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Cover image: *The Louvre under Snow* by Camille Pissarro, oil on canvas, 1902. On view at The National Gallery, London. Public domain.

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Letter from the Editor in Chief and Founding Editor for Volume 6, Issue 4

Richard J. Barohn MD

I am happy to make some opening remarks for Volume 6, Issue 4 of the RRNMF Neuromuscular Journal.

Once again Dr. Josh Freeman has written an insightful editorial on the state of health care in the United States, addressing the profits of health insurance companies.

Dr. Soontrapa, Dr. Pinto and Dr. Dyck from the Mayo Clinic reported a detailed investigation of 278 patients over a 20-year period with peripheral nerve vasculitis and examined vessel size categorization on nerve biopsy. Of the 278 patients, 125 had large-arteriole vasculitis and 153 had microvasculitis. The authors present several interesting and useful clinical comparisons between the two groups.

Dr. Johnson and the team at the University College London published a retrospective series of 100 adult spinal muscular atrophy patients, examining bone health, frequency of fractures and the relationship to ambulation, bone density, and vitamin D status.

Dr. Longde and two colleagues from India provide a case report of a Guillain-Barre Syndrome patient presenting with respiratory failure. Ultimately, the patient demonstrated other pharyngeal and limb weakness and was found to have thyroid cancer. They point out that it is uncommon for GBS to present with isolated ventilatory manifestations and raise the question of a possible paraneoplastic relationship.

In the Review Article section, we are publishing another lecture given at the University of Kansas Department of Neurology neuromuscular course, titled "The evaluation of muscle disorders after patients have been placed in a phenotypic pattern." This is a talk usually given by Dr. Todd Levine and is a follow-up talk on the 10 patterns of muscle and neuromuscular junction disorders, in which the clinician attempts to place a patient into a pattern category before ordering any laboratory tests. We published that earlier lecture in the RRNMF Neuromuscular Journal Volume 5, Issue 2 in 2024. The lecture published in this issue discusses the laboratory approach to the various disorders and refers back to the pattern they were most likely placed in.

Also, in the Review Article section, I am publishing the first in a series on the history of neurology. A number of years ago, when I was at the University of Kansas, I would give the neurology residents short vignettes on the history of neurology. I usually gave these talks immediately after morning report on Monday every week. So, I had a captive audience, and they got a dose of the history of neurology whether the wanted it or not! I enjoyed doing the research in my files to put together these presentations. Some of them I subsequently recorded and, for a time, they were on the Department of Neurology website. Alas, since I left KU so have the videos on the website. A few remain on YouTube, including the one I am publishing in this issue. It is called "The Tale of Two Toms" and it is about the incredible visionary renaissance physicians Thomas Willis and Thomas Syndenham. We have provided the link to my old YouTube video. I have not written these up and published them before and plan to publish as many as I can while I can in this journal.

We are also pleased to include a lovely poem by Dr. Ariah Leday who is an internal medicine intern in San Antonio. Dr. Leday wrote this poem based on an interview she did with a patient with ALS.

Finally, a few abstracts from the recent NMSG meeting in Italy did not appear in the last issue and we are now including them for completeness.

In December we like to have winter cover art. The painting on the cover is "The Louvre under Snow" by Camille Pissarro. It is generally housed at the National Gallery in London but is currently on loan to the Denver Art Museum until February 2026. It is a beautiful image. We are able to show this image as it is licensed for non-commercial use under a Creative Commons agreement with the National Gallery, London.

Please continue to send in your creative neuromuscular work: case reports, original contributions, review articles and yes even poems and prose.

Seasons Greetings and Happy Holidays!

Making a profit isn't enough for Wall St.: You are going to have to pay with your money (and maybe your life!)

Joshua Freeman, MD

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

Wendell Potter, in his "Health Care Un-Covered" substack, recently (Aug 6, 2025) reports that 'As Americans Struggled, Health Insurers Made a Record-Breaking $71.3 Billion in Profits. In 2024, seven big insurers posted $71.3 billion in profits and paid their CEOs more than $146 million.' There are several things being said in that sentence. First is that health insurance companies made a lot of profit. Second is that some people, specifically health insurance CEOs, are doing very well, thank you. Third is the assumption that Americans are struggling, presumably with their health insurance and healthcare. Let's think about each of these.

These health insurance companies, per the chart that Potter includes, made $71.3B in profits. That seems like a lot to me. For most, it's also more than the prior year. But not for all. Note that Humana made 33% less than in 2023, a mere $2.7B.

Fortunately, that was enough to continue to pay its CEO over $15M.

At least UnitedHealth, the largest health insurer, is doing fine, right? It increased its profits 6% over the year before, and its CEO Andrew Witty (head of UnitedHealth Group, not to be confused with the assassinated Brian Thompson, CEO of UnitedHealthCare, who worked for him), is the highest-paid health insurance CEO at $26.3M, so I guess he deserves it because the company is doing so well. That shows that I (and possibly you) are not expert in the ways of Wall St. investors. It wasn't enough for them. Just two days earlier, on Aug 4, Potter posted 'Inside the Midyear Panic at UnitedHealth'. It makes fascinating reading, although the lessons learned by an MBA student may be different from those learned by, say, a regular person needing healthcare. As far as Wall St. is concerned, it is not enough to stay profitable; corporate profits need to continually go up so that these investors can meet their expectations for their *own* profit. It is important to understand that, as much as health insurance companies can be seen to be greedy parasites who produce nothing but obstruction and cost for those providing and receiving healthcare which they sell as producing "value", private investors are a meta-level worse. They don't even pretend to produce anything; they are, as an old family friend liked

Company	CEO	2024 Compensation
UnitedHealth	Andrew Witty	$26.3M
CVS/Aetna	David Joyner	$17.8M
Cigna	David Cordani	$23.3M
Elevance	Gail Boudreaux	$20.5M
Humana	Jim Rechtin	$15.6M
Centene	Sarah London	$20.6M
Molina	Joseph Zubretsky	$22.0M
	Total:	**$146.1M**

Company	2023 Revenue	2024 Revenue	Change	2023 Profit	2024 Profit	Change
UnitedHealth	$371.6B	$400.5B	8%	$32.4B	$34.4B	6%
CVS/Aetna	$357.8B	$372.8B	4%	$13.7B	$12.0B	-12%
Cigna	$195.3B	$247.1B	27%	$7.4B	$7.4B	0%
Elevance	$171.3B	$175.2B	2%	$8.7B	$9.3B	7%
Humana	$106.4B	$117.8B	11%	$4.0B	$2.7B	-33%
Centene	$154.0B	$163.1B	6%	$2.9B	$3.8B	31%
Molina	$34.1B	$40.7B	19%	$1.6B	$1.7B	6%

to say, "in money". They invest and expect money back, more money all the time, and don't care much about how the companies they invest in get it.

Nearly 500 years ago, Shakespeare wrote the "Merchant of Venice", an excellent but anti-Semitic play about a greedy Jewish moneylender named Shylock.* Shylock has been widely decried for centuries for demanding a pound of flesh as repayment for the loan (how horrible!) But, by today's standards, particularly in health insurance, he'd be a piker. While a lot of people, including me, could afford to lose a pound (or 20) of flesh, the health insurance companies are being spurred on by their investors (along with their own lack of values), are doing much worse. The actions that they are taking to ensure Wall St. investors make what they believe to be sufficient ROI will end up *killing* people. Antonio should have been happy to give up his pound of flesh!

Of course, the financial investors in health insurance companies are not gauche enough to literally demand the killing of their clients. But they did demand changes that will undoubtedly have that result. While UnitedHealth saw an 8% increase in their Medicare Advantage plans, which they generally like because these plans allow them to do what they do with regular insurance, obstruct access, they still had to pay more out in medical claims than the shareholders were happy about. As Potter says, *"Those seniors figured out how to get at least some care despite the company's high barriers to care (aggressive use of prior authorization, "narrow" networks of providers, etc.)."* Sounds good if you're a patient, but if you're an investor, it's horrific. Remember what the insurance industry calls the percent of the premiums that they collect which they actually have to pay for medical care? The "medical loss ratio"! They *hate* it when they make less profit because they are paying for your care! Yes, UnitedHealth made *$14.3 billion in profits* during the second quarter, but it was less than the $15.8 billion they made in the second quarter of 2024, so something had to be done!

Potter describes what UnitedHealth promised its investors they would do:

- *Dump 600,000 or so enrollees who might need care next year* [after all it is much more profitable to collect premiums on people who *won't* need care]
- *Raise premiums "in the double digits" – way above the "medical trend" that PriceWaterhouseCoopers predicts to be 8.5% (high but not double-digit high)* [ie., you, the customer, pay more for less]
- *Boot more providers it doesn't already own out of network* [when they work for you, money you pay them goes back to yourself!]
- *Reduce benefits* [of course]

Yup, these changes most definitely *will kill people.*

Most insurance involves has you betting against yourself; you pay premiums to protect you if something happens that you do not want (or expect) to happen, but might. You have homeowner's insurance, but you hope your house doesn't burn down. You have auto insurance, but you hope you are not in a car accident. Originally, health insurance followed the same idea; it was not intended to pay for routine care, but to protect you if you had to be hospitalized and or have surgery for something you didn't expect. But then it began covering (or hopefully covering) regular medical care, visits, treatments, and drugs. It was paying for what you wanted – regular care, not unexpected and unanticipated "major medical" care. This is different from what insurance usually is. Actually, though, insurance companies preferred as it is predictable and relatively low cost. With Medicare Advantage plans, for example, they take money from Medicare to cover seniors who are happy to have coverage for prevention, doctor visits, drugs, and even gym membership without having to pay separately for a Part D plan, a Medicare Supplement plan (to cover the 20% of hospital costs Medicare Part A doesn't pay for), etc.

When those people get sick, however, they want their

bills paid, and not infrequently United and the others were denying it. But as Potter points out, not often enough to please their investors. People were sometimes, increasingly, getting their bills paid – indeed CMS, the Center for Medicare and Medicaid Services, was requiring that they be paid. That is what infuriated investors – all that money going to pay for medical care rather than profit and shareholder dividends! So, they will reduce benefits, increase premiums, further limit the doctors you can see and hospitals you can use, and make being sick more unpleasant than it already is. Tough luck.

But that's what you get when you have a "healthcare" system that exists primarily to make profit, not to provide healthcare. When you live in the United States. Why do we put up with this?

* Jews were moneylenders because it was an area open to them; in those quaint days Christians actually thought they had to abide on the Biblical prohibition on earning interest from lending money. It's complicated; most of the prohibitions are actually in the Old Testament, but this was often interpreted as not lending money to other Jews; Christians were OK. Of course, they were presumably lending to other Jews when New Testament describes Jesus turning over the tables of the moneylenders in the Temple, saying per Matthew 5:42 'Give to the one who asks you, and do not turn away from the one who wants to borrow from you'. Anyway, both Jews and Christians lend money – "invest" – now.

Nerve vasculitis: The importance of vessel size categorization in nerve biopsy

From "Distinctive clinical features in biopsy-proven nerve large-arteriole vasculitis and microvasculitis"

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Systemic and non-systemic vasculitic neuropathies are described by nerve biopsy showing evidence of either large-arteriole vasculitis or microvasculitis. No studies have asked whether there are different clinical features between pathologically confirmed large-arteriole vasculitis and microvasculitis. This study was conducted to investigate if vasculitis involving vasa nervorum of different sizes (<75 µm classified as microvasculitis and ≥75 µm classified as large arteriole vasculitis) results in different clinical manifestations, including associated systemic autoimmune diseases and laboratory findings. Data were retrospectively collected from patients evaluated at Mayo Clinic from 2001-2020 with pathologically confirmed nerve vasculitis comparing these two groups. 278 patients met the inclusion criteria of having robust clinical information, being evaluated by a Mayo Clinic neurologist, and having definite or highly suggestive vasculitis on nerve biopsy vasculitis, of which 125 cases were nerve large-arteriole vasculitis and 153 cases were nerve microvasculitis. The sural nerve was the most frequently sampled, followed by the superficial peroneal nerve, with a few cases involving proximal fascicular nerve biopsies.

Major findings include nerve large-arteriole vasculitis exhibiting a more acute onset (50.4 vs 26.8%, p=0.0001) being more readily diagnosed due to the clearer or more acute onset (4.3 vs 10.5 months, p<0.0001), a shorter time to plateau (3.5 vs 8.9 months, p<0.0001), and a clinical pattern of neuropathy more often presenting as distal asymmetric polyneuropathy (48.0 vs 19.6%, p<0.0001) compared to nerve microvasculitis. On the other hand, nerve microvasculitis predominantly presented as radiculoplexus neuropathy or polyradiculoneuropathy, indicating greater nerve root involvement with more proximal limb abnormalities such as shoulder or hip weakness, as can also be seen by electrophysiologic findings. Autonomic symptoms, such as bowel or bladder dysfunction, orthostatic symptoms, and erectile dysfunction were more common in nerve microvasculitis (24.2 vs 7.2%, p=0.0002). The composite autonomic scoring scale, which reflects worse autonomic function at higher values, was also higher in nerve microvasculitis group (3.7 vs 2.2, p=0.002) (Table 1).

Both nerve large-arteriole vasculitis and nerve microvasculitis span the disease spectrum of systemic and non-systemic vasculitis, but with different prevalence. Nerve large-arteriole vasculitis was more commonly in systemic vasculitis (77%), while nerve microvasculitis occurred less frequently in systemic vasculitis (29%). Many systemic vasculitis diseases were ANCA-associated vasculitis (40% of nerve large-arteriole vasculitis), especially microscopic polyangiitis (23.2% of nerve large-arteriole vasculitis), followed by rheumatoid arthritis (12.8% of nerve large-arteriole vasculitis). On the other hand, nerve microvasculitis comprised 71% of non-systemic vasculitis cases, while nerve large-arteriole vasculitis accounted for 23%. Many of non-systemic vasculitis cases were due to diabetic or non-diabetic radiculoplexus neuropathy (30.8% of nerve microvasculitis) and 94% of these diabetic or non-diabetic radiculoplexus neuropathies pathologically had nerve microvasculitis. Given that nerve large-arteriole vasculitis was more strongly associated with systemic vasculitis, it made sense that nerve large-arteriole vasculitis demonstrated a higher prevalence of systemic symptoms compared to microvasculitis including constitutional symptoms (60.8 vs 47.1%, p=0.02), asthma (8.8 vs 0.7%, p=0.0009), sinusitis (11.2 vs 0%, p<0.0001), pulmonary infiltrates (9.6 vs 2%, p=0.005), glomerulonephritis (8.0 vs 0%, p=0.0004), rash (25.6 vs 13.1%, p=0.008), and arthritis (10.4 vs 3.9%, p=0.03). Similarly, laboratory findings in large-arteriole vasculitis showed more frequent abnormalities, including anemia (12.1 vs 13.1 g/dL, p<0.0001), leukocytosis (10.5 vs 7.0 x 10^9/L, p<0.0001), eosinophilia (19 vs 6%, p=0.001), higher platelet count (344.6 vs 261.2x 10^9/L, p<0.0001), and elevated inflammatory markers such as C-reactive protein (43.3 vs 8.2 mg/L, p=0.0001) and erythrocyte sedimentation rate (39.3 vs 19.6 mm/hr, p<0.0001), reflecting more systemic involvement compared to nerve microvasculitis. In contrast, microvasculitis was more associated with having diabetes mellitus than was nerve large arteriole vasculitis (24.8% vs 13.6%, p=0.02) (Table 1).

Commentary: This study underscores the distinct clinical features of nerve large-arteriole vasculitis and nerve microvasculitis, shedding light on their pathophysiology: that is nerve microvasculitis is associated with greater proximal nerve and root involvement manifesting as proximal weakness and sensory disturbance, while nerve

Table 1: Key distinguishing clinical features between nerve biopsy-proven large-arteriole vasculitis and nerve microvasculitis

Features	Nerve large-arteriole vasculitis (*n*=125)	Nerve microvasculitis (*n*=153)	*p*-value
Systemic vasculitis - ANCA-associated	77% 40%	29% 5%	<0.0001
Constitutional symptoms	61%	47%	0.02
Non-systemic vasculitis - diabetic or non-diabetic radiculoplexus neuropathy	23% 2.4%	71% 31%	<0.0001
Underlying diabetes mellitus	14%	25%	0.02
Disease course - acute - chronic	 50% 34%	 27% 58%	0.0001
Pattern of neuropathies - Distal asymmetric polyneuropathies - Radiculoplexus neuropathy	 48% 10%	 20% 32%	<0.0001
Proximal lower limb involvement	26%	51%	<0.0001
Autonomic symptoms	7%	24%	0.0002
Composite autonomic scoring scale	2.2 ± 1.5	3.7 ± 2.2	0.002

ANCA = anti-neutrophil cytoplasm antibodies

large-arteriole vasculitis typically shows watershed infarction (occurring at mid-thigh and mid-arm levels), thus manifesting as primarily distal asymmetrical neuropathies. However, these processes represent a continuum of anatomical involvement rather than entirely distinct entities. With the unclear pathomechanism, different antigens might speculatively contribute to this variation or variations in vascular shear flow could play a role. Additionally, this study confirms the association between nerve large-arteriole vasculitis and connective tissue disorders and more systemic vasculitis whereas microvasculitis is more associated with diabetes mellitus. We plan to further publish findings on clinical outcomes and pathological distinctions between the two conditions.

References:

1. Pannathat Soontrapa, Marcus V Pinto, Kamal Shouman, Jay Mandrekar, JaNean K Engelstad, Catarina Aragon Pinto, Sean Taylor, Michelle L Mauermann, Sarah E Berini, E Peter Bosch, Devon I Rubin, Matthew J Koster, Cornelia M Weyand, Kenneth J Warrington, Christopher J Klein, Peter J Dyck, P James B Dyck, Distinctive clinical features in biopsy-proven nerve large-arteriole vasculitis and microvasculitis, *Brain*, Volume 148, Issue 3, March 2025, Pages 1031–1042, https://doi.org/10.1093/brain/awae406
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100 adults with spinal muscular atrophy at the dawn of treatment: A bone health focus

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ABSTRACT

INTRODUCTION: As disease-modifying treatments for spinal muscular atrophy (SMA) are implemented, comorbidities in adults including osteo-pathologies are increasingly recognised. Guidance for managing such issues is incomplete.
We present data on bone health from, to our knowledge, the UK's largest single-centre adult SMA cohort.

OBJECTIVES: We aimed to quantify the following in our cohort:
1. Fracture incidence and location
2. Implementation of bone density scanning
3. Vitamin D status and supplementation

METHODS: Retrospective case note review was performed for 100 adult patients (51% male; 49% female, average age 32), at the National Hospital for Neurology and Neurosurgery from 2022-2025. SMA subtypes were SMA3 (N=55), SMA2 (N=44) and SMA1 (N=1). Where available ethnicities were: White (N=57), Asian (N=13), Black (N=4), Mixed (N=2) and Other (N=4).

RESULTS: Fracture incidence was 25% (N=25), of which 85% (N=29) affected the lower limb(s). Most fractures (80%) (N=20) occurred in SMA3 patients. 50% (N=10) of SMA3 patients with a history of fractures, subsequently lost the ability to walk.
Bone density scans were recorded in 40% (N=10) of patients who had fractures (90% of scans occurred post fracture), and in 17% (N=13) of non-fracture patients.
Of the overall cohort, 39% (N=39) were vitamin D deficient or insufficient, and 60% (N=60) were prescribed cholecalciferol.

CONCLUSIONS: The high fracture rate is particularly pertinent, given that lower limb fractures can accelerate ambulation loss in SMA3 patients. Consistency in bone-density scanning is lacking and generally reactive to fracture occurrence. This highlights the importance of bone health considerations in adult SMA patients.

Keywords: Spinal muscular atrophy, Fractures, Bone, Neuromuscular disease

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive inherited neuromuscular disease characterized by degeneration of alpha motor neurons in the spinal cord. SMA is caused by loss-of-function mutations of the survival of motor neuron 1 (*SMN1*) gene, typically (>95% of cases) a deletion of exons 7 and 8.[1,2] SMA incidence is around 1 in 10,000 live births and the average carrier frequency of *SMN1* pathogenic mutations varies from 1:40 to 1:60 worldwide.[2]

SMN1 encodes the SMN protein, which is ubiquitously expressed in all cells.[1] The *SMN2* gene is highly homologous to *SMN1*. The only functional difference between *SMN1* and *SMN2* is a synonymous transition leading to alternative splicing of *SMN2* exon 7 encoding an SMN protein from *SMN2* of limited function instead of the full-length protein. Previous clinical studies have shown that the *SMN2* copy number is negatively correlated with disease severity and a higher level of functional SMN protein is associated with milder phenotypes.[3]

Consequently, the clinical features of SMA are heterogeneous, with all patients experiencing varying degrees of severity of progressive muscle weakness, hypotonia and mobility impairment with respiratory and bulbar muscle weakness in more severe cases.[4] SMA patients have, therefore, historically been characterized by their clinical phenotype, and age of disease onset into subtypes.[1-5]

Until recently, SMA was symptomatically managed with musculoskeletal, nutritional and respiratory support. However, the advent of several disease modifying therapies has changed the landscape of treatment in SMA. This includes Zolgensma (gene therapy for infants under 2 years with SMA1, 2 and 3) and Nusinersen and Risdiplam (for children and adults with SMA 1, 2 and 3) both of which act to increase SMN protein expression via the modulation of SMN2 pre-mRNA splicing.[6,7] Nusinersen and Risdiplam were recently licenced in the UK, and a health service treatment programme makes both available for all those with SMA types 1-3 who are not in the final stages of disease

(i.e. when daily ventilation use exceeds 16 hours). The initial data is promising, demonstrating not only reduced disease progression but also improved motor function scores.[8] Along with this demonstratable reduction of disability, it may be anticipated that these treatments could increase life-expectancy in the more severe forms of SMA. As these therapies are being increasingly implemented worldwide, this has led to an increasing awareness of the extent of comorbidities in SMA patients, both in paediatric and adult populations.[9]

One of these comorbidities is poor bone health. In SMA lower limb muscle weakness results in reduced loading leading to osteoporosis and gait difficulties increasing risk of falls and fractures.[10] Fractures result in loss of function and deformity which negatively impact on quality of life. Additionally, there is evidence that the SMN protein has a role in bone re-modelling. In *SMN1* gene mouse knock-out models, both an osteoporotic phenotype and increased osteoclast activity (on histochemical staining), have been demonstrated, thus further increasing the potential for osteoporosis and fracture.[11]

Despite these risk factors, there is as yet no consensus on guidelines regarding managing and maximising bone health in adults with SMA.[10]

We aimed to quantify bone health specific parameters in, to our knowledge, the largest single centre adult SMA patient cohort in the UK. We aimed to quantify:

1. Fracture incidence, location and incidence categorised by SMA subtype
2. Implementation of bone density scanning and bisphosphonate prescription
3. Vitamin D status and supplementation.

Table 1: Classification of spinal muscular atrophy subtypes.

Type	Onset	Motor Function
1	0-6 months	Never sit
2	<18months	Sit never stand
3	>18 months	Exceed the ability to sit
4	>18 years	Walk unaided

Methods

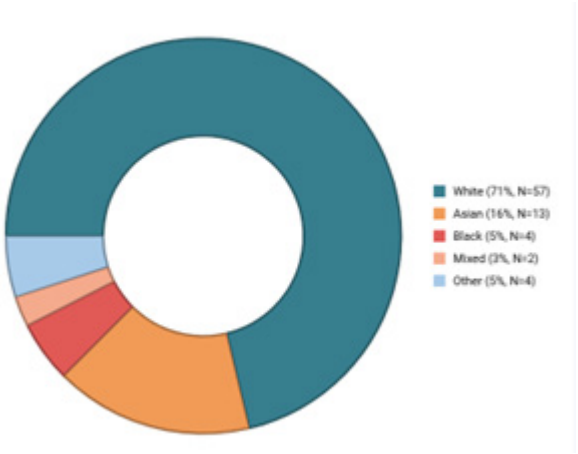
Retrospective case note review of 100 adult patients at the National Hospital for Neurology and Neurosurgery with genetically confirmed SMA was performed. When data was missing GP records were reviewed. This project is registered with the Queen Square Clinical Audit & Quality Improvement Subcommittee.

The average age of the cohort was 32 years old (range 17-67 years old), and 87% (N=87) of patients were on disease modifying treatment. Of the patients on disease modifying treatment, 77% (N=67) were on Risdiplam and 23% (N=20) on Nusinersen. The remainder of the cohort demographics are shown in table 2 and figure 1. Ethnicity data were available for (N=80) patients.

Table 2: Cohort demographics for 100 adult spinal muscular atrophy patients

Characteristics	Male (N = 51)	Female (N= 49)	Totals (N= 100)
SMA subtypes			
SMA1	0	1	1
SMA2	20	24	44
SMA3	31	24	55

Figure 1: Ethnicities (where available, N=80) of cohort of 100 adult spinal muscular atrophy patients



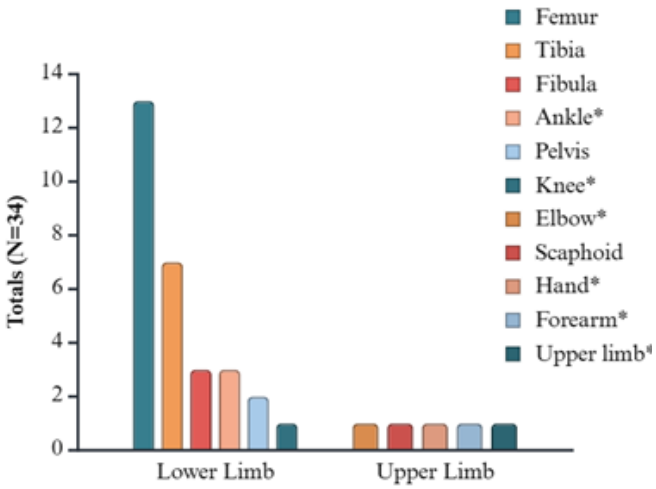
Results

Fracture incidence, location and incidence categorised by SMA subtype

Across the whole cohort 25% (N=25) had at least one fracture reported. Eight patients had a history of fracture in more than one bone, in two of these cases the fractures occurred on separates episodes, in the remaining six cases, multiple bones were fractured in one episode. 85% (N=29) of the overall fractures occurred in lower limbs. A more detailed breakdown of fracture location is shown in figure 2.

The average age in patients with a history of fracture was 35.44 years (18-65 years). 92% (N=23) of patients with a history of fracture were on disease modifying treatment, 76% (N=19) of these patients were on Risdiplam, and 16% (N=4) on Nusinersen. The majority of fractures occurred in SMA3 patients (N=20) (80% of all fractures). Of note, eleven patients reported a decline in motor function post fracture, of whom 50% (N=9) lost the ability to walk, one ambulant patient lost the ability to both ambulate and sit and one SMA2 patient lost the ability to sit.

Figure 2: Fracture location of (N=34) cases in a cohort of 100 adult spinal muscular atrophy patients

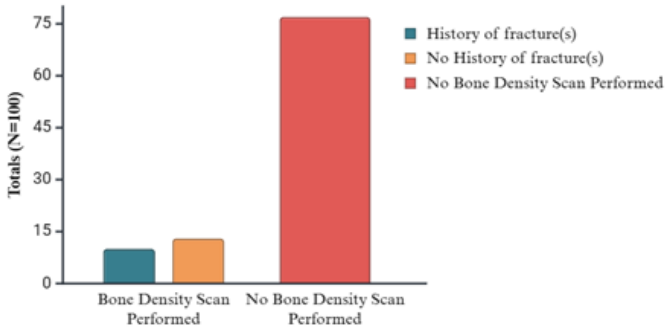


*Location of fracture not specified further. Fractures occurring in femur (N=13), tibia (N=7), fibula (N=3), ankle (N=3), pelvis (N=2), knee (N=1), elbow (N=1), scaphoid (N=1), hand (N=1), forearm (N=1) and upper limb (N=1).

Bone Density Scanning implementation and bisphosphonate prescription

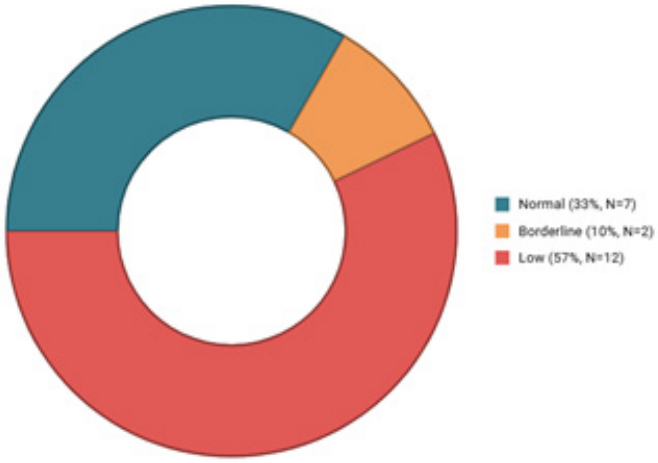
Bone density scans were performed in 23% (N=23) of the overall cohort, one further patient has also been referred but is awaiting the scan. See figure 3 for a more detailed breakdown of bone density scanning implementation. The interpretations from bone density scans (available in 21 of the 23 cases) are shown in figure 4. 4% (N=4) of the cohort were prescribed a bisphosphonate (Zoledronic acid (N=3) and Alendronic acid (N=1)).

Figure 3: Bone density scanning implementation in cohort of 100 adult spinal muscular atrophy patients.



Bone density scanning was performed in 23 patients, 10 of whom had a history of fracture, 77 patients had not had a bone density scan.

Figure 4: Interpretation of 21 bone density scans in a cohort of 100 adult spinal muscular atrophy patients.

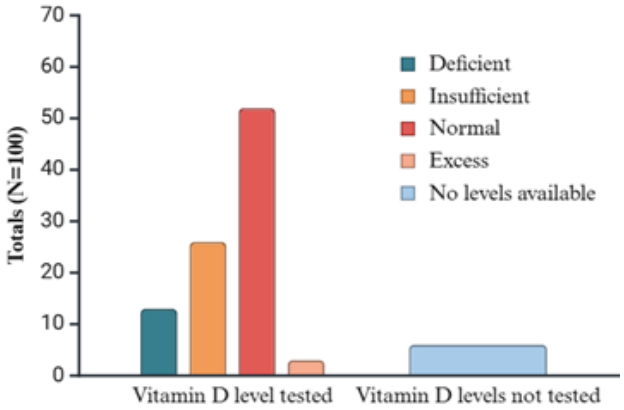


The interpretation of the bone density scans into normal, borderline and low was based on z-scores.

Vitamin D levels and supplementation

Vitamin D status was available for 94% (N=94) of the cohort. The levels are shown in figure 5. Notably, 60% (N=60) of the cohort were prescribed vitamin D replacement therapy.

Figure 5: Vitamin D level status in cohort of 100 adult spinal muscular atrophy patients



Deficient (N=13), insufficient levels (N=26), normal levels (N=52), excess (N=3), Status not available (N=6). Ranges are as follows, deficient:< 25 nmol/L, insufficient: 25-50 nmol/L and normal >50nmol/L.

Discussion

A pertinent finding from our results is the high fracture rate in this adult SMA population. One of the widely understood risks of hereditary neuromuscular disorders is the increased risk of fractures - noted especially in Duchenne muscular dystrophy (DMD), which is "less rare" than SMA (1 in 3500 to 1 in 5000 live male births) and where the recommended use of corticosteroids for disease modification has further prompted specific bone health guidance.[13,14] In their retrospective study reviewing bone health across various hereditary neuromuscular disorders, Opsomer et al. found the highest prevalence of fractures in DMD, myotonic dystrophy and SMA patients, with results comparable to our own demonstrating most fractures affecting the lower limb.[15] They also noted that the aetiology of fractures in their cohorts was a mix of low-energy traumatic and osteoporotic fractures, with nearly 30% of their SMA cohort losing ambulation due to the fracture, thus raising the possibility of a potential complex aetiological overlap and highlighting the functional impact that fractures can have in this patient population.

We found that consistency in bone density scanning is lacking in this cohort, and generally reactive to a fracture occurring. Furthermore, where bone density scans were performed, the majority were found to have borderline or low bone density. This is particularly significant, as it was noted that most fractures in our cohort affected the lower limb - with the most commonly fractured bone being the femur - and occurred in SMA3 patients, of whom a significant proportion lost the ability to ambulate post-fracture. In all populations, low bone density increases the risk of fractures. However, in vitro, preclinical and clinical studies support the notion that there is dysregulated bone metabolism in SMA from intrinsic and extrinsic mechanisms.[10,11,16] From here, a vicious cycle can ensue- intrinsically impaired bone growth and remodelling in SMA results in a fracture, which then affects mobility and weight-bearing abilities, thus further impairing bone density and increasing risk of recurrent fractures.[16]

There is scope to optimise the management of low bone density in SMA. Current guidelines (from the pre-treatment era and focussed on children and younger people) encourage supplementation with vitamin D and/or bisphosphonates in any evidence of osteopenia or frequent fractures.[17] In our cohort, testing of vitamin D levels and supplementation with cholecalciferol were the most consistently applied actions to improve bone health. Despite this and our cohort's substantial fracture rate, only 4% were prescribed bisphosphonates. Actions to improve bone health. Despite this and our cohort's substantial fracture rate, only 4% were prescribed bisphosphonates.

This implies that treating bone health in the aftermath of fractures may not be enough alone to improve bone density and reduce future fracture risk. We advocate for a proactive and prophylactic approach to be implemented in bone health management of SMA patients. Early bone health screening to identify those at highest risk of low bone density or fractures, and a multidisciplinary approach to improve bone health would be beneficial to management. Studies auditing current clinical practices in the management of bone health in SMA patients identified the need for fracture prevention and standardised screening protocols.[18,19]

Some limitations should be acknowledged in our report. Although we present- to our knowledge- the largest single centre cohort of adult SMA patients from a range of cities in the UK, we have a limited sample size, and the majority reside in the south of England. Previous studies have noted epidemiological variation of fracture incidence in both children and adults correlating with regional differences.[20,21] Additionally, identifying the aetiology and mechanism of fractures was beyond the scope of this study. Fractures were not categorised by those deemed osteoporotic or traumatic secondary to impaired mobility.

There is a lack of consensus and research when it comes to long-term post-fracture management in in the adult SMA population. For otherwise healthy patients, standard practice in the UK is to encourage early mobilisation and physiotherapy to reduce risk of deconditioning.[22] However, in adult SMA patients, decisions regarding early mobilisation are more nuanced, and consensus is yet to be reached on mobility management post-fracture due to the inherent complexities in balancing deconditioning against the risk of further fractures in this population with progressive muscle weakness. We note the recent publication of UK orthopaedic care guidelines for DMD, including aspects of post-fracture and post-operative care, as a prompt to future such work in SMA.[23]

Ultimately, bone health is an important consideration in SMA patients given its potential long-term implications for functional disability and overall morbidity. Further research in this unique demographic of adult SMA patients, with a focus on bone health, is required in order to create robust management guidelines.

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Isolated hypercapneic respiratory failure as a presentation of GBS variant: A paraneoplastic association?

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Introduction

Guillain-Barré Syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy, that classically presents with ascending weakness and generalized areflexia.[1] The Pharyngeal-Cervical-Brachial (PCB) variant is a rare GBS subtype characterised by oropharyngeal, neck and upper limb weakness with relatively preserved lower limb strength.[2] Isolated hypercapnic respiratory failure as the initial manifestation of PCB-GBS is exceedingly rare and may cause significant diagnostic delay.[3]

Although uncommon, paraneoplastic GBS has been associated with various malignancies, most commonly small cell lung cancer.[4–8] Association with thyroid neoplasm is extremely rare.[8] We report a unique case of PCB-variant GBS presenting as isolated respiratory failure as paraneoplastic manifestation of an underlying oncocytic follicular thyroid neoplasm. This case highlights the co-occurrence of extremely rare clinical presentations within the spectrum of GBS and emphasizes the importance of considering paraneoplastic triggers in atypical GBS.

Case Report

A 60-year-old male presented to the emergency department with a history of drowsiness for two days. He had recently returned to Mumbai, India from a 20-hour flight from Los Angeles, United States, where he had remained largely indoors due to the cold weather. For approximately a week prior to his return, he reported generalized weakness and somnolence. He had been self-medicating with melatonin tablets. On further questioning he recalled drooling of saliva and slurred speech over the preceding few days. There was no history of limb weakness, preceding fever, or history of travel during his stay in the United States.

On examination, he was drowsy but arousable to verbal stimuli. Vital signs revealed tachycardia (103/min, blood pressure 160/100 mmHg, respiratory rate 24/min and oxygen saturation of 61% on room air. Arterial blood gas analysis demonstrated severe hypercapnic respiratory failure (pCO_2 of 91.6 mmHg), prompting immediate initiation of non-invasive ventilation (NIV) (Table 1).

Magnetic resonance imaging (MRI) of the brain did not reveal any acute infarct or hemorrhage. Despite non-invasive ventilation, his respiratory status progressively worsened. Multiple attempts at laryngoscopy and endotracheal intubation failed. Ventilation with supraglottic airway was unsuccessful. An emergency tracheostomy had to be performed, he was shifted to an intensive care unit and invasive mechanical ventilation was initiated.

Table 1: Arterial blood gas (ABG) at arrival to the hospital and after initiation of mechanical ventilation

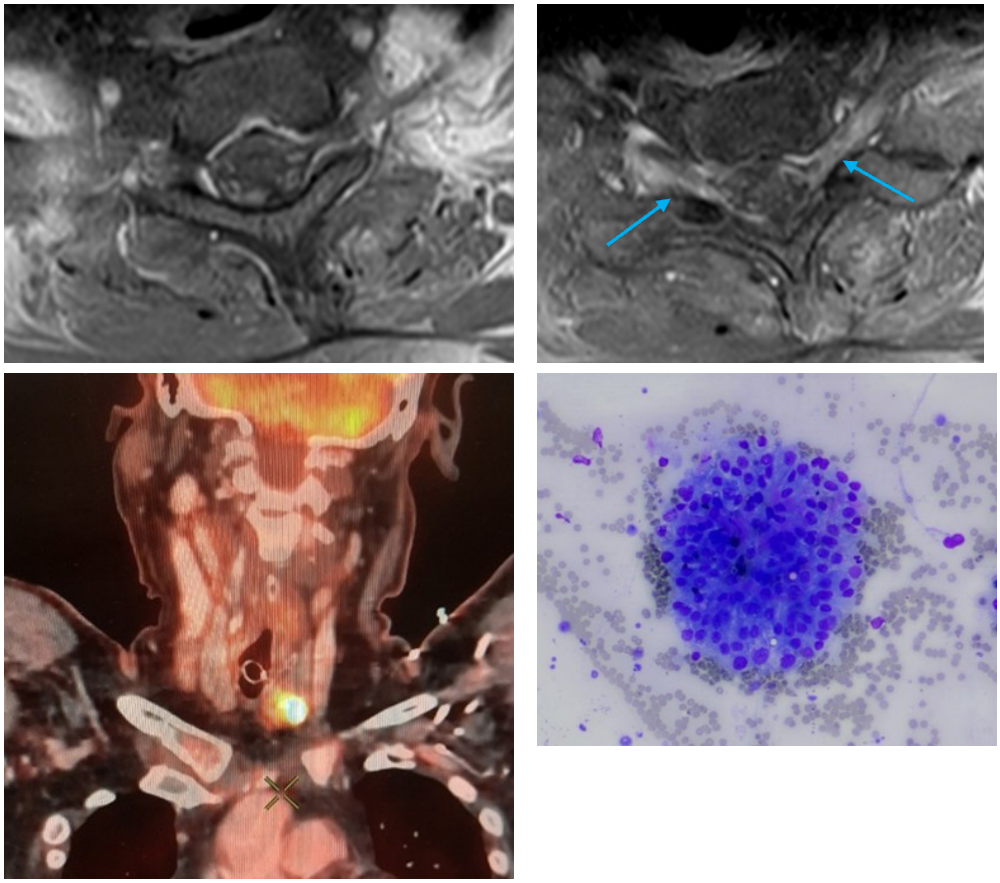
Arterial Blood gas	At arrival	After 3 hours of NIV	Post-tracheostomy and ventilation
pH	7.215	7.094	7.6
pCO2 (mmHg)	91.6	130	31.1
pO2 (mmHg)	87.5	87.8	131
HCO3 (mEq/L)	35.7	35	31.2

CT pulmonary angiography showed a thrombus in the right lower lobar segmental artery, with no evidence of deep vein thrombosis. Two dimensional echocardiography revealed features suggestive of acute pulmonary embolism without right ventricular dysfunction. He was treated with subcutaneous enoxaparin 60 mg twice a day. Though his ventilatory parameters improved, multiple attempts to wean were unsuccessful with persistent hypercapnia. The small pulmonary embolism could not explain his respiratory compromise, prompting a neuromuscular consultation.

Neurological examination revealed mild facial weakness, neck flexor weakness and distal left upper extremity weakness (C8–T1 distribution) with generalized areflexia. Lower limb strength was preserved (Medical Research Council [MRC] grade 5/5) and sensory examination was normal. Notably, he had a remote history of electric injury to the right upper limb, that accounted for pre-existing weakness. Serum creatine phosphokinase was normal. Acetylcholine receptor and muscle-specific kinase antibodies were negative. Electrodiagnostic studies revealed reduced amplitude of the left ulnar motor response recorded at abductor digiti minimi with minimal chronic denervation in left C8–T1 muscles. No myopathic motor potentials were seen. 3 Hz repetitive nerve stimulation did not reveal a significant (>10%) decremental response.

Cerebrospinal fluid analysis was unremarkable (cell count 1/µL; protein 55 mg/dL; glucose 73 mg/dL). MRI Cervical spine with contrast demonstrated enhancement of bilateral C6–T1 nerve roots. (Figure 1A and 1B). Based on above, a clinical diagnosis of Pharyngeal-Cervical-Brachial (PCB) variant of Guillain-Barré Syndrome (PCB-GBS)

Figure 1: T1-Weighted post-contrast fat-sat axial sequence at C7-T1 level showing bilateral mild thickening and abnormal enhancement of dorsal and ventral nerve roots (Yellow Arrows) and (B) exiting nerve sheaths (Blue arrows)
(C) Whole body-FDG PET showing increased uptake in left lobe of thyroid (Green arrow)
(D) Left lobe thyroid nodule fine needle aspiration cytology: Smears stained by MGG showed loosely cohesive as well as singly scattered large cells with abundant granular cytoplasm. The cells had enlarged, round to oval nuclei with open chromatin and occasional inclusions.



was made. Serum anti-ganglioside antibody panel was negative.

He was initially treated with intravenous methylprednisolone 1g daily for 5 days by the intensive care team but without clinical improvement. This was followed by intravenous immunoglobulin (IVIG) 2 g/kg administered over 5 days, resulting in prompt recovery. Due to concurrent pulmonary embolism and no preceding illness, a paraneoplastic etiology was suspected. Whole-body PET CT identified an FDG-avid thyroid nodule (Figure 1C). Fine-needle aspiration cytology confirmed oncocytic follicular neoplasm (Bethesda Category IV) (Figure 1D). He underwent total thyroidectomy by day 28.

At 6 months follow up he is neurologically asymptomatic and free of malignancy.

Discussion

This case illustrates an unusual presentation of the pharyngeal-cervical-brachial variant (PCB) of Guillain-Barré syndrome, initially manifesting as isolated hypercapnic respiratory failure. Respiratory compromise in neuromuscular disorders typically occurs in the context of generalized weakness, isolated respiratory failure as the presenting feature is uncommon.

There are several reports of type II respiratory failure as the initial presentation of undiagnosed myasthenia gravis.[9–11] However, in our patient, myasthenia gravis seemed less likely as he had no history of prior symptoms suggestive of myasthenia gravis, no demonstrable eyelid fatigability, negative antibody profile and a normal repetitive nerve stimulation study. Similarly adult-onset Pompe disease and inflammatory myopathies can present with prominent respiratory failure but were excluded based on normal serum creatine kinase levels and electromyography[12]. Rarely, amyotrophic lateral sclerosis (ALS) can present with isolated respiratory failure; however, this was inconsistent with the clinical presentation in our patient.[13,14]

Guillain-Barré Syndrome (GBS) is classically characterized by acute onset of ascending limb weakness and generalized areflexia; yet respiratory failure as the

predominant initial manifestation is rare.[3] The clinical diagnosis of GBS can be particularly challenging in such cases due to the paucity of limb weakness, normal nerve conduction study with no albumin-cytological dissociation on cerebrospinal fluid analysis. Clinical clues for GBS in our patient were presence of bulbar features (drooling of saliva, slurred speech, dysphagia), facial weakness, neck weakness and generalized areflexia. Electrophysiological testing was essentially unremarkable except for chronic C8,T1 motor axon loss which was presumed to be due to old electrical current injury. CSF analysis was unremarkable. MRI cervical spine with contrast showed enhancement of several cervical nerve roots.

Selective involvement of oropharyngeal and neck muscles, generalized areflexia and cervical nerve root enhancement was suggestive of a pharyngo-cervico-brachial variant of GBS. The PCB variant of GBS is characterized predominantly by axonal involvement rather than demyelination.[2,15] It represents a focal form of acute motor axonal neuropathy (AMAN) and is often associated with anti-GT1a IgG antibodies in 51%.[2] Recent evidence suggests that anti-GT1a antibodies frequently cross-react with GQ1b. This immunological overlap supports the concept of PCB-GBS and Fisher syndrome existing along a continuous clinical and serological spectrum.[2] The ganglioside panel that was tested in our patient did not include anti-GT1a antibody. He was initially treated with intravenous methylprednisolone 1000 mg for 3 days by the treating physician as MRI spine showed some subtle STIR hyperintensity in the cervical spine and the diagnosis of GBS was not considered initially by the Intensive care team. However, a careful Neuromuscular evaluation was consistent with the diagnosis of PCB variant of GBS. Plasmapheresis was advised however the family opted for IVIG. IVIG 2g/kg over 5 days was started to which he responded quite well and was off the ventilator by the 5th day of IVIG.

The absence of antecedent infection and concurrent pulmonary embolism raised the suspicion for an underlying malignancy. Although GBS is classically post-infectious, paraneoplastic GBS has also been described albeit rarely. Isolated reports of GBS with lung cancer, squamous cell carcinoma and renal cell carcinoma suggest a possible paraneoplastic immune-mediated mechanism.[6,16,17] Only one prior case of GBS associated with papillary thyroid carcinoma has been reported[8]. In our patient, a thyroid malignancy was found. However a causative link between GBS and cancer could not be established. We cannot establish if this co-occurrence is by chance or a paraneoplastic syndrome. Serum paraneoplastic panel was suggested however was deferred by the treating physician.

This case underscores several important points. First, PCB-GBS should be considered in patients with otherwise unexplained hypercapnic respiratory failure, even in the absence of generalized weakness. Second, electrophysiological studies may be non-diagnostic in early or atypical cases, and supportive findings such as CSF protein elevation and nerve root enhancement on MRI may be useful. Finally, the concurrent occurrence of pulmonary embolism and absence of infection prompted malignancy screening, highlighting the need for a multidisciplinary, systematic approach in atypical GBS presentations.

Conclusion

This case emphasizes the importance of considering neuromuscular causes, particularly PCB variant of Guillain-Barré Syndrome, in patients presenting with unexplained hypercapnic respiratory failure. The unusual co-occurrence of PCB-GBS with pulmonary embolism prompted evaluation for an underlying thyroid malignancy. A comprehensive evaluation and a multisystemic diagnostic approach are essential for timely diagnosis and management.

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Evaluation of muscle disorders after patients have been placed in a phenotypic pattern

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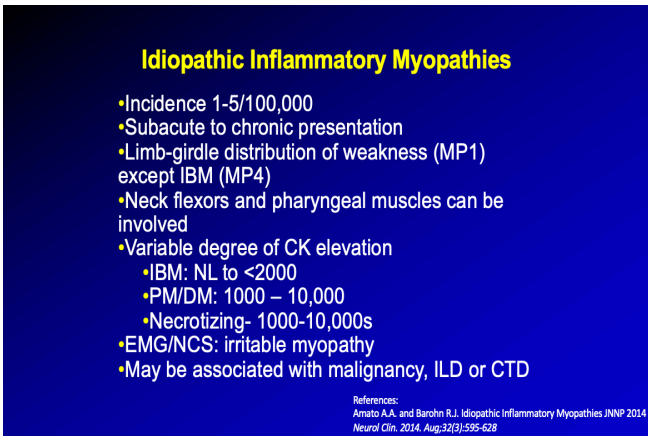
Previously we discussed the pattern recognition approach to myopathy and neuromuscular junction disorders (see Pattern Recognition Approach to Neuromuscular Disorders: Myopathy & Neuromuscular Junction Disorders in the prior issue of the Barohn RRNMF Journal Volume 5 Issue 2 September 2024). That discussion was geared to teach how to approach the patient before ordering laboratory tests and putting patients into one or more of the ten phenotypic clinical patterns. The patterns are based solely on the history and presentation of the patient. In this lecture, a patient has already been placed into one or more of the possible myopathic patterns, specific muscle diseases should be considered as the next step. Therefore, it is time to think about ordering laboratory tests to support or at times confirm the clinical suspicion based on the pattern recognition. We will briefly review a number of myopathies, describe what are the most likely patterns with the condition, and discuss the appropriate laboratory studies, and the possible treatments. The evaluation and approach to neuromuscular junction disorders will be provided in a different lecture.

Inflammatory Myopathies

Figure 1



From a historical perspective, the modern concept of inflammatory myopathies was introduced by Dr. John Walton in a 1954 article in Brain and the book titled Polymyositis authored by him and Dr. Raymond Adams in 1958. In the modern era, a classification of the inflammatory myopathies has been defined in the International Myositis Classification Criteria Project leading to the publication of the criteria by American College of Rheumatology / European Alliance of Associations for Rheumatology.

Idiopathic inflammatory myopathies are relatively rare, about 1 to 5 per 100,000. In most of them, the onset was sub-acute over months. Usually, they present for medical care in less than a year from the onset of symptoms except for inclusion body myositis (IBM) which has a delayed presentation and insidious onset over many years.

The typical pattern is limb-girdle (MP1 pattern). Because MP1 is the most common pattern, in some regards it is the least helpful because it does not distinguish between many different forms of muscle disease. An exception is IBM which presents with the MP4 pattern showing weakness in distal arms and proximal legs.

Figure 2

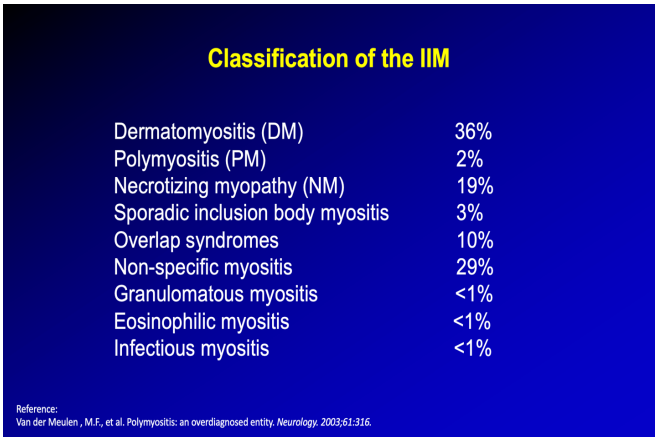
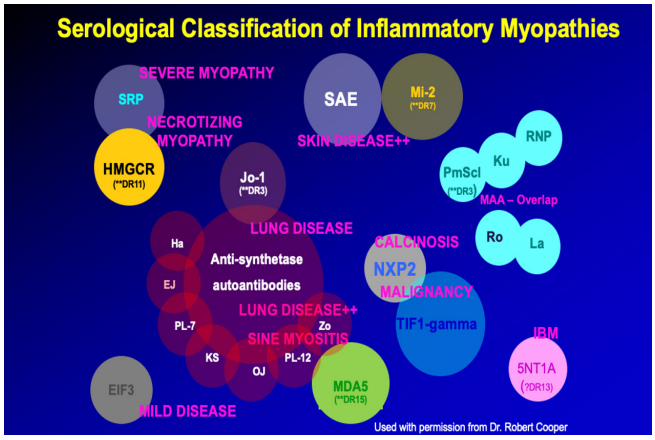


Figure 2 lists a number of different inflammatory myopathies and their frequencies according to a Dutch study. A common misbelief was that polymyositis is a frequent form of idiopathic inflammatory myopathy. But this is not the case. The Dutch study by Van der Meulen et al. showed that polymyositis accounted for only 2% of biopsy proved inflammatory myopathies. The most common inflammatory myopathy diagnosis in adults was dermatomyositis, followed by necrotizing myositis. Surprisingly, in this series, IBM made up only 3%. In our clinics in North America, IBM is more common than that. In the Database Evaluation for Muscle and Nerve Diseases (DEMAND) experience from four clinics, out of 490 inflammatory myopathy patients, 200 were IBM, 188 were polymyositis, and 102 were dermatomyositis.

Regarding laboratory studies, creatine kinase (CK) is very useful and its elevation indicates muscle damage. The magnitude of CK elevation can sometimes provide a clue as to the type of inflammatory myopathy. For example, IBM tends to have CK levels of 500 to 1000 IU/L range, whereas in polymyositis and dermatomyositis it is often over a thousand, and in necrotizing myopathy, it can be much higher. CK may be normal in DM and IBM.

Electromyography (EMG) is also helpful because it can reveal short-duration and small-amplitude motor unit potentials with irritability (denervation potentials in the form of fibrillations or positive sharp wave discharges). The presence of denervation potential suggests an active disease process. But their presence does not distinguish one muscle disease from another.

Figure 3



Some inflammatory myopathies are associated with specific serologic abnormal antibodies (Figure 3).

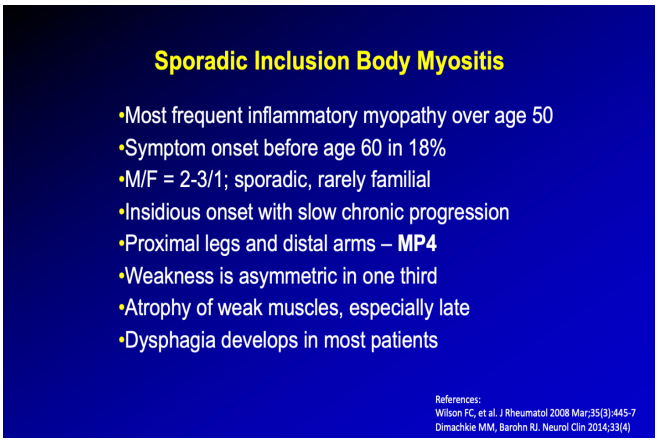
One of the first serologic antibodies that were discovered in inflammatory myopathy patients was the Jo-1 antibody. Subsequently, other tRNA synthetase antibodies were discovered. What is important about the tRNA-synthetase autoantibodies is that they predict a very high likelihood that the patient has concomitant interstitial pulmonary fibrosis. Both the muscle and the lung are targets of the autoimmune attack. The autoimmune attack on the lungs tends to be difficult to reverse with treatment. Therefore, it is important to identify these patients early and treat them aggressively.

Some of these myopathies can be associated with an increased risk for malignancy up to 4 years from disease onset. While malignancies are overall more frequent in dermatomyositis, 2 myositis specific antibodies, Anti-NXP-2 (NXP2) and TIF1-gamma, are predictive of a higher likelihood of having an underlying malignancy. In dermatomyositis, SAE and Mi-2 antibodies are more commonly seen in patients with skin diseases such as calcinosis, severe alopecia, or other forms of breakdown of the skin.

Necrotizing myopathy is associated with SRP antibodies as well as HMGCR antibodies if the patient has been on a statin-lowering agent and sometimes without identifiable statin exposure. Finally, IBM is associated with NT5C1A antibodies in approximately half of the cases (See Figure 5 below and Barohn, Dimachkie, Jackson Neurol Clin 2014 and Dimachkie, Barohn, Amato Neurol Clin 2014).

Inclusion Body Myositis

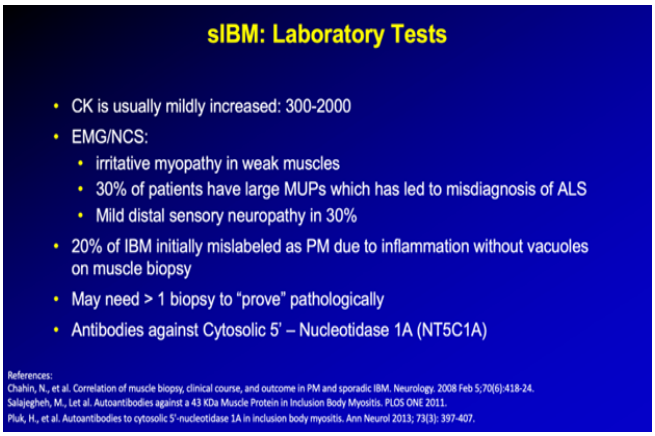
Figure 4



IBM in most series (other than the Dutch study noted above) is the most common inflammatory myopathy in older adults. It is uncommon to occur before age 50. It is more common in men. IBM has a very slow chronic progression, and the average time between onset of weakness and diagnosis is approximately 8 years. These patients may not realize they have a muscle disease for many years. They may think their weakness is simply age-related because it comes on so slowly. IBM has a unique pattern of weakness involving the proximal legs and the distal arms. It is often asymmetric. The muscle involvement is very selective in the proximal legs, the quadriceps muscles (knee extensors) are predominantly involved whereas the hamstrings (knee flexors) are relatively spared. In the arms, the involvement is selective to muscles in the flexor compartment and

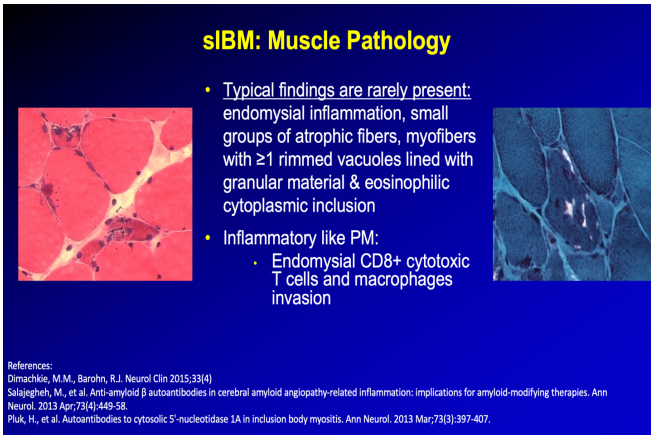
tends to spare the extensor compartment. Therefore, the weakness in the upper extremities involves finger flexors and wrist flexors. Some IBM patients also have dysphagia.

Figure 5



The CK is usually mildly elevated or normal in IBM. Many of these patients will have concomitant neuropathy based on symptoms and signs and electromyographic testing. The needle electromyography (EMG) findings can show long-duration and high-amplitude motor unit potentials which can make the diagnosis confusing and can lead to the misdiagnosis of amyotrophic lateral sclerosis (ALS). However, the pattern of weakness in IBM should make it very clear that it is unlikely to be ALS.

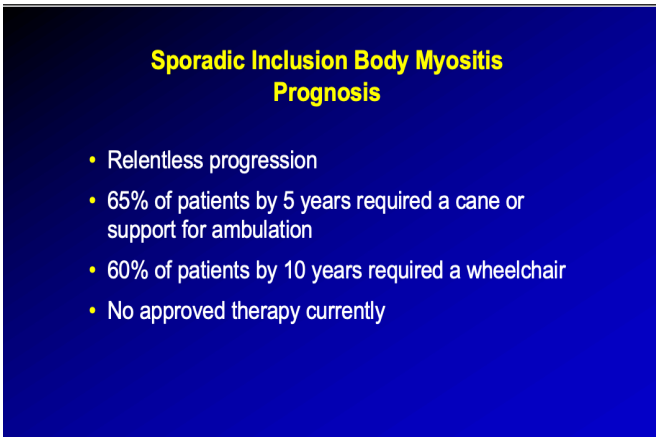
Figure 6



Historically, the standard way to diagnose IBM is via a muscle biopsy. Figure 6 shows the hematoxylin and eosin stain of a biopsied muscle from an IBM patient. There are small atrophic fibers that contain inclusions and small vacuoles. The vacuoles are easier to visualize on the trichrome stain. This type of biopsy finding is characteristic of IBM. However, sometimes the biopsy shows mild inflammation without the characteristic vacuoles. We believe the inflammation is likely a secondary phenomenon as a result of degenerative processes ongoing within muscle fibers. This can therefore lead to the erroneous diagnosis of polymyositis if vacuoles and inclusions are not seen. If the patient is mistakenly diagnosed as polymyositis this can lead to them being put on corticosteroids and other immunosuppressant agents with no clinical benefit. Ultimately, the patient may undergo a second muscle biopsy to search for the characteristic vacuoles leading to the correct diagnosis of IBM. There is a serologic test, the NT5C1A antibody that can be positive in up to 50% of the patients with IBM. However other diseases can be associated with the NT5C1A. For example, patients with Sjogren's syndrome, systemic lupus erythematosus and even some neuromuscular disorders that are non-immune mediated may have a positive NT5C1A antibody titer. Therefore, in the right clinical setting where the patient has asymmetrical proximal leg and distal arm weakness with a slow progression, obtaining a positive serologic antibody test confirms the clinical suspicion and you can probably avoid a muscle biopsy.

This antibody test is now commercially available and should be obtained in any patient where there is a clinical suspicion of IBM based on the pattern recognition. However, the absence of the NT5C1A antibody does not rule out IBM and in this setting a muscle biopsy is necessary to confirm the diagnosis.

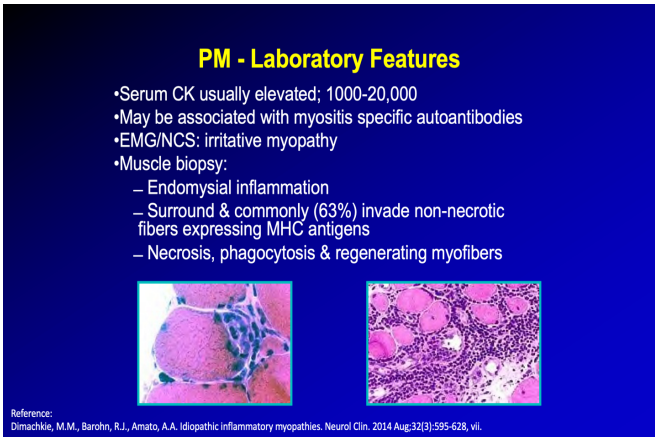
Figure 7



The course of IBM is very slow, relentless, and progressive. About 65% of patients need help with an assistive device for walking after five years and about 60% are in a wheelchair after 10 years.

Unfortunately, there is no effective therapy. A recent phase 2/3 randomized control trial of the drug arimoclomol, a heat shock protein inducer, was negative (See Machado PM, et al. Lancet Neurology 2023;10:900-911).

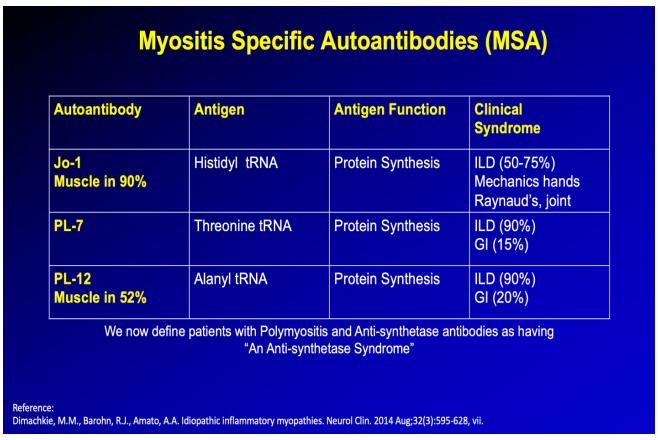
Polymyositis
Figure 8



Polymyositis presents with the classic hallmark MP1 pattern of limb-girdle weakness as previously noted. In addition to limb-girdle weakness, there can be neck flexor weakness and dysphagia. Usually, the facial muscles are not involved. The pathology of polymyositis is different from IBM. There are many inflammatory cells surrounding nonnecrotic muscle fibers that otherwise appear to be healthy (Figure 8).

What used to be called polymyositis has splintered into 4 clinically, pathologically and serologically distinct diseases: necrotizing autoimmune myopathy, overlap syndrome, anti-synthetase syndrome and inclusion body myositis.

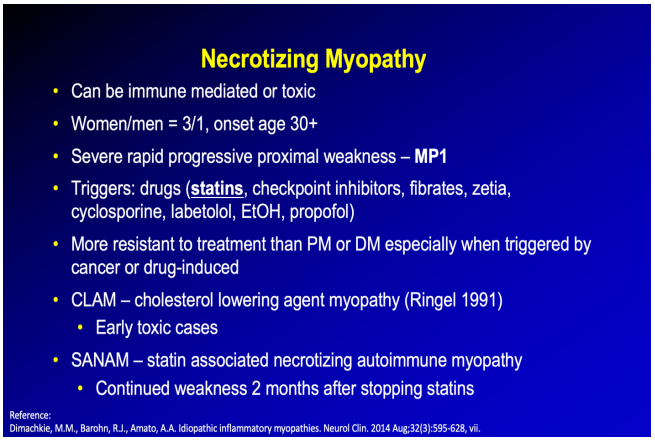
Figure 9



We believe this inflammatory cell invasion of non-necrotic fibers represents a cellular-mediated attack on the muscle fibers.

Some cases of polymyositis are associated with tRNA synthetase antibodies (Figure 9) suggestive of the anti-synthetase syndrome. Polymyositis with these antibodies is now known as anti-synthetase syndrome and is associated with interstitial lung disease. These patients need to be treated aggressively.

Necrotizing Myopathy
Figure 10



In the group of immune-mediated myopathies, necrotizing myopathy is the most recently identified. There are two forms of necrotizing myopathy. One is an acute toxic myopathy which is typically caused by drugs or toxins, and the other is a more chronic immune-mediated necrotizing myopathy. The most common class of drugs to cause acute necrotizing myopathy are the cholesterol-lowering agents. In fact, this was first identified in 1991 and was called cholesterol-lowering agent myopathy (CLAM). Rarely, acute statin induced myopathy can present as a rhabdomyolysis with myoglobinuria (MP8), but more often as a subacute MP1 pattern without rhabdomyolysis (See Barohn, Dimachkie, Jackson Neurol Clin 2014). Usually, once the offending toxic drug is withdrawn the toxic myopathy resolves. However, some patients continued to have progressive myopathy symptoms and signs and persistently elevated CK for 1-2 months after the cholesterol-lowering agent was stopped. We call these cases statin-associated necrotizing autoimmune myopathy

(SANAM) and it is believed that the statin drugs set off an immune-mediated process against muscle fibers. Other drugs or agents that can cause acute toxic myopathy include alcohol, cyclosporine, propofol or immune checkpoint inhibitors (see Figure 8 in Barohn, et al, The Pattern Recognition Approach to Neuromuscular Disorders: Volume 5 Issue 2 September 2024).

Figure 11

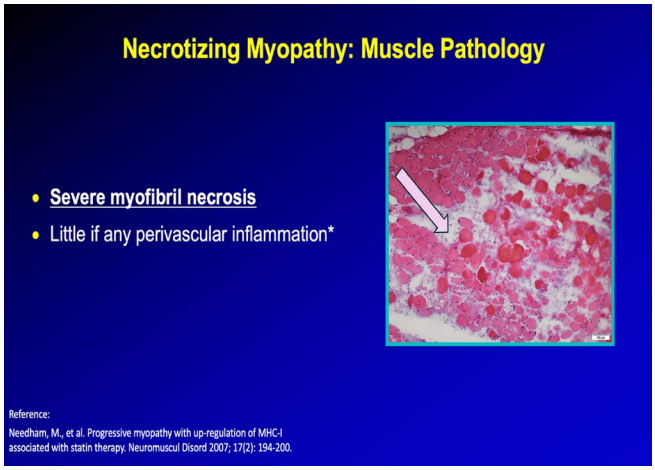


Figure 11 shows the pathology of a severe necrotizing myopathy. There is little inflammation. There is a great deal of muscle fiber necrosis. There are "ghost fibers" that have replaced healthy muscle fibers (See arrow in Figure 11).

Figure 12

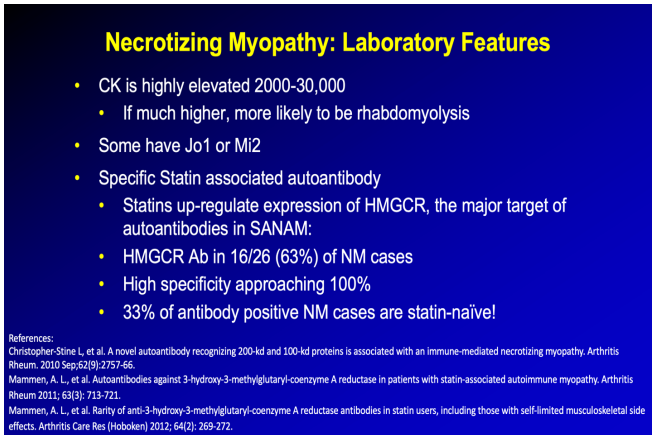
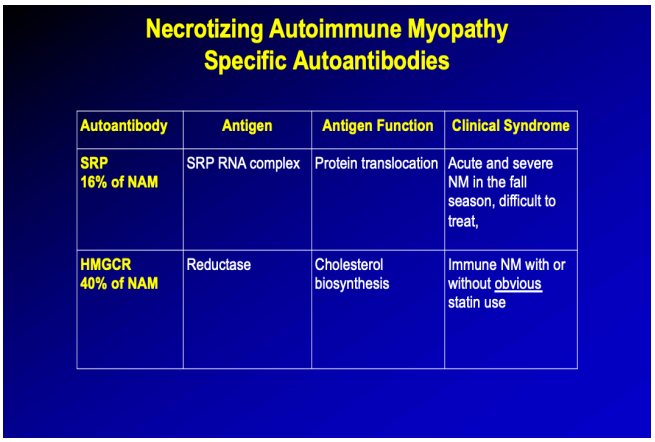


Figure 13

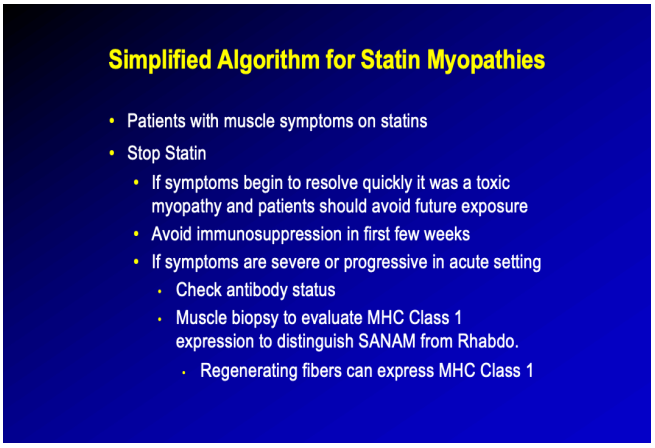


In necrotizing myopathy, CK level tends to be high, at least 1,000 IU/L sometimes over 10,000 IU/L (Figure 12).

HMGCR autoantibody is present in about two thirds of SANAM (Figures 12 and 13). It is speculated that the statins upregulate the expression of HMGCR. However, it has also been demonstrated that about one third of patients with necrotizing myopathy and HMGCR antibodies have never been previously exposed to a statin medication. So clearly in some cases, the statin alone is not the precipitating event for the autoimmune process.

Another antibody associated with necrotizing myopathy is SRP antibodies. These cases tend to be seasonal, often following a flu-like illness.

Figure 14

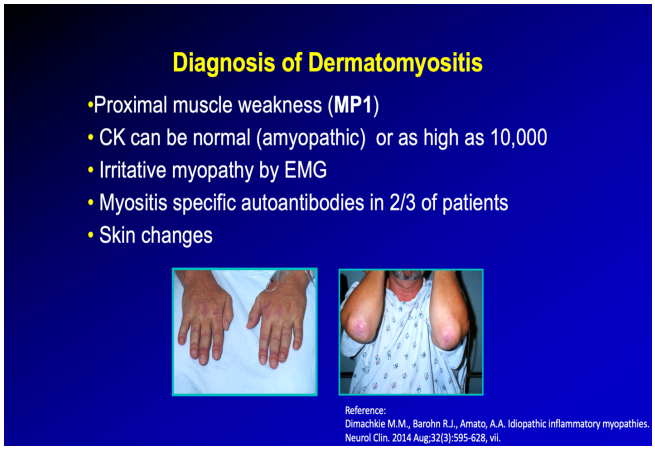


How should you handle a patient who is on statin and has muscle weakness? (Figure 14)

If the patient on a statin presents with muscle cramps and muscle aches without objective weakness the first thing to do is to stop the statin. We would recommend obtaining a serum CK to determine if there is evidence of muscle fiber damage. Usually, these patients present within eight weeks of starting the statin. If the statin is stopped and they improve there is nothing further to do other than get an additional CK if the initial one was elevated. If the statin is stopped and they do not start to get better after 8 weeks, we recommend to test for HMGCR antibody and trend CK levels. If the course continues to worsen, there is a need to consider a muscle biopsy. If the HMGCR antibody is elevated an argument can be made not to perform a muscle biopsy. In either care, immunosuppressive therapy for SANAM should be initiated.

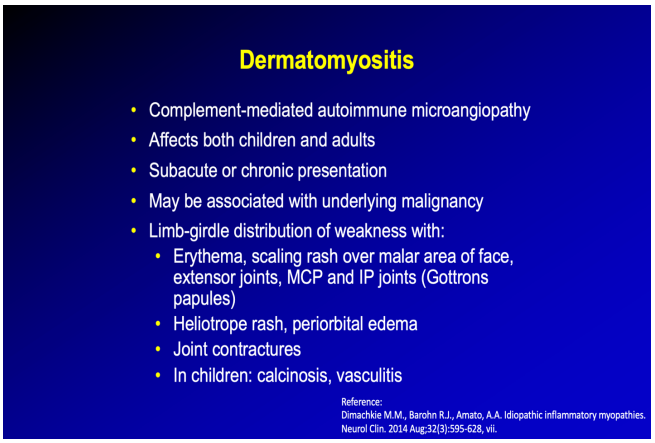
Dermatomyositis

Figure 15



Dermatomyositis has an MP1 pattern of presentation. CK is generally very high but cases with a normal CK and typical skin involvement do occur and have been called amyopathic dermatomyositis. The red skin discoloration usually appears on the extensor surfaces of the fingers, elbows or arms, as well as on the front and back of the neck (Figure 15). The facial rash can appear on the forehead, cheeks, and eyelids. EMG in dermatomyositis shows an irritable myopathy.

Figure 16



Unlike polymyositis, dermatomyositis is an autoimmune muscle disease that can occur in children (Figure 16). Other features of dermatomyositis include calcinosis, vasculitis, and joint contractures.

Before the 1950s and the availability of corticosteroids, children who had dermatomyositis tended to die very often due to ischemic bowel disease because of vasculitis and its widespread nature. Therefore, juvenile dermatomyositis is vasculitis of the muscle rather than myositis. B lymphocytes invade and circle the small capillaries inside of the muscle fascicles. There is immunoglobulin (IgM) and complement deposition around the blood vessels. This leads to entire muscle fascicles that become ischemic.

The blood vessels course through the middle of the fascicle and therefore muscle fibers on the edge of a muscle fascicle become ischemic and become smaller. That leads to the appearance perifascicular atrophy (Figure 17).

Figure 17

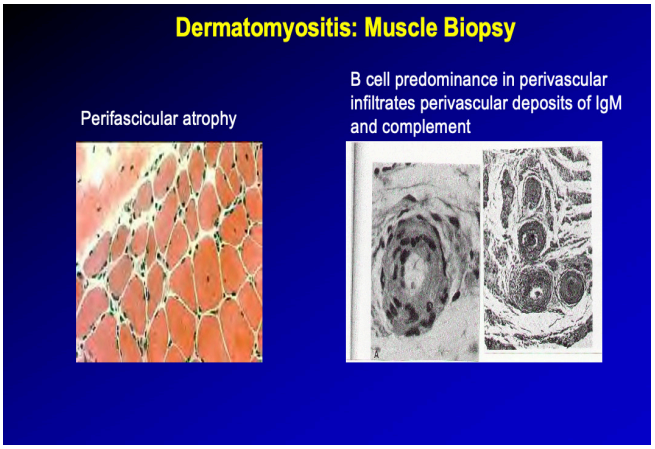


Figure 18

DM Specific Autoantibodies

Autoantibody	Antigen	Antigen Function	Clinical Syndrome
Mi-2	Helicase	Nuclear transcription	Nail fold lesions; higher in Hispanics
Anti-p155(140) TIF1γ	Transcription intermediary factor 1γ	Part of tripartite-motif (TRIM) family, interacts with SMAD 2,3,4; muscle cell regeneration	Cancer in adults; Severe skin disease in children; palmar hyperkeratotic papules, psoriasis like
MDA-5 aka CADM-140 May be weak!!	Type I IF-inducible protein 1, IFIH1	Positive regulator of the IFN response	Severe ILD & cardiopulmonary syndrome, skin ulceration, tender palmar papules
MJ (p140) Up to 40% of DM	NXP-2	Nuclear transcription	JDM with calcinosis
Anti-small ubiquitin-like modifier 1	Small ubiquitin-like modifier 1	post-translational modification; not targeting proteins for degradation	Skin presenting before muscle manifestations; dysphagia common

Figure 18 shows a number of autoantibodies that have been identified in a number of cases of dermatomyositis. Some of these cases predict interstitial lung disease and others can predict severe skin disease.

Cancer and Inflammatory Myopathies

Since many inflammatory myopathies (including IBM) are associated with an increased risk for cancer and are paraneoplastic (Figure 19), what is the standard cancer screening in a patient with inflammatory myopathy? (Figure 20)

We recommend that cancer surveillance screening be performed yearly for the first 5 years after diagnosis of inflammatory myopathy. There are two approaches of cancer surveillance as outlined in Figure 20 or a combination of these approaches can be used.

Figure 19

Cancer Screening in PM/DM/NM

- Risk is highest within the first year of diagnosis
- In those with polymyositis, the risk fell to expected rates 5 years after diagnosis
- In those with dermatomyositis, the risk is always elevated
  - Risk of ovarian, pancreatic, lung cancer remained elevated for up to 5 years
  - Pancreatic and colorectal cancer risks remained elevated past 5 years

Reference:
Hill, C.L. et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet. 2001 Jan 13;357(9250):96-100.

Figure 20

Cancer Screening in DM/PM/NM

- A matter of debate
- Best practice guidelines say to repeat yearly for 1st 5 years after diagnosis
- Approach #1
  - Complete history and physical exam
  - Routine blood and urine tests
  - Fecal occult blood
  - Chest x-ray; mammogram
  - Additional tests in case of specific signs and symptoms

Approach #2: WHOLE BODY CT OR PET

Figure 21 outlines the various immunosuppressive drug therapy options for autoimmune inflammatory myopathy. For polymyositis, dermatomyositis and autoimmune necrotizing myopathy, corticosteroids and intravenous immunoglobulin (IVIG) are often used as first-line immunotherapies. There is now an FDA-approved indication for IVIG in dermatomyositis.

Figure 21

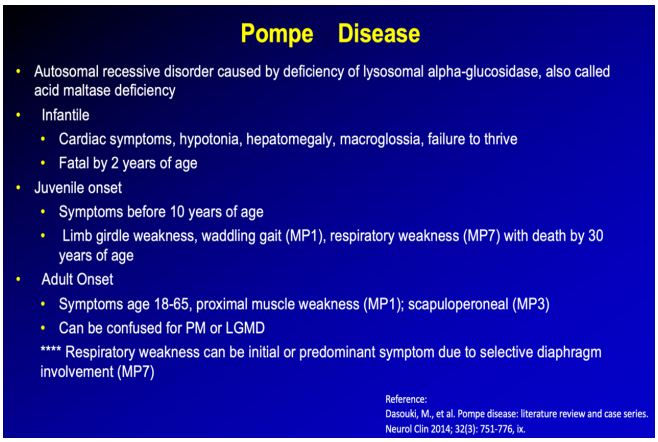
PM/DM/NM Drug Therapy

- 1st Line
  - Prednisone
  - IV methylprednisolone
  - IVIG*
- 2nd Line
  - Methotrexate
  - Azathioprine*
  - Mycophenolate mofetil
- 3rd Line
  - Rituximab*(Oddis)
  - Cyclophosphamide
  - Etanercept* (Amato)
  - Tacrolimus (Oddis)
  - Cyclosporine

*RCT

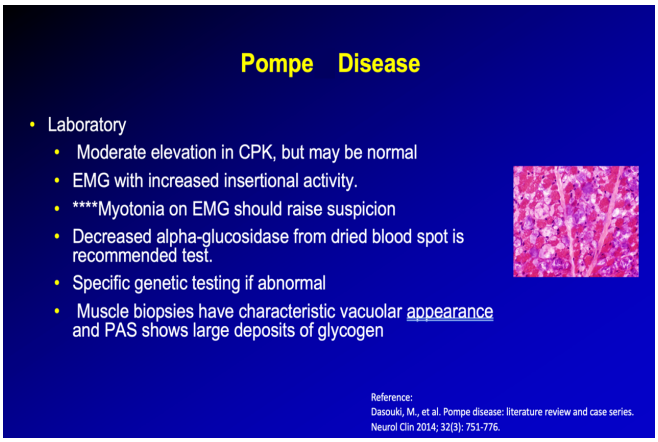
References:
van der Ploeg, et al. Rituximab therapy for myopathy associated with anti-signal recognition particle antibodies: a case series. Arthritis Care Res (Hoboken) 2010; 62(9): 1328-1334.
Amato, A.A., et al. A randomized, pilot trial of etanercept in dermatomyositis. Ann Neurol 2011; 70(3): 427-436.
Dimachkie, M. M., Barohn, R. J., Amato, A. A. Idiopathic inflammatory myopathies. Neurol Clin 2014; 32(3): 595-628, vii.
Baraliakos, X., et al. Efficacy and safety of upadacitinib in patients with active psoriatic arthritis and axial involvement: results from two phase 3 studies. Arthritis Res Ther. 2023 Apr 10;25(1):56.

Pompe's Disease
Figure 22



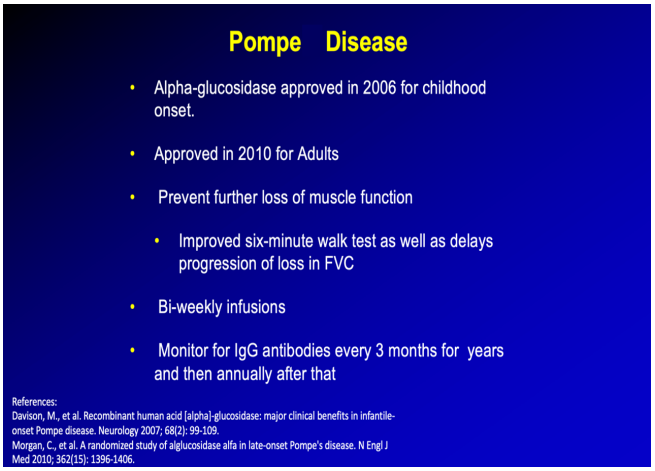
Pompe disease is also known as alpha-glucosidase deficiency or acid maltase deficiency. Pompe disease is an autosomal recessive disorder. It can present at various ages. If it presents in infancy the disease used to be often fatal by 2 years of age without enzyme replacement therapy. Juvenile onset patients used to die of the disease by the second or third decade without enzyme replacement therapy. The late-onset Pompe disease with an adult presentation usually has an MP1 pattern however can also present with an MP3 scapuloperoneal pattern. Because Pompe disease most often has an MP1 presentation it can mistakenly be diagnosed as polymyositis. As also pointed out in the pattern recognition review, Pompe disease patients often have prominent respiratory issues due to diaphragm involvement (MP7).

Figure 23



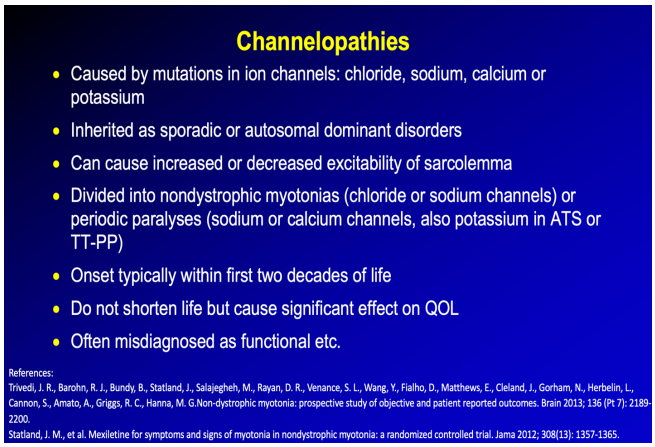
The serum CK is usually mild to moderately elevated. The EMG is interesting because in addition to short-duration small-amplitude motor unit potentials and fibrillation potentials, there can be the presence of myotonic potentials. Figure 23 shows a muscle biopsy showing H&E stained section with vacuolated muscle fibers and loss of muscle fibers and large deposits of glycogen accumulation resulting from a lack of breakdown due to enzyme deficiency.

Figure 24



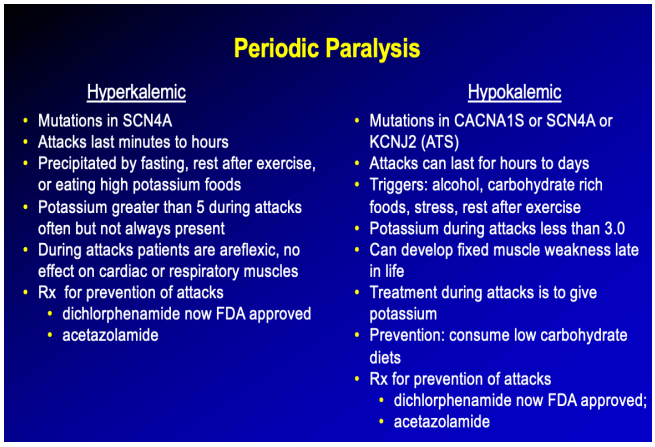
One of the biggest breakthroughs in modern medicine is the introduction of enzyme replacement therapy for Pompe disease. This was the first FDA-approved molecular therapy for a muscle disease. Initially, it was demonstrated that enzyme replacement therapy could dramatically improve infants with Pompe disease and preserve life. It was subsequently shown that chronic enzyme replacement therapy can slow down the progression of juvenile and adult Pompe disease and improve muscle function. Therefore, it is important to recognize Pompe disease early. As the possibility of enzyme replacement therapy was being studied in clinical trials, measuring alpha-glucosidase activity from a phlebotomy sample was developed. This is now a standard procedure for all patients being suspected of Pompe disease. Further genetic testing confirms the diagnosis. Therefore, the combination of an abnormally low alpha-glucosidase level on a blood sample and an abnormal genetic test for Pompe disease can avoid a muscle biopsy and enzyme replacement therapy can be initiated.

Channelopathies
Figure 25



Another group of muscle disorders are the disorders due to muscle channel dysfunction (Figure 25). This group of genetic disorders can be due to mutations in either the chloride, sodium, calcium, or potassium channels. They are inherited disorders that can either increase or decrease the excitability of the muscle fiber membrane. The two most prominent presentations of channelopathies are episodic weakness after exercise or at times unrelated to exercise (MP9), or muscle stiffness and decreased ability to relax (MP10).

Figure 26

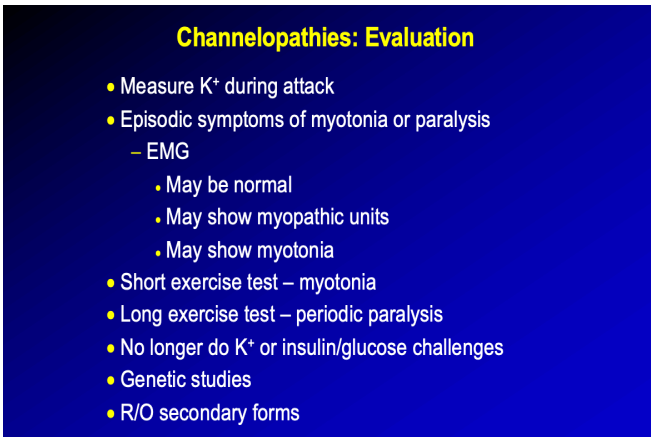


We divide the muscle channelopathies into two groups. One group is the nondystrophic myotonias due to chloride and sodium channel mutations. The other group is the periodic paralysis. These conditions often begin before the first two decades of life and they generally do not cause permanent weakness which is why they are not considered dystrophic. There are exceptions however, as some middle and late age patients with long-standing episodic symptoms of periodic weakness can eventually develop permanent weakness. These conditions do affect the patient's quality of life. These conditions can be difficult to diagnose and sometimes patients can be labeled as being functional or psychogenic.

Periodic paralysis can be further divided into two groups based on the serum level of potassium: hyperkalemic and hypokalemic (Figure 26). The hyperkalemic-associated episodes tend to last a shorter time than the hypokalemic subtype. Hyperkalemic paralysis is typically precipitated by fasting, resting after exercise, or eating high-potassium foods. Hypokalemic paralysis is typically precipitated by alcohol intake, carbohydrate-rich food, stress, and resting after exercise.

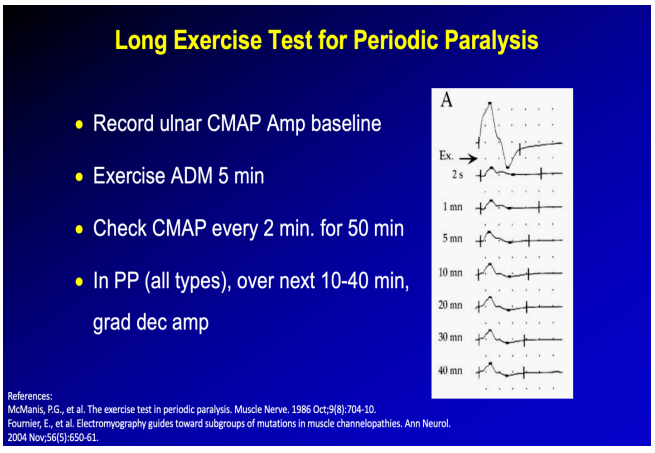
The evaluation of channelopathies is outlined in Figure 27.

Figure 27



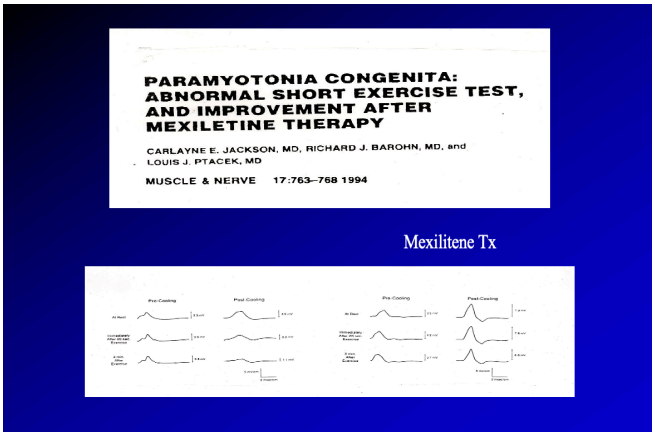
Examining a patient and measuring the potassium level during the paralysis attack is optimal but it is often difficult to have these opportunities. In hyperkalemic paralysis, EMG between attacks may be normal or may show myopathic units or myotonic discharges. However, these are not observed in the hypokalemic group. On nerve conduction studies, the long exercise test for periodic paralysis and the short exercise test for non-dystrophic myotonias can sometimes be useful to differentiate the subtypes (Figure 28).

Figure 28



The short exercise test can sometimes be used to monitor electrophysiologic improvement after treatment initiation for myotonia (Figure 29).

Figure 29

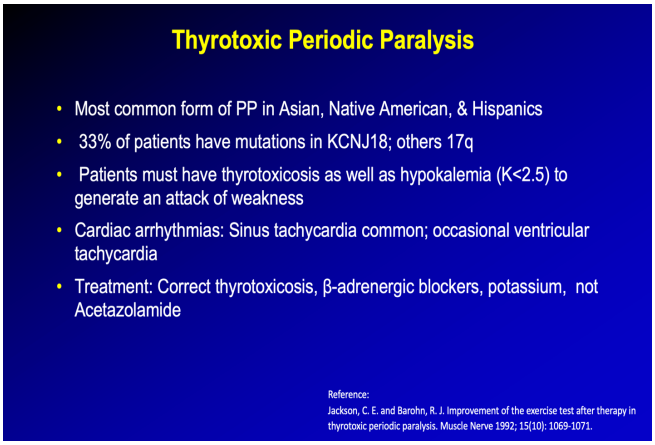


The most efficient and accurate way to diagnose channelopathies is via genetic testing for sodium, calcium, chloride, or potassium channel mutations which are now commercially available. Prior to the advent of genetic testing, an attack could be provoked by administering potassium to produce hyperkalemia and then administering insulin with glucose to produce hypokalemia. However, this is no longer needed with the availability of genetic testing.

Therapy for periodic paralysis is either dichlorphenamide which is now FDA-approved or acetazolamide. Therapy for myotonia is sodium channel-blocking agents. For decades the drug of choice was mexiletine, but more recently ranolazine and lamotrigine have been shown to be effective (See Vivekanandam, et al. Lancet Neurology 2024;10:1004-1012).

Thyrotoxic Periodic Paralysis

Figure 30



There are secondary forms of periodic paralysis. The most common etiology for secondary periodic paralysis is thyrotoxic periodic paralysis.

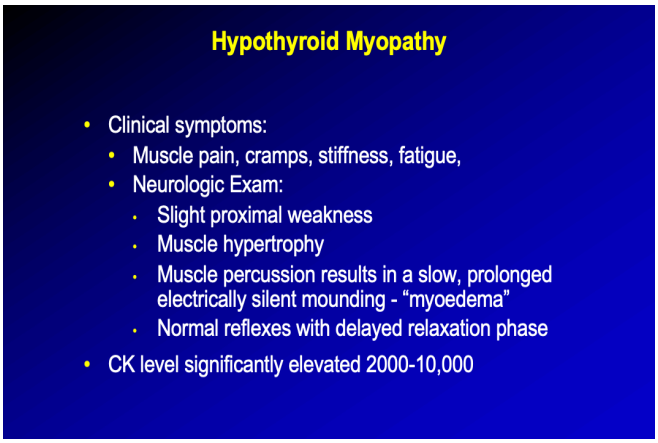
This is the most common form of paralysis in Asians, Native Americans, and Hispanics.

Many of these patients have a concomitant potassium channel defect on chromosome 18 or on chromosome 17. Clinically they have obvious thyrotoxicosis when they present with weakness and hypokalemia.

Acutely the treatment is to correct the hypokalemia, but the long-term treatment is to correct the thyrotoxicosis.

Hypothyroid Myopathy

Figure 31

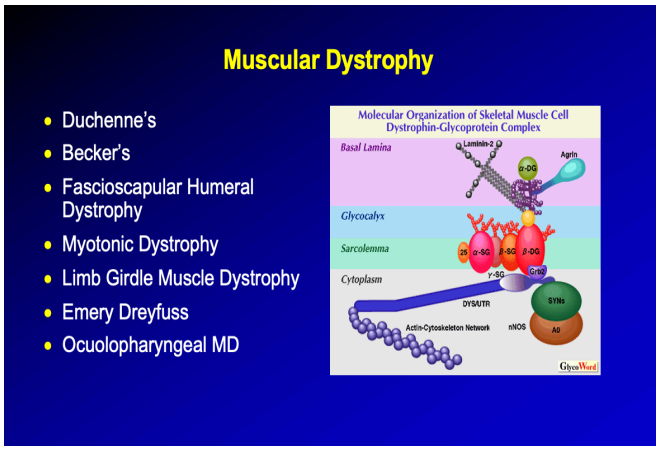


Hypothyroid myopathy patients present with cramps, stiffness, fatigue, and proximal weakness (MP1). Reflexes can exhibit a delayed relaxation phase. Serum CK is often very high. It is important to check thyroid functions in patients with unexplained elevated CK as some of these patients may not have a great deal of symptoms and signs of muscle disease or hypothyroidism.

Muscular Dystrophies

A number of different muscular dystrophies along with a diagram of the molecular organization of a skeletal muscle cell and the dystrophin glycoprotein complex is shown in Figure 32.

Figure 32

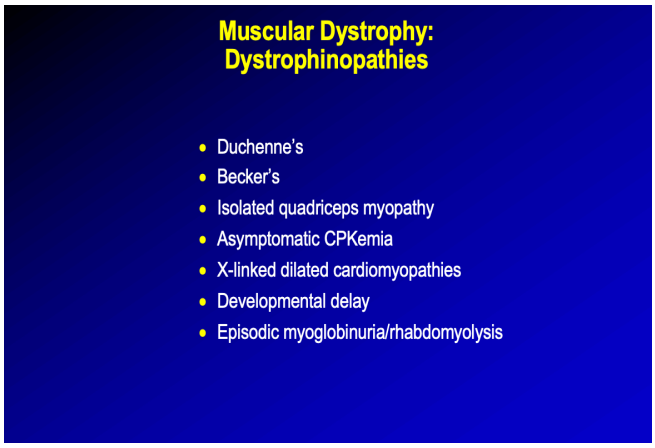


Dystrophinopathies (Duchenne's and Becker's Muscular Dystrophy)

Dystrophinopathies have a number of clinical presentations. The most common presentation is an MP1 pattern of muscle weakness for both Duchenne's and Becker's muscular dystrophy.

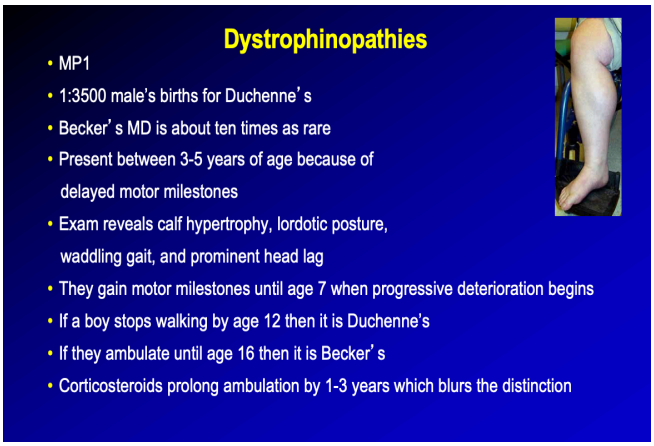
Duchenne and Becker's muscular dystrophy are due to genetic defects in the dystrophin gene and are therefore called dystrophinopathies. Other reported presentations of dystrophinopathies are shown in Figure 33.

Figure 33



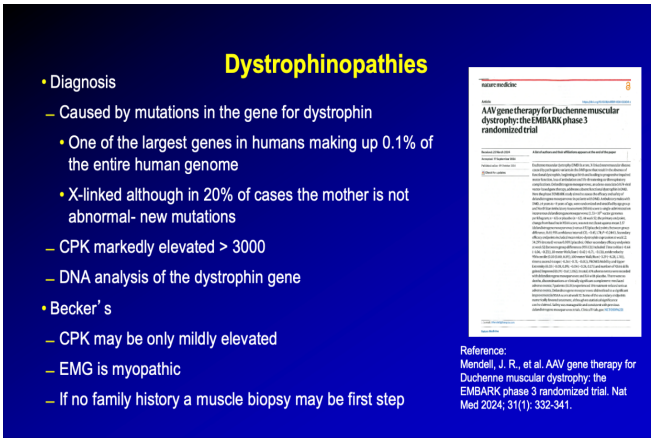
Typical patients with Duchenne muscular dystrophy present between ages 3 and 5 because of delayed motor milestones. There is often the presence of calf hypertrophy (Figure 34).

Figure 34



Boys usually stop walking by age 12 but the use of corticosteroids will prolong ambulation. There is now FDA-approved exon-skipping antisense therapy for dystrophinopathies due to a number of specific deletions in the dystrophin gene. More recently the FDA approved intravenous AAV mediated gene therapy (Elevidys). Therefore, accurate and early genetic diagnosis is important (Figure 35).

Figure 35

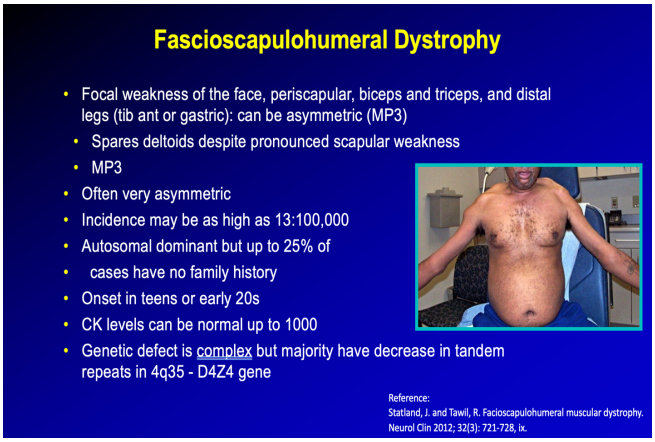


Muscle biopsies will show the absence of dystrophin, but these are no longer needed with a documented dystrophin mutation in the blood (Figure 36).

Figure 36

Facioscapulohumeral Dystrophy (FSHD)

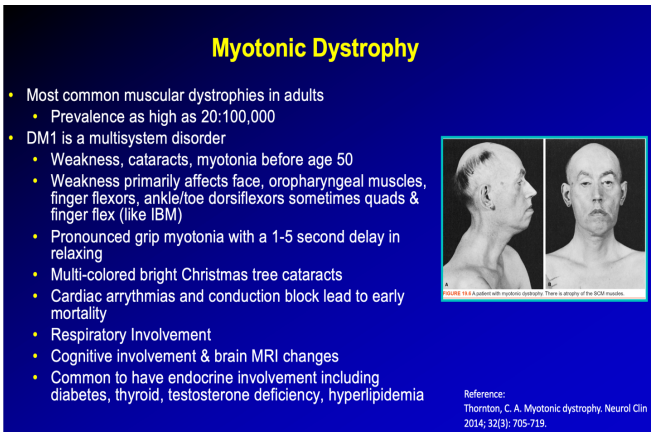
Figure 37



FSHD patients have a scapuloperoneal or MP3 weakness distribution (Figure 37). Patients have weakness of the face, periscapular muscles, biceps, and triceps. In these patients, the deltoid can appear normal with very atrophic biceps and triceps. Scapular winging is prominent and can be observed with either shoulder flexion or abduction. Most patients will provide an autosomal dominant family history but up to 25% will not. The diagnosis is based on demonstrating the genetic defect which is a decrease in the number of tandem repeats in the 4q35-D4Z4 gene.

Myotonic Dystrophy

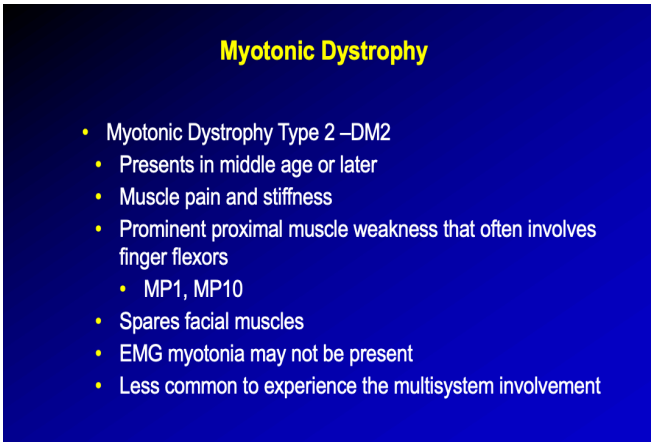
Figure 38



Myotonic dystrophy is probably the most common form of muscular dystrophy in adults. There are two forms of myotonic dystrophy. Myotonic dystrophy type 1 (DM1) is the classic form with multisystem involvement. Along with weakness, they have cataracts. They develop cardiac arrhythmias and conduction blocks which lead to very early mortality, often in the sixth decade. Some of these patients require pacemakers and automatic implantable cardioverter defibrillators. They can have various endocrine disorders, including diabetes, hypothyroidism, and testosterone deficiency. Cognitive impairment is very common.

Myotonic dystrophy can have a number of different presentation patterns including MP1, distal weakness MP2, ocular ptosis MP5, and muscle stiffness (MP10). Rarely, an adult DM1 patient can have severe knee extension weakness combined with severe finger flexor weakness MP4 pattern which is most often seen in IBM. However, the age of the patient and other typical myotonic dystrophy features help distinguish these two diseases.

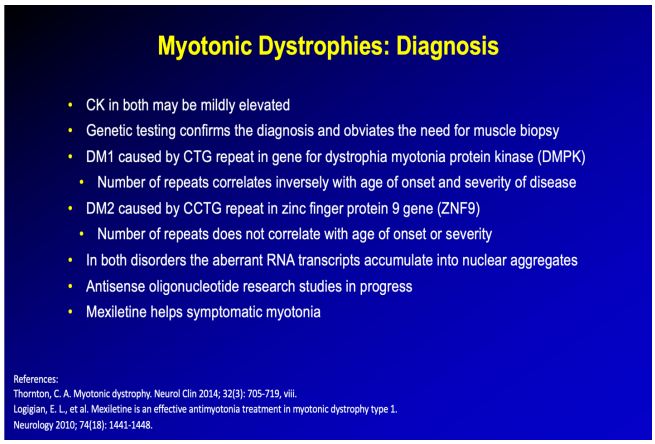
Figure 39



Myotonic dystrophy type 2 (DM2) presents later in life (Figure 39). They do not have all of the features typical for DM1. Most of these patients present with muscle pain and stiffness. On exam, they can have mild or prominent limb-girdle weakness (MP1).

One clue to DM2 is that very often their finger flexors are weak as well, but they do not have facial involvement and they may not have myotonia on exam.

Figure 40



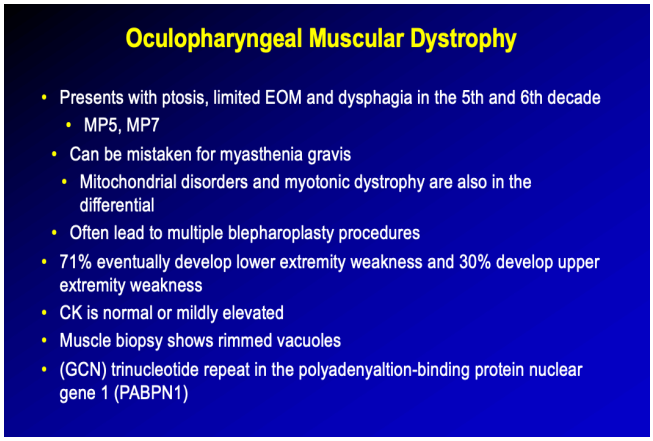
The definitive diagnosis of both types of myotonic dystrophy is via genetic testing of the blood or muscle. Genetic testing confirms the diagnosis. DM1 is caused by CTG repeat expansion of the DMPK gene. DM2 is caused by CCTG repeat expansion of the ZNF9 gene (Figure 40).

In DM1 the number of repeats correlates inversely with the onset age and the severity of the disease. In DM2 the number of repeats does not correlate well with the onset of severity.

Both seem to relate to the increase in RNA transcripts that build up because of these extra repeats and there are several research studies now trying to decrease the amount of RNA with antisense nucleotides. EMG can show classic myotonia but is often more subtle in DM2 and CK may be mildly elevated.

Although not FDA-approved, mexiletine is very helpful to treat their symptoms of muscle stiffness and pain but it does not help weakness.

Oculopharyngeal Muscular Dystrophy
Figure 41



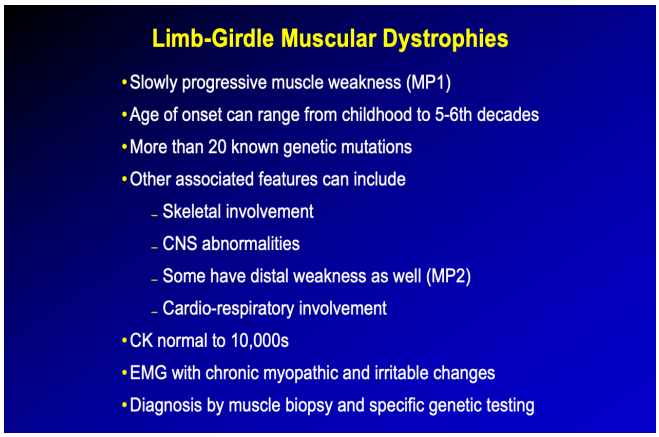
Oculopharyngeal muscular dystrophy (OPMD) is important to recognize because this can be mistaken for myasthenia gravis, as patients will come in with ptosis, extraocular muscle weakness, dysphagia, and often some facial weakness late in the course of the disease (Figure 41).

Therefore, OPMD has features of both MP5 (eyeball pattern) and MP7 (bulbar pattern). One of the clues favoring OPMD rather than MG is that because eye muscle weakness develops slowly throughout the entire lifetime in OPMD, the patient's eyes may not move at all, but they have no double vision. On the other hand, in myasthenia gravis, there may be no obvious deficit in extraocular motility on examination, but the patients complain of diplopia. Muscle biopsies may show the presence of rimmed vacuoles and subtle dystrophic features without inflammation. The definitive test demonstrates the genetic abnormality of a trinucleotide repeat expansion in the PABPN1 gene.

Limb-girdle muscular dystrophy (LGMD) (Figure 42)

Historically, limb-girdle muscular dystrophies were always lumped into one group until genetic mutations were found and there were apparent multiple limb-girdle muscular dystrophies. Most present with an MP1 pattern that is slowly progressive, however, distal presentations can occur (MP2) in some of the LGMDs.

Figure 42



The most common forms of limb-girdle muscular dystrophy are shown in Figure 43.

Figure 43

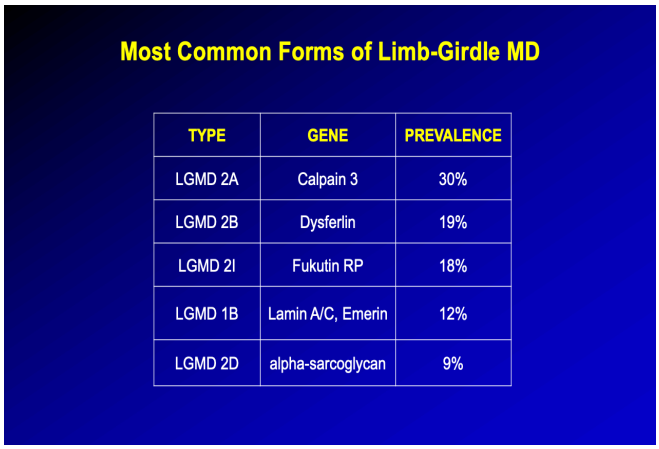
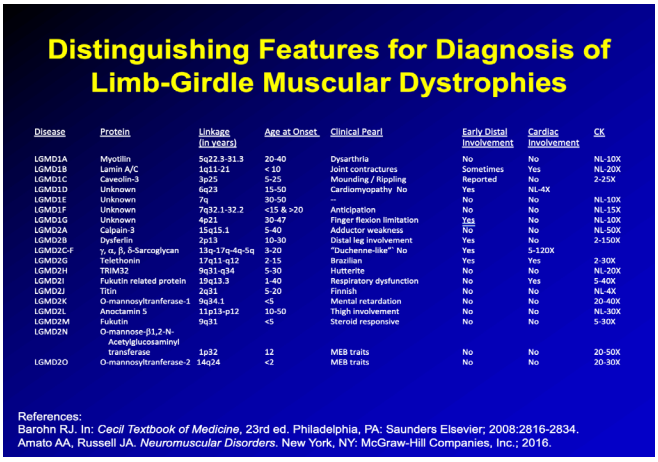


Figure 44 provides more distinguishing features between a number of the LGMDs.

Figure 44



Congenital Muscular Dystrophy

Congenital muscular dystrophies occur within the first year of life and present with prominent hypotonia. Ultimately an MP1 pattern is recognizable. Frequently other organ systems are involved including eyes, lungs, brain, and heart (Figure 45).

Figure 45

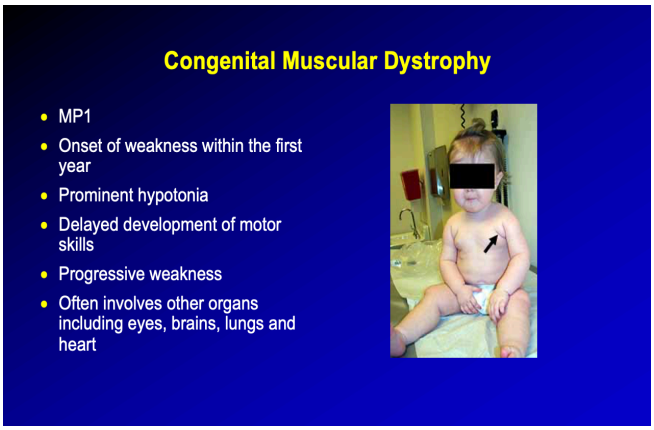


Figure 46 shows a muscle biopsy with dystrophic changes, muscle size variability, and significant replacement of muscle fibers by connective tissue. However, a muscle biopsy is now rarely indicated, and patients are diagnosed with specific genetic testing.

Figure 46

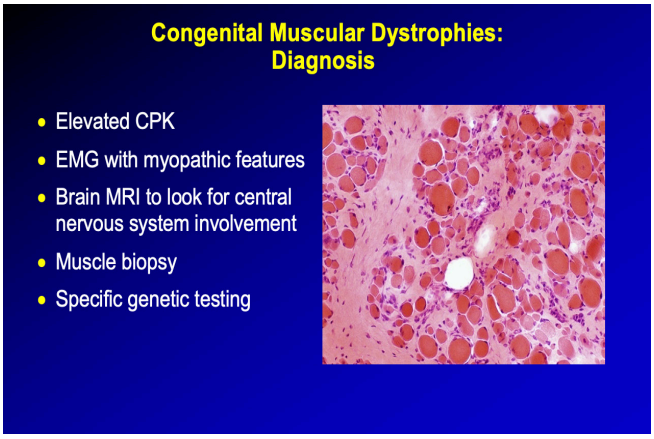


Figure 47 shows a number of different congenital muscular dystrophies with specific genetic abnormalities. While often included on this list, Bethlem myopathy is due to a genetic mutation in collagen genes rather than muscle-specific genes.

Figure 47

Congenital Muscular Dystrophies

	Respiratory	Cardiac	Brain MRI	Course
Merosin	Common	35%	T2 Abnormal	Slowly progressive
Fukuyama	Not seen	Decreased EF	migrational defects	Progressive
Musce-Eye-Brain	Not seen	Not seen	Structural abnormal	Progressive
Walker-Warburg	Not seen	Not common	Structural abnormal	Poor survival
Bethlem	Not seen	some conduction defects	Normal	Progression at 2nd decade
Ullrich	Early resp involvement	Not seen	Normal	Progressive

Congenital Myopathies

There are several congenital myopathies that usually present in childhood with an MP1 pattern. By definition, these tend to be nonprogressive in contradistinction to congenital muscular dystrophies. A number of different molecular genetic defects have now been identified for nemaline rod, congenital myopathy with central nuclei, and congenital myopathy with cores.

Figure 48

Congenital Myopathies

- MP1, occasionally MP2, MP3, MP5
- Early onset hypotonia
- Muscle weakness
- Not progressive by definition
- NI to slightly elevated CPK
- Muscle biopsy with specific pathologic findings

Figure 49

Congenital Myopathies: Nemaline Rod

- 90% are congenital but childhood and adult onset do occur
  - Can be autosomal dominant or recessive
  - 7 identified genes to date
- Weakness and hypotonia
- Cognitive involvement in younger children
- Progressive disorder in kids with death from respiratory involvement
- Adult can present with paraspinous and neck extensor involvement

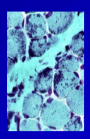


Figure 50

Congenital Myopathies

- Congenital Myopathy with Fiber Size Disproportion
- Autosomal dominant or recessive
- Onset is congenital or childhood
- Diffuse weakness and hypotonia
- 50% are static, 35% improve somewhat and
- 15% worsen

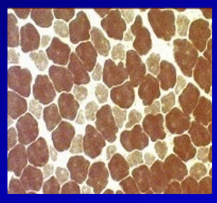


Figure 51

Congenital Myopathies

- Congenital myopathy with central nuclei
  - X-linked (Myotubularin 1) or autosomal dominant or recessive
  - Onset in infancy
  - 50% of mothers will have polyhydramnios
  - Facial and head malformations
  - Hypotonia, muscle and respiratory weakness and ocular (ptosis, EOM)
  - Many die within the first 6 months
  - Longer survivors require respiratory support

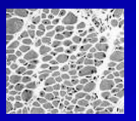
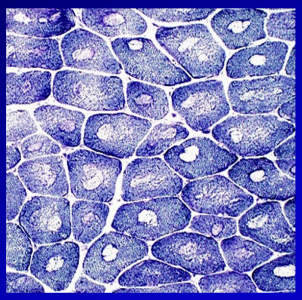


Figure 52

Congenital Myopathies: CORES

- Ryanodine receptor syndromes
- Central core myopathy
- Congenital or childhood onset
- Autosomal dominant or recessive
- Hypotonia
- Congenital hip dislocation and reduced fetal movements
- Slowly or not progressive
- Malignant hyperthermia
- Usually Limb Girdle
- MP1



Metabolic Myopathies

The last group of disorders we will consider in this lecture are the metabolic myopathies. We have already discussed Pompe disease which is included in this group and is considered a static metabolic myopathy. Another group of metabolic myopathies with static presentation

are the mitochondrial myopathies which can be associated with not only an MP1 presentation but also the eyeball presentation and ptosis with ophthalmoplegia (MP5). Other metabolic myopathies are episodic and present with rhabdomyolysis and myoglobinuria, MP8 pattern (Figure 53). These can also be considered dynamic disorders. Metabolic myopathies that have exercise intolerance and rhabdomyoma provoked by intense exercise under 10 minutes are usually glycogen disorders. On the other hand, dynamic metabolic myopathies in which symptoms are provoked by low-intensity exercise lasting longer than 10 minutes are usually lipid disorders.

Figure 53

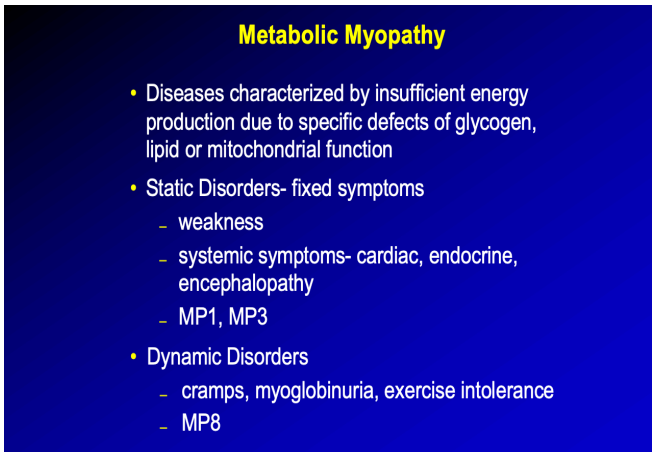


Figure 54

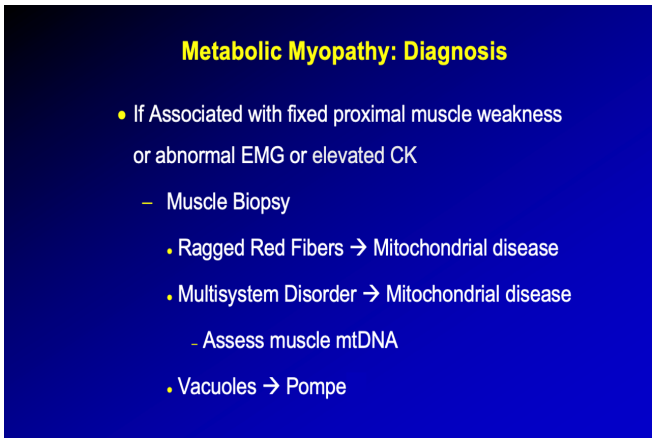


Figure 55

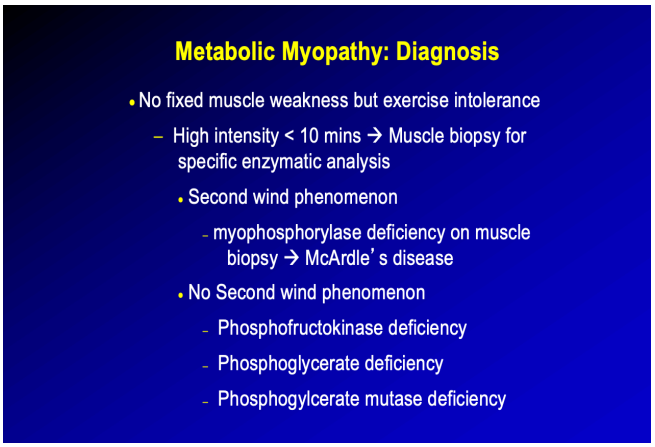
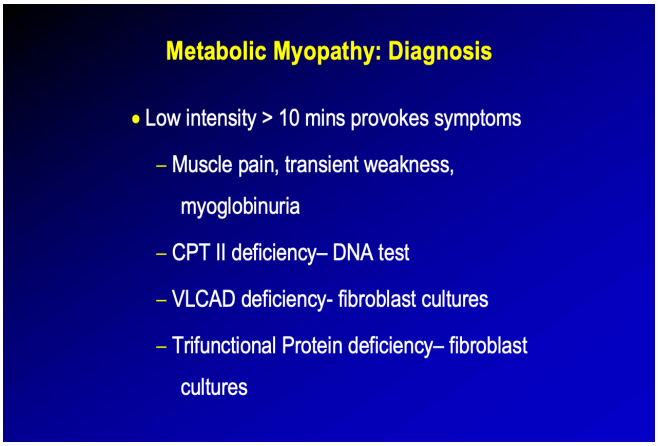


Figure 56



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History of Neurology: The Tale of Two Toms— Thomas Willis & Thomas Sydenham

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Executive Vice Chancellor for Health Affairs
Hugh E. and Sarah D. Stephenson Dean
University of Missouri School of Medicine
Columbia, Missouri

A live recording of this lecture can be viewed here: RRNMF Early, Early Neurology History The Tale of Two Toms - YouTube

This is the first in a series of short presentations where I will review some of the early historical points of neurology and neuroscience. The first story I want to tell you is the Tale of Two Toms.

The first Tom is Thomas Willis (Figure 1). He was born in the 1600s, went to school in Oxford, and while he was a medical student, the Civil War broke out. Not the U.S. Civil War. This was the British Civil War between Charles I and Oliver Cromwell, the Royalists and the Parliamentarians. Willis sided with the King. Since the Parliamentarians won the war, this delayed his education, and it took him a while to finally get his degree. While he was a student in Oxford, William Harvey was doing experiments on the heart and published *De Motu Cordis*.[1]

Figure 1

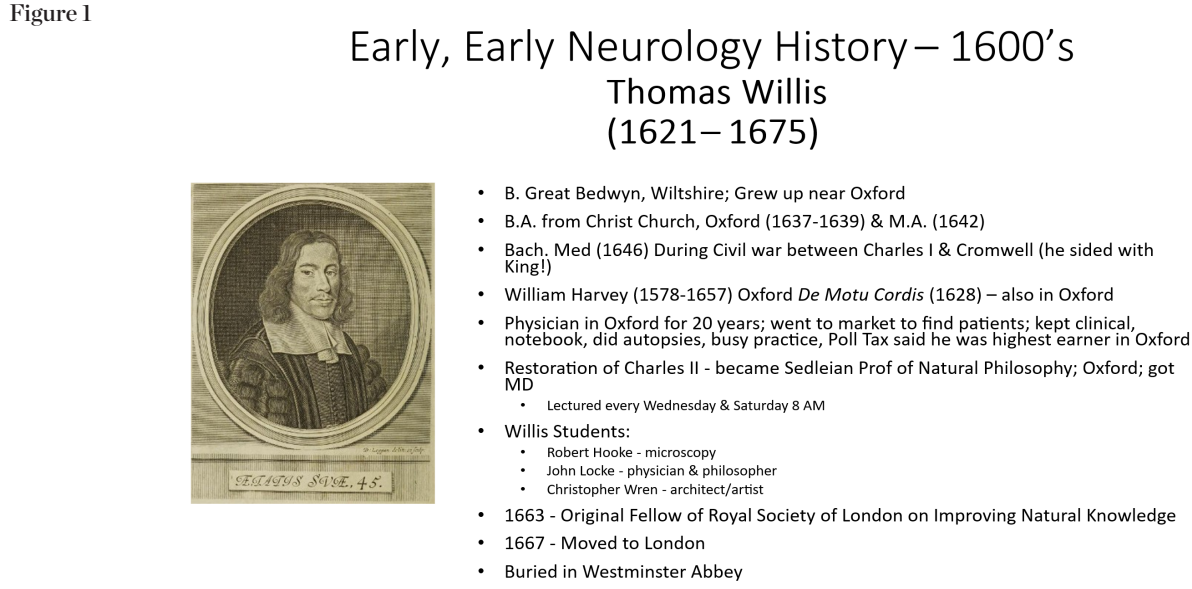
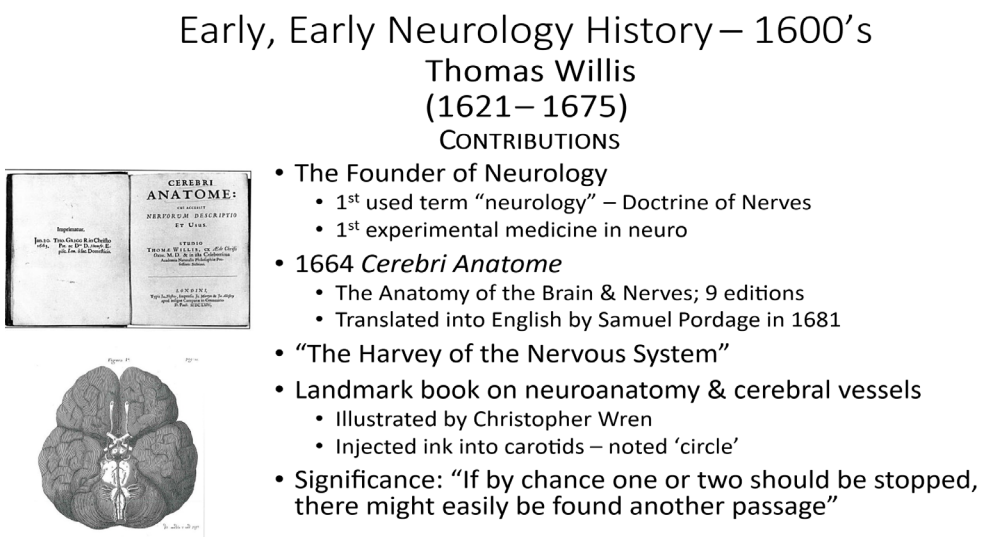


Figure 2



Willis went into practice after the Civil War in Oxford. He had a very busy practice, but he is said to have gone to the marketplace to find patients when business was slow. His practice grew, and the poll tax showed he was the highest-paid earner in Oxford. He did autopsies on his deceased patients. Interestingly, when Charles II was restored and the King was back in place, Willis was named Sedleian Professor of Natural Philosophy in Oxford, and he gave a lecture every Wednesday and Saturday morning at 8 a.m. His students became famous: Robert Hooke, John Locke, Christopher Wren. John Locke took notes on the lectures, so we know exactly what Willis was saying. Robert Hooke, who wrote *Micrographia*[2] in 1665 and pioneered the use of the microscope, was Thomas Willis' laboratory assistant. Willis recommended Hooke to Robert Boyle and these two became research partners for many years.

He was one of the original Fellows of the Royal Society and was buried in Westminster Abbey, one of the few physicians to receive such an honor.

What is Thomas Willis famous for in neurology? He's the first to use the term "neurology," calling it the doctrine of the nerves, and he's considered the first experimental medicine physician in neurology. He published his most well-known and landmark book, *Cerebri Anatome*,[3] which went through nine editions while he was alive. He is rightly known as the Harvey of the nervous system (Figure 2).

The book was illustrated by his student Christopher Wren, the legendary architect who rebuilt London after the Great Fire of 1666. In *Cerebri Anatome*, Willis describes his experiments where he would inject blood vessels with ink and showed that there was a circle of arteries around the base of the brain that we now call the Circle of Willis. He noted that if one or two vessels were blocked, another passage might easily be found. This was a monumental breakthrough in understanding brain anatomy and ultimately is the basis for what we know about stroke.

He also wrote a number of other books in his lifetime[3-13] (Figure 3). After his death, his followers had his works translated into English by Samuel Pordage. The first title "The Remaining Medical Works of That Famous and Renowned Physician Dr. Thomas Willis"[11] contained major parts of *Cerebri Anatome* with the famous brain illustrations by Christopher Wren. The most popular and frequently reprinted English translation was called *The London Practice of Physick or the whole Practical Part of Physick contained in the works of D. Willis*[12] included chapters from many of his previous books. One chapter, on "palsy", originally published in *De Anima Brutorum* (1672)[7] described what was probably the first case of myasthenia gravis—a woman who temporarily became weak and lost speech:

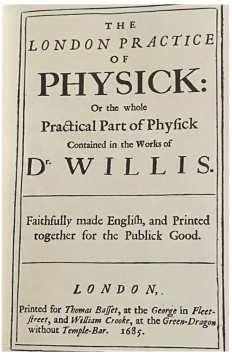
"Wherefore, in regards the Spirits residing in the Brain are conscious of the Weakness of the others plac'd in the Members, they refuse to impose local motion on their Companions, as being a task too difficult for them; for which cause the Affected are scarce led by any persuasion to try whether they are able to go or not: but those who being troubled with a scarcity of Spirits, will force them as much as they may to local Motions, are able at their first rising in the Morning to walk, move their Arms, this way and that, or to lift up a weight with strength; but before Noon, the store of Spirits which influenc'd the Muscles being almost spent, they are scarce able to move Hand or Foot. I have now a prudent and honest Woman in cure who for many years has been

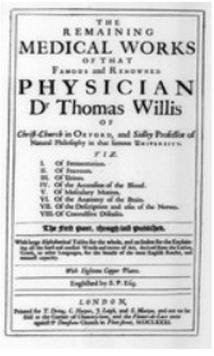
Figure 3

Early, Early Neurology History – 1600's

Thomas Willis (1621–1675)

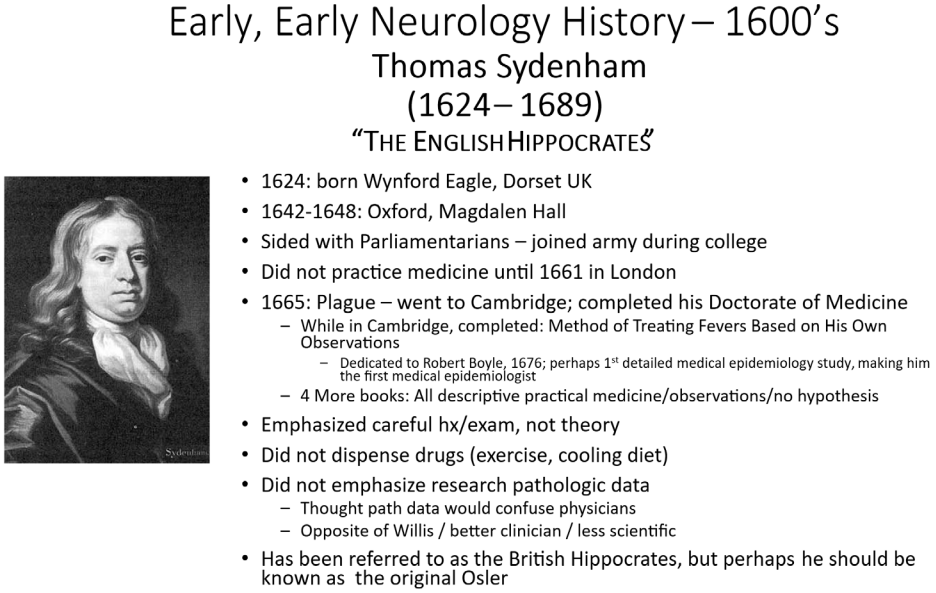
Major Bibliography


THE
LONDON PRACTICE
OF
PHYSICK:
Or the whole
Practical Part of Phyſick
Contained in the Works of
Dr WILLIS.
Faithfully made Engliſh, and Printed together for the Publick Good.
LONDON,
Printed for Thomas Baſſet, at the George in Fleet-ſtreet, and William Crooke, at the Green-Dragon without Temple-Bar. 1685.


THE
REMAINING
MEDICAL WORKS
OF THAT
Famous and Renowned
PHYSICIAN
Dr Thomas Willis
LONDON,

- 1658 *Diatribae duae medico-philosophicae*
  - Wrote hysteria was caused by brain dysfunction
- 1664 *Cerebri anatome*
- 1667 *Pathologiae Cerebri et Nervosi Generis Specimen*
- 1670 *Hysteria and Hypochondria*
  - Mental retardation and hysteria are brain disorders
- 1672 *De Anima Brutorum*
  - 1st textbook of neuropsychiatry
- 1672 *De moto musculari*
- 1672 *De Sanguiniis ascensione*
- 1675 *Pharmaceutice rationalis*
- 1681 *The Remaining Medical Works of that Famous and Renowned Physician Dr. Thomas Willis, translated from Latin by Samuel Pordage*
  - English translation of major parts of *Cerebri anatome*
- 1685 *Dr. Willis' London Practice of Physick, translated from Latin by Samuel Pordage*
  - Of the Palsey – 1st description of Myasthenia Gravis: woman temporarily lost speech and became "mute as a fish". First published in Latin in *De Anima Brutorum*

Figure 4



obnoxious to this kind of bastard Palsy not only in the Limbs, but likewise in her Tongue; This Person for some time speaks freely and readily enough, but after long, hasty, or laborious speaking, presently she becomes as mute as a fish and cannot bring forth a word, neigh, and does not recover the use of her Voice 'til after an hour or two" (From the London Practice of Physick, London, 1685:page 432; Recently republished in the Classics of Neurology and Neurosurgery Library, Division of Gryphon Editions, New York, 1991).[13]

Therefore he is credited for being the first physician to recognize what we now call myasthenia gravis.

Willis also wrote about hysterical fits. While earlier writers believed the source or cause of hysterical fits was from the uterus and therefore restricted to women, Willis believed the source was the brain and could affect both sexes. The following quote is also from the London Practice of Physick page 297 in 1685 edition:

"A motion in the lower part of the Belly... and an Ascent, a Suffocation in the Throat, ... a Giddiness, an Inversion or rotation of the Eyes, often Laughing or Weeping, a talking

Figure 5

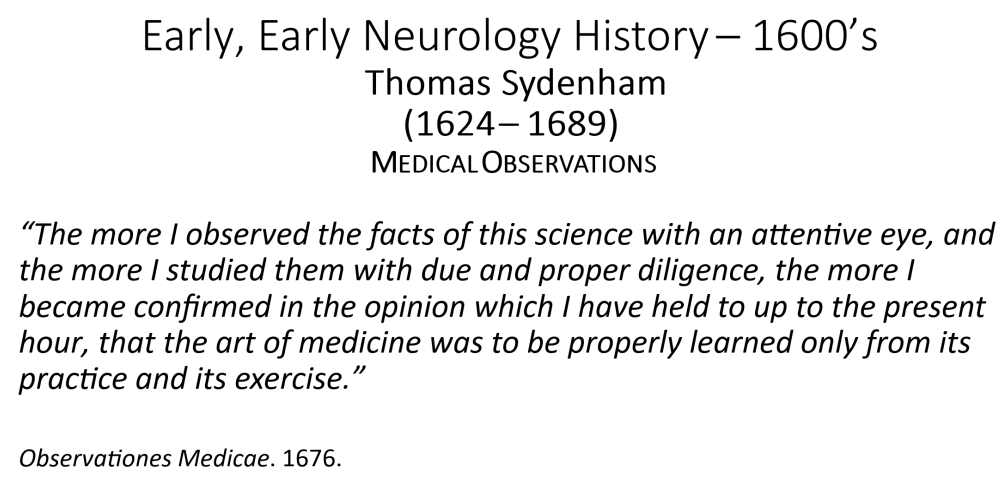
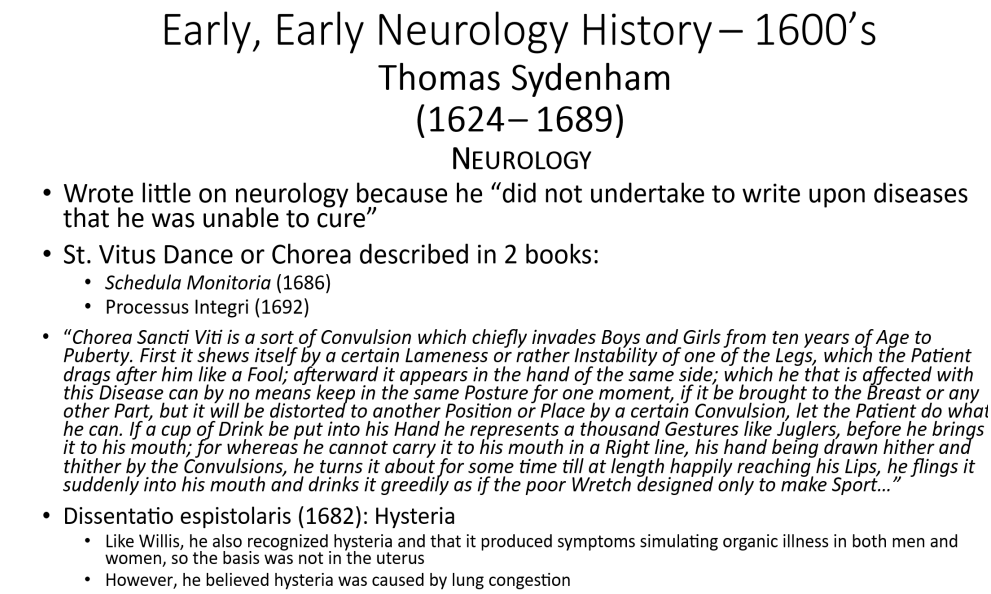


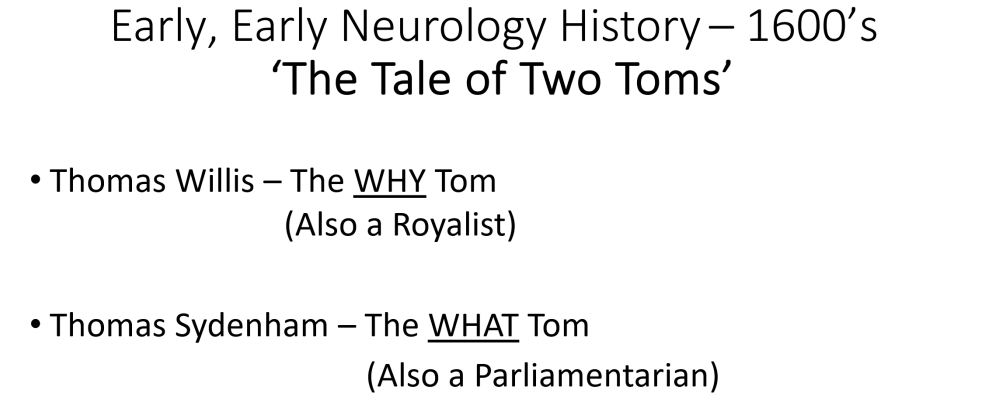
Figure 6



Idly, sometimes a Speechlessness and Immobility, with obscure or no Pulse, and a Cadaverous aspect, sometimes Convulsive Motions rais'd in the face or limb, and sometimes in the whole body.... I have observed those symptoms in Girls before the time in puberty and in old Women, and men are sometimes troubled with such kind of Passions, instances of which are not wanting. The cause of these Symptoms must not be imputed to the Ascent of the Womb, and to Vapors of the Blood into the Lungs, as the Learn'd Hughmore has Judg'd: But we say that the affect call'd Hysterical, chiefly primarily Convulsive, and depends primarily on the Brain".

The other Tom is Thomas Sydenham, sometimes called the English Hippocrates (Figure 4). He also went to Oxford around the same time as Willis, but he sided with the Parliamentarians when the civil war broke out in 1642. He joined the army during college. His whereabouts were unknown for some time during the War and under the Protectorate of Oliver Cromwell who ruled England until his death in 1658. The monarchy was restored under Charles II in 1661. Thomas Sydenham began practicing medicine in London but when the plague struck in 1665, he moved to Cambridge to complete his Doctorate in Medicine. While in Cambridge, he wrote the first book on the method of treating fevers,[14] dedicating it to Robert Boyle, another founder of the Royal Society of London, who with Robert Hooke, invented the air pump/vacuum. Boyle is probably

Figure 7



most famous for describing the inverse relationship between gas and volume, Boyle's Law. By 1676 he had written four more descriptive, practical medicine books which were observational, without scientific hypotheses. Sydenham emphasized careful history and examination rather than theory. He did not dispense drugs. His therapies usually involved exercise, cooling, and diet. He did not focus on research involving pathologic data, as he believed pathology could confuse physicians. Therefore, he was the opposite of Thomas Willis. Most considered him a better clinician than Willis but less scientific. I think of him as the original William Osler.

In his book *Medical Observations,*[15] Sydenham observed that the art of medicine was properly learned only from practice and exercise (Figure 5).

He did not publish much in neurology, avoiding topics he could not cure. He is however well known for describing chorea in two of his books,[16,17] with long descriptions of men and women suffering from what we now call "Sydenham's chorea", and he compared it to the movements in St Vitus' dance (Figure 6).

Thomas Sydenham, like Thomas Willis wrote about hysteria,[18] and also observed that it occurred in men and woman and thus did not believe the older concept that the source of hysteria was the uterus. However, he believed the cause was lung congestion while Willis believed hysteria originated in the brain and was thus a neurologic disorder.

So we have the tale of two Toms. Thomas Willis was the "why" Tom and a Royalist, while Thomas Sydenham was the "what" Tom and a Parliamentarian (Figure 7). I don't think their politics had anything to do with their "why" or "what" mentality, but we see scientists and physicians over time split into these two categories: the "why" explorers and the "what" explorers. I have always considered myself more of a "what" explorer; maybe the "why" explorers are a little smarter. I do wish I could be more of a Tom Willis rather than a Tom Sydenham.

This is the end of this brief history of neurology lecture on the "Tale of Two Toms".

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Dear Dr. L: ALS

Ariah Leday, MD

McGovern Medical School at UTHealth Houston

Dear Dr. L,

Is it strange that I feel blessed?
You can't lose what you never had,
and I thank God I lost so much.

I thank God for the beach:
for my toes touching sand and legs riding waves,
and the coolness of the breeze hitting water on my skin.
Those waves washed me clean,
now replaced by hands that are not my own
but love me all the same;
and I'd take those hands over the ocean any day.

I thank God for my Country:
for the strength to fight a battle bigger than myself
and stand for something before falling for anything.
Some may think that the wheels of my chair
restrict me from standing up for my beliefs,
but it's funny how the body learns to compensate,
how the loss of one thing becomes the gain of another,
and my mind took on the strength my body once had;
my thoughts run faster than my legs ever could,
and even when my voice fails me,
my mouth still works just fine.

I thank God for my voice:
singing was never my strong suit,
but I learned to perfect my tone.
People would rather hangout with an honest jerk
than a kind liar,
so I choose to be honest even when it turns jerk.
My voice may have faded,
but my character continues to speak for itself–
after all, its "actions over words",
and my actions are louder than my voice could ever carry my words.

I thank God for my music:
the soothing sound of the guitar,
the feeling of the strings,
the vibration of the chords–
they never truly leave you.
I still hear music in the voices of my loved ones
and feel the same rhythmic vibrations in their laughter;
and the rhythm in their heartbeat
plays the most beautiful tune.
My fingers could never replicate the same songs,
even before they began to ignore my commands.

I thank God for my daughters:
I've never known a 20-year-old to live in a 10-year-old's body,
or a 4-year-old to plan a heist,
but the maturity speaks for itself.
My daughters will always be my babies,
even after I lost the ability to carry them;
and yet, I will always carry them with me.
My fight turned fist to knowledge,
and I protect them more by teaching them,
and somehow simultaneously, they teach me
how to protect them better every day.

I thank God for my marriage:
the one thing I never lost.
My wife vowed "for better or worse,"
and somehow still made my "worst" feel better.
Her arms hold me up,
and her legs guide my steps.
I would call her perfect,
but she does have one flaw–
in how she keeps her word.
This is the only thing I'd ever change about her,
because this disease has changed the man
she made that promise to,
and she deserves all the things I lost.
I see the loving pain in her eyes
and the struggle she has with watching me struggle,
and this becomes the thing I miss the most:
the moments I'll never have with her.
A future of smiles and laughter
stolen without explanation.
She could easily find another man
who doesn't have to be so grateful for losing so much,
but while I'm forced to live through my worst,
my wife chooses to give me her best.
And I thank God for her best
because it's the greatest blessing He's ever given me.

#1212 Safety, β-Sarcoglycan Expression, and Functional Outcomes Following Bidridistrogene Xeboparvovec Treatment in Patients With LGMD2E/R4: VOYAGENE 18-Month Results

A.M. Connolly[1,2], M.P. Coughlin[3], A. Haile[3], J. Thomas-Ahner[3], P. Lebahar[3], T. Feng[3], L.R. Rodino-Klapac[3], O. Rogers[3], H. Stevenson[3], R.S. Finkel[4]

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Introduction: Limb-girdle muscular dystrophy 2E/R4 (LGMD2E/R4) is caused by pathogenetic variants in the beta-sarcoglycan (*SGCB*) gene leading to muscle loss. Bidridistrogene xeboparvovec, an adeno-associated virus vector that delivers the full-length SGCB transgene, has shown biologic efficacy and an acceptable safety profile.
Objectives: To present VOYAGENE (SRP-9003-102; NCT05876780) 18-month data evaluating bidridistrogene xeboparvovec treatment in ambulatory and nonambulatory participants with LGMD2E/R4.
Methods: Six participants (aged 17–29 years; 1 ambulatory and 5 nonambulatory; 2 females) received a single infusion of $7.41x10^{13}$ vg/kg bidridistrogene xeboparvovec. Primary endpoints were treatment-emergent adverse events (TEAEs) and day 60 SGCB expression in muscle biopsy via immunofluorescence (IF) and Western blot (WB). Secondary endpoints were day 60 muscle vector genome copies, North Star Assessment for LGMD (NSAD), and Performance of Upper Limb (PUL) 2.0 scores by month 60. Other endpoints included changes in forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and creatine kinase (CK) levels through month 60.
Results: No serious TEAEs, discontinuations, or deaths were noted. All participants had TEAEs; most were grade 1 (n=87/153) or 2 (n=63/153), with mostly mild/moderate treatment-related TEAEs (grade 1–2: 40/43; grade 3 [severe]: 3/43). At day 60, muscle biopsy showed increases in SGCB-positive fibers by IF and expression by WB; vector genome DNA was detected in myofibers in all participants. Over time NSAD, PUL 2.0, FVC, and FEV_1 remained stable and participants had reduced CK levels.
Conclusions: These findings show partial restoration of SGCB expression after bidridistrogene xeboparvovec treatment in ambulatory and nonambulatory LGMD2E/R4 individuals.
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Disclosures: AMC has served on an advisory board for Sarepta Therapeutics, Inc., unrelated to this work. MPC, AH, JTA, PL, TF, LRR-K, OR, and HS are employees of Sarepta Therapeutics, Inc., and may own stock/options in the company. RSF has served on an advisory board and on a data safety and monitoring board for Sarepta Therapeutics, Inc., unrelated to this work.

#1170 JOURNEY MRI Sub-Study: Baseline Characteristics of Limb-Girdle Muscular Dystrophies 2E/R4, 2D/R3, 2C/R5

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Introduction: Sarcoglycanopathies, accounting for ~15% of limb-girdle muscular dystrophies (LGMDs), are characterized by loss of healthy muscle fibers. However, data on the natural history of LGMDs are limited.
Objectives: To evaluate skeletal muscle magnetic resonance imaging (MRI) in a subset of participants from JOURNEY (NCT04475926), a global, prospective, longitudinal study of the natural history of participants with LGMD2E/R4, 2D/R3, 2C/R5, and 2A/R1.

Methods: MRI was used to characterize skeletal muscle structure and physiology in patients with a sarcoglycanopathy subtype (2E/R4, 2D/R3, 2C/R5).

Results: As of February 2025, baseline MRI data were available for 55 participants; 60.0% were female, and 61.8% were ambulant at baseline. The mean (SD) age was 19.4 (12.89) years for ambulatory participants and 25.5 (14.31) years for nonambulatory participants. For those with data available, lean muscle volume (LMV) was consistently higher in ambulatory participants compared with nonambulatory participants across LGMD subtypes and muscle groups (deltoid, anterolateral lower leg, and quadriceps). Muscle fat fraction (MFF) was generally higher in older ambulatory participants across LGMD subtypes and muscle groups and was highest in nonambulatory participants. Quadriceps generally had the highest mean LMV and MFF values among the muscle groups in both ambulatory and nonambulatory participants.

Conclusions: Overall, baseline muscular MRI data in a subset of JOURNEY participants indicate a more progressed degeneration of affected muscles in older and/or nonambulatory individuals, compared with ambulatory individuals with subtypes R4/2E, R3/2D, and R5/2C. These results support further investigation of muscle MRI as a potential endpoint in LGMD clinical trials.

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Disclosures: LPL, HS, GS: Employees of Sarepta Therapeutics, Inc., and may own stock/options in the company. KGC: Received speaker/advisory board honoraria from Alexion, Alnylam, Amicus Therapeutics, argenx, Biogen, CSL Behring, Ipsen, Janssen Pharmaceuticals, Lupin, Pfizer, Roche, Sanofi Genzyme, and UCB, and research funding from CSL Behring and Roche. CMP: Participated in advisory boards and as a consultant for Biogen, Genentech/Roche, Novartis Gene Therapies, Sarepta Therapeutics, Inc., and Scholar Rock. Served as a speaker for Biogen. Served as principal investigator of studies sponsored by Astellas, Biogen, Biohaven, CSL Behring,

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#1210 Long-Term Safety and Tolerability of Casimersen Treatment in Patients With Advanced DMD

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Introduction: In study 4045-101 (NCT02530905), casimersen demonstrated safety and tolerability in patients with Duchenne muscular dystrophy (DMD) amenable to exon 45 skipping, which represents about 8% of all patients with DMD.

Objectives: To evaluate the safety and tolerability of casimersen treatment in patients with advanced DMD for up to 6 years as observed in the open-label long-term extension (LTE) study (study 4045-302; NCT03532542) and study 4045-101.

Methods: Patients with advanced DMD (defined as nonambulatory or unable to walk ≥300 meters on the 6-minute walk test) were enrolled in study 4045-101. Patients who completed study 4045-101 were included in the LTE and continued receiving casimersen 30 mg/kg intravenous infusion once weekly. Adverse events, clinical laboratory tests, and cardiac assessments were monitored.

Results: Of the 12 patients enrolled in study 4045-101, 11 (91.7%) continued in study 4045-302. The mean (SD; range) duration on treatment was 5.7 (0.99; 2.5-6.2; n=12) study years. Throughout both studies, treatment-emergent adverse events (TEAEs) were generally mild (87%), unrelated to treatment (97%), and decreased during the LTE. Over 6 study years, four patients experienced 14 serious TEAEs; none were related to treatment. The most common TEAEs were nasopharyngitis (75%), headache (58%), and cough (50%). No patterns or trends in hematology, coagulopathy, chemistry, or other clinical laboratory parameters were observed. During the LTE study, no discontinuations, port-related infections, or dosage reductions were reported, and no casimersen-related cardiac or kidney toxicity signals were identified.

Conclusions: Over 6 study years, casimersen was well tolerated and demonstrated a manageable safety profile, consistent with previous clinical and real-world experience, supporting the use of casimersen in patients with advanced DMD.

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