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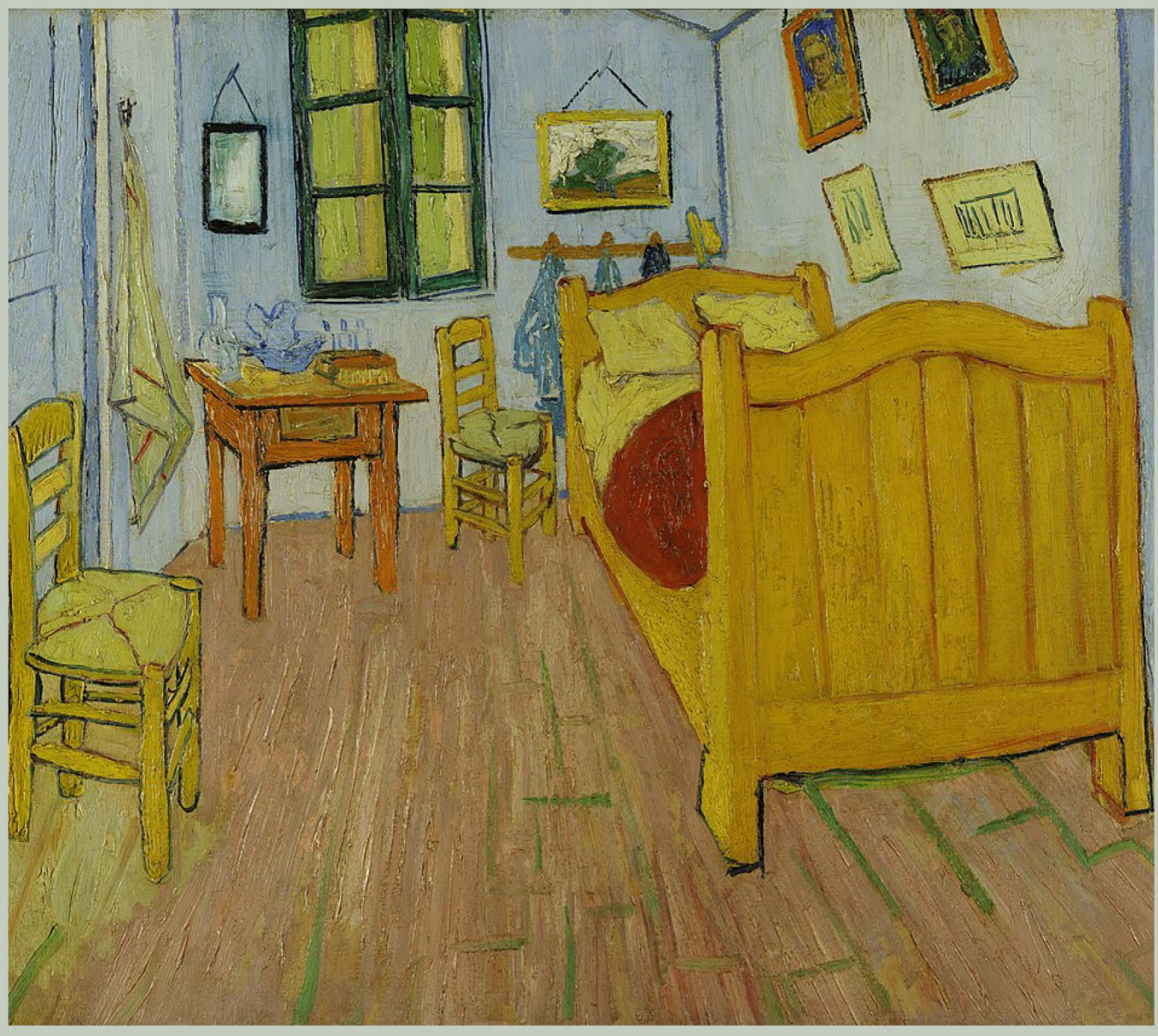

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Cover Image: *Bedroom in Arles* by Vincent van Gogh, c. 1888.
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RRNMF Neuromuscular Journal would like to acknowledge the following individuals for reviewing manuscripts for the past year:

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Message from the Founding Facilitator for Volume 5, Issue 1

Richard J. Barohn MD

Welcome to the first issue of 2024: Volume 5, Issue 1. Here is what is in this issue:

Two excellent editorials from our recuring authors regarding problems facing our health care delivery systems and society in general. Drs. Josh Freeman and Donald Frey are both leaders in family medicine and former chairs of departments of family medicine. Dr. Freeman discusses how and why the number of primary care physicians is falling, in part due to inadequate reimbursement, and he gives some ways the Center for Medicare and Medicaid Services (CMS) could provide some relief for this problem. Dr. Frey takes on the issue of the national minimum wage and asks, "what does it take to make a living wage?"

In the *New Stuff* category, our colleagues at the University of Iowa and the Iowa City Veterans Affairs Medical Center compared demographic, treatment, and survival data on ALS patients from the Iowa VA Medical Center with data published by other ALS clinics across the US and Europe. They conclude that the length of survival of patients in the VA clinic was comparable to these other multidisciplinary clinics. They also conclude that multidisciplinary clinic care provides better outcomes than care in general neurology clinics. Their data also suggests that edavarone may provide some survival benefit for ALS patients. A second manuscript on ALS comes from three leaders in the field: Dr. Bedlack at Duke, Dr. Heitzman in Dallas, and Dr. Sheffner at Barrow Neurologic Institute in Phoenix, AZ. They asked ALS clinicians to complete a survey regarding their attitude on which FDA approved drugs should be used in ALS patients and rank the barriers to getting patients on each drug. Clinicians also provided responses regarding the need for prior authorizations and denials and delays in getting prescriptions approved. They conclude insurance barriers are the main reason preventing large portions of ALS patients who should be taking edavarone and sodium phenylbutyrate/taurursodiol from actually being on these medications, and other useful insights facing clinicians and ALS patients. The final manuscript in the *New Stuff* section is by the University of Kansas neuromuscular group and myself and describes a pilot study of phenylbutyrate used in inclusion body myositis. We were able to demonstrate that phenylbutyrate is tolerated and safe in this population of patients and hope this pilot study will lead to a larger randomized controlled trial.

In the *Clinic Stuff* section we publish two nice case reports. One is from our colleagues at UT Southwestern, led by Dr. Bhai (one of the journal's associate facilitators) and his team that included several students (Ahmad, Govil, and Modi) and describes a case of rhabdomyolysis and exercise intolerance in a middle-aged man. They present the case as a diagnostic problem that posed key questions, to which they uncover answers. The elegant work-up ultimately reveals the diagnosis of McArdle's disease. We were pleased to receive a manuscript from India by Drs. Sankalp Mohan and Megha Dhamne which describes two cases that raises the quandary of distinguishing between acute and chronic inflammatory demyelinating polyneuropathy.

Finally, in the *Looking Back/Looking Forward* section we publish two rather unusual review articles that emanated from a longstanding course on neuromuscular disease that I have been involved in with Drs. Mazen Dimachkie, Todd Levine, Jonathan Katz and, more recently, David Saperstein. We began conducting this course "on the road" many years ago and delivered it dozens of times throughout the USA and Canada. During COVID, we naturally switched the course to Zoom, where it has remained. The course was recorded, and these are the first edited "transcripts" along with figures that cite the power point slides we used in the course. When you read these reviews, envision one of the authors delivering this as a lecture, which is how it was originally presented. It is conversational, in the first person. The first lecture is titled "Pattern Recognition of Neuropathy and Neuronopathy: 7 Questions / 11 Patterns." I first developed this pattern recognition approach to neuromuscular disease in the 1990s. Over the years we have made some modifications and, in this version, we have expanded the approach from the prior 6 questions / 10 patterns. To paraphrase the great William James, MD who said, "The rivalry of the patterns is the history of the world," the talk concludes "The recognition of the patterns is the key to understanding neuromuscular disease." The second review is on the laboratory approach to testing in neuropathy and neuronopathy and emphasizes that one must start with the clinical pattern, which will guide the clinician in deciding the laboratory tests to order. All the course teachers are equal authors on these publications and, at any given time, any of the authors could deliver one of the dozen lectures, so we hope to continue publishing further review articles based on course transcripts. This course has been an exciting journey for all involved. We hope that by publishing these lectures we can make them available to a wider audience in a meaningful way. Finally, I would like to thank Lauren Peck, a student at the University of Missouri, who has served as the undergraduate student editor for the journal and who provided immense help in manuscript preparation for these course publications.

For the cover art in this issue, I have chosen the famous painting Vincent van Gogh painted of his bedroom at Arles – "The Bedroom At Arles," 1888. His bedroom is so simple and in many ways heartbreaking. A true classic of art.

RRNMF Neuromuscular Journal facilitators meeting prior to publishing Volume 5, Issue 1.

Richard J. Barohn, M.D, Facilitator In Chief and Founding Facilitator; Yuebing Li, M.D., Associate Chief Facilitator; Salman Bhai, M.D., Associate Chief Facilitator; Jiji Oufattole, Managing Editor Facilitator; Himavarsha Kincharla, medical student facilitator; Michael Sherby, medical student facilitator; Alexandria Spurgeon, medical student facilitator; Marianne Reed, publishing facilitator; Eric Bader, publishing facilitator.

Not pictured: Michael T. Pulley, M.D. Ph.D., Associate Chief Facilitator; Farrell Landwehr, medical student facilitator, Lacey Raper, medical student facilitator

Primary Care, Private Equity, and Profit: How to ensure poor quality care for the American people

Joshua Freeman, MD

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

I -- and many others -- have written (frequently and recently) about the abuses of for-profit companies, especially private equity companies and "non-profits" that act like for-profits in health care (Private equity, private profit, Medicare and your health: They are incompatible, May 11, 2023; Privatizing Medicare through "Medicare Advantage" and REACH: The Wrong Way to Go!, Jan 20, 2023; "Private Equity": Profiteers in nursing homes, Medicare Advantage, DCEs, and all of healthcare, Sept 16, 2022). But despite our efforts, it doesn't get any better. Indeed it gets worse.

Drs. David Himmelstein, Steffie Woolhandler, Adam Gaffney, Don McCanne, and John Geyman, leaders in the campaign for a national health insurance plan (e.g., Medicare for All), published an article 18 months ago in 'The Nation' (March 31, 2022) titled 'Medicare for All is Not Enough'. They go through the ways in which the ownership of our health system has changed, particularly over the last decade, to focus on profit for the private owners rather than improving "health care". That is to say, while a single-payer Medicare for All program would likely limit the considerable negative impact that for-profit insurance companies wreak on our collective health, as long as for-profit companies continue to increasingly own our actual health delivery systems (in the form of hospitals, nursing homes, pharmacies, and physician practices), those single-payer dollars from such a Medicare for All program would flood into investors' pockets rather than patient care.

Insurance companies like United Health and giant pharmacy firms like CVS own large portions of our practice and health delivery sector. At least as terrifying is the role of private equity companies and investors, with their "buy 'em and burn 'em" approach to acquisition and profit, in taking over our delivery system. As the authors state:

> *At least UnitedHealth and CVS plan to stay in business for the foreseeable future, and may be constrained by the worry that substandard care will damage their reputation. Private equity companies face no such constraints. They promise investors quick profits, and often sell off the businesses they've bought within five years, often after stripping their assets and loading them with debts that hobble future operations.*

On top of who will *own* our care provision, there also is the issue of who will provide the care. Most developed countries, with more rational health delivery systems, rely on primary care physicians and other clinicians far more than the US does. In those other countries primary care is at least 30-40% of the physician workforce, while here it is closer to 20% and dropping, an issue I have written about often (see, for example, What is the problem with Primary Care? The US health system!, March 22, 2022). Primary care clinicians – family physicians, pediatricians, and general internists, and the NPs and PAs who work with them – can provide not only cost-effective care but care that is comprehensive, continuous, and reassuring to people and families because they know the person who is providing it and have a relationship with them. And the cost-effectiveness is not (only) about the fact that they earn less money (see below) but because they are in a position, as a result of taking care of the "whole person" and having a long-term relationship, to more wisely utilize resources when necessary. Nonetheless, there is a definite shortage of primary care clinicians, as anyone who has tried to find one recently can testify, because their physicians moved, or retired or had their practice bought out by a large company like Optum (a subsidiary of UnitedHealthcare, which has become UHC's major profit center as documented by former insurance executive Wendell Potter in his "Health Care Un-covered" substack), or, sometimes in response, their physician moved into a "concierge" or "boutique" practice. Elisabeth Rosenthal, editor of Kaiser Health News, notes in a recent piece in the Washington Post, "The Shrinking Number of Primary Care Physicians is Reaching a Tipping Point", that "fewer medical students are choosing a field that once attracted some of the best and brightest because of its diagnostic challenges and the emotional gratification of deep relationships with patients." And she makes the important point that:

> *One explanation for the disappearing primary-care doctor is financial. The payment structure in the U.S. health system has long rewarded surgeries and procedures while shortchanging the diagnostic, prescriptive and preventive work that is the province of primary care.*

Don't forget that one. Rosenthal discusses the terrible experience of colleague Bob Morrow, MD, who, under financial pressure, finally had to sell his decades-old practice and then left medicine, having watched how the new owner ran it (which he considered not in the best interests of the patients). Morrow is not a depressed person, but reading

about what has happened to him and thousands of other primary care doctors is enough to make one depressed.

In a data-driven "Scorecard" on primary care in the US, the Milbank Memorial Fund ranks it poorly on all fronts, although not based on the quality of the physicians:

> *This first national primary care scorecard finds a chronic lack of adequate support for the implementation of high-quality primary care in the United States across all measures, although performance varies across states. The scorecard finds:*
>
> 1. *Financing: The United States is systemically underinvesting in primary care.*
> 2. *Workforce: The primary care physician workforce is shrinking and gaps in access to care appear to be growing.*
> 3. *Access: The percentage of adults reporting they do not have a usual source of care is increasing.*
> 4. *Training: Too few physicians are being trained in community settings, where most primary care takes place.*
> 5. *Research: There is almost no federal funding available for primary care research.*

The Scorecard, created for Milbank by the Robert Graham Center (the policy arm of the American Academy of Family Physicians, AAFP) not only identifies these deficits, but also the importance of solving them for the health of the American people. One hundred million people without a primary care doctor who are only able to see a physician (if they can see *any* physician) who has a narrowly focused, disease-based practice is a real problem. We need those specialists for when we are diagnosed with a particular condition that requires their expertise, but they are often not knowledgeable about conditions outside it. Moreover, the primary care clinician does not only care for many conditions; much more important is that they care for the *person* who has those conditions.

The report also endorses the conclusions from the National Academy of Science, Engineering, and Medicine (NASEM) from 2021, recommending that the US:

> 1. *Pay for primary care teams to care for people, not doctors to deliver services.*
> 2. *Ensure that high-quality primary care is available to every individual and family in every community.*
> 3. *Train primary care teams where people live and work.*
> 4. *Design information technology that serves the patient, family, and interprofessional care team.*
> 5. *Ensure that high-quality primary care is implemented in the United States.*

Finally, for the moment, an effort is being made in Congress to try to increase the number of primary care clinicians. In an uncommon bipartisan effort, the bill is cosponsored by Bernie Sanders (I, VT), chair of the Senate HELP Committee, and Roger Marshall, MD, an OB/GYN and conservative Republican from Kansas, as reported by Jake Johnson in Common Dreams, Sept 14, 2023. Although bipartisan support is nice to see, the bill would, sadly, be unlikely to have a major effect on increasing the primary care physician supply. Funding in the bill – about $6 billion – would go mainly to Community Health Centers (CHCs), especially Federally-Qualified Health Centers (FQHCs). These centers provide care to lower-income people and communities where access to other clinicians is difficult. Republicans like them because they are not actually "government" programs, but responsible only to their boards of directors. These centers often rely heavily on primary care, and expanding them will increase the number of jobs for primary care clinicians. However, such an expansion would do nothing to increase the supply of those clinicians, such as by convincing medical students to enter family medicine, pediatrics, and general internal medicine instead of much higher-paying subspecialties.

This problem is a lot about money, as the Milbank report also mentions. Convincing students to enter fields where their income is likely to be a fraction of that of subspecialists (even if much better than that of most Americans) has become increasingly difficult, especially in the context of huge educational debt borne by these students (frequently over $250K), and in view of the lack of respect given by the medical profession and often society at large to primary care. And, not at all to be minimized, the takeover of so many practices by for-profit corporations and private equity, with situations like Dr. Morrow's becoming the norm rather than the exception. Some subspecialties make 2-3 or more times that of primary care doctors, which makes it increasingly difficult for students to decide to enter primary care. While some of these subspecialties have grueling work hours (e.g., general surgery) others have much more circumscribed work hours, often characterized by shift work with little call.

There IS certainly something the federal government could do. The Center for Medicare and Medicaid Services (CMS) sets the relative reimbursement for physician services (office visits, procedures, etc.) and virtually all private insurance companies reimburse based on multiples of the Medicare rate (traditionally more, but now often less). So, CMS could revise its fee schedule, increasing the relative value of primary care visits relative to procedures. Of course, there would likely be great opposition from other specialists; indeed the "RUC", a non-government committee that advises CMS on this ratio is completely dominated by subspecialists (Changes in the RUC: None.. How come we let a bunch of self-interested doctors decide what they get paid?, July 21, 2013). CMS is not required to follow the recommendations of the RUC, although it

usually does; CMS could ignore or adjust what the RUC recommends or reconstitute the membership of the RUC to have more primary care doctors. Primary care physicians do not need to make as much as the highest-paid subspecialists (indeed, neither do those subspecialists!), but the difference needs to be decreased. Studies have indicated that if primary care doctors earned 70% of what subspecialists do, income would no longer be a significant factor in specialty choice. [CITE]

Addressing this income gap is critical to increase the number of primary care clinicians. Of course, there is a lot more to do to improve healthcare, like getting for-profit corporations and private equity out of healthcare altogether.

For a "humorous" depiction of the takeover of primary care by for-profit companies like Optum, check out this short piece by the brilliant Dr. Glaucomflecken: https://twitter.com/i/status/1706339952857149895

What Does It Take to Make a Living Wage?

Donald R. Frey, MD

Originally published in Dr. Frey's blog "A Family Doctor Looks at the World." https://afamilydoctorlooksattheworld.com/what-does-it-take-to-make-a-living-wage/

Recently, I was asked by Nebraska Appleseed to write an opinion piece regarding a proposal to raise the Nebraska minimum wage. I immediately contacted my old friend John Kretzschmar, the Founding Director of the William Brennan Institute for Labor Studies at the University of Nebraska. He's spent a career dealing with the status of American workers and is far more knowledgeable than me. Together, we put together an article that appeared in the Omaha World-Herald. There's a link to the actual article below.

In the meantime, there's plenty about the minimum wage that simply couldn't be included in the paper because of space limitations. So here's some additional information.

First, the national minimum wage has been in place ever since the Federal Government instituted it in 1938 at a whopping 25 cents an hour. And ever since, its detractors have been trying to convince us that it's all some sort of communist plot.

Their thinking goes something like this. If employers have to pay their workers a little more, they'll either have to fire some of them or not hire anyone else. In other words, you can't raise wages and maintain profits.

It sounds plausible, but in each of the instances the minimum wage has been increased, no one has demonstrated any sort of consistent adverse effect on employment, incomes, or other major economic factors.

Every economic change, whether public or private, has winners and losers (just ask anyone who used to work at Sears, K-Mart, or Toys-R-Us). Short term, some jobs transition. The long-term consequences are usually different. And no one has been able to clearly demonstrate that increasing the minimum wage, or for that matter, even having a minimum wage in the first place, has had a negative effect on the economy.

But isn't raising wages substantially something that's bad for business? Is it even possible for a business to increase wages and increase profits at the same time?

History says yes. Enter the picture, Henry Ford.

In 1914, Ford shocked the world when the company announced that it was doubling the salary of its workers. That's right, doubling—as in a 100% raise.

In Ford's words "It is our belief that social justice begins at home. We want those who have helped us to produce this great institution and are helping to maintain it to share our prosperity. We want them to have present profits and future prospects. ... Believing as we do, that a division of our earnings between capital and labor is unequal, we have sought a plan of relief suitable for our business."

The Wall Street Journal, along with several other newspapers, went nuts. Ford had "committed economic blunders, if not crimes," the Journal's editorial page screamed. The conventional wisdom was that Ford would be bankrupt within a year.

Instead, the opposite happened. Turnover at Ford factories fell sharply, reducing training costs. Ford workers poured more money into the local economy. And many of them bought cars themselves—Fords.

Within two years, Ford doubled its profits.

Let's get one thing straight, though. The bit about Ford doing this from a concept of "social justice" is a load of crap. If you look up "nice guy" in the dictionary, Henry Ford's picture won't be there.

He was a bigoted, anti-Semitic racist. He even purchased his own newspaper, The Dearborn Independent, to spread his racist views. He hated the prospect of his workers organizing, and hired Harry Bennett, once described as "America's most reviled corporate thug" to ambush, beat, and sometimes kill workers who got out of line.

So what was the real reason Henry Ford massively raised wages in 1914? Simple. He knew it would be good for Ford.

Ford's decision proved the fallacy of the "Gee, if we have to raise wages we'll automatically lose money" thinking.

Economics is a complex field, full of human variables. It's not a hard-science, and every honest economist knows this.

A scientist can predict what will happen when two particles collide. But when humans with their own biases collide? That's much less predictable. It's what makes psychology, sociology, and economics more subjective, and in many ways, much more difficult.

And in all my reading, I've yet to find convincing evidence that paying a living wage ends up being an economic negative in the long term.

As a nation, that's where our focus really needs to be. On the future, and not just next quarter's report to corporate shareholders.

Survival and multidisciplinary amyotrophic lateral sclerosis clinic care at a United States Veterans Affairs medical center

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ABSTRACT

Introduction/Aims: The purpose of this work was to investigate survival outcomes in patients with amyotrophic lateral sclerosis (ALS) at our Veteran's Affairs Medical Center multidisciplinary ALS clinic and compare this to relevant data from several European studies.

Methods: Our sample consisted of 56 total Veterans (n=56; 54 males, 2 females) who had been seen between June 24, 2013 and February 1, 2021 at our multidisciplinary ALS clinic.

Results: The median survival time of our Veterans from symptom onset was 40.96 months (95% CI of 32.17, 76.07), and the median survival time from diagnosis was 23.77 months (95% CI of 18.64, 38.58). This was consistent with the literature. Further consistent with the literature is that multidisciplinary clinics, including ours, have survival advantage over general neurology clinics. Analyzing factors that contributed to this survival, we found a significant protective effect on survival from Edaravone use (HR = 0.32, p = 0.036). Otherwise, there was no significant effect on survival noted from use of percutaneous endoscopic gastrostomy (PEG), non-invasive ventilation (NIV), or Riluzole.

Conclusion: We found no significant difference in survival rates between our U.S. Veterans in our multidisciplinary ALS clinic and European multidisciplinary ALS clinics, and both are better than general neurology clinics. We also found that Edaravone use may provide some benefit to survival in this patient population.

Keywords: ALS, multidisciplinary, PEG, NIV, Edaravone, survival

1 Background

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder characterized by progressive loss of upper and lower motor neurons. There is currently no cure for ALS, and treatment options are limited and focus on slowing disease progression and improving quality of life. Until the recent approval of sodium phenylbutyrate and taurursodiol in September 2022, pharmacological therapy has been restricted to two FDA-approved drugs, Riluzole and Edaravone, which have shown modest benefit in survival time or benefit in delaying functional decline.[1,2] Symptom-based palliative care that includes use of non-invasive ventilation (NIV), percutaneous endoscopic gastrostomy (PEG), and assistive equipment has also been shown to positively modify outcomes in affected patients.[3,4]

Guidelines from professional societies in the United States (American Academy of Neurology [AAN])[5] and Europe (European Federation of the Neurological Societies [EFNS])[6] recommend ALS multidisciplinary clinics (MDCs) for managing patients with ALS to optimize healthcare delivery and prolong survival. This recommendation has Level B ("Probably effective") evidence, based primarily on two European studies from Ireland[7] and Italy[8] which showed an increase in time of survival from symptom onset and from diagnosis compared to similar patients managed in general neurology clinics (GNC). A single study from Italy[9] did not show a survival benefit from MDC care. MDC care is also recommended for improving quality of life in patients with ALS, based on a study from the Netherlands[10] with Level C ("Possibly effective") evidence. No similar studies have been done in the United States or with U.S. Veterans as the study population.

U.S. Veterans are at increased risk of developing ALS. In 2008, the U.S. Institute of Medicine released a report that determined that there was evidence of a relationship between military service and later development of ALS.[11] The evidence from reviewing 30 studies was too limited, however, and found "no strong evidence that any particular military exposure is associated with ALS etiology".[12] Persistent exposures to neurotoxicants that accumulate in the central nervous system, as well as service-linked trauma, are thought to contribute to ALS pathogenesis.[13]

In September 2008, the VA established ALS as a service-connected disability for Veterans who served 90 days consecutive active duty and who later were diagnosed with ALS.[14] In January 2012, the VA determined that the service-connection for ALS would automatically be rated as 100% disabling.[15] This service-connected disability status entitles Veterans with ALS to a substantial package of financial and healthcare benefits that includes providing free medical care, equipment, transportation, monthly compensation for work lost, and nursing home coverage.

In 2013, our VA Healthcare System developed an ALS multidisciplinary clinic (MDC). The multidisciplinary team

Table 1. Results for VA MDC together with relevant results from comparison studies. VA = Veterans Affairs medical center; PEG = percutaneous endoscopic gastrostomy; NIV = noninvasive ventilation; MDC = multidisciplinary clinic; GNC = general neurology clinic; N/A = not applicable; * *Respiratory subtype also included generalized onset disease causing relatively large number*

	Traynor et. al. 2003 [7]	Chio et. al. 2006 [8]	Zocollela et. al. 2007 [9]	Paipa et. al. 2019 [16]	Aridegbe et. al. 2012 [17]	Martin et. Al. 2017 [19]	VA MDC
Total number of patients (n) included in each cohort	82	221	84	344	254	330	56
Mean age at symptom onset (years)	59.0	60.8	63.5	62	62.6	58.1	64.9
Mean age at diagnosis (years)	60.1	N/A	64.2	N/A	N/A	N/A	66.5
Delay to diagnosis from symptom onset (months)	13.0	N/A	N/A	10	16.6	12.0	16.5
Mean age at death (years)	61.95	N/A	65.7	N/A	N/A	N/A	71.4
Percent limb onset	58.5% (N=48)	N/A	75% (N=63)	66.65% (N=229)	73% (N=185)	73.6% (N=243)	60.7% (N=34)
Percent bulbar onset	34.1% (N=28)	N/A	19% (N=16)	29.9% (N=103)	27% (N=69)	25.5% (N=84)	17.9% (N=10)
Percent bulbar *p* value vs. VA	0.0515	N/A	>0.9999	0.0776	0.1765	0.2428	Reference
Percent respiratory onset	7.4% (N=6)	N/A	6% (N=5)	3.5% (N=12)	N/A	N/A	21.4% (N=12)*
Percent PEG tube use	N/A	32% (N=unknown)	6% (N=5)	32.3% (N=111)	26% (N=66)	N/A	46.4% (N=26)
Percent PEG *p* value vs. VA	N/A	N/A	<0.0001	0.0480	0.0035	N/A	Reference
Percent NIV use	6.1% (N=5)	15.4% (N=unknown)	2.5% (N=2)	48.8% (N=168)	29% (N=73)	13.3% (N=44)	80.4% (N=45)
Percent NIV *p* value vs. VA	<0.0001	N/A	<0.0001	<0.0001	<0.0001	<0.0001	Reference
Percent use of Riluzole	98.8% (N=80)	N/A	66% (N=55)	88.7% (N=305)	89% (N=222)	60.9% (N=201)	44.6% (N=25) (53.6% used a medication)
Riluzole *p* value vs. VA	<0.0001	N/A	0.0144	<0.0001	<0.0001	0.0275	Reference
Median time of survival from symptom onset in MDC	N/A	1080 days (35.5 months)	26 months	40 months	36.8 months	N/A	1239 days (40.96 months)
Median time of survival from symptom onset in GNC	N/A	775 days (25.5 months)	33.3 months	34 months	28 months	N/A	N/A
Median time of survival from diagnosis in MDC	677 days (22.2 months)	N/A	17.6 months	N/A	19 months	21.6 months	719 days (23.77 months)
Median time of survival from diagnosis in GNC	448 days (14.7 mos)	N/A	18 months	N/A	11 months	N/A	N/A

at our MDC includes a physiatrist, specialist nurse, social worker, dietitian, psychologist, occupational therapist, physical therapist, speech and language pathologist, pulmonologist and respiratory therapist, and a palliative care physician. (Table A.1 in supplement)

In this retrospective chart review, we evaluated data from the ALS MDC at our VA medical center as it more closely resembles that of the European model in terms of access to and financial coverage of care compared to private practices in the United States. Outcomes regarding survival time, medication use, and symptom-based treatments of patients treated in MDCs were compared to those reported in prior studies.

2 Methods

2.1 Study Design

The previously mentioned studies on which current ALS multidisciplinary clinic recommendations from the AAN and EFNS are based were retrieved electronically using PubMed.gov.[7-10] By reviewing the references of these papers; searching PubMed using keywords "amyotrophic lateral sclerosis," "motor neuron disease," "ALS," and "multidisciplinary"; and using editorial suggestions, we also identified four newer studies from Paipa et al.[16], Aridegbe et al.[17], Rooney et. al.[18], and Martin et. al.[19]. Survival, intervention use, and type of ALS onset data reported for the multidisciplinary clinics in these studies is included in Table 1 except for the study by Rooney et. al. which did not include comprehensive survival data for the Irish multidisciplinary clinic studied. This data was recorded to be used for comparison with the corresponding data obtained from our VA MDC.

A list of VA MDC attendees from June 24, 2013 to February 1, 2021 was obtained from VA records. This list included a total of 56 patients (n = 56) which is consistent with the rarity of ALS and catchment area of our VA medical center. 41 of these patients were deceased on or before February 1, 2021. A retrospective chart review was then performed on our 56-patient cohort to identify patient gender; age at symptom onset; age at diagnosis; age of death (if applicable); onset type (bulbar, limb, or respiratory/generalized onset); use of a PEG; use of NIV, including continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), and/or average volume assured pressure support (AVAPS); use of Riluzole; and use of Edaravone. If only the month was noted for time of symptom onset or diagnosis, the first of the month was used as the date of symptom onset or diagnosis for age calculation. If only the year was noted for time of symptom onset or diagnosis, the first of the year was used as the date of symptom onset or diagnosis for age calculation. Of note, we defined the subtypes based on what the charts mentioned as the first symptom at onset.

2.2 Ethical Approval

This study was approved by the Institutional Review Board of our VA Medical Center (IRB # 202101656). A waiver of the requirement for informed consent was obtained because of the retrospective design of the study.

2.3 Statistical Analysis

For survival analysis, two patients with ALS in our sample were involved in the MDC from the beginning of the clinic and survived for the entire duration of the study. These observations were censored beginning on February 1, 2021, the last day that patients were monitored. A Kaplan-Meier survival curve was constructed to find the distribution of the survival times of the patients in our study. The median survival time for our study was determined, along with its corresponding 95% confidence interval (CI), and this was compared with the median survival estimates from the other studies of interest.

Pairwise differences for PEG and NIV use rates between our MDC and each of the other relevant studies with sufficient data were assessed using Fisher's exact test. To account for multiple comparisons, a Bonferroni correction was employed for the PEG and NIV rate comparisons, such that the alpha threshold for the PEG comparisons was $0.05/3 = 0.0167$, and the alpha threshold for the NIV, bulbar, and Riluzole comparisons was $0.05/4 = 0.0125$.

The impact of Edaravone on survival times was assessed using Cox proportional hazards models to determine a hazard ratio (HR). A multivariate model was constructed for both survival time from symptom onset and survival time from diagnosis, in which Edaravone was assessed, along with the effects of age and gender. Schoenfeld residuals were also obtained to ensure that the Cox model was appropriate for the analysis.

Results

3.1 Demographics

Our cohort was comprised of 56 Veterans (n = 56). There were two females (4%), which is consistent with our VA population.[20,21] Our results, together with results from the literature, are presented in Table 1.

3.2 Survival from Time of Symptom Onset and Time of Diagnosis

The median survival time from symptom onset and from diagnosis in our VA MDC was 40.96 months (95% CI of 32.17, 76.07) and 23.77 months (95% CI of 18.64, 38.58) respectively. The survival probability is plotted as a function of time from symptom onset in Figure 1.

Figure 1. Survival probability as a function of days from symptom onset and diagnosis

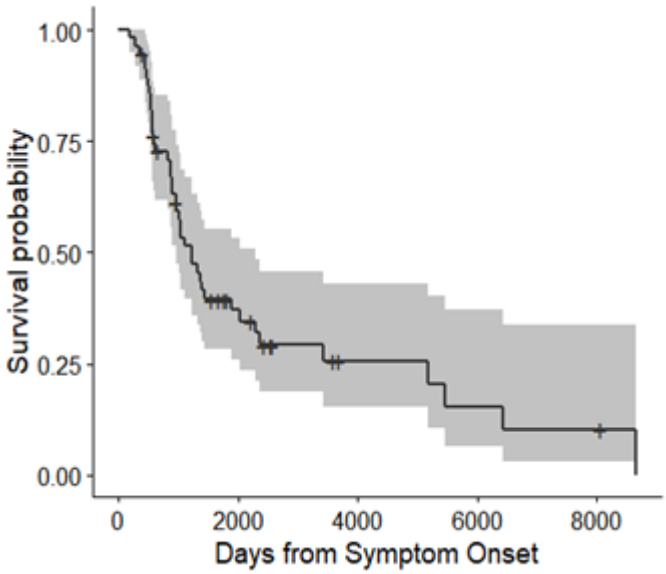

Figure 1a. Survival probability as a function of days from symptom onset

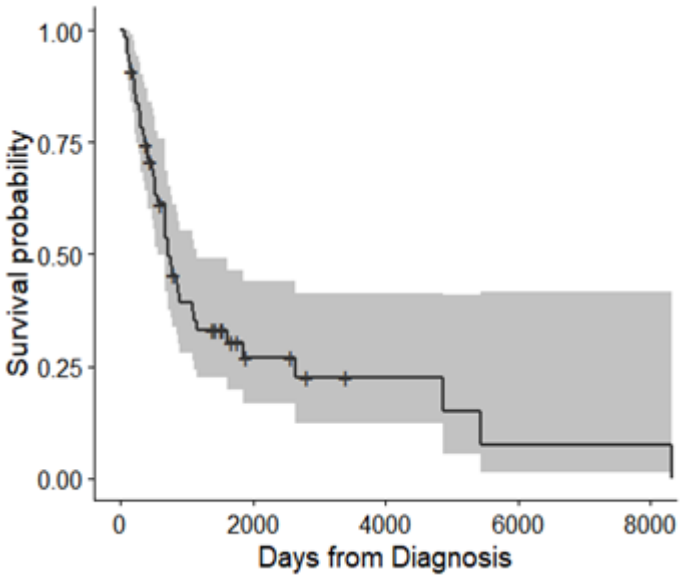

Figure 1b. Survival probability as a function of days from diagnosis.

3.3 Effect of Age and Gender on Survival

Using time to death from symptom onset as the outcome, and after adjusting for gender and Edaravone use, our model found age at symptom onset (Age_SO) to be a substantial risk factor (HR = 1.06, $p < 0.001$; Table 2). The Age_SO HR is interpreted as follows: at any given timepoint, the likelihood of a patient dying is 6% greater than that of a patient who is one year younger. This model found no noteworthy effect related to gender after adjusting for Edaravone use and age (HR = 0.79, $p = 0.80$; Table 2).

Table 2. Effect of age at symptom onset on survival, controlling for gender and Edaravone use

Characteristic	HR[1]	95% CI[1]	p-value
Edaravone	0.32	0.11, 0.93	**0.036**
Age at Symptom Onset	1.06	1.03, 1.10	<**0.001**
Gender			
F	—	—	
M	0.79	0.18, 3.40	0.8

[1]HR = Hazard Ratio, CI = Confidence Interval

3.4 Survival by ALS Subtype

The Cox proportional hazards model demonstrated that the location of symptom onset had an effect on patient survival from symptom onset. Specifically, patients who had limb onset subtype had greater lengths of survival from time of symptom onset relative to those with bulbar onset (HR = 0.26, $p = 0.002$). This effect remained significant after adjusting for Edaravone use, gender, and age at symptom onset (HR = 0.34, $p = 0.020$; Figure 2a; Table A.2a in appendix).

Similarly, survival from time of diagnosis was also longer in limb onset vs. bulbar onset. The results of the unadjusted effect of limb onset type on patient survival time from diagnosis, relative to bulbar onset were statistically significant (HR = 0.34, $p = 0.010$). When the model accounted for the effects of Edaravone usage, gender, and age at diagnosis, the effect of limb onset was similar, but no longer statistically significant (HR = 0.46, $p = 0.071$; Figure 2b; Table A.2b in appendix).

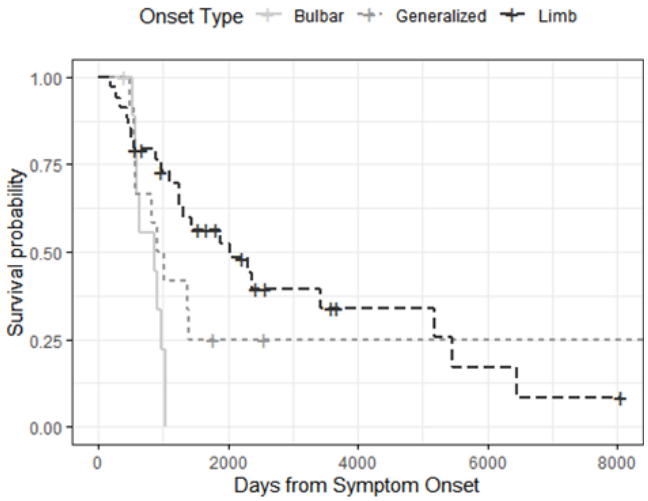

Figure 2a. Survival probability as a function of time from symptom onset by ALS subtype

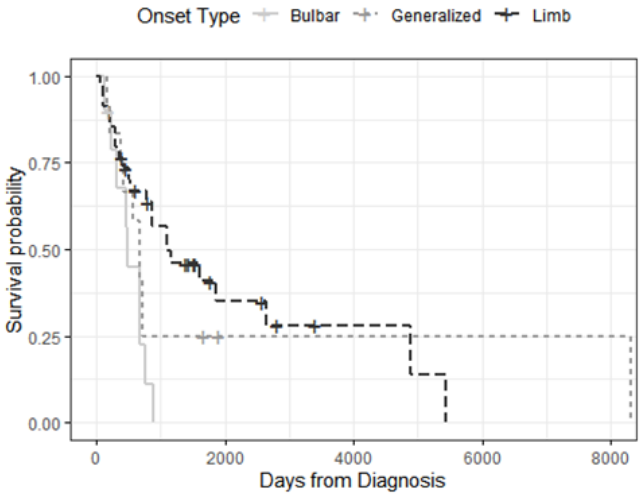

Figure 2b. Survival probability as a function of time from diagnosis by ALS subtype

3.5 Use of Equipment: PEG or NIV

The PEG use rate among patients in our study was 46.4%. If it was noted in a patient's chart that PEG had not been used yet, the data were analyzed as PEG not being used, although PEG might have been used at a later date. Figure A.3a and Table A.3a show the effect of PEG use on survival from symptom onset, and Figure A.3b and Table A.3b show survival from time of diagnosis (see appendix). In both univariate and multivariate (aka adjusted) models, we did not detect a relationship between PEG use and survival times from symptom onset (Table A.3c; see appendix) or diagnosis time (Table A.3d; see appendix).

80.4% of the patients in our study used NIV. In both univariate and multivariate (aka adjusted) models, we did not detect a relationship between NIV use and survival times from symptom onset (Table A.3e; see appendix) or diagnosis time (Table A.3f; see appendix).

3.6 Use of Riluzole

Riluzole was prescribed in 44.6% of our patients. We investigated a multivariate model (controlling for age and subtype), and the effect of Riluzole was not statistically significant in both survival from symptom onset (p = 0.8) and survival from diagnosis (p = 0.6); similarly, the univariate model also was not significant. (Figure A.4a-A.4b and Table A.4a-A.4b; see appendix).

3.7 Edaravone Effect on Survival

Fourteen of our patients (25% of our sample) were using Edaravone. When investigating the survival time from symptom onset, the Cox proportional hazards model found that Edaravone had a significant protective effect on our patient population (HR = 0.32, p = 0.036). The global Schoenfeld test of this model resulted in a p value of 0.9948, implying that the use of the Cox model is justified.

Using the Cox proportional hazards model to predict survival time from diagnosis, results were similar to those of survival from symptom onset. Edaravone is found to have a protective effect on the survival of our patient population (HR = 0.29, p = 0.023), while age at diagnosis was shown to be a risk factor (HR = 1.07, $p < 0.001$), and gender was not found to influence survival times (HR = 0.94, $p > 0.9$). The global Schoenfeld test of this model resulted in a p value of 0.9994, implying that the use of the Cox model is justified. Additionally, univariate Cox proportional hazards models were used to predict the survival time of patients with ALS from symptom onset (Table A.5a; see appendix) and diagnosis (Table A.5b; see appendix). In both instances, Edaravone usage is shown to increase survival times.

The effect of Edaravone on survival from symptom onset and diagnosis while controlling for age and gender of the patient is presented in Figure 3 and Tables 2 and 3.

Figure 3. Survival from Symptom Onset (SO) and diagnosis in patients on Edaravone vs patients not using it

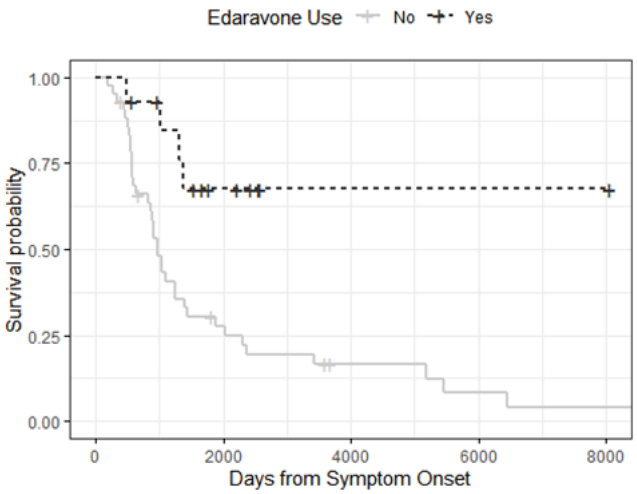

Figure 3a. Survival from Symptoms Onset in patients on edaravone vs patients not using it

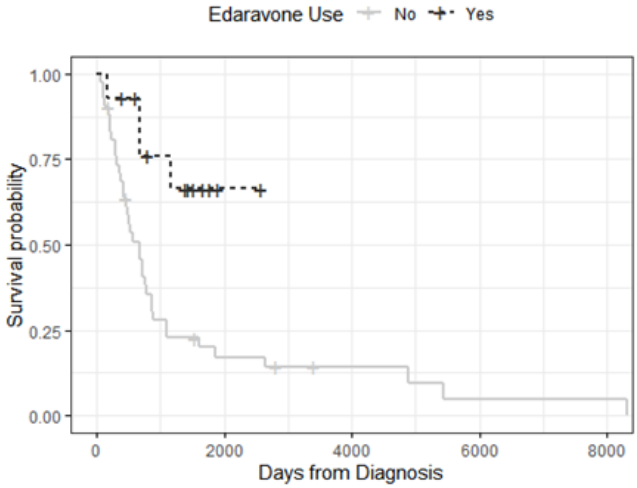

Figure 3b. Survival from diagnosis in patients using edaravone vs. patients not using it

Table 3. Effect of Edaravone on survival from time of diagnosis, controlling for age and gender

Characteristic	HR[1]	95% CI[1]	p-value
Edaravone	0.29	0.10, 0.84	**0.023**
Age at Diagnosis	1.07	1.03, 1.10	<**0.001**
Gender			
F	—	—	
M	0.94	0.22, 4.01	>0.9

[1]HR = Hazard Ratio, CI = Confidence Interval

4 Discussion

The median survival time of Veterans in our MDC from symptom onset was significantly greater than the median estimate provided in Zocollela et al.[9], whereas no significant difference is shown between the median survival time from symptom onset and the estimates provided in other similar studies.[7,8,16,17,19] Similarly, the median survival from time of diagnosis is significantly greater than the median estimate provided in Zocollela et al.[9] Apart from the Zocollela study,[9] all the other studies[7,8,16,17,19] showed that their MDC improved survival compared to the care provided at a general neurology clinic (GNC). The Zocollela study is one of the oldest studies (recruited in the 1990s), so it is possible their MDC did not provide the same level of care that is provided in MDCs more recently, such as fewer medications and less equipment support (Table 1). In the study by Chio,[8] their MDC used more NIV and PEG than what was used in their GNC; the MDC in Paipa[16] also used more PEG, NIV, and Riluzole vs. GNC; and similarly, the MDC studied by Traynor[7] used more NIV and Riluzole. Use of PEG, NIV, and Riluzole have all shown some benefit on survival,[22-24] but it is possible that the combination of these treatments, along with daily psychosocial support, contribute to improved survival in MDC clinics, with up to an additional 9-10 months in some cases.[7,8,23] Furthermore, quality of life was improved in patients with ALS in MDC clinics independent of the use of aids and appliances.[10,23]

Our results also agree with the hypothesis that MDC care improves median survival relative to GNC care. The 95% confidence intervals for our survival times were 32.17–76.07 for time of survival from symptom onset and 18.64–38.58 for time of survival from diagnosis. Comparing the time of survival seen in our study with that reported by GNCs in the included studies (data summarized in Table 1), our survival values fall outside of the range for survival from symptom onset reported for GNCs in Chio and Aridegbe[8,17] and outside of the range for survival from diagnosis reported for GNCs in Traynor, Zocollela, and Aridegbe.[7,9,17] The time of diagnosis is a more definite starting point than symptom onset and therefore possibly more likely to accurately reflect a difference.

4. 1 Survival by ALS Subtype

We found that Veterans who had limb onset ALS survived longer from time of symptom onset or time of diagnosis relative to those with bulbar onset ALS. This remained true even after controlling for Edaravone usage, gender, and age. Our findings are consistent with the literature where bulbar onset ALS is thought to have a poorer prognosis than spinal onset ALS (recorded as limb or respiratory/generalized onset in Table 1), although this can be variable.[25] Furthermore, we found no statistically significant difference in the number of bulbar onset cases in

our study versus all five relevant studies from which this was reported suggesting that our sample make up is consistent with the literature.

4. 2 Survival by Age and Gender

Our model found that age at symptom onset is a substantial risk factor and that at any given time point, the likelihood of a patient dying is 6% greater than that of a patient who is one year younger. This is consistent with the literature.[26] This model also found no noteworthy effect of survival based on gender. This is consistent with the literature, where most studies did not find a role for gender in the prognosis.[26]

4.3 Equipment Use

The rate of PEG use in our study was significantly greater than that of patients in the study from Zocollela et al. ($p < 0.0001$) and from Aridegbe et al. ($p = 0.0035$).[9,17] No significant difference was detected between PEG use rates from our study and the study from Paipa et al. ($p = 0.0480$).[16] Chio et al. and Martin et al. did not report the percentage PEG use.[8,19] We did not find that PEG use added survival advantage. Burkhardt et al.[27]found that PEG ($p < 0.01$) had a significant impact on survival. They initially did not find benefit for PEG use, but after adjustments for diagnostic delay, region of onset, predicted ALS-FRS (ALS-functional rating scale), gender, age at diagnosis, and BMI loss, they found significant benefit. We repeated a similar analysis but did not find a survival advantage. Although PEG use is widely accepted in ALS care to prevent starvation and dehydration and to improve quality of life, survival benefit of PEG is not universally demonstrated.[26]

The reason for increased PEG use in the VA MDC is not clear. In the VA MDC, PEG use is discussed early but generally, patients are not referred for the procedure until they have significant weight loss (>10%), dysphagia, aspiration, or fatigue with eating which is in accordance with AAN guidelines.[27] All patients are seen quarterly by nutrition, speech pathology, and pulmonology. Weights, pulmonary function tests, and bedside swallows are monitored quarterly. Video swallows are done when deemed indicated by speech pathology. Patients are referred to gastroenterology for consultation if/when they want to proceed with a PEG and they perform the procedure if they feel it is indicated. If patients choose a PEG, the procedure is performed when FVC is still >50%.

The percentage of our patients using NIV was greater than the percentage of NIV use in any of the other studies ($p < 0.0001$ for each comparison), but we did not find a survival advantage. This is consistent with the literature, where survival advantage was found in some studies,[28-32] but not universally.[33] It is possible that this result was confounded by NIV use for non-ALS purposes such as obstructive sleep apnea. Overall, there is a higher use of CPAP and BiPAP in the U.S., possibly due to a higher prevalence of sleep apnea in the U.S. vs. Europe. Therefore, we hypothesize that the percentage of NIV use in our sample is diluted by patients using NIV for other reasons, though we did not perform an analysis of who was started on NIV initially for alternative reasons and did not require adjustments based on weakness due to ALS progression.

4.4 Medication Use: Riluzole

Significant differences were detected in Riluzole use rates between our VA MDC and the studies performed by Traynor, Paipa, and Aridegbe et. al.[7,16,17] The difference between Riluzole use rates of our VA MDC and the studies performed by Zocolella and Martin et. al. was marginally significant,[9,19] but not statistically significant, after applying the Bonferroni correction for multiple comparisons.

This difference in Riluzole use is most likelyrelated to patient preference. All patients at the VA MDC are offered medications unless they have a contraindication to use. Since ALS care is palliative by nature, it is not unreasonable for a patient concerned about quality of life to decline Riluzole use given minimal clinical benefit. Some VA MDC patients used both Riluzole and Edaravone; 30 of 56 patients used either one or both medications (53.6%). Because our Riluzole use was very low, we could not detect survival advantage.

4.5 Medication Use: Edaravone

Our Cox proportional hazards model found that Edaravone had a significant protective effect on our patient population and improved survival from symptom onset, as well as from time of diagnosis (HR = 0.29, $p = 0.023$). No other identified study has reported Edaravone use in MDC.

Edaravone is a relatively newly approved medication for ALS and therefore was not included as a variable in any of the European comparison studies. A clinical trial published in 2017 showed benefit in reducing the decline in the ALS-FRS in well-selected patients with ALS,[2] but survival advantage has not been well-established. Two recent studies with small cohorts of 45 and 57 patients, both conducted in Japan, demonstrated evidence for improvement in survival with Edaravone use.[34,35] A larger retrospective review in the U.S. also showed survival benefit,[36] while a study conducted in Germany showed no survival benefit or slowing of clinical decline.[37] Twenty-five percent of our cohort used Edaravone and we were able to show a statistically significant increase in life expectancy in the patients that had used Edaravone relative to those who had not, though we did not record dosage or dosing frequency amongst these patients. We did not perform an analysis on comorbidities, other medication use, or personal opinions in the patients who opted to take Edaravone, though it seems possible that those patients who chose to take this medication preferred a maximum treatment approach as opposed to a comfort-focused approach. While this philosophy may confer survival benefit, it is beyond the scope of this retrospective review. Our data

may still contribute to recent findings that Edaravone may in fact prolong life in ALS patients.

Limitations

There are several limitations in our research. First, the diagnosis of ALS is clinical, often with the assistance of electromyography (EMG) to help support the diagnosis. The El Escorial criteria, which provide a unified set of ALS diagnostic criteria, were first published by the World Federation of Neurology in 1994.[38] These criteria remain a standard of diagnosis for ALS. Unfortunately, we do not know what criteria were used to make a diagnosis of ALS for the patients in our study, because most patients in the VA MDC were not diagnosed at the VA hospital but were initially seen by a non-VA neurologist. While all of the VA MDC referrals came from neurologists, making proper criteria usage more likely, we cannot say whether the patients in our cohort would be defined as having definite, probable, or possible ALS based on El Escorial criteria. A misdiagnosis could certainly affect survival data and should be mentioned. The most recent Gold Coast criteria has simplified the ALS diagnostic categories and would be used moving forward.[39]

Second, we lacked the exact date for onset of symptoms for most patients given that this date is generally subjective and based on patient history. We suspect this is not unique to our study since ALS is insidious.

Third, our clinic is a relatively small ALS clinic with less than 8 new patients added per year. It is not a typical multidisciplinary ALS center, and the findings might not be applicable to larger, much busier clinics as the amount of time available to each patient would be significantly higher in our clinic.

Finally, we did not compare our results to a local GNC, because the veterans with ALS in our study were enrolled only in the VA MDC. In the future, as veterans have options to go to community neurologists, our study will provide a basis against which to compare survival of veterans in VA MDCs vs. GNCs.

In conclusion, we found that Veterans enrolled in a US-based multidisciplinary ALS clinic had similar survival to those cared for at European MDCs, and both have survival advantage over those cared for by general neurologists reported in the literature. This becomes relevant if more Veterans choose to seek care outside the VA, in locations where only general neurologists exist. Fortunately, according to the recent Veterans Health Administration Directive 1101.07, Amyotrophic Lateral Sclerosis (ALS) System of Care, released on August 30, 2021, "Community care referrals will include approval for interdisciplinary ALS care".[40] Future research should compare ALS care at VA MDC versus that at academic center MDC and private general neurologists. We also showed agreement with recent literature suggesting that Edaravone was associated with a prolonged life expectancy.

Disclosure of conflict of interest

None of the authors has any conflict of interest to disclose.

Ethical publication statement

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

Data availability statement

Any data not published within the article will be available upon request.

References

1. Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. N Engl J Med. 1994;330(9):585-91. doi: 10.1056/NEJM199403033300901. PMID: 8302340.

2. Writing Group; Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2017;16(7):505-512. doi: 10.1016/S1474-4422(17)30115-1. Epub 2017 May 15. PMID: 28522181.

3. Khairoalsindi OA, Abuzinadah AR. Maximizing the Survival of Amyotrophic Lateral Sclerosis Patients: Current Perspectives. Neurol Res Int. 2018; 12; 2018:6534150. doi: 10.1155/2018/6534150. PMID: 30159171; PMCID: PMC6109498.

4. Oliver DJ. Palliative care in motor neurone disease: where are we now? Palliat Care. 2019; Jan 21;12:1178224218813914. doi: 10.1177/1178224218813914. PMID: 30718958; PMCID: PMC6348498.

5. Miller RG, Jackson CE, Kasarskis EJ, et al. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2009;73(15):1227-33. doi: 10.1212/WNL.0b013e3181bc01a4. PMID: 19822873; PMCID: PMC2764728.

6. EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis:, Andersen PM, Abrahams S, Borasio GD, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)--revised report of an EFNS task force. Eur J Neurol. 2012;19(3):360-75. doi: 10.1111/j.1468-1331.2011.03501.x. Epub 2011 Sep 14. PMID: 21914052.

7. Traynor BJ, Alexander M, Corr B, et al. Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996-2000. J Neurol Neurosurg Psychiatry. 2003; 74(9):1258-61. doi: 10.1136/jnnp.74.9.1258. PMID: 12933930; PMCID: PMC1738639.

8. Chiò A, Bottacchi E, Buffa C, et al. PARALS. Positive effects of tertiary centres for amyotrophic lateral sclerosis on outcome and use of hospital facilities. J Neurol Neurosurg Psychiatry. 2006; 77(8):948-50. doi: 10.1136/jnnp.2005.083402. Epub 2006 Apr 13. PMID: 16614011; PMCID: PMC2077622.

9. Zoccolella S, Beghi E, Palagano G, et al. ALS multidisciplinary clinic and survival. Results from a population-based study in Southern Italy. J Neurol. 2007; 254(8):1107-12. doi: 10.1007/s00415-006-0401-y. Epub 2007 Apr 13. PMID: 17431705.

10. Van den Berg JP, Kalmijn S, Lindeman E, et al. Multidisciplinary ALS care improves quality of life in patients with ALS. Neurology. 2005;65(8):1264-7. doi: 10.1212/01.wnl.0000180717.29273.12. PMID: 16247055.

11. Institute of Medicine. Amyotrophic Lateral Sclerosis in Veterans: Review of the Scientific Literature. Washington, DC: The National Academies Press.2006; https://doi.org/10.17226/11757.

12. Beard JD, Engel LS, Richardson DB, et al. Military service, deployments, and exposures in relation to amyotrophic lateral sclerosis survival. PLoS One. 2017;12(10):e0185751. doi: 10.1371/journal.pone.0185751. PMID: 29016608; PMCID: PMC5634564.

13. Re DB, Yan B, Calderón-Garcidueñas L, et al. A perspective on persistent toxicants in veterans and amyotrophic lateral sclerosis: identifying exposures determining higher ALS risk. J Neurol. 2022. doi: 10.1007/s00415-021-10928-5. Epub ahead of print. PMID: 34973105.

14. Office of the Federal Register, National Archives and Records Administration. (2009, November 3). 74 FR 57072 - Presumption of Service Connection for Amyotrophic Lateral Sclerosis. [Government]. Office of the Federal Register, National Archives and Records Administration. https://www.govinfo.gov/app/details/FR-2009-11-04/E9-26580

15. Office of the Federal Register, National Archives and Records Administration. (2011, December 19). 76 FR 78823 - Schedule for Rating Disabilities; Evaluation of Amyotrophic Lateral Sclerosis. [Government]. Office of the Federal Register, National Archives and Records Administration. https://www.govinfo.gov/app/details/FR-2011-12-20/2011-32531

16. Paipa AJ, Povedano M, Barcelo A, et al. Survival benefit of multidisciplinary care in amyotrophic lateral sclerosis in Spain: association with noninvasive mechanical ventilation. J Multidiscip Healthc. 2019;12:465-470. doi: 10.2147/JMDH.S205313. PMID: 31354285; PMCID: PMC6590410.

17. Aridegbe T, Kandler R, Walters SJ, et al. The natural history of motor neuron disease: assessing the impact of specialist care. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14(1):13-9. doi: 10.3109/17482968.2012.690419. Epub 2012 May 29. PMID: 22642305.

18. Rooney J, Byrne S, Heverin M, Tobin K, Dick A, Donaghy C, Hardiman O. A multidisciplinary clinic approach improves survival in ALS: a comparative study of ALS in Ireland and Northern Ireland. J Neurol Neurosurg Psychiatry. 2015 May;86(5):496-501. doi: 10.1136/jnnp-2014-309601. Epub 2014 Dec 30. PMID: 25550416.

19. Martin S, Trevor-Jones E, Khan S, Shaw K, Marchment D, Kulka A, Ellis CE, Burman R, Turner MR, Carroll L, Mursaleen L, Leigh PN, Shaw CE, Pearce N, Stahl D, Al-Chalabi A. The benefit of evolving multidisciplinary care in ALS: a diagnostic cohort survival comparison. Amyotroph Lateral Scler Frontotemporal Degener. 2017 Nov;18(7-8):569-575.doi:10.1080/21678421.2017.1349151. Epub 2017 Jul 18. PMID: 28719997.

20. Fattal D, Hester S, Wendt L. Body Weight and Obstructive Sleep Apnea: a Mathematical Relationship between Body Mass Index and Apnea Hypopnea Index in Veterans: For every 7-lb. drop in weight, expect a 7% drop in AHI. Submitted, J Clin Sleep Med. 2022.

21. United States Census Bureau. (2020, June 2). Release Number CB20-TPS.30 - Census Bureau Releases New Report on Veterans. https://www.census.gov/newsroom/press-releases/2020/veterans-report.html

22. Lacomblez L, Bensimon G, Leigh PN, et al. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. Lancet. 1996;347(9013):1425-31. doi: 10.1016/s0140-6736(96)91680-3. PMID: 8676624.

23. Aboussouan LS, Khan SU, Meeker DP, et al. Effect of noninvasive positive-pressure ventilation on survival in amyotrophic lateral sclerosis. Ann Intern Med. 1997; 127(6):450-3. doi: 10.7326/0003-4819-127-6-199709150-00006. PMID: 9313002.

24. Chiò A, Finocchiaro E, Meineri P, et al. Safety and factors related to survival after percutaneous endoscopic gastrostomy in ALS. ALS Percutaneous Endoscopic Gastrostomy Study Group. Neurology. 1999;53(5):1123-5. doi: 10.1212/wnl.53.5.1123. PMID: 10496278.

25. Turner MR, Scaber J, Goodfellow JA, et al (2010). The diagnostic pathway and prognosis in bulbar-onset amyotrophic lateral sclerosis. J Neurol Sci. 2010;294(1-2):81-5. doi: 10.1016/j.jns.2010.03.028. Epub 2010 May 10. PMID: 20452624.

26. Chiò A, Logroscino G, Hardiman O, et al (2009). Eurals Consortium. Prognostic factors in ALS: A critical review. Amyotroph Lateral Scler. 2009;10(5-6):310-23. doi: 10.3109/17482960802566824. PMID: 19922118; PMCID: PMC3515205.

27. R G Miller, C E Jackson, E J Kasarskis, J D England, D Forshew, W Johnston, S Kalra, J S Katz, H Mitsumoto, J Rosenfeld, C Shoesmith, M J Strong, S C Woolley; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug,

nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2009 Oct 13;73(15):1218-26. doi: 10.1212/WNL.0b013e3181bc0141.

28. Burkhardt C , Neuwirth C , Sommacal A, et al. Is survival improved by the use of NIV and PEG in amyotrophic lateral sclerosis (ALS)? A post-mortem study of 80 ALS patients. PLoS One. 2017;12(5):e0177555. doi: 10.1371/journal.pone.0177555. eCollection.

29. Shoesmith CL, Findlater K, Rowe A, et al. Prognosis of amyotrophic lateral sclerosis with

respiratory onset. J Neurol Neurosurg Psychiatr. 2007;78:629–31. [PubMed: 17088331]

30. Tysnes O-B, Vollset SE, Aarli JA. Epidemiology of amyotrophic lateral sclerosis in Hordaland

county, western Norway. Acta Neurol Scand. 1991;83:280–5. [PubMed: 2063649]

31. Pinto AC, Evangelista T, Carvalho M, et al. Respiratory assistance with a

non-invasive ventilator (Bipap) in MND/ALS patients: survival rates in a controlled trial. J Neurol

Sci. 1995;129(Suppl):19–26. [PubMed: 7595610]

32. Pinto A, deCarvalho M, Evangelista T, et al. Nocturnal pulse oximetry: a new

approach to establish the appropriate time for non-invasive ventilation in ALS patients.

Amyotroph Lateral Scler Other Motor Neuron Disord. 2003;4:31–5. [PubMed: 12745616]

33. Chio A, Mora G, Leone M, et al. for the Piemonte and Valle

d'Aosta Register for ALS. Early symptom progression rate is related to ALS outcome: a

prospective population-based study. Neurology. 2002;59:99–103. [PubMed: 12105314]

34. Houzen H, Kano T, Horiuchi K, Wakita M, Nagai A, Yabe I. Improved Long-Term Survival with Edaravone Therapy in Patients with Amyotrophic Lateral Sclerosis: A Retrospective Single-Center Study in Japan. Pharmaceuticals (Basel). 2021 Jul 21;14(8):705. doi: 10.3390/ph14080705. PMID: 34451802; PMCID: PMC8398196.

35. Okada M, Yamashita S, Ueyama H, Ishizaki M, Maeda Y, Ando Y. Long-term effects of edaravone on survival of patients with amyotrophic lateral sclerosis. eNeurologicalSci. 2018 May 17;11:11-14. doi: 10.1016/j.ensci.2018.05.001. PMID: 29928711; PMCID: PMC6006910.

36. Brooks BR, Berry JD, Ciepielewska M, Liu Y, Zambrano GS, Zhang J, Hagan M. Intravenous edaravone treatment in ALS and survival: An exploratory, retrospective, administrative claims analysis. EClinicalMedicine. 2022 Aug 4;52:101590. doi: 10.1016/j.eclinm.2022.101590. PMID: 35958519; PMCID: PMC9358426.

37. Witzel S, Maier A, Steinbach R, Grosskreutz J, Koch JC, Sarikidi A, Petri S, Günther R, Wolf J, Hermann A, Prudlo J, Cordts I, Lingor P, Löscher WN, Kohl Z, Hagenacker T, Ruckes C, Koch B, Spittel S, Günther K, Michels S, Dorst J, Meyer T, Ludolph AC; German Motor Neuron Disease Network (MND-NET). Safety and Effectiveness of Long-term Intravenous Administration of Edaravone for Treatment of Patients With Amyotrophic Lateral Sclerosis. JAMA Neurol. 2022 Feb 1;79(2):121-130. doi: 10.1001/jamaneurol.2021.4893. Erratum in: JAMA Neurol. 2022 Jun 13;:null. PMID: 35006266; PMCID: PMC8749709.

38. Brooks BR, Miller RG, Swash M, Munsat TL, World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;1(5):293-9. doi: 10.1080/146608200300079536.

39. Steve Vucic, Toby A Ferguson, Catherine Cummings, Michael T Hotchkin, Angela Genge, Robert Glanzman, Kasper C D Roet, Merit Cudkowicz, Matthew C Kiernan. Gold Coast diagnostic criteria: Implications for ALS diagnosis and clinical trial enrollment. Muscle Nerve. 2021 Nov;64(5):532-537. doi: 10.1002/mus.27392. Epub 2021 Aug 24.

40. Department of Veterans Affairs. Veterans Health Administration. (2021, August 30). VHA Directive 1101.07. Amyotrophic Lateral Sclerosis System of Care. https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=9423

Appendix

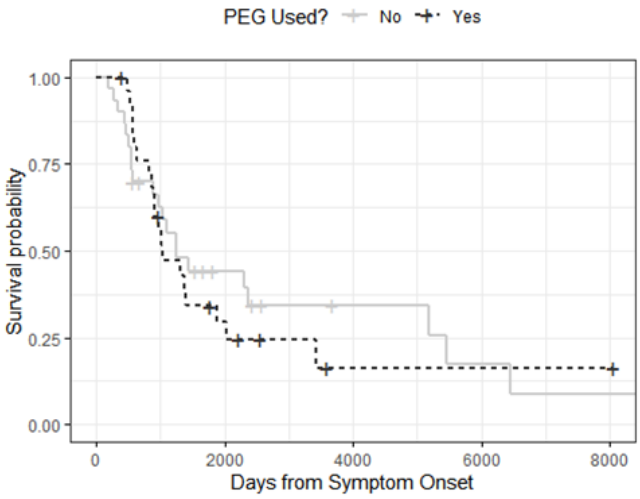

Figure A.3a. Survival probability as a function of time from symptom onset by PEG tube use

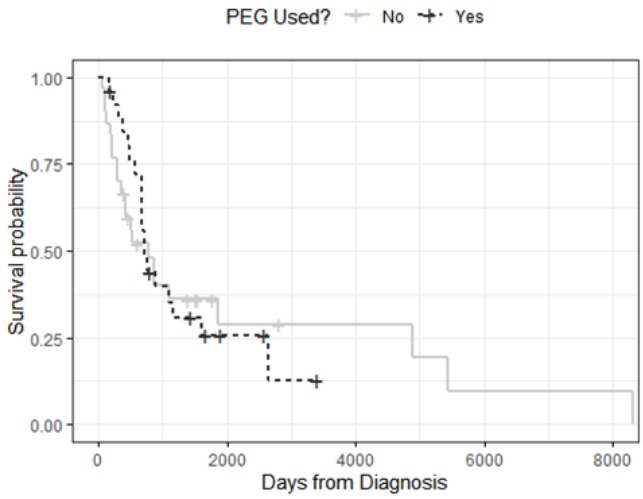

Figure A.3b. Survival probability as a function of time from diagnosis by PEG tube use

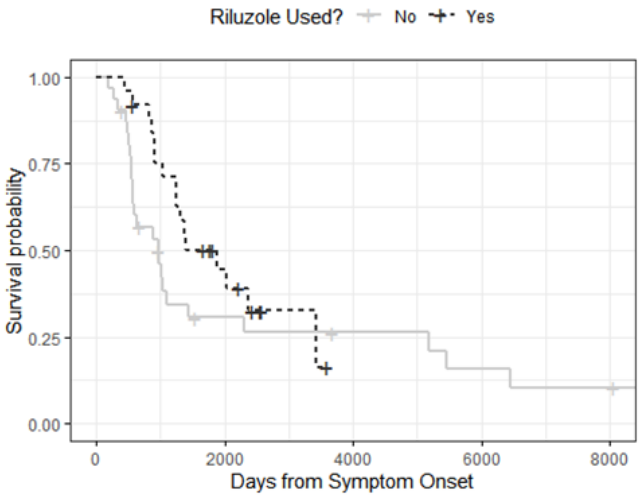

Figure A.4a. Survival from diagnosis in patients using riluzole vs. patients not using it

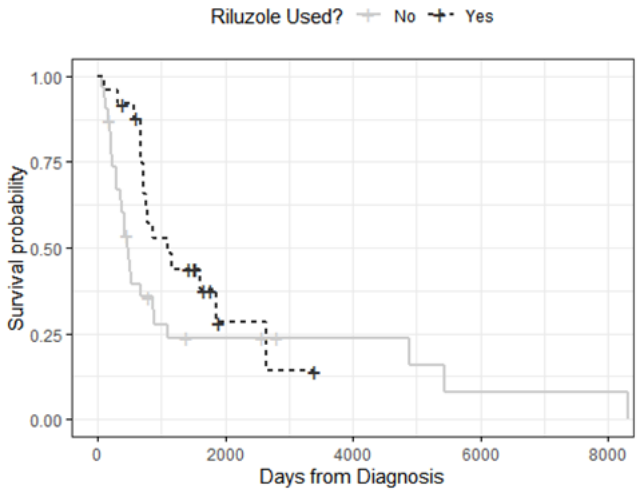

Figure A.4b. Survival from diagnosis in patients using riluzole vs. patients not using it

Table A1. ALS clinic roles

ALS Clinic team member	**Role**
RN Case Manager	Pre-clinic check-in call to complete ALS FRS-R; rooming veterans, vitals
Respiratory Therapist	Complete respiratory testing at the start of the clinic day
Physiatrist/PA	Medical management; medication management
Social Worker	Assists with support system and VA/community benefits & resources
Dietitian	Diet and nutritional assessment; feeding tube formulas management
Psychologist	Adjustment/grief/loss support; brief counseling support
Occupational Therapist	Strategies/tools/equipment for managing ADL/IADLs
Physical Therapist	Home and community mobility support; transfers; wheelchair assessments
Speech and language pathologist	Swallowing changes; augmentative and alternative communication (AAC) strategies for managing speech changes
Pulmonologist	Management of neuromuscular respiratory failure
Palliative care physician	Ongoing palliative care support, care planning, and hospice coordination

Table A.2a. Model for survival from symptom onset by ALS subtype

Full model: This table provides our estimates for the effect of onset type on survival time from symptom onset after adjusting for the potential confounders of edaravone usage, age at symptom onset, and gender.

Characteristic	HR[1]	95% CI[1]	*p* value
Edaravone usage	0.32	0.11, 0.96	**0.042**
Age at Symptom Onset	1.06	1.03, 1.10	<**0.001**
Gender			
F	—	—	
M	0.62	0.14, 2.75	0.5
Onset Type			
Bulbar	—	—	
Generalized	0.63	0.22, 1.75	0.4
Limb	0.34	0.14, 0.85	**0.020**

[1]HR = Hazard Ratio, CI = Confidence Interval

Unadjusted model: This table provides our estimates for the effect of Onset Type on survival time from symptom onset without adjusting for patient age, gender, or edaravone usage

Characteristic	HR[1]	95% CI[1]	*p* value
Onset Type			
Bulbar	—	—	
Generalized	0.39	0.15, 1.04	0.059
Limb	0.26	0.11, 0.62	**0.002**

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.2b. Model for Survival from time of diagnosis by ALS subtype

Full model: This table provides our estimates for the effect of onset type on survival time from diagnosis after adjusting for the potential confounders of edaravone usage, age at diagnosis, and gender.

Characteristic	HR[1]	95% CI[1]	p-value
Edaravone	0.30	0.10, 0.88	**0.028**
Age at Diagnosis	1.06	1.03, 1.10	<**0.001**
Gender			
F	—	—	
M	0.76	0.17, 3.35	0.7
Onset Type			
Bulbar	—	—	
Generalized	0.79	0.29, 2.12	0.6
Limb	0.46	0.19, 1.07	0.071

[1]HR = Hazard Ratio, CI = Confidence Interval

Unadjusted Model: This table provides our estimates for the effect of Onset Type on survival time from diagnosis without adjusting for a patient's age, gender, or edaravone intake.

Characteristic	HR[1]	95% CI[1]	p-value
Onset Type			
Bulbar	—	—	
Generalized	0.46	0.18, 1.19	0.11
Limb	0.34	0.15, 0.77	**0.010**

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.3a. PEG and survival from symptom onset

Characteristic	HR[1]	95% CI[1]	p-value
PEG	1.38	0.71, 2.66	0.3
Age_SO	1.07	1.04, 1.11	<**0.001**
Gender			
F	—	—	
M	0.72	0.16, 3.18	0.7

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.3b. PEG use and survival from time of diagnosis

Characteristic	HR[1]	95% CI[1]	p-value
PEG	1.14	0.59, 2.21	0.7
Age_Diag	1.07	1.04, 1.11	<**0.001**
Gender			
F	—	—	
M	0.76	0.17, 3.33	0.7

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.3c. Model: PEG use and survival from symptom onset

Characteristic	HR[1]	95% CI[1]	p-value
PEG	0.90	0.36, 2.23	0.8
Age_SO	1.06	1.03, 1.10	<**0.001**
Gender			
F	—	—	
M	0.52	0.10, 2.59	0.4
Onset_type			
Bulbar	—	—	
Generalized	0.41	0.15, 1.14	0.086
Limb	0.32	0.10, 1.02	0.054
Delay to Diagnosis	1.00	1.00, 1.00	0.10

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.3d. Model: PEG use and survival from time of diagnosis

Characteristic	HR[1]	95% CI[1]	p-value
PEG	0.56	0.21, 1.50	0.3
Age_Diag	1.07	1.03, 1.10	<**0.001**
Gender			
F	—	—	
M	0.41	0.08, 2.07	0.3
onset_type			
Bulbar	—	—	
Generalized	0.45	0.16, 1.26	0.13
Limb	0.23	0.07, 0.82	**0.023**
Delay to Diagnosis	1.00	1.00, 1.00	>0.9

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.3e. Survival from symptom onset model and NIV use

Characteristic	HR[1]	95% CI[1]	p-value
NIV	1.50	0.58, 3.83	0.4
Age_SO	1.07	1.03, 1.11	<**0.001**
Gender			
F	—	—	
M	0.62	0.14, 2.78	0.5
Onset_type			
Bulbar	—	—	
Generalized	0.37	0.13, 1.04	0.060
Limb	0.34	0.14, 0.84	**0.020**
Delay to Diagnosis	1.00	1.00, 1.00	0.12

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.3f. Survival from symptom onset model and NIV use

Characteristic	HR[1]	95% CI[1]	p-value
NIV	1.30	0.50, 3.36	0.6
Age_Diag	1.07	1.03, 1.12	<**0.001**
Gender			
F	—	—	
M	0.64	0.14, 2.89	0.6
Onset_type			
Bulbar	—	—	
Generalized	0.50	0.18, 1.34	0.2
Limb	0.39	0.16, 0.93	**0.035**
Delay to Diagnosis	1.00	1.00, 1.00	0.8

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.4a. Effect of riluzole on survival from symptom onset, controlling for age and gender

Characteristic	HR[1]	95% CI[1]	p-value
Riluzole	0.89	0.44, 1.82	0.8
Age at Symptom Onset	1.06	1.03, 1.10	<**0.001**
Onset_type			
Bulbar	—	—	
Generalized	0.43	0.16, 1.15	0.092
Limb	0.30	0.12, 0.75	**0.010**

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.4b. Effect of riluzole on survival from time of diagnosis, controlling for age and gender

Characteristic	HR[1]	95% CI[1]	p-value
Riluzole	0.82	0.40, 1.67	0.6
Age at Diagnosis	1.06	1.03, 1.10	<**0.001**
Onset_type			
Bulbar	—	—	
Generalized	0.54	0.20, 1.41	0.2
Limb	0.39	0.17, 0.90	**0.028**

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.5a. Model demonstrating that edaravone is a preventative factor against death from ALS from symptom onset

Characteristic	HR[1]	95% CI[1]	p-value
Edaravone	0.24	0.09, 0.68	**0.007**

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.5b. Model demonstrating that edaravone is a preventative factor against death from ALS from diagnosis

Characteristic	HR[1]	95% CI[1]	p-value
Edaravone	0.25	0.09, 0.70	**0.009**

[1]HR = Hazard Ratio, CI = Confidence Interval

A worsening problem in ALS: insurance barriers between drug approvals and patient access

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For most of the past 150 years, clinicians have had few treatments to offer patients with ALS. Riluzole was approved in 1995,[1] and this ushered in an era initially characterized by hope for the rapid development of new therapeutics. However, despite great progress in the development of disease models, breakthroughs in understanding ALS pathophysiology, and large federal and pharma investment, more than 20 years elapsed before the next positive phase 3 trial.[2,3]

In the past six years, three new drugs have been FDA-approved for ALS: edaravone (an antioxidant that slows accumulation of disability by about 30% over 6 months),[3] sodium phenylbutyrate/taurursodiol (a combination with multiple intracellular actions which similarly slows disability and also prolongs survival by 4-6 months)[4] and tofersen (an antisense oligonucleotide which lowers mutant SOD1 protein and neurofilament light chain levels).[5] This progress is much welcomed, but it has led to a worsening problem in ALS: insurance barriers between drug approvals and patient access. The most extreme examples are payors who deny coverage for newer FDA-approved medications, claiming they are "experimental" (ex. 6). Other payors have instituted "step therapy"[7] and are only covering the newer medications for those who "fail" riluzole.[8] Some only cover the newer medications for patients who meet certain clinical criteria, similar to the entry criteria for the pivotal trials.[8-11] In our experience, these insurance barriers are resulting in already-stretched clinicians and clinic staff needing to spend time on prior authorization forms, appeals of denials, and peer-to-peer reviews. More importantly, all of this results in potentially harmful delays between a medication being prescribed and a patient being able to start taking it.

To better quantify and understand the impact of these insurance barriers across more providers and clinics, we conducted and herein report the results of a survey of our colleagues in the Northeast ALS Consortium (NEALS).

We created a 16-question survey to better understand ALS Clinician perspectives on the barriers associated with riluzole, edaravone, and sodium phenylbutyrate/taurursodiol treatments (Figure 1). We did not include tofersen because it was not FDA-approved at the time our survey launched. An electronic link to the survey was sent to 128 clinicians identified as primary site investigators in the Northeast ALS Consortium (NEALS). The link was sent three times between May 14 and May 30, 2023.

Twenty-eight clinicians completed the survey, for a response rate of 22%. The average number of patients with ALS being followed by the respondents was 168.

Clinicians were asked about the percentage of patients they felt *should be* taking each of the 3 drugs, versus the percentage that *are* taking it (Table 1). There was a large amount of variability in responses between different clinicians. The gap between these estimates for riluzole was 10%; it was 19% for edaravone and 38% for sodium phenylbutyrate/taurursodiol.

Clinicians were asked to rank the barriers to getting more patients on each drug, from biggest (1) to smallest (4, Table 2). For riluzole, the biggest barrier was a lack of patient interest. For edaravone and sodium phenylbutyrate/taurursodiol, the biggest barrier was payor restrictions.

Clinicians were asked about the percentage of prescriptions on which they encountered a need for prior authorization, denials with options to appeal, and final insurance denials (Table 3). All of these barriers were rare with riluzole. Denials with options to appeal occurred with more than half the prescriptions for edaravone and for sodium phenylbutyrate/taurursodiol. Less than 1% of riluzole prescriptions were met with a final insurance denial, while more than 25% of those for the newer medications met this fate. Given the frequency of these insurance barriers, it is not surprising that the average clinician time per script for riluzole was only 7 minutes, but it was more than 100 minutes for the newer medications. The delay between the script being written and patients being able to access the drug averaged only 4 days for riluzole, but it was around a month for edaravone or sodium phenylbutyrate/taurursodiol. Although not universal, clinicians felt on average that the delays between scripts for sodium phenylbutyrate/taurursodiol and access were more than 50% likely causing patients harm (Figure 2).

Our small survey confirms our impressions across a wider sample of clinicians. Insurance barriers, while not the only reasons, are the *main* reasons for the large gaps between the percentage of patients with ALS who *should be* taking edaravone and sodium phenylbutyrate/taurursodiol versus the percentage that *are* taking these. Prior authorizations and appeals of denials are commonly encountered in the prescribing of the newer ALS medications; these cause significant time burdens for physicians and delays between script and patient access. At least in the case of sodium phenylbutyrate/taurursodiol, these delays are perceived by experts as more than 50% likely harmful to patients. This perception is supported by open-label extension data showing that patients who receive sodium phenylbutyrate/taurursodiol early do much better on functional measures, risk of hospitalization, and survival compared to those who receive it after a delay.[12,13]

There are limitations to this study. First, we did not address the pricing of the newer ALS medicines, which, given the small effect sizes and lack of replication trials for edaravone and sodium phenylbutyrate/taurursodiol, some have understandably criticized.[14,15]Determining how many ALS trials or what effect size is needed to establish confidence in an ALS drug, or to determine its cost, are beyond the scope of this paper. We refer readers to an excellent editorial that touches on some of these complex questions.[16] Second, we did not survey payors nor patients to get their perspectives. Finally, the response rate of our survey was low, which may have introduced bias. Nonetheless, we believe we have identified an important and worsening problem facing ALS clinicians.

These types of insurance barriers are not unique to ALS treatments,[7,8] but they are especially problematic due to the aggressive and fatal nature of the disease. And they are not evidence-based. FDA-approved therapies are not "experimental." The idea of a patient needing to "fail" riluzole is farcical since essentially all ALS patients will worsen over time. Using clinical trial inclusion criteria as a basis for coverage reflects misunderstanding both of the differences between clinical trial methodology and clinical care, as well lack of understanding of the nature of ALS. Clinical trials attempt to reach efficacy conclusions as efficiently as possible, while practice entails treating as many patients as effectively as possible. The idea that a clinical trial population in ALS is somehow etiologically different than those needing care is not supported by any available data. Indeed, at this time, the authors of this paper do not believe there is a point in ALS progression where the available drugs would no longer be effective. Roadblocks to the use of effective drugs in combination with riluzole mean that patients get access either late or not at all. As ALS involves the inexorable death of motor neurons, delaying treatment is a guarantee of inadequate treatment.

For other diseases, advocacy has been effective in reducing insurance barriers.[17] Laws have even been enacted to ensure insurance coverage for treatments that experts felt were important.[8,17,18]We hope that discussion of this important topic will result in recognition from payors that ALS patients deserve access to care that meaningfully impacts their disease. If not, then perhaps it will galvanize advocates and lawmakers toward addressing the unacceptable insurance barriers to newer ALS treatments. People affected by this disease have waited long enough for these treatments.

References

1. Approval of Riluzole. FDA Website, https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=072792. Accessed June 21, 2023.
2. Petrov D, Mansfield C, Moussy A, Hermine O. ALS clinical trials review: 20 years of failure. Are we any closer to registering a new treatment? *Front Aging Neurosci* 2017;9:68. doi: 10.3389/fnagi.2017.00068
3. Writing Group;Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis: a randomized, double-blind, placebo-controlled trial. *Lancet Neurol* 2017;16:505-512. doi: 10.1016/S1474-4422(17)30115-1.
4. Paganoni S, Macklin E, Hendrix S, et. al. Trial of sodium phenylbutyrate-taurursodiol for amyotrophic lateral sclerosis. *NEJM* 2020;383:919-930. doi: 10.1056/NEJMoa1916945
5. Miller T, Cudkowicz M, Genge A, et. al. Trial of antisense oligonucleotide tofersen for SOD1 ALS. *NEJM* 2022;387:1099-1110. doi: 10.1056/NEJMoa2204705
6. Cigna National Formulary Coverage Policy for sodium phenylbutyrate/taurursodiol. Cigna Website, https://static.cigna.com/assets/chcp/pdf/coveragePolicies/cnf/cnf_777_coveragepositioncriteria_neurology_relyvrio_pa.pdf. Accessed June 22, 2023.
7. Washington Post page about step therapy. Washington Post website, https://www.washingtonpost.com/wellness/2023/02/06/prior-authorization-fail-first-step-therapy/. Accessed June 22, 2023.
8. Tufts Medical Center page anticipating payor restrictions on new ALS drugs. Tufts Medical Center website, https://cevr.tuftsmedicalcenter.org/news/2022/how-might-us-health-plans-cover-amx0035-relvyrio-for-als-lessons-from-the-spec-database. Accessed June 22, 2023.
9. Aetna page about edaravone coverage. Aetna website, https://www.aetna.com/cpb/medical/data/900_999/0918.html. Accessed June 22, 2023.
10. Wellmark page about sodium phenylbutyrate/taurursodiol coverage. Wellmark website, https://www.wellmark.com/-/media/sites/public/files/provider/pharmacy/relyvrio.pdf?sc_lang=en&hash=909B3F893ECD41B7DE790429E3B8CA04. Accessed June 22, 2023.
11. Pacific Source page about edaravone and sodium phenylbutyrate/taurursodiol coverage. Pacific Source website, https://pacificsource.com/sites/default/files/2023-01/Exchange%20and%20PDL%20PA%20Criteria%202023%20With%20Medical%2001222023.pdf. Accessed June 22, 2023.
12. Paganoni S, Hendrix S, Dickson S, et. al. Effect of sodium phenylbutyrate/taurursodiol of tracheostomy/ventilation-free survival and hospitalization in amyotrophic lateral sclerosis: long-term results from the CENTAUR trial. *J Neurol Neurosurg Psych* 2022;93:871-875. doi: 10.1136/jnnp-2022-329024
13. Paganoni S, Hendrix S, Dickson S, et. al. Long-term survival of patients in the CENTAUR trial of sodium phenylbutyrate-taurursodiol in amyotrophic lateral sclerosis. *Muscle Nerve* 2021;61:31-39. doi: 10.1002/

mus.27091
14. ICER page on the cost of AMX0035 and oral edaravone for amyotrophic lateral sclerosis. ICER website, https://icer.org/wp-content/uploads/2022/02/ICER_ALS_Draft-Evidence-Report_061422.pdf. Accessed August 17, 2023.
15. Lewis-Kraus G. When dying patients what unproven drugs. New York Post. June 19, 2023.
16. Cudkowicz M, Shefner J. Regulatory approval in ALS; when is a single trial enough? Ann Neurol 2022;91:737-739.
17. Resolve page summarizing the impact of advocacy and efforts on insurance barriers to in vitro fertilization drugs. Resolve website, https://resolve.org/advocacy-in-action-update/. Accessed June 22, 2023.
18. Rettig R. Origins of the Medicare Kidney Disease Entitlement: The Social Security Amendments of 1972. In Hanna K, ed. Biomedical Politics: Institute of Medicine (US) Committee to Study Decision Making. Washington (DC): National Academies Press (US); 1991.

Table 1. Based upon what you know today about these drugs, what percentage of the people with ALS that you care for should be/are taking:

	Riluzole	Edaravone	NaPB/TURSO
Should Be Taking	88% (0, 100)	51% (0, 100)	76% (0, 100)
Are Taking	78% (30, 98)	32% (5, 95)	38% (5, 90)
Difference in Means	10%	19%	38%

Data presented are means and (ranges).

Table 2. Rank the barriers to getting more patients on each drug, from biggest (1) to smallest (4):

	Riluzole	Edaravone	NaPB/TURSO
Lack of physician confidence in benefits	1.9 (0.88)	2 (0.82)	2.6 (0.79)
Lack of physician confidence in safety	3.1 (0.65)	3.8 (0.52)	3.1 (0.88)
Lack of patient interest	1.7 (0.98)	2.8 (0.84)	3.1 (0.94)
Payor restrictions	3.3 (1.0)	1.5 (0.74)	1.2 (0.69)

Data presented are means (and standard deviations)

Table 3. On what percentage of prescriptions do you encounter the following:

	Riluzole	Edaravone	NaPB/TURSO
Prior Authorization	20.7% (36.4)	87.2% (9.7)	90.3% (9.7)
Insurance Denial with Option to Appeal	5.6% (3.3)	56.2% (22.1)	65.2% (26.5)
Final Insurance Denial	0.3% (0.42)	26.1% (20.4)	28.8% (17.1)

Data presented are means (and standard deviations)

Table 4. Time To Get Each Drug

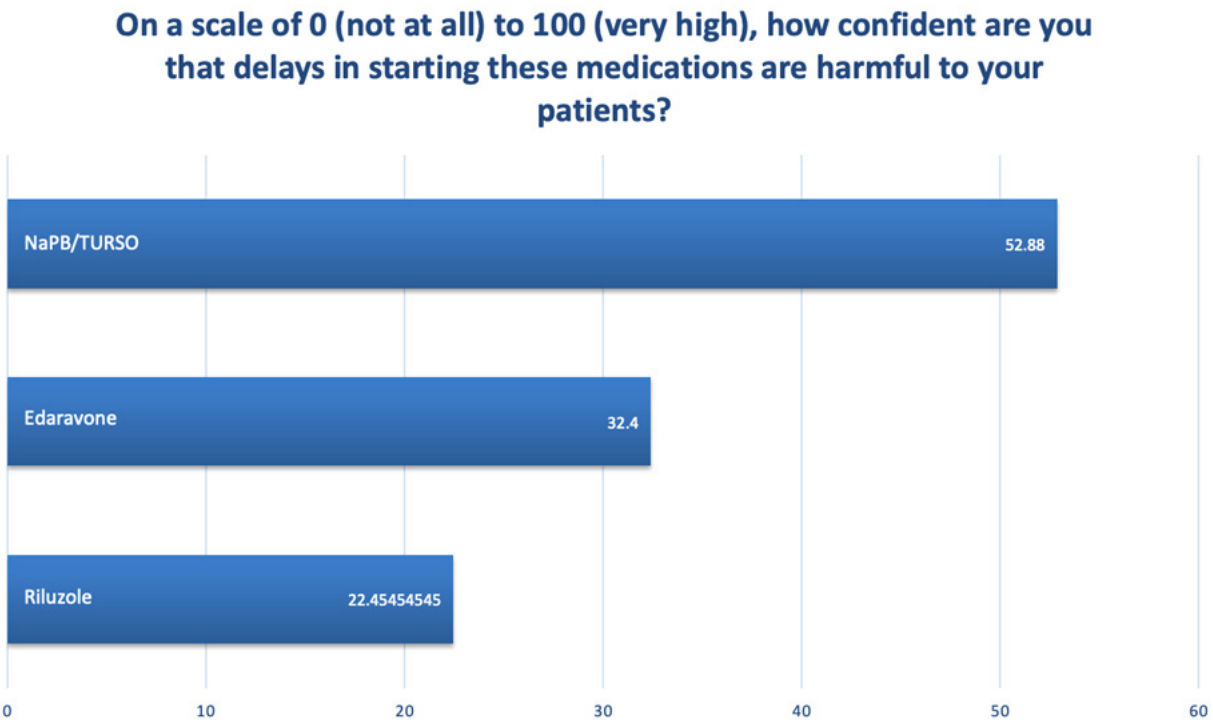
	Riluzole	Edaravone	NaPB/TURSO
Clinician Time Per Script	7 minutes (0, 30)	110 minutes (15, 360)	126 minutes (15, 360)
Delay Between Script and Patient Access	4 days (0, 30)	29 days (5, 60)	32 days (2, 60)

Data presented are means and (ranges).

Figure 1. Survey Questions

1. Based upon what you know today about these drugs, what percentage of the people with ALS that you care for should be taking riluzole, edaravone, sodium phenylbutyrate/taurursodiol?
2. In your estimation, what percentage of the patients you care for are currently taking riluzole, edaravone, sodium phenylbutyrate/taurursodiol.?
3. Rank the barriers to getting more patients on riluzole from biggest (at the top) to smallest (at the bottom):
    a. Lack of physician confidence in benefits
    b. Lack of physician confidence in safety
    c. Lack of patient interest
    d. Payor restrictions
4. Rank the barriers to getting more patients on edaravone from biggest (at the top) to smallest (at the bottom):
    a. Lack of physician confidence in benefits
    b. Lack of physician confidence in safety
    c. Lack of patient interest
    d. Payor restrictions
5. Rank the barriers to getting more patients on sodium phenylbutyrate/taurursodiol.from biggest (at the top) to smallest (at the bottom):
    a. Lack of physician confidence in benefits
    b. Lack of physician confidence in safety
    c. Lack of patient interest
    d. Payor restrictions
6. On what percentage of riluzole prescriptions to you encounter the following:
    a. Prior authorization
    b. Insurance denial with option to appeal
    c. Final insurance denial
7. On what percentage of edaravone prescriptions to you encounter the following:
    a. Prior authorization
    b. Insurance denial with option to appeal
    c. Final insurance denial
8. On what percentage of sodium phenylbutyrate/taurursodiol prescriptions to you encounter the following:
    a. Prior authorization
    b. Insurance denial with option to appeal
    c. Final insurance denial
9. How much effort (in average minutes per prescription) does it take your team to get a patient on:
    a. Riluzole
    b. Edaravone
    c. Sodium phenylbutyrate/taurursodiol.
10. How much time passes (in average days) between your prescription for riluzole and your patient getting it from their pharmacy?
11. How much time passes (in average days) between your prescription for edaravone and your patient getting it from their pharmacy?
12. How much time passes (in average days) between your prescription for sodium phenylbutyrate/taurursodiol and your patient getting it from their pharmacy?
13. On a scale from 0 (not at all) to 100 (very), how confident are you that delays in starting riluzole are harmful to your patients?
14. On a scale from 0 (not at all) to 100 (very), how confident are you that delays in starting edaravone are harmful to your patients?
15. On a scale from 0 (not at all) to 100 (very), how confident are you that delays in starting sodium phenylbutyrate/taurursodiol are harmful to your patients?
16. How many people with ALS do you currently provide care for?

Figure 2. Clinician Confidence in Delays Causing Harm



Data presented are means. Standard deviations: Riluzole (30.6), Edaravone (28.1), NaPB/TURSO (32.2)

Safety and tolerability of phenylbutyrate in inclusion body myositis

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ABSTRACT

Introduction

Phenylbutyrate (PBA) showed a positive effect on the muscle cell model of Inclusion Body Myositis (IBM) by improving lysosomal activity, ameliorating consequences of impaired autophagy, and decreasing vacuolization. This provides a rationale to study this medication in patients with IBM.

Objectives

To evaluate the safety and tolerability of phenylbutyrate in IBM and monitor for any early signal of effectiveness.

Methods

Open-label study of 10 subjects with IBM who received treatment with PBA for 3 months after a 3-month run-in period. The PBA dose was 3 gm twice daily. The primary outcome measure was adverse event reporting. Secondary outcome measures included manual muscle testing, timed up and go test, IBM functional rating scale, and grip strength, along with exploratory biomarkers evaluating the mitochondrial function, stress response, degenerative process, and apoptosis.

Results

Ten subjects completed the study. PBA was well tolerated with no serious adverse events related to it. The most common adverse events were gastrointestinal-related and did not require stopping treatment. One of the biomarkers (MitoTracker) showed a statistically significant drop over the treatment period of the study (p-value of 0.02 for the mean change). There were no statistically significant changes in other secondary outcome measures, but the study was limited by a small sample size and short treatment period.

Conclusions

Phenylbutyrate was safe and well tolerated in patients with IBM in this pilot study. The change in the MitoTracker suggests target engagement, but a Phase II study is needed to confirm and study the efficacy of PBA in IBM.

Introduction

Inclusion body myositis (IBM) is the most common acquired muscle disorder after age 50. The prevalence of IBM varies from study to study and ranges in United States from 10.7 per million (28.9 per million for age 45 and older)[1] to 70.6 per million[2] with male to female ratio of 2:1 to 3:1.[3] While IBM does not change life expectancy, it causes significant disability.

IBM was classically classified as inflammatory myopathy considering inflammatory infiltrate found on muscle biopsy. The lack of response to treatment raised the impression that IBM is a degenerative disorder with secondary inflammation.[4] This was further supported by other findings on muscle biopsy like inclusions and amyloid deposits as can be seen in other neurodegenerative disorders.

The abnormal accumulation of amyloid-beta protein precursor, and its proteolytic fragment amyloid-beta, associated with intracellular aging of muscle fibers, is thought to be the key pathogenic event.[5] Low-molecular amyloid-beta oligomers, which are highly cytotoxic, have been demonstrated in IBM muscle tissues with immunoblots but not in control muscle tissue.[6]

Studies have suggested that cultured human muscle fibers (CHMFs) with experimentally inhibited autophagy and lysosomal activity had pronounced vacuolization, in addition to significantly increased amyloid-beta and its oligomers.[7-8]

Many similar neurodegenerative disorders, termed "protein-misfolding disorders" are characterized by the accumulation of intracellular or extracellular protein aggregates. These aggregates, or more likely their intermediate oligomeric precursor forms, can act to catalyze the process of additional aggregation.[9]

A highly conserved class of proteins called molecular chaperones has evolved to prevent inappropriate interactions within and between non-native polypeptides, to enhance the efficiency of *de novo* protein folding, and to promote the refolding repair of proteins that have become misfolded as a result of cellular stress.[10-11] In addition to this protein repair activity, chaperones can mediate targeting to the proteasome system or to lysosomes, resulting in selective degradation of the misfolded protein when the chaperones cannot repair the misfolded proteins.

Phenylbutyrate, an orally active chemical chaperone approved by the US Food and Drug Administration for the treatment of urea cycle disorders, mimics the function of intracellular molecular chaperones in preventing protein aggregation and oligomerization.[12]

Nogalska et al. reported a novel function of phenylbutyrate, namely that in lysosomal activity-inhibited CHMFs it substantially: (a) improved the phenotype of muscle fibers by decreasing their vacuolization; (b) increased cathepsins D and B activities, accompanied by a decrease of NBR1, p62 and LC3-II; (c) decreased

Aβ42 and Aβ42 oligomers; and (d) decreased γ-secretase activity.[13] This improvement of lysosomal activity and striking ameliorative consequences of experimentally impaired autophagy provide a rationale for considering phenylbutyrate as a potentially beneficial drug for IBM.

Study design

We conducted a pilot study (phase 1 clinical trial) to evaluate the safety and tolerability of phenylbutyrate in IBM. In this open-label study, the plan was to enroll 10 patients with sporadic inclusion body myositis who would be treated with phenylbutyrate (3 gm twice daily) for 3 months. There would be a run-in period of 3 months, during which no study medication would be taken, and certain exploratory biomarkers would be measured at baseline and at the end of the run-in period in addition to final measurement at the end of the treatment period.

These biomarkers evaluate the mitochondrial function, stress response, degenerative process and apoptosis and include mitochondrial membrane potentials through MitoTracker red (shows overall mitochondrial mass), MitoSox (a mitochondrial biomarker which detects mitochondrial superoxide levels), tetramethylrhodamine ethyl ester (determine mitochondrial membrane potential and a marker of overall mitochondrial activity), Annexin binding in lymphocytes (apoptosis marker). We have previously assayed TDP-43 and its derivative, phosphorylated TDP-43 (pTDP-43) in peripheral blood platelets in our laboratory (Dr. Agbas). TDP43 positive cytoplasmic aggregates have been described in ALS motor neurons and IBM skeletal muscle tissue with significant up-regulation of *TARDBP* (the gene expresses TDP-43 protein) and *SQTM1* (Sequestosome-1) gene expression.[14] Therefore, we planned to measure blood-derived platelet total TDP-43 and pTDP-43 as surrogate biomarker for skeletal muscle TDP-43 profile of IBM patients. Our laboratory had demonstrated analytical capability of the measurement of platelet TDP-43 and pTDP-43 in human platelets.[15,16,17]

Primary outcome measures included adverse event reporting. Secondary outcome measures included multiple strength and functional measures: manual muscle testing, timed up and go test (TUG), IBM functional rating scale (IBMFRS), and grip strength. These clinical outcome measures were commonly used in evaluating progression of IBM and in clinical trials of this disease. [18,19,20,21] In addition, safety laboratory tests and electrocardiogram would be monitored regularly. As mentioned above, the biomarkers would be repeated at the end of the treatment period.

Study Eligibility

Inclusion Criteria

1. Fulfill ENMC 2011 diagnostic criteria for IBM
2. Age ≥ 18 years
3. Women must be post-menopausal (no menses in >12 months) or status post hysterectomy.
4. Able to give informed consent
5. Subjects must be able and willing to remain on stable concomitant medications throughout the duration of the study.

Exclusion Criteria

1. Presence of any one of the following medical conditions: chronic infection; chronic renal insufficiency; cancer other than skin cancer less than five years prior; multiple sclerosis or prior episode of central nervous system demyelination; or other chronic serious medical illnesses
2. Presence of any of the following on routine blood screening: WBC<3000; Platelets < 100,000; hematocrit < 30%; BUN > 30 mg/dl; creatinine > 1.5 mg/dl; liver disease with serum albumin < 3 g/dl
3. Women who are pregnant or lactating
4. History of non-compliance with other therapies
5. Coexistence of other muscular disease
6. Drug or alcohol abuse within the past three months
7. Known bleeding disorder
8. Known liver disease
9. Known congestive heart failure
10. Known hypernatremia

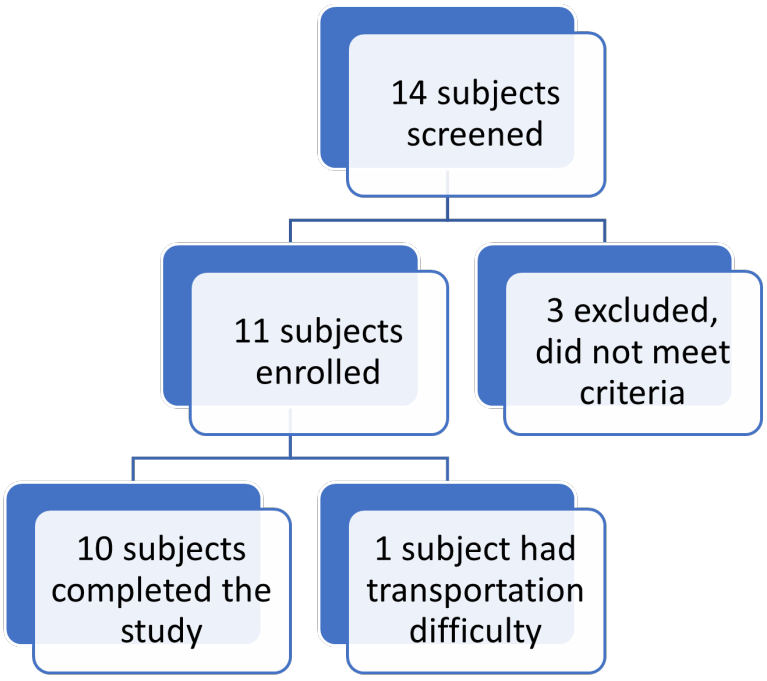
Statistical Method

This is a pilot study with a sample size of n=10 subjects. For both the primary and secondary outcomes, statistical reporting would be in the form of descriptive statistics.

Demographic variables are reported using mean and standard deviation (or median) for continuous variables (age, weight, height) and frequency counts for categorical variables (gender, race, ethnicity). The disposition to complete or not complete treatment would be recorded as a 'Yes/No' dichotomous response and would be reported using frequency counts.

For the primary outcome of safety, the frequency of Adverse Events (AEs) and Serious Adverse Events (SAEs) by grade, would be reported. This would be done for each follow-up visit as well as for all visits combined.

For the secondary outcomes, the measurements at baseline, month-3, and month-7 would be reported using mean and standard deviation (or median and interquartile range for skewed measurements) along with a corresponding 95% confidence interval. These measurements would be visually compared using box plots to detect the presence of a trend over time by drawing a trend line on the means (or median). Due to the small sample size, this comparison would be done visually, and no formal statistical test would be done routinely but it would be considered to further study a trend.



Results

Fourteen patients with IBM were screened for this study. Three patients were excluded from the study due to not meeting the inclusion/exclusion criteria. Ten patients were enrolled in the study, but one subject dropped out of the study due to transportation difficulties. After getting IRB approval, one additional subject was enrolled, and all 10 subjects completed the study.

The demographic characteristics can be seen in **Table 1 (a, b)**. F:M ratio was 7:4 and median age was 73 (67, 76).

Table 1a. Demographics Characteristics

	Participants
Enrolled, N	11
Female N (%)	7 (63.6%)
Caucasian N (%)	10 (90.9%)
Age (years median (IQR))	73 (67, 76)

Table 1b – Detailed Demographics

Subject number (enrolled only, n=11)	Gender	Age	Race
1	F	73	Caucasian
2	F	72	Caucasian
4	F	77	Caucasian
5	M	91	Caucasian
6	F	74	Caucasian
7	M	57	Caucasian
9	F	76	Hispanic or Latina
10	M	80	Caucasian
11	F	77	Caucasian
13	F	68	Caucasian
14	M	67	Caucasian

The study drug was well tolerated, and all enrolled subjects were able to continue it throughout the treatment period. There was one serious event (a fall that required a hospital visit) that was not related to the study drug. No study drug-related serious events were reported.

Two subjects had mildly elevated liver enzymes at baseline before the treatment period. No other significant laboratory changes were noted. One subject had hair loss which was considered possibly related. The most common adverse events were related to gastrointestinal symptoms (n=9), **(Tables 2 and 3)**.

The IBMFRS did not seem to change during the study (Median was 23 at baseline, 24 at the beginning of the treatment period, and 23 at the end of it), (**Figure 1)**.

There were no meaningful changes in the other clinical outcome measures either (TUG, Total MMT, Dynamometer of the knee extension or hand grips), **(Figure 2).**

Figure 1- IBMFRS Changes

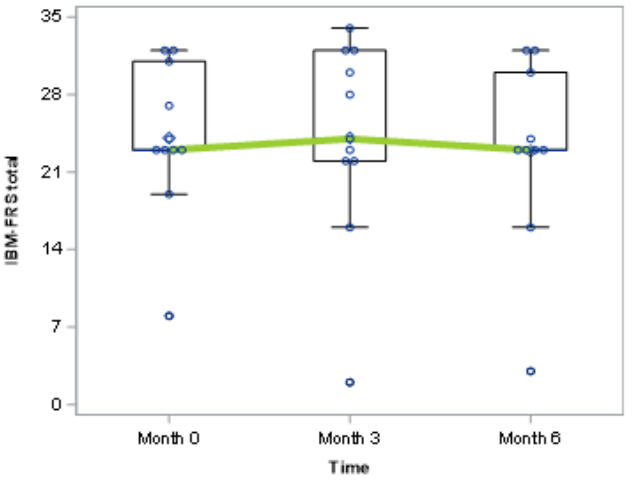


Table 2 – Adverse Events (considered possibly or probably related)

Adverse Events (possibly or probably related)		Number of occurrences	Number of subjects
Gastrointestinal AEs		9	9
	Heartburn	4	4
	Nausea	2	2
	Urgency	1	1
	Constipation	1	1
	Oral Aphthous Lesion	1	1
Musculoskeletal Pain		2	2
Drowsiness		1	1
Tremor		1	1
Hair Loss		1	1
Two Itchy Skin Lesions		1	1
Nasal Congestion		1	1

Table 3 – Adverse Events (considered unrelated)

Adverse Events (considered unrelated)	Number of occurrences	Number of subjects
Falls	9	6
Urinary Urgency	2	2
Elevated blood pressure	2	2
Elevated liver enzymes	2	2
Low blood pressure	1	1
Headache	1	1
Chills	1	1
Numbness in the Legs	1	1
Back Pain	1	1
Elevated White Blood Count	1	1
Right Bundle Branch Block	1	1
Strep. Throat Infection	1	1

Figure 2 – TUG, MMT and Dynamometer changes

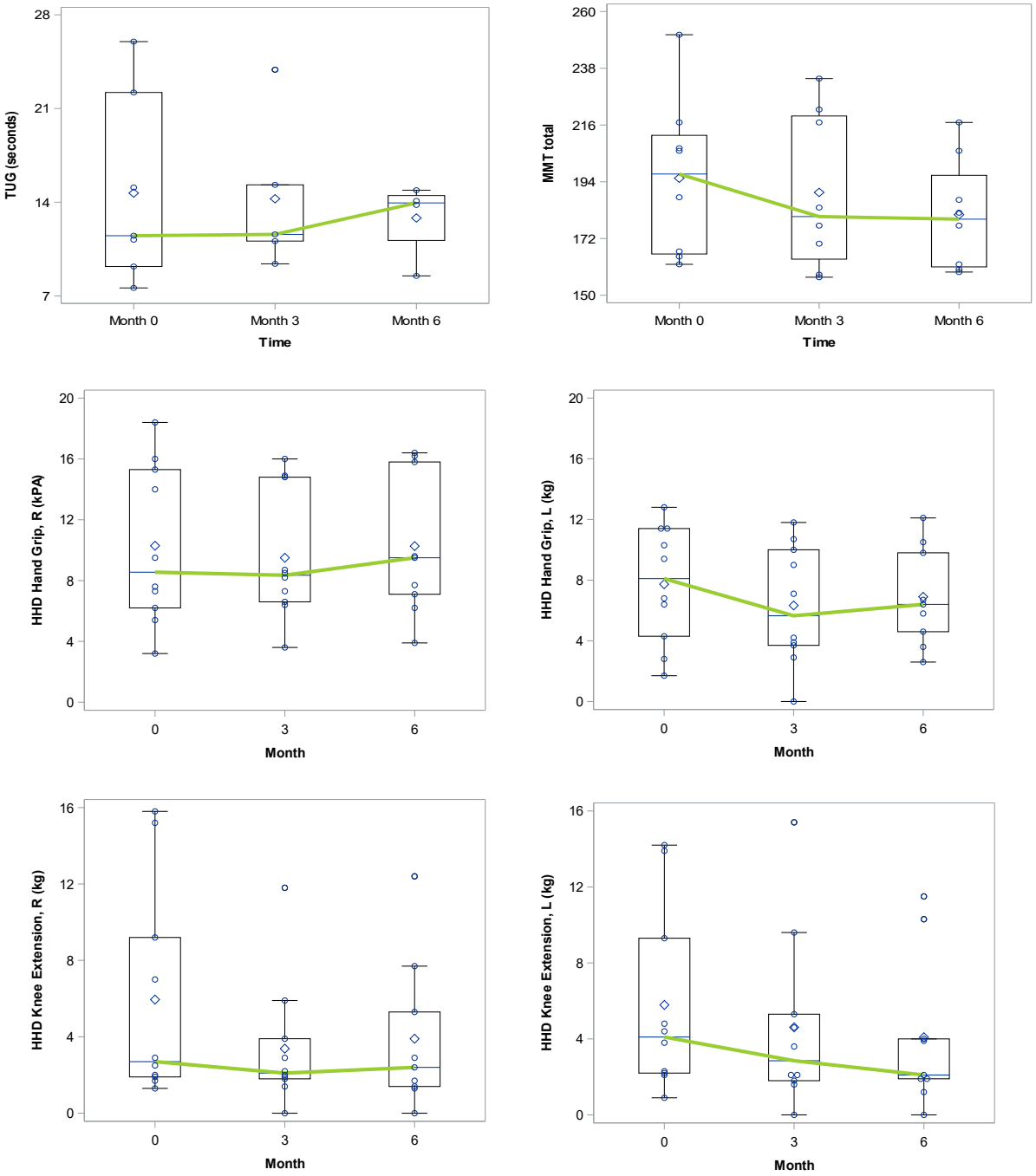
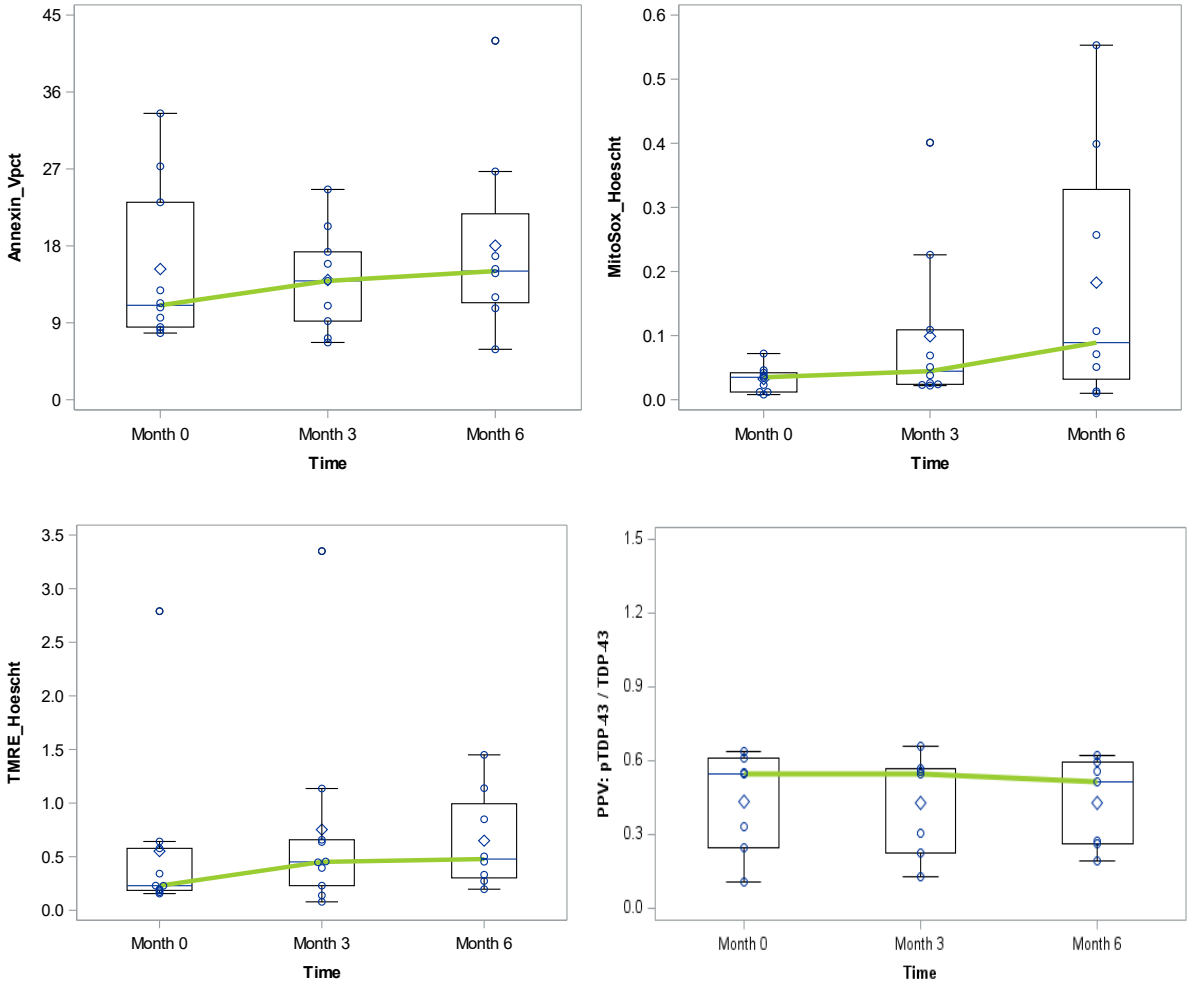
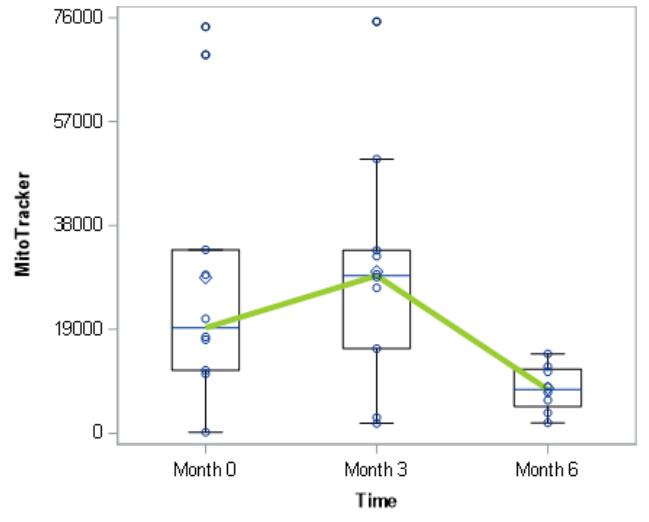


Figure 3 – Changes in Annexin, TMRE, MitoSox and TDP 43



While there was no meaningful change in most exploratory biomarkers used in this study **(Figure 3)**, the MitoTracker dropped at the end of the treatment period (median of 8010 comparing to 19299 at the baseline and 28823 at the beginning of the treatment period **(Figure 4)**. This was investigated further with a statistical analysis (detailed below in **Table 4 and Figure 5**) which showed that the mean change between the run-in period and treatment period was statistically significant (p=0.0243).

Figure 4 – Changes in MitoTracker



Statistical Analysis

Box plots of outcomes provide for visual inspection of the observed values as well as a representation of the median, inter-quartile range, and mean.

The trend observed in the boxplots of MitoTracker data warranted further exploration with a post hoc analysis. A generalized linear mixed model was used to estimate mean values of MitoTracker at each timepoint. 10 of 11 subjects had measurements at all 3 timepoints. Time was used as a categorical value and correlation among an individual's repeated measurements was accounted for with

Table 4 – statistical model

Effect	Estimated coefficient (95% CI)	Std Err	df	p-value
Intercept	29,574 (15,596, 43,552)	6,274	10	0.0008
Month			2/15	0.0724[F]
Month 0	-1,128 (-20,038, 17,782)	8,872	15	0.9005
Month 3	0	reference		
Month 6	-21,344 (-41,402, -1,287)	9,410	15	0.0385
	Mean Estimated Change (95% CI)	**Std Err**	**df**	**p-value**
On treatment – Off treatment	20,780 (3,091, 38,469)	8299	15	0.0243[t]

F: An F-test of fixed effects

t: t-test comparing mean change to zero.

a random effect for subject. The fixed effect, month, was not statistically significant (p=0.0724). Although, MitoTracker values after treatment are statistically significantly different from pre-treatment, months 0 and 3 combined (p=0.0243). The results from the model are exploratory.

Discussion

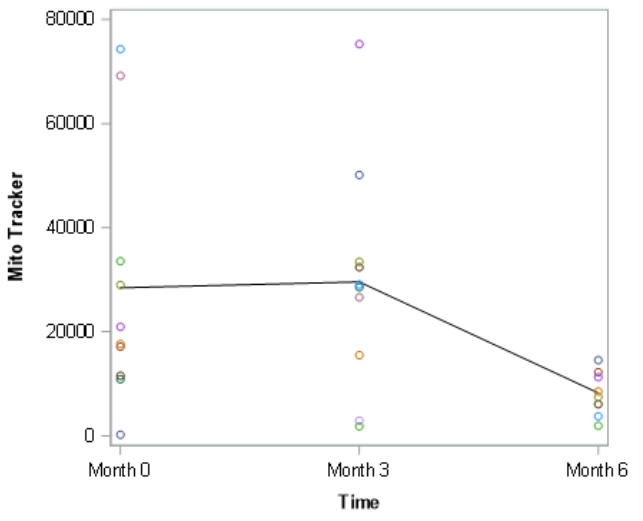
This is the first clinical trial of phenylbutyrate (PBA) in inclusion body myositis (IBM), and it was justified by the potential benefits of PBA in IBM as detailed above. This is a phase 1 trial to study the safety and tolerability of PBA in IBM.

We found PBA to be safe and well-tolerated in subjects with IBM. There were no concerning safety findings in this study and the only serious event reported (a fall) was related to the disease itself, not the study drug.

There were no meaningful changes in all clinical and most biological outcome measures. This was not unexpected considering the short duration of this study and the small sample size. Despite these limitations, the MitoTracker showed a significant drop with treatment. Reduced MitoTracker with treatment could be due to reduced mitochondrial number/mass. We propose that PBA induces autophagy/mitophagy as it is known to reduce protein aggregation and one way to process aggregates is to ship them to mitochondria and then induce mitophagy.

A phase 2 study is needed to verify the MitoTracker change and to further evaluate for any clinical or biological outcome measures changes that might have been missed due to the small sample size and short duration of our pilot study. Studying the muscle tissue should be considered in any future trial to evaluate for histopathological changes

Figure 5 – Mean Change of MitoTracker



secondary to treatment with PBA considering the changes found in the muscle cell model of IBM when exposed to PBA.[13]

In addition, PBA with tauroursodeoxycholic acid (TUDCA) showed positive results in a phase 2 clinical trial in another neurodegenerative disorder, amyotrophic lateral sclerosis (ALS). This further supports the need for a larger and longer study to evaluate its efficacy in IBM, which likely shares pathophysiological mechanisms with ALS.

Conclusion

Phenylbutyrate was safe and well tolerated in patients with IBM in this small pilot study. The change in the

MitoTracker suggests target engagement, but a longer and larger study is needed to confirm that and study the efficacy of PBA in IBM. Such Phase II study may include tissue markers to further evaluate PBA effect on the treated muscles. If PBA is found to be beneficial for the treatment of IBM, it would represent the first effective treatment for this progressive and debilitating disease.

Acknowledgement

We would like to acknowledge and thank Dr. Valerie Askanas for sharing her research findings on phenylbutyrate with us which inspired this pilot study of inclusion body myositis.

We would also like to thank Sigmapharm Laboratories for providing the study drug which made it possible to translate this research idea to a clinical trial.

References

1. Felice KJ, North WA. Inclusion body myositis in Connecticut: observation in 35 patients during an 8-year period. Medicine (Baltimore) 2001:80:320-7

2. Wilson FC, Ytterberg SR, St Sauver JL, Reed AM. Epidemiology of sporadic inclusion body myositis and polymyositis and Olmsted County, Minnesota. J Rheumatol. 2008:35:445-7

3. Dimachkie MM, Barohn RJ. Inclusion body myositis. Curr Neurol Neurosci Rep. 2013;13:321

4. Machado PM, Dimachkie MM, Barohn RJ. Sporadic inclusion body myositis: new insights and potential therapy. Curr Opin Neurol. 2014 Oct;27(5):591-8.

5. Askanas V, Engel WK. Inclusion-body myositis: a myodegenerative conformational disorder associated with Abeta, protein misfolding, and proteasome inhibition. Neurology 2006;66(2 Suppl 1):S39-48

6. Nogalska A, D'Agostino C, Engel WK, Klein WL, Askanas V. Novel demonstration of amyloid-β oligomers in sporadic inclusion-body myositis muscle fibers. Acta Neuropathol 2010;120(5):661-6

7. Nogalska, A., D'Agostino, C., Terracciano, C., Engel, W.K., Askanas, V., 2010b. Impaired autophagy in sporadic inclusion-body myositis and in endoplasmic reticulum stress-provoked cultured human muscle fibers. Am. J. Pathol 2010;177:1377–1387

8. Nogalska A, D'Agostino C, Engel WK, Askanas V. Activation of the γ-secretase complex and presence of γ-secretase-activating protein may contribute to Aβ42 production in sporadic inclusion-body myositis muscle fibers. Neurobiol Dis. 2012;48(1):141-9

9. Forloni G, Terreni L, Bertani I et al. Protein misfolding in Alzheimer's and Parkinson's disease: genetics and molecular mechanisms. Neurobiol Aging. 2002;23:957-976

10. Hartl F, Hayer-Hartl M. Molecular chaperones in the cytosol: from nacent chain to folded protein. Science. 2002;295:1852-1858

11. Sherman MY, Goldberg AL. Cellular defenses against unfolded proteins: a cell biologist thinks about neurodegenerative diseases. Neuron 2001; 29(1): 15-32.

12. Papp E, Csermely P. Chemical chaperones: Mechanisms of action and potential use. Handb Exp Pharmacol 2006;172:405-16

13. Nogalska A, D'Agostino C, Engel K.W, Askanas V. Sodium phenylbutyrate reverses lysosomal dysfunction and decreases amyloid-β42 in an in vitro model of inclusion-body myositis, Neurobiol. Dis 2014;65:93-101

14. Cykowski MD, Powell SZ, Appel JW et al. Phosphorylated TDP-43 (pTDP-43) aggregates in the axial skeletal muscle of patients with sporadic and familial amyotrophic lateral sclerosis. Acta Neuropathol Commun. 2018;6(1):28

15. Statland JM, Moore D, Wang Y et al. Rasagaline for amyotrophic lateral sclerosis: A randomized, controlled trial. Muscle Nerve. 2019;59:201-207

16. Wilhite R, Sage JM, Bouzid A, Primavera T, Agbas A. Platelet phosphorylated TDP-43: an exploratory study for a peripheral surrogate biomarker development for Alzheimer's disease. Future Sci OA. 2017;3:FSO238

17. Sage JM, Hall L, McVey A, Barohn RJ et al. Use of capillary electrophoresis immunoassay to search for potential biomarkers of amyotrophic lateral sclerosis in human platelets. J Vis Exp. 2020:156

18. Jackson CE, Barohn RJ, Gronseth G, Pandya S, Herbelin L; Muscle Study Group. Inclusion body myositis functional rating scale: a reliable and valid measure of disease severity. Muscle Nerve. 2008;37:473-6

19. Jørgensen AN, Aagaard P, Nielsen JL et al. Physical function and muscle strength in sporadic inclusion body myositis. Muscle Nerve. 2017;56:E50-E58.

20. Lin AY, Siener CS, Faino AV et al. Optimizing hand-function patient outcome measures for inclusion body myositis. Neuromuscul Disord. 2020;30;807-814

21. Sangha G, Yao B, Lunn D et al. Longitudinal observational study investigating outcome measures for clinical trials in inclusion body myositis. J Neurol Neurosurg Psychiatry. 2021;jnnp-2020-325141

Rhabdomyolysis and exercise intolerance in a 45-year-old man

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ABSTRACT
A 45-year-old man presented to neuromuscular clinic after a first-time episode of non-traumatic rhabdomyolysis after aerobic exercise. Prior to his diagnosis, he had an extensive medical workup to evaluate for elevated transaminases and creatinine, including liver and renal biopsies. On history, the patient confirmed a lifelong history of exercise intolerance. Creatine kinase evaluation revealed an elevated baseline value. Genetic testing disclosed homozygous variants of uncertain significance and required exercise testing and muscle biopsy to identify the underlying etiology. This case demonstrates pitfalls of genetic testing and an approach to identify this form of myopathy.

Section 1

A 45-year-old man presented to neuromuscular clinic for an episode of non-traumatic rhabdomyolysis. He had a history of elevated transaminases for which he underwent two liver biopsies, seven years and one year prior to his clinic visit, and was diagnosed with fatty liver disease. He was noted to have an elevated creatine kinase (CK) to the 3800s U/L after his second liver biopsy. He had repeat CK values that were elevated but less than 1000 U/L. After performing routine aerobic exercise, he developed muscle weakness and dark colored urine. He was admitted for further work-up. CK was >35,000 U/L and creatinine (Cr) peaked at 6.66. A renal biopsy was performed and was normal. His CK and Cr improved with intravenous fluids. MRI of his proximal lower limbs and EMG were normal. During his initial clinic visit, he described difficulty with exercise since childhood. He had no prior identifiable episodes of rhabdomyolysis or myoglobinuria. He denied weakness, cramping, contractures, rashes, dyspnea, and dysphagia. There was no family history of muscle or metabolic disorders. The neurological exam was normal. There were no rashes and lungs were clear to auscultation bilaterally.

Questions for consideration:

1. What diagnoses should be considered?
2. What tests would you perform next?

Section 2

The patient's symptoms localize to the muscles given the elevated CK and rhabdomyolysis. Normal EMG and strength exam do not eliminate a myopathy from the differential. The patient's reported persistent exercise difficulty since childhood and rhabdomyolysis were most suggestive of a metabolic (glycolysis/glycogenolysis and fatty acid oxidation disorders) or mitochondrial myopathy. Typically, glycogen-storage disorders present during periods of high-intensity exercise, whereas fatty acid oxidation disorders and mitochondrial myopathies present during longer duration endurance-type activities or periods of metabolic stress such as surgery or infection. Given the non-specific history of exercise intolerance, further investigation was needed to differentiate between these. There were no systemic features which could point to a specific subtype of fatty acid oxidation disorder. There were no specific features such as proximal weakness or a rash that would suggest an inflammatory myopathy. The patient was not taking statins or cortico- or anabolic steroids, which excluded forms of drug-induced myopathy.

Comprehensive testing was performed to narrow the diagnosis. Repeat CK was 609 U/L. A neuromuscular disorders gene panel (Invitae, next-generation sequencing) was obtained and revealed a pseudodeficiency allele in *GAA* and homozygous variant of uncertain significance in *PYGM* (c.403G>A [p.Gly135Arg]). Non-ischemic forearm test (NIFT) (Table 1A) and cycle exercise test (Table 1B) were performed. Cycle exercise test showed elevated heart rate (HR) and rate of perceived exertion (RPE) at low workloads with a reduction of HR (31 beats per minute from minute 8 to 16) and RPE with better tolerance to higher workloads, a physiologic response known as the second wind phenomenon, seen in McArdle disease (GSD V).

Table 1

A. Non-ischemic forearm test

Time	Absolute Force (kg)	Grip Force (% max)	Lactate mM	Ammonia µM/L	Serum CK
rest	30.0	100	0.67	31	1834
1 sec	15.6	52			
30 sec	19.4	65			
60 sec	12.9	43	0.68	97	
post exer					
1 min			0.41	121	
2 min			0.46	74	
5 min			0.55	41	
10 min			0.56	34	

Lactate response was blunted, and ammonia production was increased in the context of a baseline elevated CK value.

B. Cycle exercise test

Time (min)	WL (watts)	RPE Overall	O_2 sat. (%)	BP (mmHg/mmHg)	HR (bpm)	VO_2 (L/min)	Q (L/min)	a-vO_2diff (mlO_2/dlQ)	ΔQ/ ΔVO_2	lactate (mM)
0	rest		98	130/98	78	0.376	5.97	6.3		0.63
1	10	11	98	181/107	112					
2	20	12	98	166/92	119					
3	30	14	98		125					
4	30		98		135					
5	30	16	99	196/93	145	1.180	19.07	6.2		0.40
6	30									
7	30	16	98		156					
8	20	17	98		162					
9	20	15	97							
10	20	14	97	192/91	155					
11	20	14	97		150					
12	20	13	97	169/92	142					
13	20	13	97		136					
14	20	13	97		133					
15	20	13	96	181/85	132	1.533	14.81	10.4		0.51
16	30	13	96		131					
17	30	14	97		134					
18	40	15	97	174/96	136					
19	50	14	98		146					
20	60				148					
21	70	16	98	187/91	153					
22	70	17	97		162					
23	70	17	97	209/83	165	2.010	18.67	10.8	7.29	0.42

The exercise test showed reduced peak VO_2, blunted lactate production, second wind phenomenon, and a defect in oxidative phosphorylation.

WL: workload, RPE: Rate of Perceived Exertion (6-20, no exertion to maximal exertion), BP: blood pressure, HR: heart rate, VO_2: oxygen consumption, Q: cardiac output, a-vO_2 diff: arteriovenous oxygen difference

Questions for consideration:

1. What additional testing would you obtain to determine the diagnosis?

Section 3

A lifetime of exercise intolerance, non-traumatic rhabdomyolysis, and chronically elevated muscle enzymes are all highly suggestive of a metabolic myopathy. While primary mitochondrial myopathies (PMM) and fatty acid oxidation disorders (FAOD) can present with exercise intolerance and rhabdomyolysis, the lack of lactate production on NIFT and the second wind phenomenon argue in favor of a glycogen storage disorder (GSD), specifically McArdle disease. His genetic results and absence of symptoms with fasting, illness, and exposure to cold temperatures argue against FAOD and mitochondrial myopathies. It is therefore unnecessary to order mitochondrial DNA testing or urine organic acids, serum acylcarnitine, and carnitine profiles. We pursued a vastus lateralis muscle biopsy to test for the defective enzyme in GSD V, myophosphorylase (PYGM gene). The patient's myofibers revealed a complete absence of reactivity (Figure 1) and provided the diagnosis. His homozygous VUS was recharacterized as pathogenic per American College of

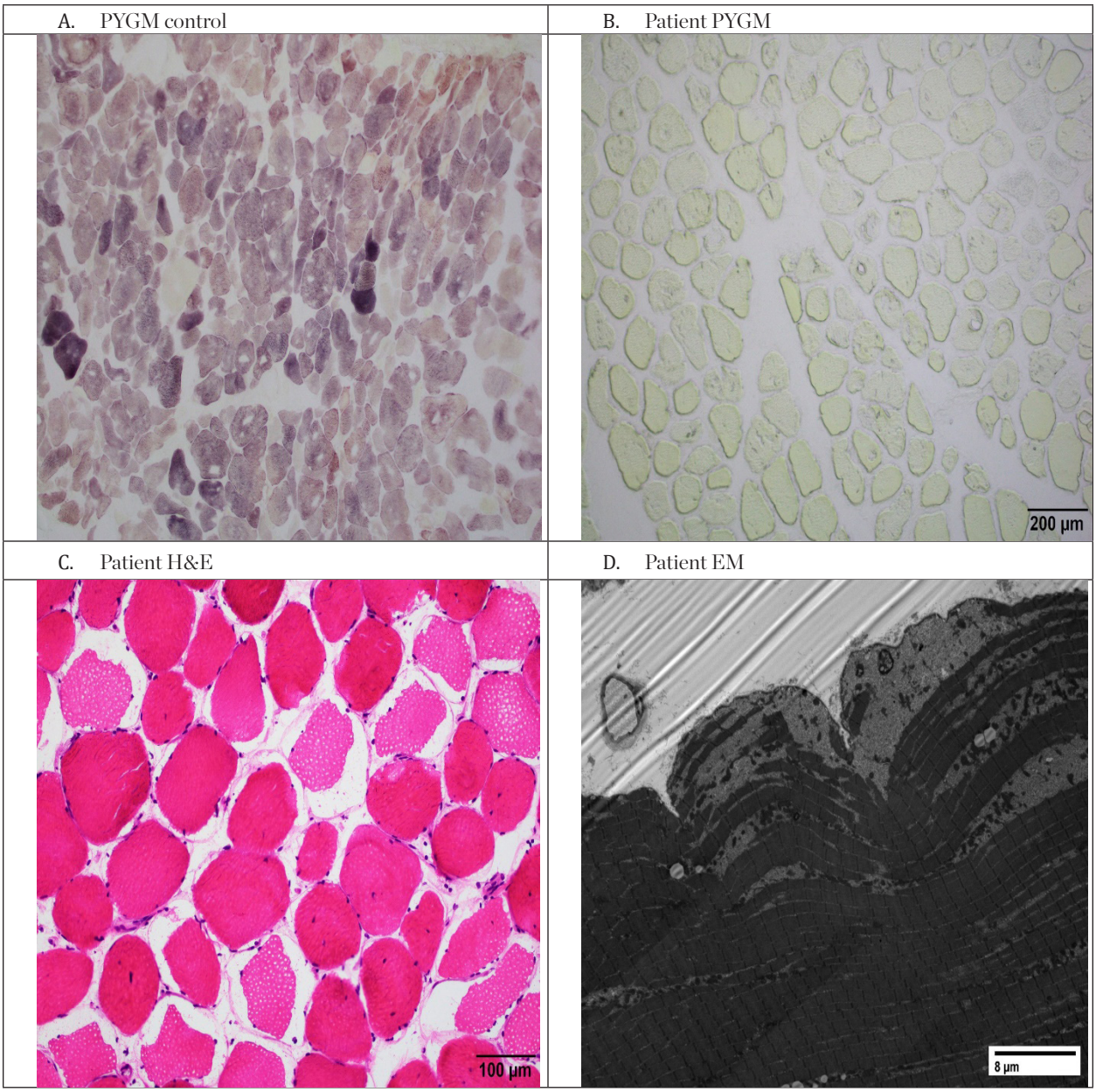

Figure 1: Quadriceps muscle biopsy showed a vacuolar myopathy with subsarcolemmal vacuoles (arrows) in a subset of myofibers (C), complete absence of myophosphorylase reactivity in all myofibers (B) compared to a control myophosphorylase image (A), and accumulation of free glycogen particles in subsarcolemmal space in some fibers on EM (D). Periodic acid-Schiff is not shown as there was no increased PAS staining.

Medical Genetics and Genomics guidelines given the low frequency of this mutation in the population, established clinical testing, and *in silico* analysis.

The patient was educated on the second wind phenomenon, benefits of high carbohydrate diet, and high-risk activities that could trigger rhabdomyolysis. We recommended low and moderate intensity aerobic exercises with modest use of sports drinks prior to activity. After implementing these measures, he reported an improvement in muscle symptoms and has not had a recurrence of rhabdomyolysis.

Discussion

McArdle disease[1] is an autosomal recessive disorder caused by a *PYGM* gene defect, encoding for myophosphorylase, a muscle-specific isoform of glycogen phosphorylase that catalyzes the degradation of glycogen into glucose-1-phosphate. Nearly all mutations in *PYGM* lead to complete loss of enzyme activity, thus blocking glycogenolysis.[2,3] In the initial stages of exercise and during intense activities, skeletal muscle predominantly depends on anaerobic glycogenolysis for energy. Thus, within minutes of starting the activity, patients describe fatigue that progresses to muscle cramps, contractures, and rhabdomyolysis if the activity is continued. Since glycogen is also needed for oxidative metabolism, patients have a low capacity for moderate exercise as well. Sustained moderate activity leads to fatigue, tachycardia, and dyspnea. After resting or maintaining a low level of activity, patients experience the pathognomonic second wind phenomenon related to greater mobilization of fatty acids to fuel oxidative metabolism.[4,5,6]

Although exercise intolerance is present in childhood, the diagnosis is almost never made until at least the second decade of life due to misdiagnoses like "growing pains" or "being unfit." Patients typically present in early adulthood with exercise intolerance, cramps, and recurrent rhabdomyolysis that can progress to fixed proximal weakness.[1] Work-up often begins at the time of non-traumatic rhabdomyolysis. CK is typically elevated to 5-10 times the upper limit of normal. Importantly, AST and ALT are present in myofibers and are not specific for liver pathology and can lead to unnecessary invasive procedures, such as liver biopsy. Significant delays in diagnosis are common, with a high rate of misdiagnosis (up to 90%). Women are substantially more likely to receive a psychiatric or psychological misdiagnosis.[6]

NIFT is classically performed rather than ischemic forearm testing, which can lead to muscle contractures and rhabdomyolysis.[7,8] During NIFT, a block in glycogenolysis is demonstrated by absent lactate and increased ammonia production. Cycle testing demonstrates and helps patients recognize the second wind phenomenon. Molecular testing may obviate the need for exercise testing and muscle biopsy in patients with the typical clinical phenotype and known pathogenic *PYGM* mutations. When *PYGM* VUS are found, a normal NIFT can exclude GSDs. If NIFT is abnormal, a muscle biopsy should be performed to assess for myophosphorylase activity.

The goal of management is to reduce episodes of rhabdomyolysis and improve exercise tolerance. Avoidance of intense activities, especially those requiring isometric, repetitive, and eccentric actions, is recommended. Low-to-moderate aerobic exercise (no greater than approximately 70% of maximal HR) improves muscle oxidative capacity and increases the threshold for muscle injury due to exertion.[9] Patients should warm-up at a low intensity for at least 10 minutes to help achieve the second wind phenomenon. Pre-exercise simple sugars improve exercise tolerance and reduce the risk of rhabdomyolysis during activity.[10-12] Because McArdle disease patients are at risk of obesity, consuming sugar prior to all activity is not recommended. Additionally, carbohydrate-rich diets are beneficial by bolstering hepatic glycogen stores and glucose mobilization.

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References

1. McArdle B. Myopathy due to a defect in muscle glycogen breakdown. Clin Sci 1951; 10:13.
2. Llavero F, Sastre AA, Montoro ML, Gálvez P, Lacerda HM, Parada LA, et al. McArdle disease: new insights into its underlying molecular mechanisms. Int J Mol Sci 2019;20. doi:10.3390/ijms20235919.
3. Nogales-Gadea G, Brull A, Santalla A, et al. McArdle Disease: Update of Reported Mutations and Polymorphisms in the PYGM Gene. Hum Mutat 2015; 36:669.
4. Pearson CM, Rimer DG, Mommaerts W. A metabolic myopathy due to absence of muscle phosphorylase. Am J Med 1961;30:502–17. doi:10.1016/0002-9343(61)90075-4.
5. Tarnopolsky, Mark A. "Metabolic Myopathies." CONTINUUM: Lifelong Learning in Neurology, vol. 22, no. 6, 2016, pp. 1829–1851, https://doi.org/10.1212/con.0000000000000403.

6. Scalco RS, Morrow JM, Booth S, et al. Misdiagnosis is an important factor for diagnostic delay in McArdle disease. Neuromuscul Disord 2017; 27:852.
7. Kazemi-Esfarjani P, Skomorowska E, Jensen TD, et al. A nonischemic forearm exercise test for McArdle disease. Ann Neurol 2002; 52:153.
8. Hogrel JY, et al. Diagnostic power of the non-ischaemic forearm exercise test in detecting glycogenosis type V. Eur J Neurol 2015;22;933-940)
9. Haller RG. Treatment of McArdle disease. Arch Neurol 2000; 57:923.
10. Vissing J, Haller R. The effect of oral sucrose on exercise tolerance in patients with McArdle's disease. N Engl J Med 2003;349:2503–9. doi:10.1056/nejmoa031836.
11. Andersen ST, Haller RG, Vissing J. Effect of oral sucrose shortly before exercise on work capacity in McArdle disease. Arch Neurol 2008;65:786–9. doi:10.1001/archneur.65.6.786.
12. Haller RG, Vissing J. Spontaneous "second wind" and glucose-induced second "second wind" in McArdle disease oxidative mechanisms. Arch Neurol 2002;59:1395–402. doi:10.1001/archneur.59.9.1395

Guillain-Barré Syndrome vs acute onset CIDP – a clinical dilemma for the neurologist

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ABSTRACT

The most common acquired immune mediated polyneuropathies are acute inflammatory demyelinating polyradiculoneuropathy (AIDP), a form of Guillain-Barré syndrome (GBS), and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Sixteen percent of cases ultimately diagnosed as CIDP may present acutely and be indistinguishable initially from AIDP. While GBS is typically thought of as a monophasic illness, 10% may show treatment related fluctuations. Therefore, distinguishing acute onset CIDP (A-CIDP) from GBS with treatment-related fluctuations may be difficult early in the disease course but it's important to distinguish between the two entities to guide further treatment strategies. We present 2 illustrative cases of A-CIDP, diagnosed as GBS who eventually required long term immunosuppression for sustained recovery.

Introduction

Guillain-Barré syndrome (GBS) is an acute immune mediated polyradiculoneuropathy that presents with acute flaccid paresis. Although GBS is considered to be monophasic, recurrences are reported in 2 to 5% of patients. [1,2]

Acute inflammatory demyelinating polyradiculoneuropathy (AIDP), a subtype of GBS, is characterized by its acute onset and progression up to four weeks and is often preceded by an infection. However chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) progresses slowly over weeks to months or in a relapsing remitting manner [3,4]. Five percent of patients initially diagnosed with GBS may evolve into CIPD and 16% of patients with CIDP present with an acute GBS-like illness [5]. Distinguishing between GBS, GBS with treatment related fluctuation (TRF) and A-CIDP is important as patients with A-CIDP require long-term immunotherapy. Treatment related fluctuation in GBS is defined as worsening by at least one grade in the GBS disability scale or by at least 5 points in MRC sum score after initial improvement or stabilization with the initial treatment with immunotherapy by either plasmapheresis or intravenous immunoglobulin therapy, not occurring more than 2 times and within the first two months of onset of symptoms. A-CIDP should be considered when a patient with GBS deteriorates after 9 weeks of onset or deterioration occurs more than 3 times [5,6].

Here we present 2 cases: one presenting as recurrent GBS and the other one as GBS with TRF and relapses which posed a diagnostic dilemma of A-CIDP vs GBS. Both required initiation of immunosuppression and achieved remission after rituximab infusion.

Case 1

A 17-year-old girl presented to the emergency department with a history of low-grade fever lasting for 1 day followed by rapidly progressive weakness of all four limbs over the next 2 days. On examination she had bilateral lower motor neuron facial nerve palsy, absent gag reflexes, strength 0/5 (MRC grade) in all 4 extremities. She developed bulbar and severe respiratory weakness requiring mechanical ventilation. She had a previous history of similar illness on two occasions.

The first episode of weakness was in 2016 when she was diagnosed with Guillain-Barré Syndrome. She was treated with intravenous immunoglobulin (IVIG) followed by plasmapheresis due to no response to IVIG. A second episode of GBS occurred in 2020 where she again received IVIG in an outside hospital. This was followed by plasmapheresis with improvement. In between the above episodes, she had complete recovery and was walking independently. This was treated as recurrent GBS. Nerve conduction studies (NCS) revealed absent F responses in bilateral median, ulnar and common peroneal nerves with mildly prolonged latency in the peroneal motor nerve and a sural sparing pattern. Cerebral spinal fluid (CSF) examination showed albumino-cytological dissociation. Serum acetyl choline receptor binding antibody was negative. Urine porphobilinogen was negative.

In the current episode she was treated with plasmapheresis due to no response to IVIG in previous two episodes. Since she had no response by the fifth session, we she received two more sessions of plasmapheresis. Over the next 3 weeks she showed gradual improvement and was weaned off the ventilator. She showed complete improvement in weakness over one month and could walk independently at discharge. In view of this third episode of severe GBS-like presentation, she was treated with rituximab infusion 1000 mg followed by another 1000 mg 2 weeks apart with premedication. Since she had three GBS episodes, CIDP was considered and a nodopathy panel was sent which was positive for NF-155 and NF-186 antibodies. She received maintenance dose of 500 mg rituximab at 6 months follow up. She is in remission with minimal left facial weakness.

Case 2

A 35-year-old female presented to the hospital with a history of tingling in hands and feet for 4 days prior to admission. She also had imbalance on walking. This was

preceded a week prior with fever and upper respiratory infection. She was admitted with a clinical diagnosis of GBS with proximal and distal weakness in the lower extremities (MRC grade 3) and upper extremities (MRC grade 4-/5 in proximal and distal muscles). No sensory impairment was present. There was generalized hypo/areflexia. An NCS was performed (table 1). Examination of CSF revealed albuminocytological dissociation. Treatment was initiated with IVIG 2g/kg divided over 5 days. However, on the second day of IVIG she developed bulbar symptoms with dysphagia, diplopia and strength in the upper and lower extremities worsened to grade 0-1/5. She progressed rapidly to respiratory failure requiring mechanical ventilation. There was an initial slight improvement after IVIG but she deteriorated again to grade 1/5 in arm strength. Hence, she received another course of IVIG. However, there was no improvement and she remained dependent on ventilator at week 3 of illness. A repeat NCS was performed at week 3 (table 1). Since there was no improvement after IVIG, she underwent plasmapheresis 2 weeks after IVIG. She showed remarkable improvement and after the fourth session of plasmapheresis, she was weaned off the ventilator, strength in the upper extremities improved to 4-/5 and was shifted out of the intensive care unit. However, four days after the initial response, strength in shoulder abduction worsened to 2/5. She underwent two more sessions of plasmapheresis in view of this treatment related fluctuation. She was also started on oral prednisolone 40 mg once a day with azathioprine 50 mg twice a day and physiotherapy were continued. Strength in the upper extremity gradually improved. She was discharged in a week and started walking 2 months later. Prednisolone was gradually tapered off over next 2 months. She developed pancytopenia at that time which was thought to be due to azathioprine. Hence it was stopped at 3 months from the onset of her illness.

However, one month after stopping immunosuppression, (5 months from initial symptom onset) she noticed worsening of gait imbalance, diplopia with weakness in both lower (MRC grade 2/5) and upper extremities (MRC grade 4-/5). She was treated with plasmapheresis. This was the first relapse after the initial episode of GBS like presentation.

2 months later, she presented for the third time with gait imbalance, this time with predominant sensory ataxia,

Table 1: Case 2: Nerve conduction study at week 1 (day2) and week 3 of illness

	Recording site	Peak Latency (ms)		Amplitude (microV)		Velocity (m/s)		F wave latency (ms)	
SENSORY		Week 1	Week 3	Week 1	Week 3	Week 1	Week 3	Week 1	Week 3
R Sural	Lateral malleolus	2.60	2.86	54.6	11.9				
R Superficial peroneal	Lower leg	2.60	2.70	27.2	13.0				
R Median	Digit II	2.76	NR	15.3					
R Ulnar	Digit V	2.40	NR	23.4					
R Radial	Thumb	2.03	2.40	42.8	11.8				
MOTOR	Recording site	Distal latency (ms)		Amplitude (mV)		Velocity (m/s)		F wave latency (ms)	
		Week 1	Week 3	Week 1	Week 3	Week 1	Week 3	Week 1	Week 3
R Peroneal Ankle	EDB	9.17	22.86	2.6	0.9			45.10	Absent
Fibular head		15.31	30.36	2.5	0.5	48.8	40.0		
Pop fossa		17.45	34.79	2.3	0.4	42.1	20.3		
R Tibial Ankle	AH	7.40	14.90	5.7	1.1			47.10	Absent
Pop fossa		16.46	30.57	5.1	1.1	40.8	22.3		
R Median Wrist	APB	8.07	24.38	1.1	2.6			Absent	Absent
Elbow		12.71	31.82	1.1	2.5	49.6	30.9		
R Ulnar Wrist	ADM	4.43	14.74	2.0	2.5			Absent	Absent
B elbow		7.92	20.00	1.8	2.1	54.4	36.1		
A elbow		9.84	28.07	1.4	1.5	51.9	12.4		

areflexia, and weakness in her extremities (MRC grade 4-/5 in the upper and 2/5 in the proximal lower extremities). She responded to IVIG with improvement in the strength, sensory symptoms and gait. She received rituximab infusion 1000 mg followed by another dose of 1000 mg after 2 weeks in view of these frequent relapses. Since then, her disease is in remission for last 3 years with no neurological deficit.

Discussion

Guillain-Barré syndrome (GBS) is an acute immune mediated polyradiculoneuropathy affecting 0.8–1.9 subjects per 100,000 every year worldwide [7]. A preceding infection can be identified in about 70% of cases. GBS represents a model for post-infectious auto-immune disorders [7] The most common preceding infection causing GBS has been shown to be *Campylobacter jejuni* enteritis, responsible for 50% of cases. Recurrences of GBS are rare, reported in 2-5% of patients.

CIDP is a chronic progressive or relapsing condition that develops over at least 2 months. Studies have shown that up to 16% of CIDP patients may present acutely like AIDP, developing in <8 weeks.[8] This entity is defined as acute-onset CIDP (A-CIDP) which presents acutely like GBS but followed by a chronic course beyond 2 months.

Treatment-related fluctuations (TRF) may be observed during the course of GBS, during which clinical deterioration after treatment is observed but <8 weeks after symptom onset. Acute onset with more than three fluctuations after treatment and progression beyond 9 weeks was considered as A-CIDP as against GBS with TRF. [5]

A-CIDP patients in Dionne et al. and Alessandro et al. studies [8,9] were significantly more likely to have prominent sensory signs with proprioceptive disturbances and sensory ataxia, which was noted in both our patients. Cranial nerve involvement including bulbar weakness (defined as dysphagia, dysarthria), and respiratory tract involvement are atypical features of CIDP, which was however present in both our patients.

A sural-sparing pattern or elevated sensory ratio, when observed, might be useful to differentiate a length-dependent axonal polyneuropathy from an acquired demyelinating and potentially treatable polyneuropathy. According to the study by Dione et al., this pattern is observed with similar frequency in both AIDP and CIDP, at least when studied acutely. None of the electrophysiological parameters studied could reliably differentiate between AIDP and A-CIDP. [9,10]

Kerasnoudis et al. observed that nerve ultrasound score called Bochum ultrasound score could be a useful tool in distinguishing CIDP from AIDP. The score includes measurement of cross-sectional area of (a) the ulnar nerve in Guyon's canal, (b) the ulnar nerve in upper arm, (c) the radial nerve in spiral groove and (d) the sural nerve between the lateral and medial head of the gastrocnemius muscle. [11]

The spectrum of CIDP is expanding and patients with antibodies against nodal or paranodal antigens seem to constitute a distinct group, referred to as the autoimmune nodopathies[12]. Antibodies against CNTN1 have been reported in these patients, they may present acutely as GBS, have a severe disease course with predominant distal weakness and sensory ataxia, with no or poor response to IVIG. Antibodies against NF155 have been observed mainly in young adults with a subacute or chronic disease course, distal more than proximal weakness, sensory ataxia, tremor, and poor response to IVIG. CIDP with anti-Caspr1 antibodies had more frequent respiratory failure and cranial nerve involvement.[12]

Plasma exchange after initial IVIG in GBS was not associated with improved short-term outcomes but rather with increased cost and hospital stay[13]. However, we believe there is a subgroup of patients who do not respond to IVIG may benefit with plasmapheresis. These may be A-CIDP as in our patients or nodopathies. We need prospective studies to identify this subgroup of patients.

Our first patient clinically behaved like recurrent AIDP. However, this was the third relapse of weakness with severe illness each time requiring ventilatory support with prolonged recovery. She received IVIG despite non-responsiveness to initial IVIG at an outside hospital. Given the 3 relapses of GBS-like presentation, and non-responsiveness to IVIG she was treated at our hospital with plasmapheresis. She had dual positive Neurofascin NF-155 and NF-186 antibodies and was given Rituximab to prevent further relapses. Hence, her clinical presentation was that of A-CIDP.

The second patient presented as GBS, with prominent cranial nerve and respiratory involvement at the onset. In her subsequent relapses there was prominent proprioceptive impairment with sensory ataxia in addition to severe proximal and distal weakness. With more than 3 relapses and progression beyond 9 weeks, she was also treated as CIDP. Given the severe clinical course with sensory ataxia, GBS-like presentation and poor response to IVIG, nodopathy was considered. Neurofascin NF-155, anti-contactin and anti-CASPR antibodies were negative.

Both the patients had poor response to IVIG and responded well to plasmapheresis and rituximab raising the possibility of nodopathies which show poor response to conventional IVIG treatment [14]. They both showed improvement with remission after treatment with rituximab.

Conclusion

Patients presenting as GBS with treatment related fluctuations or recurrent relapses may be A-CIDP. IVIG unresponsive patients with a fluctuating clinical course may benefit with aggressive treatment with plasmapheresis. It is important to recognize this subgroup of patients while treating them as GBS as they may require long term immunosuppressive treatment.

References

1. Grand'Maison F, Feasby TE, Hahn AF, et al. Recurrent Guillain–Barre´ syndrome. Clinical and laboratory features. Brain 1992;115:1093–1106.

2. Das A, Kalita J, Misra UK. Recurrent Guillain–Barre´ syndrome. Electromyogr Clin Neurophysiol 2004;44:95–10.

3. Latov N. Diagnosis and treatment of chronic acquired demyelinating polyneuropathies. *Nat Rev Neurol.* 2014;10:435–446.

4. Dalakas MC. Advances in the diagnosis, pathogenesis and treatment of CIDP. *Nat. Rev. Neurol.* 2011;7:507–517.

5. Ruts L, Drenthen J, Jacobs BC, van Doorn PA; Dutch GBS Study Group. Distinguishing acute-onset CIDP from fluctuating Guillain-Barre syndrome: a prospective study. Neurology. 2010 May;74(21):1680–6.

6. Kleyweg RP, van der Meché FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barré syndrome. *Muscle Nerve.* 1991;14:1103–9.

7. Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology. 2011;36(2):123–33.

8. Jacobs BC, Rothbarth PH, van der Meché FG, Herbrink P, Schmitz PI, de Klerk MA, et al. The spectrum of antecedent infections in Guillain-Barré syndrome: a case-control study. Neurology. 1998;51(4):1110–5.

9. Alessandro L, Rueda JMP, Wilken M, et al. Differences between acute-onset chronic inflammatory demyelinating polyneuropathy (A-CIDP) and acute inflammatory demyelinating polyneuropathy (AIDP) in adult patients. *J Peripher Nerv Syst*. 2018;

10. Dionne A, Nicolle MW, Hahn AF. Clinical and electrophysiological parameters distinguishing acute-onset chronic inflammatory demyelinating polyneuropathy from acute inflammatory demyelinating polyneuropathy. *Muscle Nerve*. 2010; **41**(2): 202- 207.

11. Kerasnoudis A, Pitarokoili K, Behrendt V, Gold R, Yoon MS. Nerve ultrasound score in distinguishing chronic from acute inflammatory demyelinating polyneuropathy. Clin Neurophysiol. 2014 Mar;125(3):635-4

12. Van den Bergh PYK , van Doorn PA , Jacobs BC , Querol L , Bunschoten C , Cornblath DR. Boundaries of chronic inflammatory demyelinating polyradiculoneuropathy. J Peripher Nerv Syst. 2020;25(1):4–8.

13. Oczko-Walker M, Manousakis G, Wang S, Malter JS, Waclawik AJ. Plasma exchange after initial intravenous immunoglobulin treatment in Guillain-Barré syndrome: critical reassessment of effectiveness and cost-efficiency. J Clin Neuromuscul Dis. 2010 Dec;12(2):55-61.

14. Querol L, Rojas-García R, Diaz-Manera J, Barcena J, Pardo J, Ortega,et-al. Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins. Neurol Neuroimmunol Neuroinflamm. 2015 Sep 3;2(5):e149

Pattern recognition of neuropathy and neuronopathy: 7 Questions / 11 Patterns

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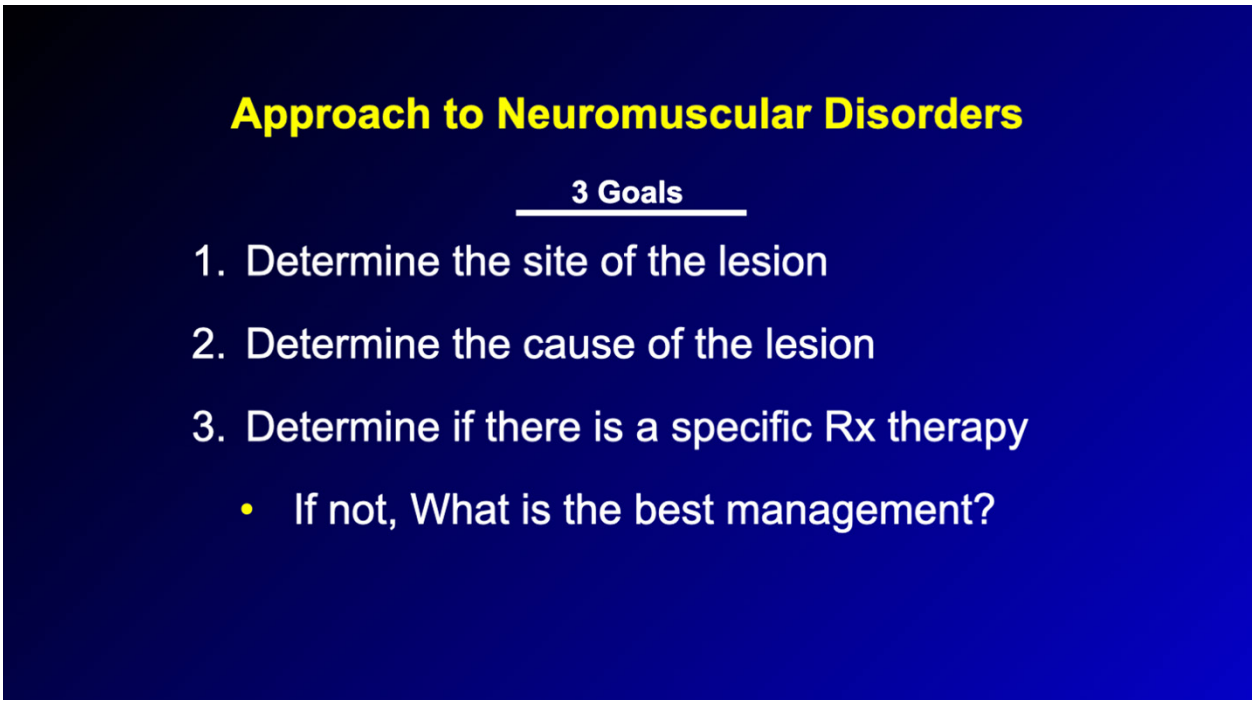
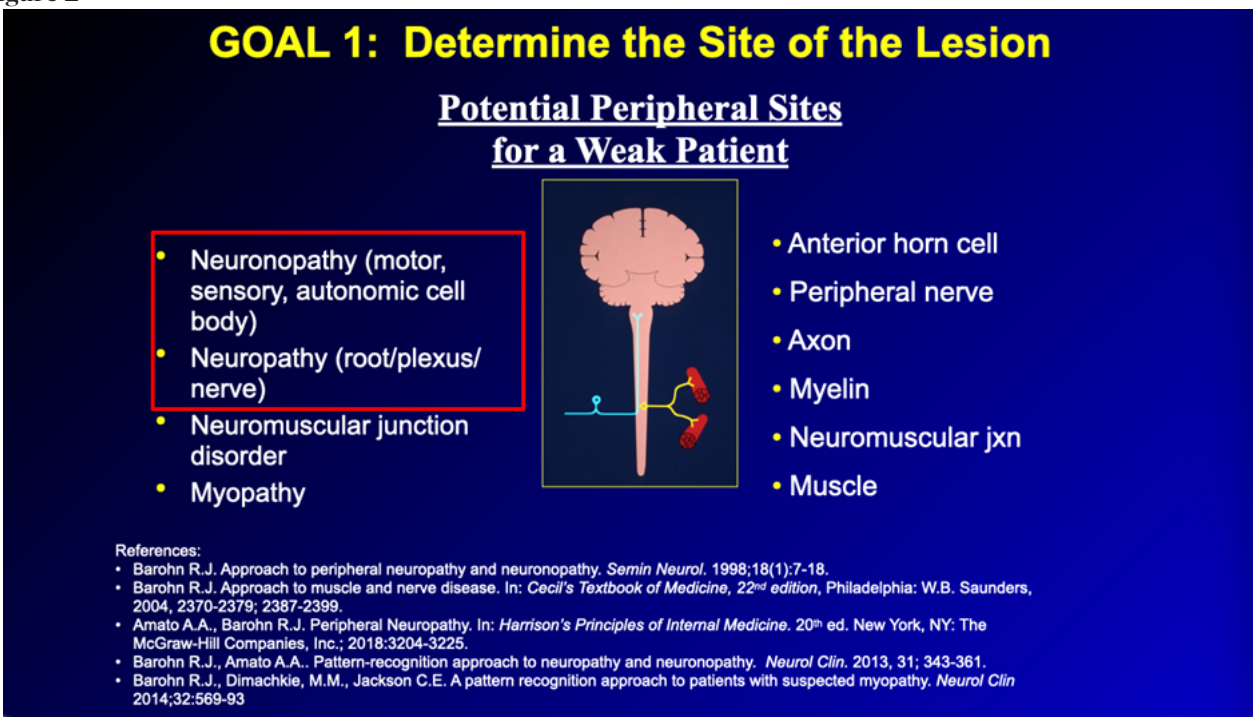
Every neurologist has three goals when they see a patient: 1. To determine the site of the lesion; 2. To determine the cause of the lesion; 3. To determine the specific therapy for the patient's problem and if not a specific therapy, what the best management is. (Figure 1)

Figure 1



This discussion will concern the peripheral nervous system components that include the lower neuron nerve cell bodies, roots, plexus, and nerves. (Figure 2)

Figure 2



Therefore, this includes both lower motor neurons (anterior horn cells) and sensory neuron cell bodies or the dorsal root ganglia.

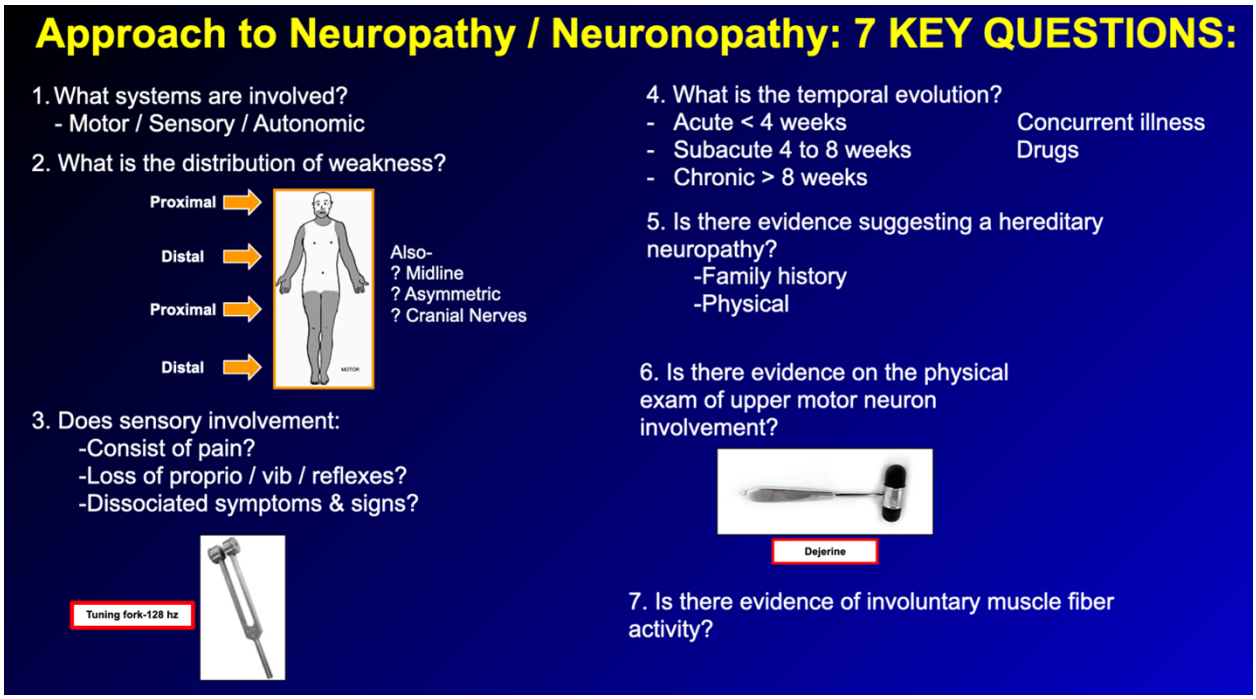
Using the pattern recognition approach to neuropathies and neuronopathies, clinicians can place a patient in a clinical pattern before ordering a single laboratory test.

In order to do that there are seven key questions that you need to be asking yourself when you take the history and when you do the physical exam. When you have the answers to these seven key questions, then you will put the patient into one of the patterns. Then after you put the patient into one of the patterns, it is time to think about ordering laboratory tests to finalize the diagnosis.

In previous publications and lectures, we taught the 6-question/10-pattern approach. We have now added question #7 on excessive muscle activity and created pattern 11 to accommodate some of these patients.

What are the **SEVEN KEY QUESTIONS** you need to answer to put the patient into a pattern? (Figure 3)

Figure 3



Question 1: What systems are involved?

When we ask, "What systems are involved?", what we are asking is if there is motor, sensory, or autonomic involvement. To determine if there is motor involvement you need to determine if the patient complaining of weakness. In addition, if the patient complains of muscle twitches or fasciculations, this could also indicate motor involvement. If there is sensory involvement, the patient will complain of numbness, tingling, pain, and poor gait or clumsiness.

If there is autonomic involvement, the patient will complain of lightheadedness when standing (orthostasis) or issues involving sweating, gastric motility, or impotence. Patients may complain of a combination of motor, sensory, and autonomic symptoms.

Question 2: What is the distribution of the weakness?

Once the patient says that they are weak, then you need to examine them and determine the distribution of the weakness.

Is the weakness exclusively distal, such as in an axonopathy or is it proximal and distal such as in an acquired myelinopathy? Is the weakness symmetric or asymmetric?

Does the weakness involve midline musculature such as cervical and thoracic paraspinous muscles, oropharyngeal muscles, other cranial nerve innervated muscles, and the diaphragm?

Question 3: What is the nature of the sensory involvement?

Question 3 further investigates sensory involvement and has several sub-questions. If the patient complains of numbness and tingling, then you know there is most likely sensory involvement. Additional questions regarding sensory involvement are as follows:

Does the patient have neuropathic pain?

If there is severe pain, then that will lead you down certain pattern pathways.

Also, if there is severe pain you know that you will need to treat the patient's neuropathic pain.

Next, you need to determine if there is severe proprioception loss, vibration loss, or loss of reflexes.

If the patient has numbness and tingling, and if proprioception, vibration, and reflexes are normal, then there is a possibility that this is a small fiber neuropathy. If vibration, proprioception, or reflexes are abnormal the neuropathy involves large fibers as well. If proprioception and vibration are severely involved, the lesion could also be either in the dorsal root ganglion or posterior columns.

Finally, are there **dissociated sensory symptoms and signs**?

The phrase "**dissociated sensory symptoms and signs**" may be unfamiliar to you.

The concept of dissociated cerebrospinal fluid findings in Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy (CIDP) with elevated protein and normal cell count is well known. This is a dissociated laboratory finding.

What do we mean by dissociated sensory symptoms and signs? The concept of dissociated sensory loss is sometimes a finding in cervical syringomyelia when due to a central cavity in the spinal cord, crossing spinothalamic pathways are disrupted causing pain and temperature loss bilaterally in the upper extremities with preservation of posterior column function. This has been termed dissociated sensory loss. But the concept of dissociated sensory symptoms and signs is a different concept and can be explained as follows:

When the patient presents with distal weakness (foot drop or hand weakness) and they do not complain of numbness and tingling, but on examination, you find a significant loss of either light touch, vibration, proprioception, temperature, or pinprick, that implies that there has been a long-standing disorder over many years and the etiology is most likely hereditary.

Question 4: What is the temporal evolution of the neuropathic disorder?

How fast or how slow is the condition progressing?

Acute is less than 4 weeks, chronic is more than 8 weeks, and subacute is 4-8 weeks.

This temporal framework comes from our understanding of Guillain-Barré syndrome which always evolves over less than 4 weeks and CIDP which by definition has to progress longer than 8 weeks.

But we use this temporal evolution to apply to all neuromuscular disorders and indeed it can be used for all neurologic disorders.

While we are considering the temporal evolution, we also want to know if the patient was exposed to any drugs that could cause neuropathic disorders, were they exposed to an infection that could have precipitated a neuropathic disorder, and do they have another underlying systemic condition that could predispose them to a neuropathic disorder.

Question 5: Is there evidence of a hereditary neuropathy?

To determine if there is a hereditary neuropathy, one needs to take a careful family history. In addition, on examination, one needs to determine if there are high arches, hammer toes, or scoliosis. One may have to examine family members as well. If there are dissociated sensory symptoms and signs as described above this strongly suggests a hereditary neuropathy.

Figure 4 shows a picture of three successive generations (grandmother bottom picture, mother middle picture, daughter top picture) of Charcot-Marie-Tooth disease patients demonstrating high arches and hammertoes that worsen as the patient ages.

Figure 4

Question 6: Is there evidence on the physical exam of upper motor neuron involvement?

Are there brisk reflexes, Hoffman's signs, any increased tone, or extensor plantar responses?

Question 7: Is there evidence of excessive muscle fiber activity?

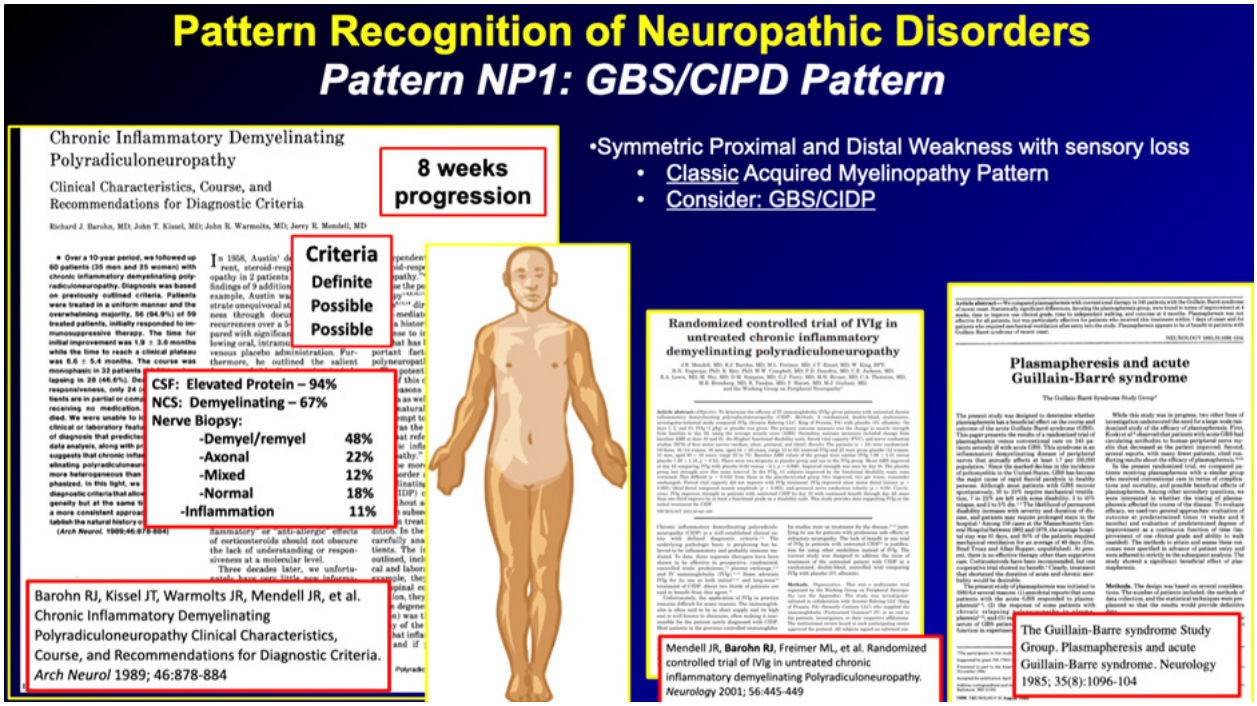
First, you should ask the patient if they have noticed muscle twitches. If the answer is "yes" then ask them which muscles have had twitches and how frequently they occur and what time of day. They can also ask if the twitches are exacerbated by exercise or drinking caffeine. Then, examine the patient once they have disrobed and carefully look for fasciculations. Sometimes fasciculations can be elicited by gently tapping a muscle with a reflex hammer or with the tip of the examiner's finger. More complex spontaneous muscle activity can be classified as myokymia. To classify an excessive muscle movement as myokymia it is necessary to do a needle EMG and determine if the spontaneous muscle activity is regular and periodic. Fasciculations are usually irregular and have no periodicity. Fasciculations can ultimately be benign in etiology or could indicate underlying nerve damage. Question 7 only addresses excessive muscle activity due to neuropathic disorders and not myopathic (see discussion below).

Once the answers to these seven key questions are obtained, you can place the patient into one of the **ELEVEN NEUROPATHIC PATTERNS.**

The **ELEVEN NEUROPATHIC PATTERNS** (NP) are as follows:

NP1: **Symmetrical, proximal, and distal weakness with sensory loss.** (Figure 5)

Figure 5

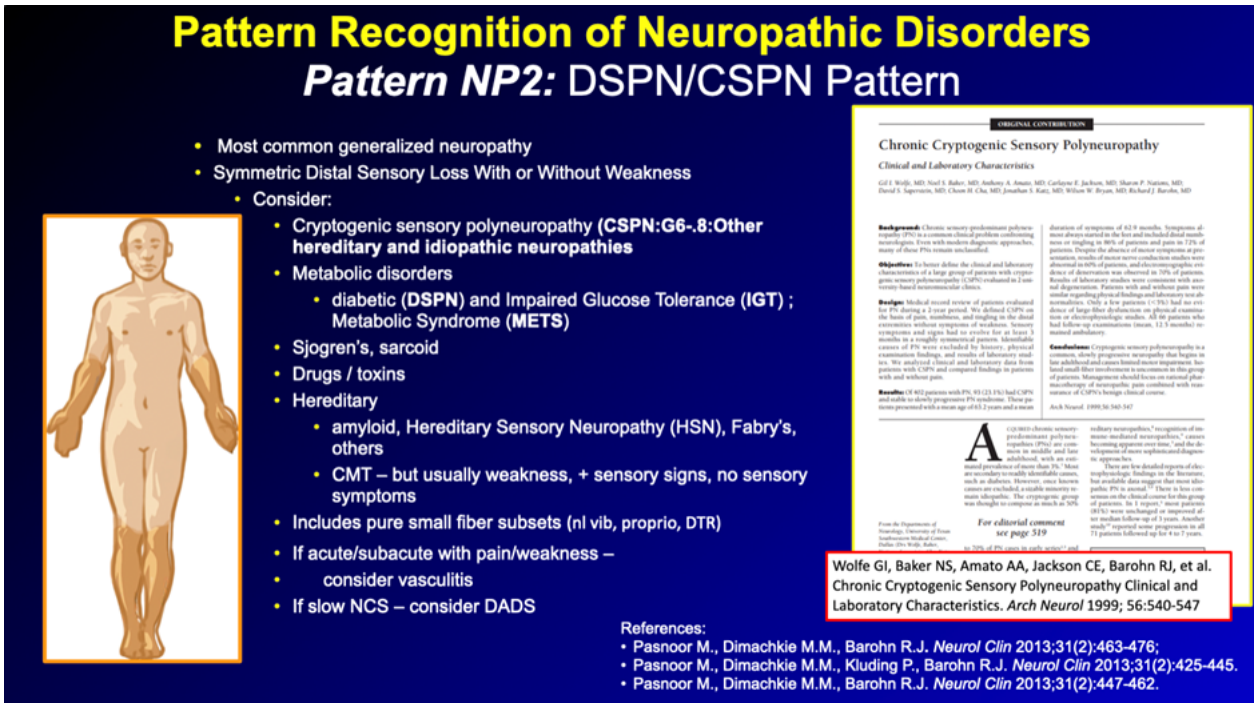


We also refer to this as the GBS/CIDP pattern. These patients have numbness, tingling, and weakness, and on examination, they have weakness in proximal and distal muscles.

It is extremely important to identify the NP1 pattern because it is the hallmark of classic acquired myelinopathy and is treatable with either immunomodulating or immunosuppressive therapy. While a temporal distinction is the primary determination between acute GBS (less than four weeks) and chronic CIDP (greater than eight weeks), there are other features that are more consistent with GBS such as significant autonomic and respiratory involvement.

NP2: **Symmetric distal sensory loss with or without weakness.** (Figure 6)

Figure 6



This is also referred to as the DSPN/CSPN pattern.

This is the most common generalized neuropathy pattern. In the NP2 pattern, patients often have no or very little weakness, although prominent distal weakness can occur. The most common causes of this pattern are diabetic sensory polyneuropathy (DSPN), or cryptogenic sensory polyneuropathy (CSPN). More recently, the metabolic syndrome has also emerged as a cause. We, therefore, believe this pattern also occurs in metabolic syndrome and painful neuropathy associated with impaired glucose intolerance.

Other causes of this pattern are toxicity from drugs or other toxins.

Hereditary neuropathy, also known as Charcot-Marie-Tooth disease (CMT) also falls into this category. However, in hereditary neuropathy, the weakness is out of proportion to the sensory involvement as noted above.

Amyloid neuropathy, both hereditary and acquired, can have an NP2 presentation. Hereditary or familial amyloidosis is very important to recognize because we now have treatments for this disorder.

We group all small and large fiber neuropathies in the NP2 pattern.

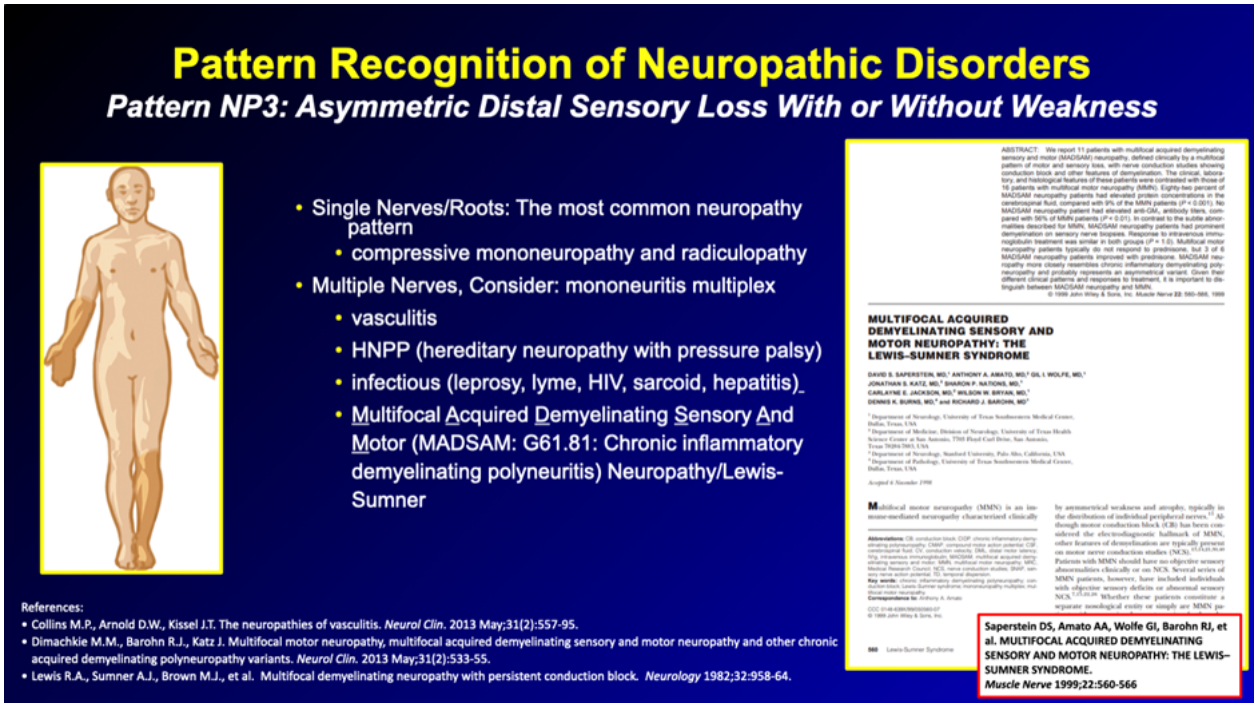
Based on the clues from the physical exam you will determine if the patient is likely to have a small fiber neuropathy, as noted above. Then, laboratory tests such as nerve conduction studies and skin biopsies can further support the clinical impression that only small fibers are involved.

Usually, vasculitis presents as mononeuritis multiplex (see NP3 below) but rarely, vasculitis presents with an NP2 pattern. When this occurs, there is usually intense pain, significant distal lower extremity weakness with sensory loss, and the temporal evolution is more often acute or subacute.

In addition, while most chronic acquired demyelinating polyneuropathies have an NP1 pattern, one variant called distal acquired demyelinating symmetric neuropathy (DADS) will have an NP2 pattern.

NP3: Asymmetric distal sensory loss with or without motor weakness (Figure 7).

Figure 7



This is the most common neuropathy when it is a single nerve or root.

Examples are median neuropathy at the wrist, ulnar compressive neuropathy, peroneal compressive neuropathy, or a cervical or lumbar radiculopathy (ex., C5, C6, L5, S1).

On the other hand, if two or more distal peripheral nerves are involved, then that is mononeuropathy multiplex.

It is important to recognize mononeuritis multiplex quickly as one of the causes is vasculitis which is serious and can be life-threatening.

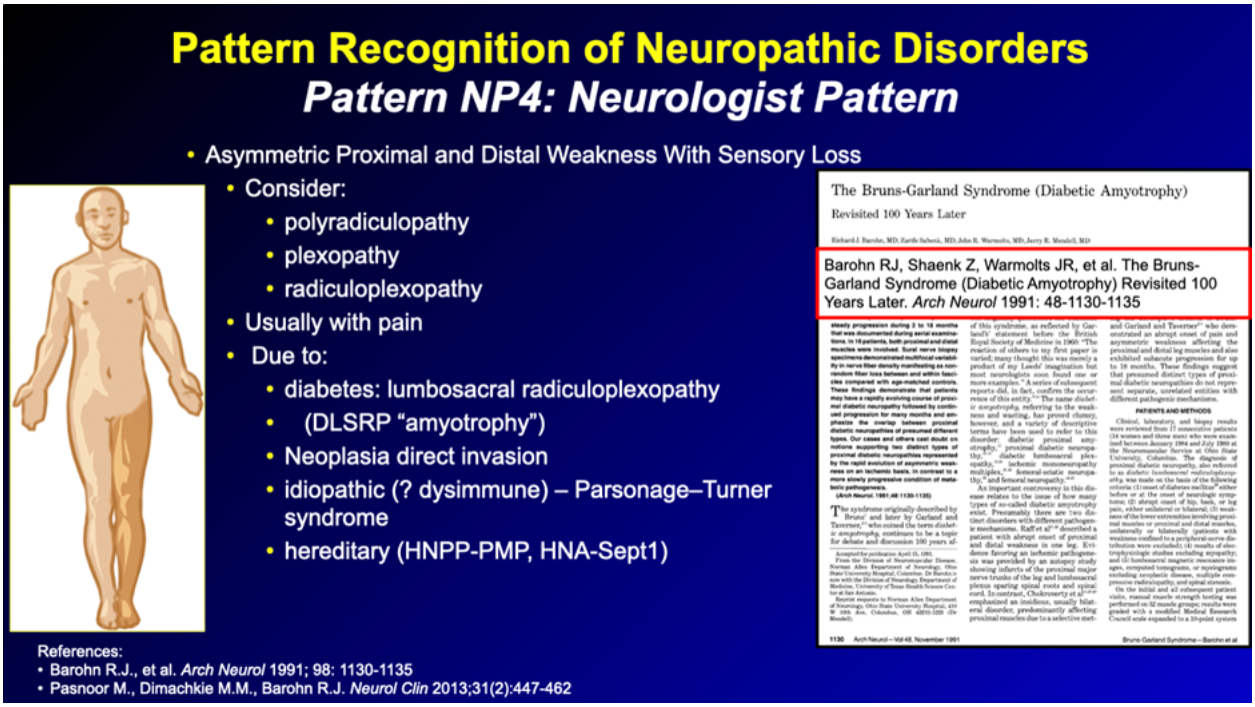
Vasculitis typically occurs subacutely or acutely. There also is a hereditary form of mononeuropathy multiplex, hereditary neuropathy with liability to pressure palsy (HNPP) which evolves over months or years with different episodes of compressive neuropathy.

A variety of infectious diseases can produce mononeuropathy multiplex in which case it is then referred to as mononeuritis multiplex (Figure 8).

There is another variant of chronic acquired demyelinating neuropathy that presents with mononeuritis multiplex and that presents multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), this is also referred to as the Lewis Sumner syndrome. This is another CIDP variant.

NP4: **Asymmetric proximal-distal weakness with sensory loss** (Figure 8).

Figure 8



We call this "The Neurologist's Pattern" because it is usually the neurologist who makes the diagnosis after others have incorrectly diagnosed the patient.

The key distinguishing variable that distinguishes NP3 from NP4 is the presence of **proximal** weakness in NP4.

Patients will present with an entire arm or leg involved, proximally and distally, from nerve roots C5 to T1 or from L1 to S1.

All of these segments do not have to be equally involved but both proximal and distal muscles are involved to some extent. When this occurs, the lesion has to be in either multiple roots, (polyradiculopathy) or in the plexus, or in both-radiculoplexopathy.

These patients usually have severe pain at the onset.

The most common cause of NP4 is diabetes and therefore we call this diabetic lumbosacral radiculoplexopathy. In the older literature, it was called diabetic amyotrophy, but we do not use that term any longer as it is nonspecific and simply implies loss of muscle mass in a diabetic. Another term for diabetic lumbosacral radiculoplexopathy (DLSRP) that we have used in the past is Bruns-Garland syndrome (Figure 9).

Usually, the patients have been misdiagnosed and they may have had back surgery for presumed compressive radiculopathy, but they are still getting worse.

The neurologist often will then be consulted after lumbar surgery and make the diagnosis of DLSRP. Hence, as noted above, we call this "The Neurologist's Pattern".

Other causes of NP4 are neoplasia, either direct invasion into the plexus or the meninges (either carcinomatous meningitis or lymphomatous meningitis).

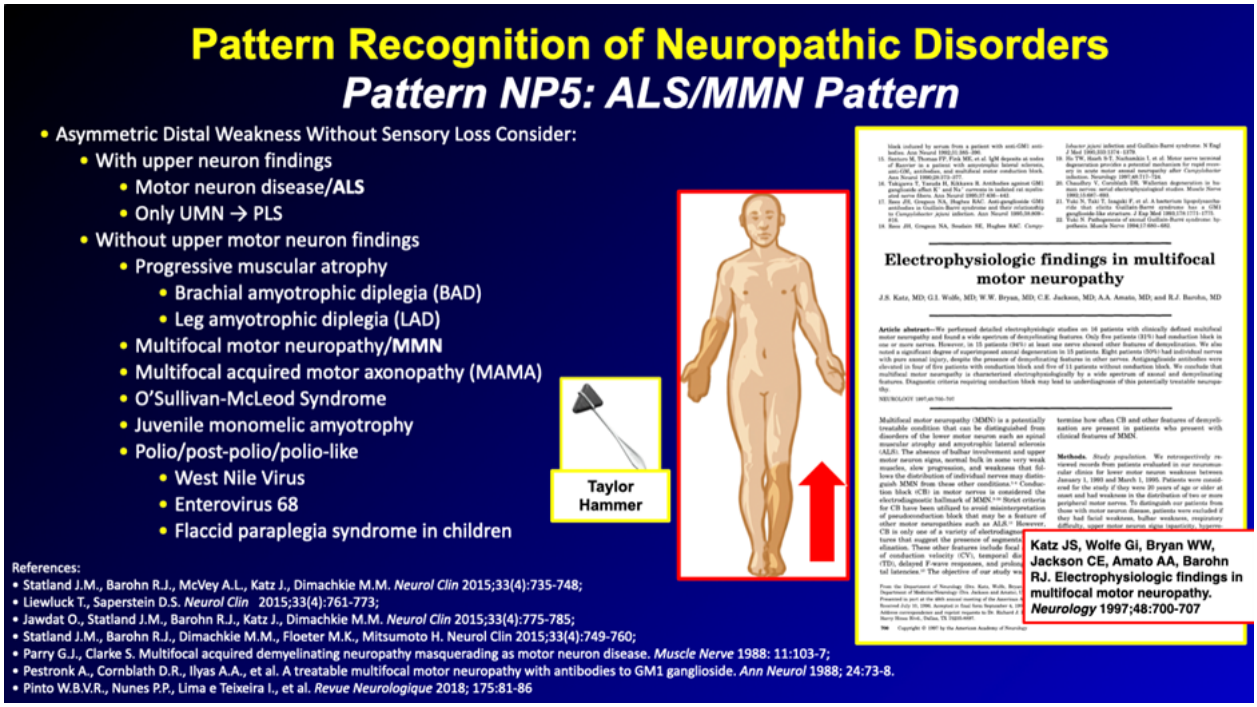
Other causes of NP4 are idiopathic or immune-mediated such as the Parsonage-Turner Syndrome that occurs in the brachial plexus.

There is also a lumbosacral idiopathic variant as well.

There are also hereditary causes of plexopathy due to hereditary neuralgic amyotrophy (HNA) related to SEP9 mutations. SEP9 mutations account for approximately 50% of HNA and other gene mutations have been identified with this phenotype. These are generally autosomal dominant. HNPP can occasionally present with a painless recurrent plexopathy. Hereditary plexopathy cases generally are painless in contrast to acquired cases which are usually painful.

NP5: Asymmetric distal weakness without sensory loss (Figure 9)

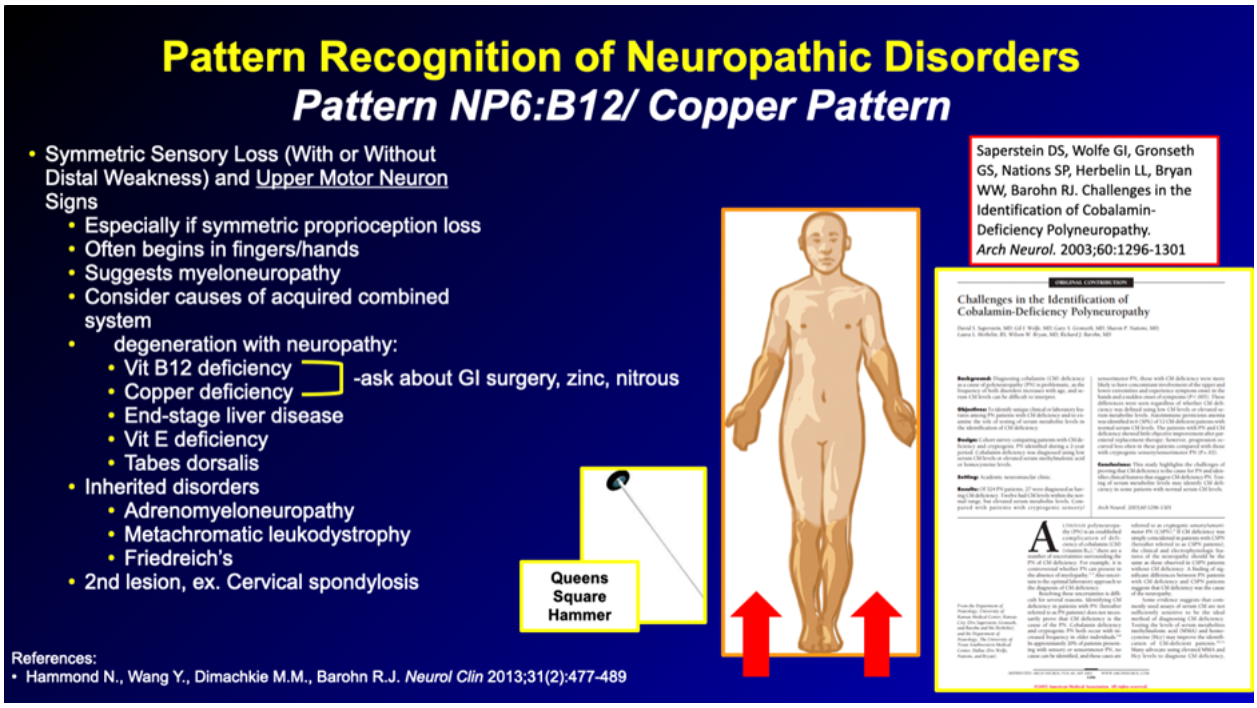
Figure 9



NP5 is also known as the "ALS/MMN pattern". With this pattern, the patient presents with progressive foot drop or progressive hand weakness typically for six to twelve months. There are no sensory symptoms or signs. After you have established that the patient is weak in this distribution then you need to assess for upper motor neuron signs. You need to determine if there are hyperactive reflexes or increased tone or pathologic reflexes. If they have upper motor neuron signs the diagnosis is almost always going to be amyotrophic lateral sclerosis (ALS). Occasionally, with exclusively upper motor neuron signs the diagnosis can be primary lateral sclerosis (PLS). ALS is much more common than PLS. If they do not have upper motor neuron signs, then the differential diagnosis is more challenging. The patient could have progressive muscular atrophy (PMA) which is the lower motor neuron form of ALS. If the weakness begins in one hand, the diagnosis could be multifocal motor neuropathy, which is treatable. There are a few other diagnoses that can present with this pattern such as juvenile monomelic atrophy, polio or polio-like viruses that can cause weakness, and multifocal acquired motor axonopathy, which we call MAMA.

NP6: Symmetric sensory loss with or without distal weakness and upper motor neuron signs. (Figure 10)

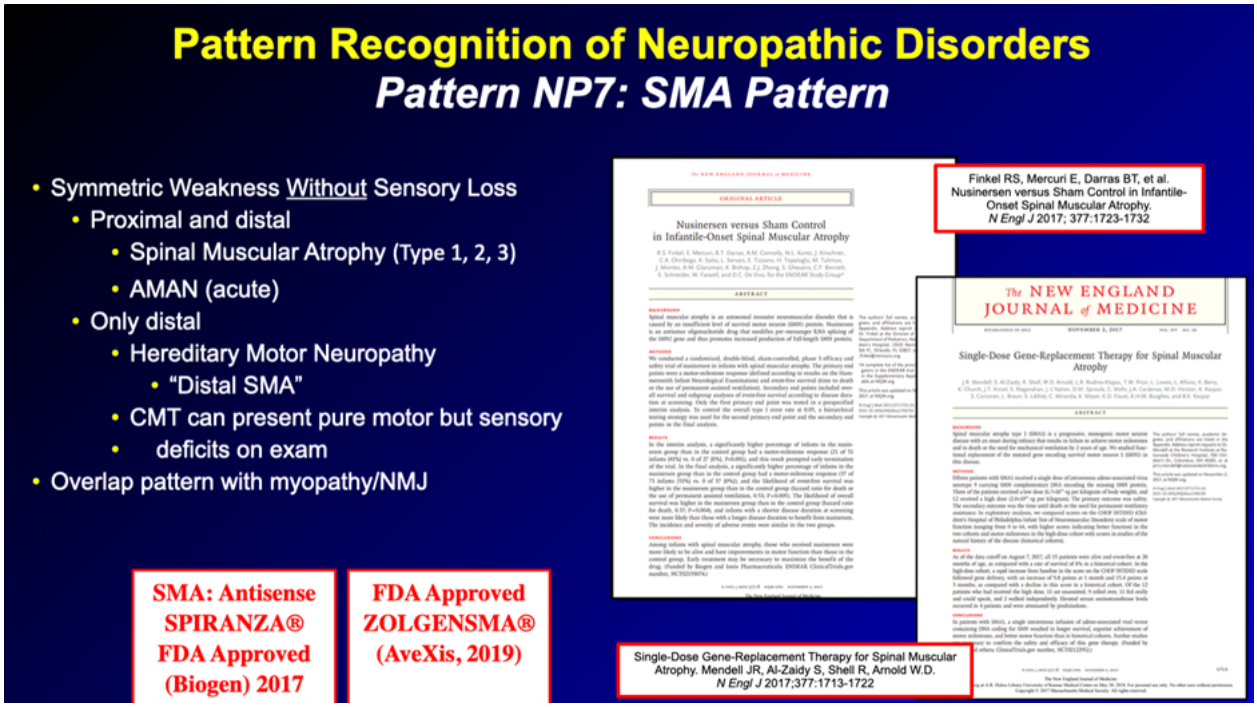
Figure 10



This is similar to the NP2 but with upper motor neuron signs. The patient presents with numb hands and feet. Sometimes the sensory symptoms can begin in the hands before the feet. They have significant gait instability, and they have significant proprioceptive and vibration loss, more than is seen in a typical DSPN or CSPN patient. They have brisk reflexes, pathologic reflexes, and they may have increased tone. All of these features in combination suggest myeloneuropathy. Both the peripheral nerves and the spinal cord are involved. That is why these sensory symptoms can begin in the hands and also why there is extensive proprioception and vibration loss due to posterior column damage. The patient may not have all of the abnormal symptoms and signs noted above and the evidence of upper motor neuron signs could be subtle. Therefore, a high index of suspicion is indicated. For example, the patient with a typical NP2 pattern may have a loss of ankle reflexes but have crossed adductor reflexes at the knees and Hoffman's reflexes in the fingers. Or the patient may have an NP2 pattern with easily obtainable ankle reflexes, crossed adductors, and Hoffman's signs. Any of these combinations would put the patient in the NP6 category. The next step is to search for combined system generation due to B12 and/or copper deficiency. Therefore, you have to ask about prior gastrointestinal surgery, excessive zinc use, and illicit nitrous oxide use. Other rare entities that can have a combination of upper and lower motor neuron signs with motor and sensory involvement include inherited disorders such as Friedreich's ataxia, adrenomyeloneuropathy, and metachromatic leukodystrophy. On the other hand, the NP6 pattern can also be produced when a second lesion is superimposed on CSPN or DSPN, such as cervical spondylosis or bilateral strokes. Therefore, these patients usually have to have MRI imaging of the cervical spine and the brain to exclude second lesions.

NP7: Symmetric weakness without sensory loss. (Figure 11)

Figure 11

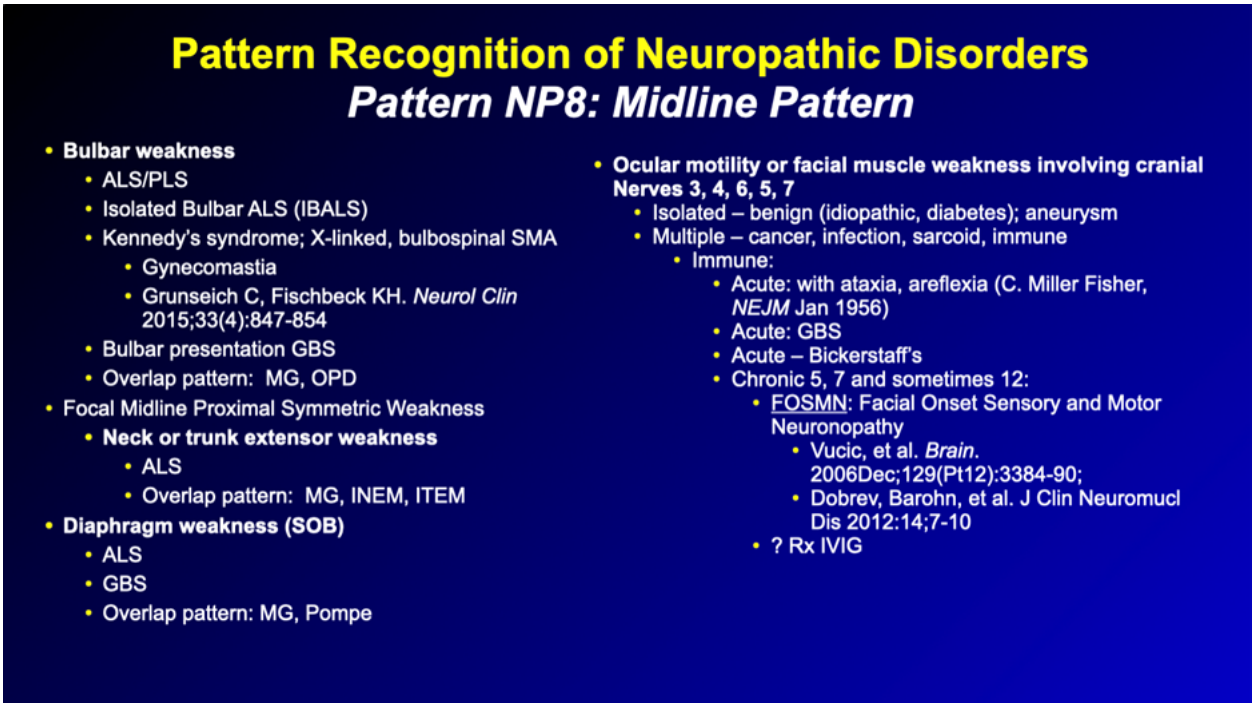


In the NP7 pattern, the weakness is usually proximal and distal and when this occurs, the diagnosis is usually spinal muscular atrophy (SMA), either type 1, 2, or 3. This is extremely important to recognize as autosomal recessive SMA is now treatable with gene therapy and antisense therapy. While SMA can present at birth or shortly after birth it is considered a chronic condition. On the other hand, if this pattern occurs acutely in either adults or children, the diagnosis may be acute motor axonal neuropathy (AMAN). If the presentation is chronic and only distal, then we refer to this entity as hereditary motor neuropathy. In the older literature hereditary motor neuropathy was referred to as distal SMA.

NP7 overlaps with myopathic and neuromuscular junction patterns which can present with proximal and distal weakness with no sensory loss.

NP8: The Midline Pattern (Figure 12)

Figure 12



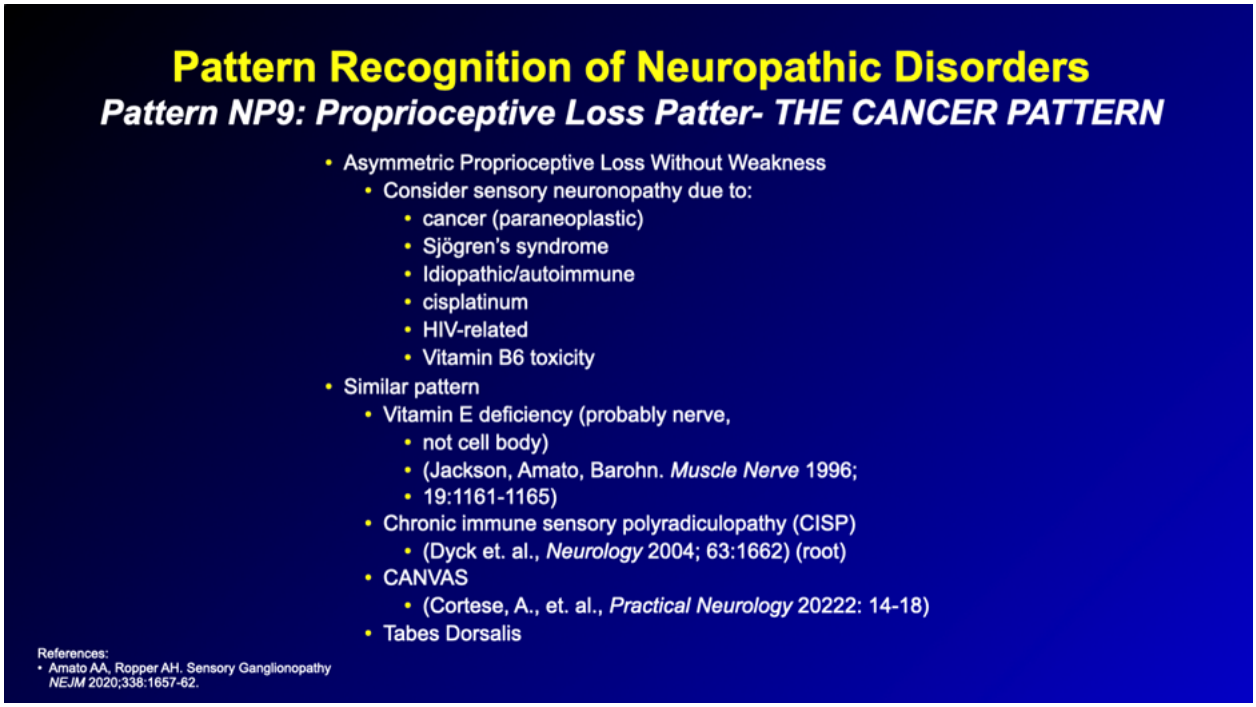
The "midline pattern" term is used when there is weakness of midline muscles involving bulbar or cervical or thoracic musculature, or the diaphragm. When a neuropathic patient presents with chronic progressive bulbar weakness the diagnosis is most likely going to be ALS, PMA, or PLS. Alternatively, it could be Kennedy's syndrome, X-linked bulbospinal SMA. If it is an acute presentation the diagnosis may be a bulbar presentation of GBS. Also in the midline pattern are patients who present with neck or trunk drop. When it is neuropathic, the most likely cause is motor neuron disease, ALS, or PMA. If they present with progressive shortness of breath over months ALS is a consideration and if it occurs acutely then GBS is a consideration.

Also included in the midline pattern are muscle disorders involving ocular motility or facial musculature. In other words, any disorder involving cranial nerves the oculomotor nerve (cranial nerve 3), trochlear nerve (cranial nerve 4), abducens nerve (cranial nerve 6), or facial nerve (cranial nerve 7). Most of the time individual cranial nerve disorders involving these nerves are benign and often idiopathic and they improve over time. Multiple cranial nerves can be involved in Guillain-Barré syndrome. When multiple cranial nerves are involved subacutely or chronically and the disorder is progressive this could be due to an underlying malignancy or infectious process. Occasionally, multiple cranial nerves are due to an idiopathic condition called facial onset sensory and motor neuropathy, also known as FOSMN. These patients present with numbness beginning in the lower face and oral cavity that progresses over several years to involve the scalp, neck, shoulder, and arms. The muscles of the facial nerve (cranial nerve 7) and hypoglossal nerve (cranial nerve12) are involved and eventually, the patients develop dysphagia due to involvement in the glossopharyngeal nerve (cranial nerve 9) and the vagus nerve (cranial nerve 10).

NP8 midline patterns can overlap with myopathic and neuromuscular junction patterns. For example, bulbar weakness occurs in myasthenia gravis and oculopharyngeal muscular dystrophy (OPMD). Also, neck and trunk weakness can be a prominent feature of myasthenia gravis, isolated neck extensor myopathy (INEM), and isolated trunk extensor myopathy (ITEM). Finally, both myasthenia gravis and myopathies such as Pompe disease can have predominant diaphragm weakness causing shortness of breath.

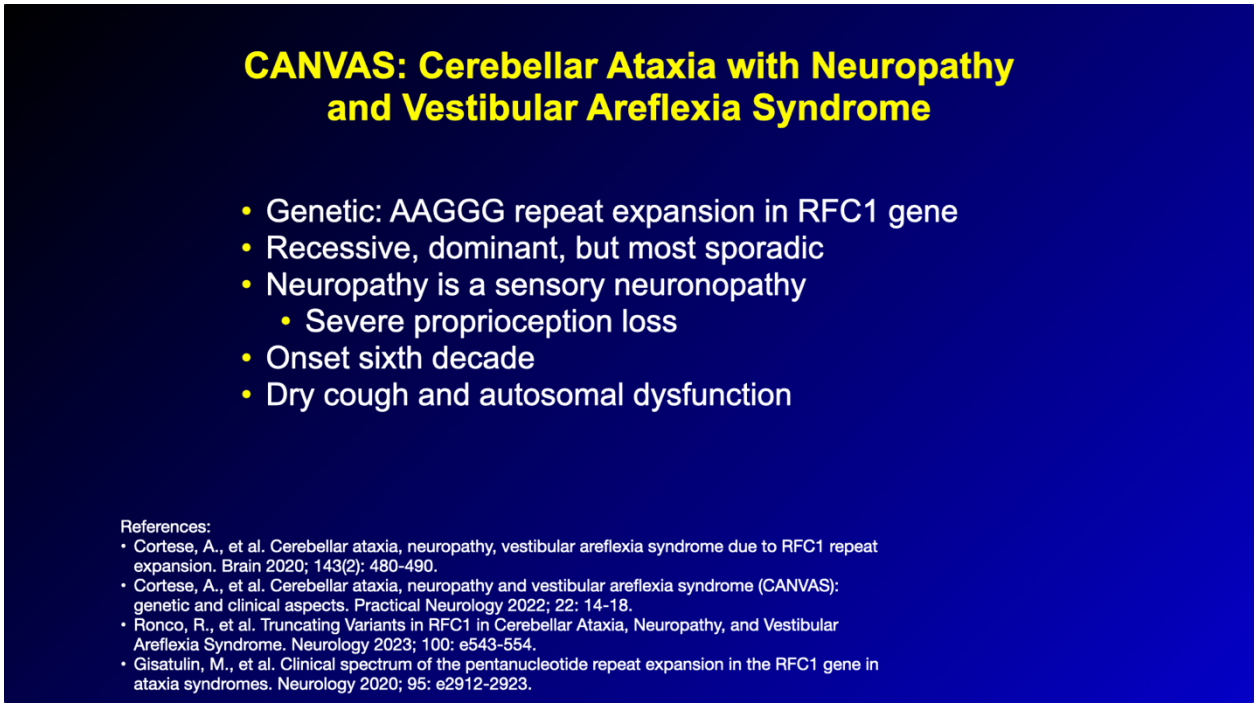
NP9: Asymmetric proprioceptive loss without weakness. (Figure 13)

Figure 13



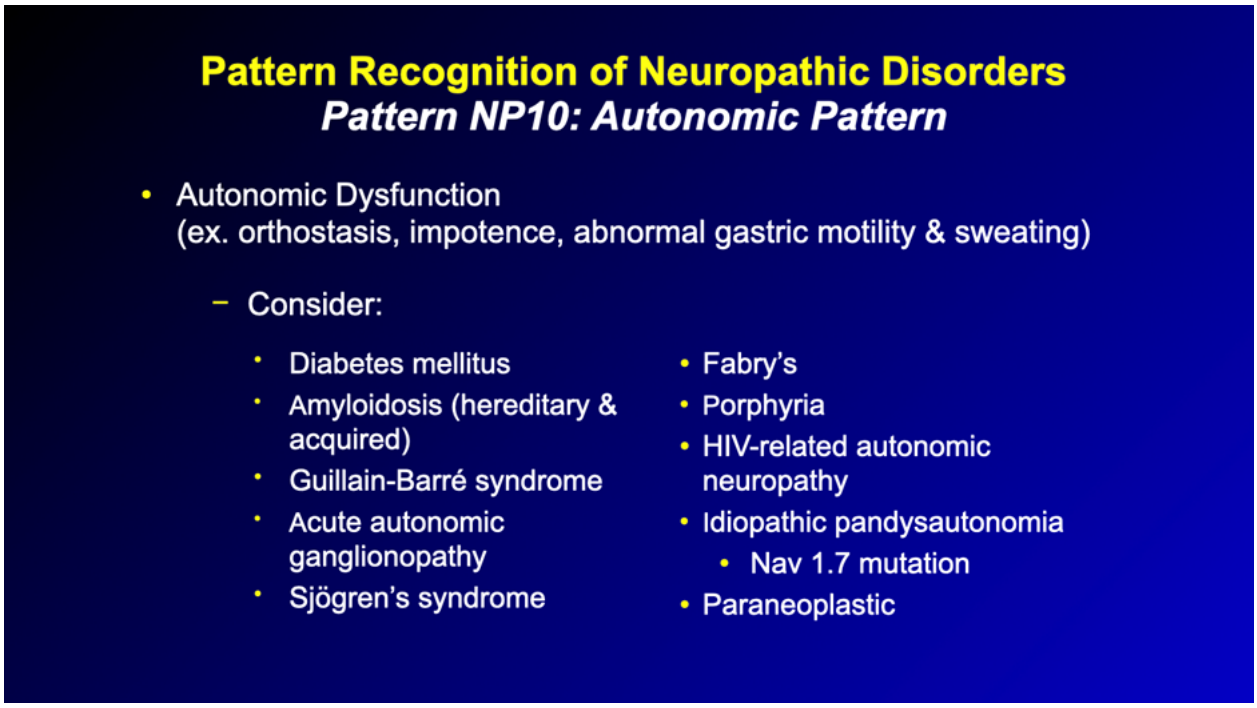
This is often due to an underlying malignancy with a paraneoplastic presentation. Therefore, we refer to this as "The Cancer Pattern". These patients present with numbness and tingling in either one leg or one arm or poor control of that limb which is due to proprioceptive loss. When you examine the patient, in addition to decreased touch and pin sensation, they have severely decreased proprioception either at the toes, ankles, and knees or the fingers, wrists, and elbows. When this occurs, the lesion is in the dorsal ganglion and the most common cause is cancer. Causes other than cancer include an autoimmune disorder such as Sjogren's disease. There may be other autoimmune causes of this pattern that may be associated with newly discovered antibodies to FGFR-3 and TS-HDS. Vitamin E deficiency neuropathy, either acquired or hereditary, can have the NP9 pattern. Another variant of CIDP, chronic immune sensory polyradiculopathy (CISP) presents with a classic NP9 pattern. CISP is presumably due to inflammation and demyelination of the sensory roots proximal to the dorsal root ganglion, and it is potentially treatable with IVIG. Some of these patients reportedly respond to intravenous immune globulin therapy, however, 2 small randomized, placebo-controlled trials showed no benefit from IVIG. CISP and sensory neuronopathy can clinically look very similar. The way to distinguish them is by the sensory nerve conduction studies which are preserved in CISP and abnormal in sensory neuronopathy. Other considerations with this pattern are toxicity due to drugs such as the platinums. HIV infection has been associated with neuropathies that have this pattern. A new entity has recently been described called CANVAS- cerebellar ataxia, neuropathy (most likely a neuronopathy), and vestibular dysfunction. This is due to a genetic defect in the RFC1 gene with a repeat expansion of AAGGG. These patients have severe proprioceptive loss and ataxia for multiple reasons including sensory neuronopathy. One of the clues to diagnosing these cases is that patients have recurrent coughing for which no etiology has been found.

Figure 14



NP10: The Autonomic Pattern (Figure 15)

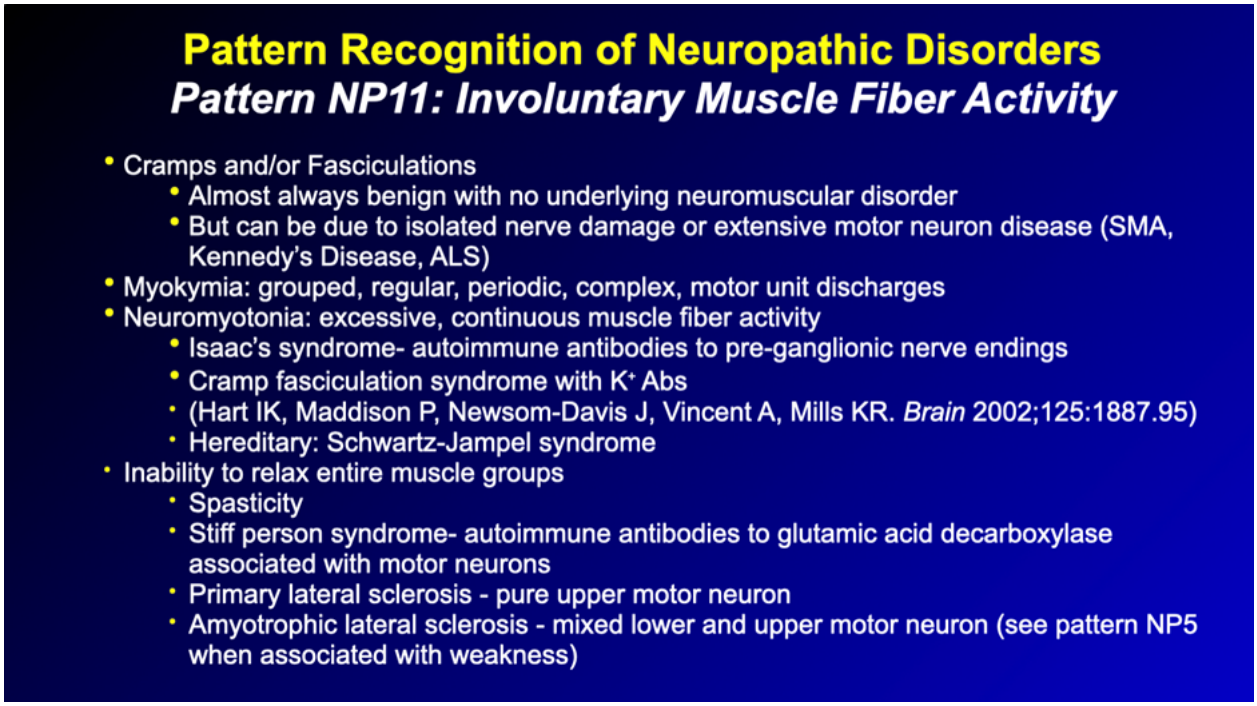
Figure 15



With the autonomic pattern patients present with orthostasis, impotence, abnormal gastrointestinal motility, and abnormal sweating symptoms. The most common cause is diabetes. But there are other causes such as hereditary amyloidosis and it is important to recognize this entity because it is treatable. Acutely, Guillain-Barré syndrome can have significant autonomic symptoms and signs.

NP11: Excessive muscle activity. (Figure 16)

Figure 16



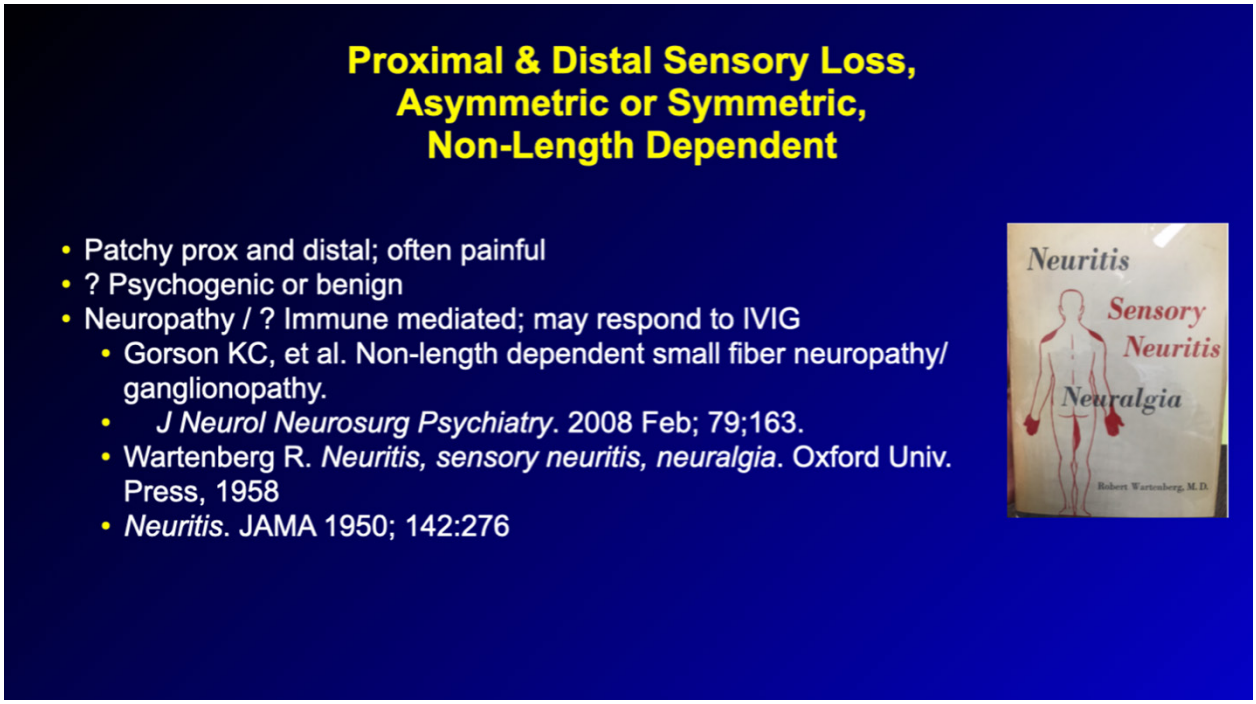
There are a variety of types and etiologies of excessive muscle activity that range from benign to ominous. Most fasciculations are indeed benign and do not represent any underlying medical problem or diagnosis. It is very common to experience muscle twitches and to visibly see them, particularly in the calf muscles such as the gastrocnemius, arm muscles such as the deltoid or biceps, or facial muscles such as the orbicularis oculi. These can occur when an individual is overly fatigued, after exercise, or after drinking an excessive amount of caffeine. Pyridostigmine for myasthenia gravis commonly causes fasciculations in the extremities and facial muscles. On the other hand, fasciculations can occur as a result of many types of peripheral nerve damage. This can be due to a relatively simple median nerve damage from carpal tunnel syndrome. Fasciculations can also occur in multiple skeletal muscles as a result of motor neuron disease from spinal muscular atrophy or amyotrophic lateral sclerosis. More complex, repetitive, and regular muscle twitches are often termed myokymia. However, determining the regular periodicity of myokymic twitches usually requires a needle EMG examination. Myokymia also can be the result of median nerve damage in carpal tunnel syndrome. Myokymic potentials can also occur after radiation therapy for cancer in muscles that are exposed to the radiation window. For example, radiation to the neck as a treatment for head and neck cancers can produce a brachial plexopathy with myokymic potentials in arm muscles. More dramatic excessive and continuous muscle fiber activity can produce what has been called neuromyotonia. Neuromyotonia can superficially look like multiple fasciculations, but a needle EMG examination will reveal the characteristic high-frequency neuromyotonic discharges. Neuromyotonia is usually the result of an autoimmune process at the presynaptic nerve endings and is due to antibodies directed to presynaptic potassium channels. This is also called Isaac's syndrome. The Schwartz-Jampel syndrome due to a mutation of the HSPG2 gene which codes for perlecan is a hereditary disorder that can produce an unusual continuous muscle fiber activity and muscle stiffness. This rare autosomal recessive disorder appears to cause an instability of neuromuscular junction transmission causing continuous muscle discharges. Therefore, while it is considered to cause a form of continuous muscle fiber activity it is probably better categorized as an unusual muscle-based myotonic disorder rather than neurogenic muscle stiffness. This entire category can be considered to overlap with muscle stiffness due to other common myotonic disorders due to hereditary mutations of sodium channel, chloride channel, and other genes related to muscle function.

A whole limb that is stiff from multiple involuntary muscle contractions could be due to something as common as spasticity due to upper motor neuron damage. Of course, any case of corticospinal tract damage can result in spasticity. However, in the context of neuromuscular disorders, motor neuron disease is the primary consideration for spasticity due to upper motor neuron damage. If both upper and lower motor neuron findings are present, the diagnosis is generally amyotrophic lateral sclerosis. In this case, there is almost always distal asymmetric weakness which would be recognized as an NP5 pattern. If there is only spasticity and other upper motor neuron findings in a case of presumed motor neuron

disease, then the diagnosis is primary lateral sclerosis. Whole-muscle involuntary contractions can rarely be due to stiff person syndrome due to antibodies directed against glutamic acid decarboxylase on neurons. Stiff person syndrome most often involves all four extremities but at times can be two or three limbs.
In this discussion, we are not considering rigidity and excessive movements due to extrapyramidal disorders.

Bonus/ Exception Concept:
The Non-Length Dependent Sensory Neuropathy. (Figure 17)

Figure 17



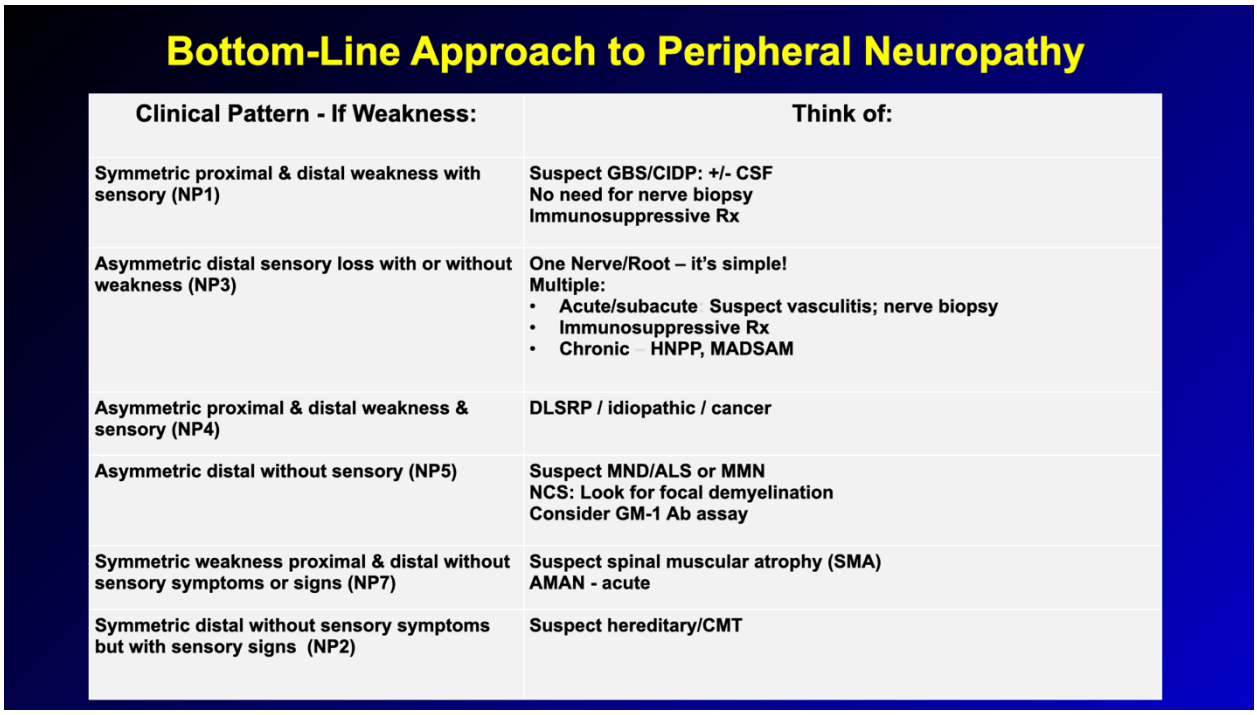
An exception to isolated sensory involvement being predominantly distal is the isolated sensory neuropathy that is non-length dependent. This was first described by Dr. Robert Wartenberg, and he even wrote a book on this entity (see Figure 18). Therefore, in the older literature, this has been referred to as Wartenberg's Sensory Neuritis. These patients have odd patches of numbness, tingling, and pain anywhere on their body including the trunk and face. The distribution can be proximal, distal, or proximal and distal and can be symmetric or asymmetric therefore if the sensory loss is both proximal, distal, and symmetric it would probably fit into the NP-1 pattern but there would be no weakness; if distal and symmetric- NP-2; if distal and asymmetric- NP-3; if proximal, distal, and asymmetric- NP-4; if only midline face or trunk- NP-8. Often these patients are thought to be psychogenic, but we now know that this can be a true non-length-dependent sensory neuropathy. Many of these cases only involve small fibers and electrodiagnostic studies would be normal. In these small fiber cases, a skin biopsy to assess epidermal nerve fiber loss is often needed to make the diagnosis. Some of these patients reportedly respond to intravenous immune globulin therapy. It is important that the clinician be aware of this sensory pattern and not immediately dismiss the patient as being psychogenic without further workup.

Some of the cases that Dr. Wartenberg described involved multiple distal sensory nerves and would fit the pattern of a sensory mononeuritis multiplex- NP-3. Another neuropathy that could be put in this pattern are the truncal diabetic sensory radiculopathies which can produce odd and asymmetric areas of sensory loss on the thorax and abdomen sometimes these cases are associated with the classic diabetic radiculopathy involving the lower and occasionally upper extremities described in the NP-4 pattern but sometimes they can occur in isolation without the extremity involvement.

Summary

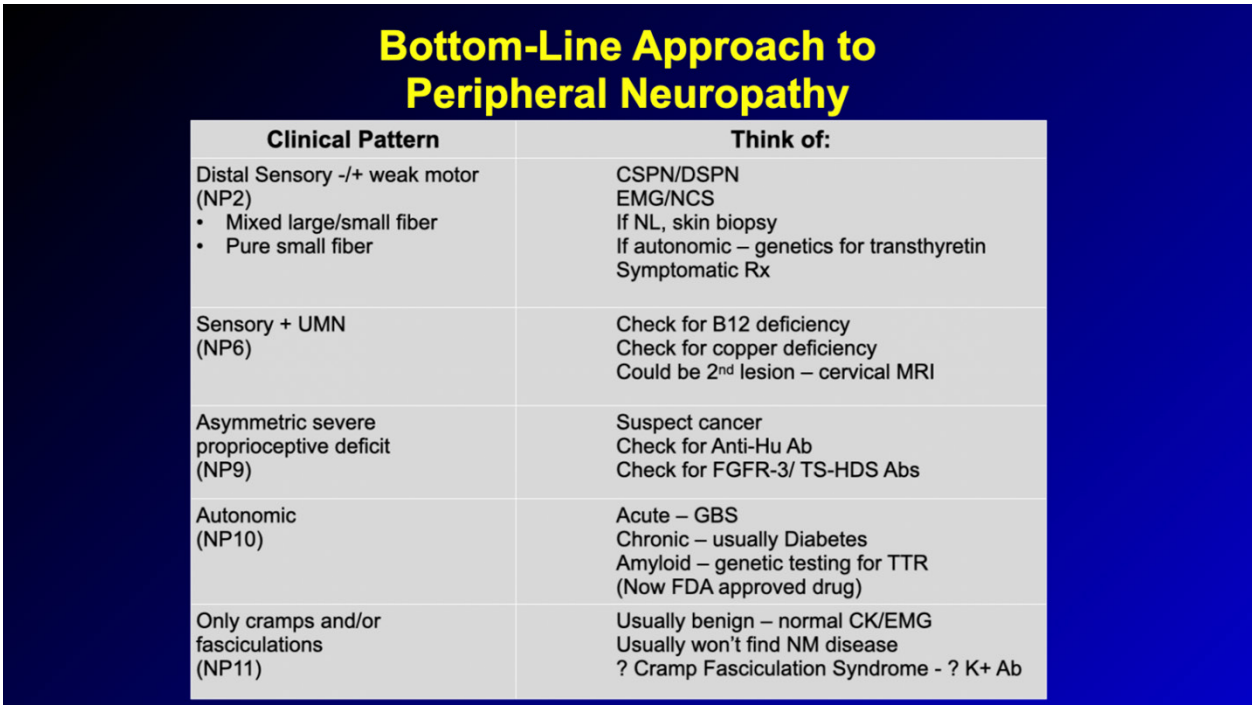
The following two figures summarize the patterns. Figure 18 involves patterns with motor involvement and Figure 19 involves patterns with predominant or exclusive sensory involvement.

Figure 18



If the pattern is symmetrical, proximal, and distal weakness with sensory loss then it is NP1- GBS or CIDP pattern. If it is asymmetric, distal weakness, and sensory loss and only one nerve or root are involved it is probably a simple mononeuropathy or radiculopathy. If multiple nerves or roots are involved, then it is mononeuropathy multiplex. If the pattern is asymmetric proximal and distal weakness with sensory loss, then it is most likely DLSRP until proven otherwise. If the pattern is asymmetric distal weakness without sensory loss, then this is the ALS/MMN pattern. The majority of these patients usually have motor neuron disease. If the pattern is symmetric weakness that is proximal and distal without sensory symptoms or signs, then this is most likely SMA which is now treatable. This is also the AMAN pattern when it is acute, a pure motor GBS variant. When the patient presents with distal weakness but without sensory signs, this is the dissociated sensory pattern and is likely to be a hereditary neuropathy.

Figure 19



If the neuropathic presentation is predominantly sensory, symmetrical, and distal this is the NP2 pattern (Figure 19). In the NP2 pattern, there may be mixed large or small fiber involvement, and the diagnosis is usually CSPN, DSPN, or the neuropathy associated with the metabolic syndrome, but isolated small fiber involvement can occur. If it is the same pattern but with upper motor neuron signs, then check for B12 and copper as this could be a myeloneuropathy- NP6. But the NP6 pattern can also imply that there could be an NP2 neuropathy with a second lesion such as a cervical spinal cord lesion or bihemispheric strokes. If it is an asymmetric severe proprioceptive deficit, NP9, suspect cancer but there are other causes as well. If there is autonomic involvement (NP10) and it is acute, consider GBS and if it is chronic, consider diabetes and familial amyloidosis. If the patient presents with only cramps or fasciculations it is most likely benign (NP11).

In Figure 20 we summarize all eleven clinical patterns of neuropathic disorders.

Summary of Eleven Clinical Neuropathic Patterns

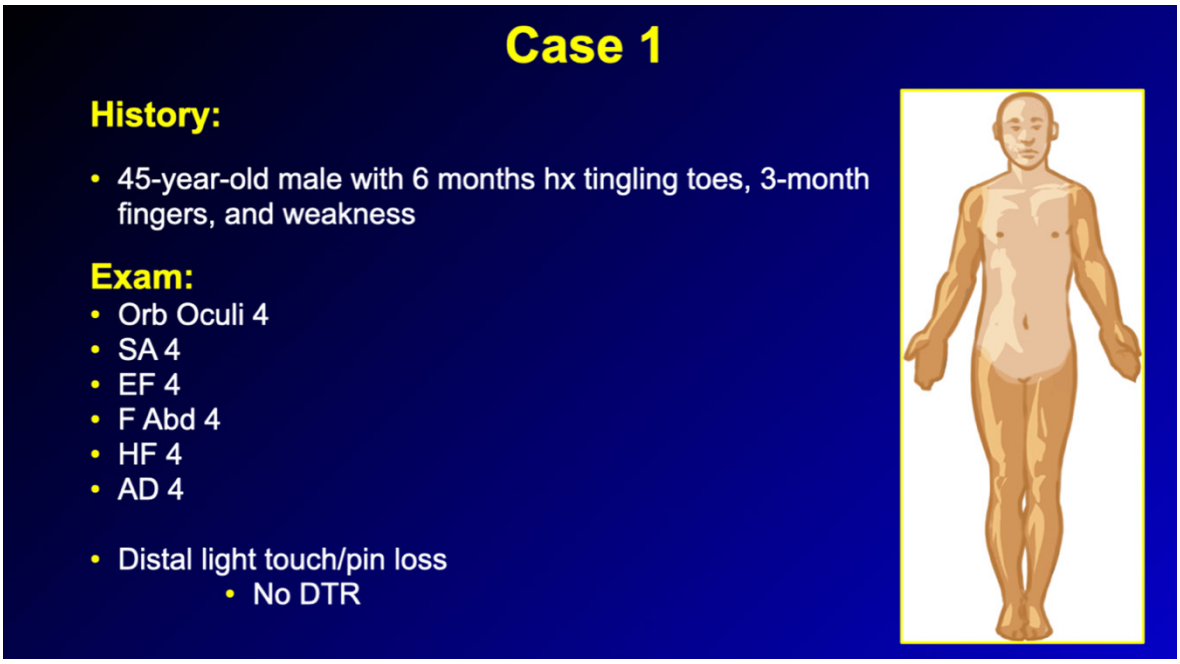
Figure 20

PATTERN	Proximal	Distal	Asymmetrical	Symmetrical	Sensory Symptoms	Severe Proprioceptive Loss	UMN Signs	Autonomic Symptoms/ Signs	Diagnosis
NP1-Symmetric, proximal, distal weakness w/ sensory loss	+	+		+	+				GBS / CIDP
NP2-Distal sensory loss w/without weakness		+		+	+				CSPN, metabolic, diabetes, drugs, hereditary, DADS
NP3-Asymmetric distal weakness w/ sensory loss		+	+		+				Multiple-vasculitis, HNPP, MADSAM, infection Single-Mononeuropathy, radiculopathy
NP4-Asymmetric proximal, distal weakness w/ sensory loss	+	+	+		+				Polyradiculopathy, plexopathy, DLSRP, cancer, idiopathic, infection
NP5-Asymmetric distal weakness w/ out sensory loss		+	+				+/-		+UMN-ALS/PLS -UMN-MMN
NP6-Symmetric sensory loss & upper motor neuron signs		+			+	+	+		B12 / copper deficiency; Friedreich's, ALD
NP7-Symmetric weakness w/out sensory loss*	+/-	+			+				Prox & Distal-SMA Distal-Hereditary motor neuropathy
NP8-Focal midline weakness*	+ Neck/trunk extensor +Bulbar +Diaphragm +CN 3,4,5,6,7			+ +			+ +		ALS ALS/ PLS CBS Isolated CN 3,4,5,6, 7-benign Multiple CN 3,4,5,6,7-underlying disease
NP9-Asymmetric proprioceptive loss w/out weakness			+		+	+			Sensory neuronopathy (ganglionopathy) CISP
NP10-Autonomic dysfunction								+	Diabetes, GBS, amyloid prophyria
NP11-Excessive muscle activity	+	+	+	+					Fasciculations, myokymia, neuromyotonia, stiff-person syndrome

CASE EXAMPLES
The following case studies demonstrate four of these patterns.

Case #1: 45-year-old male with 6 months of tingling in the toes, and 3 months in the fingers and he tells you he is weak. (Figure 21)

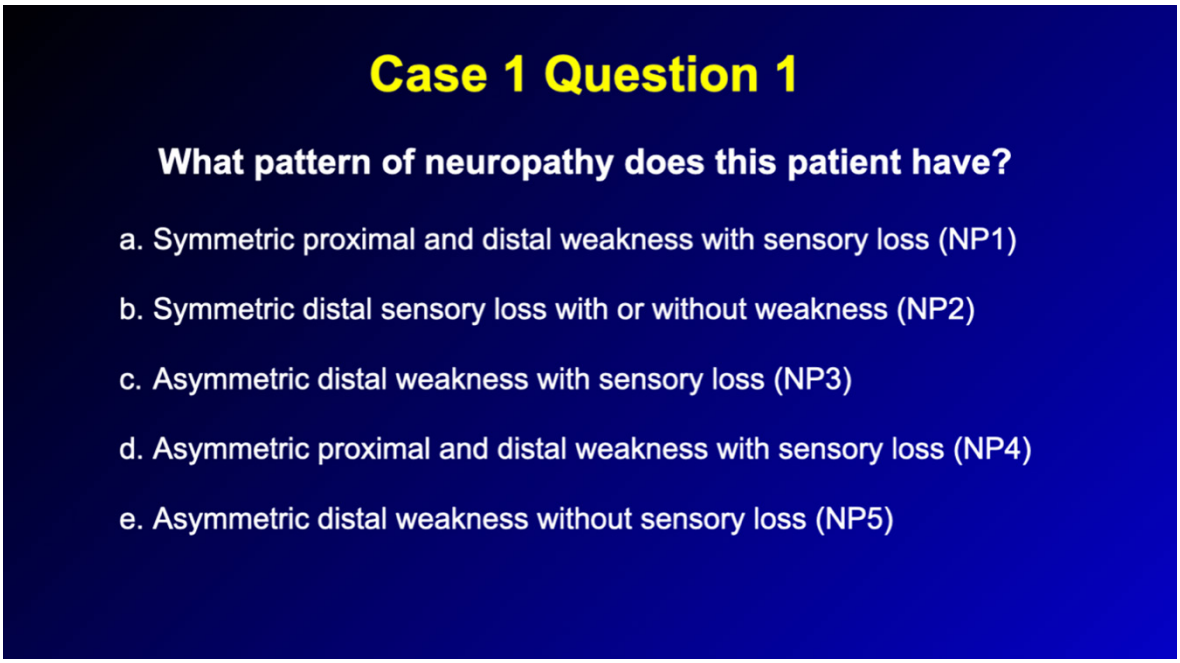
Figure 21



When you examine him, he has grade 4 weakness proximally and distally: orbicularis oculi, shoulder abduction, elbow flexion, finger abduction, hip flexion, and ankle dorsiflexion. There is a distal light touch and pinprick loss, and he has no reflexes.

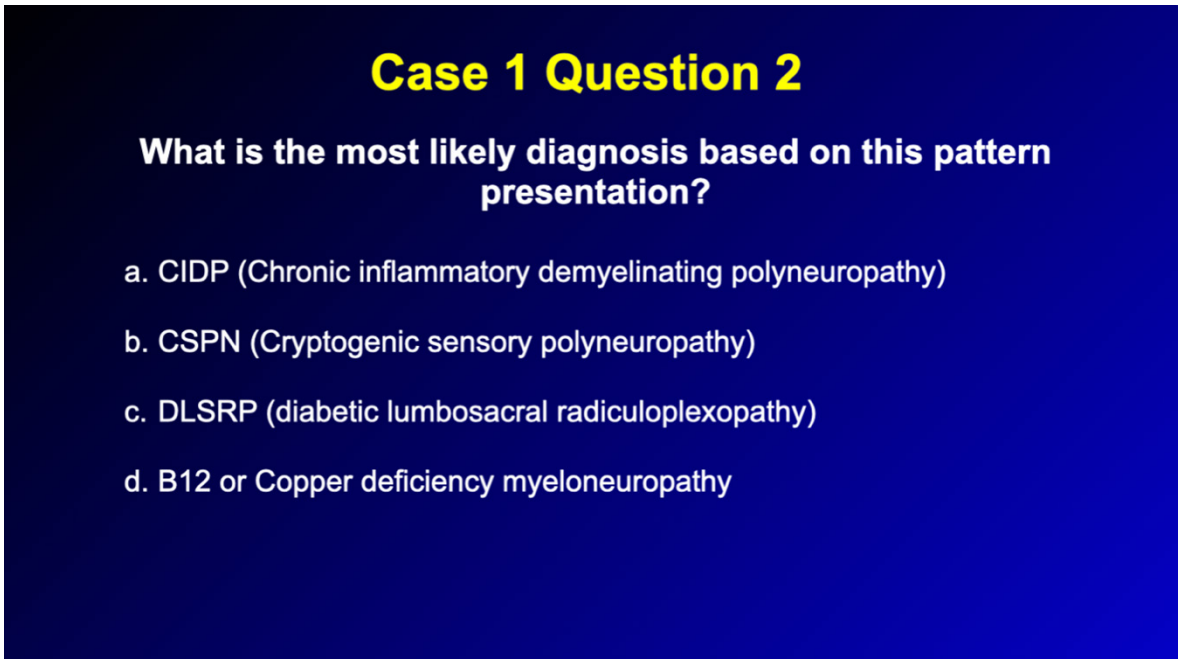
What pattern of neuropathy does this patient have? (Figure 22)

Figure 22



Answer: Symmetric proximal and distal weakness with sensory loss.
What is the most likely diagnosis based on this pattern? (Figure 23)

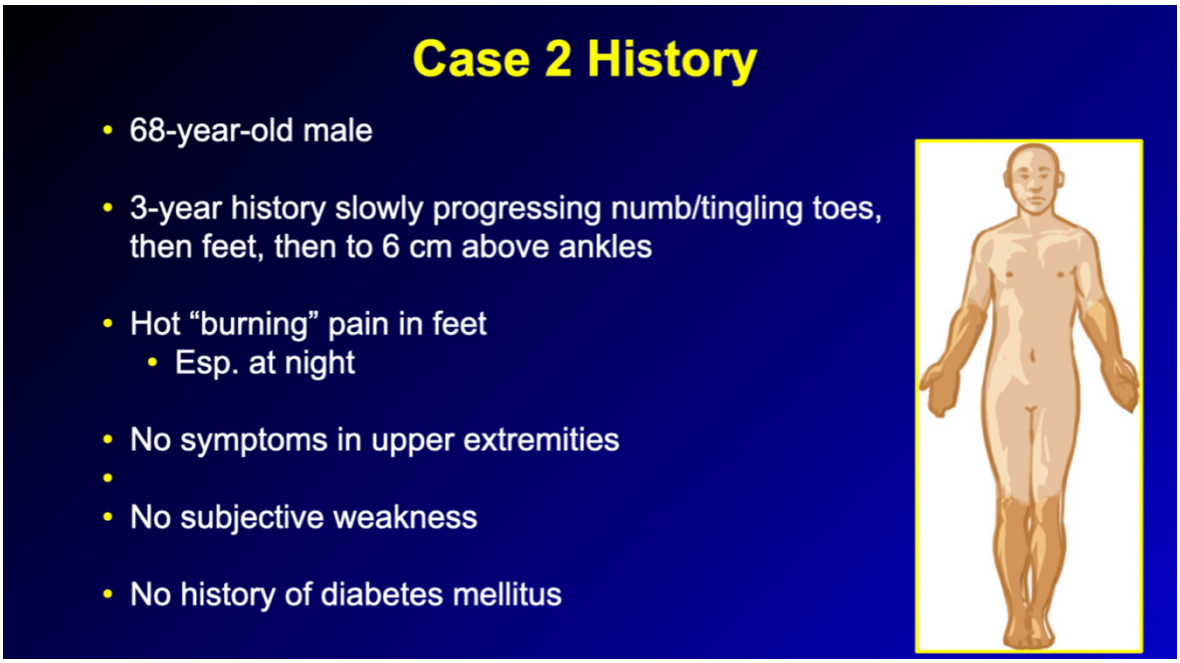
Figure 23



Answer: CIDP or Chronic inflammatory demyelinating polyradiculoneuropathy.

Case #2: 68-year-old male with a 3-year history of slowly progressive numbness and tingling of the toes that then progressed to the feet and eventually progressed to approximately 6 cm above the ankles. This occurred over 5 years. (Figure 24)

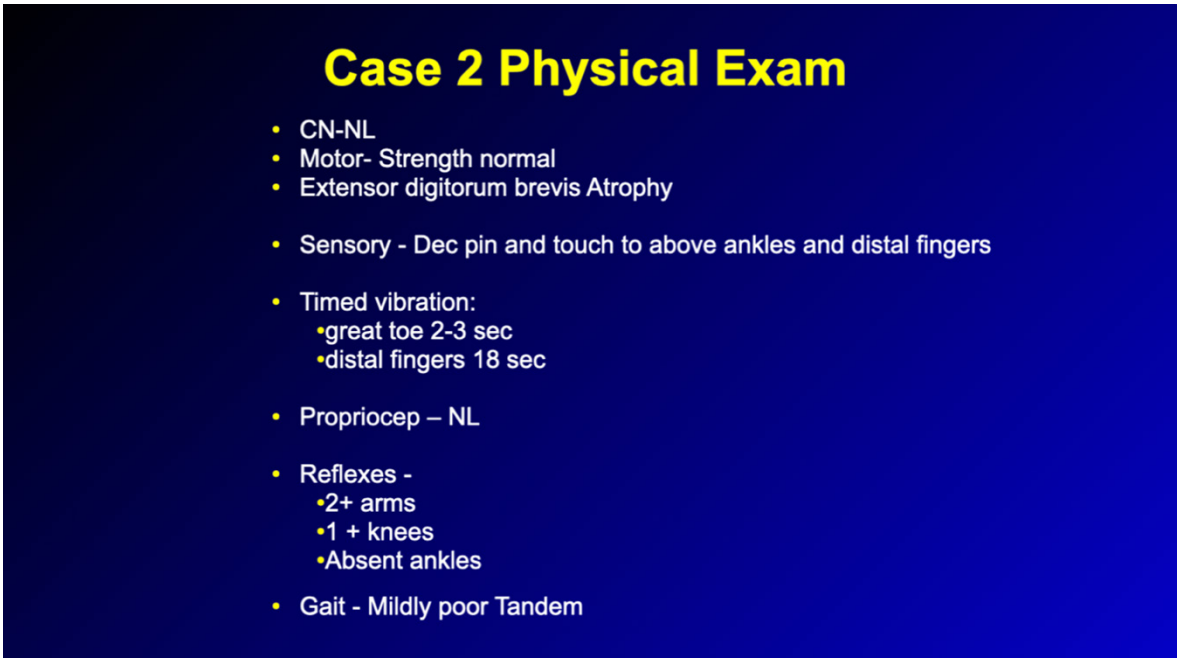
Figure 24



There is no hand involvement. The pain is a hot and burning sensation in the feet, especially at night. There is no subjective weakness and no history of diabetes.

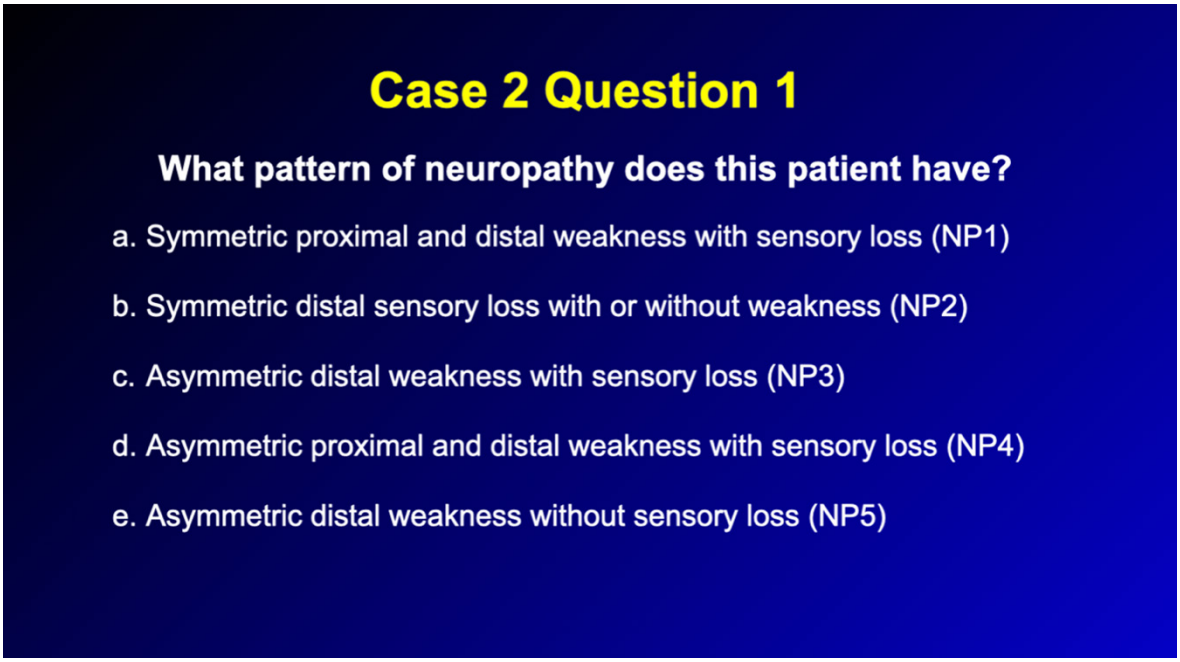
On exam (Figure 25), the cranial nerves are normal. The motor exam has normal strength although there is some extensor digitorum brevis atrophy in the feet. On sensory exam, there is decreased pinprick and touch above the ankles and also a slight decrease in the perception of these modalities in the fingertips. Timed vibration testing of the great toes is 2-3 seconds which is probably abnormal for his age. Proprioception is normal. Reflexes are 2 at the arms, 1 at the knees, and absent at the ankles. His routine gait is normal but when he tries to tandem walk he is unsteady.

Figure 25



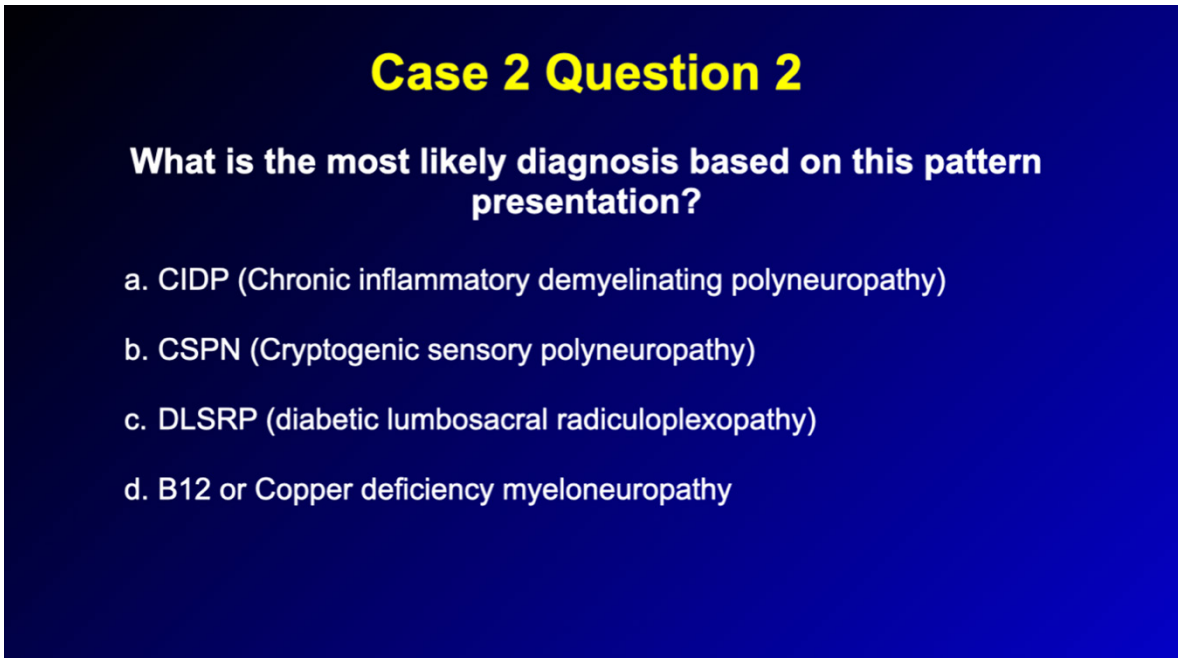
What pattern of neuropathy does this patient have? (Figure 26)

Figure 26



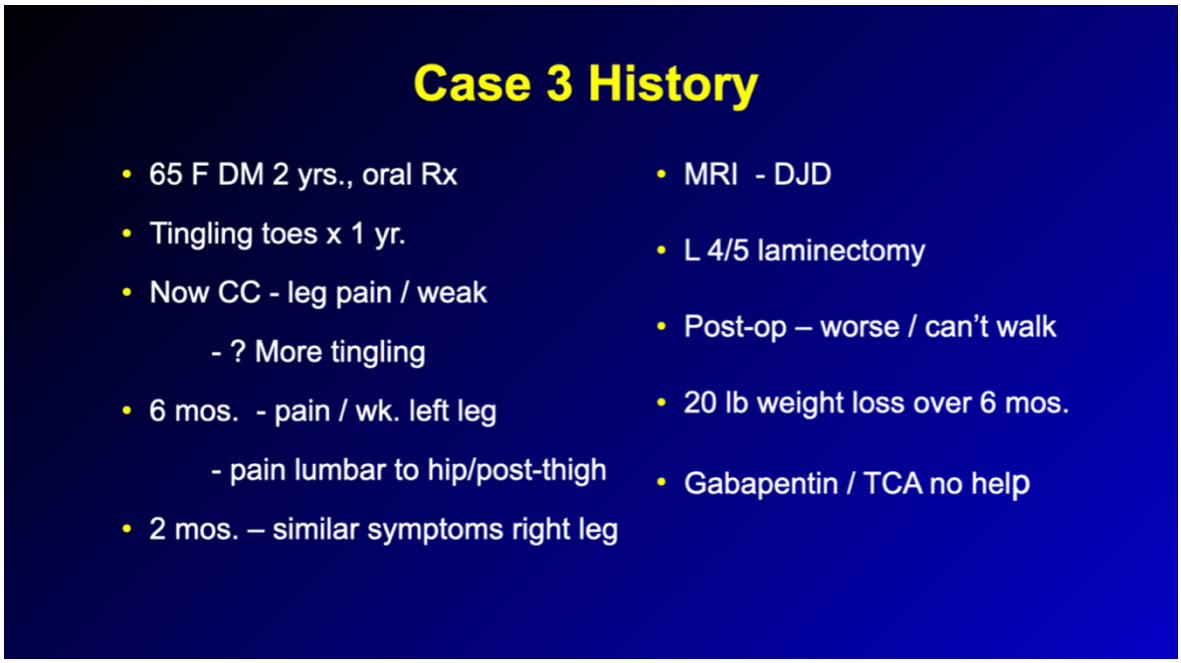
Answer: Symmetric distal sensory loss with or without weakness, NP2

What is the most likely diagnosis based on this pattern? (Figure 27)
Figure 27



Answer: Cryptogenic sensory polyneuropathy or CSPN.

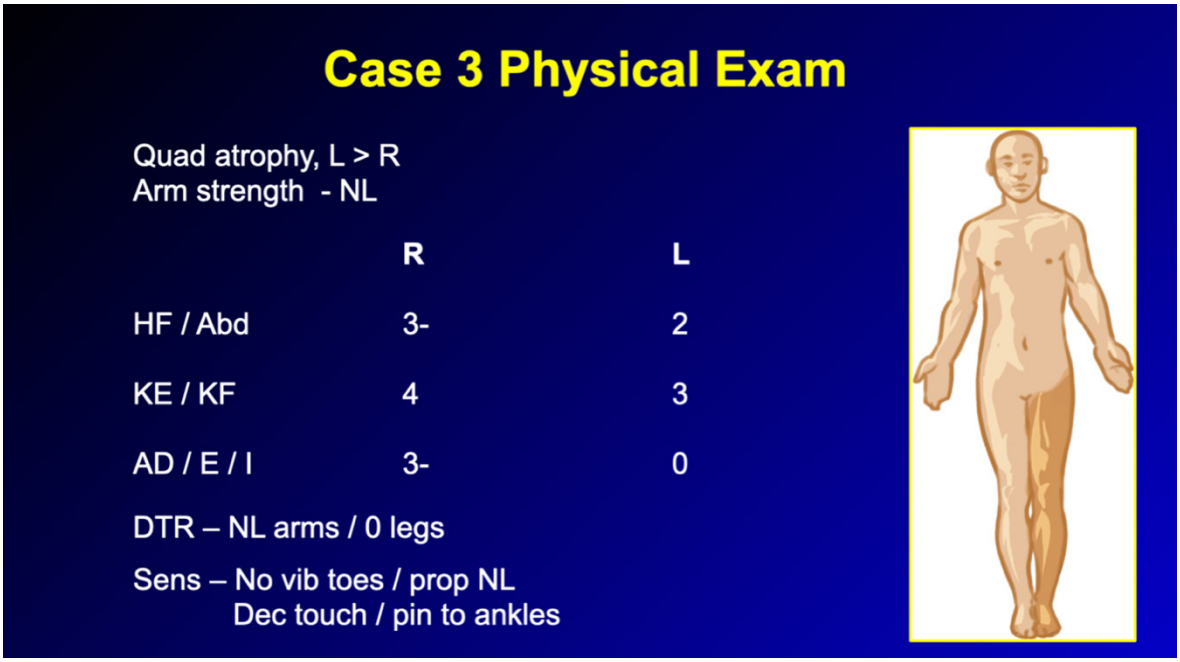
Case #3: 65-year-old diabetic female. She has been diabetic for 2 years and is on oral hypoglycemics. (Figure 28)
Figure 28



For the last year, she has had some tingling in the toes. For 6 months she has had leg pain and weakness, and it began 6 months ago in the left leg with severe back pain radiating in the hip and posterior thigh in the leg became weak and 2 months ago similar symptoms occurred in the right leg. This led her to a surgeon who did an MRI, and she then had an L4-L5 laminectomy. Post-operatively she continued to worsen. By the time a neurologist was consulted, she could not walk. The neurologist obtained the history that there was a 20lb weight loss over 6 months. She has been on gabapentin and tricyclic antidepressants for pain without help.

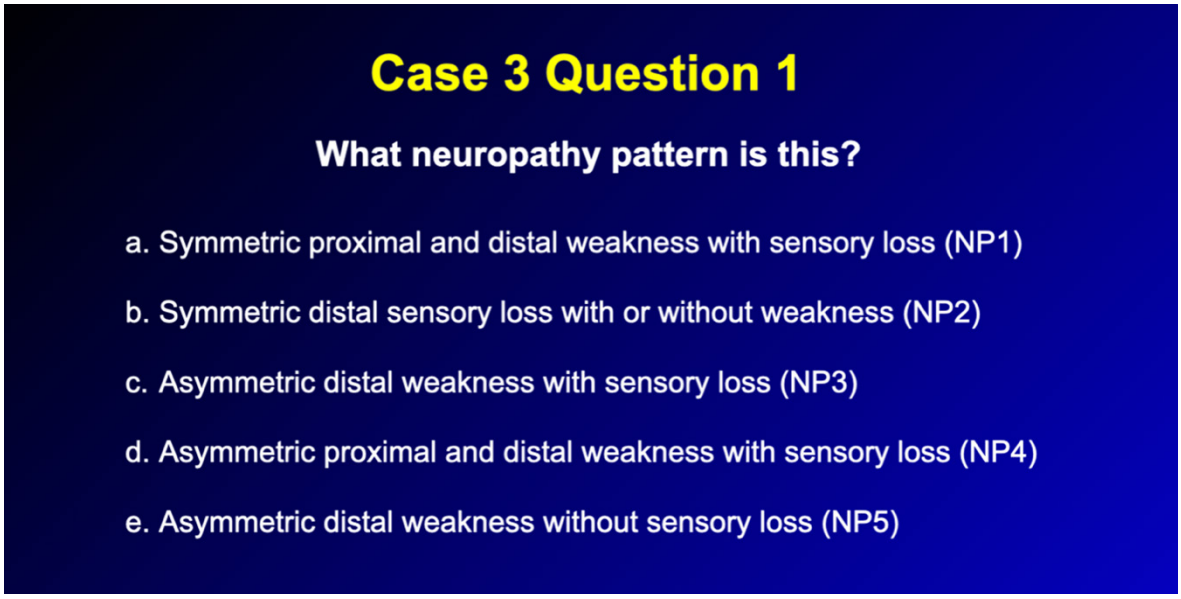
On examination, (Figure 29) there is severe quadriceps atrophy, worse on the left. Arm strength is completely normal. In the lower extremities, hip flexors and hip abductors are 3- on the right and 2 on the left; knee extensors and flexors are 4 on the right and 3 on the left; and ankle dorsiflexors and evertors and inverters are 3- on the right and zero on the left. Reflexes in the arms are normal but there are no reflexes at the knees or ankles. There is no vibration at the toes; proprioception is normal, and there is decreased pin and touch to the ankles.

Figure 29



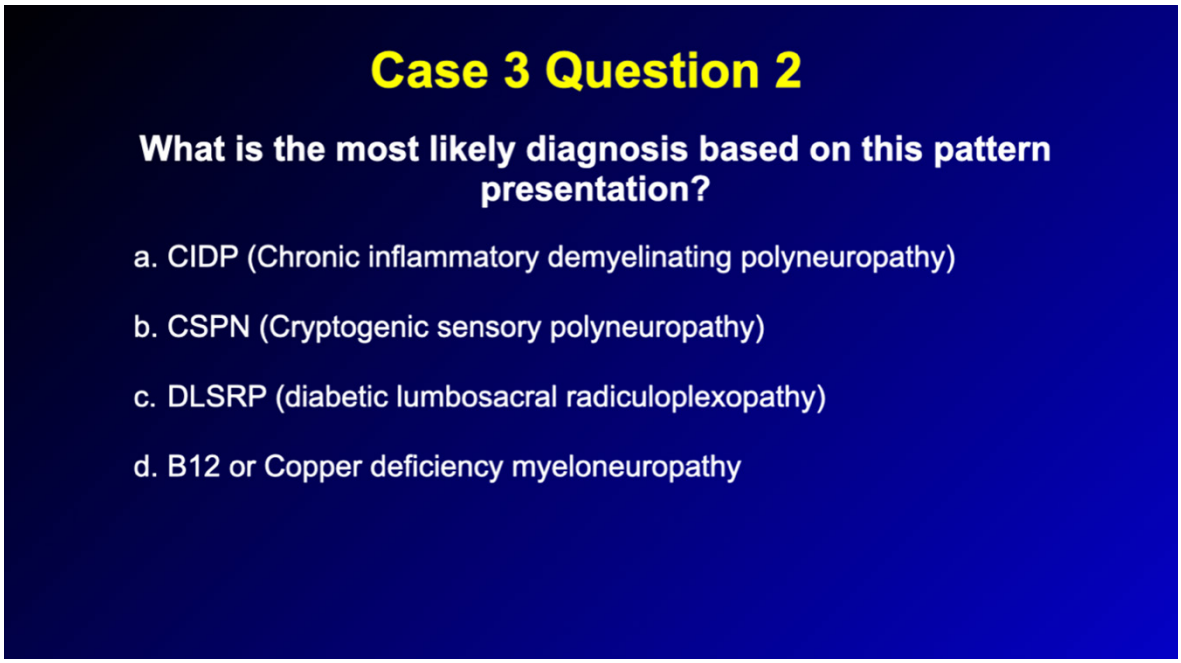
What neuropathy pattern is this? (Figure 30)

Figure 30



Answer: Asymmetric proximal and distal weakness with sensory loss
What is the most likely diagnosis based on this pattern? (Figure 31)

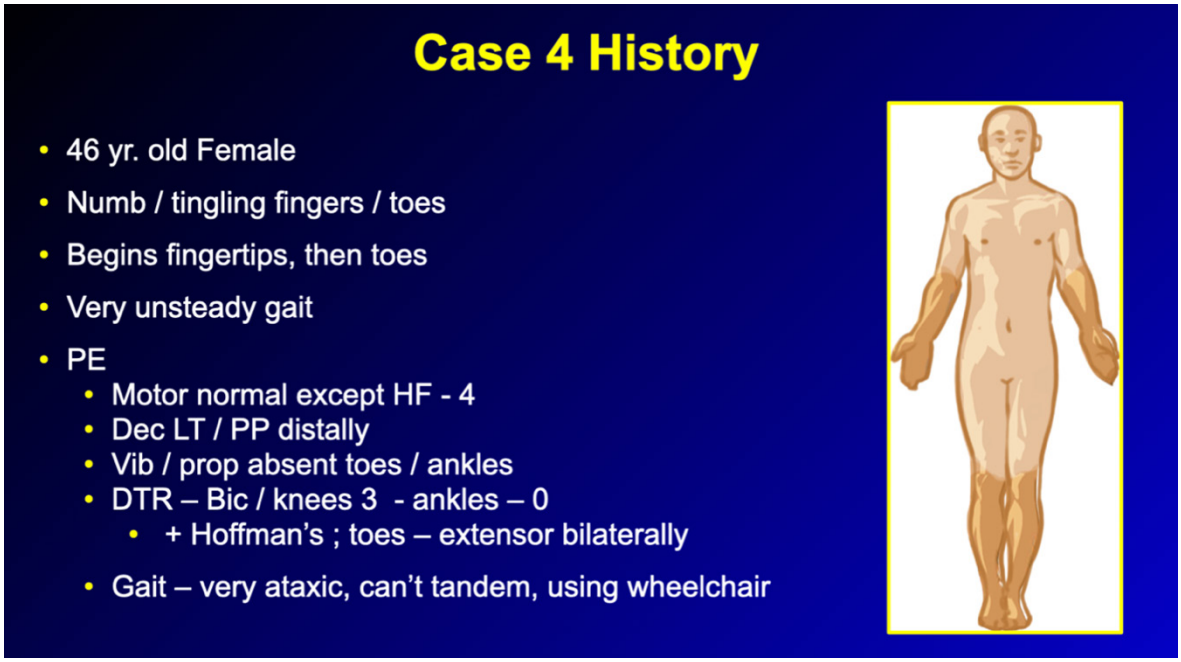
Figure 31



Answer: Diabetic lumbosacral radiculoplexopathy

Case #4: 46-year-old female with numbness and tingling in the fingers and toes. (Figure 32)

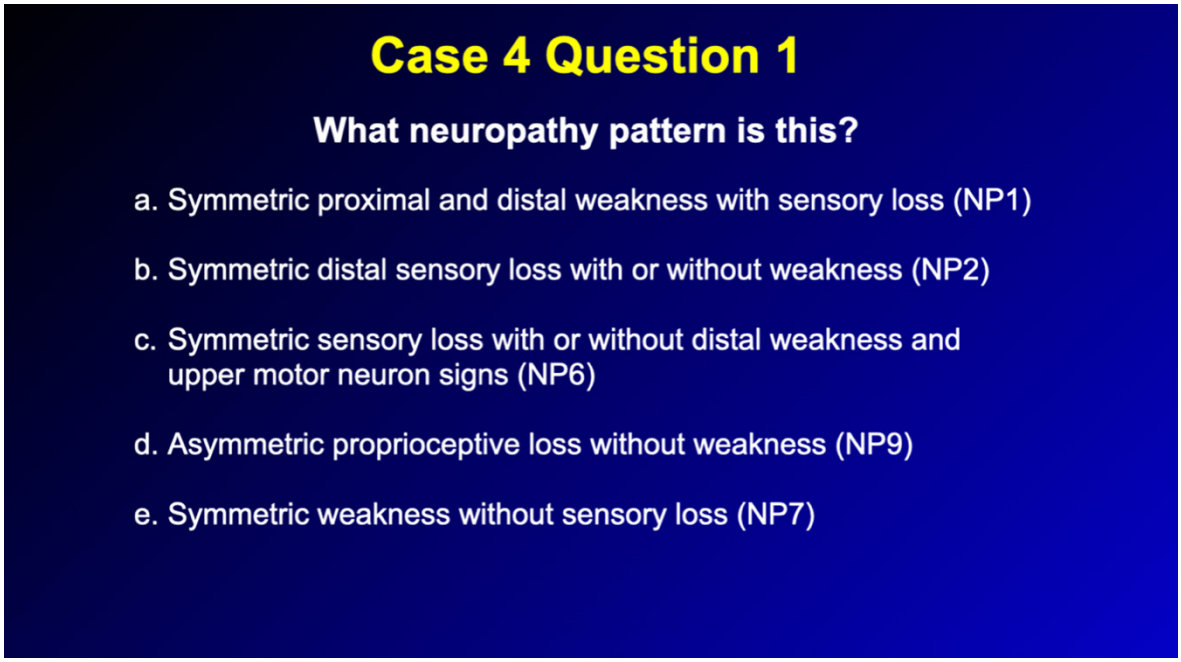
Figure 32



It began in the fingertips then went into the toes and has been gradually worsening over the last year and a half. She complains of a very unsteady gait. On examination, her motor strength is normal except for hip flexors that are grade 4. She has decreased light touch and pinprick distally, but her vibration and proprioception are absent at the toes and ankles. The reflexes are 3 at the biceps and knees and absent at the ankles. She has a positive Hoffman's reflex bilaterally and plantar responses are extensor bilaterally. Her gait is very ataxic, and she cannot tandem walk. She comes to the office in a wheelchair.

What neuropathy pattern is this? (Figure 33)

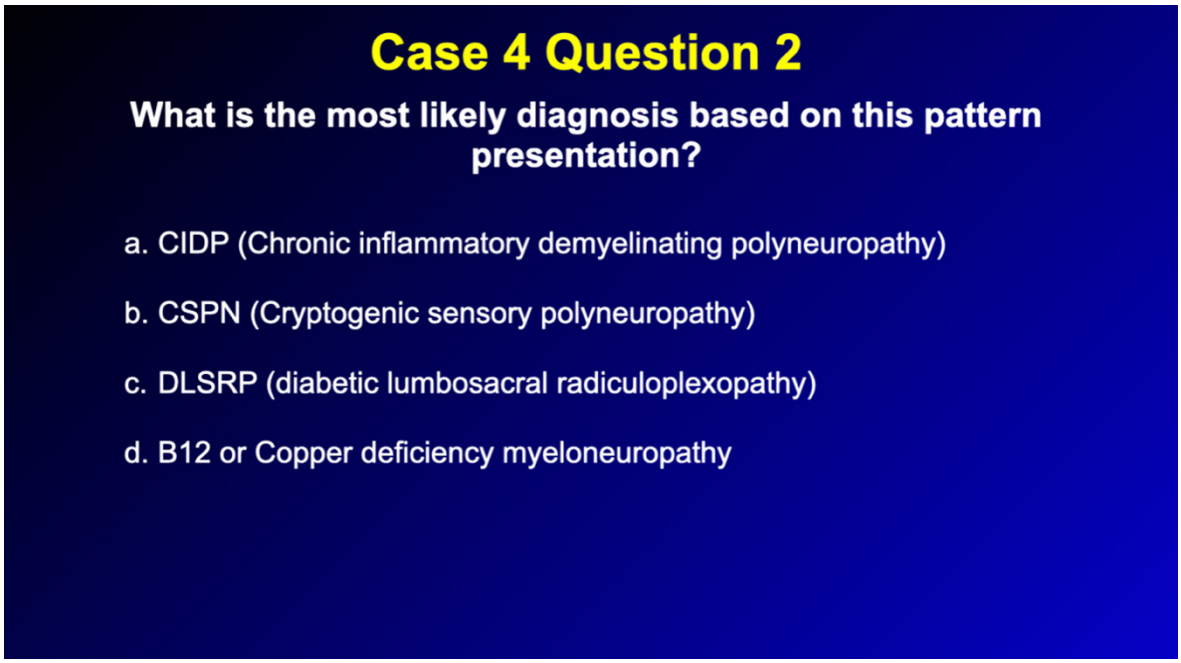
Figure 33



Answer: Symmetric sensory loss with or without distal weakness and upper motor neuron signs or NP6

What is the most likely diagnosis? (Figure 34)

Figure 34



Answer: B12 or copper deficiency myeloneuropathy

Conclusion

We end this review by showing a quote by William James who said, "The rivalry of the patterns is the history of the world" (Figure 35). We have paraphrased William James in the following ways:

The recognition of the patterns is the key to understanding neuromuscular disease

And

The patterns are like the operating systems for how we are supposed to think about neuromuscular disease (Figure 36).

Figure 35

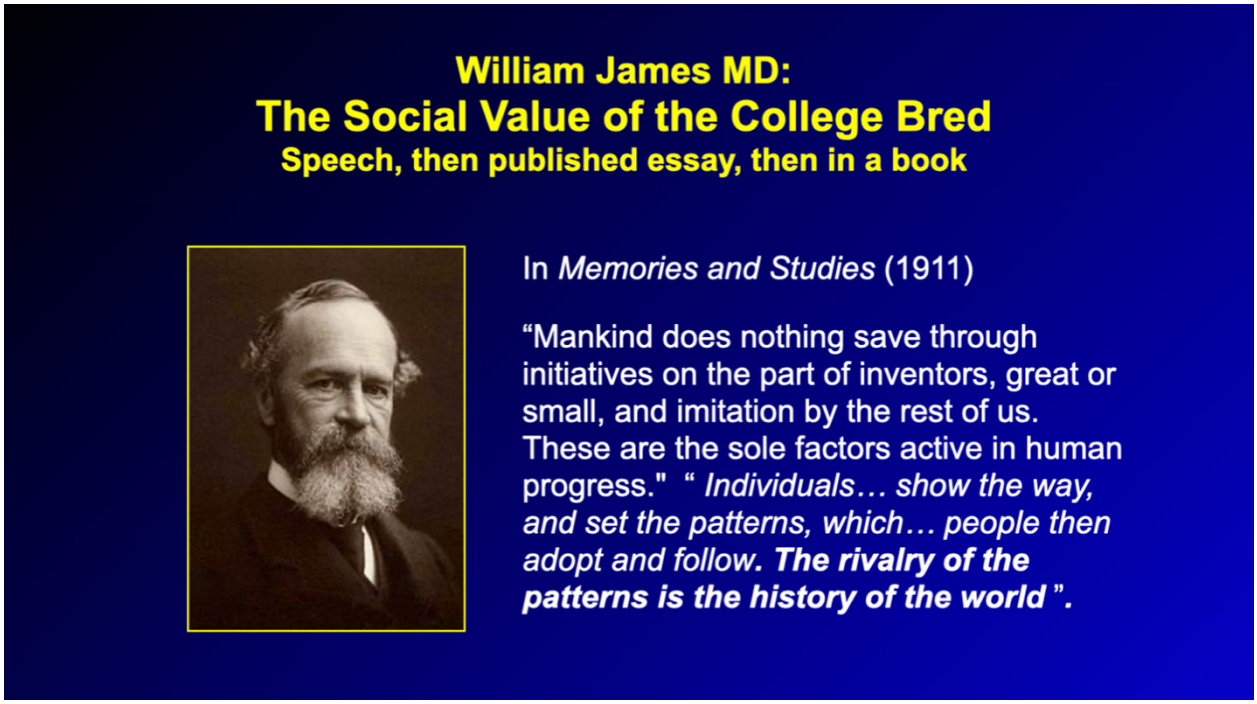


Figure 36

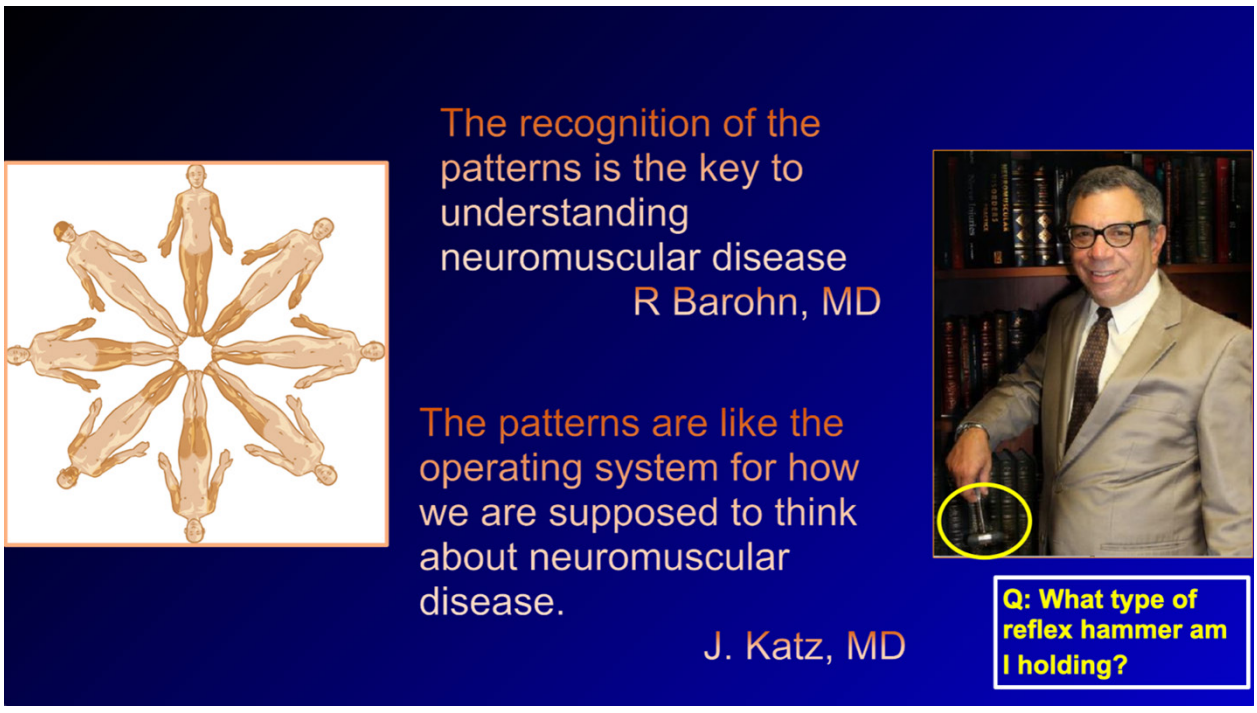


Figure 37

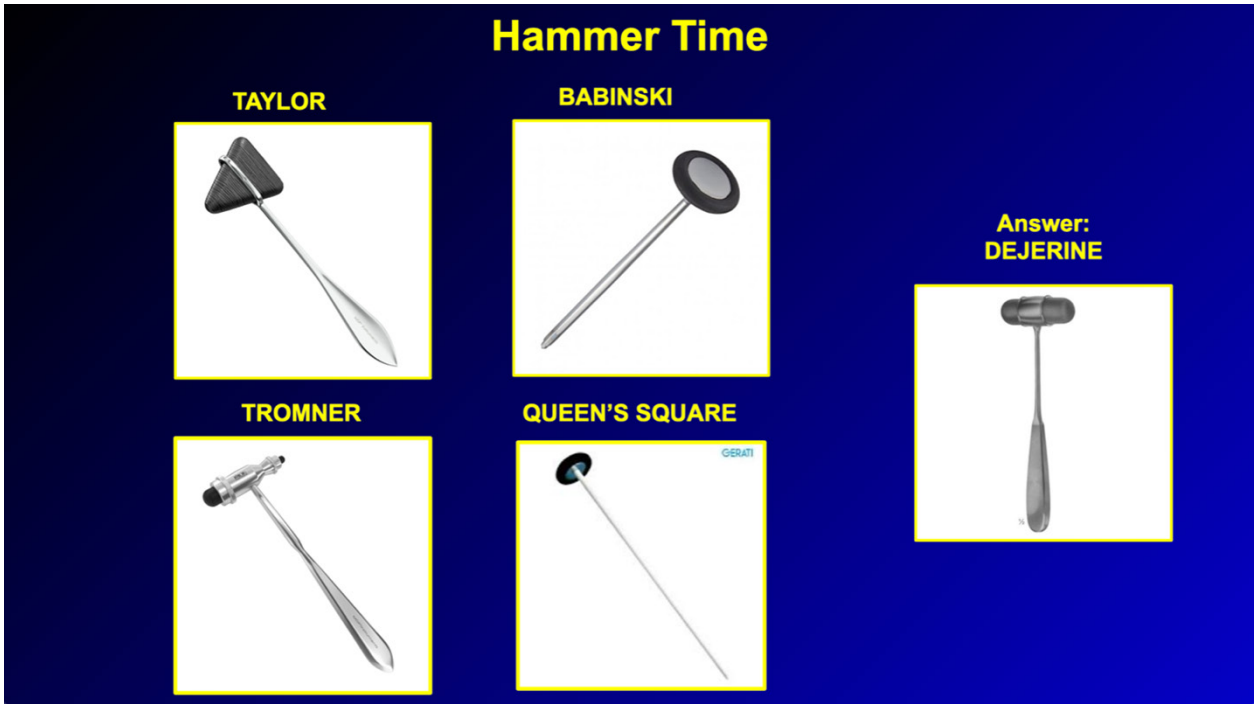


Figure 38

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References

Amato, A. A. and Barohn, R. J. Peripheral neuropathy. Harrison's Principles of Internal Medicine 20th J. L. Jameson, A. S. Fauci, D. L. Kasper et al. New York, NY, McGraw-Hill 2018; 3204 -3225

Amato, A. A. and Ropper, A. H. Sensory ganglionopathy. N Engl J Med 2020; 383(17): 1657-1662.

Barohn, R. J., Kissel, J. T., Warmolts, J. R., Mendell, J. R. Chronic inflammatory demyelinating polyradiculoneuropathy. Clinical characteristics, course, and recommendations for diagnostic criteria. Arch Neurol 1989; 46(8): 878-884.

Barohn, R. J., Sahenk, Z., Warmolts, J. R., Mendell, J. R. The Bruns-Garland syndrome (diabetic amyotrophy). Revisited 100 years later. Arch Neurol 1991; 48(11): 1130-1135.

Barohn, R. J. Approach to peripheral neuropathy and neuronopathy. Semin Neurol 1998; 18(1): 7-18.

Barohn, R. J. Approach to muscle and nerve disease. Cecil's Textbook of Medicine 22nd, L. Goldman, D. A. Ausiello. Philadelphia, PA. Saunders 2004; 2370-2379; 2387-2399

Barohn, R. J. and Amato, A. A. Pattern-recognition approach to neuropathy and neuronopathy. Neurol Clin 2013; 31(2): 343-361.

Barohn, R. J., Dimachkie, M.M., Carlayne, J.E. A pattern recognition approach to patients with a suspected myopathy. Neurol Clin 2014; 32(3): 569-593, vii.

Barohn R. J., Fink J. K., Heiman-Patterson T., Huey E. D., Murphy J., Statland, J. M., Turner M.R., Elman L. The clinical spectrum of primary lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener*. 2020; (sup1):3-10.

Campbell, W. W. and Barohn, R. J. Reflexes. DeJong's the Neurologic Examination. W. W. Campbell, R. J. Barohn and R. N. DeJong. Philadelphia, PA, Lippincott Williams & Wilkins 2020; 579-594.

Campbell, W. W. and Barohn, R. J. Reflexes. DeJong's the Neurologic Examination. W. W. Campbell, R. J. Barohn and R. N. DeJong. Philadelphia, PA, Lippincott Williams & Wilkins 2020; 542.

Collins, M. P., Arnold, D. W., Kissel, J.T. The neuropathies of vasculitis. Neurol Clin 2013; 31(2): 557-595.

Cortese, A., Tozza, S., Yau, W. Y., Rossi, S., Beecroft, S. J., Jaunmuktane, Z., Dyer, Z., Ravenscroft, G., Lamont, P. J., Mossman, S., Chancellor, A., Maisonobe, T., Pereon, Y., Cauquil, C., Colnaghi, S., Mallucci, G., Curro, R., Tomaselli, P. J., Thomas-Black, G., Sullivan, R., Efthymiou, S., Rossor, A. M., Laurá, M., Pipis, M., Horga, A., Polke, J., Kaski, D., Horvath, R., Chinnery, P. F., Marques, W., Tassorelli, C., Devigili, G., Leonardis, L., Wood, N. W., Bronstein, A. Giunti, P., Züchner, S., Stojkovic, T., Laing, N., Roxburgh, R. H., Houlden, H., Reilly, M. M. Cerebellar ataxia, neuropathy, vestibular areflexia syndrome due to RFC1 repeat expansion. Brain 2020; 143(2): 480-490.

Cortese, A., Curro, R., Vegezi, E., Yau, W. Y., Houlden, H., Reilly, M. M. Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS): genetic and clinical aspects. Practical Neurology 2022; 22: 14-18.

Dimachkie, M. M., Barohn, R. J., Katz, J. Multifocal motor neuropathy, multifocal acquired demyelinating sensory and motor neuropathy, and other chronic acquired demyelinating polyneuropathy variants. Neurol Clin 2013; 31(2): 533-555.

Dobrev, D., Barohn, R. J., Neil, A. E., Kilfoyle, D., Khan, S. McVey, A. L., Herbelin, L., Dimachkie, M. M. Facial onset sensorimotor neuronopathy syndrome: a case series. J Clin Neuromuscul Dis 2012; 14(1): 7-10.

Dyck, P. J. B., Sinnreich, M., Klein, C.J., Engelstad, J., Spinner, R. J. Chronic immune sensory polyradiculopathy: a possibly treatable sensory ataxia. Neurology 2004; 63(9): 1662-1669.

Finkel, R. S., Mercuri, E., Darras, B. T., Connolly, A. M., Kuntz, N. L., Kirschener, J., Chiribogs, C. A., Saito, K., Servais, L., Tizzano, E., Topaloglu, H., Tulinis, M., Montes, J., Glanzman, A. M., Bishop, K., Zhong, J. Z., Gheuens, S., Bennett, F. C., Schneider, E., Farwell, W., De Vivo, D. C. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. The New England Journal of Medicine 2017; 377(18): 1723-1732.

Geerts M, de Greef BTA, Sopacua M, van Kuijk SMJ, Hoeijmakers JGJ, Faber CG, Merkies ISJ. Intravenous Immunoglobulin Therapy in Patients With Painful Idiopathic Small Fiber Neuropathy. Neurology. 2021 May 18;96(20):e2534-e2545.

Gibbons CH, Rajan S, Senechal K, Hendry E, McCallister B, Levine TD. A double-blind placebo-controlled pilot study of immunoglobulin for small fiber neuropathy associated with TS-HDS and FGFR-3 autoantibodies. Muscle & Nerve. 2023 May;67(5):363-370.

Gisatulin, M., Dobricic, V., Zühlke, C., Hellenbroich, Y., Tadic, V., Münchau, A., Isenhardt, K., Bürk, K., Bahlo, M., Lockhart, P. J., Lohmann, K., Helmchen, C., Brüggemann, N. Clinical spectrum of the pentanucleotide repeat expansion in the RFC1 gene in ataxia syndromes. Neurology 2020; 95: e2912-2923.

Gorson, K. C., Herrmann, D. N., Thiagarajun, R., Brannagan, T. H., Chin, R. L., Kinsella, L. J., Ropper, A. H. Non-length dependent small fibre neuropathy/ganglionopathy. J Neurol Neurosurg Psychiatry 2008; 79(2): 193-200.

Grunseich, C. and Fischbeck, K. H. Spinal and bulbar muscular atrophy. Neurol Clin 2015; 33(4): 847-854.

The Guillain-Barre Syndrome Study Group. Plasmapheresis and acute Guillain-Barre syndrome. Neurology 1985; 35(8): 477-489

Hammond, N., Wang, Y., Dimachkie, M. M., Barohn, R. J. Nutritional neuropathies. Neurol Clin 2013; 31(2): 477-489.

Hart, I. K., Maddison, P., Newsom-Davis, J., Vincent, A., Mills, K. R. Phenotypic variants of autoimmune peripheral nerve hyperexcitability. Brain 2002; 125(8): 1887.

Jackson, C. E., Amato, A. A., Barohn, R. J. Case of the month: Isolated vitamin E deficiency. Muscle Nerve 1996; 19(9): 1161-1165.

Jawdat, O., Statland, J. M., Barohn, R. J., Katz, J. S., Dimachkie, M. M. Amyotrophic Lateral Sclerosis Regional Variants (Brachial Amyotrophic Diplegia, Leg Amyotrophic Diplegia, and Isolated Bulbar Amyotrophic Lateral Sclerosis). Neurol Clin 2015; 33(4): 775-785.

Katyal, N., Attele, P., Hoelscher, B., Ensrud, E., Barohn, R.J. Ear of the Lynx. Radiological Sign in a Patient with Primary Lateral Sclerosis. RRNMF Neuromuscular Journal 2022; 3(3), 32-35

Katz, J. S., Wolfe, G.I, Bryan, W. W., Jackson, C. E., Amato, A. A., Barohn, R. J. Electrophysiologic findings in multifocal motor neuropathy. Neurology 1997; 48(3): 700-707.

Lewis, R.A., Sumner, A. J., Brown, M. J., Asbury, A. K. Multifocal demyelinating neuropathy with persistent conduction block. Neurology 1982; 32(9): 958-964.

Liewluck, T. and Saperstein, D. S. Progressive muscular atrophy. Neurol Clin 2015; 33(4): 761-773.

Mendell, J. R., Al-Zaidy, S., Shell, R., Arnold, W. D., Rodino-Klapac, L.R., Prior, T. W., Lowes, L., Berry, K., Church, K., Kissel, J. T., Nagendran, S., L'Italien, Sproule, D. M., Wells, C., Cardenas, J. A., Heitzer, M. D., Kaspar, A., Corcoran, S., Braun, L., Likhite, S., Miranda, C., Meyer, K., Foust, K. D., Burghes, A. H. M., Kaspar, B. K. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. The New England Journal of Medicine 2017; 377(18): 1713-1722.

Mendell, J.R., Barohn, R. J., Freimer, M. L., Kissel, J. T., King, W., Nagaraja, H. N., Rice, R., Campbell, W. W., Donofrio, P. D., Jackson, C. E., Lewis, R. A., Shy, M., Simpson, D. M., Parry, G. J., Rivner, M. H., Thornton, C. A., Bromberg, M. B., Tandan, R., Harati, Y., Giuliani, M. J. Randomized controlled trial of IVIg in untreated chronic inflammatory demyelinating Polyradiculoneuropathy. Neurology 2001; 56(4): 445-449.

Mendell, J. R., Kissel. J. T., Cornblath D. R. Diagnosis and Management of Peripheral Nerve Disorders. Contemporary Neurology Series. New York, NY, Oxford University Press. 1999; 49.

Mitsumoto, H., Nagy, P., Gennings, C., Murphy, J., Andrews, H.F., Goetz, R., Floeter, M.K., Hupf J, Singleton J, Barohn, R.J., Nations, S., Shoesmith, C.L., Kasarskis, E.J., Factor-Litvak, P. Phenotypic and Molecular Analyses of Primary Lateral Sclerosis (PLS): *Neurol Genet.* 2015; 1(1): e3.

Parry, G.J. and Clarke, S. Multifocal acquired demyelinating neuropathy masquerading as motor neuron disease. Muscle Nerve 1988; 11(2): 103-107.

Pasnoor, M., Dimachkie, M. M., Barohn, R. J. "Diabetic neuropathy part 2: proximal and asymmetric phenotypes." Neurol Clin 2013; 31(2): 447-462.

Pasnoor, M., Dimachkie, M. M., Kluding, P., Barohn, R. J. Diabetic neuropathy part 1: overview and symmetric phenotypes. Neurol Clin 2013; 31(2): 425-445.

Pestronk, A., Cornblath, D. R., Ilyas, A. A., Quarles, R. H., Griffin, J. W., Alderson, K., Adams, R. N. A treatable multifocal motor neuropathy with antibodies to GM1 ganglioside. Ann Neurol 1988; 24(1): 73-78.

Pinto, W. B. V. R., Nunes, P. P., Teixeira, I. L. E., Assis, A. C. D., Naylor, F. G. M., Chieia, M. A. T., Souza, P. V. S., Oliveira, A. S. B. O'Sullivan-McLeod syndrome: Unmasking a rare atypical motor neuron disease. Rev Neurol (Paris) 2019; 175(1-2): 81-86.

Pocock, K., and Vu, T. Progression of Charcot-Marie-Tooth Foot Deformities in a Family With CMT1A. RRNMF Neuromuscular Journal 2020; 1:3: 32-33.

Ronco, R., Perini, C., Currò, R., Dominik, N., Facchini, S., Gennari, A., Simone, R., Stuart, S., Nagy, S., Vegezzi, E., Ouartesan, I., El-Saddig, A., Lavin, T., Tucci, A., Szymura, A., Novis De Farias, L. E., Gary, A., Delfeld, M., Kandikatla, P., Niu, N., Tawde, S., Shaw, J., Polke, J., Reilly, M. M., Wood, N. W., Crespan, E., Gomez, C., Chen, J. Y. H., Schmahmann, J. D., Gosal, D., Houlden, H., Das, S., Cortes, A. Truncating Variants in RFC1 in Cerebellar Ataxia, Neuropathy, and Vestibular Areflexia Syndrome. Neurology 2023; 100: e543-554.

Saperstein, D. S., Amato, A. A., Wolfe, G. I., Katz, J. S., Nations, S. P., Jackson, C. E., Bryan, W. W., Burns, D. K., Barohn, R. J. Multifocal acquired demyelinating sensory and motor neuropathy: the Lewis-Sumner syndrome. Muscle Nerve 1999; 22(5): 560-566.

Singer, M.A., Kojan, S., Barohn R.J., Herbelin, L., Nations, S.P., Trivedi, J.R., Jackson, C.E., Burns, D.K., Boyer, P.J., Wolfe, G.I. Primary lateral sclerosis: Clinical and laboratory findings in 25 patients. J Clin Neuromusc Dis, 2005; 7:1-9.

Singer, M.A., Statland, J.M., Wolfe, G.I., and Barohn, R.J. Primary lateral sclerosis. Muscle and *Nerve* 2007; 35(3): 291-302.

Saperstein, D. S., Wolfe, G. I., Nations, S. P., Herbelin, L. L., Bryan, W. W., Barohn, R. J. Challenges in the identification of cobalamin-deficiency polyneuropathy. Arch Neurol 2003; 60(9): 1296-1301.

Statland, J. M., Barohn, R. J., Dimachkie, M. M., Floeter, M. K., Mitsumoto, H. Primary lateral sclerosis. Neurol Clin 2015; 33(4): 749-760.

Statland, J. M., Barohn, R. J., McVey, A. L., Katz, J. S., Dimachkie, M. M. Patterns of weakness, classification of motor neuron disease, and clinical diagnosis of sporadic amyotrophic lateral sclerosis. Neurol Clin 2015; 33(4): 735-748.

Turner, M.R., Barohn, R.J., Corcia, P., Fink, J.K., Harms, M.B., Kiernan, M.C., Ravits, J., Silani, V., Simmons, Z., Statland, J.M., van den Berg L.H.; Delegates of the

2nd International PLS Conference, Mitsumoto H. Primary lateral sclerosis: consensus diagnostic criteria. J Neurol Neurosurg Psychiatry. 2020; 9:373-377.

Vucic, S., Tian, D., Chong, P. S., Cudkowicz, M. E., Hedley-Whyte, E. T., Cros, D. Facial onset sensory and motor neuronopathy (FOSMN syndrome): a novel syndrome in neurology. Brain 2006; 129(12): 3384-3390.

Wartenberg, R. Neuritis, Sensory Neuritis, Neuralgia. Oxford Univ. Press 1958.

Wartenberg, R. Neuritis. JAMA 1950; 142(4): 275.

Wolfe, G. I., Baker, N. S., Amato, A.A., Jackson, C. E., Nations, S. P., Saperstein, D. S., Cha, C. H., Katz, J. S., Bryan, W. W., Barohn, R. J. Chronic cryptogenic sensory polyneuropathy: clinical and laboratory characteristics. Arch Neurol 1999; 56(5): 540-547.

Zeidman LA, Kubicki K. Clinical Features and Treatment Response in Immune-Mediated Small Fiber Neuropathy with Trisulfated Heparin Disaccharide or Fibroblast Growth Factor Receptor 3 Antibodies. Journal of Clinical Neuromuscular Disease. 2021 Jun 1;22(4):192-199.

Laboratory testing in peripheral nerve disorders

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The goal of this review is to guide the physician in ordering laboratory tests for a patient with a neuropathic disorder after the patient has been placed in one of the eleven neuropathic patterns (See this issue: Barohn et al. Pattern Recognition to Neuropathy and Neuronopathy, Pages 4-27, 2023). Once the patient has been placed into one of these eleven patterns, the physician is well on their way to a correct diagnosis for the neuropathic disorder that will ultimately lead to a targeted approach, including treatment. The neuropathic pattern will determine what laboratory tests should be ordered to confirm the diagnosis.

There are many tests one can order in the evaluation of peripheral neuropathy or neuronopathy; however, without using the pattern recognition approach to direct the appropriate laboratory tests the clinician can be left to process multiple laboratory studies that are not relevant to the patient's problem. We sometimes use the phrase when this occurs: "going down the rabbit hole". The danger is that you could end up treating a test result and not the relevant diagnosis for that patient.

The most common form of neuropathy that any neurologist or physician sees is the NP2 pattern, symmetric distal sensory loss with or without weakness. These individuals present with distal numbness and tingling in the toes and often burning sensations. Figure 1 lists the blood tests that are reasonable to obtain on a patient with the NP2 pattern. It also lists the tests that should **not** be obtained on a patient with a typical NP2 pattern.

Regarding tests we do not order routinely, we discourage ordering what are often referred to as autoantibody panels. These panels test for antibodies to neural antigens but often combine motor, sensory, and sensorimotor syndromes which may not be relevant to the patient's clinical phenotype. Rather we suggest only ordering specific antiganglioside antibodies that are appropriate for the clinical pattern in your patient. We will discuss these more later in this review.

Heavy metals do not need to be tested in the blood or urine unless there is a definite history of exposure. Chronic heavy metal exposure does not cause the NP2 pattern of distal sensorimotor neuropathy.

Folate deficiency does not cause peripheral neuropathy; however, it is mistakenly ordered frequently along with B12.

Figure 1

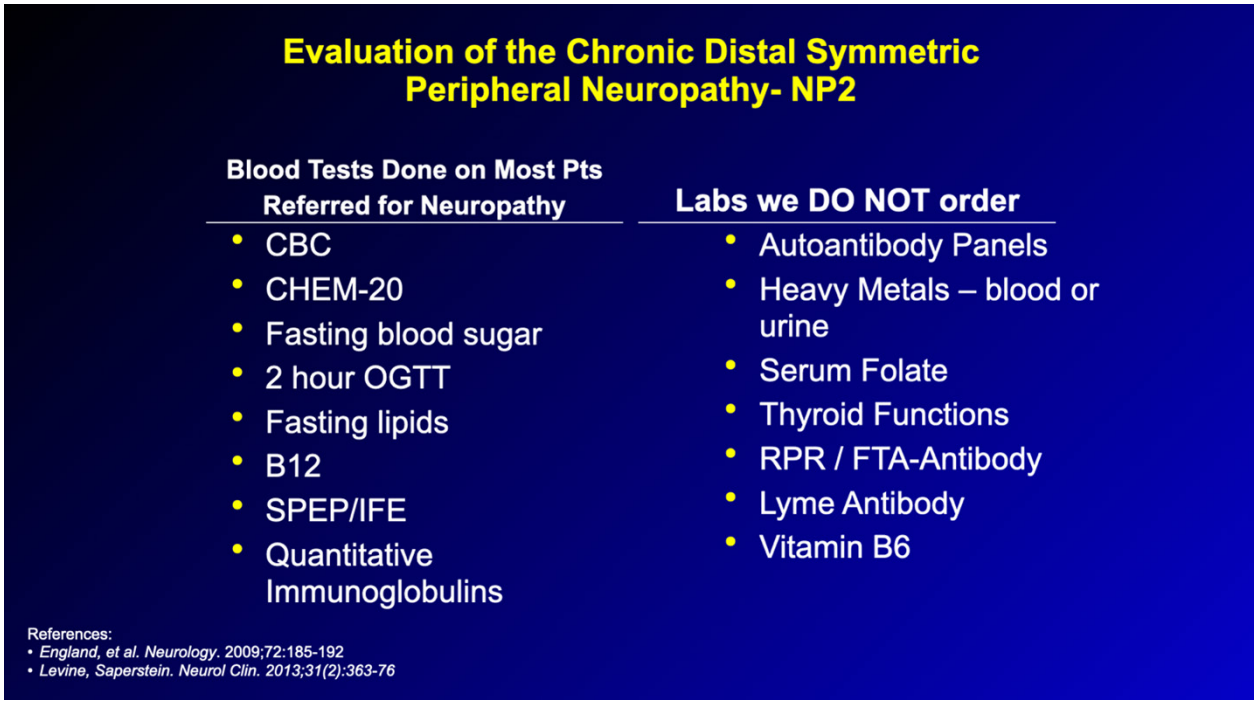
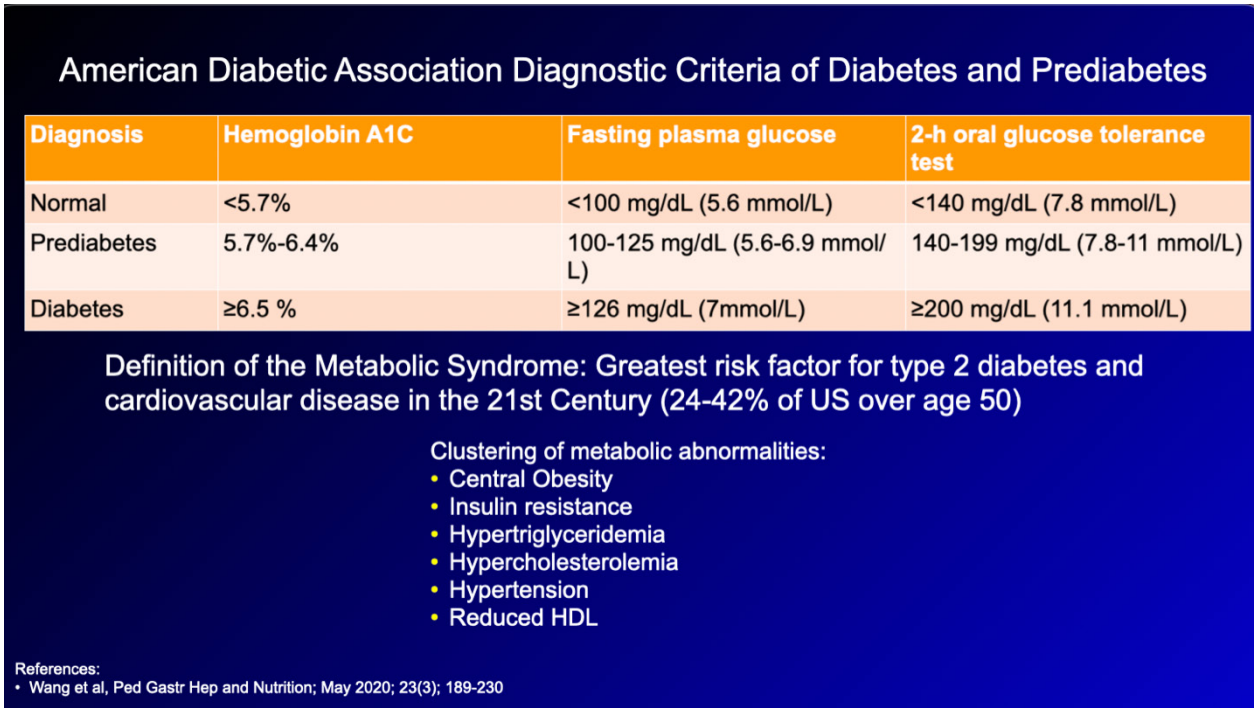


Figure 2



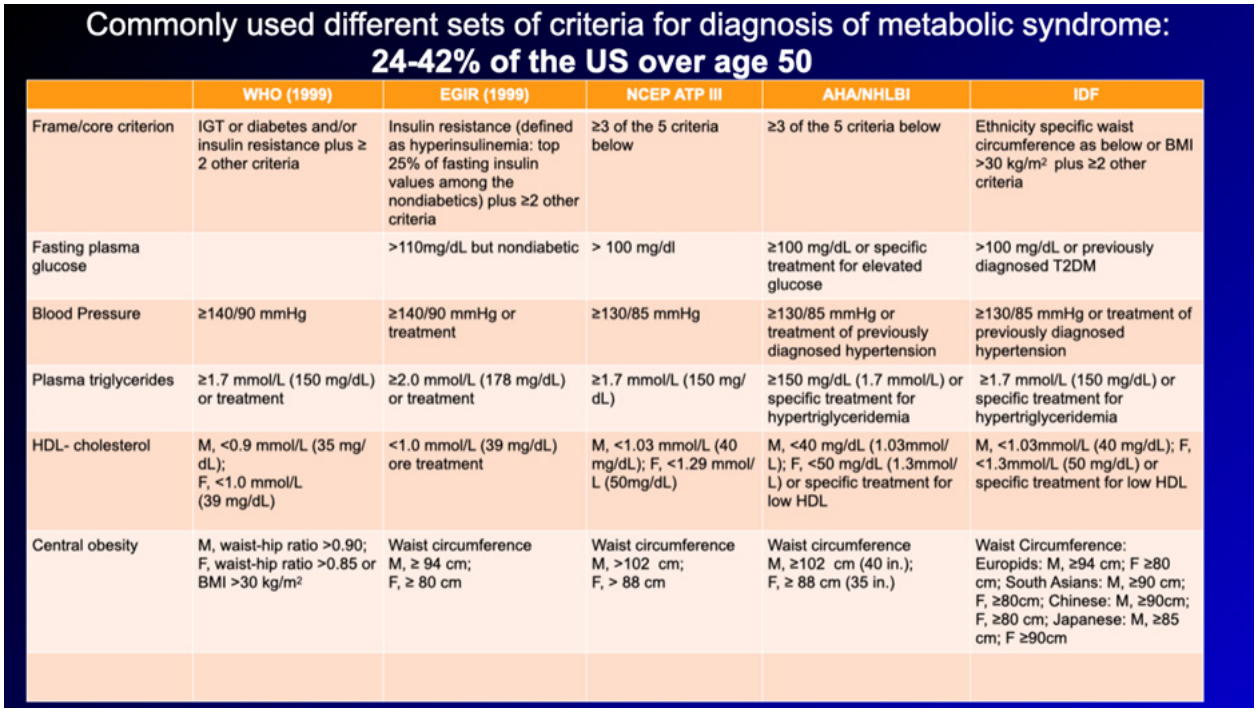
Syphilis can cause a variety of different peripheral and central nervous system disorders, but it will not present with an NP2 pattern. While there are certainly reports of excessive B6 causing neuropathies, these cases involve extremely high chronic ingestion of B6 supplements, and this information should be acquired by obtaining the history of the patient. Without such a history there is no need to check B6 levels. Thyroid hormone excess or deficiency does not cause peripheral neuropathy. Finally, unless one is in a region in which Lyme disease is common, we do not routinely recommend testing for this disorder.

Regarding the laboratory tests that should be done routinely, it is important to check for diabetes and prediabetes in patients presenting with the NP2 pattern. There are three different measures of glucose metabolism. The hemoglobin A1C is a measure for following someone who has diabetes but not for diagnosing diabetes. Fasting blood glucose, often referred to as fasting blood sugar or FBS is an easy, inexpensive, sensitive, and specific test. The FBS in a healthy person should be less than 100 mm/dL. In a patient with prediabetes, the FBS will be between 100-125 mm/dL. If the FBS is over 125 mm/dL this meets the definition of diabetes mellitus. The two-hour glucose tolerance test is a bit more cumbersome to obtain but it does increase the sensitivity for diagnosing diabetes. (Figure 2)

Therefore, the FBS and the 2-hour glucose tolerance test are both excellent screening tools for diabetes in a patient with the NP2 pattern and are preferable to the hemoglobin A1C.

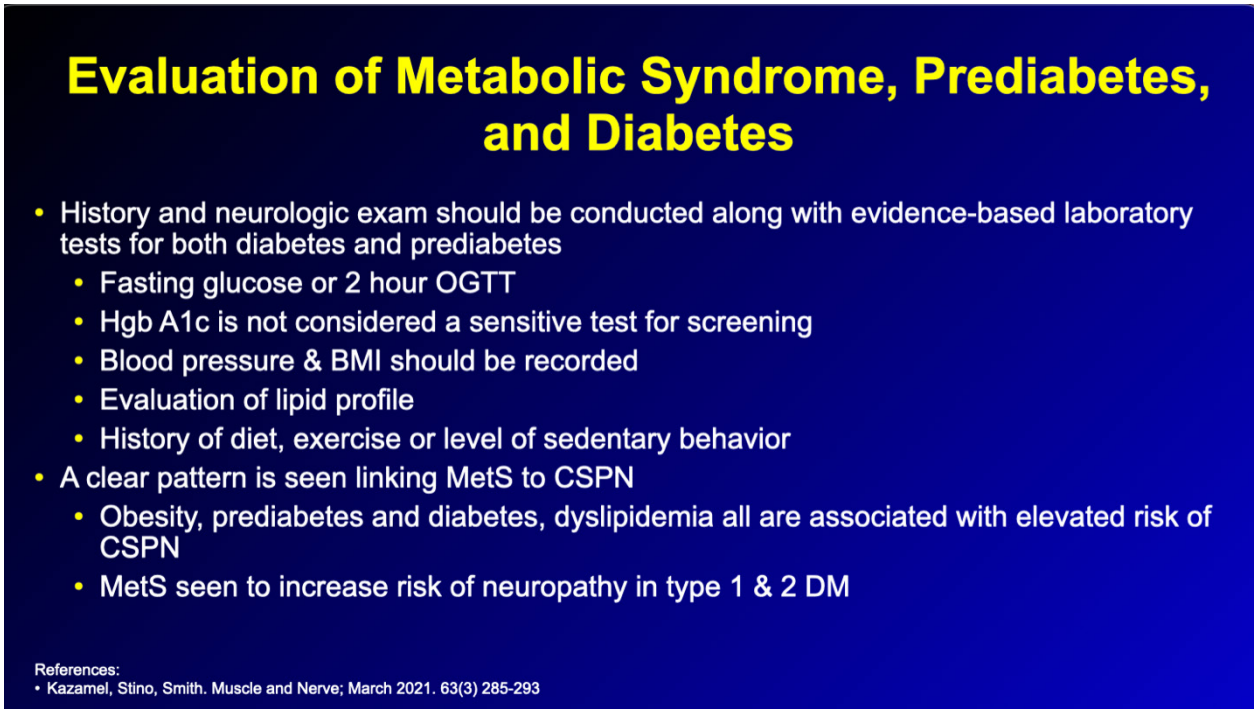
Metabolic Syndrome is a growing area of interest and is the single biggest risk factor for diabetes or cardiovascular disease (Figure 3). Metabolic syndrome is present in about 1/3 of the population in the United States and consists of a clustering of metabolic abnormalities that include central obesity, insulin resistance, hypertriglyceridemia, hypercholesterolemia, hypertension, and reduced HDL. Figure 3 shows a number of different sets of criteria for the definition of metabolic syndrome. For example, in the Metabolic and Heart Association criteria, three of the following abnormalities would constitute the metabolic syndrome: elevated FBS, treated hypertension, elevated triglycerides, low HDL, or central obesity.

Figure 3



	WHO (1999)	EGIR (1999)	NCEP ATP III	AHA/NHLBI	IDF
Frame/core criterion	IGT or diabetes and/or insulin resistance plus ≥ 2 other criteria	Insulin resistance (defined as hyperinsulinemia: top 25% of fasting insulin values among the nondiabetics) plus ≥2 other criteria	≥3 of the 5 criteria below	≥3 of the 5 criteria below	Ethnicity specific waist circumference as below or BMI >30 kg/m² plus ≥2 other criteria
Fasting plasma glucose		>110mg/dL but nondiabetic	> 100 mg/dl	≥100 mg/dL or specific treatment for elevated glucose	>100 mg/dL or previously diagnosed T2DM
Blood Pressure	≥140/90 mmHg	≥140/90 mmHg or treatment	≥130/85 mmHg	≥130/85 mmHg or treatment of previously diagnosed hypertension	≥130/85 mmHg or treatment of previously diagnosed hypertension
Plasma triglycerides	≥1.7 mmol/L (150 mg/dL) or treatment	≥2.0 mmol/L (178 mg/dL) or treatment	≥1.7 mmol/L (150 mg/dL)	≥150 mg/dL (1.7 mmol/L) or specific treatment for hypertriglyceridemia	≥1.7 mmol/L (150 mg/dL) or specific treatment for hypertriglyceridemia
HDL- cholesterol	M, <0.9 mmol/L (35 mg/dL); F, <1.0 mmol/L (39 mg/dL)	<1.0 mmol/L (39 mg/dL) ore treatment	M, <1.03 mmol/L (40 mg/dL); F, <1.29 mmol/L (50mg/dL)	M, <40 mg/dL (1.03mmol/L); F, <50 mg/dL (1.3mmol/L) or specific treatment for low HDL	M, <1.03mmol/L (40 mg/dL); F, <1.3mmol/L (50 mg/dL) or specific treatment for low HDL
Central obesity	M, waist-hip ratio >0.90; F, waist-hip ratio >0.85 or BMI >30 kg/m²	Waist circumference M, ≥ 94 cm; F, ≥ 80 cm	Waist circumference M, >102 cm; F, > 88 cm	Waist circumference M, ≥102 cm (40 in.); F, ≥ 88 cm (35 in.)	Waist Circumference: Europids: M, ≥94 cm; F ≥80 cm; South Asians: M, ≥90 cm; F, ≥80cm; Chinese: M, ≥90cm; F, ≥80 cm; Japanese: M, ≥85 cm; F ≥90cm

Figure 4



Therefore, it is important to take into account all of these parameters when evaluating a patient for the NP2 pattern of neuropathy (Figure 4). There is a clear association between the metabolic syndrome and diabetic distal sensory polyneuropathy (DSPN) and cryptogenic sensory polyneuropathy (CSPN) or the NP2 pattern of peripheral neuropathy. We also know that in a patient who has diabetes, type 1 or type 2, if they have metabolic syndrome in addition to their diabetes their risk of neuropathy goes up significantly. Therefore, metabolic syndrome does seem to be an independent risk factor even separate from glucose that links the metabolic syndrome to the NP2 pattern of neuropathy.

Figure 5

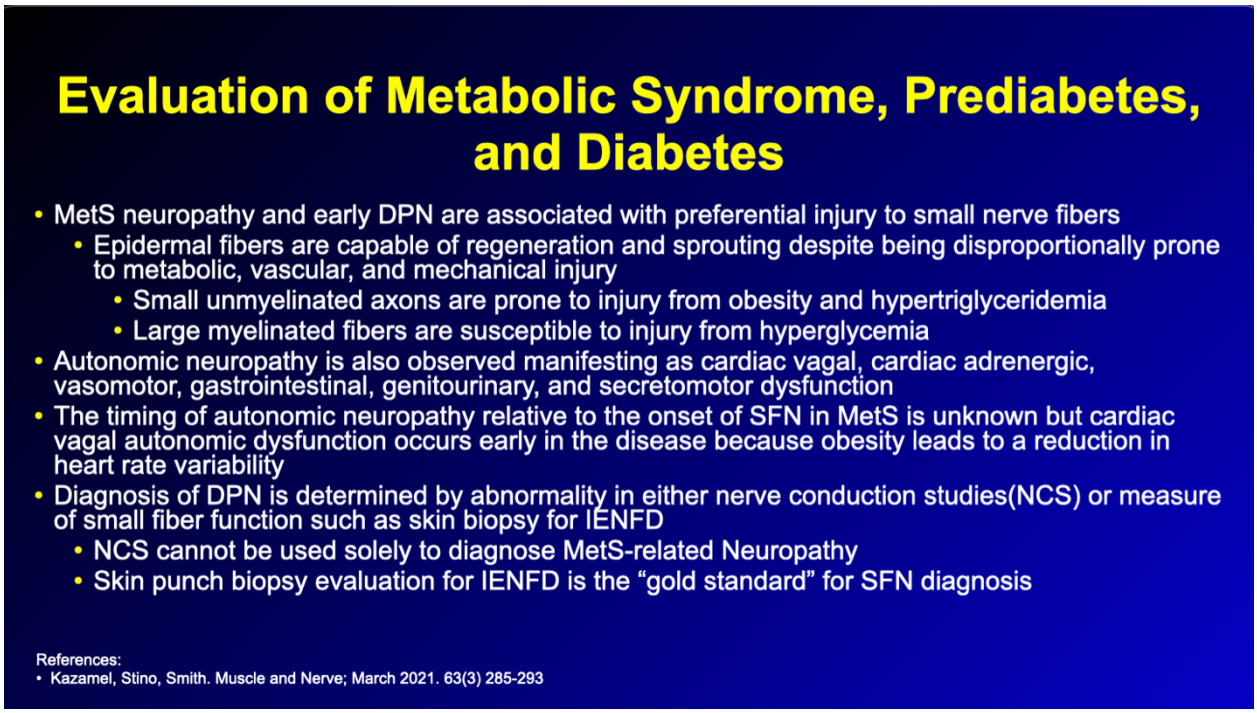
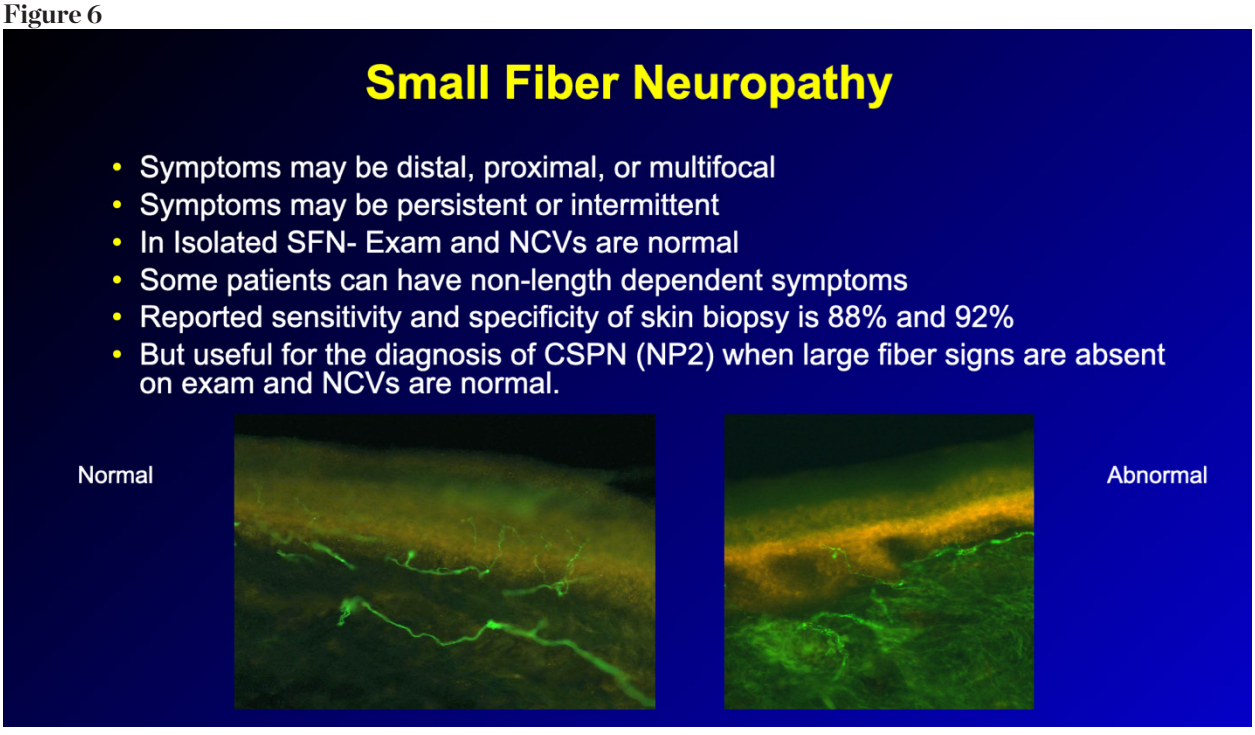


Figure 6

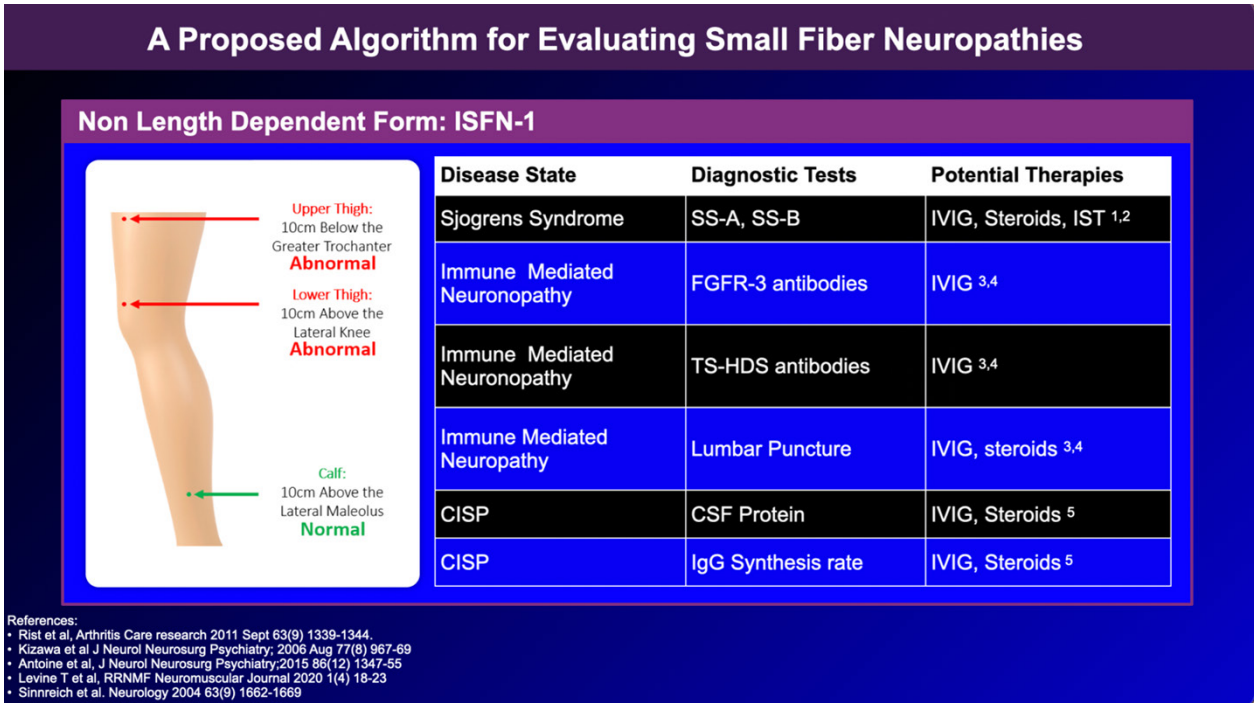


Metabolic syndrome in the early phases of diabetic neuropathy tends to affect the smallest nerves first (Figure 5).

These small nerves, the epidermal sensory nerve fibers, seem to be very susceptible to injury from obesity and hypertriglyceridemia. The large, myelinated fibers seem to be more susceptible to damage from hyperglycemia. Autonomic symptoms and signs can be associated with small fiber involvement. Nerve conduction studies alone may not be able to diagnose the neuropathy associated with metabolic syndrome. Nerve conduction studies measure large fiber physiology and cannot detect neuropathy when only small nerve fibers are involved. Rather, skin punch biopsies assessing small intradermal nerve fibers is probably a more sensitive test to look for nerve damage (Figure 6).

What do we mean when we talk about intraepidermal

Figure 7



nerve fiber densities? Figure 6 shows two skin punch biopsies. The area at the top is the epidermal layer. Just beneath that is the basement membrane and the melanocytic layer and below that is the dermis. The figure on the left shows normal intraepidermal nerve fiber density and the figure on the right shows decreased intraepidermal nerve fiber density.

In skin biopsies for intraepidermal nerve fiber density, the nerves come in parallel to the surface of the skin and then they branch upwards. These small unmyelinated nerve fibers are the nerve fibers that provide sensation throughout our body. When these small nerve fibers are damaged, this typically results in distal sensory loss or abnormal sensory sensations. Therefore, the pattern is the distal NP2 in most cases. Rarely some small fiber neuropathies can have proximal or multifocal patches of sensory involvement. When only small fibers are involved, vibration and proprioception, and reflexes on the neurologic exam are normal and nerve conduction studies are normal. In these cases, a skin biopsy can be helpful in documenting and quantifying small fiber sensory loss. If the patient presents with distal sensory loss and/or neuropathic pain distally, and either proprioception or vibration, or reflexes are abnormal then you know that both large and small fibers are involved, and the nerve conduction studies are likely to be abnormal. In these cases, a skin biopsy is probably not going to be useful as you have already documented a neuropathy. In other words, if the nerve conduction studies are abnormal you will not learn anything additional from the skin biopsy. The skin biopsy is most useful as a tool in cases where a patient has sensory symptoms and a normal exam and normal nerve conductions studies. In these cases, the skin biopsy has a sensitivity and specificity of about 90%. We recommend that skin biopsies are taken from three sites: one from just above the ankle, one from just above the knee, and one from below the hip. The reason for doing this is to demonstrate objectively the pattern of small fiber loss.

Based on the patient's symptoms, signs, and skin biopsy, there are four different intraepidermal small fiber neuropathy presentations- IFSN-1; IFSN-2; IFSN-3; IFSN-4. If you have a patient with upper thigh skin biopsies that are abnormal, but lower thigh and calf biopsies are normal, this is referred to as the ISFN-1 presentation (Figure 7) This is a non-length-dependent small fiber neuropathy which has been shown to predict an autoimmune etiology.

The length-dependent distal pattern, where the skin punch biopsy is abnormal at the lower thigh and calf and normal at the upper thigh is the IFSN-2 presentation of small fiber neuropathy. This falls in the spectrum of the clinical NP2 pattern and most often due to diabetes (DSPN), cryptogenic (CSPN), or chemotherapy-induced neuropathy (CIN). (Figure 8)

There is an entity called Wartenberg's sensory neuritis which is a patchy distribution of sensory loss and pain both proximally and distally. In other words, there is multifocal patchy sensory loss and pain. For example, the calf and upper thighs may be involved clinically but the lower thigh is normal, and this can be at times documented or supported

Figure 8

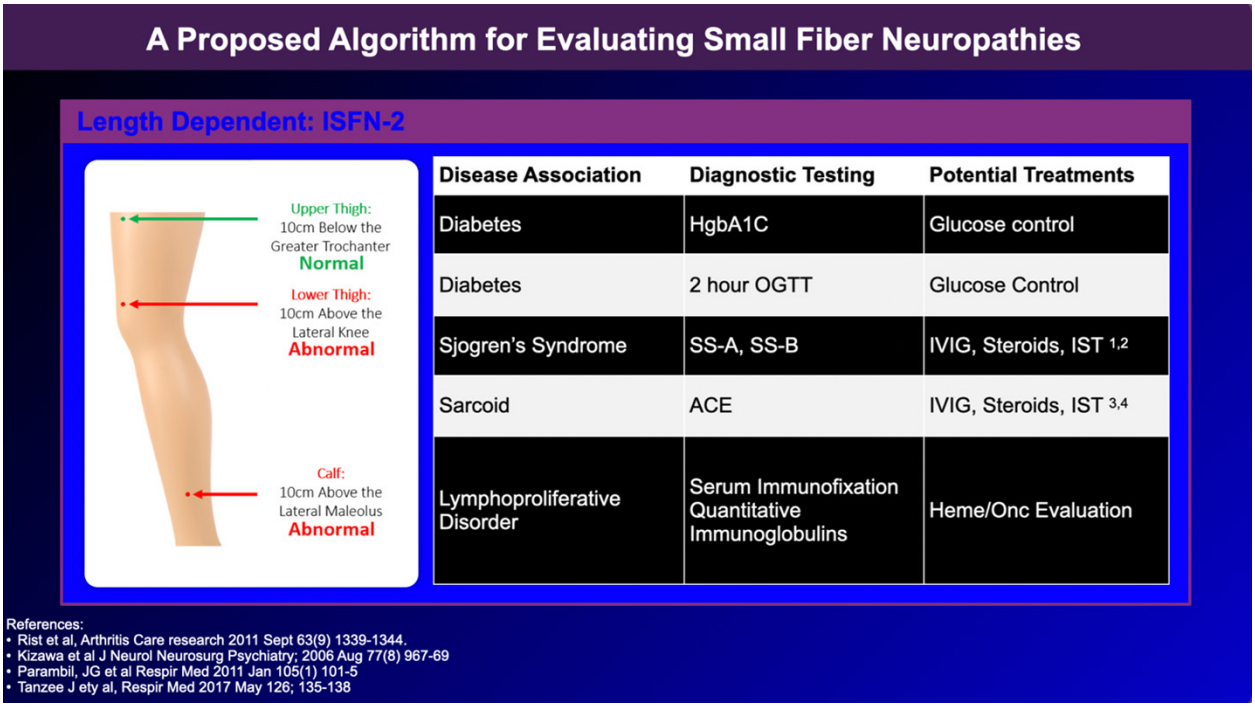
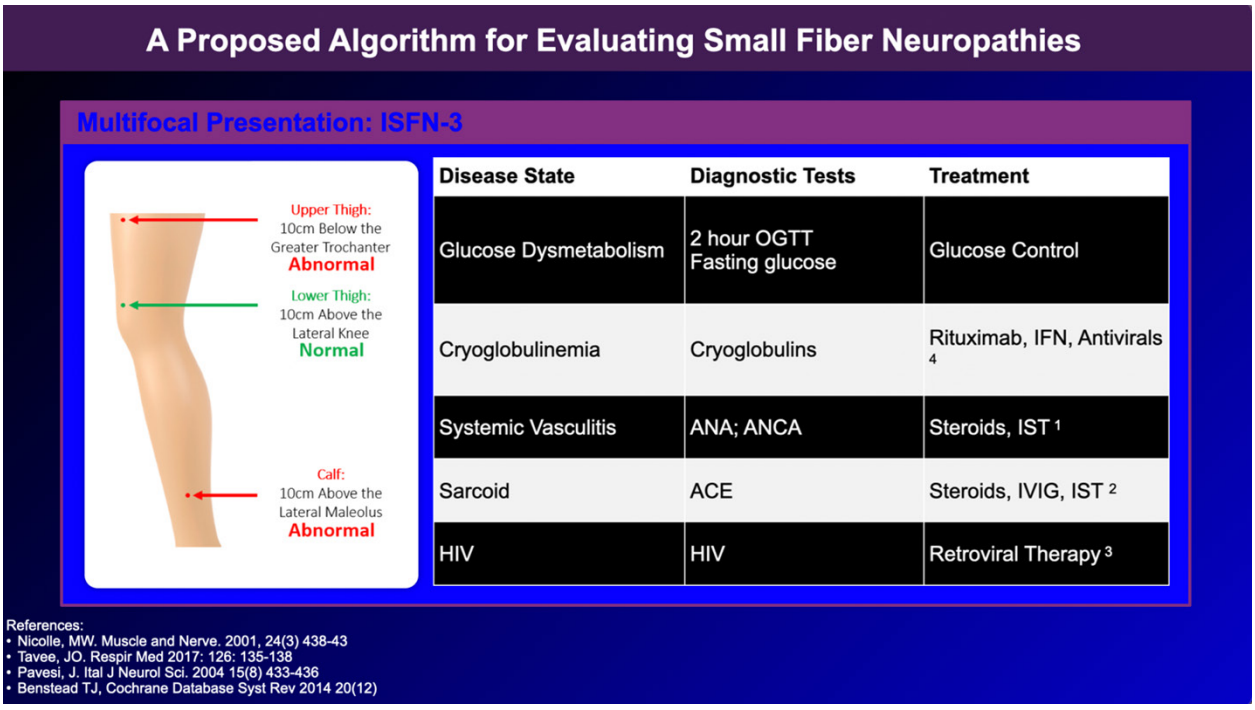


Figure 9



by skin biopsies showing a similar distribution of small fiber sensory loss. We have referred to this as the ISFN-3 presentation. (Figure 9)

There are some pure autonomic neuropathies in which the intraepidermal nerve fiber density is normal but the nerve fiber density in the sweat glands in the skin are reduced. This has been referred to as the ISFN-4 presentation. (Figure 10)

Regarding B12 deficiency, serum B12 is often a poor measure of B12 deficiency. In B12 deficiency, methylmalonic

Figure 10

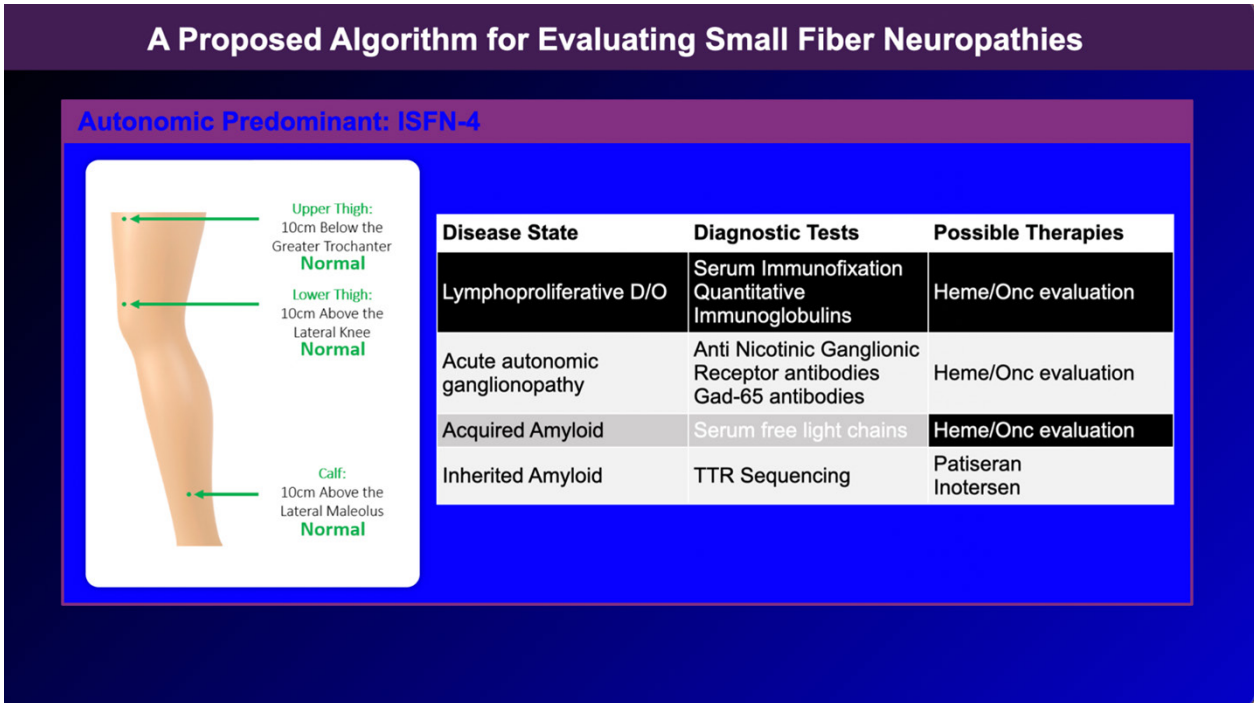
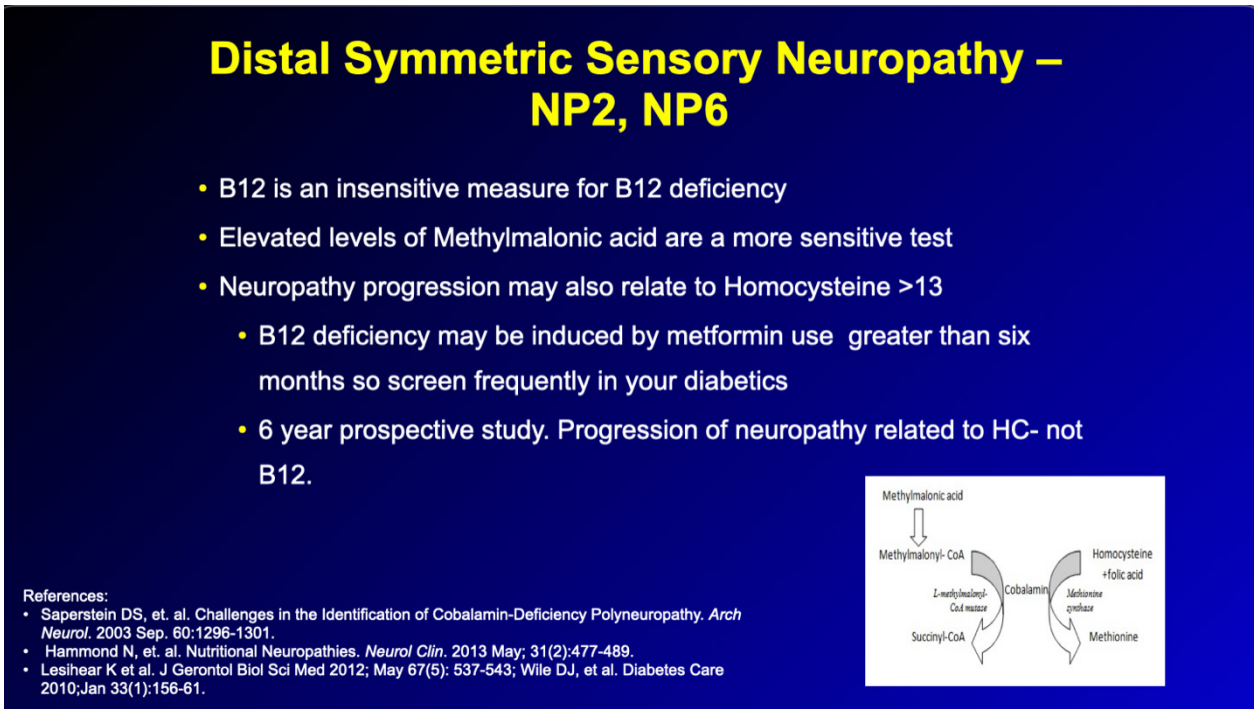


Figure 11



acid builds up and is toxic to nerves. Therefore, in evaluating for possible B12 deficiency it is recommended to do a serum B12 level with a serum methylmalonic acid level. Blood methylmalonic levels are elevated in B12 deficiency. Blood homocysteine levels can also be elevated. Homocysteine is probably not a direct cause of neuropathy. However, when homocysteine is elevated, it does predict a faster progression of the neuropathy. Elevated homocysteine may be a measure of metabolic syndrome, and it may be that it is the metabolic syndrome that is causing the progression of their neuropathy. For diabetic patients who are on metformin, it should be recognized that this drug can induce a B12 deficiency. Therefore, we recommend that diabetics on metformin have B12, methylmalonic acid, and homocysteine levels checked if they have a worsening neuropathy to make sure there is not a second cause due to the metformin.

Figure 12

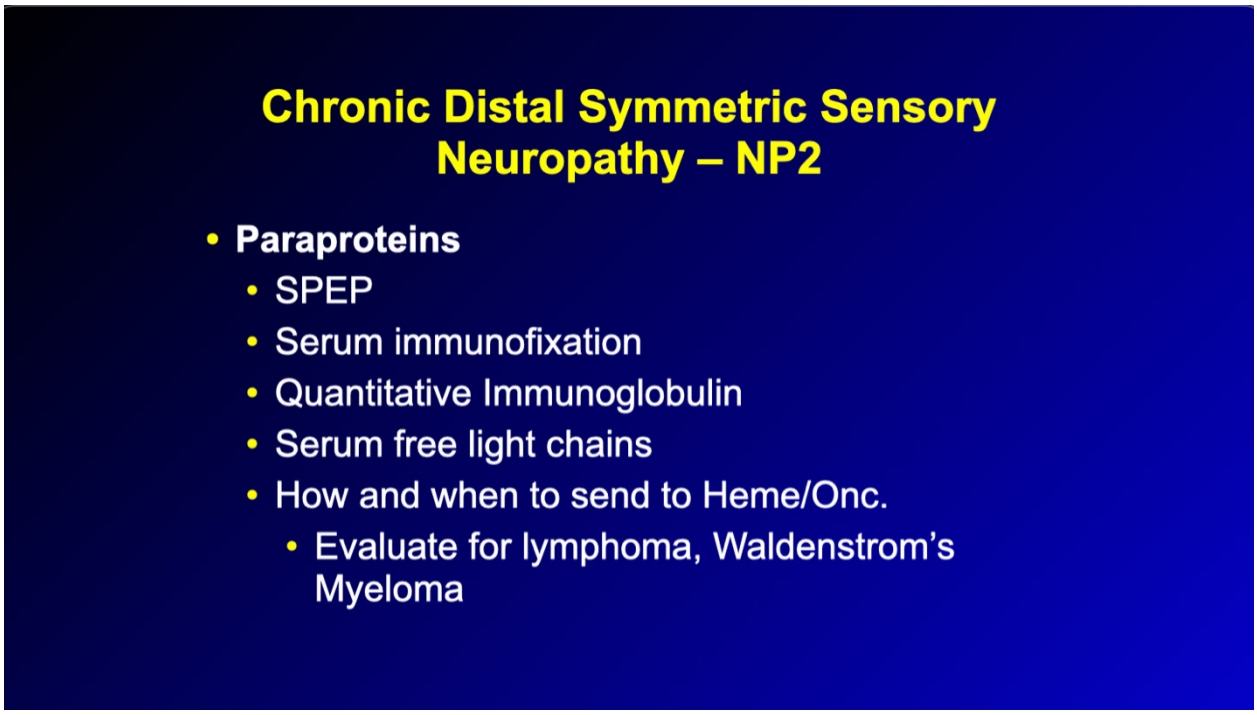
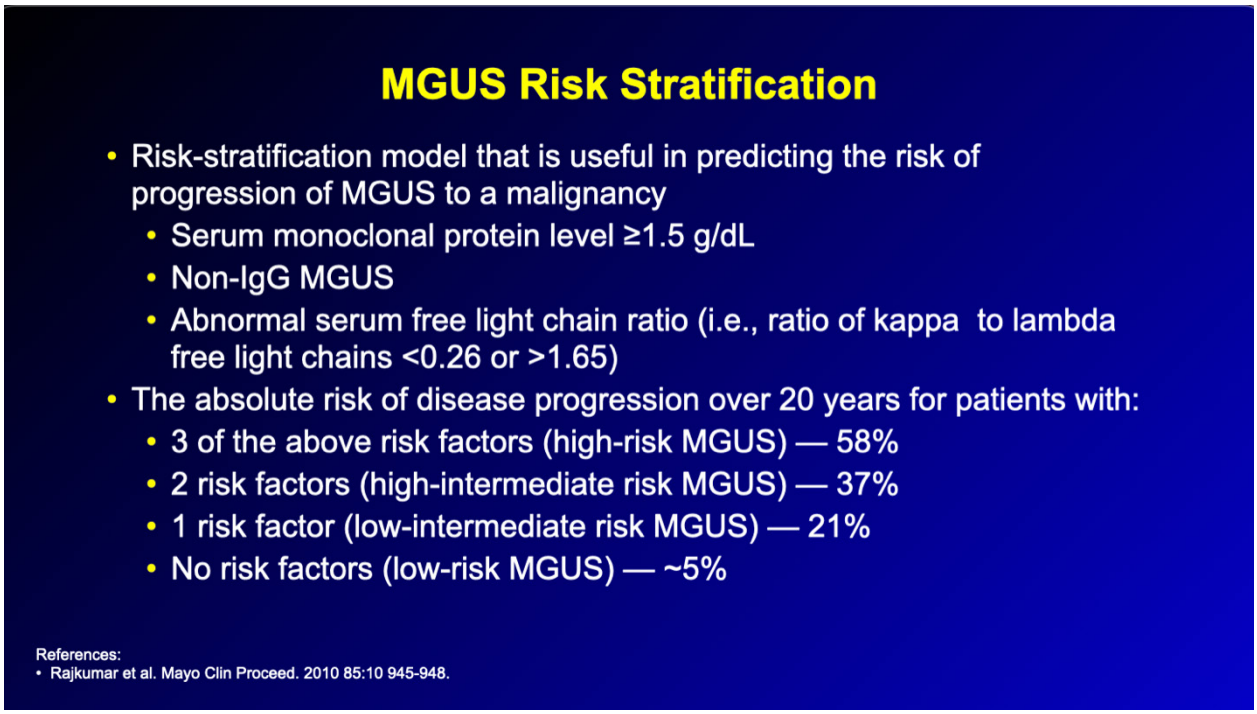


Figure 13



Regarding testing for a paraprotein in the setting of a neuropathy, it is recommended that patients have a serum protein electrophoresis (SPEP) blood test or quantitative immunoglobulins to evaluate the total of the antibody classes. In addition, we recommend a serum immunofixation to look for small spikes of abnormal proteins. If any of these are abnormal an additional test for serum-free light chains and urine for light chains should be obtained as an evaluation for underlying blood-based dyscrasias. All of the tests for serum paraproteins are designed to search for an underlying lymphoproliferative disorder. However, not all patients with a serum paraprotein have an identifiable lymphoproliferative disorder and in these cases, we classify the abnormality as a monoclonal gammopathy of unknown significance (MGUS). The incidence of paraproteins increases with age. Over the age of 75, up to 5% of the population may have a MGUS. If a paraprotein is found (also often called monoclonal protein) attention needs to

Figure 14

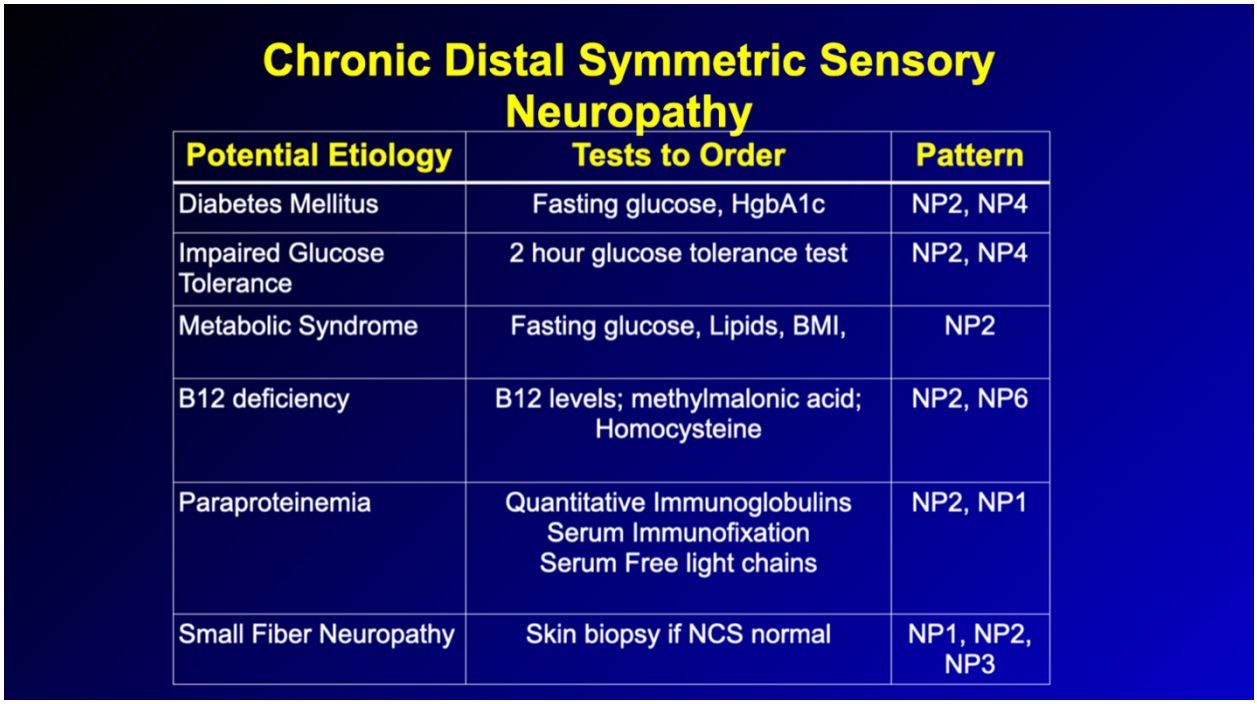
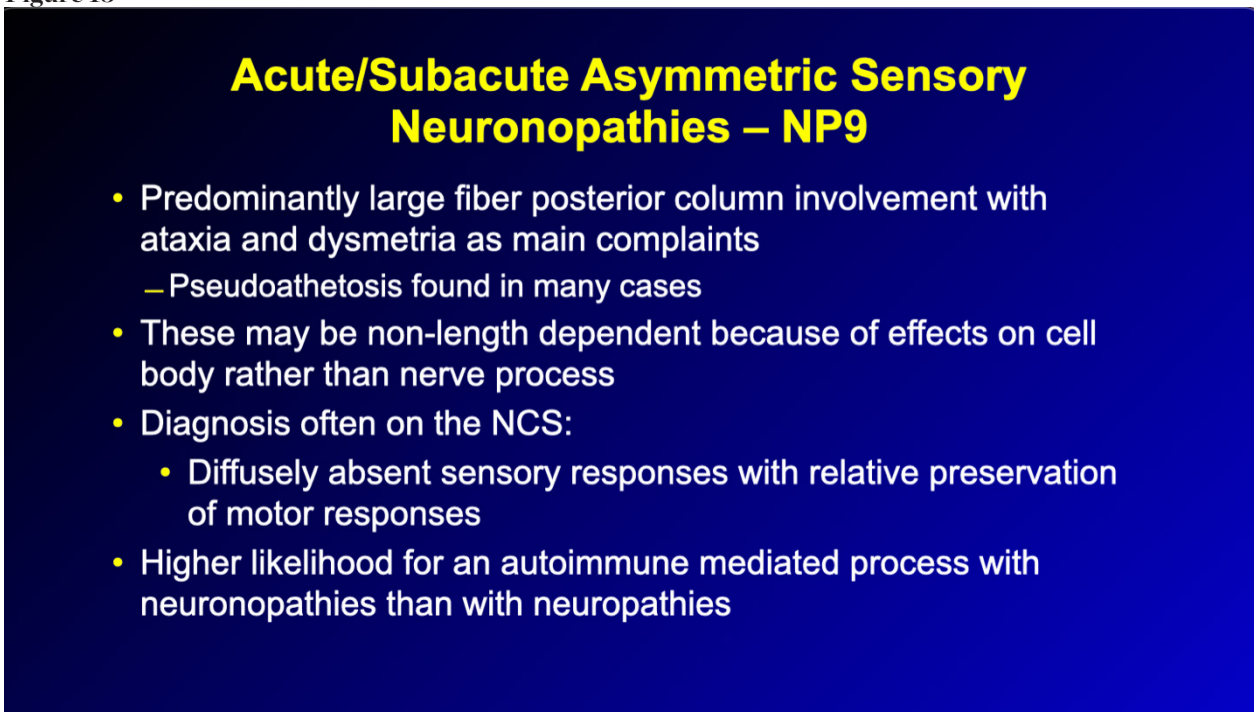


Figure 15



be focused on three aspects: the amount of the monoclonal protein, the type of monoclonal protein, and whether there are any free light chains.

If we look at the stratification in approaching a patient with a MUGS outlined in Figure 13, there are three risk factors that we identify. The type of Ig (IgM, IgG), the amount of the protein, and the ratio of kappa to lambda light chains. If the patient has an IgG level below 1.5gm/dl and a normal light chain ratio, the chance of any malignancy is very low. On the other hand, a patient with 3 gm/dL of paraprotein that is IgM and an abnormal free light chain ratio, has a very high likelihood of malignancy and needs a referral to hematology.

Figure 14 summarizes the information we have reviewed up to this point regarding diabetes, metabolic syndrome, B12 deficiency, paraproteins, small fiber neuropathy, and the pattern most often associated with these abnormalities.

Figure 16

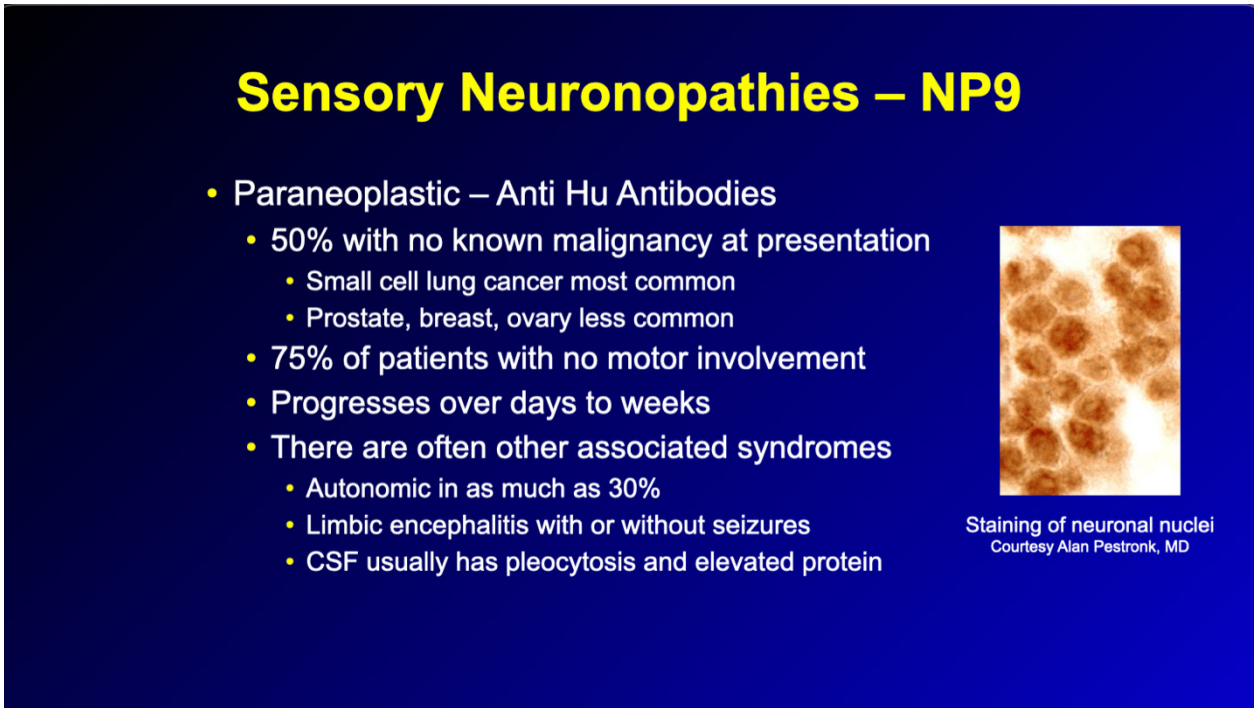
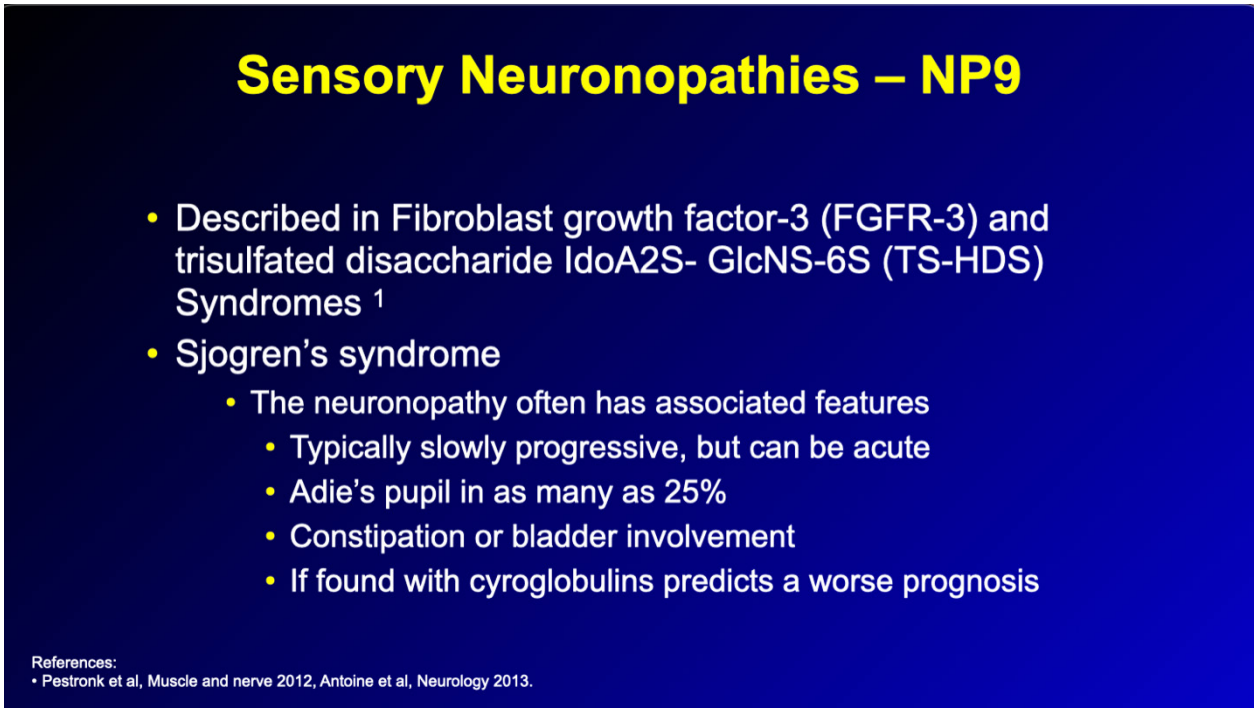


Figure 17



The NP9 pattern often indicates a neuronopathy where the damage is to the sensory cell body (Figure 15). NP9 affects large sensory fibers and can lead to ataxia, dysmetria, and very often astereognosis. This can be non-length dependent and asymmetric. Nerve conduction studies show that sensory responses are absent and motor responses are normal. These disorders are most likely to be autoimmune.

Often there is an underlying malignancy as in the presence of anti-Hu antibodies. (Figure 16)

However, occasionally a malignancy is not found (Figure 17). In these instances, some cases have been associated with autoantibodies to FGFR-3 and TS-HDS. Other cases are associated with Sjogren's syndrome and

Figure 18

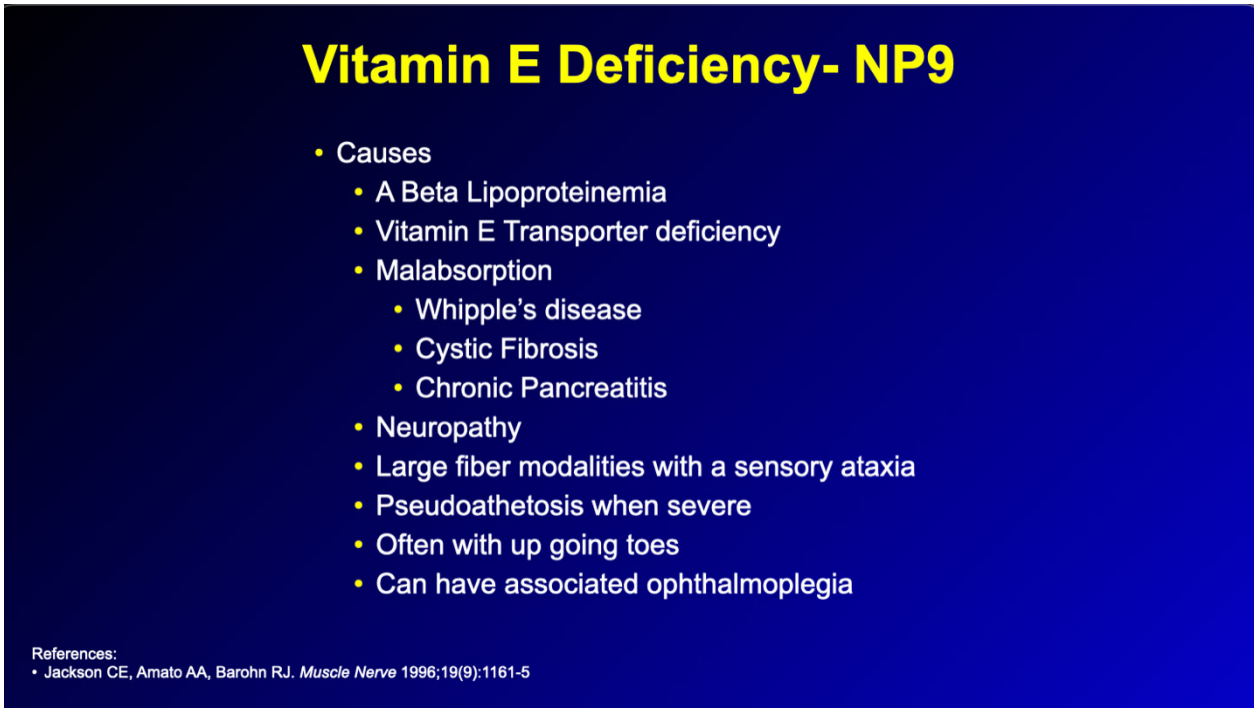
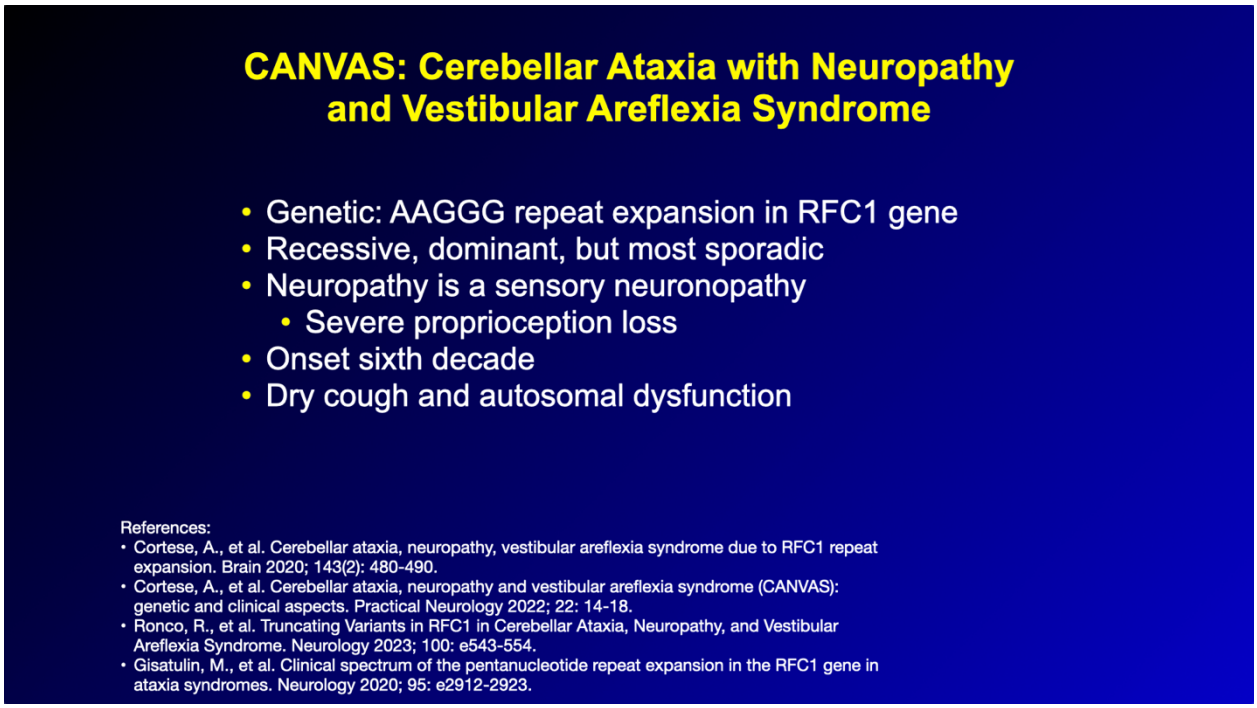


Figure 19



may have SS-A or SS-B serum positivity. Clinically some of these Sjogren's patients with neuronopathy can also have Adie's pupil, severe constipation, and bladder involvement suggesting autonomic issues.

Vitamin E deficiency can also present with an NP9 pattern (Figure 18). Vitamin E deficiency is generally only seen in patients with a severe malabsorption issue or if they have a specific deficiency like abetalipoproteinemia or vitamin E transporter deficiency. In many vitamin E deficiency patients, there are also central nervous system findings including upgoing toes and ophthalmoplegia.

Recently, a genetic syndrome has been described consisting of cerebellar ataxia, neuropathy, and vestibular dysfunction called CANVAS. The neuropathy is believed to be a sensory neuronopathy with profound proprioceptive sensory loss. Many patients have a chronic cough, and

Figure 20

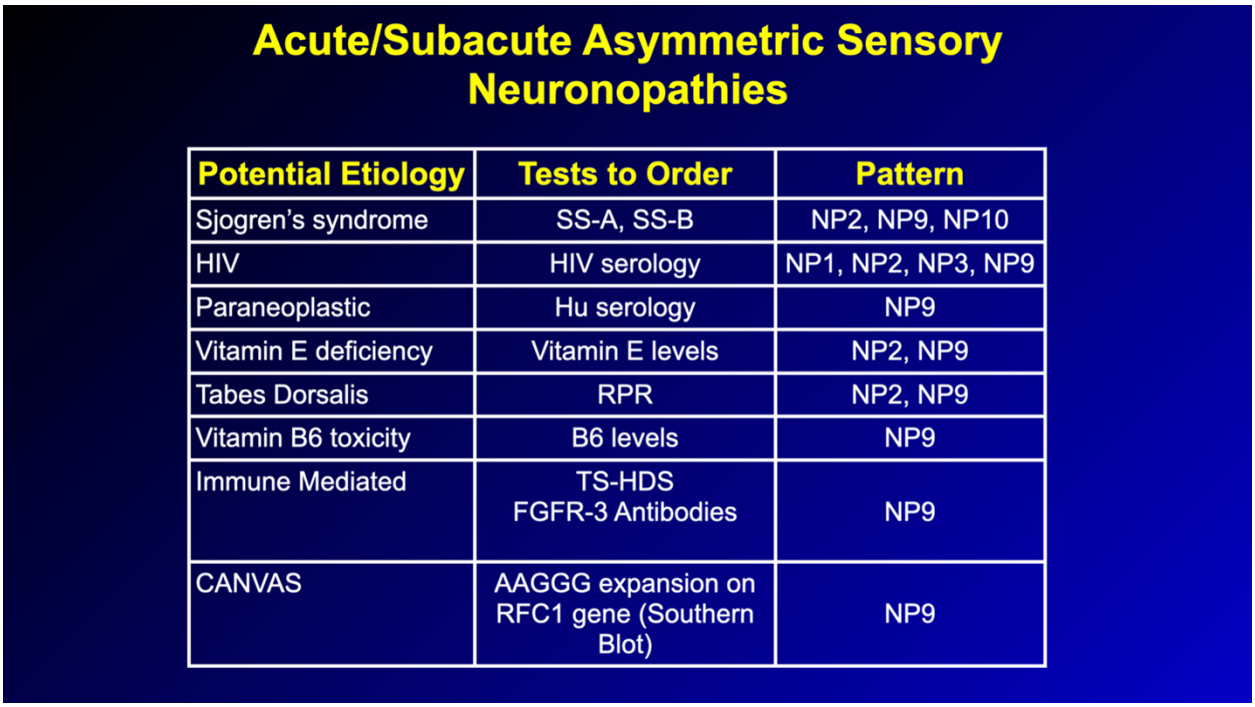
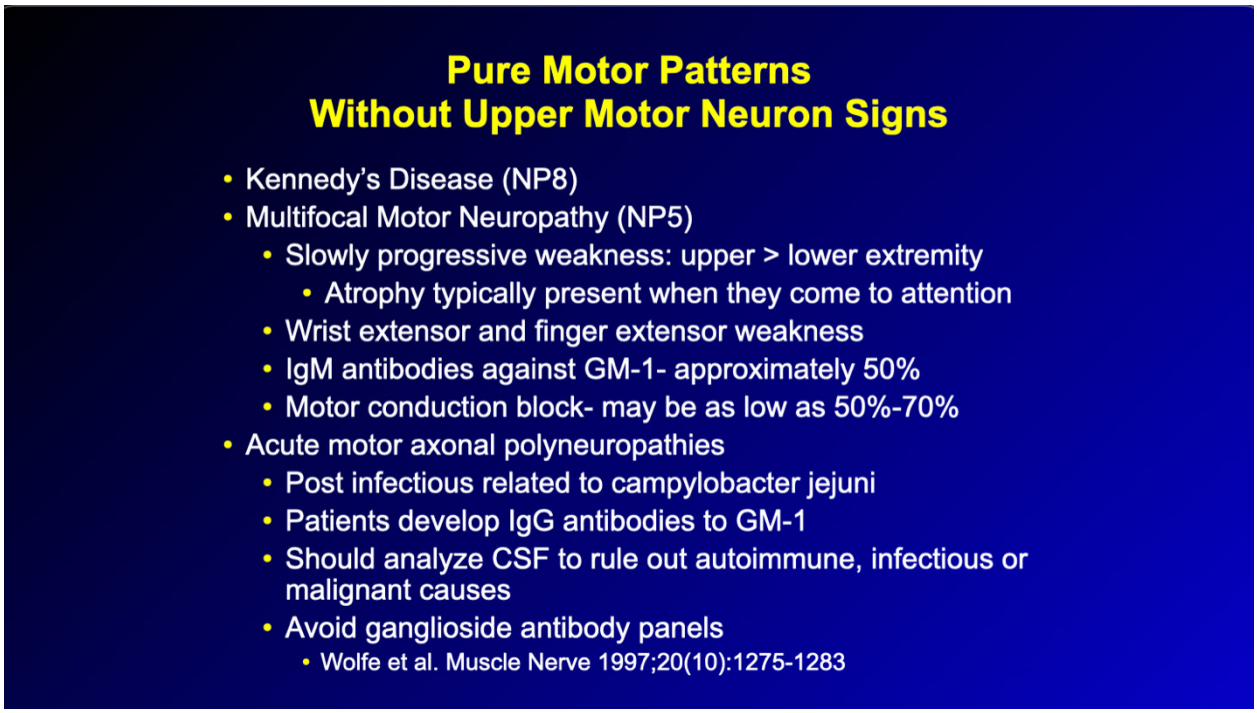


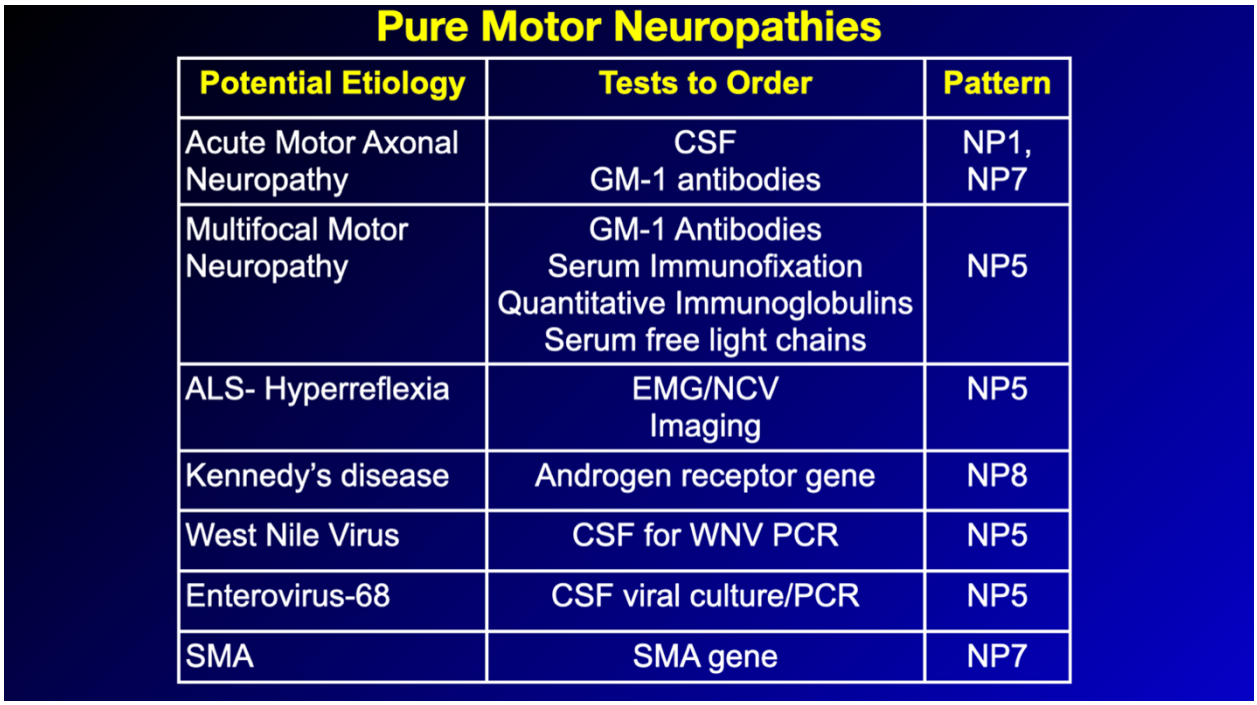
Figure 21



some have autonomic dysfunction the genetic defect is a novel biallelic AAGGG expansion in the replication factor subunit 1 complex (RFC1). The repeat expansion cannot be detected on currently available next-generation sequencing panels and requires identification by time-consuming southern blotting. This condition is now thought to be one of the most common causes of late-onset genetically mediated cerebellar ataxia. A patient with a combination of cerebellar ataxia and sensory neuronopathy may have this disorder.

Figure 20 summarizes the information about sensory neuronopathy discussed above. It also mentions that rarely HIV, Tabes Dorsalis, and vitamin B6 toxicity can have an NP9 presentation.

Figure 22



Pure Motor Neuropathies

Potential Etiology	Tests to Order	Pattern
Acute Motor Axonal Neuropathy	CSF GM-1 antibodies	NP1, NP7
Multifocal Motor Neuropathy	GM-1 Antibodies Serum Immunofixation Quantitative Immunoglobulins Serum free light chains	NP5
ALS- Hyperreflexia	EMG/NCV Imaging	NP5
Kennedy's disease	Androgen receptor gene	NP8
West Nile Virus	CSF for WNV PCR	NP5
Enterovirus-68	CSF viral culture/PCR	NP5
SMA	SMA gene	NP7

Pure motor patterns are often some of the most difficult cases mainly due to the fact that if a patient comes in with pure motor weakness as a result of neuropathic disorder, it is more likely to be due to amyotrophic lateral sclerosis- NP5 (Figure 21). If upper motor neuron signs are present ALS is definitely the most likely diagnosis. On the other hand, if upper motor neuron signs are not present the diagnosis may be a pure lower motor neuron disease often referred to as progressive musculature atrophy (PMA). However, there are other causes that can produce pure motor patterns without upper motor neuron signs. Kennedy's disease also known as X-linked spinobulbar atrophy is a genetic disorder affecting men and in addition to limb involvement has tongue, face, and pharyngeal motor weakness (NP8). It is usually symmetric and proximal more than distal weakness in the extremities. The diagnostic test is a genetic assay showing an excess number of triplet repeats in the SMA gene on the X chromosome.

Multifocal motor neuropathy (NP5), like ALS, can present with distal unilateral hand weakness but without upper motor neuron signs and the weakness may be confined at an early stage to one or two nerves. MMN has a predilection for radial nerves, so wrist and finger drop are prominent. It is important to recognize as it is treatable. Half of these patients have serum GM1 antibodies in the serum. Conduction block may only be seen in 50-70% of patients, so a clinical diagnosis is critical in these cases.

Some acute motor neuropathy syndromes are acute and symmetric and mimic the Guillain-Barré syndrome but without sensory symptoms, signs, or objective sensory abnormalities on nerve conduction studies or nerve biopsy. These GBS variants are usually axonal polyneuropathies and not demyelinating. The usual term for these disorders is acute motor axonal neuropathy (AMAN). AMAN usually follows a gastrointestinal infection with *Campylobacter jejuni* and has IgG antibodies to GM-1. AMAN cases are treated like typical GBS but often have a poor prognosis.

Autosomal recessive spinal muscular atrophy presents with the NP7 pattern with symmetric proximal and distal weakness and can present from infancy to young adulthood. The diagnosis is based on genetic testing for SMN-1 gene deletions and also determining the number of copies of SMN-2. Now that we have therapies for SMA it is important to consider this diagnosis even in the non-pediatric population.

West Nile virus can present as a polio-like syndrome at any age. Enterovirus can produce a paralytic polio-like syndrome in infancy and childhood.

Figure 22 summarizes the entities discussed above, and the associated patterns and laboratory tests.

Figure 23

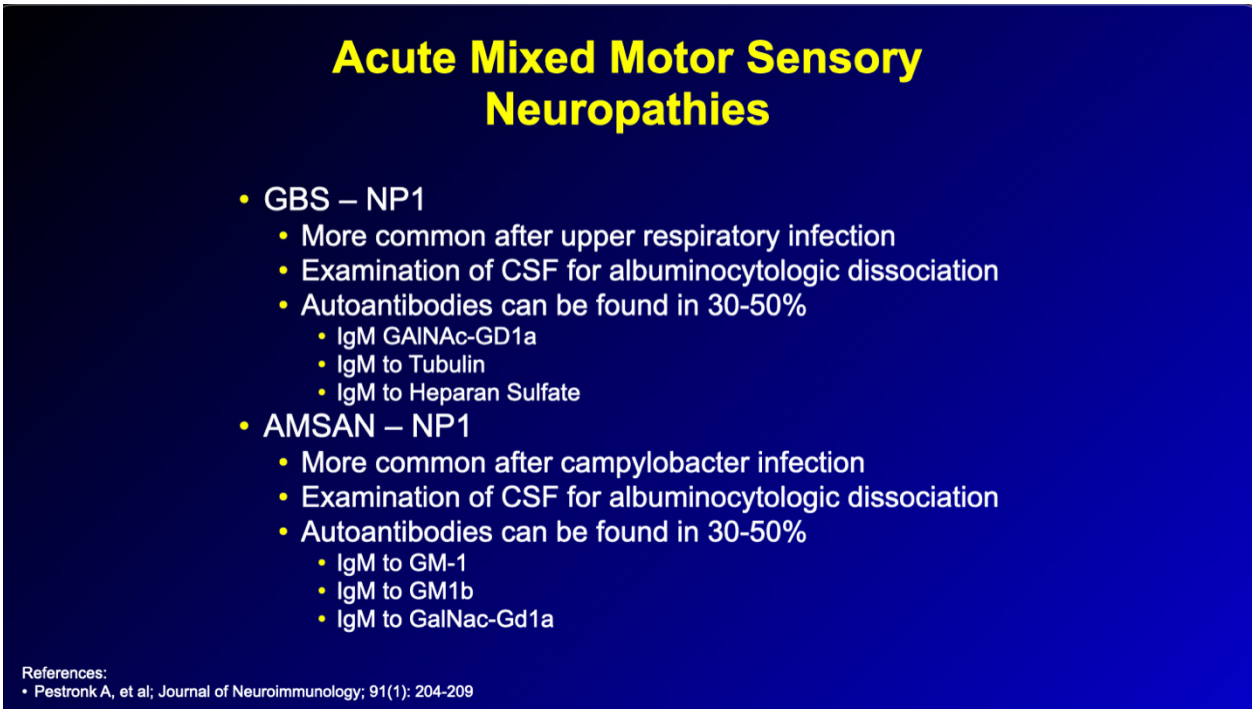
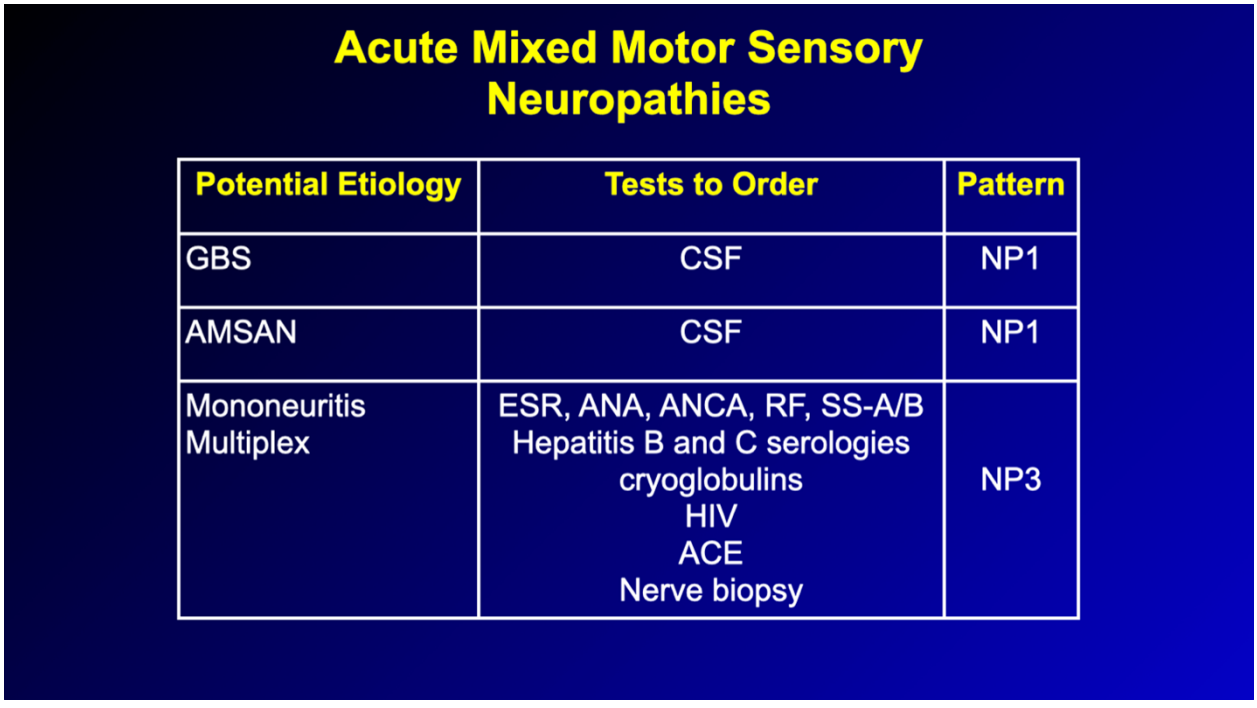
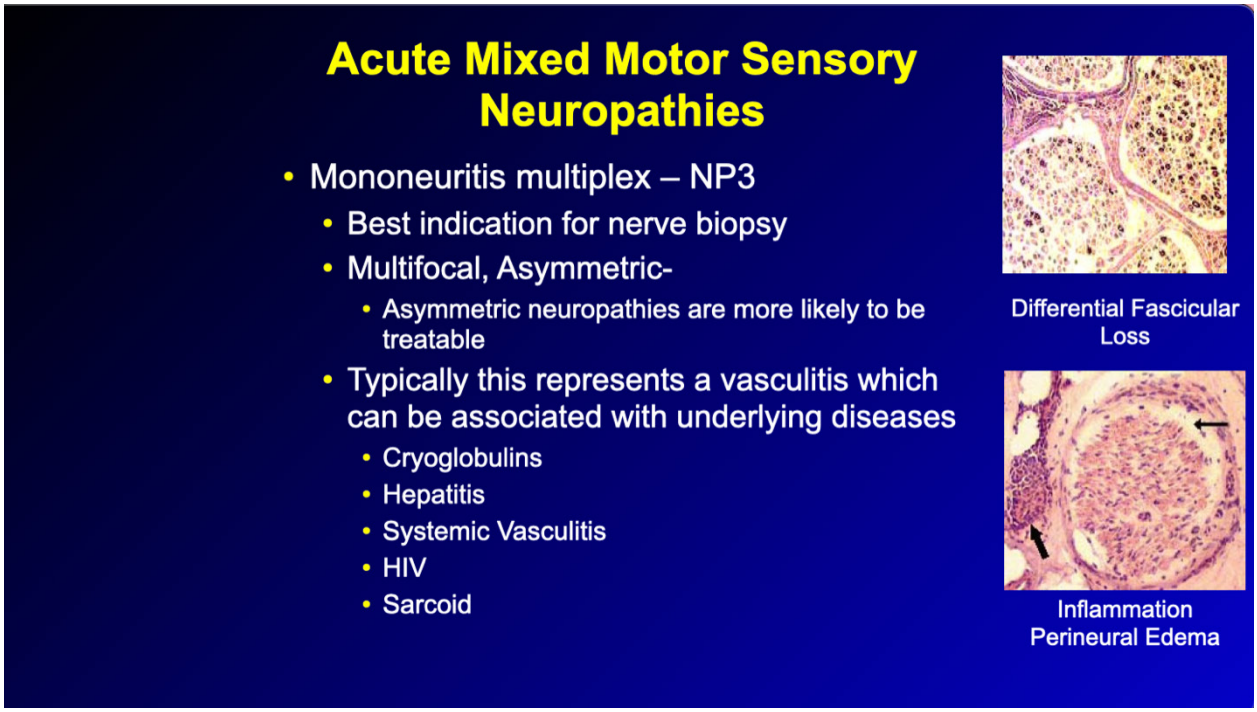


Figure 24



Guillain-Barre syndrome, while often appearing predominantly motor usually has sensory symptoms and signs and often can have sensory nerve conduction study abnormalities (Figure 23, 24). Occasionally IgG and IgM antibodies to a number of nerve glycoproteins have been identified. The pure axonal form of motor and sensory Guillain-Barré is often referred to as acute motor sensory and motor sensory axonopathy (AMSAN), and like AMAN has a poorer prognosis than GBS. GBS, AMSAN, and AMAN all typically have elevated CSF protein without an elevated cell count, or the so-called albumin-cytologic dissociation.

Figure 25



Why have nerve biopsies decreased? Only rarely are nerve biopsies now needed as a supportive laboratory test for the diagnosis of neuropathy. This is usually performed in cases of possible vasculitic neuropathy that presents with the NP3 pattern (Figure 25). However, other than in vasculitis nerve biopsies are rarely performed in the modern era. Why? We have gained a better understanding of clinical phenotypes and we have gotten better at interpreting nerve conduction studies; we use more genetics, imaging, and spinal fluid than we did previously. If you make a provisional diagnosis using pattern recognition and tests short of a nerve biopsy, and the patient continues to deteriorate despite therapies, this may be an indication of the need for a nerve biopsy. On the other hand, if the patient has an acute presentation with pain as part of the NP3 pattern, you might consider treating the patient with prednisone.

Figure 26

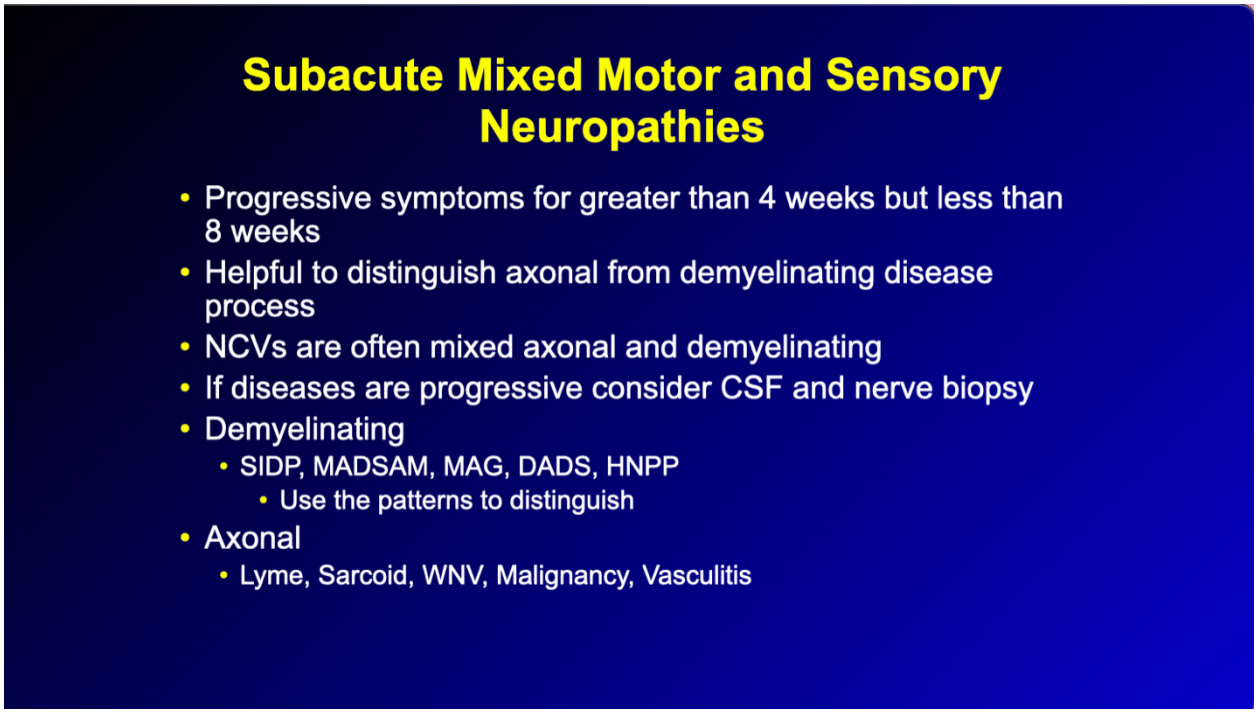
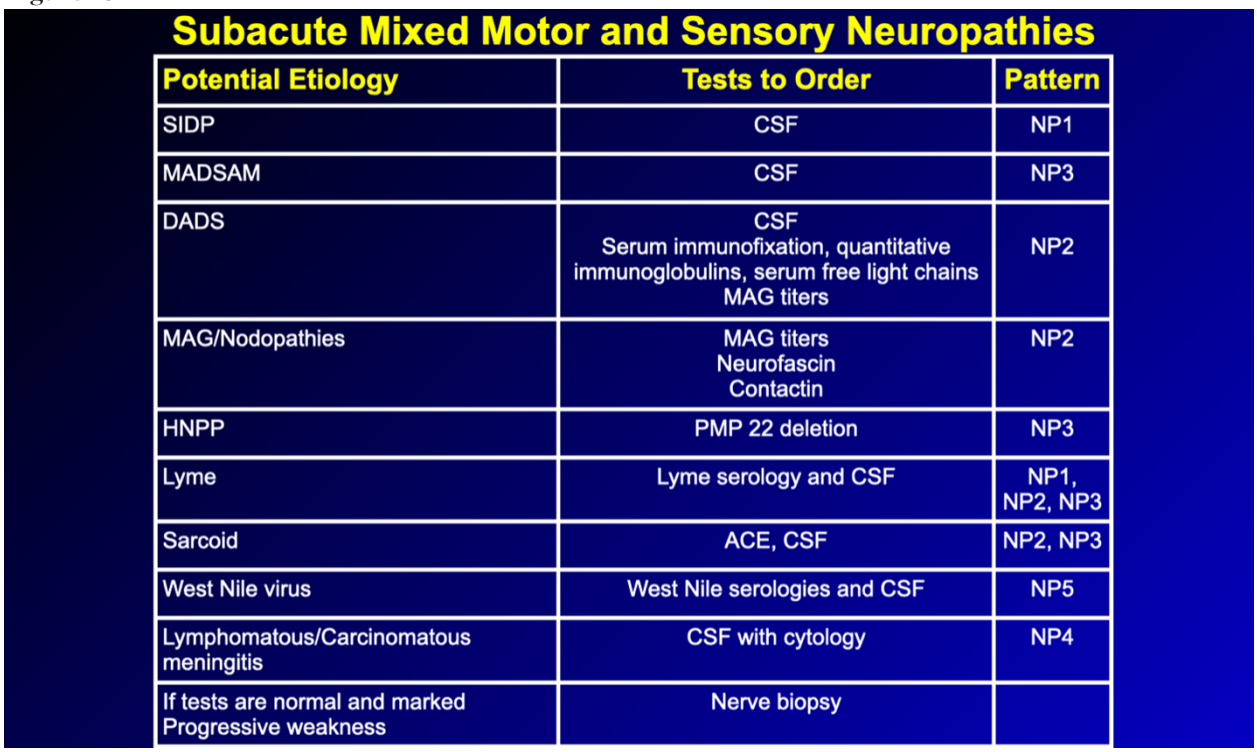


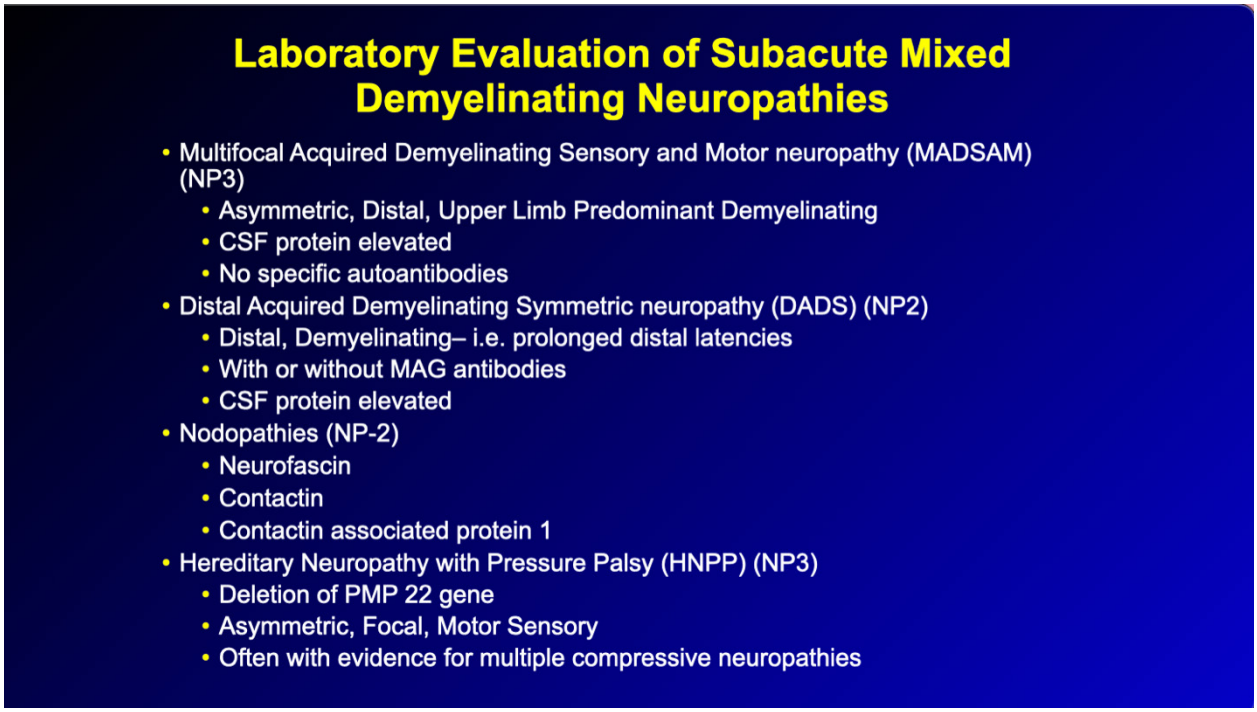
Figure 27



Acute neuropathies are defined as disorders with a duration under four weeks. Chronic neuropathy has a duration of over eight weeks with progression. Neuropathic disorders with progression between four and eight weeks are considered subacute. Subacute immune demyelinating polyneuropathy or SIDP falls into this category, between GBS and CIDP (Figure 26, 27). These cases remain difficult to approach. The dilemma is often: Should one treat them as Guillain-Barré only for a limited time or as CIDP on a chronic basis?

Nerve conduction studies can be helpful in subacute mixed motor and sensory neuropathies. Progressive weakness that is subacute or chronic that is associated with demyelinating electrophysiologic abnormalities

Figure 28

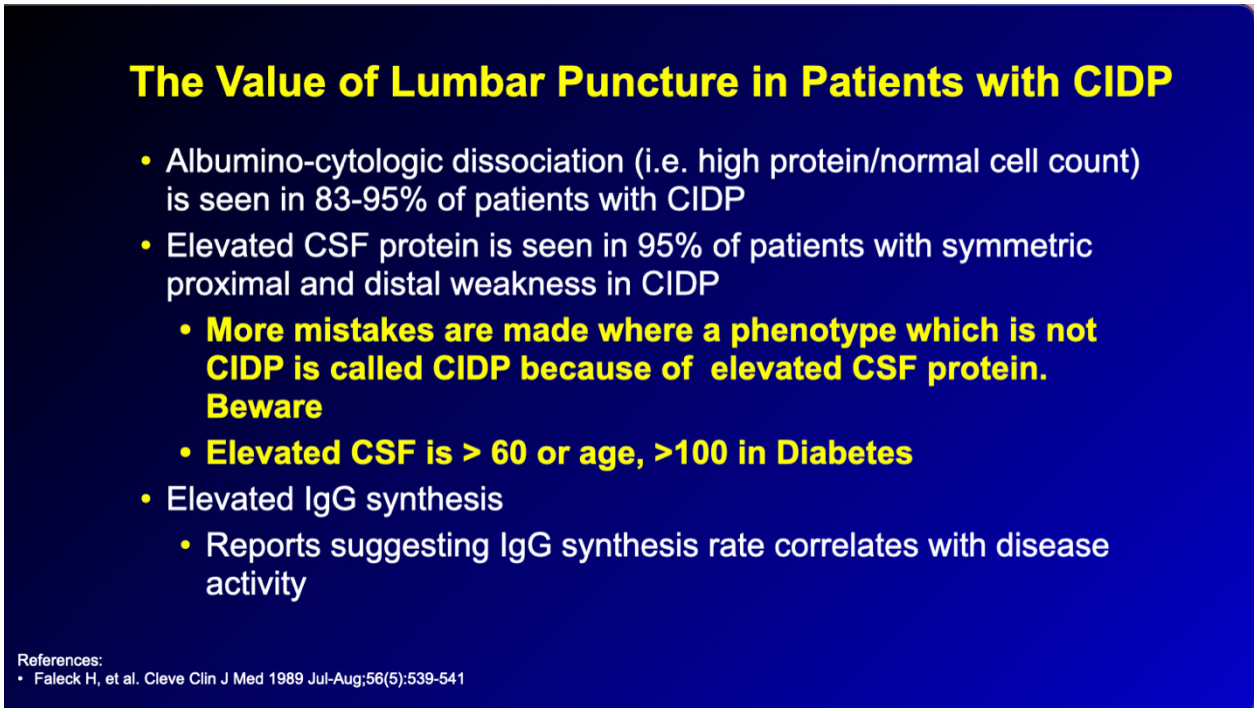


superimposed on axonal changes should prompt aggressive therapy with immunomodulating agents.

There are a series of disorders called nodopathies (NP-2) (Figure 28). In nodopathies, there is an antibody-mediated attack on the nodes of Ranvier, so it is not directly demyelinating but it is interfering with conduction. In those patients, their exam and nerve conduction studies may look like a CIDP-type patient, but these patients are difficult to treat and do not respond to IVIG and steroids. The antibody in these cases is an IgG 4 and may respond much better to rituximab than they do IVIG or steroids. Therefore, if a patient does not respond to IVIG with a subacute or chronic inflammatory demyelinating polyneuropathy consider searching for antibodies associated with the nodopathies.

Hereditary neuropathy with pressure palsy (HNPP) can also present with a mononeuritis multiplex NP5 pattern. The supporting laboratory test is a genetic test for the deletion in the CMT1A gene.

Figure 29



Should a lumbar puncture be performed?

Another value that comes up frequently when evaluating patients with neuropathies is whether or not a lumbar puncture needs to be done in order to distinguish between CIDP and diabetes (Figure 29). In immune neuropathy such as CIDP, approximately 90% of the time there will be an albuminocytologic dissociation. The problem arises when the clinical phenotype is not the typical NP1 CIDP pattern. It is known that patients with typical diabetic neuropathy can have elevated CSF protein as well, but the presentation is usually an NP2 pattern. Therefore, if one did a CSF examination in a typical NP2 DSNP patient and found an elevated protein it would be a mistake to consider this CIDP and treat the patient with immunomodulating drugs. In other words, if the patient has a small amount of toe weakness and numbness distally, a distal axonal sensory-motor neuropathy (NP2), and the CSF protein is 150 mg/dL, this does not mean the patient has CIDP just because of the elevated CSF protein. The patient does not have the pattern of weakness associated with CIDP-NP1. This is why you must be very cautious about over-interpreting spinal fluid protein values. Therefore, whether or not one obtains a CSF study should be based on the clinical pattern and the disease progression.

In addition, one needs to take age into consideration when evaluating CSF protein. CSF protein increases the more we age. For example, 60mg/dL is normal for a 60 year old.

In the evaluation of very chronic neuropathies, for example, over 10 years, it will be unlikely to find an

Figure 30

Chronic Mixed Motor and Sensory Neuropathies

Potential Etiology	Tests To Order	Pattern
CIDP	CSF, NCS	NP1
Diabetes	Fasting glucose, HgbA1c	NP2
Impaired glucose tolerance	2 hour glucose tolerance test	NP2
B12 deficiency	Vitamin B12, methylmalonic acid	NP6, NP2
Paraproteinemia	Serum immunofixation, Quantitative Immunoglobulins, serum free light chains	NP1, NP2
CMT1	PMP duplication/ deletion, Cx32, MPZ	NP2
CMT2	EGR2, FIG4, GARS, GDAP1, HSPB1, LMNA, MFNA2, MFN2, MPZ, Periaxin, RAB7, RFC1	NP2
Hereditary amyloidosis	Transthyretin	NP2, NP3, NP10
Sjogren's syndrome	SS-A, SS-B	NP2, NP9, NP10
If tests are normal but there is marked progressive weaknes	CSF, possible nerve biopsy	

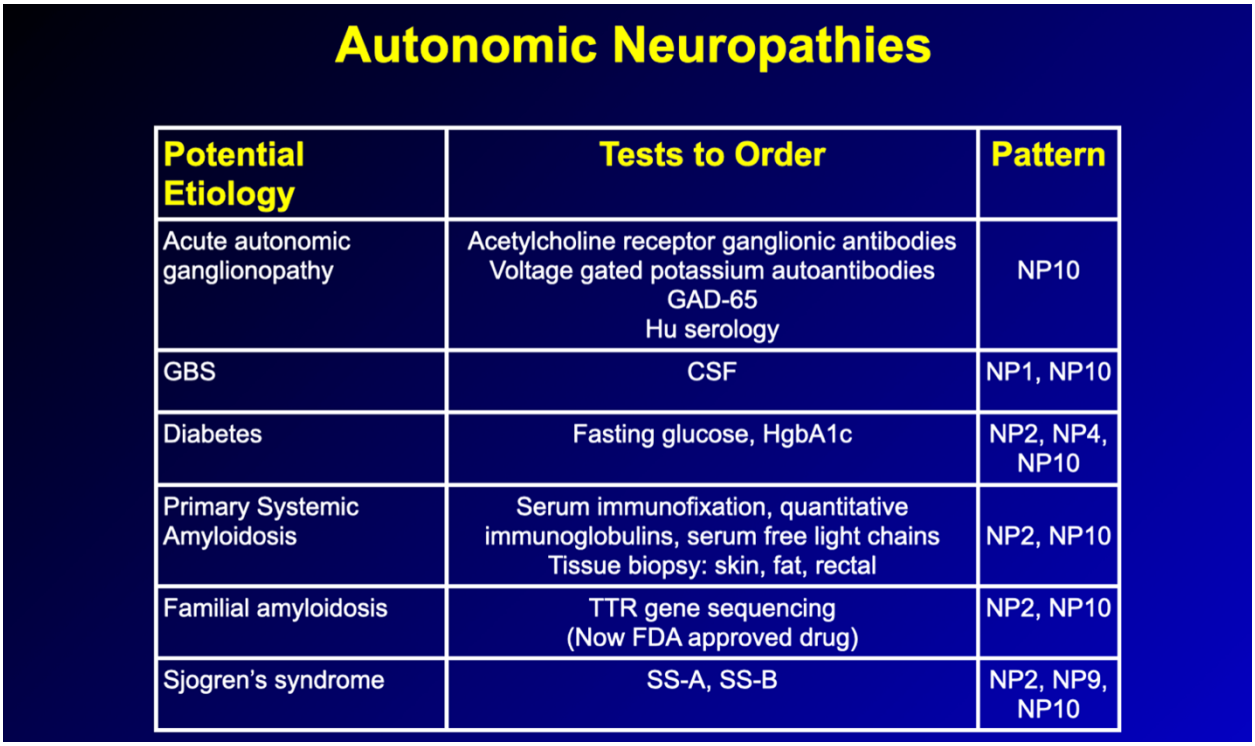
Figure 31

Autonomic Neuropathies

- Cardiac, gastrointestinal, thermoregulation, pupillary abnormalities, sexual dysfunction
- Often confused for IBS, fibromyalgia, malingering
- Helpful to get autonomic testing to confirm presence of autonomic dysfunction
  - Can segregate POTS from Dysautonomia
  - Consider other objective tests of neuropathy
    - Gastric emptying study
    - Skin biopsy
- Skin biopsy can be useful to look at small nerve fibers and at the innervation of the sweat glands

effective therapy (Figure 30). Nevertheless, an initial evaluation for chronic neuropathies is important. In the modern era, genetic testing plays more of a role than ever before. For this reason, it is important to pay attention to clues from the history and physical exams for a possible hereditary basis such as a family history of neuropathy, high arches, and hammer toes. One exception would be hereditary amyloidosis for which genetic diagnosis testing for transthyretin mutations and therapy is now available. If a diagnosis still is not established after appropriate blood work and nerve conduction studies but the patient continues to deteriorate and have ambulation problems, then it might be reasonable to consider a CSF examination or a nerve biopsy.

Figure 32



We are seeing an increase in autonomic neuropathies in patients with cardiac, GI, thermoregulation, pupillary abnormalities, and sexual dysfunction (Figure 30, 31). These patients are often confused with IBS, fibromyalgia, and malingering. It can be difficult to tell the difference between patients who have autonomic disorders and patients who do not. If you have access to autonomic testing this is where this process should begin. If you do not have access to this testing, you can use a skin biopsy which can be useful to look at small nerve fibers as well as the sweat gland innervation involved in the autonomic nervous system. There are numerous causes.

Occasionally there is a need to order laboratory studies for a patient with fasciculations which are likely benign. In this situation, if the fasciculations are of great concern to the patient, a serum creatine kinase and an electromyogram to reassure the patient they do not have motor neuron disease is reasonable. For patients with florid fasciculations and myokymia and in the setting of an NP2 neuropathy, voltage-gated potassium channel antibodies can be obtained to search for Isaac's syndrome, which can be paraneoplastic. Patients with Schwartz-Jampel syndrome have excessive muscle activity, particularly in axial and facial muscles, and on EMG have continuous motor unit high-frequency discharges. These patients have a characteristic "pinched" facial appearance with a tendency to keep their eyes closed due to hyperexcitable facial muscles. The diagnosis is made by finding a mutation in the *HSPG2* gene which codes for perlecan. Patients with stiff limbs due to unexplained upper motor dysfunction can be tested for glutamic acid decarboxylase antibodies found in stiff person syndrome (Figure 33)

Figure 33

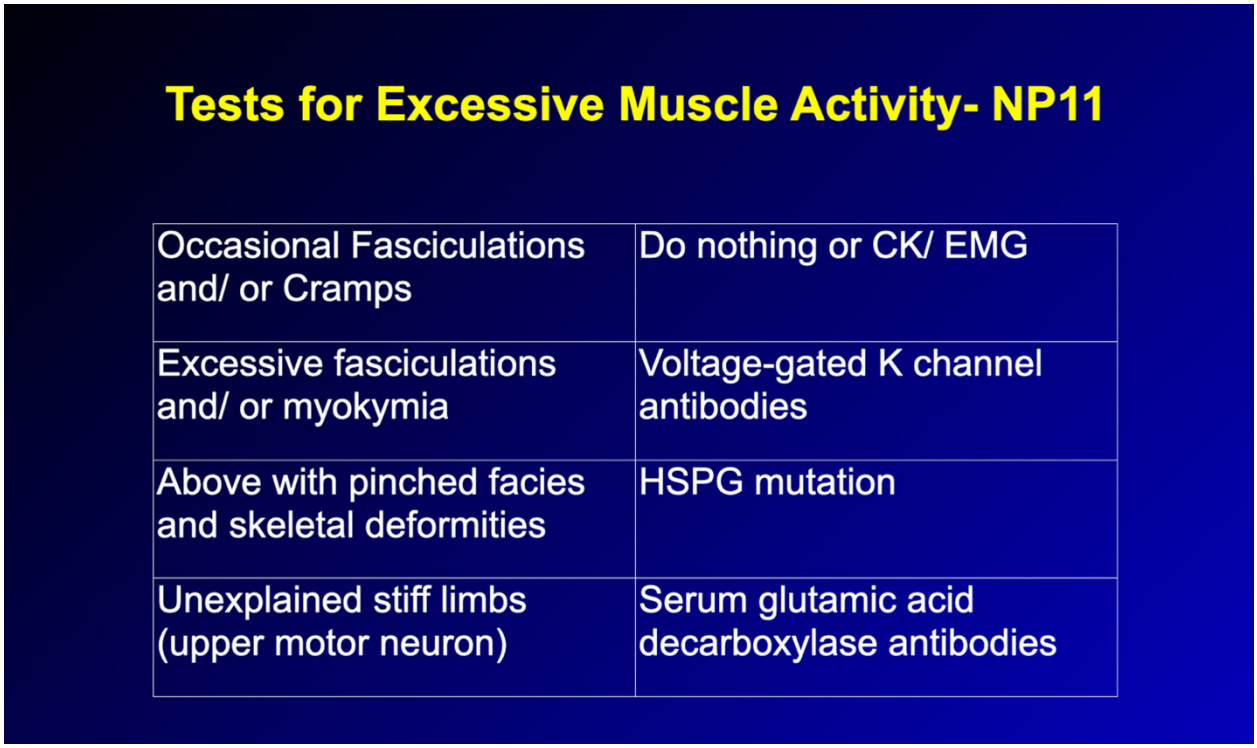
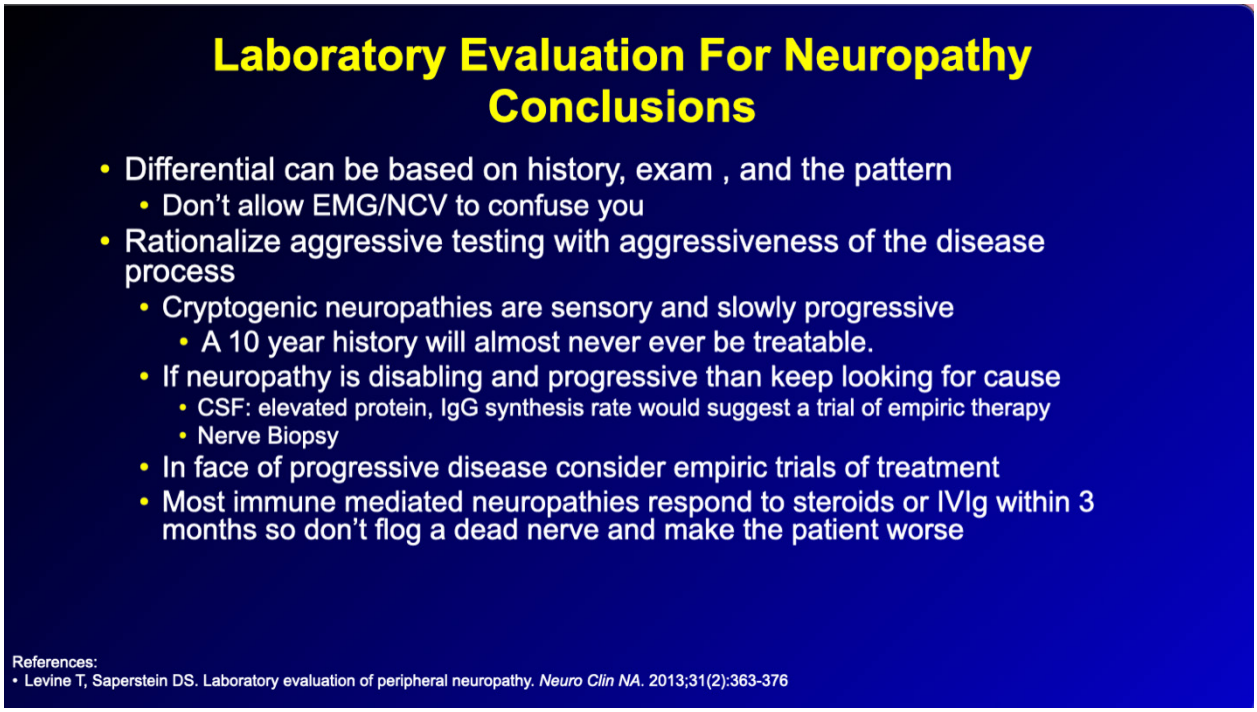


Figure 34



In conclusion, differential diagnoses should be established by the history, exam, and by the pattern (Figure 34). Nerve conduction studies can be helpful but often be very confusing and if it does not correlate with what you are seeing in the history, the exam and the pattern always focus on the history, exam, and pattern when interpreting laboratory tests.

Aggressive testing needs to be rationalized against the aggressiveness of the disease. A patient who has a 10-year history of peripheral neuropathy which is slowly progressive and purely sensory is very unlikely to be able to be treated to stop the neuropathy from progressing. However, if the patient has pain that can be treated. On the other hand, if the neuropathy is progressive and disabling, causing

weakness and balance difficulties, that is where you want to be aggressive with spinal fluid and perhaps a nerve biopsy.

Response to immunosuppressive and immunomodulating therapy can be a diagnostic tool in itself. If IVIG or steroids are used the patient should respond within three months. If they do not respond, it is very likely that the presumptive diagnosis of an immune-mediated neuropathy is wrong, and that the patient most likely has an untreatable neuropathy.

References

Adams, D., Ando, Y., Beirão, J.M., Coelho, T., Gertz, M.A, Gillmore J.D. (2021). "Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy." J Neurol 268(6): 2109-2122.

Antoine, J. C., Boutahar, N., Lassablière, F., Reynaud, E., Ferraud, K., Rogemond, V., Paul, S., Honnorat, J., Camdessanché, J. P. Antifibroblast growth factor receptor 3 antibodies identify a subgroup of patients with sensory neuropathy. Journal of neurology, neurosurgery, and psychiatry 2015; 86(12): 1347-1355.

Benstead, T. J., Chalk, C. H., Parks, N. E. Treatment for cryoglobulinemic and non-cryoglobulinemic peripheral neuropathy associated with hepatitis C virus infection. Cochrane Database Syst Rev 2014; (12).

Cortese, A., Tozza, S., Yau, W. Y., Rossi, S., Beecroft, S. J., Jaunmuktane, Z., Dyer, Z., Ravenscroft, G., Lamont, P. J., Mossman, S., Chancellor, A., Maisonobe, T., Pereon, Y., Cauquil, C., Colnaghi, S., Mallucci, G., Curro, R., Tomaselli, P. J., Thomas-Black, G., Sullivan, R., Efthymiou, S., Rossor, A. M., Laurá, M., Pipis, M., Horga, A., Polke, J., Kaski, D., Horvath, R., Chinnery, P. F., Marques, W., Tassorelli, C., Devigili, G., Leonardis, L., Wood, N. W., Bronstein, A. Giunti, P., Züchner, S., Stojkovic, T., Laing, N., Roxburgh, R. H., Houlden, H., Reilly, M. M. "Cerebellar ataxia, neuropathy, vestibular areflexia syndrome due to RFC1 repeat expansion." Brain 2020; 143(2): 480-490.

Cortese, A., Curro, R., Vegezi, E., Yau, W. Y., Houlden, H., Reilly, M. M. "Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS): genetic and clinical aspects "Practical Neurology 2022; 22: 14-18.

Cruz, M. W. (2019). "Tafamidis for autonomic neuropathy in hereditary transthyretin (ATTR) amyloidosis: a review." Clin Auton Res 29(Suppl 1): 19-24.

England, J. D., Gronseth, G. S., Franklin, G., Carter, G. T., Kinsella, L. J., Cohen, J. A., Asbury, A. K., Szigeti, K., Lupski, J. R., Latov, N., Lewis, R. A., Low, P. A., Fisher, M. A., Herrmann, D. N., Howard, J. F., Jr., Lauria, G., Miller, R. G., Polydefkis, M., Sumner, A. J. "Practice Parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation." Neurology 2009; 72(2): 185-92.

Gisatulin, M., Dobricic, V., Zühlke, C., Hellenbroich, Y., Tadic, V., Münchau, A., Isenhardt, K., Bürk, K., Bahlo, M., Lockhart, P. J., Lohmann, K., Helmchen, C., Brüggemann, N. "Clinical spectrum of the pentanucleotide repeat expansion in the RFC1 gene in ataxia syndromes " Neurology 2020; 95: e2912-2923.

Hammond, N., Wang, Y., Dimachkie, M. M., Barohn, R. J. "Nutritional neuropathies." Neurol Clin 2013; 31(2): 477-489.

Jackson, C. E., Amato A. A., Barohn R. J. "Isolated vitamin E deficiency." Muscle Nerve 1996; 19(9): 1161-1165.

Kaku, M. and J. L. Berk (2019). "Neuropathy Associated with Systemic Amyloidosis." Semin Neurol 39(5): 578-588.

Kazamel, M., Stino, A. M., Smith, A. G. (2021). "Metabolic syndrome and peripheral neuropathy." Muscle Nerve 63(3): 285-293.

Kizawa, M., Mori, K., Iijima, M., Koike, H., Hattori, N., Sobue, G. Intravenous immunoglobulin treatment in painful sensory neuropathy without sensory ataxia associated with Sjögren's syndrome. Journal of neurology, neurosurgery, and psychiatry 2006; 77(8): 967-969.

Leishear, K., Ferrucci, L., Lauretani, F., Boudreau, R. M., Studenski, S. A., Rosano, C., Abbate, R., Gori, A.M., Corsi, A. M., Di Iorio, A., Guralnik, J. M., Bandinelli, S., Newman, A. B., Strotmeyer, E. S. "Vitamin B12 and Homocysteine Levels and 6-Year Change in Peripheral Nerve Function and Neurological Signs." The Journals of Gerontology: Series A 2011; 67A(5): 537-543.

Levine, T. D. and Saperstein, D. S. "Laboratory evaluation of peripheral neuropathy." Neurol Clin 2013; 31(2): 363-76.

Levine, T. D., Bellaire, B., Arellano, A., Barohn, R. J., Dimachkie, M., & Katz, J. A Proposed Taxonomy of Isolated Small Fiber Neuropathy. RRNMF Neuromuscular Journal 2020; 1(4), 18–23.

Parambil, J. G., Tavee, J. O., Zhou, L., Pearson, K. S., Culver, D. A. Efficacy of intravenous immunoglobulin for small fiber neuropathy associated with sarcoidosis. Respir Med 2011; 105(1): 101-105.

Pavesi, G., Medici, D., Lusvardi, M., Gemignani, F., Macaluso, G. M., Magnani, G., Mancia, D. Migrant sensory neuritis associated with AIDS: case report. Ital J Neurol Sci 1994; 15(8): 433-436.

Nicolle, M. W., Barron, J. R., Watson, B. V., Hammond, R. R., Miller, T. A. Wartenberg's migrant sensory neuritis. Muscle Nerve 2001; 24(3): 438-443.

Pestronk, A., Choksi, R., Yee, W. C., Kornberg, A. J., Lopate, G., Trotter, J. "Serum antibodies to heparan sulfate glycosaminoglycans in Guillain-Barré syndrome and other demyelinating polyneuropathies." J Neuroimmunol 1998; 91(1-2): 204-209.

Pestronk, A., Schmidt, R. E., Choksi, R. M., Sommerville, R. B., Al-Lozi, M. T. "Clinical and laboratory features of neuropathies with serum IgM binding to TS-HDS." Muscle Nerve 2012; 45(6): 866-872.

Rajkumar, S. V., Kyle, R. A., Buadi, F. K. "Advances in the diagnosis, classification, risk stratification, and management of monoclonal gammopathy of undetermined significance: implications for recategorizing disease entities in the presence of evolving scientific evidence." Mayo Clin Proc 2010; 85(10): 945-948.

Rist, S., Sellam, J., Hachulla, E., Sordet, C., Puéchal, X., Hatron, P., Benhamou, C., Sibilia, J., Mariette, X. Experience of intravenous immunoglobulin therapy in neuropathy associated with primary Sjögren's syndrome: A national multicentric retrospective study. Arthritis Care & Research 2011; 63(9): 1339-1344.

Ronco, R., Perini, C., Currò, R., Dominik, N., Facchini, S., Gennari, A., Simone, R., Stuart, S., Nagy, S., Vegezzi, E., Ouartesan, I., El-Saddig, A., Lavin, T., Tucci, A., Szymura, A., Novis De Farias, L. E., Gary, A., Delfeld, M., Kandikatla, P., Niu, N., Tawde, S., Shaw, J., Polke, J., Reilly, M. M., Wood, N. W., Crespan, E., Gomez, C., Chen, J. Y. H., Schmahmann, J. D., Gosal, D., Houlden, H., Das, S., Cortes, A. "Truncating Variants in RFC1 in Cerebellar Ataxia, Neuropathy, and Vestibular Areflexia Syndrome " Neurology 2023; 100: e543-554.

Saperstein, D. S., Wolfe, G. I., Gronseth, G. S., Nations, S. P., Herbelin, L. L., Bryan, W. W., Barohn, R. J. "Challenges in the identification of cobalamin-deficiency polyneuropathy." Arch Neurol 2003; 60(9): 1296-1301.

Sinnreich, M., Klein, C. J., Daube, J. R., Engelstad, J., Spinner, R. J., Dyck, P. J. Chronic immune sensory polyradiculopathy: a possibly treatable sensory ataxia. Neurology 2004; 63(9): 1662-1669.

Tavee, J. O., Karwa, K., Ahmed, Z., Thompson, N., Parambil, J., Culver, D. A. Sarcoidosis-associated small fiber neuropathy in a large cohort: Clinical aspects and response to IVIG and anti-TNF alpha treatment. Respir Med 2017; 126: 135-138.

Wang, H. H., Lee, D. K., Liu, M., Portincasa, P., Wang, D. Q. "Novel Insights into the Pathogenesis and Management of the Metabolic Syndrome." Pediatr Gastroenterol Hepatol Nutr 2020; 23(3): 189-230.

Wile, D. J. and Toth, C. "Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy." Diabetes Care 2010; 33(1): 156-161.

Wolfe, G. I., El-Feky, W. H., Katz, J. S., Bryan, W. W., Wians, F. H., Jr., Barohn, R. J. "Antibody panels in idiopathic polyneuropathy and motor neuron disease." Muscle Nerve, 1997; 20(10): 1275-1283.

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