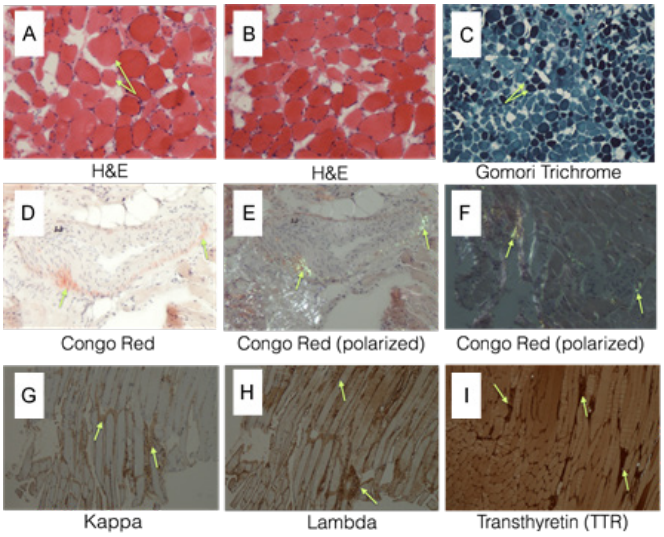
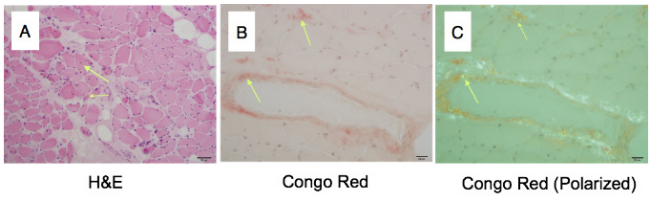


Figure 1. Biopsy of the biceps muscle. A) and B) Hematoxylin-Eosin (H&E) and C) Gomori-Trichrome stains showing muscle fiber size variability. There is no inflammation or vacuolation. D) Congo red stain showing salmon-pink amyloid deposits in blood vessel wall. E) and F) Congo red stain under polarized light showing apple-green birefringent amyloid deposits in blood vessel and muscle fibers. G), H) and I) Immunohistochemical staining showing immunoreactivity against kappa light chain (G), lambda light chain (H) and transthyretin (I).

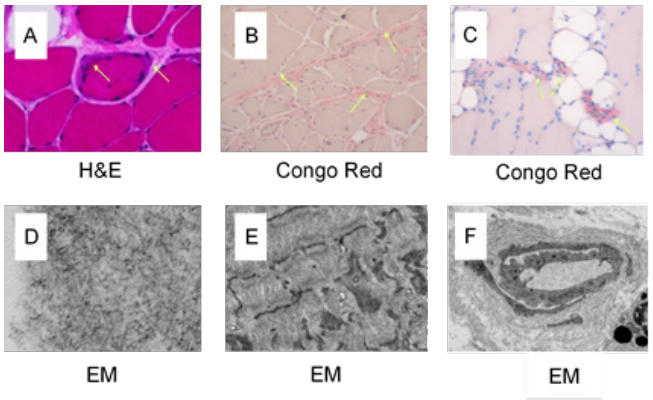
Case 2: A 76-year-old male presented with progressive dysphagia for four years and thigh predominant leg weakness for four to five years. Around dysphagia onset, he was diagnosed with heart and renal failure due to primary amyloidosis. Despite chemotherapy, cardiac function declined. Neuromuscular examination demonstrated mild flaccid dysarthria and symmetric limb weakness. Leg weakness was mostly proximal, barely antigravity in quadriceps muscles. Arm weakness was most prominent distally with finger flexors involvement. There was no sensory loss or tongue enlargement. Initially, the patient was suspected to have IBM, despite known systemic amyloidosis diagnosis. EMG revealed myopathy with increased insertional activity. Vastus lateralis muscle biopsy revealed endomysial and perivascular amyloid deposits (Supplementary Fig. 2). There were no rimmed vacuoles nor inflammation. He died of presumed cardiac arrhythmia or aspiration one month following myopathy diagnosis.



Supplementary Figure 2. Biopsy of the vastus lateralis muscle of case 3. A) H&E stain showing muscle fiber size variability. B) Congo red stain showing salmon-pink amyloid deposits in blood vessel wall and muscle fibers. C) Congo red stain under polarized light showing apple-green birefringent amyloid deposits in blood vessel and muscle fibers.

Case 3: An 82-year-old male presented with 3 years of progressive proximal weakness. He had difficulty initially lifting arms above his head, followed by difficulty standing up and keeping his head up, then difficulty with buttoning and imbalance leading to falls. He also experienced swallowing difficulties and chronic constipation. Weakness was noted on neck flexion and extension, right greater than left proximal arms, and finger flexors greater than extensors, as well as antigravity strength in proximal legs and knee extensors. Reflexes were absent in the legs with reduced vibration. Lambda free light chain was elevated. EMG showed an irritative myopathy. Deltoid muscle biopsy showed myofiber necrosis, type II atrophy, mild fibrosis and upregulated HLA class 1 expression (Supplementary Fig. 3). Congo red stains revealed amyloid within arteriolar walls and endomysial connective tissues. Bone marrow biopsy showed presence of Lambda Bence Jones protein without evidence of amyloid deposition on Congo red stain.

Case 4: A 62-year-old male presented with a one and a half-year history of progressive bilateral hand weakness, worse on the left. Examination showed weakness of flexor digitorum profundus 4+/3 (digits 3, 4 and 5) and 3+/2 (digits 1 and 2), right and left respectively. CK was 280 IU/L. He had normal serum and urine electrophoresis, immunofixation electrophoresis, and kappa to lambda free light chain ratio. EMG showed irritative myopathy. He was initially thought



Supplementary Figure 3. Biopsy of the right deltoid muscle. A) H&E stain showing muscle fiber size variability and subsarcolemmal aggregates. B) Congo red stain showing muscle fiber size variability and interstitial thickening/amyloid. C) Congo red stain showing vascular (right) and interstitial (center) amyloid. D) Electron microscopy (EM) 30,000x with interstitial amyloid fibrils, 8-10 nm. E) EM 4800x showing sarcomere Z line disruption. F) EM 2900x of affected vessel.

to have IBM. Left biceps muscle biopsy revealed prominent perivascular deposition of amyloid leading to the diagnosis of amyloid myopathy. There was also rare rimmed vacuoles, fiber muscle necrosis and perivascular inflammation. There was HLA Class 1 sarcolemmal expression, CD3+ T cells with rare invasion of non-necrotic muscle fibers, and variable expression of phosphorylated neurofilaments on SMI-31 antibody staining (Fig. 2). Immunochemistry for transthyretin was weakly positive but negative for beta-amyloid protein and kappa and lambda light chains. A search for systemic amyloidosis, including bone marrow and rectal biopsy, echocardiography and genetic testing for transthyretin mutations was unfruitful.

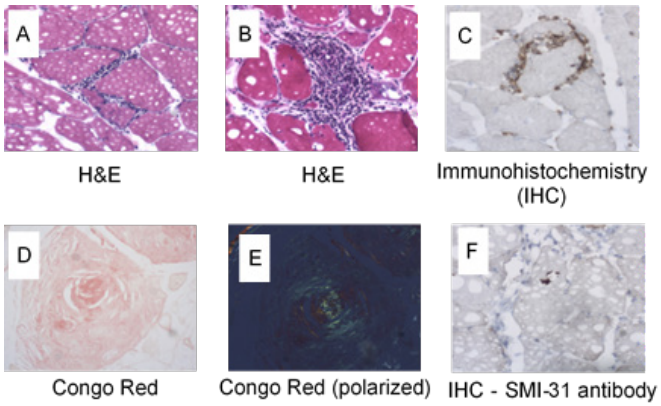


Figure 2. Biopsy of left biceps muscle. A) H&E stain showing endomysial inflammation. B) H&E stain showing perivascular inflammation. C) IHC showing predominantly CD3+ T-cells. D) Non-polarized Congo red stain showing amyloid deposits in blood vessel wall. E) Polarized Congo Red stain confirming the presence of amyloid in thickened blood vessel walls. F) IHC SMI-31 Ab showing phosphorylated neurofilament deposition.

Discussion

IBM classically causes distal arm and proximal leg weakness also known as MP4 but can have a pleomorphic presentation (Table 1). The differential diagnosis of IBM includes inflammatory, autoimmune and genetic diseases, and in some cases, degenerative or even metabolic disorders. Table 1 lists confounders of IBM by phenotypic presentation.

Recognition and description of the clinical pattern of weakness remains an essential part of the diagnostic approach to myopathies. The patients described here, however, illustrate that tissue diagnosis is of key importance. While our patients had clinical presentations consistent with IBM as determined by neuromuscular experts, muscle histopathology revealed a different diagnosis with quite different management.

The clinical scenario was slightly different in our cases. Cases 1, 3 and 4 presented for evaluation of myopathy and were ultimately diagnosed with amyloidosis. Case 2 had an established diagnosis of systemic amyloidosis and only later amyloid myopathy. In cases 1, 2 and 3, the distribution of weakness was striking and notable for distal arm and proximal leg weakness. In case 4, there was weakness more notable in the finger flexors when compared to finger extensors without lower extremity weakness. Therefore, all patients required muscle biopsy to disprove the initial erroneous diagnosis of IBM.

Our study has several limitations. The number of cases is small. The data was retrospectively abstracted. We did not measure antibody titers to cyclic nucleotidase-1A as patients were evaluated before the availability of these autoantibodies. Furthermore, these autoantibodies have been increasingly described to be non-specifically elevated in various inflammatory myopathies and autoimmune rheumatologic disorders. For example, these are found in Sjögren's syndrome (23-36%), systemic lupus erythematosus (14-20%) and dermatomyositis (15%).[14,15]

For case 4, follow up duration was short. Though histopathologic evidence of inflammation was described previously in amyloid myopathy leading to an erroneous diagnosis of polymyositis, rare rimmed vacuoles would be quite an unusual finding.[4] The rarity of these vacuoles renders them

Table 1: IBM phenotypes and differential diagnosis according to clinical patterns.

IBM Phenotypes [1]	Differential diagnosis
Distal Arm/Proximal Leg (MP4)	Myotonic MD[2], Sarcoidosis[3], Amyloid Myopathy[4]
Distal Weakness (MP2)	Myotonic MD[2], ALS[5]
Quadriceps Atrophy	Becker MD[6], LGMD[6], Emery-Dreifuss[6], PM[6], SMA[6]
Limb-girdle pattern (MP1)	Polymyositis[7], LGMD, Pompe[8], Amyloid Myopathy[4], Sarcoidosis[9]
Bulbar (MP7) - dysphagia	MG[2], LEMS[2], ALS[2], LGMD[2]

1. Dimachkie *et al.*, 2014;[6] 2. Barohn *et al.*, 2014;[7] 3. Wolfe *et al.*, 1987;[9] 4. Gert *et al.*, 1996;[3] 5. Barohn *et al.*, 2013;[10] 6. neuromuscular.west.edu/muscdist/quad.html; 7. Dimachkie *et al.*, 2014;[11] 8. Manganelli *et al.*, 2013;[12] 9. Hinterbuchner *et al.*, 1964.[13]

non-diagnostic. Furthermore, these have been non-specifically observed in other disorders such as polymyositis, hereditary IBM, and neurogenic atrophy.[16]

All of our cases fulfilled the 2011 ENMC clinical and laboratory criteria for IBM (Supplementary Table 1).[17] Cases 3 and 4 even fulfilled criteria for clinically defined IBM and probable IBM respectively. This is given pathologic evidence of HLA class 1 expression in Case 3 and inflammation with myofiber invasion in Case 4. This highlights the importance of obtaining muscle biopsy in patients with IBM and that Congo Red staining should be part of the routine evaluation of IBM muscle. Beyond that, it raises questions about the specificity of the ENMC 2011 IBM criteria. For instance, if Congo Red stain was not done in cases 3 and 4, the diagnosis would have been IBM based on these criteria (Supplementary Table 1).

Clinical & Laboratory Features	Classification	Pathological Features
Duration >12 months Age at onset > 45 yrs Quads weak ≥ hip flex **and/or** FF weak > should abd sCK not > 15xULN	**Clinico-Pathologically Defined IBM**	Endomysial inflammation **&** Rimmed vacuoles **& either** Protein accumulation (amyloid or other proteins) **or** 15-18nm filaments
Same as in Clinico-pathologically Defined IBM except Quads weak ≥ hip flex **and** FF weak > should abd	**Clinically-Defined IBM**	***One or more of:*** Endomysial inflammation Rimmed vacuoles ↑ MHC1 Protein accumulation* (amyloid or other proteins) 15-18nm filaments
Same as in Clinico-pathologically Defined IBM except Quads weak ≥ hip flex **or** FF weak > should abd	**Probable IBM**	*Same as clinically defined IBM* *amyloid = Congo-red, crystal violet, or thioflavine T/S other proteins = p62, SMI-31, or TDP-43

Supplementary Table 1: IBM diagnostic criteria (adapted from The ENMC IBM research diagnostic criteria 2011[17]).

Conclusion

Amyloid myopathy may clinically mimic IBM and manifest as an initial or delayed presentation of primary systemic amyloidosis. Despite the availability of antibody testing, muscle biopsy remains critically important in the evaluation of patients suspected to have IBM and serves to distinguish IBM from its many mimics.

Corresponding author:
Anai C. Hamasaki, MD
Email: Anai-Hamasaki@ouhsc.edu

Bibliography

[1] Kyle, R.A. and M.A. Gertz, Systemic amyloidosis. Crit Rev Oncol Hematol, 1990. 10(1): p. 49-87.

[2] Kelly, J.J., Neurologic complications of primary systemic amyloidosis. Rev Neurol Dis, 2006. 3(4): p. 173-81.

[3] Gertz, M.A. and R.A. Kyle, Myopathy in primary systemic amyloidosis. J Neurol Neurosurg Psychiatry, 1996. 60(6): p. 655-60.

[4] Smestad, C., et al., Amyloid myopathy presenting with distal atrophic weakness. Muscle Nerve, 2004. 29(4): p. 605-9.

[5] Tuomaala, H., et al., Amyloid myopathy: a diagnostic challenge. Neurol Int, 2009. 1(1): p. e7.

[6] Dimachkie, M.M. and R.J. Barohn, Inclusion body myositis. Neurol Clin, 2014. 32(3): p. 629-46, vii.

[7] Barohn, R.J., M.M. Dimachkie, and C.E. Jackson, A pattern recognition approach to patients with a suspected myopathy. Neurol Clin, 2014. 32(3): p. 569-93, vii.

[8] Abuzinadah, A.R., J.T. Joseph, and L. Korngut, Amyloid myoneuropathy mimicking inclusion body myositis. Can J Neurol Sci, 2013. 40(2): p. 255-8.

[9] Wolfe, S.M., et al., Myopathy in sarcoidosis: clinical and pathologic study of four cases and review of the literature. Semin Arthritis Rheum, 1987. 16(4): p. 300-6.

[10] Barohn, R.J. and A.A. Amato, Pattern-recognition approach to neuropathy and neuronopathy. Neurol Clin, 2013. 31(2): p. 343-61.

[11] Dimachkie, M.M., R.J. Barohn, and A.A. Amato, Idiopathic inflammatory myopathies. Neurol Clin, 2014. 32(3): p. 595-628, vii.

[12] Manganelli, F. and L. Ruggiero, Clinical features of Pompe disease. Acta Myol, 2013. 32(2): p. 82-4.

[13] Hinterbuchner, C.N. and L.P. Hinterbuchner, Myopathic Syndrome in Muscular Sarcoidosis. Brain, 1964. 87: p. 355-66.

[14] Lloyd, T.E., et al., Cytosolic 5'-Nucleotidase 1A As a Target of Circulating Autoantibodies in Autoimmune Diseases. Arthritis Care Res (Hoboken), 2016. 68(1): p. 66-71.

[15] Herbert, M.K., et al., Disease specificity of autoantibodies to cytosolic 5'-nucleotidase 1A in sporadic inclusion body myositis versus known autoimmune diseases. Ann Rheum Dis, 2016. 75(4): p. 696-701.

[16] Dimachkie, M.M. and R.J. Barohn, Distal myopathies. Neurol Clin, 2014. 32(3): p. 817-42, x.

[17] Rose, M.R. and E.I.W. Group, 188th ENMC International Workshop: Inclusion Body Myositis, 2-4 December 2011, Naarden, The Netherlands. Neuromuscul Disord, 2013. 23(12): p. 1044-55.

Myasthenia Gravis Exacerbation with Shingrix Vaccine

Lakshmi P. Digala, MBBS and
Raghav Govindarajan, MD
Department of Neurology, University of Missouri Health Care, Columbia, MO, USA 65201

Keywords: *Shingrix, Myasthenia exacerbation, Auto-immunity, Adjuvants.*

Introduction

Shingrix is a non-live recombinant vaccine approved to prevent herpes zoster infection, and its efficacy, and safety are well studied. The risk of vaccine-related complications in myasthenia symptoms is higher with live vaccines. However, Shingrix, a non-live vaccine causing exacerbation of the myasthenia symptoms, has not been reported to date. Herein, we present a case of stable myasthenia gravis that got exacerbated after a single dose of Shingrix vaccination.

Case

Our patient is a 73-year-old man diagnosed with stable seropositive generalized myasthenia gravis (MG) for the last eight years. He was on prednisone 10 mg every other day and Pyridostigmine 60 mg twice daily. He presented to the Neurology clinic with worsening ocular symptoms including horizontal diplopia worse with right lateral gaze, generalized weakness, and fatigue. He also complained about difficulty swallowing and orthopnea. 5 days before the presentation, he received the Shingrix vaccine. There was no change in medications or infections in the interim. On examination, he had fatigable ptosis with Cogan's Sign, fatigable arm weakness, and single breath count test of 38. He was admitted and treated with IVIg (1g/kg body weight) for five days, which improved dysphagia and orthopnea but did not improve the diplopia. His dose of prednisone was increased to 30 mg every other day and Pyridostigmine 60 mg, three times a day, which improved his ocular symptoms 2 months later.

Discussion

Herpes zoster (HZ) is a painful dermatomal, vesicular rash commonly seen in the elderly, also known as Shingles.[1] It is caused by the reactivation of the latent Varicella-zoster virus (VZV),[1] a member of the α-herpes virus family.[2]

Shingrix is an adjuvanated non-live recombinant vaccine for herpes zoster, which was approved by the Food and Drug Administration (FDA) in October 2017 for adults over 50 years.[3]

It consists of glycoprotein E (gE) and an adjuvant component called AS01B, which enhances the potency, quality, and immune response's longevity.[4]

Vaccines, although beneficial, have proposed to be implicated in the development of autoimmune disorders. The definite mechanism is unknown, but one probable cause could be the vaccine components eliciting an exaggerated immune response.

However, studies also reported the role of adjuvants in causing autoimmunity by simulating an immune reaction in animal models or humans similar to bacterial or viral infections.[5,8]

As stated earlier, the Shingrix vaccine consists of the glycoprotein E and adjuvant AS01B. Adjuvants, by definition, are substances that augment antigen-specific immune response.[6]

Our patient had been stable for the past eight years and developed an exacerbation of MG 5 days after the vaccination. Chung et al. described a case that described the possible association between vaccination and myasthenia exacerbation. They reported a case in a young woman who developed myasthenia gravis within three days of the human papillomavirus vaccination.[7]

Another vaccine associated with the onset or exacerbation of myasthenia gravis is the recombinant Hepatitis B vaccination. Stuben described various autoimmune neuromuscular diseases developed after the HBV vaccine.[8] He described three cases, and the predisposition to auto-immunity is explained by their history of atopic allergy.[8] Although uncommon, the temporal association of myasthenia is reported in three patients after Hepatitis B vaccination.[8,9,10]

In our case, we hypothesize that either the gE or AS01B may have led to an alteration in the host immune response, and the release of inflammatory cytokines resulted in an exaggerated T cell response and worsening of the patient's symptoms. However, further studies are required to evaluate Shingrix vaccine safety, especially in Myasthenia Gravis patients.

Corresponding author:
Raghav Govindarajan MD
Email: govindarajanr@health.missouri.edu

References

[1] Cunningham A.L. et al.(2016) Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older. N Engl J Med. 15;375(11):1019-32. doi: 10.1056/NEJMoa1603800.

[2] Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. (2007) A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction, Mayo Clin Proc, vol. 82(pg. 1341-9) doi: 10.4065/82.11.1341.

[3] Hesse E M., Shimbakuro T T. et al. (2019) Postlicensure Safety Surveillance of Recombinant Zoster Vaccine (Shingrix) — United States, October 2017–June 2018. MMWR Morb Mortal Wkly Rep1;68(4):91-94. doi: 10.15585/mmwr.mm6804a4.

[4] F. Maltz, B. Filder. (2019) Shingrix: A New Herpes Zoster Vaccine. P.T. 44(7): 406-409,433.

[5] Vered Molina, Yehuda Shoenfeld. (2005) Infections, Vaccines and Other Environmental triggers of Auto-immunity. Autoimmunity. 38(3):235-45. doi: 10.1080/08916930500050277.

[6] E. Israeli, N. Agmon-Levin, M. Blank, Y.Shoenfeld. (2009) Adjuvants and autoimmunity, vol. 18pp. 1217-1225 doi: 10.1177/0961203309345724.

[7] Chung, J.Y., Lee, S.J., Shin, B. et al. (2018) Myasthenia gravis following human papillomavirus vaccination: a case report. BMC Neurol 18, 222. https://doi.org/10.1186/s12883-018-1233-y

[8] Stübgen JP. (2010) Neuromuscular disorders associated with hepatitis B vaccination. J Neurol Sci. 292(1–2):1–4. Doi: 10.1016/j.jns.2010.02.016.

[9] Biron P., Montpetit P., Infante-Rivard C., and Léry L. (1988) Myasthenia gravis after general anesthesia and hepatitis B vaccine. Arch Int Med. 148: pp. 2685 doi: 10.1001/archinte.1988.00380120123025.

[10] Louzir B, Othmani S, Battikh R, Ben Abdelhafidh N, Bahri M, Taalouche L, et al. (2003) Myasthenia after hepatitis B vaccination. Therapie. 58(4):378–9. Doi: https://doi.org/10.2515/therapie:2003059.

2020 Muscle Study Group Annual Scientific Meeting

The MSG meeting is scheduled for Sept 25, 26, and 27 and we published Issue 4 of the *RRNMF Neuromuscular Journal* which contains the abstracts from the meetings prior to the first day of the meeting.

This year due to COVID-19 the MSG meeting has gone 100% virtual. While this will be a challenge it has some opportunities. Typically, about 175 neuromuscular specialists sign up for the meeting which for several years has been in Snowbird, Utah, but this year was scheduled to be in Georgetown, Washington DC. We have also had meetings in Oxford, England and the early years of MSG were held in upstate New York, in Beaver Hollow, outside of Buffalo.

But this year it is being held in your own home/office! And as a result, we have over 500 individuals registered not only from the US, UK and Europe but from 17 other countries! The planning committee had to be creative in organizing the conference. First, we decided to begin early in the morning and end around noon or 1, because we have many attendees from the UK and Europe, and now as it turns out from all over the world. Most of our speakers we had invited agreed to do their talk virtually. Some were pre-recorded. The challenge was the scientific "platform" presentations from MSG members and posters from attendees. We have a few 15-minute scientific platform presentations from MSG members, especially from prior, current and future MSG funded neuromuscular fellows. But most were in the "poster" category. We debated on having a virtual "poster room". But we opted to give each "poster" instead a 5-minute FLASH presentation followed by 5 minutes of Q and A. At the end of the morning sessions we plan to have "rooms" with the FLASH presenters from that day that any conference attendee can visit and ask more questions. Welcome to the virtual era. I am anxious to see how this year's conference works out.

We are indebted to the Planning Committee who was able to be nimble and adjust to the COVID pandemic for this meeting; to the executive committee, and especially to our administrative director, Liz (Elizabeth) Paulk who has worked very, very hard to make this a successful meeting for us all. Thank you Liz! In addition, we would like to thank all of the sponsors who continued to support this meeting even when the decision was made to go virtual. Their generous support was appreciated even more because of that. And thank you to all the invited speakers, the FLASH presenters, and attendees. MSG hired Amardeep Gill, a virtual event producer in New York City to put this all together and "Gill" has been a pleasure to work with. Next year we tentatively plan to have the meeting take place in Georgetown on September 24-26, 2021.

But who knows.. we may prefer to keep this virtual! Let us know how you like this one.

Thanks,
Rick

2020 Planning Committee
Carolina Barnett-Tapia, M.D., Ph.D. // Chair University of Toronto
Chafic Karam, M.D. //Oregon Health and Science Hospital
Gita Ramdharry, Ph.D. //Queen Square MRC Centre for Neuromuscular Disease
James B. Lilleker, MBChB, Ph.D. //The University of Manchester
Kimberly A. Hart, M.A. //University of Rochester Medical Center
Lindsay Alfano, DPT //Nationwide Children's Hospital
Richard Barohn, M.D. // MSG Chair University of Missouri
Prof Michael Hanna, M.D. // MSG Co-Chair University College London

MSG Executive Committee
Richard Barohn, M.D. // Chair University of Missouri
Prof Michael Hanna, M.D. // Co-Chair University College London
Robert Griggs, M.D. // Former Chair University of Rochester Medical Center
Mazen Dimachkie, M.D. // Investigator Member, Treasurer University of Kansas Medical Center
Valeria Sansone, M.D. // Investigator Member NEMO Clinical Center
Michael McDermott, Ph.D. // Biostatistician University of Rochester Medical Center
Rabi Tawil, M.D. // Director, MSG Coordination Center, University of Rochester Medical Center
William David, M.D., Ph.D. // Massachusetts General Hospital
Melissa Mcintyre, DPT, DPT // Evaluator Member University of Utah
Marie Wencel, CCRP // Coordinator Member University of California, Irvine

Elizabeth Paulk, MSG Administrative Manager, epaulk@kumc.edu. 913.945.6939
Amardeep Gill, ZOOM Event Producer, customerservice@streamguru.net

MEETING SUPPORT //
Thank You!

MUSCLE STUDY GROUP

GOLD LEVEL SPONSORS

Genentech
A Member of the Roche Group

PTC THERAPEUTICS®
measured by moments

SAREPTA THERAPEUTICS

SILVER LEVEL SPONSOR

UCB Inspired by **patients.** Driven by **science.**

Ra Pharma now a part of UCB

BRONZE LEVEL SPONSORS

Argenx
Biogen
Cytokinetics
MT Pharma
Orphazyme

CORPORATE LEVEL SPONSORS

Catalyst Pharmaceuticals
Spark Therapeutics, Inc.

AGENDA // Friday, September 25

Carolina Barnett-Tapia, M.D., Ph.D. & Chafic Karam, M.D. // *Moderators*

8-8:15 A.M. **WELCOME** Richard J. Barohn, M.D., Prof Michael G. Hanna, M.D.

8:20-8:30 A.M. **UPDATE ON THE PHASE 2/3 STUDY OF ARIMOCLOMOL IN IBM ***
Mazen Dimachkie, M.D. // *University of Kansas Medical Center*

8:32-8:42 A.M. **MSG INTERNATIONAL INCLUSION BODY MYOSITIS (IBM) GENETICS CONSORTIUM UPDATE *** Alaa Khan, Ph.D. // *UCL Queen's Square*

8:45-8:55 A.M. **INFLUENCE OF NT5c1A ANTIBODIES ON DISEASE PROGRESSION, CLINICAL PHENOTYPE AND BLOOD AND MUSCLE BIOMARKERS IN SPORADIC INCLUSION BODY MYOSITIS: A PROSPECTIVE EVALUATION *** Tahseen Mozaffar, M.D. // *University of California, Irvine*

9:00-9:20 A.M. **DEVELOPMENT WORK FOR AN APP-BASED INTERVENTION TO PROMOTE PHYSICAL ACTIVITY IN PEOPLE LIVING WITH AND BEYOND CANCER**
Dr. Abi Fisher // *Associate Professor, UCL School of Behaviour Change*

9:25-9:55 A.M. **CHALLENGES OF HEALTH ECONOMIC ASSESSMENT FOR SPINRAZA AND ZOLGENSMA**
Rick Chapman, Ph.D. // *Institute for Clinical & Economic Review*

10-10:20 A.M. **INCORPORATING IMPLEMENTATION SCIENCE QUESTIONS INTO CLINICAL EFFECTIVENESS TRIALS**
Geoff Curran, Ph.D. // *Professor, University of Arkansas for Medical Sciences*

10:25-10:50 A.M. **THE HEALEY ALS PLATFORM TRIAL: INNOVATIVE TRIAL DESIGN AND COLLABORATION TO ACCELERATE DRUG DEVELOPMENT**
Sabrina Paganoni, M.D., Ph.D. // *Healey Center for ALS, Massachusetts General Hospital*

10:55-11:10 A.M. **BREAK**

**Not for CME Credit*

MUSCLE STUDY GROUP

11:10-11:25 A.M. **PROXIMAL NERVE IMAGING IN CMT1A**
Reza Sadjadi, M.D. // *MSG Fellow, Massachusetts General Hospital*

10:27-11:37 A.M. **LONG-TERM SAFETY AND EFFICACY OF GOLODIRSEN IN MALE PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY AMENABLE TO EXON 53 SKIPPING**
Francesco Mutoni, M.D. // *Chair of Paediatric Neurology, UCL GOS Institute of Child Health*

11:39-11:49 A.M. **SATISFACTION WITH ANKLE FOOT ORTHOSES IN INDIVIDUALS WITH CHARCOT-MARIE-TOOTH**
Riccardo Zuccarino, M.D., PMR // *Fondazione Serena Onlus, Centro Clinico Nemo*

11:50 A.M.-12 P.M. **EXPLORING MUSCLE STRUCTURE, FUNCTION AND GAIT PATTERNS IN PEOPLE WITH DISTAL HEREDITARY MOTOR NEUROPATHY: NATURAL HISTORY AND THE EFFECT OF REHABILITATION INTERVENTIONS, STUDY PROTOCOL**
Aljwhara Alangary, PT // *Ph.D. Student, UCL institute of Neurology, UK*

12-12:20 P.M. **EXPANDING POSSIBILITIES IN THE TREATMENT OF SPINAL MUSCULAR ATROPHY**
Perry Shieh, M.D., Ph.D. // *Representative, Genentech*

12:25-12:45 P.M. **SAREPTA PIPELINE OVERVIEW AND THE EVOLUTION OF REMOTE ASSESSMENT AND STRATEGIES FOR IMPLEMENTATION IN THE COVID-19 ERA AND BEYOND**
Linda P. Lowes, PT, Ph.D. // *Associate Professor, The Ohio State University of College of Medicine*
Louise Rodino-Klapac, Ph.D. // *Senior Vice President, Gene Therapy, Sarepta Therapeutics, Inc.*

12:45 P.M. **CLOSING** Richard J. Barohn, M.D., Prof Michael G. Hanna, M.D.

12:45-1:30 P.M. **FLASH PRESENTER AND SPONSOR NETWORKING ZOOM BREAKOUT ROOMS (OPTIONAL)**

All times US Central Time

AGENDA // Saturday, September 26

Lindsay Alfano, DPT & James B. Lilleker, MBChB, Ph.D. // *Moderators*

8-8:10 A.M. **OPENING** Richard J. Barohn, M.D., Prof Michael G. Hanna, M.D.

8:10-9:05 A.M. **ROBERT C. GRIGGS, M.D. ANNUAL MSG LECTURE: HOW THE FSHD PUZZLE WAS SOLVED**
Rabi Tawil, M.D. // *Fields Endowed Professor of Neurology, University of Rochester Medical Center*

9:07-9:27 A.M. **RARE DISEASES: WHY CONSIDER ECONOMICS?** Karen Lee // *CADTH*

9:30-9:50 A.M. **A NOVEL APPROACH TO OPTIMIZING MOVEMENT IN TREATED CHILDREN WITH SPINAL MUSCULAR ATROPHY** Megan Iammarino, PT, DPT // *Nationwide Children's Hospital*

9:55-10:10 A.M. **BREAK**

10:10-10:25 A.M. **MOLECULAR BIOMARKERS IN MYOTONIC DYSTROPHY TYPE 2**
Paloma Gonzalez Perez, M.D., Ph.D. // *MSG Fellow, Massachusetts General Hospital*

10:27-10:37 A.M. **RESULTS FROM A NATIONAL CROSS-SECTIONAL STUDY OF DISEASE-BURDEN IN AMYOTROPHIC LATERAL SCLEROSIS (ALS): RESULTS FROM A NATIONAL CROSS-SECTIONAL STUDY** Jennifer Weinstein, MS // *University of Rochester*

10:39-10:49 A.M. **EXOME SEQUENCING IDENTIFIES NOVEL CANDIDATE GENES AND PHENOTYPIC EXPANSION IN A NEUROMUSCULAR COHORT**
Daniel Calame, M.D., Ph.D. // *Baylor Medical College*

10:51-11:01 A.M. **A SAFETY STUDY OF WEEKLY STEROIDS IN MUSCULAR DYSTROPHY (WSIMD)**
Senda Ajroud-Driss, M.D. // *Associate Professor of Neurology, Northwestern University Feinberg School of Medicine*

11:03-11:13 A.M. **AAV GENE THERAPY FOR TNNT1-ASSOCIATED NEMALINE MYOPATHY**
Eleonora D'Ambrosio, M.D. // *University of Massachusetts*

11:15-11:25 A.M. **FOLLOW-UP CARE IN MYASTHENIA GRAVIS DURING COVID-19: COMPARISON OF TELEMEDICINE AND IN-PERSON ENCOUNTERS**
Constantine Farmakidis, M.D. // *Assistant Professor, University of Kansas Medical Center*

11:28-11:38 A.M. **POST-COVID GUILLAIN-BARRE SYNDROME MIMICKING MYOSITIS**
Sai Si Thu, M.D. // *SUNY Downstate Medical Center, USA*

11:38-11:45 A.M. **BREAK**

11:45 A.M.-12:05 P.M. **TOTALITY OF EVIDENCE: CONTROLLING DYSTROPHIN AS AN ANTIGEN IN DUCHENNE MUSCULAR DYSTROPHY (DMD)**
Brian E. Pfister, Ph.D., MBA // *Executive Director, US Medical Head-Neurology, PTC Therapeutics*

12:10-12:30 P.M. **THE FUTURE OF MYASTHENIA GRAVIS TREATMENT, SPECIFICALLY THINKING ABOUT WHEN AND WHERE COMPLEMENT AND FCRN INHIBITORS MIGHT BE USED MOST EFFECTIVELY BASED ON AVAILABLE DATA** James Howard, M.D. // *Representative, UCB*

12:30 P.M. **CLOSING** Richard J. Barohn, M.D., Prof Michael G. Hanna, M.D.

12:30-1:30 P.M. **FLASH PRESENTER AND SPONSOR NETWORKING ZOOM BREAKOUT ROOMS (OPTIONAL)**

All times US Central Time

MUSCLE STUDY GROUP

AGENDA // Sunday, September 27

Kimberly A. Hart, M.A & Gita Ramdharry, Ph.D. // *Moderators*

MUSCLE STUDY GROUP

8–8:15 A.M. **OPENING** Richard J. Barohn, M.D. Prof Michael G. Hanna, M.D.

8:20–9:45 A.M. **SHARK TANK SESSION ($10K GRANT AWARDED TO BEST PRESENTATION)**
Vera Bril, BSc, M.D., FRCPC, Laurie Gutmann, M.D., James Lilleker, MBChB, Ph.D., William David, M.D., Ph.D. // *Sharks*
Will Meurer, M.D. // *Moderator*

- **HEAD TO HEAD** Dr. Vino Vivekanandam // *UCL Institute of Neurology*
- **CLASH OF THE TITINS** Jennifer Roggenbuck, MS, LGC // *The Ohio State University College of Medicine*
- **PROJECT NMD MUSE: INSPIRING A DEEPER UNDERSTANDING OF MOTOR UNIT BEHAVIOR IN NEUROMUSCULAR DISEASE** Kristina M. Kelly, PT, DPT, EdM, NCS, CPT, PES // *The Ohio State University*
- **EXPLORING CSF BIOMARKERS IN PREPARATION FOR CLINICAL TRIALS TARGETING CNS IN DM1** Carola Rita Ferrari-Aggradi // *Medical Student, University of Milan*

9:45–10 A.M. **BREAK**

10–10:10 A.M. **RESPIRATORY FUNCTION AND THE ROLE OF NON-INVASIVE VENTILATION IN MYOTONIC DYSTROPHY TYPE 1: A RETROSPECTIVE STUDY**
Carola Rita Ferrari-Aggradi // *Medical Student, University of Milan*

10:13–10:23 A.M. **MAGNETIC RESONANCE IMAGING (MRI) IN PERIODIC PARALYSIS**
Dr. Vinojini Vivekanandam // *UCL Institute of Neurology*

10:25–10:35 A.M. **INCIDENCE AND RISK FACTORS FOR PATELLOFEMORAL DISLOCATION IN ADULTS WITH CHARCOT-MARIE-TOOTH DISEASE: AN OBSERVATIONAL STUDY**
Enza Leone, PT, MSc // *UCL Great Ormond Street Institute of Child Health*

10:35–10:45 A.M. **ANNOUNCEMENT OF SHARK TANK AWARD**

10:45–10:55 A.M. **REFRACTORY CIDP: CHARACTERISTICS, ANTIBODIES AND RESPONSE TO ALTERNATIVE TREATMENT**
Jamila Godil // *Medical Student, Oregon Health and Science University*

10:57–11:07 A.M. **TIMED MOTOR FUNCTION TESTS IN BOYS WITH NONSENSE DMD MUTATIONS**
Darina Dinov, DO // *PGY-2 Child Neurology Resident, Virginia Commonwealth University*

11:09–11:19 A.M. **PATIENT ACCEPTABLE SYMPTOM STATES (PASS) IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)** Meg Mendoza, Ph.D. // *Research Analyst I, UHN*

11:21–11:31 A.M. **SCREENING FOR GENETIC MUTATIONS IN PATIENTS WITH NEUROPATHY WITHOUT DEFINITE ETIOLOGY IS USEFUL** Braden Vogt // *Medical Student, Brown University*

11:33–11:43 A.M. **OPTIMIZING HAND-FUNCTION PATIENT OUTCOME MEASURES FOR INCLUSION BODY MYOSITIS**
Ava Lin, M.D., Ph.D. // *Clinical Assistant Professor, University of Michigan*

11:45–11:55 A.M. **FURTHER INSIGHT INTO DYSPHAGIA USING MBS-IMP IN ADULT PATIENTS WITH NEPHROPATHIC CYSTINOSIS AND MYOPATHY**
Stacey Sullivan MS, CCC-SLP // *Massachusetts General Hospital*

11:57 A.M.–12:07 P.M. **LIVE CELL-BASED ASSAY FOR ANTIBODIES TO CLUSTERED ACETYLCHOLINE RECEPTOR IN MYASTHENIA GRAVIS, CROSS VALIDATION, INTER-ASSAY STABILITY AND UTILITY IN A PAEDIATRIC COHORT SUSPECTED FOR MG** Hans Frykman, M.D., Ph.D., FRCPC // *Clinical Assistant Professor, The University of British Columbia*

12:09–12:19 P.M. **DIAGNOSTIC OUTCOME OF GENETIC TESTING ON NEUROMUSCULAR DISORDERS IN A TERTIARY CENTER** Husam Al Sultani, M.D. // *Nerve and Muscle Center of Texas*

12:20–12:30 P.M. **PATIENT PREFERENCE IN VIRTUAL VERSUS IN-PERSON VISITS IN NEUROMUSCULAR CLINICAL PRACTICE** Komal Naeem // *Neurology Resident (3rd Year), Baylor College of Medicine*

12:30 P.M. **CLOSING** Richard J. Barohn, M.D., Prof Michael G. Hanna, M.D.

12:35–1:35 P.M. **FLASH PRESENTER AND SPONSOR NETWORKING ZOOM BREAKOUT ROOMS (OPTIONAL)**

All times US Central Time

ABSTRACTS FROM THE 2020 MUSCLE STUDY GROUP ANNUAL SCIENTIFIC MEETING

Title: **Timed motor function tests in boys with nonsense DMD mutations**

Author: *Darina Dinov, Heather Gordish-Dressman, Mathula Thangarajh; CINRG investigators.*

Abstract: **Introduction:** Boys with nonsense DMD mutations have worse motor outcomes but the natural history of timed motor function tests are not known.
Objective: To learn the natural history of decline in motor function from boys with confirmed nonsense DMD mutations using the DMD Natural History data.
Method: A total of 27 boys with 144 observations over 10 years were studied. The three timed function tests evaluated were time to run/walk 10 m velocity, time to climb 4 stairs and time to stand from supine. Data was analyzed using mixed linear model.
Result: All three timed function tests declined over time. Walk velocity declined by 0.2 m/sec each year. Corticosteroid treatment was protective with current steroid user having a walk velocity of 0.4 units greater than those not on steroids.
Conclusion: Increased knowledge of motor outcomes in nonsense DMD mutations can help with clinical trial design in this subset of patients.

Title: **Patient Preference in Virtual Versus In-Person Visits in Neuromuscular Clinical Practice**

Author: *H. Al Sultani, K. Hafeez, A.Shaibani, A. Habib*, H. Kushlaf**, K. Johnson***, N. Robbins*****, Z. Siddiqi ***** (Houston, Tx, Irvin, CA*; Cincinnati, OH**; Jefferson, LA***; Hanover, NH****; Edmonton, AB*****)*

Abstract: The COVID-19 pandemic has led to increased utilization of tele-health services. To inform future decisions on the subject, we phone surveyed patient preference of virtual vs in-person visits in 12 neuromuscular centers in the USA and Canada. The survey consisted of 11 questions. The Data from the first 278 collected surveys revealed that 24.82% preferred virtual visits and 53.96% preferred in-person visits. 67.99% reported physical face-to-face interaction as "very important". For receiving a new diagnosis, 58.99% preferred in-person vs 30.58% reported no preference. Fewer patients were worried about not having physical examination or routine vitals recording (38.49% and 21.22% respectively). 82.73% believed virtual visits were sufficiently private. 68.35% didn't consider expenses a factor in their decision. While 91.73% were comfortable with communication technology. 52.16% preferred video communications, and 23.74% preferred phone calls. **Conclusion:** Although neither technology, privacy or finance burdened patients in our study, more patients preferred physical interaction over virtual communication especially to receive a new diagnosis. This emphasizes the importance of the healing effect of the physician's touch.

Title: **Diagnostic Outcome Of Genetic Testing on Neuromuscular Disorders in a Tertiary Center**

Author: *H. Al Sultani, K. Naeem*, A. Mendez-Zaidi**, A. Shaibani* (Houston, Tx)*

Abstract: Utilization of diagnostic genetic testing in neuromuscular disorders has been expanding and the methods have been progressively improving. To illustrate this trend, we collected genetic testing data in a tertiary neuromuscular clinic from 2014-2020. A total of 514 tests were ordered. 64.57% were neuromuscular panels, 25% single gene tests and 9.84% WES. Results: 28.6% of the total were positive for a pathogenic variant (PV). Per method, positive testing was 43% for single gene testing, 23.17% for panels and 30% for WES. For specific disorders positive outcome was; 18% for MND, 38% for myopathy, and 19% for neuropathy. Diagnostic predictability of panels after negative single gene testing was 44% and that of WES after negative panels was 38%. Conclusions: genetic testing has improved diagnosis of neuromuscular disorders. Compared to other studies, our data showed higher diagnostic yield, reflecting the progressive improvement in the diagnostic outcome of genetic testing.

Title: **Live Cell-Based Assay For Antibodies To Clustered Acetylcholine Receptor In Myasthenia Gravis, Cross Validation, Inter-Assay Stability And Utility In A Paediatric Cohort Suspected For MG**

Authors: *H. Frykman and A. Cruz (Vancouver, CA)*

Abstract: **Introduction:** A live cell-based assay (CBA) expressing clustered acetylcholine receptor (AchR) on the cell surface through co-expression of rapsyn has been shown to detect AchR antibodies (Ab) in 16%-60% of myasthenia gravis (MG) patients that do not have measurable AchR Ab or muscle-specific tyrosine kinase antibodies by radioimmunoprecipitation assay (RIPA).
Objective: To validate the CBA for testing of clustered AchR Ab in the diagnosis of MG
Methods: 49 AchR Ab RIPA positive and 50 healthy control sera were blinded and assayed three times by CBA. Additionally, a cohort of RIPA negative sera from 45 Canadian children age 16 years and younger with suspect MG were assayed.
Results: In all three assays, 48 tested CBA positive and 51 negative. 7 children samples were CBA positive. Follow-up showed 3 have ocular MG and 4 have generalized MG.
Conclusion: The clustered AchR CBA is highly sensitive and replicable and improves diagnostic sensitivity of MG in children.

Title: **Respiratory Function and the Role of Non-Invasive Ventilation in Myotonic Dystrophy Type 1: a Retrospective Study**

Author: *C.R. Ferrari Aggradi, A. Lizio, E. Falcier, E. Roma, F. Rao, A. Zanolini, A. Barp, J. Casiraghi, S. Pozzi, E. Carraro, A. Pirola, V.A. Sansone (The NEMO Clinical Center, Neurorehabilitation Unit, University of Milan, Italy)*

Abstract: **Introduction:** The factors that influence respiratory function decline, one of the main causes of death in myotonic dystrophy type 1, need to be further explored.
Objectives: To analyze respiratory function and the role played by NIV initiation over time.
Methods: 152 adult patients with DM1 were subjected to: arterial blood gas analysis, spirometry, cough efficacy, nocturnal oximetry and respiratory muscle strength.
Results: 75 of 152 had normal respiratory function (49,34%, mean age: 37 years, mean BMI: 23,51, mean disease duration: 10 years), 77 received NIV indication (50,66%, mean age: 48 years, mean BMI: 25,88, mean disease duration: 14 years) but only ¼ were NIV compliant (19/77, 24,68%, mean follow-up: 4,95 years). 5 were lost to follow up.
Conclusions: Compliance is a limiting factor in respiratory care in DM1. Ongoing analysis of longitudinal respiratory, neuromotor and psychological assessments will provide insights into respiratory function decline including the role of NIV.

Title: **Perceptions of current myasthenia gravis (MG) therapies and unmet needs of neurologists and patients in the USA: a blinded retrospective survey with patient chart review**

Authors: *C. Karam[1], D. Gelinas[2], M. Jefferson[2], G. Buckland[3], N. Silvestri[4]*
Affiliations: 1Oregon Health & Science University, Portland, OR, USA; 2argenx, Boston, MA, USA; 3Collective Acumen, Greenwich, CT, USA; 4 University at Buffalo, Buffalo, NY, USA

Abstract: **Introduction:** Perceived satisfaction with MG therapy may influence treatment decision-making by physicians.
Objectives: To categorize the spectrum of disease control perceived by patients and neurologists to gain insight on unmet need and to optimize potential treatment selection.
Methods: This blinded survey of 60 neurologists included retrospective chart review of 180 patient charts identified as three target populations: "controlled but dissatisfied," "controlled but at-risk," and "uncontrolled, unstable." Descriptive statistics were performed.
Results: Neurologists reported only 25% of patients had "uncontrolled, unstable" disease but 34% lacked satisfactory outcome, suggesting >50% of patients may have unmet needs. Despite the perception of disease control, dissatisfaction was high among "controlled" patients and neurologists. "At-risk" patients were more likely to have moderate disease with more comorbidities and more complex treatment regimens, including novel agents.
Conclusions: While MG is considered a treatable disease, this study supports the need for novel, more effective therapies with fewer sides effects.
Disclosures: Author contributions: All authors critically interpreted the results, reviewed and/or revised drafts of this abstract, and approved the final version for publication. Funding disclosure: This study was funded by argenx US. Inc., manufacturer of efgartigimod. Collective Acumen conducted the study and analyzed the data. C. Karam 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. D. Gelinas and M. Jefferson are employees of argenx. G. Buckland is an employee of Collective Acumen. N. Silvestri has served as a consultant for argenx and Alexion Pharmaceuticals.

Title: **A case of hemiplegic migraine (HM) in a girl with initial diagnosis of congenital muscular dystrophy: a challenging diagnosis.**

Author: *E. Albamonte, A. Barp, F. Salmin, E. Carraro, M. Moscardi, S. Bergamoni*, V.A. Sansone Neurorehabilitation Unit, the NEMO Clinical Center in Milan, University of Milan, Milan, Italy *Pediatrics Division, Niguarda Ca' Granda Hospital, Milan, Italy.*

Abstract: **Introduction:** Hemiplegic migraine (HM) is a rare form of migraine in which attacks are accompanied by aura manifestations such as unilateral/bilateral weakness and sometimes with chronic ataxia; it usually starts in the first or second decade of life.
Case Report: we describe an eight-years old girl with hypotonia at birth, absent tendon reflexes and psychomotor delay with an initial diagnosis of a congenital muscular dystrophy, due to a muscle biopsy which was consistent with a dystrophic process. At seven years-old, the patient started having recurrent episodes of loss of consciousness and falls, often associated with transitory limb paresis and drowsiness. Brain MRI revealed mild cerebellar atrophy and vermian hypoplasia. Genetic test for HM revealed the presence of a heterozygous mutation c.4503_4505 del in CACNA1A gene. A therapy with acetazolamide was started with a marked reduction of the attacks.
Conclusions: Early onset, hypotonia and recurrent falls in hemiplegic migraine may mimic a neuromuscular disease.

Title: **Post-COVID GBS Mimicking Myositis**

Author: *S.S. Thu, Z. Charmchi, Y. Anziska*

Abstract: **Introduction:** Cases of Guillain-Barre syndrome (GBS) have been reported in patients infected with SARS-coronavirus-19 (COVID-19). However, all cases occurred in acute infection. We describe GBS occurring in a patient 3.5 weeks after his first COVID-symptoms, from which he had fully recovered weeks earlier, and whose repeated SARS-CoV-2-RNA was negative. This case was atypical in that patient complained of severe bilateral thighs pain and tenderness preceding weakness. Unlike most reported cases, we utilized plasma exchange as treatment to avoid thrombotic complications common in COVID.
Objectives: To report a case with atypical post-COVID GBS, diagnosed on nerve conduction studies.
Methods: Data was extracted from the hospital's electronic medical record.
Results: The patient improved considerably after 5 rounds of plasma exchange and was discharged to inpatient rehabilitation.
Conclusions: GBS can occur both in acute and post-COVID infection, sometimes with unusual presentations. Neurologists should be alert to this complication occurring even weeks after recovery.

Title: **Further insight into dysphagia using MBS-ImP in adult patients with nephropathic cystinosis and myopathy**

Authors: *S. Sullivan, N. Grant, F. Eichler, R. Sadjadi (Boston, MA)*

Abstract: **Introduction:** Nephropathic cystinosis is a lysosomal storage disorder with known myopathic features such as dysphagia which has significant implications for social eating and overall quality of life. Dysphagia is not well characterized in this patient population and there is no guidance towards potential treatment targets.
Objectives: We applied advanced MBS-ImP analysis for more granular description of swallowing impairments with aim to capture deficit that correlated with patient symptom description, not adequately demonstrated with previous examinations.
Methods: We retrospectively evaluated 10 video fluoroscopic swallowing studies from patients with nephropathic cystinosis with various levels of oral and pharyngeal stage dysphagia.
Results: We demonstrated significant oral stage involvement related to lingual strength and control that impacts bolus hold, transport and clearance.
Conclusions: This study provides better insight to dysphagia in this patient population and paves the path for future studies of treatment targets and outcome measures.

Title: **Exome sequencing identifies novel candidate genes and phenotypic expansion in a neuromuscular cohort**

Author: *D. Calame, D. Marafi, J. Fatih, T.E. Lotze, P. Mancias, S. Biliciler, F. Abid, K. Sheikh, O. Yesilbas*, H. Erdem**, N. Elcioglu***, B. Tuysuz***, J.E. Posey, D. Pehlivan, J.R. Lupski (Houston, TX; Van, TR*; Ankara, TR**; Instabul, TR***)*

Abstract: **Introduction:** Recent advances in exome sequencing (ES) have revolutionized the approach to neuromuscular disorders (NMDs). Significant challenges remain due to overlapping phenotypes, genetic heterogeneity, and the rarity of individual conditions. Around 40-75% of NMD patients lack a molecular diagnosis, a critical step to inform expectant management and guide development of precision therapy.
Objectives: To identify novel NMD genes.
Methods: Family-based ES analysis was applied to a cohort of 43 NMD families.
Results: Preliminary analysis identified two novel candidate genes, DHX9 (autosomal dominant axonal CMT) and COL19A1 (autosomal recessive arthrogryposis multiplex congenita), a 4.6% novel gene discovery rate. Other novel discoveries include biallelic PNPT1 variants causing CMT, heterozygous ATP7A variants causing distal arthrogryposis and axonal neuropathy, congenital muscular dystrophy due to biallelic TNNT3 splice-site variants, and biallelic EPG5 variants causing congenital myopathy and intellectual disability.
Conclusion: ES is a powerful tool to identify novel NMD genes and reveal new genotype-phenotype relationships not predicted by current knowledge.

Title: **Results from a National Cross-Sectional Study of Disease-Burden in Amyotrophic Lateral Sclerosis (ALS): Results from a National Cross-Sectional Study**

Author: *Christine Zizzi, BA[1]; Ellen Wagner, MS[1]; Jennifer Weinstein, MS[1], Jamison Seabury, BS[1], Nuran Dilek, MS[2]; Michael McDermott, PhD[2]; Sumaira Hussain, BSc[3]; Joanne Wuu, ScM[3]; James Caress, MD[4]; Richard Bedlack, MD, PhD[5]; Volkan Granit, MD, MSc[3]; Jeffrey Statland, MD[6]; Paul Mehta, MD[7]; Michael Benatar, MD, PhD[3]; Chad Heatwole, MD, MS-CI[1, 2]*

[1]Center for Health + Technology, 265 Crittenden Blvd, CU 420694, Rochester, NY 14642 [2]University of Rochester, Department of Neurology, 601 Elmwood Ave, Box 673, Rochester, NY 14642 [3]University of Miami Miller School of Medicine, Department of Neurology, 1120 NW 14th Street, Suite 1300, Miami, FL 33136 [4]Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157 [5]Duke University School of Medicine, Department of Neurology, 311 Research Dr, Durham, NC 27710 [6]University of Kansas Medical Center, Department of Neurology, 3901 Rainbow Blvd, Kansas City, KS 66160 [7]Centers for Disease Control and Prevention National ALS Registry, Agency for Toxic Substances and Disease Registry, 4770 Buford Highway NE, Atlanta, GA 30341

Abstract: **Introduction:** Patients with ALS experience a wide range of clinical symptoms that affect how they feel and function.

Objectives: To identify the most common and important disease manifestations in ALS.

Methods: We conducted a cross-sectional study of 532 patients from the Centers for Disease Control and Prevention National ALS Registry to identify the relative importance of 189 individual symptoms.

Results: ALS participants provided over 89,000 symptom rating responses. The symptomatic themes with the highest prevalence in ALS were inability to do activities (93.8%), fatigue (92.6%), problems with hand and finger function (87.7%), and limitations with mobility or walking (86.7%). Symptomatic theme prevalence was widely associated with assistive ventilation reliance, impaired speech, and unemployment.

Conclusions: ALS symptoms, some under-recognized, vary based on disease characteristics and demographic features. These symptoms represent potential targets for future therapeutic interventions.

Study Supported By: Funding for this project was provided by the ALS Association. Research activities were conducted in collaboration with the Center for Disease Control and Prevention and the CReATe Consortium (U54 NS092091).

Title: **Satisfaction with Ankle Foot Orthoses in Individuals with Charcot-Marie-Tooth**

Author: *Riccardo Zuccarino MD [*,***], Kirsten M. Anderson [**], Michael E. Shy MD[*], Jason M. Wilken[**]*

**Department of Neurology, The University of Iowa Carver College of Medicine, Iowa City, IA; **Department of Physical Therapy and Rehab Science, The University of Iowa Carver College of Medicine, Iowa City, IA ***Neuromuscular Omnicentre (NEMO)- Fondazione Serena Onlus, Via del Giappone 3, Arenzano, GE, Italy*

Abstract: **Introduction:** Ankle foot orthoses (AFOs) are commonly prescribed to individuals with Charcot Marie Tooth (CMT). The aim of this study was to evaluate patient reported satisfaction with orthotic devices and services in individuals with CMT to provide baseline knowledge prior to advance AFO care for individuals with CMT.

Methods: A survey including the Orthotics and Prosthetics Users Survey (OPUS) was emailed to individuals with CMT using the INC Contact Registry. The OPUS includes 11 device specific questions and 10 service related questions.

Results: 314 individuals completed the survey. Over one third of participants provided negative responses, including dislike of AFOs appearance, discomfort, experience with abrasions or irritations and pain. Ratings of orthotic services were generally positive.

Conclusions: Lower scores related to comfort, abrasions and pain identified clear areas for AFO improvement. Continued research in these areas will be beneficial to informing and advancing AFO development and improving clinical care.

Title: **Systemic Gene Transfer of Adeno-Associated Alpha-Sarcoglycan for Limb-Girdle Muscular Dystrophy in Young and Aged Mice**

Author: *Eric R. Pozsgai, Danielle A. Griffin, Ellyn L. Peterson, Amber Kempton, Oliver Rogers, Young-Eun Seo, Louise R. Rodino-Klapac*
Sarepta Therapeutics, Inc., Cambridge, MA, USA

Abstract

Introduction: LGMD2D, due to an SGCA gene mutation, is progressive and debilitating.
Objectives: Report findings of SGCA gene transfer in mice.
Methods: Single systemic delivery of $1.0x10^{12}$, $3.0x10^{12}$, and $6.0x10^{12}$ vg of scAAVrh74.tMCK.hSGCA was administered in 4-to-5-week-old mouse model of LGMD2D (sgca-/-). The same vector was delivered to 12-month-old sgca-/- mice to assess effects on older, more severely affected muscle.
Results: All three doses showed robust protein expression of α-SG at the sarcolemma, improved histopathology, increased locomotor activity and specific-force generation, protection against eccentric force loss, and reduced serum CK compared with controls. No vector toxicity was detected. In aged mice, treatment resulted in widespread, high-level protein expression in muscles analyzed, reduced fibrosis, and increased resistance to contraction-induced injury in tibialis anterior muscle.
Conclusions: Systemically delivered scAAVrh74.tMCK.hSGCA may offer clinical treatment for LGMD2D, and may be efficacious when delivered in older subjects with more severely diseased muscle.
Disclosures: This study was funded by Sarepta Therapeutics, Inc. All authors are employees of Sarepta Therapeutics and may have stock options.

Title: **Follow-up care in myasthenia gravis during COVID-19: comparison of telemedicine and in-person encounters**

Author: *C. Farmakidis, S. Hunt, M. Pasnoor, O. Jawdat, D. Jabari, R. Barohn*, M.M. Dimachkie (Kansas City, KS; Columbia, MO*)*

Abstract: **Introduction:** Telemedicine may have a role in myasthenia gravis.
Objective: Compare videoconferencing (ZM), telephone (TEL) and in-person (PER) follow-up encounters.
Methods: Retrospective analysis of follow-up encounters March through June 2020.
Results: N=94 encounters. Differences in patient age and distance from clinic were not statistically significant while median MG-ADL scores appeared to differ [ZM 3.6, TEL 2.8, PER 5, p=0.02]. Mean encounter duration [ZM 24.3, TEL 22.8, PER 31.5, minutes, p<0.01] and MG-specific physical exam regions mean [ZM 2.4, TEL 1.1, PER 3, p<0.01] differences appeared to be significant. However, the median number of medical actions after each encounter type did not appear to differ [ZM 3, TEL 2.5, PER 3, p=0.34].
Conclusion: Telehealth encounters occurred without respect to age/distance. Patients with higher MG-ADL scores were more likely to be evaluated in person. While duration and exam content appear to differ between ZM, TEL and PER encounters, clinical decision-making remained similar.

Title: **Deflazacort Or Prednisone Treatment For Duchenne Muscular Dystrophy (DMD): Real-World Outcomes At Cincinnati Children's Hospital Medical Center (CCHMC)**

Author: *Jessica Marden[1], Jonathan Freimark[1], Zhiwen Yao[1], James Signorovitch[1], Cuixia Tian[2], Brenda Wong[3]*
[1]Analysis Group, Inc., Boston, Massachusetts
[2]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
[3]University of Massachusetts Medical School, Worcester, Massachusetts

Abstract: **Introduction:** Corticosteroids are the standard of care for Duchenne muscular dystrophy.
Objective: This study assessed real-world deflazacort and prednisone treatment, and ambulatory, pulmonary, and growth outcomes.
Methods: Among 200 boys, ~75% received deflazacort, ~13% prednisone, and ~12% were prednisone-to-deflazacort switchers.
Results: From adjusted regressions, deflazacort patients compared with prednisone had: 0.59 stairs/second greater 4-stair climb velocity, 4.6 points higher NSAA score, and 9.9% higher FVC %-predicted ($P<0.05$ each). Total body mass was 6.9kg lower, height was 6.2cm lower, and % lean body mass was 4.4% higher. In Kaplan-Meier analyses, by age 15 (age 20), 56.4% (85.1%) of prednisone-initiated patients were wheelchair-bound, compared to 43.7% (78.7%) of deflazacort-initiated patients ($P<0.01$). By age 15 (20), 13.7% (64.8%) of prednisone-initiated patients had scoliosis compared to 8.9% (33.7%) of deflazacort-initiated patients ($P=0.05$).
Conclusions: This study adds evidence associating deflazacort with greater functional and lean body mass preservation, and delay of scoliosis vis-à-vis prednisone.

Title: **Pulmonary function in non-ambulatory patients with nmDMD from the STRIDE Registry and CINRG Duchenne Natural History Study: a matched cohort analysis.**

Author: *Andrés Nascimento Osorio,[1] Már Tulinius,[2] Filippo Buccella,[3] Isabelle Desguerre,[4] Janbernd Kirschner,[5] Eugenio Mercuri,[6] Francesco Muntoni,[7] Joel Jiang,[8] Allan Kristensen,[8] Panayiota Trifillis,[8] Claudio L. Santos,[8] and Craig M. McDonald[9] on behalf of the STRIDE and CINRG DNHS investigators*

[1]Hospital Sant Joan de Déu, Unidad de Patología Neuromuscular, Universidad de Barcelona, Barcelona, Spain; [2]Department of Pediatrics, Gothenburg University, Queen Silvia Children's Hospital, Gothenburg, Sweden; [3]Parent Project APS , Rome, Italy; [4]Hôpital Necker – Enfants Malades, Paris, France; [5]Medical Center – University of Freiburg, Freiburg, Germany; [6]Department of Pediatric Neurology, Catholic University, Rome, Italy; [7]University College London, Great Ormond Street Institute of Child Health, London, UK; [8]PTC Therapeutics Inc., South Plainfield, New Jersey, USA; [9]University of California Davis School of Medicine, Davis, CA, USA.

Abstract: **Introduction:** The STRIDE registry provides observational data on ataluren use in patients with nmDMD.

Objective: Decline in pulmonary function was compared between non-ambulatory nmDMD patients receiving ataluren+ standard of care (SoC; corticosteroid/palliative therapies) and DMD patients receiving SoC [CINRG DNHS].

Methods: Propensity score matching identified comparable non-ambulatory patients from STRIDE and CINRG DNHS using predictors of disease progression. Kaplan–Meier analyses estimated age at loss of ambulation (LOA) and pulmonary function decline.

Results: Median age at LOA for STRIDE vs CINRG DNHS cohorts (each n=22) was 12.4y vs 11.1y. Mean Ataluren exposure for patients in STRIDE up to LOA was 302d. Median Age at %-predicted forced vital capacity (FVC) <60% was delayed for patients from STRIDE vs the CINRG DNHS (18.7y vs 15.6y). Mean Ataluren exposure for patients in STRIDE up to %-predicted FVC <60% was 661d.

Conclusion: Aaluren+SoC treatment may slow pulmonary disease progression in non-ambulatory nmDMD patients.

Title: **Demographics and safety data from patients with nonsense mutation Duchenne muscular dystrophy receiving ataluren in the STRIDE Registry.**

Author: *Francesco Muntoni,[1,2] Filippo Buccella,[3] Isabelle Desguerre,[4] Janbernd Kirschner,[5] Andrés Nascimento Osorio,[6] Már Tulinius,[7] Joel Jiang,[8] Allan Kristensen,[8] Panayiota Trifillis,[8] and Claudio L. Santos[8]*

[1]Dubowitz Neuromuscular Centre & MRC Centre for Neuromuscular Diseases, University College London, Institute of Child Health & Great Ormond Street Hospital for Children Foundation Trust, London, UK; [2]NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Institute of Child Health, University College London, Great Ormond Street Hospital Trust, London, UK; [3]Parent Project Italy APS, Rome, Italy; [4]APHP Necker – Enfants Malades Hospital, Paris V Descartes University, Neuromuscular Network FILNEMUS, Paris, France; [5]Medical Center – University of Freiburg, Freiburg, Germany; [6]Hospital Sant Joan de Déu Unidad de Patología Neuromuscular, Universidad de Barcelona, CIBERER, ISCIII, Barcelona, Spain; [7]Department of Pediatrics, Gothenburg University, Queen Silvia Children's Hospital, Gothenburg, Sweden; [8]PTC Therapeutics Inc., South Plainfield, NJ 07080-2449, USA.

Abstract: **Introduction:** Ataluren promotes the production of a functional dystrophin and is indicated for the treatment of patients with nonsense mutation Duchenne muscular dystrophy (nmDMD). STRIDE is an ongoing registry providing real-world data on ataluren use in nmDMD patients.

Objectives: Describe the demographics of the STRIDE population and interim safety results as of January 2019.

Method: Patients' data are collected at the consent date; Patients are followed for ≥5 years.

Results: As of January 2019, 220 boys (210 confirmed nmDMD) were enrolled in STRIDE in 11 countries and received ≥1 ataluren dose. Mean ataluren exposure (SD) was 822±368 days. Safety outcomes were consistent with the known ataluren profile. Mean age at consent date (SD) was 10.6±3.6 years. Mean age at first symptoms and nmDMD confirmation was 2.8±1.8 years, and 5.2± 2.9 years, respectively.

Conclusions: STRIDE constitutes the first drug registry for nmDMD. STRIDE data analyses provide insights into the real-world ataluren effectiveness/safety.

Title: **A safety study of Weekly Steroids in Muscular Dystrophy (WSiMD)**

Author: *Senda Ajroud-Driss, Aaron Zelikovich, Glenn Walter, Abhinandan Batra, Benjamin Joslin, Patricia Casey, Robert Sufit, Elizabeth McNally*
Dept of Neurology, Center for Genetic Medicine, Department of Medicine (Cardiology) Northwestern University Feinberg School of Medicine. Department of Physiology and Functional Genomics, University of Florida.

Abstract: **Introduction:** Corticosteroids are known to improve strength and prolong ambulation in Duchenne Muscular Dystrophy, where common dosing strategies include daily or high dose weekend steroids. Steroid use in Becker Muscular Dystrophy or Limb Girdle Muscle Dystrophy (LGMD) has been less well studied, with at least one study showing adverse outcomes in dysferlin-related LGMD. Recently, once weekly steroid dosing was found to promote strength and lean muscle in preclinical models including the mdx mouse and two mouse models of LGMD.
Objective: To report the results of an open label safety and efficacy clinical trial of oral weekly corticosteroids in adults with BMD and LGMD subtypes.
Methods: Participants received prednisone at 0.75-1g/kg orally on Mondays after the evening meal. Participants completed strength and functional assessments, a quality of life questionnaire, safety laboratory testing, DEXA scans, exploratory biomarkers as well as muscle MRI imaging before starting steroid treatment and at the end of the 6-month period.
Results: Twenty patients completed 6 months of once weekly prednisone (1 BMD and 19 with different LGMD subtypes, 13 male, 7 female.) 12 of 20 (60%) were ambulatory. Once weekly prednisone was overall well tolerated. We observed no significant negative impact on body weight, blood pressure, forced vital capacity, bone density or safety labs. There was a significant decrease in serum CK, accompanied by an increase in lean mass without an increase in fat mass on DEXA that was significant in the upper and lower extremities. For ambulatory patients we noted an improvement in 6min walk and 10 m run test. MRI analysis revealed a reduction in water T2 in at least one muscle in 80% of the subjects and in all except for one of the ambulatory patients.
Conclusions: Once weekly steroids, given as 0.75-1gm/Kg was well tolerated in LGMD. Although underpowered for efficacy, this study suggests improved lean mass and function in the study cohort and warrants additional investigation of once weekly steroids.
This study was funded by Kurt & Peter Foundation.

Title: **Oral Suspension Formulation of Edaravone for Amyotrophic Lateral Sclerosis: Human Pharmacokinetics and Development Plan**

Author: *Koji Takei, Tomoyuki Omura, Tomohiro Takahashi, Munetomo Matsuda, Yoshinobu Nakamaru, Hidetoshi Shimizu, Manabu Hirai, Steven Toler*, Joseph Palumbo*, Stephen Apple***

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

Abstract: **Introduction:** An investigational oral formulation of edaravone is being developed as a potential alternative option to the current intravenous (IV) formulation.

Objectives: To describe progress in the clinical development plan for an oral suspension formulation of edaravone.

Methods: A pharmacokinetic (PK) bridging study with long-term safety data and a dosing optimization study were conducted. A Phase 3 safety study in patients with amyotrophic lateral sclerosis (ALS) is ongoing.

Results: The oral formulation was shown to have similar PK to the IV formulation. Safety will be investigated in a 48-week safety study in adult ALS patients (N=150). The efficacy and safety of daily dosing will be assessed in a 48-week, Phase 3b study (N≈400). PK data and study designs will be presented.

Conclusions: The clinical development plan for oral edaravone is intended to help establish the data needed to seek registration for marketing authorization pending further discussion with health authorities.

Acknowledgments: Funded and conducted by Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan (MTPC). ST is an employee of Mitsubishi Tanabe Pharma Development America, Inc (MTDA). TO and JP are former employees of MTPC and MTDA. SA is an employee of Mitsubishi Tanabe Pharma America, Inc (MTPA). All other authors are employees of MTPC.

Title: **Magnetic Resonance Imaging (MRI) in Periodic Paralysis**

Authors: *Vinojini Vivekanandam*[*1], *Sachit Shah*[2], *Emma Matthews*[1], *Karen Suetterlin*[1], *Iwona Skorupinska*[1], *Jasper Morrow,* [1], *Tarek Yousry*[2], *Michael G Hanna*[1].
Affiliations: 1. MRC Centre for Neuromuscular Diseases, QS Institute of Neurology, UCL. 2. Neuromuscular MRI Research Group, UCL Institute of Neurology.

Abstract: **Introduction:** The primary periodic paralyses (PP) include hypokalaemic periodic paralysis (HypoPP), hyperkalaemic periodic paralysis(HyperPP) and Andersen Tawil Syndrome (ATS). To date, very few studies have reported neuromuscular MRI changes in these groups.
Objectives: 1. Define the presence, frequency and pattern of lower limb neuromuscular MRI abnormalities in PP.
Methods: Ethics approval was attained (Joint National Hospital for Neurology and Institute of Neurology Research Ethics Committee.) Lower limb MRI scans of patients with genetically proven PP and 10 controls were attained. 38 muscles were scored using the Modified Mercuri semi-qualitative scale. Clinical data was retrospectively collated.
Results: A total of 77 scans were identified. Distinct changes exist in patients with periodic paralysis which consists predominantly of fatty infiltration. Changes are more marked in the thighs, and are most severe in the subset of patients with hypoPP.
Conclusions: This will be the largest review of neuromuscular MRI in patients with PP. Despite the episodic nature of symptoms, there are definite fatty infiltration changes suggesting the disease course is not benign. Differences between subsets also exist.

Title: **Patient and Treatment Characteristics of a Large US Sample of Patients With Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) Initiating Intravenous Immunoglobulin (IVIG) Therapy**

Author: *C. Anderson-Smits*, J.B. Layton**, M.E. Ritchey**, V. Hayden*, S. Chavan*, N. Souayah*** (Shire US Inc., a Takeda company, Cambridge, MA, USA*; RTI Health Solutions, Research Triangle Park, NC**; Department of Neurology, Rutgers University, Newark, NJ***)*

Abstract: **Introduction:** CIDP is a rare immune-mediated neuropathy with significant burdens. Per guidelines, IVIG is first-line therapy.

Objectives: Describe characteristics of US patients with CIDP initiating IVIG treatment.

Methods: Adult immunoglobulin-naïve patients with CIDP from 2008–2018 were identified via diagnosis coding using the IBM® Watson Health™ MarketScan® Research Databases.

Results: Demographics were similar between new IVIG users (n=3975) and the full cohort (n=32 090). IVIG users, compared with the full cohort, had greater comorbidity and symptom burden (eg, weakness and/or difficulty walking, neuropathic pain, diabetes, hypertension, leukemia/lymphoma, hypothyroidism, rheumatoid arthritis, other autoimmunity disorders). Patient characteristics were similar by initial IVIG product, except for index treatment year.

Conclusions: There was a trend to initiate IVIG in patients with CIDP who had greater comorbidity and symptom burden. Patient characteristics were not correlated with initial IVIG selection; rather, difference in selection varied by year.

Title: **Phase 3 Study of HyQvia for Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP): ADVANCE-CIDP 1 Infusion Protocol**

Author: *S. Hasan*, K. Duff**, A. Nagy***, L. Yel** (Shire US Inc., a Takeda company, Cambridge, MA, USA*; Baxalta US Inc., a Takeda company, Cambridge, MA, USA**; Baxalta Innovations GmbH, a Takeda company, Vienna, Austria***)*

Abstract: **Introduction:** HYQVIA® (Immune Globulin Infusion [Human] 10% with recombinant human hyaluronidase [rHuPH20]; fSCIG) allows for dispersion and absorption of large-dose subcutaneous immunoglobulin.
Objectives: Describe infusion protocol for fSCIG in ADVANCE-CIDP1 (NCT02549170).
Methods: Planned enrollment is 174 adults. The primary outcome is relapse rate (proportion of patients with increase ≥1 point in adjusted Inflammatory Neuropathy Cause and Treatment disability scale score from baseline). Recommended sites for infusion are upper to middle abdomen and thighs with 24G needle(s). Number of infusion sites can be 1, 2, or 3, and a needle set can be single, bifurcated, or trifurcated. Maximum infusion volume per site is 600 mL for patients ≥40 kg and 300 mL for patients <40 kg.
Results: This study is ongoing and blinded.
Conclusion: fSCIG is being evaluated as a novel maintenance therapy for CIDP.
Baxalta (a Takeda company) funded this study; Shire (a Takeda company) provided medical writing support.

Title: **Infusion Parameters And Demographics Of Patients With Chronic Inflammatory Demyelinating Polyneuropathy During Scig Self-Administration Training**

Author: *Robert McNeill[1], Elyse Murphy[1], Chris Vanname[2], Melody Bullock[2], Ayman Kafal[1]*
[1]CSL Behring LLC, King of Prussia, [2]Specialty Pharmacy Nursing Network (SPNN) Inc.

Abstract: **Introduction:** Subcutaneous immunoglobulin (SCIg) was approved for maintenance therapy in adult patients with chronic inflammatory demyelinating polyneuropathy (CIDP) in 2018.
Objectives: Here, we analyzed training data from patients with CIDP as they transitioned to SCIg (Hizentra®).
Methods: This was a retrospective, observational study utilizing data collected by specialty pharmacy nurses on self-administration training, discontinuations, and infusion parameters between 3/2018–12/2019 in patients with CIDP.
Results: Overall, 310 adult patients completed 1–7 training visits. SCIg discontinuations due to side effects occurred in 5.8%. Of successfully-trained patients, 54.5% required ≤3 training visits. By their final visit, most patients (92.8%) had increased their infusion rate, mL/hr/site (mean increase of 43.37% [standard deviation 66.91%]) and over half (53.8%) were able to reduce their infusion sites by ≥1.
Conclusions: Ongoing training after completion of formal training can improve patients' ability to optimize and individualize their SCIg self-administration technique. Training techniques may need to differ depending on individual patient need.
Funding: CSL Behring

Title: **Patient Acceptable Symptom States (PASS) in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)**

Author: *M. Mendoza, C. Tran, C. Barnett (Toronto, ON)*

Abstract: **Background:** At present, we do not have a patient-anchored definition of what constitutes as a "good" outcome during CIDP treatment.
Objective: We aim to understand how CIDP patients value their current health; by estimating patient acceptable symptom state (PASS) thresholds for common CIDP outcome measures.
Methods: We conducted an online-survey asking North American CIDP patients questions on symptom satisfaction, general demographic and clinical characteristics.
Results: In total, 128 individuals were satisfied with their disease burden (PASS-positive) while 190 participants were not (PASS-negative). In comparison to PASS-negative, PASS-positive patients had better average outcome scores with no differences in age, sex or disease duration. We estimated PASS thresholds for EQ5D (0.57), RODS (32), ONLS (3), INCAT (2) and CAPPRI (14).
Conclusions: Our PASS thresholds represent a global state of "being well" and can be applied as secondary endpoints for CIDP research and aid in clinical decision-making.

Title: **Refractory CIDP: characteristics, antibodies and response to alternative treatment**

Author: *Jamila Godil*, Nizar Chahin*, Alan Pestronk**, Erik Ensrud*, Matthew J. Barrett*** and Chafic Karam* (*Department of Neurology, Oregon Health & Science University, Portland, OR, USA.*
***Department of Neurology, Washington University School of Medicine*
****Department of Neurology, Virginia Commonwealth University, Richmond, VA, USA.*

Abstract: **Introduction:** CIDP is the most common immune mediated neuropathy. Patients usually respond well to high doses of immunoglobulins (intravenous (IV) or subcutaneous), steroids, or plasmapheresis. However, approximately 20-30% of patients with CIDP do not respond well to these therapies, which are considered first-line treatments, and approximately 15% of patients remain refractory to all treatment modalities.
Objective: To review the characteristics, antibodies, and response to alternative treatments in a cohort of patients with refractory CIDP.
Methods: We performed a retrospective chart review of all CIDP patients seen at Oregon Health & Science University Neuromuscular clinic between 2017-2019. We extracted information regarding demographics, clinical characteristics, antibodies, and response to alternative treatments. During this time period it was routine clinical practice of our group to test all CIDP patients for neurofascin (NF) and contactin antibodies.
Results: Among 45 CIDP patients studied, 34 (76%) showed improvement with first-line therapy (steroids, IVIG and/or plasmapheresis) and 11 (24%) were considered refractory to first line therapy. Of the latter, seven (64%) responded to alternative treatment (cyclophosphamide or rituximab). Three were refractory to all treatment. One patient was not prescribed alternative treatment. At the end of study, 39 patients (87%) were ambulatory without aid and 5 (11%) were in remission. One patient died from complications of alcoholic liver cirrhosis. Thrombosis was seen in three patients receiving IVIG. Six patients (13%) tested positive for NF antibodies. Four tested positive for NF155 IgM antibodies only and of those, one responded to IVIG, two partially responded to IVIG and one was refractory. One patient tested positive for NF155 IgG4. Another tested positive for NF155 IgG4 and NF155 IgM. Both patients with IgG4 antibodies were refractory to IVIG, but one responded to rituximab and one was refractory to all treatment.
Conclusion: Less than a quarter of patients did not respond to steroids, IVIG, and/or plasmapheresis. Most of the refractory patients responded to rituximab or cyclophosphamide. Patients with NF antibodies tended to be more resistant to IVIG. The majority of refractory CIDP patients were seronegative and disease management relied on clinical judgment.

Title: **Incidence and risk factors for patellofemoral dislocation in adults with Charcot-Marie-Tooth disease: an observational study**

Author: *E. Leone, S. Davenport, C. J. Robertson, M. Laurà, G. Ramdharry (London, UK)*

Abstract: **Introduction:** Patellofemoral dislocation is frequently reported by people with Charcot-Marie-Tooth disease (CMT). To date, the frequency and the risk factors for patellofemoral dislocation in adults with CMT are unknown.

Objectives: To determine the incidence and the risk factors for patellofemoral dislocation in adults with CMT.

Methods: A cross-sectional, observational study was conducted among adults with different CMT subtypes attending a specialist neuromuscular centre. Participants were invited to undergo a knee examination.

Results: The incidence of patellofemoral dislocation was 32.3% (10/31). Patellar dislocation was associated with CMT-1A (p=0.013) and younger age at disease onset (p=0.004). Patella alta (p=0.001), J-sign (p=0.017), lateral patellar glide (p=0.001), generalised hypermobility (p=0.012) and hamstring weakness (p=0.012) were associated with higher risk of patellofemoral dislocation.

Conclusions: Patellofemoral dislocation was common among adults with CMT and was associated with multiple risk factors. The identified predictors may be addressed by clinicians through preventive, supportive and corrective measures.

Title: **Exploring muscle structure, function and gait patterns in people with Distal Hereditary Motor Neuropathy: natural history and the effect of rehabilitation interventions, Study Protocol.**

Authors: *A. Alangary, J. Morrow, M. Laura, A. Rossor, M. M. Reilly, G. Ramdharry* (London, UK*)*

Abstract: **Background:** Distal Hereditary Motor Neuropathy (dHMN) is a rare inherited neuromuscular disorder. It is characterised by distal weakness. Though patients usually have a normal lifespan it is a disabling condition and most eventually need aids to walk. In order to improve walking quality in patient with dHMN, research is needed to understand the impairments that lead to altered gait patterns, and to develop interventions to correct walking gait conservatively.

Aims: Primary: (1) To explore the natural history of muscle structure and function in dHMN over one year. Secondary: (2) To ascertain relationships between intramuscular fat fraction, muscle volume, isokinetic muscle strength and moments/power generation. (3) To explore the effect of bilateral carbon fibre ankle foot orthoses (AFO) on the kinetics and kinematics of gait of people with dHMN. (4) To explore the effect of resistance training of the ankle muscles in people with ankle muscle strength over grade 4 MRC scale on muscle structure, function, and gait patterns.

Methods: Objective1&2: dHMN participants aged over 18 will undergo the following measures: MRI scans of the calves and thighs muscles, isokinetic strength and power measures of the lower limb using the HUMAC Norm dynamometer,3D motion analysis to capture kinetic and kinematic data of complete gait cycles. For direct comparison of gait deviations, twenty age and gender matched health controls will also be recruited to undergo the same measures. Scans, dynamometry and clinical measures will be repeated after one year to explore the natural history of the disease. Objective3: dHMN participants will undergo additional gait analysis: wearing just shoes (control condition), wearing their own prescribed orthoses (where appropriate), and wearing bilateral carbon fiber AFOs. Objective4: up to 15 dHMN participants will be prescribed a home based, resistance training program for 16 weeks, supervised through weekly phone calls, monthly visits and an exercises diary. Response to training will be analysed by: MRI scans, myometry, and 3D motion analysis.

Title: **Screening for genetic mutations in patients with neuropathy without definite etiology is useful**

Author: *B. Vogt, N. Chahin, W. Wiszniewski, T. Ragole, C. Karam (Portland, OR)*

Abstract: **Introduction:** Many genetic neuropathies are misdiagnosed. Recently, the first therapeutic for a genetic neuropathy, namely hATTR Amyloidosis, has been approved. The two companies who created these therapeutics are currently sponsoring free genetic neuropathy panels.

Objective: To determine the clinical usefulness of systemic genetic testing in neuropathies without definite etiology.

Methods: We systematically performed genetic testing in all patients with neuropathy who did not have a definite etiology, seen between 2017 and 2020. The testing consisted of an inherited neuropathy panel (72 to 81 genes).

Results: Pathogenic mutations were found in 30/200 (15%). The management was altered in 4/200 (2%) overall, and 4/108 (5.6%) of patients not suspected to have an inherited neuropathy.

Conclusion: Screening for genetic mutations in patients with neuropathy without a definite etiology is useful. While only a minority of patients with unsuspected inherited neuropathy tested positive, the findings altered management in some, improving morbidity and, perhaps, mortality.

Title: **Optimizing hand-function patient outcome measures for inclusion body myositis**

Author: *Ava Y Lin, Catherine S Siener, Anna Faino, Michelle Seiffert, Conrad C Weihl, Leo H Wang*

Abstract: Inclusion body myositis (IBM) is the most common acquired myopathy after the age of 45. The slowly progressive and heterogeneous disorder is a challenge for measuring clinical trial efficacy. One current method for measuring progression utilizes the IBM Functional Rating Scale (FRS). We have found that the hand domain scores in the IBM-FRS do not consistently change until there is extreme loss of grip and finger flexor strength. Therefore, we performed a cross-sectional observational study of 83 IBM and 38 control patients recruited at the 2019 Annual Patient Conference of The Myositis Association. We evaluated new hand function patient-reported outcome measures modified from the NIH Patient-Reported Outcomes Measurement Information System (PROMIS). We find that hand-function PROs have a higher correlation with pinch and grip strength than the IBM-FRS.

Title: **Top 10 research priorities for patients with primary mitochondrial disease and their carers**

Author: *T. D. Graves1,2, L. Butterworth3, C. Feeney4, S. Holmes1, A. Hunter5, J. Lowndes6, S. Rahman7 J. Sharpe8, R. H. Thomas9, S. Upadhyaya10, M. Vortruba11, L. Weaver12, R. Wheeler13 (The Rare Mitochondrial Diseases Priority Setting Partnership Steering Committee)*

Abstract: Primary mitochondrial diseases encompass a number of clinical presentations with a spectrum of severity, lack effective disease-modifying therapies and have high mortality. It is therefore vital to know that research meets the needs of people with mitochondrial disease. Priority setting partnerships are an established collaborative methodology bringing patients, charity representatives and clinicians together to establish the most pressing and unanswered research priorities. We developed a web-based questionnaire, asking patients affected by primary mitochondrial disease, their carers and clinicians to pose their research questions.

Results: 709 questions were received (from 50 patients, 47 carers and 50 clinicians). Unanswerable questions were excluded, this left 42 answerable questions. Individuals were invited to prioritise these questions from 'important' to 'less important' using a web-platform. The top 24 questions were then discussed at a face-to-face workshop where a definitive top 10 of unanswered research questions for primary mitochondrial disease was decided.

Conclusions: These questions will be presented and should be taken forward by researchers to ensure that their research is relevant to those affected by primary mitochondrial disease.

Title: **AAV gene therapy for TNNT1-associated nemaline myopathy**

Author: *E.S. D'Ambrosio, M. Sena-Esteves, H.L. Gray-Edwards, M. Otero, H. Grimason, L. Labdi (Worcester, MA, University of Massachusetts)*

Abstract: Nemaline myopathy is one of the most common congenital myopathies. It is characterized by early onset muscular weakness and rod-like inclusions in myocytes.
A non-sense mutation in exon 11 of the TNNT1 gene (encoding for the slow skeletal muscle isoform of troponin T) results in selective atrophy of slow-twitch myofibers and in a unique form of nemaline myopathy, named Amish Nemaline Myopathy (ANM).
Currently there is no treatment for ANM. The development of an AAV gene therapy is viable, but requires the expression of TNNT1 to slow-twitch fibers only.
We designed AAV8 vectors carrying a muscle-specific promoter (MHCK7) and incorporated both TNNT1 and suppressive microRNAs (miR208a and miR-133, characteristic of cardiac and fast-twitch myofibers respectively). This approach enabled the expression of TNNT1 in slow-twitch myofibers, while preventing its ectopic expression in other tissues or myofibers.
We will then test the designed vector in Tnnt1-/- mice and quantify its transduction efficiency.

Title: **Systemic Gene Transfer with AAVrh74.MHCK7.SGCB Increased β-Sarcoglycan Expression in Patients with Limb Girdle Muscular Dystrophy Type 2E**

Author: *Louise R. Rodino-Klapac,[1,3] Eric R. Pozsgai,[1,3] Sarah Lewis,[1,3] Danielle A. Griffin,[1,3] Aaron S. Meadows,[1,3] Amanda Nicholl,[1] Carrie Nease,[1] Kelly J. Lehman,[1] Kathleen Church,[1] Natalie F. Miller,[1] Megan A. Iammarino,[1] Linda P. Lowes,[1] Jerry R. Mendell[1,2]*
[1]Center for Gene Therapy, The Research Institute at Nationwide Children's Hospital, Columbus, Ohio, USA; [2]Department of Pediatrics and Neurology, The Ohio State University, Columbus, OH, USA; [3]Sarepta Therapeutics, Inc., Cambridge, MA, USA

Abstract: **Introduction:** LGMD2E is progressive and debilitating.
Objectives: Report findings of AAVrh74.MHCK7.SGCB gene transfer (NCT03652259).
Methods: Patients: 4-15y, SGCB mutation, >40%n on 100-meter walk test. Cohort 1 (n=3) and Cohort 2 (n=3) received single IV infusion of $5x10^{13}$ vg/kg AAVrh74.MHCK7.SGCB and $2x10^{14}$ vg/kg, respectively. Prednisone 1 mg/kg/day initiated 1d before (30d-[Cohort 1] and 60d-[Cohort 2] taper). Endpoints: Primary—safety. Secondary—SGCB expression 8w posttreatment. Other–CK decrease, function.
Results: Immunohistochemistry Cohort 1: mean 51% SGCB-positive fibers expressing mean 47% intensity; mean 36.1% SGCB expression vs normal (western blot). Cohort 2: mean 72% SGCB-positive fibers expressing mean 73% intensity; mean 62.1% SGCB expression vs normal. Functional improvements in all Cohort 1 patients (Table 1). Mean CK decreased from baseline by 72% at 1y in Cohort 1, 89% at 90d in Cohort 2. Two Cohort 1 patients had elevated liver enzymes (returned to baseline); one Cohort 2 patient had vomiting/dehydration (resolved).
Conclusions: The results of this study reflect optimized rAAVrh74.MHCK7.SGCB construct design. We observed increased β-sarcoglycan expression across all patients at a systemic dose of $2x10^{14}$ vg/kg compared to the dose of $5x10^{13}$ vg/kg, substantial reduction in CK in both cohorts, sustained improvement in all functional measures in patients in Cohort 1, and similar safety and tolerability profiles in both Cohorts.

Table 1. Summary of Functional Data at 1 Year

Patient	Assessment	NSAD	Time to Rise (sec)	4-Stair Climb (sec)	100 MWR (sec)	10 MWR (sec)
1	Baseline	40	5.0	2.4	52.0	5.0
	1-year	44	3.8	2.2	48.4	4.5
	Δ from Baseline	4	1.2	0.2	3.6	0.5
2	Baseline	48	1.5	1.6	35.1	3.4
	1-year	54	1.0	1.1	31.8	2.9
	Δ from Baseline	6	0.5	0.5	3.3	0.5
3	Baseline	41	3.5	2.8	48.8	5.2
	1-year	48	2.9	2.0	39.9	4.3
	Δ from Baseline	7	0.6	0.8	8.9	0.9

NSAD, North Star Assessment for Dysferlinopathy; 100MWR, 100-Meter Walk/Run; 10MWR, 10-Meter Walk/Run

Disclosures: This study was sponsored by Sarepta Therapeutics, Inc. (NCT03652259). L.R. Rodino-Klapac, E.R. Pozsgai, S. Lewis, D.A. Griffin, and A.S. Meadows are employees of Sarepta. A. Nicholl, C. Nease, K.J. Lehman, K. Church, N.F. Miller, M.A. Iammarino, L.P. Lowes, and J.R. Mendell have nothing to disclose.

Title: **Long-Term Safety and Efficacy of Golodirsen in Male Patients with Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping**

Author: *Francesco Muntoni;[1-3] Laurent Servais;[4,5] Volker Straub;[6] Michela Guglieri;[6] Ashish Dugar;[7] Meaghan Whalen-Kielback;[7] Deb Steiner;[7] Erica Koenig;[7] Tao Feng;[7] Baoguang Han;[7] Xiaodong Wang;[7] Eugenio Mercuri;[8] on behalf of the SKIP-NMD study group*
[1]Dubowitz Neuromuscular Centre, UCL Institute of Child Health and Great Ormond Street Hospital for Children, London, UK; [2]Great Ormond Street Hospital, London, UK; [3]NIHR Great Ormond Street Hospital Biomedical Research Centre, London, UK; [4]Institute I-Motion, Hôpital Armand-Trousseau, Paris, France; [5]Neuromuscular Reference Center, CHU Liège, Liège, Belgium; [6]Newcastle University John Walton Muscular Dystrophy Research Centre and the Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK; [7]Sarepta Therapeutics, Inc., Cambridge, MA; [8]Paediatric Neurology and Centro Clinico Nemo, Catholic University and Policlinico Gemelli, Fondazione Policlinico Universitario Agostino Gemelli IRCSS, Rome, Italy

Abstract: **Introduction:** Golodirsen restores mRNA reading frame in patients with Duchenne muscular dystrophy (DMD) mutations amenable to exon 53 skipping.
Objectives: To report golodirsen long-term safety and efficacy in this first-in-human, phase 1/2, multicenter trial.
Methods: Patients (n=25) received open-label golodirsen 30 mg/kg/week IV until week 168. Safety (up to 189 weeks) and pulmonary/motor/muscle function (144 weeks) were assessed.
Results: Majority of reported AEs were mild, nonserious, and assessed as unrelated to golodirsen, with no discontinuations due to safety. Ambulation benefits of golodirsen were suggested by post hoc comparisons vs matched natural history controls (Table). Cumulative percent predicted forced vital capacity decline of 8.4% over 3 years (144 weeks) in golodirsen-treated patients compares favorably with published DMD natural history decline of ~5% annually.
Conclusions: Long-term golodirsen treatment had acceptable safety and was well tolerated. These data support golodirsen as a treatment option in patients with DMD amenable to exon 53 skipping.

Table. Functional Outcomes in Golodirsen-Treated Patients Compared with Matched Exon 53 Skipping-Amenable Natural History External Controls Identified from a Longitudinal Multicenter Cohort Study[1]

	Golodirsen (N=25)	Matched Natural History Controls (N=19)
6-minute walk test mean (SE) change from baseline to Year 3, m	-99.0[a]	-181.4
Loss of ambulation at Year 3, %	9	26

[a]P=0.067 vs controls
1. Brogna C, et al. PLoS ONE 2019; 14: e0218683.

Funding: This study was funded by Sarepta Therapeutics, Inc.
Disclosures: FM: consultant fees (Sarepta Therapeutics); support (NIHR Great Ormond Street Hospital Biomedical Research Centre). LS: advisory board participation (Sarepta Therapeutics); VS: speaker honoraria (Sanofi Genzyme), advisory board participation (Audentes Therapeutics, AveXis, Biogen, Exonics Therapeutics/Vertex, Roche, Sarepta Therapeutics, Wave Therapeutics), research collaborations (Ultragenyxx, Sanofi Genzyme); EM: consultant fees (Serapta Therapeutics); MG: speaker honoraria and research collaboration (Sarepta), advisory board participation (Pfizer), study chair with no financial interest (ReveraGen VBP15-004 study); AD, MW-K, DS, EK, TF, BH, XW: employees of Sarepta Therapeutics, Inc.

Title: **Combined Prospective and Retrospective Analysis of Duchenne Muscular Dystrophy Patient Outcomes Following 7 Years of Eteplirsen Treatment Compared With Natural History External Control Cohorts**

Author: *Olga Mitelman MD;[1] Hoda Abdel-Hamid MD;[2] Barry J. Byrne MD, PhD;[3] Anne M. Connolly MD;[4] Peter Heydemann PhD;[5] Crystal Proud MD;[6] Perry B. Shieh MD;[7] Kathryn R. Wagner MD, PhD;[8] Ash Dugar PhD;[1] Sourav Santra PhD;[1] James Signorovitch PhD;[9] Katherine Tsai PhD;[1] and Jerry R. Mendell MD[4]*

[1]Sarepta Therapeutics, Cambridge, MA, USA; [2]UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA; [3]University of Florida, Gainesville, FL, USA; [4]Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH, USA; [5]Rush University Medical Center, Chicago, IL, USA; [6]Children's Hospital of The King's Daughters, Norfolk, VA, USA; [7]David Geffen School of Medicine at UCLA, Los Angeles, CA; [8]Kennedy Krieger Institute, Johns Hopkins School of Medicine, Baltimore, MD, USA; [9]Analysis Group Inc., Boston, MA, USA

Abstract: **Introduction:** Study 201/202 (n=12) evaluated eteplirsen over 4 years in patients with Duchenne muscular dystrophy and confirmed genetic mutations amenable to exon 51 skipping.

Objective: To describe long-term clinical outcomes of patients from Study 201/202 by retrospective chart review (Study 4658-405).

Methods: Total follow-up time was 7 years of eteplirsen treatment. Functional outcomes included loss of ambulation (LOA) and annual change in forced vital capacity percent predicted (FVC %p). Outcomes were compared with natural history external control cohorts treated with standard-of-care with adjustment for baseline characteristics.

Results: Data from 10 participants were available for chart review. Median age at LOA was 15.2 years. Comparison with natural history controls showed that median time to LOA was 2.09 years longer in eteplirsen-treated patients (P=0.01), and eteplirsen-treated patients had a significant attenuation in pulmonary decline (P<0.0001; Table).

Conclusion: Study 4658-405 highlights the functional benefits of eteplirsen up to 7 years.

Table. Functional Outcomes Over 7 Years in Eteplirsen-Treated Patients and External Natural History Controls

	Study 201/202/405 (n=12)	Natural History Comparators
Median age at LOA[a]	15.2	12.0[b], 13.0[c]
Time to LOA, years, KM estimate (95% CI)	5.09 (4.87, -)	3.00 (2.29, -)[d]
P value vs comparator	0.01	
FVC%p annual rate of change	-3.3	-6.0[e]
P value vs comparator	<0.0001	

[a]Descriptive analysis based on published data
[b]DuchenneConnect, untreated exon 51 skipping-amenable patients receiving steroids (n=106)
[c]Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DHNS) untreated exon 51 skipping-amenable patients receiving steroids (n=30)
[d]Standard of care treated, exon 51 skipping-amenable patients from the Fondazione Telethon NMD Italian Network Registry (n=8), the Leuven NMRC Registry (n=3), and the placebo arm of the DEMAND III trial (n=60)
[e]CINRG DHNS exon 51 skipping–amenable untreated male patients (n=20)

Funding: This study was funded by Sarepta Therapeutics, Inc.
Disclosures: OM, AD, SS, and KT: Employees of Sarepta Therapeutics, Inc. HZA-H: Served on advisory boards for Avexis, Audentes, Biogen, and Sarepta. BJB: Is the co-founder Aavanti Bio, Inc AMC: Served on advisory boards for Acceleron, Avexis, Genentech, and Sarepta, and on DMSB for Catabasis. PH: Has no conflict of interest to declare. CP: Served on advisory boards for AveXis, Biogen, Sarepta, is a speaker for AveXis, Biogen, has or is conducting research for AveXis, Astellas, Biogen, Catabasis, CSL Behring, PTC, Pfizer, Sarepta, Scholar Rock. PBS: Consultant (AveXis, Biogen, PTC Therapeutics, and Sarepta Therapeutics, Inc.), and speakers' bureaus (Alexion, Biogen, and Grifols). KRW: Consultant (AskBio, Dynacure, PTC Therapeutics, Roche, and Sarepta Therapeutics, Inc.), and serves on the DSMB for Fibrogen and on a dose escalation committee for Wave. JS: Employee of Analysis Group Inc., Boston, MA, USA. JRM: Has received Grants from the Parent Project Muscular Dystrophy and has received personnel fees from Sarepta and National Children's Hospital