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Cover image: *North Italian Landscape* by Albert Bierstadt, oil on canvas, ca. 1856-57. For more information, see "About the Cover," page 83.

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Letter from the Founding Editor for Volume 7, Issue 1

Richard J. Barohn, MD

This is the first issue of the year for Volume 7 of the RRNMF Neuromuscular Journal. My colleague of many years, Dr. Josh Freeman, has allowed us to publish two of his recent pieces on the state of medicine in the United States. The article on the problems with pre-authorization was originally published as an opinion piece in the Arizona Star. Dr. Freeman's second article is timely, as it deals with the potential problems with AI as a communication vehicle to patients. In the section on original research, the University of Kansas neuromuscular group, to which I still have a long distance connection, is publishing the interesting phase 1B dose escalation study of oxaloacetate (OAA) in patients with amyotrophic lateral sclerosis (ALS). This drug had previously been used in an Alzheimer's disease trial by our colleagues at KU (Swerdlow and Burns), and that is were we got the idea for the mitochondrial approach to neurodegenerative disease. We believe we now have good information from this phase 1B study, which can inform a potential phase 2 randomized controlled trial.

Also in original contributions is a description by Dr. Hussain and Dr. Shabani on how to operate a high volume clinical research program when you are not in an academic setting. Dr. Shabani has done this for many years at his large neuromuscular private practice in the Texas Medical Center. Dr. Hussain is a mentee of Dr. Shabani's, and he is emulating his mentor in his Austin practice. It is very impressive how both of these neuromuscular specialists have been successful in making clinical trials a significant part of the practice portfolio. Dr. Hussain presented this information at the NMSG meeting last year in Italy, and I asked him and Dr, Shabani to turn it into a manuscript. I am so pleased they have done that.

In the case reports section, Dr. Yuebing Li and Dr. Sakhi Bhansali report a fascinating case of a patient with Charcot-Marie-Tooth (CMT) that had a chronic cough as part of the clinical phenotype. The authors then provide a nice review of potential causes of neuropathic cough. Dr. Isho, Dr. Gonzales and Dr. Ma at the University of Washington Medical Center report a case of Lambert-Eaton syndrome and underlying prostate adenocarcinoma, an unusual relationship. The final case in this issue is reported by Leah Naasz, a medical student, and her mentors at the University of South Dakota Sanford School of Medicine. They describe a patient who had human herpesvirus 6 (HHV-6) infection discovered when they were being worked up for a case that resembles the acute motor and sensory axonal neuropathy (AMSAN) form of the Guillain-Barre syndrome.

In the review article section, we again publish an article based on a lecture given in the neuromuscular review course that a number of colleagues have been involved in for over a decade. This lecture on motor neuron disease was given by Dr. Jonathan Katz. The co-authors are Dr. Todd Levine, Dr. David Saperstein, Dr. Mamatha Pasnoor, Dr. Mazen Dimachkie and myself. This is the sixth lecture from that course we have transcribed, heavily edited, and referenced. We believe these publications will be helpful to both those doctors who have taken the course, but perhaps even more to those who have not had that opportunity. We are working now on writing another lecture by Dr. Katz on immune mediated neuropathies which will appear in an upcoming issue. While I no longer give lectures in the course, the group is still going strong and puts on the course, usually by zoom, regularly. The upcoming course dates are July 25, August 29, and December 5. If you are interested in joining the course to hear these wonderful lectures, contact Dr. Mazen Dimachkie (mdimachkie@kumc.edu), the course director.

In our Art and Creative Works section, Dr. Michael Abraham has provided a beautiful prose piece about the joy of fatherhood and that our time on this earth is "borrowed".

In the last issue of this journal, I published a History of Neurology piece I called "The Tale of Two Toms"—about Thomas Willis and Thomas Sydenham. Studying neuroscience history has been a hobby of mine for many years. When I was chairman of neurology at KU Medical Center I would give the residents a short history of neurology talk after morning report. I am not sure how well received these were, but I enjoyed putting them together. And I videoed a number of these that have since migrated to YouTube. I have now begun to go back to those talks and videos and turn them into brief manuscripts with the PowerPoint slides as figures. In this issue, I am publishing three more History of Neurology vignettes. The first I call "The Sparkling Italians" – focusing on the brilliant scientists in the late 18th century, Alessandro Volta and Luigi Galvani, who were pioneers in experimental neurophysiology. I also touch on another incredible Italian physician, Giovanni Morgagni, from a generation earlier, who made major contributions to how we study and understand human diseases by publishing a book in which he describes over 600 autopsies and makes clinical correlations—in 1761! The next History of Neurology article is about a giant in neurology, Charles Edouart Brown-Sequard. He is of course now known through the ages as the physician who first described the clinical phenotype of spinal cord hemi-section. In addition, he was a fascinating individual who went back and forth from Mauritius (his birthplace), to Paris, to various stops in the United States, to London where he was one of the original professors at Queen's Square, and finally back in Paris to succeed Claude Bernard. I call him "the first international neurologist", and before airplanes. The last history of neurology article is on two famous American neurologists from the time of the Civil War: Dr. Silas Weir Mitchell and Dr. William Hammond. I call them "the Civilian and the General". Dr. Hammond was

Surgeon General, and he appointed his friend Dr. Mitchell to see injured soldiers at the Turners Lane neurology hospital in Philadelphia during the war. Dr. Mitchell, of course, made insightful observations about pain syndromes as a result of bullet wounds, which he called "causalgia". Dr. Hammond went on to practice neurology in New York City. He published the first textbook of neurology in the United States, and he described the phenomenon of athetosis and hypothesized the site of the lesion was in the basal ganglia.

At the end of this issue, we remind readers that the Neuromuscular Study Group meeting this year is in San Antonio, September 24 to 27. I hope to see many of you there. I also want to remind you that the NMSG, in partnership with the American Brain Foundation and the American Academy of Neurology, provides funding for two-year neuromuscular fellowships. The window for applications to the ABF is mid-June to October 1. See the information about both the NMSG meeting and the fellowships to take advantage of these opportunities.

Finally, for the art on the cover of this issue, I chose another beautiful painting from the University of Missouri Museum of Art and Archeology. I again chose an image of north Italy because it reminds me of last year's NMSG meeting in Stresa (outside of Milan) and Lake Maggiore. The artist is Albert Bierstadt, a very prominent American painter who was born in Germany in the mid- to late-19th century. The large paintings most know Bierstadt by are of American landscapes, but he did travel in Europe, and this painting came from those journeys. Marie Hunter, the interim director of the museum, has provided some information about the painting and the artist, which was recently featured in the museum's Art in Bloom exhibit.

Yes, Rep. Van Drew, there IS a solution!

Joshua Freeman, MD

This piece appeared in the Arizona Star opinion section, Dec 30, 2025

A headline in the Star on December 27 is "Out-of-pocket-pain means skimping on care". It is from KFF HealthNews, and you already know what it says. We all know. In the rare cases where we or our families or close friends haven't experienced it ourselves, our newspapers and other media are full of such stories. Every day we read about how people delay or forgo care, get sick, and even die because of costs: co-pays, deductibles, and other surprise charges, all in addition to the premiums they pay, which increase yearly. This is in addition to the other obstacles to care: prior authorization requirements and outright denials of care by insurance companies, and lack of access because of a shortage of health care clinicians.

Does it have to be this way? Is there no way out? Many politicians seem to take the same position as Representative Jeff Van Drew (R-NJ), who said "Other than world peace, honest to God, health care is the toughest issue ever. It is really hard, but I think it behooves us to come up with something." The last part is true, but not the first. There is a way, not only in theory but one that has been tested and re-tested all over the world. It is the system used by *every* wealthy country, and many with fewer resources: Universal health coverage. Really. It's true. It is done in different ways, but they all cover everybody, for low, or no, out-of-pocket cost, funded by taxes. They are not all perfect, but the other thing that they have in common is that NO country that has adopted universal health coverage has gone back. Ever.

Could it be done in the US? Sure. The "Medicare for All Acts" (S. 1506 and HR. 3069) would do exactly that, expand the Medicare system to include us all. Everyone. Birth to death. No patchwork system, no falling through the cracks. *Everybody in, nobody out*. Medicare has served as a single-payer universal health care program for seniors and people with disabilities since 1965, so the structure is there. Just add the rest of us. These bills would also improve Medicare, by covering everything, including mental health, vision, hearing, long-term care, and the full cost of hospitalization (not 80% as now). It's all good.

But how could we afford it? Wouldn't taxes go up? They would, for some, but then all these other costs – premiums, co-pays, deductibles, etc. – would go away, and most people would see a net financial benefit, especially those who cost and pay the most – those who are sick. Most of the additional cost of providing healthcare to everyone would be made up for by eliminating insurance company administrative costs and profits. It is thus doubly good; not only does it save money, it creates a system whose goal is providing health care for the American people rather than making profit for insurance and private equity companies. Imagine that! The current US health "non-system" not only costs a lot more per capita than other comparable countries, but leads to worse health outcomes.

So why would the American people not support this? Actually, they do, in poll after poll. A recent one from Data for Progress shows 65% of us do, including about 75% of Democrats and Independents, and about 50% of Republicans! What about politicians? Why are there not more senators and representatives supporting the Medicare for All bills? You can guess, but let's say that a system designed to make huge profits for insurance and other private companies provides them with the resources and incentives to make large donations to congresspeople; perhaps that's part of it.

Time for them to hear from us! Sen. Gallego supported Medicare for All when he was in the House, as did the late Rep. Raul Grijalva. Write to our senators, Gallego and Kelly, and our representatives including Rep. Ciscomani, and tell them what you think and demand that they sign onto the Medicare for All bills.

It's time to have a health system that serves the people!

References

Blumenthal D, Gumas ED, Shah A, Gunja MZ, Williams II RD. Mirror, Mirror 2024: A Portrait of the Failing U.S. Health System — Comparing Performance in 10 Nations [Internet]. Commonwealth Fund; 2024 Sep 19. Available from: https://www.commonwealthfund.org/publications/fund-reports/2024/sep/mirror-mirror-2024

Medicare for All Is Popular — Even When Put Up Against Attacks [Internet]. Data for Progress; 2025 Nov 26. Available from: https://www.dataforprogress.org/blog/2025/11/medicare-for-all-is-popular-even-when-put-up-against-attacks

Once Again, Health Care Proves to Be a Bitter Political Pill for G.O.P. [Internet]. *The New York Times*; 2025 Dec 18. Available from: https://www.nytimes.com/2025/12/18/us/politics/health-care-gop.html

Physicians for a National Health Program (PNHP). The Medicare for All Act of 2025 [Internet]. PNHP; 2025 Apr 29. Available from: https://pnhp.org/the-medicare-for-all-act-of-2025/#:~:text=On%20April%2029%2C%202025%2C%20Rep,costs%20for%20all%20U.S.%20residents

Does AI Communicate Better Than Real Doctors? If so, Why is That?

Joshua Freeman, MD

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

The *New York Times* recently ran an article titled "Empathetic, Available, Cheap: When A.I. Offers What Doctors Don't", which should be very concerning to the medical profession as it emphasizes three things that they are often not. But probably won't concern the real decision makers in healthcare – the corporate owners, "health systems", insurance companies, and private equity. After all, their concern is solely making money, and they are doing just fine, thank you.

The article indicates that AI seems to be responsive to and nice to people, and seems to show respect, concern, and empathy; *"seems to"* is important, because these are computer programs, not people, and they don't have any feelings. Nonetheless, people feel better when they are addressed with respect, concern, and compassion. Even if it is programmed and not real. The truth is that doctors and other actual people do not always do so, for a variety of reasons. And they don't even have the chance to if the patient cannot contact them, which is so common as to be routine these days

For many years, I told medical students that, while they had worked very hard to master the language of medicine, learning idioms, jargon, eponyms, and acronyms so they could fit in and impress their seniors, residents and attending physicians, regular people would not understand them if they spoke like that. They had to be able to translate that back into their first language, English (or whatever their vernacular was). This is an important skill, for without it people ("patients") won't understand what you are saying, and won't know what is going on with them. And that is important. It takes effort, and it takes intentionality – you must want the person to understand what you are saying. That's is true even if what you are telling them is bad news, something that will make them upset or unhappy.

I thought about this after a recent conversation with a couple of current medical students. I made the points above, about the importance of communicating in a way people can understand, and observed that, in fact, often people did not understand. This was based on, among other things, the number of times I had to try to explain to my patients, as a family doctor, what their specialist was saying. And the number of times I had to try to figure out, as a family member or friend, what my family member or friend's doctor had been telling them that led them come away with what seemed to be an incorrect understanding of the situation. I have even said "If you assume that no one ever understands anything their doctor tells them, you will be correct a distressing percent of the time".

The students agreed, but when they gave examples from their experience, I became more concerned.

> *A surgeon I worked with was unable to get all of the cancer out, but when telling the patient used all kinds of technical and unfamiliar terms, like 'clean margins'. It was like they were trying to not lie, but to obfuscate what they were saying by talking in words and phrases that were technically true but not meaningful to the patient. I was left, after the surgeon had gone, to try to respond to the patient who asked me 'What did they just say?'"*

Obviously, this should not be the job of the medical student, but of the surgeon. And while it is tempting to say, "Well, they're surgeons; communication is not their strength" (and while, as a family doctor, I like to think we are better at it), most or all doctors are guilty of this sometimes. (It is also true that it is even harder when you have to acknowledge that the bad news may, in fact, be the result of something you did wrong, but this is a separate area.)

I have recently had experience with close family members who had complications during procedures. One, during an endoscopy, had their blood oxygen level drop and had to have a breathing treatment afterwards, receiving a new diagnosis of asthma. This was upsetting, but at least they were told everything. Another, in a much more concerning episode, had major lung surgery. After the surgery, they had terrible, persistent pain which was not adequately treated. Several months later, visiting another doctor (not the surgeon), they were told that their oxygen level had also dropped severely, as a result of having a pneumothorax, a serious, potentially dangerous condition where air gets into the chest cavity and can partially collapse the lung. More relevant, it can be terribly painful. This might explain why the nurses, following their pain-management algorithms, did not give the patient sufficient pain medication. It is still not clear if they were told their patient had a pneumothorax, but it is definitely clear that the patient, my family member, was not told. They should, of course, have been.

There are a lot of potential problems with AI providing people medical information, some of which are discussed in the *Times* article. For one thing, it could be wrong. It doesn't really know you, and part of the reason that you are consulting the medical AI (or real clinician) is that you don't actually know either exactly what is wrong with you, or how to put it in terms that will get you the correct answer to your question even if the AI is capable of getting the correct answer. Of course, sadly, the same can be true of real doctors, especially when you don't actually speak to them; the article leads with the story of a person who wanted advice on how to increase the protein in their diet, and received generic—and

unhelpful—answers from the physician on line (presumably a "patient portal"). For all we know, they could have been AI produced.

It would be much better – some of us would say essential—for doctors to communicate fully and honestly with their patients, using language that they can understand, even when the news is not good. And for them to be there, being, well, *patient,* while their patient tries to formulate questions, and answer them. But there are a lot of reasons that they don't, or can't.

A part of it may be that they are poor communicators, or uninterested in having their patients understand everything, especially if it could be embarrassing or take a lot of time. But AI doesn't have that problem. It is not paid by the patient, and it has no set number of people it has to see in a given amount of time the way that real clinicians do. These actual clinicians often work in hamster-wheel conditions (time spent not only seeing patients but having to do electronic charting aimed at maximizing profit via upcoding as much as possible) which are not the fault of the doctor, but of their employers who are interested in "throughput" to make as much money as possible. Saliently, procedures are relatively well reimbursed but spending the time necessary to talk to a person to be sure that they completely understand what is going on is not. Of course, this is also part of the reason that there are fewer students entering primary care and more are entering better-paid procedure-based specialties.

Having a health care system that valued, and paid for, communication would be good. It would have to start with a system designed to maximize the health of our people, not corporate profit. Yes, there would still be some doctors who communicated poorly, and even made poor medical decisions, but those could be dealt with as individuals, rather than having them intrinsically encouraged by the system.

Doctors could and should do better, and maybe there is a place for AI. But there is no place for profit in healthcare.

Trial of Oxaloacetate in ALS (TOALS)

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Abstract

Background: Mitochondrial dysfunction is a critical therapeutic target in amyotrophic lateral sclerosis (ALS). Oxaloacetate (OAA) is a promising candidate therapy as it crosses the blood-brain barrier, reaches motor neurons, and enhances mitochondrial bioenergetics with positive preclinical data in ALS.

Methods: We conducted a prospective, phase 1B, dose escalation study using a standard 3+3 design to assess the safety profile and determine the maximum tolerated dose. Dose-limiting toxicity (DLT) was defined as any serious adverse event (SAE) requiring hospitalization or any adverse event (AE) attributed to OAA that required discontinuation of the medication. Dosages evaluated started at 1000 mg twice daily in Cohort 1 and, if tolerated, were escalated by 500 mg up to 2500 mg twice daily in the maximal dose Cohort 4. To determine target engagement, we evaluated a panel of mitochondrial biomarkers, platelet TDP-43 levels, and MR spectroscopy of brain glutathione from baseline and at the end of treatment.

Results: A total of 19 participants were screened, 18 enrolled, and one patient at the 2500 mg BID dose withdrew due to a DLT. OAA was overall well tolerated up to a dose of 2500 mg BID. Among the small sample of participants, no consistent signal of target engagement was observed, although in aggregate, post-exposure MRS determined that brain glutathione levels increased.

Conclusions: This study supports the safety and tolerability of OAA at doses up to 2500 mg BID in patients with ALS. A future trial would be warranted to confirm the maximum tolerated dose, to assess efficacy, and further explore target engagement.

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder of the upper and lower motor neurons with a multifactorial pathophysiology. The majority of patients with ALS are deceased within 3 to 5 years from symptom onset. The standard approach to multidisciplinary care has extended survival and includes 2 FDA-approved drugs, riluzole and edaravone, which together have a modest effect on survival and slowing of functional decline. There is an urgent need for better ALS therapies.[1,2]

While the exact underlying cause of this motor neuron degeneration remains uncertain, candidate mechanisms include glutamate excitotoxicity, free radical-mediated oxidative cytotoxicity, neuroinflammation, mitochondrial dysfunction, autoimmune processes, protein aggregation, and cytoskeletal abnormalities. Mitochondrial dysfunction may play a critical role in ALS neurodegeneration, an observation supported by human, animal model studies, and patient autopsies.[3-9]

Oxaloacetate (OAA), a small molecule that has a crucial role in cell metabolism, acts as a key intermediate in the Krebs cycle and is involved in gluconeogenesis. OAA may have neuroprotective effects by reducing glutamate levels and enhancing mitochondrial function. In pre-clinical studies, OAA reduces neuroinflammation, a known ALS pathological mechanism.[10] A phase 2 trial of OAA in Alzheimer's Disease (AD) was conducted at the University of Kansas Medical Center (KUMC, PI: R. Swerdlow), but at a lower dose than the current study.[11] We are interested in OAA as a potential therapeutic agent in ALS as it crosses the blood-brain barrier, accesses motor neurons, activates mitochondrial bioenergetics, and increases respiratory and glycolytic capacity. Furthermore, superoxide dismutase 1 (SOD1) G93A transgenic mice treated with OAA showed significantly delayed limb paralysis and demonstrated a trend of increased lifespan compared to untreated animals.[12] Here, we tested the safety, maximum tolerated dose, and biomarkers of target engagement of OAA in ALS.

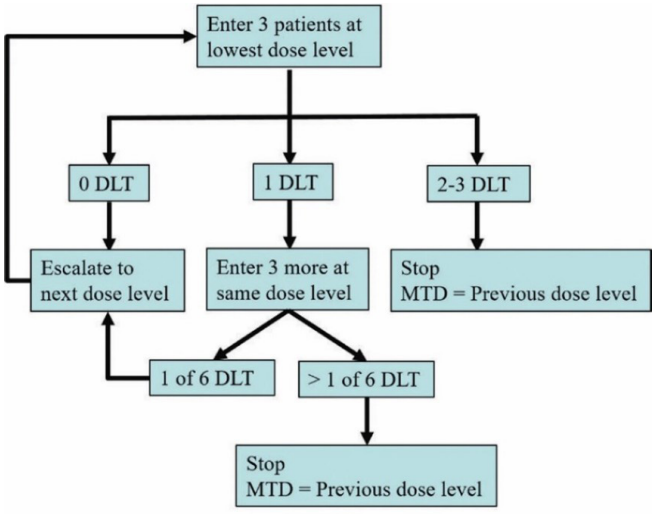
Methods

Trial Design:

We conducted a 28-day open-label, prospective 3+3 dose-ascending study of OAA in ALS to assess the safety profile and determine the maximum tolerated dose. The study was completed at KUMC from March 2020 to August 2023 (Figure 1). The trial was approved by the Institutional Review Board at the University of Kansas Medical Center. Written informed consent was obtained and documented from all participants in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The trial was registered on clinicaltrials.gov (NCT04204889).

The inclusion criteria included: a clinical diagnosis by a study investigator of laboratory-supported probable, probable, or definite ALS, according to the modified El Escorial criteria, 21 to 80 years of age, forced vital capacity (FVC) greater or equal to 50% of predicted, diagnosis of ALS within 3 years prior to enrollment, if patients took riluzole, edaravone, and/or sodium phenylbutyrate/taurursodiol for ALS, they were on a stable dose for at least thirty days prior to the baseline visit.[13] The exclusion criteria included: tracheotomy ventilation or non-invasive ventilation for > 23 hours per day, diagnosis of other neurodegenerative diseases (e.g., Parkinson disease, Alzheimer disease), clinically significant history of unstable medical illness (e.g., unstable angina, advanced cancer) 30 days prior to screening, current pregnancy or lactation, limited mental capacity such that the patient cannot provide written informed consent or comply with evaluation procedures, or receipt of any investigational drug within 30 days prior to enrollment. Study participants were recruited from the KUMC multidisciplinary ALS clinic. The oxaloacetate was provided by Terra Biological LLC as 500 mg capsules.

Figure 1. 3 + 3 research design



DLT = Dose Limiting Toxicity

MTD = Maximum Tolerable Dose

Outcomes and Measures:

Baseline characteristics included age, sex, and self-reported race and ethnicity. At the screening and baseline visits, we collected vitals, safety labs (complete blood count and comprehensive metabolic panel), concomitant medications, adverse events, physical exam, forced vital capacity, Magnetic Resonance Spectroscopy (MRS), and pharmacokinetic blood samples. At weeks 1, 2, and 3, participants were contacted by phone to capture adverse events and concomitant medication changes. On day 28 or the end of the study, we collected safety labs, medication use, adverse events, completed a physical exam, and MRS. Blood biomarkers were collected at baseline and day 28, or at the end of the study.

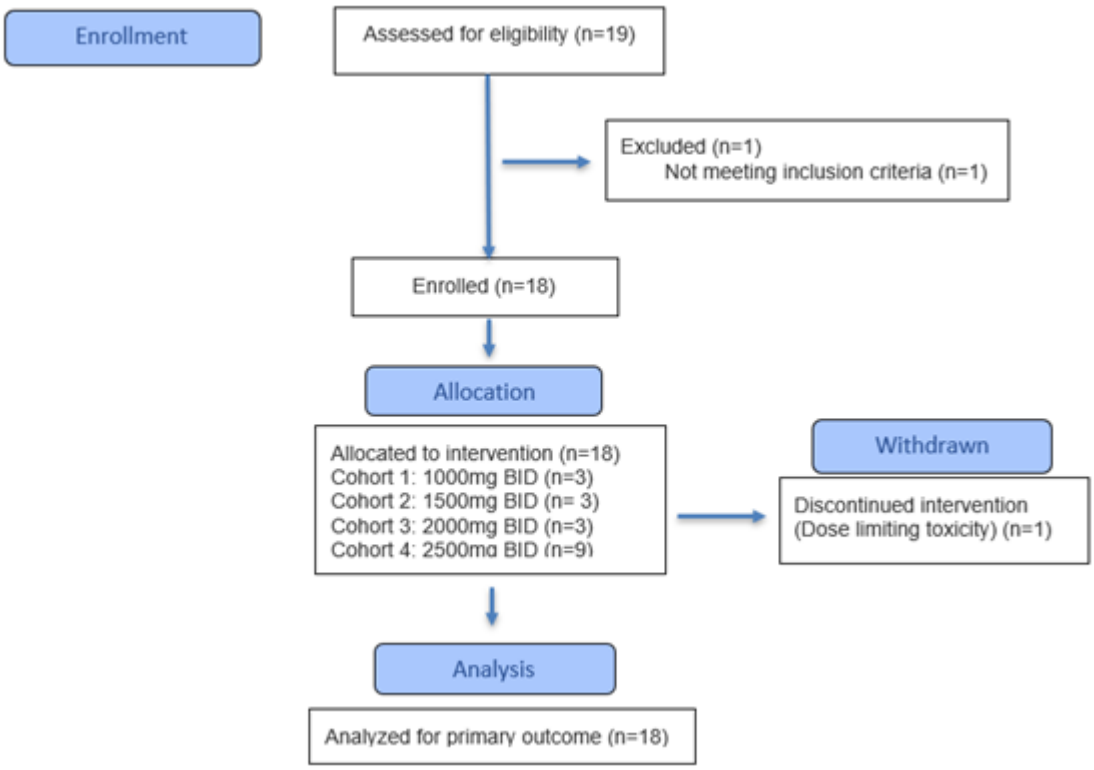
The primary outcome for the study was dose-limiting toxicities (DLT). We defined DLT as any serious adverse event related to OAA requiring hospitalization, or any AE related to OAA requiring stopping the medication, including a twofold increase in AST and/or ALT, and/or a 1.5 times increase in creatinine level. The maximum tolerated dose was defined as the maximal dose at which there were ≤ 30% DLTs.

To evaluate secondary target engagement, we included the following secondary outcomes: MRS, blood pharmacokinetics (PKs), blood mitochondrial biomarkers, and platelet TDP43. PK was measured pre-dose, 1 hour post dose, and 4 hours post dose at the baseline visit.

A panel of blood mitochondrial biomarkers was examined in peripheral blood mononuclear cells (PBMCs), and the mitochondrial functional index (MFI) was calculated. Blood was collected in ACD tubes and processed within 30 hours of blood draw. PBMCs were isolated using Accuspin tubes, histopaque 1077, and differential centrifugation. Approximately 2 million PBMCs were stained with Annexin V+MitoTracker, MitoSox+ Hoechst, and TMRE+ Hoechst as previously described.[14] Briefly, cells were incubated with 40 nM MitoTracker, 5 μM MitoSox/10 ng Hoechst, and 200 nM TMRE/10 ng Hoechst (in separate tubes) for 30 minutes at 37°C/5% CO2 in Hanks Balanced Salt Solution (HBSS with Ca2+/Mg2+). MitoTracker cells are washed and then stained with Annexin V in binding buffer, then diluted for flow cytometry analysis. MitoSox and TMRE stained cells are washed with HBSS and diluted for flow cytometry analysis, where 10,000 cells per tube were analyzed. All values were normalized to Hoechst signal. Fluorescent measures were completed within 30 hours of blood draw. The MFI algorithm; MFI = log [MitoTracker x TMRE)/ (MitoSox x Annexin V)] provides an overall picture of mitochondrial health and function. The MFI biomarker is listed in the utility patent no. 63/824,391 (Mitochondrial Functional Index) as of June 16, 2025.[14,15]

Platelet TDP-43 was assessed using capillary electrophoretic immunoassay (CEI).[16,17] Briefly, protein concentrations were determined using a BCA assay, and equal protein concentrations were used for CEI as previously described to measure total TDP43 (Proteintech Cat# 10782-2-AP) and p S409/410/12 TDP-43 (Proteintech Cat# 80007-1-RR).

Figure 2. CONSORT flow diagram



CEI data were used to calculate the Predicted Phosphorylation Value (PPV), defined as the ratio of pTDP-43 to total TDP-43 (PPV = pTDP-43 / total TDP-43). This algorithmic approach provides a practical and internally normalized surrogate measure of the relative extent of TDP-43 phosphorylation. The PPV thus serves as a useful metric for assessing TDP-43 post-translational modification in platelets and may offer insight into its relevance to platelet biology and neurodegenerative disorders such as ALS.

MRS: Brain glutathione (GSH) levels were measured via an advanced MR spectroscopy method, the multiple quantum chemical shift imaging (CSI) technique that is specially designed for GSH at 3T (Skyra, Siemens, Erlangen, Germany).[18-20] GSH is a vital antioxidant in the cerebral antioxidant defense system and is known to be a sensitive, quantitative indicator of oxidative stress, which is a major contributing factor in ALS.[21] We have demonstrated lower brain GSH in patients with progressive multiple sclerosis (MS) and patients with Alzheimer's disease (AD) compared with their age- and sex-matched controls.[18,22,23] In our previous study, we observed significant increases in brain GSH concentrations following one month of OAA treatment in patients with AD, particularly in the frontal and frontoparietal regions.[24] Accordingly, in the present study, we chose to measure brain GSH from a slab encompassing the frontal and parietal regions, consistent with our previous studies. GSH CSI acquisition parameters were TR/ TE = 1500/115 ms, FOV = 200 x 200 mm2, matrix size = 10 x 10, slice thickness = 2.5 cm, number of averages = 8. GSH signals were quantified using simultaneously measured creatine signals as internal concentration references.[20]

MRI: T1-weighted MRI (MPRAGE sequence, TR/TE/TI = 2000/3.98/830 ms, matrix = 176 × 256 × 256, FOV = 176 × 256 × 256 mm3, GRAPPA acceleration factor = 2) was also acquired for GSH quantification as well as regional brain volumes and cortical thickness using FreeSurfer software.[25]

Statistical Analysis:

The primary and secondary outcome measures were assessed with each dosing cohort in the 3+3 study design. For each dose, three subjects were enrolled and assessed for a dose-limiting toxicity (DLT). If none of the three subjects had a DLT, then three new subjects were enrolled at the next (higher) dose level. However, if one of the three had a DLT, then three additional patients were enrolled at the current dose. If none of the next three patients (i.e., so only 1/6 in total) experienced a DLT, then we continued to enroll three new subjects at the next (higher) dose. If any of the three additional subjects, or two or more of the original three subjects, at a given dose experience a DLT, dosing would be stopped. The next lower dose was then defined as the maximum tolerated dose. The sample size for this study was determined based on our 3+3 dose escalation design.

Additional analyses for this study included assessments of pre- versus post-treatment changes in biomarker measures as a function of dose. Pharmacokinetic samples were collected at baseline visit, pre-dose, 1 hour, and 4 hours post-dose. We treated dose as a continuous measure, so there were three

to six replicates at each dose for analysis. We used ordinary least square regression for analysis and conducted residual analysis to assess model assumptions. We planned to create spaghetti plots of individual subject trajectories and generate descriptive statistics as a case study approach to initially assess PK.

Results

Between March 2020 and August 2023, we screened 19 subjects, and 18 received OAA (Figure 2). One participant's screen failed due to low (less than 50%) forced vital capacity. One subject discontinued treatment on day 10/11 due to adverse events of nausea, vomiting, and diarrhea. These gastrointestinal events were considered DLT (Table 1). There were no deaths during the study. Data was analyzed for 18 subjects.

Participants were mostly middle-aged Caucasian white males with limb-onset ALS. The average time from symptom onset at the time of screening was 1.9 years.

Outcomes and measures:

Across the four cohorts, 34 adverse events were reported (Table 2). The highest incidence of adverse events was gastrointestinal and occurred in cohort 4 with a dose of 2500mg BID.

Table 1. Baseline demographics

Variable	Summary
Enrolled, (N) %	18
Sex, (N) %	
Female	3 (17%)
Male	15 (83%)
Age (years), median (IQR)	61 (54, 66)
Non-Hispanic/Non-Latino N (%)	18 (100%)
Caucasian, N (%)	18 (100%)
Participant Status, N (%)	
Completed Study	17 (94%)
Discontinue/DLT	1 (6%)
Mean symptom duration years (SD/range)	1.93 (1.13/ 0.59-4.74)
Vital status deceased as of 2026	12 (67%)
Taking riluzole	17 (94%)
Taking edaravone	13 (72%)
Taking sodium phenylbutyrate/ taurursodiol	3 (17%)

Table 2. Adverse events

System Organ Class Verbatim Term	Cohort 1 Dose 1000 mg BID (N=3)	Cohort 2 Dose 1500 mg BID (N=3)	Cohort 3 Dose 2000 mg BID (N=3)	Cohort 4 Dose 2500 mg BID (N=9)	All Subjects (N=18)
Subjects with ≥1 AE (%)	***3 (100%)***	***2 (66.7%)***	***3 (100%)***	***7 (77.8%)***	***15 (83.3%)***
Gastrointestinal	***3 (100%)***	***1 (33.3%)***	***3 (100%)***	***5 (55.6%)***	***12 (66.6%)***
Nausea	1 (33.3%)	0	0	3 (33.3%)	4 (22.2%)
Heartburn	1 (33.3%)	1 (33.3%)	0	2 (22.2%)	4 (22.2%)
Upset Stomach	0	0	2 (66.7%)	1 (11.1%)	3 (16.7%)
Diarrhea	0	0	0	1 (11.1%)	1 (5.6%)
Episodes of Sporadic Diarrhea	0	0	0	1 (11.1%)	1 (5.6%)
Intermittent Heartburn	1 (33.3%)	0	0	0	1 (5.6%)
Intermittent Indigestion	0	0	1 (33.3%)	0	1 (5.6%)
Stomach Pain	1 (33.3%)	0	0	0	1 (5.6%)
Vomiting	0	0	0	1 (11.1%)	1 (5.6%)
General Disorders	***0***	***0***	***1 (33.3%)***	***1 (11.1%)***	***2 (11.1%)***
Chills	0	0	0	1 (11.1%)	1 (5.6%)
Fatigue	0	0	1 (33.3%)	0	1 (5.6%)
Fever	0	0	0	1 (11.1%)	1 (5.6%)
Influenza-A	0	0	0	1 (11.1%)	1 (5.6%)
Musculoskeletal	***0***	***1 (33.3%)***	***0***	***1 (11.1%)***	***2 (11.1%)***
Increased Muscle Cramping	0	0	0	1 (11.1%)	1 (5.6%)
Increased Muscle Fasciculations	0	1 (33.3%)	0	0	1 (5.6%)
Shoulder Aches	0	0	0	1 (11.1%)	1 (5.6%)
Respiratory	***0***	***0***	***0***	***2 (22.2%)***	***2 (11.1%)***
Cough	0	0	0	2 (22.2%)	2 (11.1%)
Shortness of Breath	0	0	0	1 (11.1%)	1 (5.6%)
Cardiac Disorder	***0***	***0***	***1 (33.3%)***	***0***	***1 (5.6%)***
Tachycardia	0	0	1 (33.3%)	0	1 (5.6%)
Nervous System	***0***	***0***	***1 (33.3%)***	***0***	***1 (5.6%)***
Headache	0	0	1 (33.3%)	0	1 (5.6%)
Psychiatric Disorder	***0***	***0***	***0***	***1 (11.1%)***	***1 (5.6%)***
Insomnia	0	0	0	1 (11.1%)	1 (5.6%)
Skin and Subcutaneous Tissue Disorders	***0***	***0***	***1 (33.3%)***	***0***	***1 (5.6%)***
Hyperhidrosis	0	0	1 (33.3%)	0	1 (5.6%)
Vascular	***0***	***0***	***0***	***1 (11.1%)***	***1 (5.6%)***
Thrombus	0	0	0	1 (11.1%)	1 (5.6%)

N= # of subjects
N= # of events

The mitochondrial function index (previously MHI) was analyzed for 17 participants at screening and day 28.

Figure 3: MFI by cohort pre-dose and post-dose.

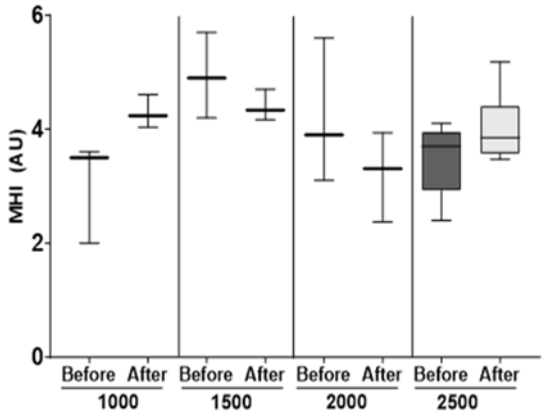
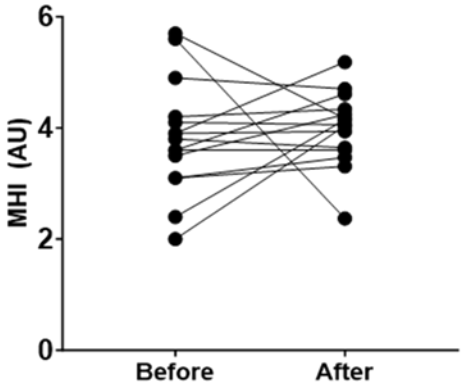


Figure 4: MFI collective pre-dose and post-dose.



Analysis of Predictive Phosphorylation Value (P-TDP-43 / Total TDP-43), PPV

Figure 5: PPV by cohort pre-dose and post-dose.

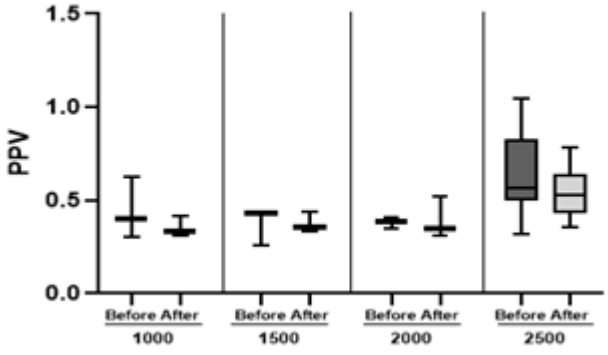
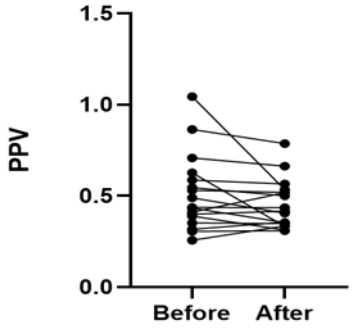


Figure 6: PPV collective pre-dose and post-dose.



MRS: Among 18 subjects, 12 of them successfully completed the MR scanning procedures. We observed consistent GSH spectral patterns across the frontal and parietal regions and across time, as shown in Figure 7. When all dose groups were combined, brain GSH levels increased significantly following OAA treatment ($p = 0.036$, $n = 12$, two-tailed, paired t-test).

Discussion

In the study, OAA was overall safe and well-tolerated in ALS patients up to 2500 mg twice daily. Across the four dosing cohorts, a total of 34 adverse events were reported. Of these, 12 of the 18 patients enrolled (66.7%) reported an adverse event that was determined to be related to OAA and classified as mild in severity. There was one serious adverse event, Influenza-A, which was assessed as not related to OAA. The highest incidence of adverse events was seen in cohort 4 with a dose of 2500 mg BID. Of the adverse events in cohort 4, 55.6% were gastrointestinal. Specifically, the adverse events included nausea, heartburn, upset stomach, diarrhea, stomach pain, and vomiting.

Due to one patient experiencing a DLT at the 2500mg BID dose, an additional 3 subjects were enrolled with no further DLTs. Gastrointestinal adverse events were reported in dosing cohorts 1, 3, and 4, with the highest prevalence in the 2500mg BID cohort. The higher frequency of adverse events in the 2500mg BID dosing cohort may influence the choice of OAA dosage in future ALS trials.

The mitochondrial biomarker, MFI indicated that lower and higher doses may better target mitochondrial function. However, n=3 in most cohorts limits a definite conclusion. Future studies should examine target engagement of mitochondrial function, as preclinical and in vitro studies show that OAA modulates mitochondrial function.[10,26]

Figure 7: Brain GSH maps before and after OAA treatment in a patient with ALS. (SEE FIGURE LEGEND BELOW)

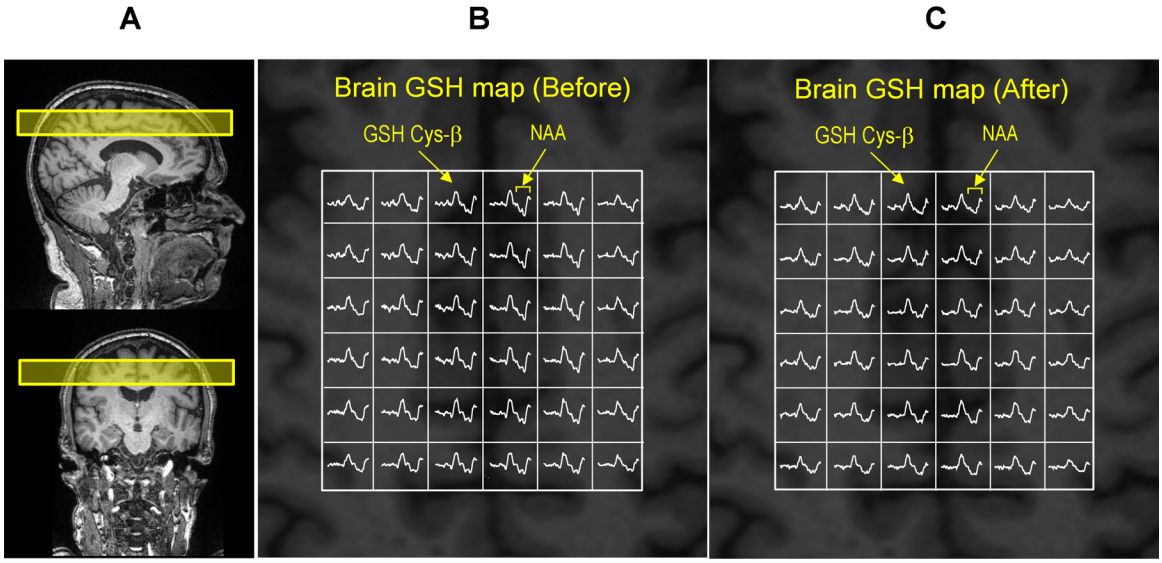


Figure 7. Representative brain GSH maps from longitudinal measurements before and after OAA treatment in a patient with ALS.

(A) T1-weighted MR images in two orientations (top: sagittal, bottom: coronal) with brain GSH chemical shift imaging (CSI) slab (2.5 cm thickness) indicated in yellow rectangles. (B) Partial views of brain GSH CSI demonstrate consistent detection of GSH signals in the brain of a patient with ALS before (left) and after (right) OAA treatment at 3 T. Brain GSH CSI spectra from the same participant are overlaid on anatomical MR images. The spectral range shown for GSH is 3.5-2.5 ppm.
PK: OAA was not detected in the PK samples. We cannot determine the exact reason for this observation.

The observed increase in brain GSH levels following OAA treatment is consistent with previously reported brain GSH increases in patients with AD, suggesting potential target engagement of the treatment.[24] In contrast, regional brain volume and cortical thickness measures in the precentral, thalamus, and brainstem regions did not show significant changes.

PPV - Predicted Phosphorylation Value (PPV), defined as the ratio of pTDP-43 to total TDP-43, showed no statistically significant difference before and after OAA intake. This potential biomarker may require further validation in ALS.

Study limitations include a small study sample, short duration of drug exposure, and inability to measure OAA levels. The COVID-19 pandemic caused trial recruitment to be slow, limited the number of subjects with MRS data collection, and the number of participants willing to stay onsite for the 4-hour post dose PK sample collection.

In this study, OAA was safe and well-tolerated in ALS patients at 2500 mg twice daily. Despite a small sample size, we observed positive target engagement based on MRS data, and TDP-43 PPV remained overall stable. We could not measure a reliable OAA plasma signal. This may be due to assay limitation or rapid metabolism of OAA, though we cannot exclude limited oral bioavailability of OAA. A reasonable next step would be to explore OAA in a larger trial powered to further evaluate efficacy and target engagement

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References

1. Rowland, L.P. and N.A. Shneider, *Amyotrophic lateral sclerosis.* N Engl J Med, 2001. **344**(22): p. 1688–700.
2. Statland, J.M., et al., *Patterns of Weakness, Classification of Motor Neuron Disease, and Clinical Diagnosis of Sporadic Amyotrophic Lateral Sclerosis.* Neurol Clin, 2015. **33**(4): p. 735–48.
3. Bowling, A.C., et al., *Superoxide dismutase activity, oxidative damage, and mitochondrial energy metabolism in familial and sporadic amyotrophic lateral sclerosis.* J Neurochem, 1993. **61**(6): p. 2322–5.

4. Fujita, K., et al., *Decreased cytochrome c oxidase activity but unchanged superoxide dismutase and glutathione peroxidase activities in the spinal cords of patients with amyotrophic lateral sclerosis.* J Neurosci Res, 1996. **45**(3): p. 276–81.
5. Vielhaber, S., et al., *Mitochondrial DNA abnormalities in skeletal muscle of patients with sporadic amyotrophic lateral sclerosis.* Brain, 2000. **123 (Pt 7)**: p. 1339–48.
6. Wiedemann, F.R., et al., *Impairment of mitochondrial function in skeletal muscle of patients with amyotrophic lateral sclerosis.* J Neurol Sci, 1998. **156**(1): p. 65–72.
7. Swerdlow, R.H., *Treating neurodegeneration by modifying mitochondria: potential solutions to a "complex" problem.* Antioxid Redox Signal, 2007. **9**(10): p. 1591–603.
8. Swerdlow, R.H., *The Neurodegenerative Mitochondriopathies.* J Alzheimers Dis, 2009.
9. Swerdlow, R.H., et al., *Role of mitochondria in amyotrophic lateral sclerosis.* Amyotroph Lateral Scler Other Motor Neuron Disord, 2000. **1**(3): p. 185–90.
10. Wilkins, H.M., et al., *Oxaloacetate enhances neuronal cell bioenergetic fluxes and infrastructure.* J Neurochem, 2016. **137**(1): p. 76–87.
11. Swerdlow RH, L.K., Khosla SK, Nashatizadeh M, Pahwa R., *A Pilot Study of Oxaloacetate 100 mg Capsules in Parkinson's Disease Patients.* J Parkinsons Dis Alzheimer Dis, 2016. **3**(2): p. 4.
12. Tungtur, S.K., et al., *Oxaloacetate treatment preserves motor function in SOD1G93A mice and normalizes select neuroinflammation-related parameters in the spinal cord.* Scientific Reports, 2021. **11**(1): p. 11051.
13. Brooks, B.R., et al., *El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis.* Amyotroph Lateral Scler Other Motor Neuron Disord, 2000. **1**(5): p. 293–9.
14. Hauger, B.M., et al., *A blood based mitochondrial functional index biomarker for Alzheimer's disease.* Alzheimers Dement, 2025. **21**(12): p. e71061.
15. Kemna, R.E., et al., *Mitochondrial blood-based biomarker is related to cardiorespiratory fitness and aging in a sex-dependent manner.* Alzheimers Dement (N Y), 2025. **11**(4): p. e70163.
16. Luthi-Carter, R., et al., *Location and function of TDP-43 in platelets, alterations in neurodegenerative diseases and arising considerations for current plasma biobank protocols.* Sci Rep, 2024. **14**(1): p. 21837.
17. Sage, J.M., 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. Choi, I.Y., et al., *Lower levels of glutathione in the brains of secondary progressive multiple sclerosis patients measured by 1H magnetic resonance chemical shift imaging at 3 T.* Mult Scler, 2011. **17**(3): p. 289–96.
19. Choi, I.Y. and P. Lee, *Doubly selective multiple quantum chemical shift imaging and T(1) relaxation time measurement of glutathione (GSH) in the human brain in vivo.* NMR Biomed, 2013. **26**(1): p. 28–34.
20. Lee, P., et al., *Brain Glutathione Levels Associate With Cognitive Performance in Older Adults.* J Neurochem, 2026. **170**(1): p. e70343.
21. Ferrante, R.J., et al., *Evidence of increased oxidative damage in both sporadic and familial amyotrophic lateral sclerosis.* J Neurochem, 1997. **69**(5): p. 2064–74.
22. Choi, I.Y., et al., *Longitudinal changes of cerebral glutathione (GSH) levels associated with the clinical course of disease progression in patients with secondary progressive multiple sclerosis.* Mult Scler, 2017. **23**(7): p. 956–962.
23. Choi, I.Y., et al., *In vivo evidence of oxidative stress in brains of patients with progressive multiple sclerosis.* Mult Scler, 2018. **24**(8): p. 1029–1038.
24. Vidoni, E.D., et al., *Safety and target engagement profile of two oxaloacetate doses in Alzheimer's patients.* Alzheimers Dement, 2021. **17**(1): p. 7–17.
25. Fischl, B., *FreeSurfer.* Neuroimage, 2012. **62**(2): p. 774–81.
26. Wilkins, H.M., et al., *Oxaloacetate activates brain mitochondrial biogenesis, enhances the insulin pathway, reduces inflammation and stimulates neurogenesis.* Hum Mol Genet, 2014. **23**(24): p. 6528–41.

Developing and sustaining an independent neuromuscular clinical trial site: A practical model from concept to maturity

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Abstract

Independent neuromuscular clinical trial sites serve a vital role in expanding access to novel therapies and improving research efficiency outside traditional academic environments.

This paper outlines the framework, infrastructure, and operational model developed by the Austin Neuromuscular Center (ANC) since 2017. Key elements include facility and safety design, staffing evolution, standard operating procedures (SOPs), regulatory compliance, patient recruitment strategies, budgeting, billing systems, and investigator-initiated trial (IIT) development. The ANC model demonstrates how an independent site can achieve sustainability, regulatory excellence, and innovation, serving as a blueprint for other centers.

Introduction

The rapid expansion of targeted therapies and gene-based treatments in neuromuscular medicine has created an urgent need for a well-organized, community-based research infrastructure. While academic centers have traditionally led this area, independent neuromuscular trial sites now play a crucial role in expanding patient access and speeding up trial processes. These sites combine clinical flexibility, sponsor responsiveness, and strong patient relationships with strict adherence to GCP and FDA standards. This paper shares the journey of the Austin Neuromuscular Center (ANC)—founded in 2017—from its beginnings as a small research extension of a private neurology practice to becoming a recognized, high-performing neuromuscular clinical research site.

Facility and Space Requirements

Establishing a high-quality research environment requires purpose-built space, equipment, and workflow design that prioritize both patient safety and data integrity. The ANC model integrated research operations within an outpatient neurology practice while maintaining regulatory independence and physical separation for audit readiness.

Core Facility Design

- **Research Suite:** Dedicated offices for CRCs and RNs, private monitoring rooms for sponsors, secure storage cabinets for source documents and signed consent forms, and keycard access to restricted areas.
- **Laboratory Infrastructure:** Equipped with centrifuges, calibrated pipettes, -20°C and -80°C freezers, continuous temperature monitoring with alarm logs, and validated shipping containers. Equipment calibration logs and deviation documentation are maintained in accordance with SOP.
- **Pharmacy and Drug Storage:** Controlled-access room with double-lock system, continuous temperature monitoring, and alarmed cold storage units. Accountability logs and segregation between blinded and unblinded staff ensure regulatory compliance.
- **Infusion Suite:** Two reclining chairs, infusion pumps, continuous vitals monitoring, and ACLS-certified RNs. The suite includes a crash cart, emergency oxygen, an AED, and spill kits.
- **Safety Infrastructure:** The site maintains adverse event management SOPs, annual emergency response drills, and sponsor notification procedures to ensure 24/7 readiness.

Core Team Development and Expansion

Staffing was designed to scale with study volume while maintaining flexibility. Early operations relied on shared roles, with the PI overseeing coordination, budgeting, and recruitment. As the research portfolio expanded, dedicated full-time staff were added.

Table 1. Team Composition and Evolution (2017–2025)

Phase	Team Composition	Key Milestones
2017–2018	PI and 1 CRC	SOP development, first site initiation visit (SIV), first patient enrolled
2019–2021	PI, 2 CRCs, 1 Sub-Investigator, 1 part-time RN	Infusion studies added; expanded sponsor relationships
2022–2025	6 CRCs (2 RNs), 2 RAs, 2 Sub-Is, PRN PT/OT, Research Manager	FDA audits passed, IITs launched, QA oversight established

Staff growth aligned with site expansion.

Standard Operating Procedures (SOPs) and Compliance

The foundation of ANC's operational integrity is a robust SOP framework developed through mentorship and consultation with experienced research organizations. SOPs are reviewed annually, updated as needed, and logged in a master file with version control. In addition, periodic

Figure 1. SOPs Starter Pack (top 12)

Core SOPs needed for compliant site operations.

internal audits ensure readiness for sponsor or FDA inspections. All personnel undergo GCP certification, IATA shipping training, and site-specific competency assessments.

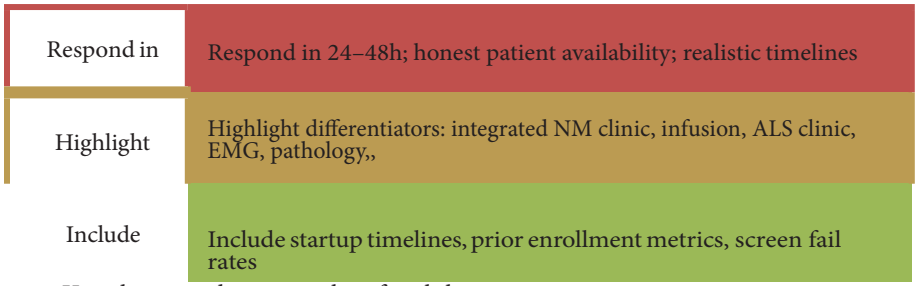
Study Feasibility and Recruitment Strategy

The site's success in trial acquisition stems from proactive engagement and data-driven feasibility assessment. The team maintains an internal diagnostic registry of neuromuscular disorders — allowing rapid estimation of eligible subjects for new protocols.

Feasibility Development

- Registered with major CRO and sponsor portals.
- Attended national and international research conferences for visibility.
- Quarterly searches on ClinicalTrials.gov and sponsor websites.
- Maintained a "Site Capability Profile" summarizing infrastructure, historical enrollment, and recruitment strategies, submitted to sponsors during feasibility rounds.

Figure 2. Feasibility Questionnaire Mastery



Key elements that strengthen feasibility responses.

Patient Recruitment

Recruitment combines both internal and external strategies:

- Clinic EMR database of >3,000 neuromuscular patients.
- Referral network of community neurologists.
- Social media and website campaigns.
- Periodic ads in local media and newsletters.
- Incentive program rewarding CRCs and assistants for identifying eligible participants.

This integrated approach allows high recruitment efficiency while maintaining patient retention and engagement.

Budget Development and Billing Management

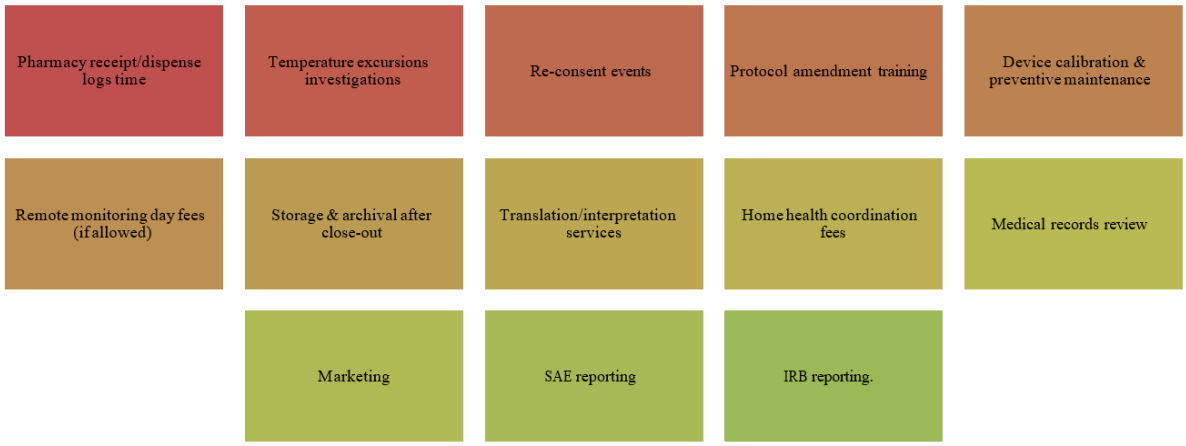
Transparent and realistic budgeting was essential for sustainability. The ANC team created an internal "Budget Builder Framework" that links each task to an estimated time per role, adjusted for overhead and administrative support.

Table 2. Budget Builder Framework

Category	Example	Notes
Startup Fees	Regulatory packet, SOP training, pharmacy and lab setup	Non-refundable after SIV
Per-Visit Fees	CRC time, PI/Sub-I review, procedures	Based on time per task
Non-Visit Fees	SAE follow-up, query responses, IRB reports	Often underbudgeted by sponsors
Pass-Through Costs	Labs, shipping, ECG, pharmacy fees	Billed as incurred
Closeout Fees	Archiving, record retention, final QA	Triggered after site closure

Main cost categories used in budgeting.

Figure 3. Commonly Missed Billable Items

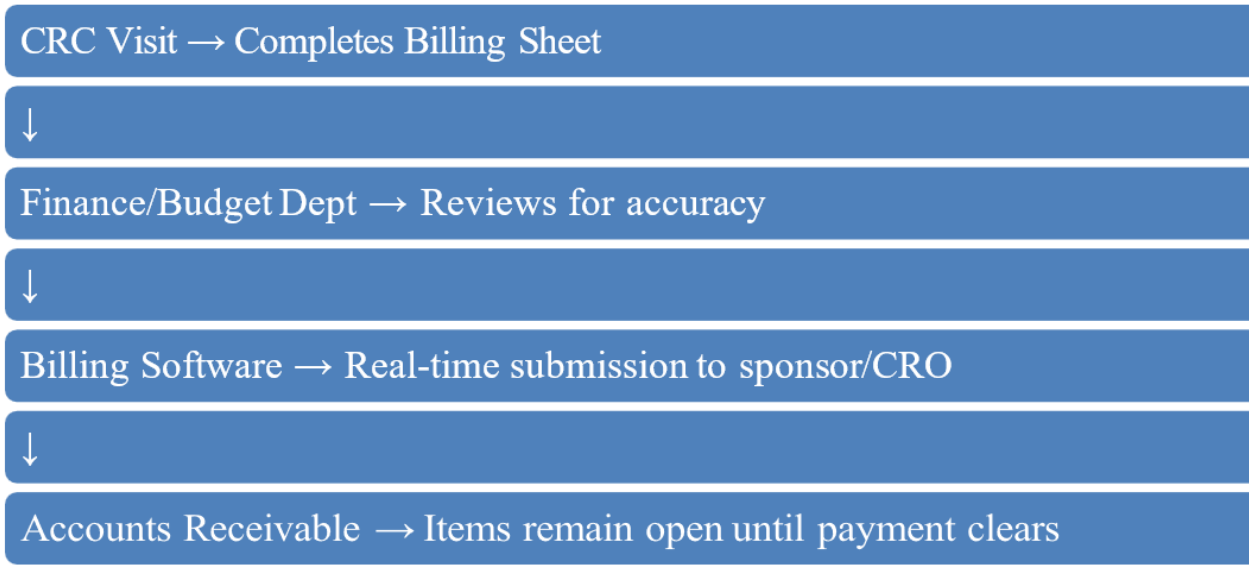


Common tasks that should be captured as billable.

Billing and Invoicing Workflow

Each CRC completes a visit-level billing sheet during each patient encounter, noting protocol-specific billable activities. These forms are reviewed by the Research Manager and entered into real-time billing software for monthly reconciliation.

Figure 4. Invoicing Workflow Diagram



Overview of the internal billing and payment process.

Study Start-Up Timelines

Efficient study start-up is vital for independent neuromuscular clinical trial sites. Unlike academic centers with less efficient administrative processes, private sites like ANC streamline regulatory, contractual, and operational tasks to enable rapid activation and ensure compliance with IRB, GCP, and FDA standards.

1. **IRB Approval (Central vs Local)**

Central IRBs review applications faster (7–14 days) than local IRBs (4–6 weeks). Many sites prefer central IRBs to minimize delays and enable parallel task initiation.

2. **Contract and Budget Negotiation**

ANC uses concurrent processes for contracts, budgets, and regulatory approval. This approach typically takes 4–6 weeks for complete agreement, much quicker than academic timelines that may take months.

3. **Site Qualification to SIV**

The Site Qualification Visit (SQV) assesses site readiness. After SQV approval, ANC aims for 45–60 days to reach Site Initiation Visit (SIV), during which the site begins enrollment.

Prompt responses and pre-prepared SOPs support these timelines.

4. **First Patient Screening**

From SIV to the first screened patient, ANC achieves 2–4 weeks, thanks to EMR-based recruitment, clinic volume, and trained staff ready to activate recruitment immediately after SIV.

Figure 5. Study Start-Up Timeline

Shows the streamlined activation steps and timeline.

Early-Stage Challenges

Establishing an independent site without institutional backing presented multiple challenges:

- **Human Resources:** Recruiting experienced CRCs was financially difficult during the early phase, with only one or two trials. The solution was to hire part-time coordinators or cross-train clinical staff.
- **Infrastructure and Training:** Initial lack of laboratory and regulatory templates required consultation with experienced PIs and third-party specialists.
- **Financial Risk:** Budget negotiation was handled directly by the PI with mentorship from colleagues; early payment delays from sponsors strained cash flow.
- **Operations:** Infusion studies were initially deferred until infusion capacity and staff competency were developed in later phases.

Despite these barriers, the site achieved steady growth through a stepwise approach emphasizing reinvestment, mentorship, and continuous quality improvement.

Investigator-Initiated Trials (IITs)

Investigator-initiated research represents the most academic and innovative tier of independent site activity. ANC has successfully launched two active and two pending IITs — all open-label pilot studies exploring neuromuscular therapies.

Table 3. Investigator-Initiated vs Industry-Sponsored Trials

Category	Investigator-Initiated Trials	Industry-Sponsored Trials
Funding Source	Institutional or grant-based	Sponsor-funded
Protocol Design	PI-driven and flexible	Sponsor-defined
Cost Efficiency	High, low logistics	Higher operational cost
Oversight	Local QA/IRB	CRO or Sponsor-managed
Innovation	Focused on emerging hypotheses	Focused on registrational endpoints

Quick comparison of operational differences.

IITs enhance clinical creativity and foster academic partnerships, though they demand more internal regulatory oversight and dedicated funding structures.

Operational Performance

ANC's operational efficiency and regulatory performance highlight the viability of this independent model.

Table 4. Operational Performance Summary

Domain	Outcome
Enrollment	Consistently top 10% across sponsored sites
Retention	<5% subject dropout rate
FDA Audits	Three successful inspections, no major findings
Financial Performance	Timely billing with 95% on-time payment
Team Capacity	6 CRCs, 2 RNs, 2 Sub-Is, PT/OT, Research Manager

Summary of key operational metrics.

Future Directions

The next stage in ANC's evolution includes:

- Initiation of **Phase 1 and translational studies**, leveraging local pharmacology partnerships.
- Expansion to **satellite research sites** across Texas, following the same SOPs and QA framework.
- Implementation of centralized data systems for remote monitoring and sponsor access.
- Development of a regional **neuromuscular trial network** integrating clinical care, research, and patient advocacy.

Conclusion

The Austin Neuromuscular Center's evolution demonstrates that independent neurology practices can build sustainable, high-performing clinical trial programs through strategic infrastructure investment, cross-trained personnel, and robust compliance systems.

This model shows that clinical excellence, operational agility, and financial accountability are compatible within an independent framework.

The ANC experience provides a replicable roadmap for other community-based centers aiming to integrate research and clinical care under a unified, scalable model.

Abbreviation Table

Abbreviation	Full Term
ACLS	Advanced Cardiac Life Support
AE	Adverse Event
AED	Automated External Defibrillator
ANC	Austin Neuromuscular Center
CRO	Contract Research Organization
CRC	Clinical Research Coordinator
ECG	Electrocardiogram
EMR	Electronic Medical Record
FDA	U.S. Food and Drug Administration
FPI	First Patient In
GCP	Good Clinical Practice
IATA	International Air Transport Association
ICF	Informed Consent Form
IIT	Investigator-Initiated Trial
IP	Investigational Product
IRB	Institutional Review Board
Sub-I	Sub-Investigator
Lab	Laboratory
NM	Neuromuscular
OT	Occupational Therapist / Occupational Therapy
PI	Principal Investigator
PRN	As needed
PT	Physical Therapist / Physical Therapy
QA	Quality Assurance
RA	Research Assistant
RN	Registered Nurse
SAE	Serious Adverse Event
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
SQV	Site Qualification Visit
V	Study Visit

A man with coughing spells for 20 years

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Introduction

Charcot-Marie-Tooth (CMT) disease or hereditary sensory motor neuropathy (HSMN) is the most common hereditary neuropathy with an estimated prevalence of 1 in 2500 people.[1] The characteristic findings in CMT include progressive sensory symptoms and weakness in the distal limbs, imbalance, and foot and ankle deformities.[2] Various atypical features of CMT have been described, including ptosis, tonic pupil, optic atrophy, deafness, diaphragmatic weakness, vocal cord palsy, chronic cough, facial or bulbar weakness, tongue atrophy, dysautonomia, cerebellar ataxia, and upper motor neuron signs.[2] The present case describes a patient with long standing numbness, imbalance, chronic cough, and a strong family history of similar symptoms.

Case Presentation

A 53-year-old man presented with complaints of daily coughing spells for the last 20 years. He described it as spells of constant intense coughing until he became lightheaded and almost passed out. The cough was always dry and could be triggered by pungent smells, temperature changes, eating or drinking. During these episodes he felt as if his throat was tightening. Hoarseness of his voice was not present in his symptomology. He was initially diagnosed with mild asthma, but pulmonary function tests were normal and the cough was not responsive to standard asthma treatment. Multiple laryngoscopy examinations were unrevealing.

He had an uneventful birth and perinatal history. He had no foot, ankle, or spine surgeries, wounds or injuries. He only participated in cross country running while in school. He first noticed imbalance when he was ice skating 10 years ago. His imbalance slowly progressed that led to his first fall approximately five years prior. More recently, he noted difficulty climbing stairs and buttoning clothes. He also reported a difficulty sensing temperature in his hands and feet, which resulted in multiple injuries in these regions.

Family history is significant on his maternal side with his mother and uncle having similar symptoms of imbalance and chronic coughing spells. His mother also had vocal cord paralysis and issues with aspiration. His brother and sister were both diagnosed with sensory neuropathy without further details.

Mental status, cranial nerves and muscle strength were all normal on the initial neurological exam. Deep tendon reflexes were hypoactive. Impaired sensation of pinprick and vibration was noted in the distal extremities, more significantly in the lower and sensation of proprioception was reduced in the toes bilaterally. Gait was unsteady and wide based. No hammer toes or high arches were observed.

Sensory nerve conduction studies showed diffusely reduced sensory nerve action potentials (SNAPs) in the upper and lower extremities. Motor nerve conductions of the upper and lower extremities were normal. Needle examination of selected muscles revealed evidence of chronic denervation in a length dependent pattern.

Laboratory workup for the aetiologies of neuropathy revealed slightly reduced B12 level that was quickly corrected with B12 supplementation, without leading to changes in his symptoms of neuropathy and coughing spells. Due to the chronic slowly progressive course and significant family history of similar symptoms, a genetic cause of neuropathy was considered. The initial testing revealed the following changes in the MFN2 gene: c.708+11_708+13delCTC (intronic). Variants of uncertain significance (VUS) were noted in the DNAJB2, MFN2NDRG1, and SPG11 genes. The changes noted above in the MFN2 gene were initially classified as being VUS but reclassified as being pathogenic and being associated with autosomal dominant or autosomal recessive CMT2A. The final diagnosis for this patient was CMT2A with involvement of laryngeal nerve causing chronic neuropathic cough. His coughing spells were relatively treatment refractory to standard asthma inhalant medications, amitriptyline, and gabapentin.

Discussion

Neuropathic cough has been associated with a variety of hereditary, nutritional, infectious/post infectious, infiltrative, and iatrogenic causes that have been summarized in **Table 1.** In hereditary neuropathies, chronic cough is hypothesized to arise from vagal neuropathy with consequent autonomic dysfunction. This may include impaired vagal control of the distal oesophageal sphincter, promoting gastroesophageal reflux and causing reflux laryngitis, and secondary laryngeal irritation–induced cough.[3] Denervation hypersensitivity is another mechanism for neuropathic cough, whereby impaired sensory function of the superior and recurrent laryngeal branches of the vagal nerve, which form the afferent limb of the sensory cough pathway, lowers the threshold required to trigger coughing. Due to the length dependent nature of CMT, the recurrent laryngeal nerve is preferentially affected, making vocal cord paralysis a well-known cause of morbidity in advanced stages of CMT.[4]

Table 1. Causes of neuropathic cough

Type	Causes	Associated features
Nutritional	B12 deficiency	Small and large fibre sensory myeloneuropathy, macrocytosis
Infection/post infectious	Post viral vagal neuropathy	Recent viral infection, dry cough, throat paraesthesia
Genetic	CMT	Imbalance, chronic pain
	HSAN	Distal sensory loss, SNHL
	CANVAS	Ataxia, vestibular areflexia
Infiltrative	Neurofibroma in vagal nerve	Cutaneous neurofibromas, family history
	Amyloidosis/sarcoidosis	Small fibre neuropathy, other cranial neuropathies, heart failure
Traumatic/iatrogenic	Post intubation/surgical	Recent surgery/instrumentation
Structural	Mediastinal mass, cervical spine disease (C2-C5)	Smoking history, myelopathic findings or radicular pain

Abbreviations: CMT: Charcot-Marie-Tooth, HSAN: Hereditary Sensory Autonomic Neuropathy, SNHL: Sensory Neural Hearing Loss, CANVAS: Cerebellar Ataxia, Neuropathy, with Vestibular Areflexia Syndrome

In clinical practice, it is essential to systematically exclude common cardiac, pulmonary, and gastrointestinal causes of chronic cough while identifying features suggestive of neuropathic cough.[5] Characteristic features of cough hypersensitivity syndrome or neuropathic cough include: (i) a persistent or intermittent irritating sensation in the pharyngeal or laryngeal region; (ii) a globus or choking sensation in the throat or chest; and (iii) cough triggered by temperature changes, laughing, talking, or exposure to pungent smells or aerosols, although triggers may be absent.[6]

Attributable to shared mechanisms, including denervation hypersensitivity and

central reflex sensitization, neuropathic cough and neuropathic pain are treated using similar therapeutic approaches. Gabapentin and amitriptyline have been tried and tested in randomized clinical trials with promising results.[7]

This case highlights the importance of periodic re-evaluation of genetic testing results in cases with VUS. The initial testing identified VUS in multiple genes, including MFN2, the most common gene associated with CMT2. Five years later, this variant was reclassified as being pathogenic.

There were certain features in this case that did not fit the common phenotype of MFN2 related CMT2. Unlike the current case, motor weakness typically predominates over sensory impairment. Most affected individuals develop symptoms in the first or second decade of life, with foot drop being a common presenting feature. Concomitantly, MFN2 associated CMT2 has several atypical features apart from chronic cough which include upper motor signs like mild increased reflexes, increased tone, extensor plantar responses without a frank spastic gait, and cranial neuropathies leading to optic atrophy, trigeminal neuralgia, facial weakness, diaphragmatic weakness, and hoarse voice.[8-10]

Conclusions

Hereditary neuropathies are common and exhibit a broad spectrum of presentations. This case underscores the importance of maintaining diagnostic vigilance in identifying neuropathic cough as an atypical manifestation of hereditary neuropathies and in periodically re-evaluating genetic testing to achieve a definitive diagnosis.

References

1. Barreto LCLS, Oliveira FS, Nunes PS, et al. Epidemiologic study of Charcot-Marie-Tooth Disease: A systematic review. *Neuroepidemiology*. 2016;46(3):157-165. doi:10.1159/000443706, PMID 26849231
2. Nagappa M, Sharma S, Taly AB. Charcot-Marie-Tooth Disease. 2024 Jun 22. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan–. PMID: 32965834.
3. Chung KF, McGarvey L, Mazzone SS. Chronic cough as a neuropathic disorder. *Lancet Respir Med*. Lancet Publishing Group. 2013;1(5):414-422. doi:10.1016/S2213-2600(13)70043-2, PMID 24429206
4. Sulica L, Lovelace RE, Blitzer A, Kaufmann P. Vocal fold paresis of Charcot-Marie-Tooth Disease. *Annals of Otology, Rhinology & Laryngology*. 2001;110(11):1072-1076. doi:10.1177/000348940111001115. PMID 11713921
5. Sakin YS, Vardar R, Sezgin B, et al. The diagnostic value of 24-hour ambulatory intraesophageal pH-impedance in patients with laryngopharyngeal reflux symptoms comparable with typical symptoms. *United European Gastroenterol J*. 2017;5(5):632-640. doi:10.1177/2050640616675040, PMID 28815026
6. Khan D, Chaudhry H, Iqbal P, et al. Cough-hypersensitivity syndrome-A new paradigm in the evaluation of

chronic refractory cough and its novel therapeutic horizons-A Review. *J Community Hosp Intern Med Perspect*. 2024;14(6):75-81. doi:10.55729/2000-9666.1417, PMID 39839174

7. Jeyakumar A, Brickman TM, Haben M. Effectiveness of amitriptyline versus cough suppressants in the treatment of chronic cough resulting from postviral vagal neuropathy. *Laryngoscope*. 2006;116(12):2108-2112. doi:10.1097/01.mlg.0000244377.60334.e3, PMID 17146380
8. Parmar JM, Laing NG, Kennerson ML, Ravenscroft G. Genetics of inherited peripheral neuropathies and the next frontier: looking backwards to progress forwards. *J Neurol Neurosurg Psychiatry.* BMJ Publishing Group. 2024;95(11):992-1001. doi:10.1136/jnnp-2024-333436, PMID 38744462
9. Di Meglio C, Bonello-Palot N, Boulay C, Milh M, Ovaert C, Levy N, Chabrol B. Clinical and allelic heterogeneity in a pediatric cohort of 11 patients carrying MFN2 mutation. *Brain Dev.* 2016 May;38(5):498-506. doi: 10.1016/j.braindev.2015.11.006. Epub 2015 Dec 10. PMID: 26686600.
10. Aho TR, Wallace RC, Pitt AM, Sivakumar K. Charcot-Marie-Tooth disease: extensive cranial nerve involvement on CT and MR imaging. *AJNR Am J Neuroradiol.* 2004 Mar;25(3):494-7. PMID: 15037479; PMCID: PMC8158541.

Lambert-Eaton syndrome and prostate adenocarcinoma, a case report

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Introduction

Lambert-Eaton Myasthenic Syndrome (LEMS) is a rare neuromuscular disease characterized by progressive muscle weakness due to a disruption of acetylcholine neurotransmission within the neuromuscular junction (NMJ). It has similar clinical features to myasthenia gravis (MG), but exhibits electrographic facilitation upon exercise.[6] Unlike MG, LEMS is due to dysfunction of the presynaptic calcium channels rather than the postsynaptic acetylcholine receptors in MG. LEMS occurs about 46 times less than MG, and is more likely to affect males, whereas MG is known to have higher prevalence in the female population.[1] Literature has shown that LEMS is predominantly associated with small cell lung cancer (SCLC). It is thought that paraneoplastic autoantibodies target the P/Q voltage-gated calcium channels within the presynaptic terminal at the NMJ.[1,5] Although some cases have been reported, the association of LEMS with other malignancies is much more rare and cases in the literature are lacking.[7,8] Here, we present a case of LEMS diagnosed in a male patient with metastatic prostate adenocarcinoma.

Case Description

A 75-year-old male with a known history of metastatic prostate cancer status-post radiation and chemotherapy treatment was admitted to the hospital for planned lumbar radiation treatment and chemotherapy. The neurology team was consulted due to progressive weakness most notably in the proximal lower extremities as well as increased difficulty breathing for 8 months. The patient denied diplopia, dysarthria, dysphagia, dizziness, or voice changes. The weakness was not associated with sensory changes or pain beyond mild muscle aches. Weakness started in the lower limbs then gradually progressed to involve the proximal upper extremities bilaterally, as well as diaphragmatic muscles, resulting in dyspnea on exertion, and eventually made the patient bedridden. However negative inspiratory force was persistently normal throughout the hospitalization. Spine MRI showed potential sites of bony metastases of prostate cancer but did not show evidence of significant spondylosis. The patient denied saddle anesthesia and bowel or bladder incontinence.

Physical examination revealed normal cranial nerve exam, 4+/5 strength throughout the bilateral upper extremities, and predominantly proximal weakness in the lower limbs with 4-/5 strength in the iliopsoas, quadriceps, and hamstrings, normalizing at the ankle. There were diminished reflexes in the biceps, triceps, brachioradialis, and the ankles. Labs were significant for mild hyponatremia, normocalcemia, and normal blood counts. Voltage gated calcium channel antibodies were elevated at 142.5 pmol/L (Normal 0-30 pmol/L). CT scan of the chest revealed clear lung parenchyma without nodules, infiltrates, or effusions, which ruled out a primary lung malignancy. Small subsegmental pulmonary emboli were visualized incidentally.

EMG/NCS was performed which demonstrated normal sensory conduction of the left superficial peroneal nerve. However, motor nerve conduction of the right ulnar at the abductor digiti minimi muscle demonstrated low compound muscle action potential (CMAP) amplitude which more than doubled upon exercising for 10 seconds (Fig. 1). 3Hz repetitive nerve conduction of the bilateral ulnar nerves demonstrated decremental response of ~30% in amplitude with subsequent post-exercise facilitation (Fig 2).

The patient was then treated with a 5-day course of intravenous immunoglobulin and amifampridine for LEMS, resulting in improvements in strength testing as well as subjective dyspnea and was subsequently discharged home on a prolonged prednisone taper.[2] He eventually transitioned to hospice care and passed away due to the underlying metastatic prostate cancer.

Discussion

Compared with MG, LEMS is a much rarer. In the literature, paraneoplastic cases are mostly associated with lung malignancy. However, our case of a patient with prostate cancer highlights the importance of considering LEMS as a cause of weakness in patients with other forms of cancer. Electrodiagnostically, one must be alert to a pattern of widespread low CMAP amplitudes on nerve conduction studies, which may alert the diagnostician to perform exercise testing to look for electrographic facilitation and subsequently pursue repetitive nerve stimulation. The treatment of paraneoplastic LEMS is primarily directed at the underlying neoplasm but also consists of immunosuppression and a trial of pyridostigmine. Additionally, amifampridine, an FDA approved agent for LEMS that may help reduce symptoms.[3,4] Amifampridine works by facilitating the release of acetylcholine within the neuromuscular junction via potassium channel blockade. Unlike SCLC, there are no clear studies of how prostate adenocarcinoma cells trigger the immune system leading to LEMS, but we theorize the mechanism may be similar to that of SCLC. Future studies should focus on understanding this pathophysiology and highlighting the mechanism at the molecular level.

Fig 1. Motor nerve conduction of the right ulnar nerve at the wrist of the ADM muscle demonstrating A) baseline reduced CMAP amplitude of 1.8mV at the wrist B) post exercise (for 10 seconds) facilitation of the same muscle to 4.4mV C) 5 minutes post exercise showed a return to baseline/post exercise exhaustion to 1.4mV.

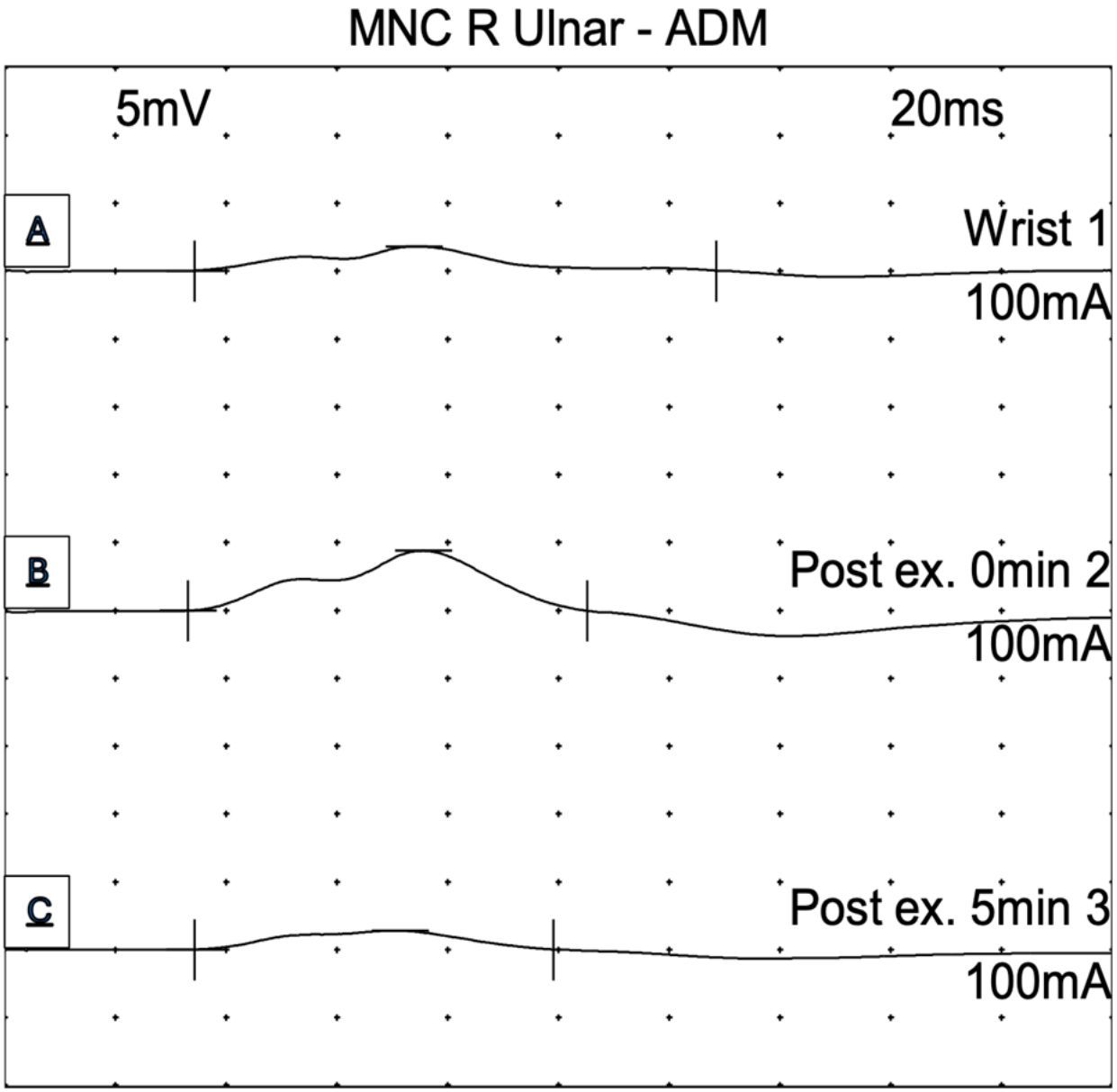
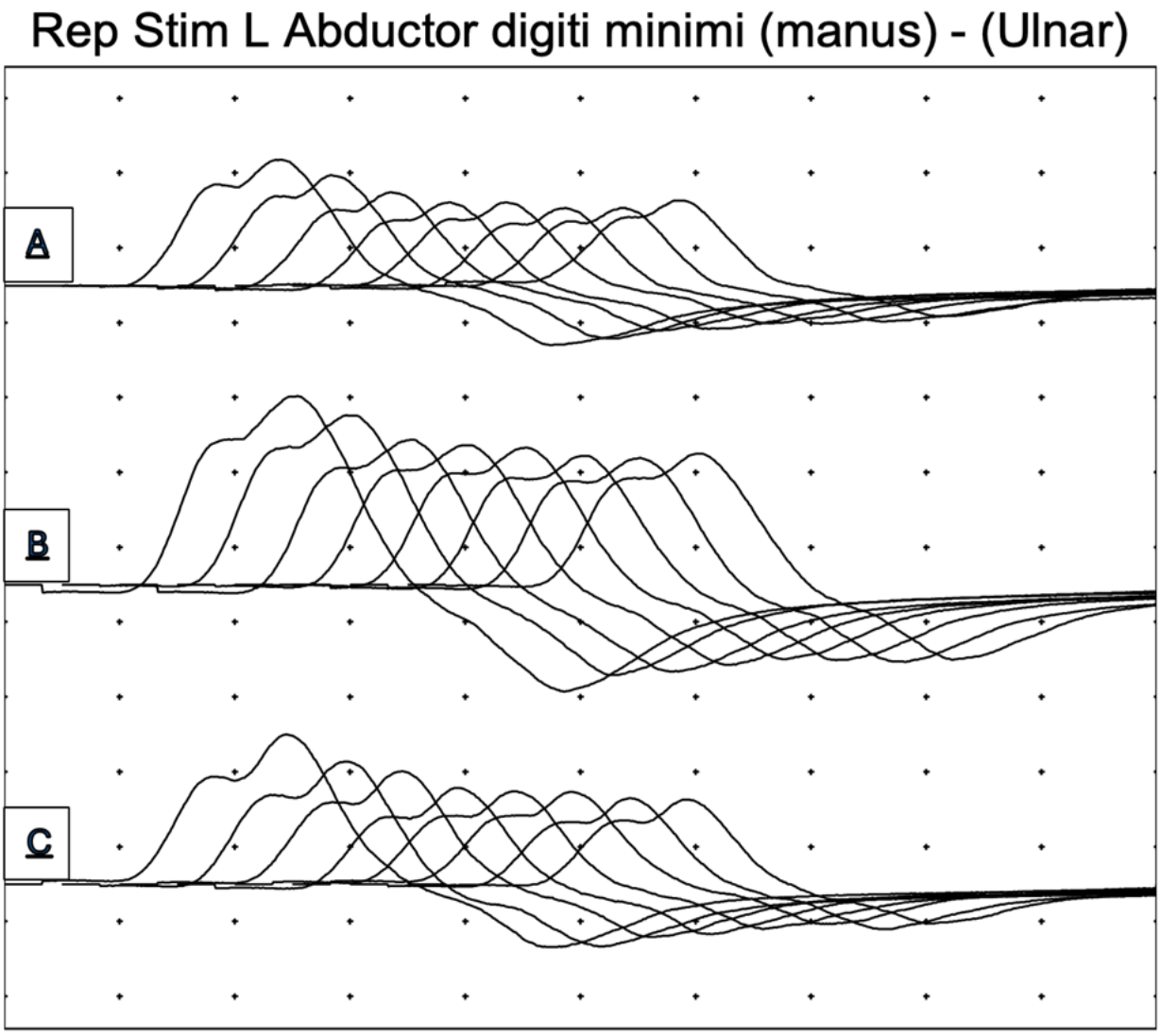


Fig 2. Repetitive nerve stimulation (3Hz) of the left ADM muscle demonstrating: A) 1.6mV at baseline. B) Facilitation immediately post exercise to 2.6mV (60% increase). C) Return to near baseline at 1.9mV 30 seconds post exercise.



References

1. Jayarangaiah A, Lui F, Kariyanna PT. Lambert-Eaton myasthenic syndrome. Treasure Island (FL): StatPearls Publishing; 2023 Oct 23. Available from: https://www.ncbi.nlm.nih.gov/books/
2. Mayo Foundation for Medical Education and Research. Amifampridine (oral route). Rochester (MN): Mayo Clinic; n.d. Available from: https://www.mayoclinic.org/
3. Firdapse (amifampridine) [prescribing information]. Coral Gables (FL): Catalyst Pharmaceuticals Inc; 2024 May.
4. Lindquist S, Stangel M. Update on treatment options for Lambert-Eaton myasthenic syndrome: focus on use of amifampridine. Neuropsychiatr Dis Treat 2011;7:341–349. doi:10.2147/NDT.S10464.
5. Lang B, Pinto A, Giovannini F, Newsom-Davis J, Vincent A. Pathogenic autoantibodies in the Lambert-Eaton myasthenic syndrome. Ann N Y Acad Sci 2003;998:187–195. doi:10.1196/annals.1254.019.
6. Baslo MB, Deymeer F, Serdaroglu P, Parman Y, Ozdemir C, Cuttini M. Decrement pattern in Lambert-Eaton myasthenic syndrome is different from myasthenia gravis. Neuromuscul Disord 2006;16(7):454–458. doi:10.1016/j.nmd.2006.05.009.
7. Delahunt B, Abernethy DA, Johnson CA, Nacey JN. Prostate carcinoma and the Lambert-Eaton myasthenic syndrome. J Urol 2003;169:278–279. doi:10.1016/S0022-5347(05)64091-8.
8. Tetu B, Ro JY, Ayala AG, Ordonez NG, Logothetis CJ, von Eschenbach AC. Small cell carcinoma of prostate associated with myasthenic (Eaton-Lambert) syndrome. Urology 1989;33(2):148–152. doi:10.1016/0090-4295(89)90017-4.

Case report: acute motor and sensory axonal Guillain-Barre variant in association with HHV-6 infection

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Introduction

Guillain-Barre syndrome (GBS) is an encompassing term that refers to a group of acute autoimmune-mediated polyneuropathies and is one of the most common neuromuscular emergencies. Infections are the most common antecedent event before the clinical development of GBS, yet several noninfectious factors have also been reported as preceding the condition, such as trauma, surgery, or medications.[1] Human herpesvirus 6 (HHV-6) is an etiological cause of roseola infection—a common childhood infection that manifests as exanthem subitum or benign febrile disease and has been observed as a concomitant infection in GBS but the association has been rarely reported. [2] While rare, HHV-6 has been observed as an infectious agent responsible for the development of GBS, and possibly a concomitant infection.[2] According to an article published by the Journal of Clinical Virology, patients observed to have GBS in the setting of HHV-6 infections often have HHV-6 specific antibodies in their CSF and is a strong indication of active virus replication within the central nervous system.[2] However, while HHV-6 has been linked to classic GBS, there has yet to be an identified association between HHV-6 and development of GBS variant disease. The variants of GBS include axonal variants, localized variants, and Miller Fischer Syndrome. Classification of these variants is based on clinical, pathophysiological, and pathologic features. The focus of this case report will be on axonal variants, which can be further divided into acute motor axonal neuropathy (AMAN) and acute motor-sensory axonal neuropathy (AMSAN). While these two axonal variants can be distinguished based on sensory involvement, they also have differing clinical courses. AMAN is more common in Asia, is preceded by diarrheal illness, and usually affects children. AMSAN, however, is less associated with geographical location, is preceded by respiratory illness, and is more prevalent in adults.[1] This case study aims to outline the presence of GBS variant disease, specifically AMSAN, in the setting of HHV-6 infection.

Case Presentation

The patient was a 44-year-old male with a past medical history significant for seropositive rheumatoid arthritis, recently started on adalimumab, who was initially hospitalized for acute necrotizing pancreatitis thought to be secondary to alcohol use disorder. The patient was treated with fluid resuscitation and had clinically improved. Upon preparation for discharge, physical therapy assessed the patient and noted profound weakness in the distal lower extremities, which the patient reported had been progressing over the last several days.

When neurology saw him, he had intact mental status, intact speech, and intact cranial nerve examination. However, motor examination was as follows in Table 1.

Table 1. Motor examination at time of consultation.

Motor movement	Right side	Left side
Ankle dorsiflexion	2/5	4/5
Ankle plantar flexion	2/5	4/5
Knee extension	5/5	5/5
Knee flexion	5/5	5/5
Hip Flexion	4/5	4/5
Digital interossei	3/5	3/5
Wrist extension	3/5	4/5
Wrist flexion	3/5	4/5
Upper arm flexion	5/5	5/5
Upper arm extension	5/5	5/5

Muscle bulk and tone were normal, and no pronator drift was noted. All reflexes were 2/2 and Babinski was down going bilaterally. Repeat exam after one week showed diminished and symmetric patellar and Achilles reflex. Sensory exam showed intact sensation to light touch and pinprick in the bilateral upper extremities, with notable diminished sensation to light touch and pinprick to ankle in the right lower extremity and to mid-shin in left lower extremity. Temperature sense was intact in bilateral upper and lower extremities. Vibration sense was 50% diminished in bilateral upper extremities, 50% diminished left lower extremities over the big toe and ankle, and 75% diminished over big toe and ankle in right lower extremity. Proprioception was impaired bilaterally over big toes and wrists. Gait was not assessed due to profound weakness.

Over the course of several days, both his weakness and sensory loss gradually progressed to involve the proximal upper and lower extremities, with the distal extremities being more profoundly affected. The patient had complete loss of grip strength bilaterally as well as progressive weakness of his lower extremities. In addition to sensory and motor changes, there was prominent pitting edema of bilateral lower extremities. There were also noted skin changes with necrosis over the right metacarpophalangeal (MCP) joint, the distal end of his digits bilaterally, and the distal end of his first hallux bilaterally.

The physical exam findings were localized to an ascending asymmetric sensorimotor neuropathy. Given

Table 2: Sensory nerve conduction study results.

Sensory Nerve	Side	Parameter	Patient Value	Normal Range
Median (2nd digit)	Right	Amplitude (microVolts)	NR	>10.0
		Velocity (m/s)	NR	>36.0
		Distal latency (ms)	NR	<4.0
Median (2nd digit)	Left	Amplitude (microVolts)	NR	>10.0
		Velocity (m/s)	NR	>36.0
		Distal latency (ms)	NR	<4.0
Radial	Left	Amplitude (microVolts)	4.9	>7.0
		Velocity (m/s)	43	
		Distal latency (ms)	2.3	<2.8
Superficial Fibular	Right	Amplitude (microVolts)	NR	>3.9
		Velocity (m/s)	NR	>30.0
		Distal latency (ms)	NR	<4.2
Superficial Fibular	Left	Amplitude (microVolts)	NR	>3.9
		Velocity (m/s)	NR	>30.0
		Distal latency (ms)	NR	<4.2
Sural	Right	Amplitude (microVolts)	NR	>4.0
		Velocity (m/s)	NR	>30.0
		Distal latency (ms)	NR	<4.5
Sural	Left	Amplitude (microVolts)	NR	>4.0
		Velocity (m/s)	NR	>30.0
		Distal latency (ms)	NR	<4.5
Ulnar	Right	Amplitude (microVolts)	3.8	>6.0
		Velocity (m/s)	45	>36.0
		Distal latency (ms)	3.1	<4.0
Ulnar	Left	Amplitude (microVolts)	3.8	>6.0
		Velocity (m/s)	47	>36.0
		Distal latency (ms)	3	<4.0

the acute course and asymmetric pattern, an inflammatory process was suspected. Laboratory workup was notable for an elevated CRP and ESR, 141.9 and 101, respectively. ANCA, serum autoimmune, acute hepatitis panel, HIV, and Lyme panel came back normal. MRI with and without contrast showed no cord abnormality or severe stenosis.

Cerebrospinal fluid (CSF) studies from lumba r puncture performed within the first 5 days of presentation demonstrated mild elevation of white blood cells with a cell count of 6 cells/uL, protein of 27.6, and red blood cell count of 3 cells/uL. Viral meningitis and encephalitis panel returned positive for HHV-6 on PCR and negative for HSV, CMV, and West Nile.

Nerve conduction studies were performed on day 5 of symptom onset and was notable for absent CMAP and SNAP responses in multiple nerves and reduced amplitude with preserved velocity in other nerves (see table 2 and 3). This is consistent with severe axonal sensorimotor neuropathy affecting the upper and lower extremities. Needle EMG could not be performed at bedside due to lack of availability.

Table 3: Muscle nerve conduction study results.

Motor Nerve	Side	Parameter	Patient Value	Normal Range
Common Peroneal (Tibial)	Left	Amplitude (microVolts)	0.5 fib, 0.4 pop	NA
		Velocity (m/s)	62	NA
		Distal latency (ms)	3.8 fib, 5.4 pop	<4.9
		F-wave	NA	NA
Common Peroneal (Tibial)	Right	Amplitude (microVolts)	NR	NA
		Velocity (m/s)	NR	NA
		Distal latency (ms)	NR	<4.9
		F-wave	NA	NA
Common Peroneal (Extensor Digitorum Brevis)	Left	Amplitude (microVolts)	NR	>1.3
		Velocity (m/s)	NR	>36
		Distal latency (ms)	NR	<6.5
		F-wave	NA	NA
Common Peroneal (Extensor Digitorum Brevis)	Right	Amplitude (microVolts)	NR	>1.3
		Velocity (m/s)	NR	>36
		Distal latency (ms)	NR	<6.5
		F-wave	NA	NA
Median	Left	Amplitude (microVolts)	0.4 wrist, 0.4 elbow	>4
		Velocity (m/s)	39	>48
		Distal latency (ms)	3.3 wrist, 9.4 elbow	<4.5
		F-wave	34.06	<33
Median	Right	Amplitude (microVolts)	NR	>4
		Velocity (m/s)	NR	>48
		Distal latency (ms)	NR	<4.5
		F-wave	NR	<33
Tibial	Left	Amplitude (microVolts)	NR	>4.4
		Velocity (m/s)	NR	>34
		Distal latency (ms)	NR	<6.1
		F-wave	NR	<61
Tibial	Right	Amplitude (microVolts)	NR	>4.4
		Velocity (m/s)	NR	>34
		Distal latency (ms)	NR	<6.1
		F-wave	NR	<61
Ulnar	Left	Amplitude (microVolts)	3.6 wrist, 3.4 B elbow, 3.5 A elbow	>6
		Velocity (m/s)	60 B/A elbow, 67 wrist/B elbow	>51
		Distal latency (ms)	3.2 wrist, 6.7 B elbow, 8.2 A elbow	<3.7
		F-wave	29.33	<36
Ulnar	Right	Amplitude (microVolts)	3.0 wrist, 2.8 B elbow, 2.8 A elbow	>6
		Velocity (m/s)	68 B elbow/A elbow, 71 wrist/B elbow	>51
		Distal latency (ms)	3.2 wrist, 6.3 B elbow, 7.7 A elbow	<3.7
		F-wave	26.86	<36

With positive HHV-6 in CSF in the setting of an axonal peripheral neuropathy, there was a high concern for reactivation of HHV-6 infection leading to a variant form of GBS. Rheumatology and infectious disease consulted due to immunocompromised status in the setting of HHV-6 infection and determined to hold the patient's upcoming dose of adalimumab. The patient was started on a treatment course of valganciclovir 900 mg twice daily for 3 days as well as intravenous (IV) solumedrol 1000 mg daily for 3 days for a presumed autoimmune process. After initiation of treatment, patient was responsive and had mild, gradual improvement in both sensory and motor symptoms bilaterally. He was deemed steroid-responsive and the duration of IV solumedrol was extended to five days. In addition, the patient underwent five days total of plasma exchange therapy. There continued to be mild improvement through hospital course. The patient worked aggressively with physical therapy and after several days desired to return home with therapy. Following discharge, results from ganglioside antibody panel returned positive for IgM Disialo, GD1b. Given this finding and the nerve conduction studies showing axonal involvement, as well as the clinical findings of loss of motor and sensory capabilities, this patient was found to have an acute motor and sensory axonal neuropathy in the setting of HHV-6 infection.

Discussion

Human herpesvirus 6 (HHV-6) is a double-stranded deoxyribonucleic acid (DNA) virus that further targets CD4+ T lymphocyte cells. It can be further categorized into HHV-6A and HHV-6B within the herpesvirus family.[3] HHV-6B is most known for infecting infants and children and often presents as an undifferentiated febrile illness, though a small subset of patients will develop the classic roseola infantum (also known as exanthem subitum).[3] The primary infection is generally self-limiting and requires no treatment other than supportive measures such as antipyretics. Alternatively, HHV-6A is more commonly associated with immunocompromised hosts, and less is known about this variant, which is thought to be acquired in adulthood and primarily presents as asymptomatic infections.[3] Currently, there is no serologic testing available to differentiate between HHV-6A and HHV-6B.[4] Incidence of HHV-6 is ubiquitous, with an estimated 95% of individuals over the age of two suspected to test seropositive for either HHV-6A or HHV-6B variant.[4] The detection method for HHV-6 is polymerase chain reaction (PCR).[5]

Following the primary infection, the virus tends to remain latent with the viral DNA residing in peripheral mononuclear blood cells, and those carrying it will generally remain asymptomatic.[6] However, HHV-6 has now been recognized as an opportunistic infection in immunocompromised patients, leading to reactivation of the virus.[3] Both HHV-6A and 6B are thought to play a role in development of opportunistic infections in immunocompromised patients.[5] In the setting of immunosuppression, HHV-6 has been recognized to enter reactivation phase and is associated with a wide variety of disease processes, including but not limited to diseases affecting the central nervous system (CNS).[7-9]

Additionally, this patient's CSF contained anti-GD1b antibodies, and in the clinical context, was pointing towards immune-mediated axonal neuropathy. Although anti-GD1b antibodies are most commonly associated with motor-predominant axonal neuropathies such as AMAN, emerging evidence supports their relevance to AMSAN. AMAN and AMSAN are increasingly understood as part of a pathophysiologic continuum, sharing overlapping immunologic profiles and nodal pathology rather than representing distinct entities.[11] Mechanistic studies demonstrate that anti-GD1b antibodies can disrupt nodal function in both motor and sensory fibers, providing a biologic basis for the combined axonal involvement seen in AMSAN.[12] Thus, the presence of anti-GD1b antibodies in this case supports the diagnosis of an axonal Guillain-Barré spectrum disorder involving both motor and sensory fibers.

In two-thirds of cases, GBS is preceded by a prodromal illness, most commonly gastrointestinal or respiratory symptoms.[10] Although noninfectious antecedents such as trauma, surgery, medications (including immune checkpoint inhibitors), and systemic disorders have been reported, infections remain the most common trigger preceding the clinical onset of GBS.[11] GBS can be further categorized into two subtypes: demyelinating, which is by far the most common and represents 85-90% of cases, and axonal forms.[13] Typically, GBS is associated with more motor neuropathy as opposed to sensory and presents with ascending weakness, which is often accompanied by hyporeflexia or areflexia. The presented case had findings consistent with an ascending sensorimotor neuropathy and findings as discussed above, which is most consistent with an acute motor and sensory axonal neuropathy. It is presumed in this case that the GBS was potentially triggered by reactivation of HHV-6 infection. Patients observed to have GBS in the setting of HHV-6 infections often have HHV-6-specific antibodies in their CSF, which is a strong indication of active virus replication within the central nervous system.[2] As mentioned, the patient described was immunocompromised from treatment with TNF-alpha inhibitors, making him more susceptible to reactivation of HHV-6 infection. Of note, there have been prior case reports which described GBS associated with HHV-6 reactivation in immunocompromised hosts, specifically after hematopoietic stem cell transplants.[7,8] GBS in the setting of HHV-6 reactivation is uncommon, and this is the first report of the AMSAN variant of GBS in this setting.

The association between HHV-6 and GBS has not been well studied, and therefore, treatment options are also not well understood.[14] HHV-6 virus has been shown to be effectively treated with ganciclovir, foscarnet, and cidofovir.[15] The patient in this case was started on valganciclovir as opposed to ganciclovir due to concern for toxicity. While IVIG and plasma exchange are typically used in GBS, we did not do so in this case because of the evidence of the HHV6

infection and we elected to treat with antivirals and high dose solumedrol. Steroids have been reported to provide benefit in some cases of inflammatory neuropathies, although their use in GBS remains controversial.[16,17]

Conclusion

While rare, HHV-6 has been observed as a concomitant infection in some GBS cases.[2] However, while HHV-6 has been linked to classic GBS, there has yet to be an identified association between HHV-6 and development of GBS variant disease. We report a case of AMSAN-variant GBS in association with HHV-6 in an immunocompromised patient. The patient received antiviral treatment and high dose steroids with improvement of symptoms.

Citations

1. Continuum (Minneap Minn). Peripheral nerve and motor neuron disorders. *Continuum (Minneap Minn).* 2023;29(5):1327–56. *(PMID not found in PubMed.)*
2. Galvan M, Rotola A, Govoni V, et al. Simultaneous Guillain-Barré syndrome and active human herpesvirus 6 infection in the central nervous system. *J Clin Virol.* 2007;38(3):271–2. doi:10.1016/j.jcv.2006.12.003. PMID: 17222581 dokumen.pub+6pubmed.ncbi.nlm.nih.gov+6scribd.com+6
3. King O, Syed HA, Al Khalili Y. Human herpesvirus 6 [Updated 2025 May 5]. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. Available from: https://www.ncbi.nlm.nih.gov/books/NBK540998/ *(No PMID assigned, as this is an online book chapter.)*
4. Braun DK, Dominguez G, Pellett PE. Human herpesvirus 6. *Clin Microbiol Rev.* 1997;10(3):521–67. *(PMID not retrieved.)*
5. Agut H, Bonnafous P, Gautheret-Dejean A. Update on infections with human herpesviruses 6A, 6B, and 7. *Med Mal Infect.* 2017;47(2):83–91. doi:10.1016/j.medmal.2016.09.004. *(PMID not retrieved.)*
6. Caserta MT, Mock DJ, Dewhurst S. Human herpesvirus 6. *Clin Infect Dis.* 2001;33(6):829–33. doi:10.1086/322691. *(PMID not retrieved.)*
7. Rodriguez V, Kuehnle I, Heslop HE, et al. Guillain-Barré syndrome after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transpl.* 2002;29:515–7. *(PMID not retrieved.)*
8. Tomaszewska A, Nasilowska-Adamska B, Dzieciatkowski T, et al. Simultaneous human herpesvirus 6-associated encephalitis and Guillain-Barré syndrome in a patient after matched unrelated donor haematopoietic stem cell transplantation. *Arch Med Sci.* 2010;6(2):288–90. doi:10.5114/aoms.2010.13912. *(PMID not retrieved.)*
9. Zerr DM, Corey L, Kim HW, et al. Clinical outcomes of human herpesvirus 6 reactivation after hematopoietic stem cell transplantation. *Clin Infect Dis.* 2005;40:932–40. *(PMID not retrieved.)*
10. Doets AY, Verboon C, van den Berg B, et al. Regional variation of Guillain-Barré syndrome. Brain J Neurol 2018;141(10):2866-2877. doi:10.1093/ brain/awy232
11. Kuwabara S, Yuki N. Axonal Guillain-Barré syndrome: concepts and controversies. Lancet Neurol. 2013 Dec;12(12):1180-1188. PMID: 24229616. doi:10.1016/S1474-4422(13)70215-1.
12. Susuki K, Yuki N, Schafer DP, Hirata K, Zhang G, Funakoshi K, Rasband MN. Dysfunction of nodes of Ranvier: a mechanism for anti-ganglioside antibody-mediated neuropathies. Exp Neurol. 2011 Dec 8;233(1):534-542. PMID: 22178332. doi:10.1016/j.expneurol.2011.11.039.
13. Habib AA, Waheed W. Guillain-Barré syndrome. *Continuum (Minneap Minn).* 2023;29(5):1327–56. doi:10.1212/CON.0000000000001289. *(PMID not found.)*
14. Sokolovska L, Cistjakovs M, Matroze A, et al. From viral infection to autoimmune reaction: Exploring the link between human herpesvirus 6 and autoimmune diseases. *Microorganisms.* 2024;12(2):362. doi:10.3390/microorganisms12020362. PMID: 38399766 continuum.aan.com+1pubmed.ncbi.nlm.nih.gov+1
15. Prichard MN, Whitley RJ. The development of new therapies for human herpesvirus 6. *Curr Opin Virol.* 2014;9:148–53. doi:10.1016/j.coviro.2014.09.019. *(PMID not retrieved.)*
16. Hughes, R. A., Brassington, R., Gunn, A. A., & van Doorn, P. A. (2016). Corticosteroids for Guillain-Barré syndrome. *The Cochrane database of systematic reviews*, *10*(10), CD001446. https://doi.org/10.1002/14651858.CD001446.pub5
17. van Lieverloo, G. G. A., Peric, S., Doneddu, P. E., Gallia, F., Nikolic, A., Wieske, L., Verhamme, C., van Schaik, I. N., Nobile-Orazio, E., Basta, I., & Eftimov, F. (2018). Corticosteroids in chronic inflammatory demyelinating polyneuropathy : A retrospective, multicentre study, comparing efficacy and safety of daily prednisolone, pulsed dexamethasone, and pulsed intravenous methylprednisolone. *Journal of neurology*, *265*(9), 2052–2059. https://doi.org/10.1007/s00415-018-8948-y

Motor Neuron Disease

A lecture from the Neuromuscular Review Course

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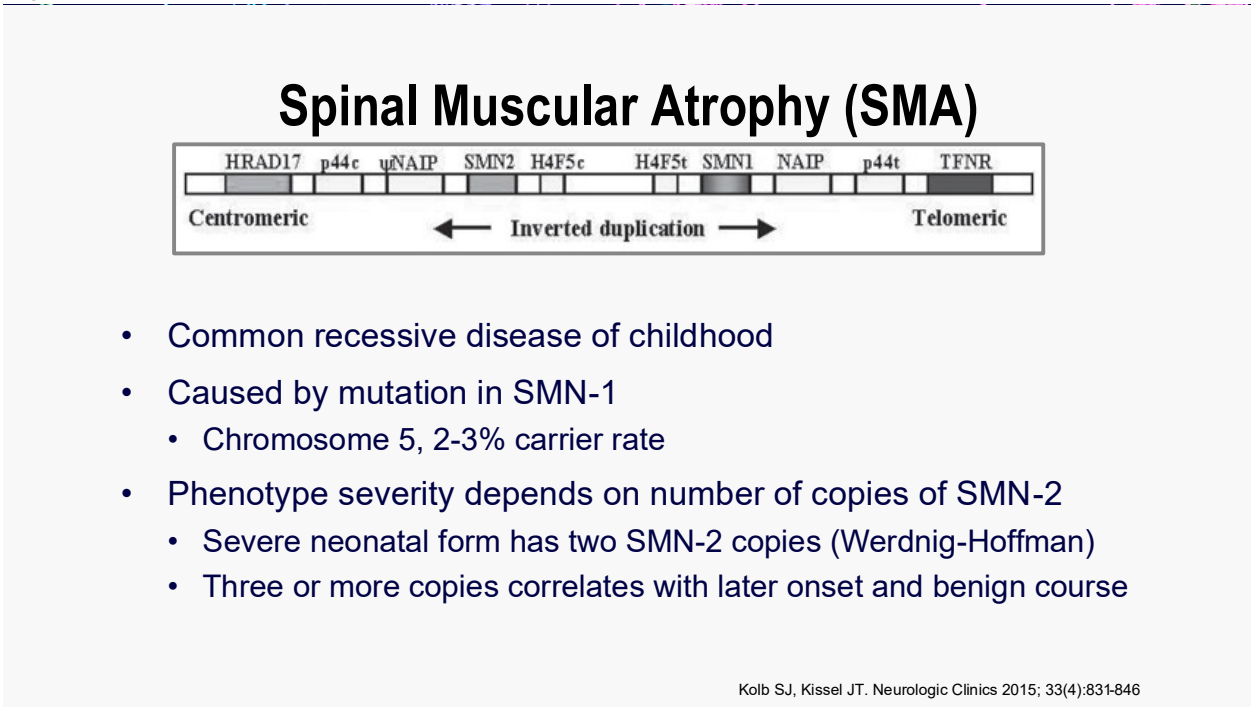
Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is an autosomal recessive, predominantly childhood disease due to a mutation in the SMN-1 gene on chromosome 5.

Figure 1

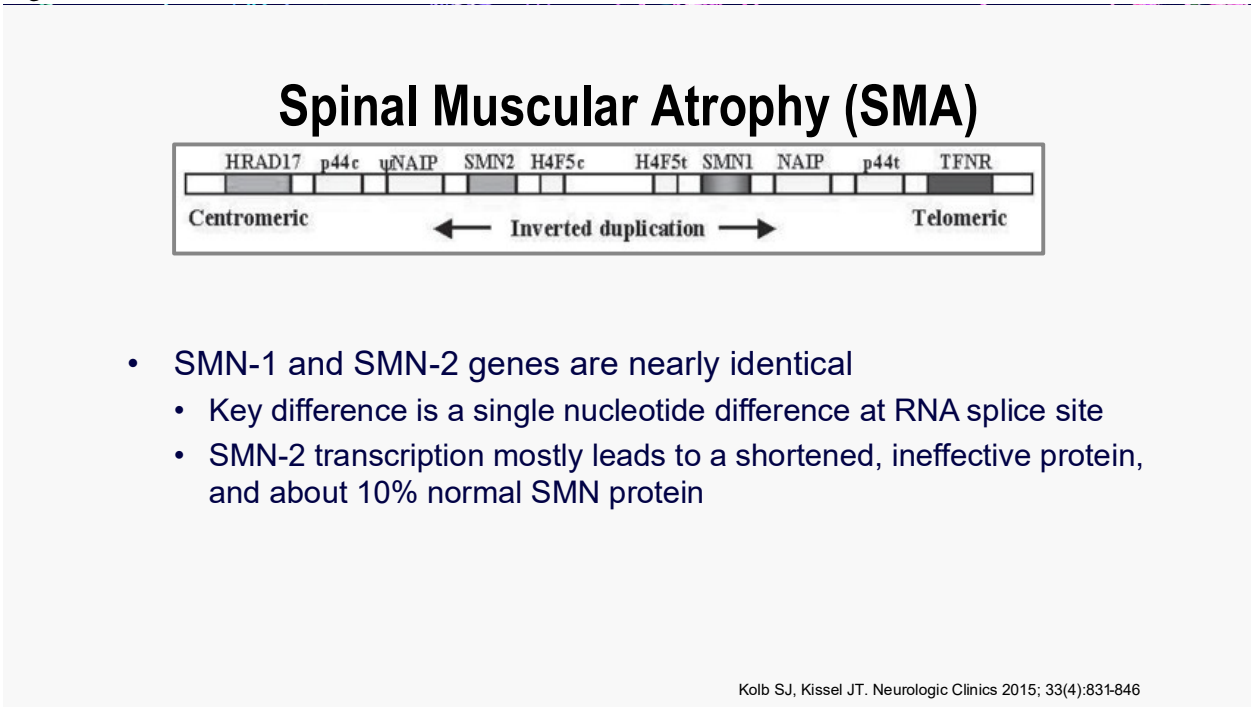


The SMN-1 gene is located in the inverted region of chromosome 5 and has a carrier rate of 2–3%. Before the gene was identified, the diagnosis was clinical, with supportive information from electromyography (EMG) and muscle biopsy. Infants were described as “floppy babies” who would not live through the first year of life. Historically, the infantile form of SMA was referred to as Werdnig-Hoffman disease. Later childhood and adult forms were also identified in the pre-genetic era.

The phenotype for most SMA patients, whether infants, children, or adults, is symmetric proximal and distal pure motor weakness without sensory loss, which corresponds to the neuropathic pattern 7 (NP7) phenotype (Barohn et al., 2024, 2025).

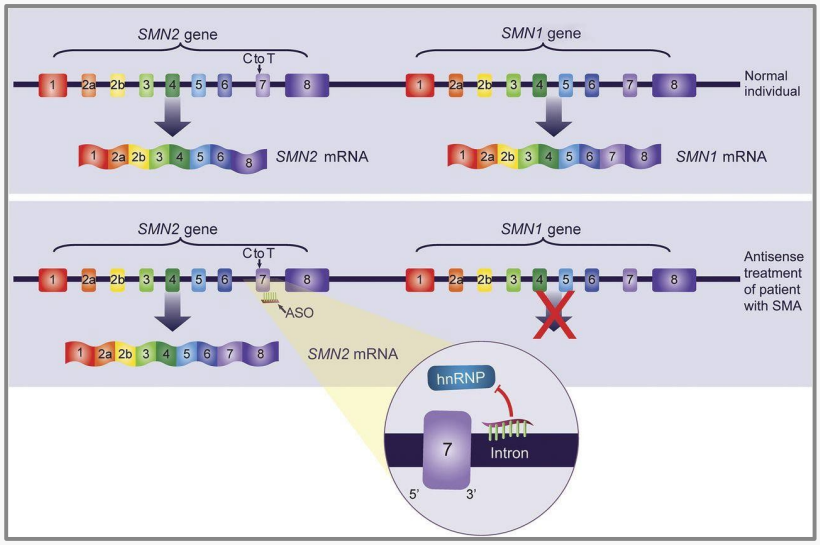
When the gene was discovered in 1995, two genes encoding the same protein were identified in the same region: SMN-1 and SMN-2 (Lefebvre et al., 1995). These genes differ by a single nucleotide at an RNA splice site. As a result, the SMN-2 gene produces a shortened and largely ineffective protein with only minimal activity.

Figure 2



All patients with autosomal recessive SMA have a mutation in the SMN-1 gene, but patients may have multiple copies of the SMN-2 gene. The severity of the phenotype depends on the number of SMN-2 copies present. Fewer copies (1 or 2) lead to a severe, usually infantile phenotype. Patients with 3 to 5 copies of the SMN-2 gene have a less severe phenotype because they produce more of the ineffective protein, which delays or mitigates clinical severity.

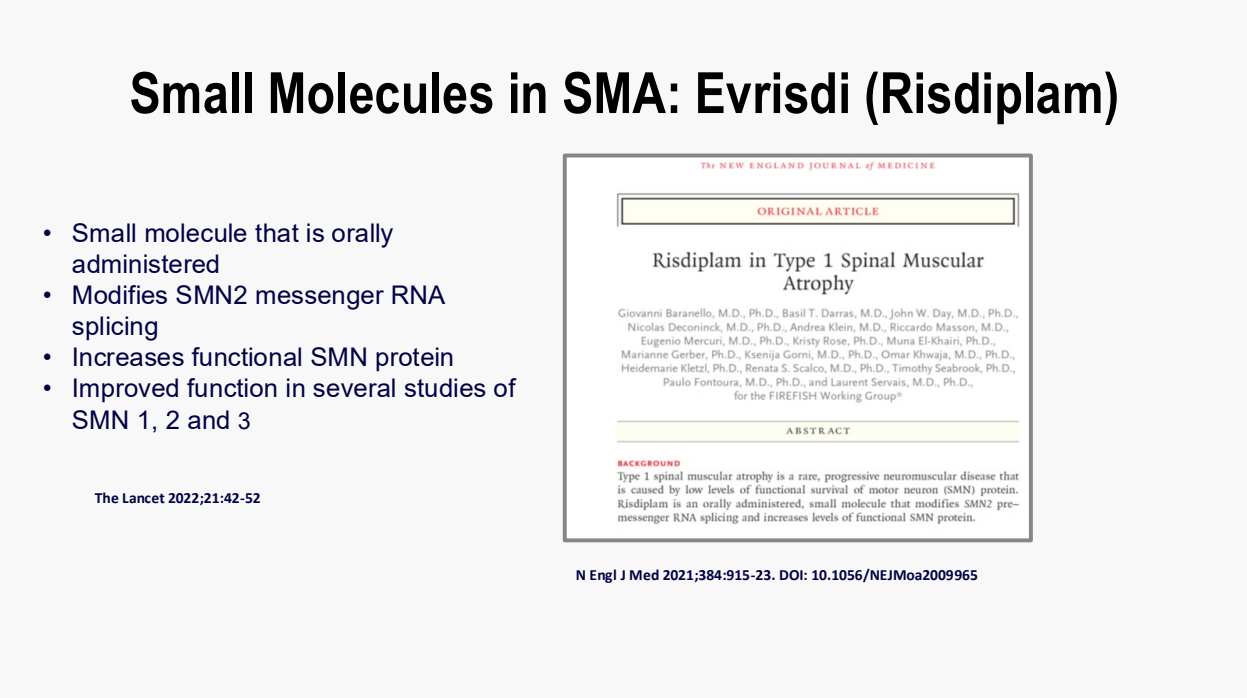
Figure 3



https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm534611.htm

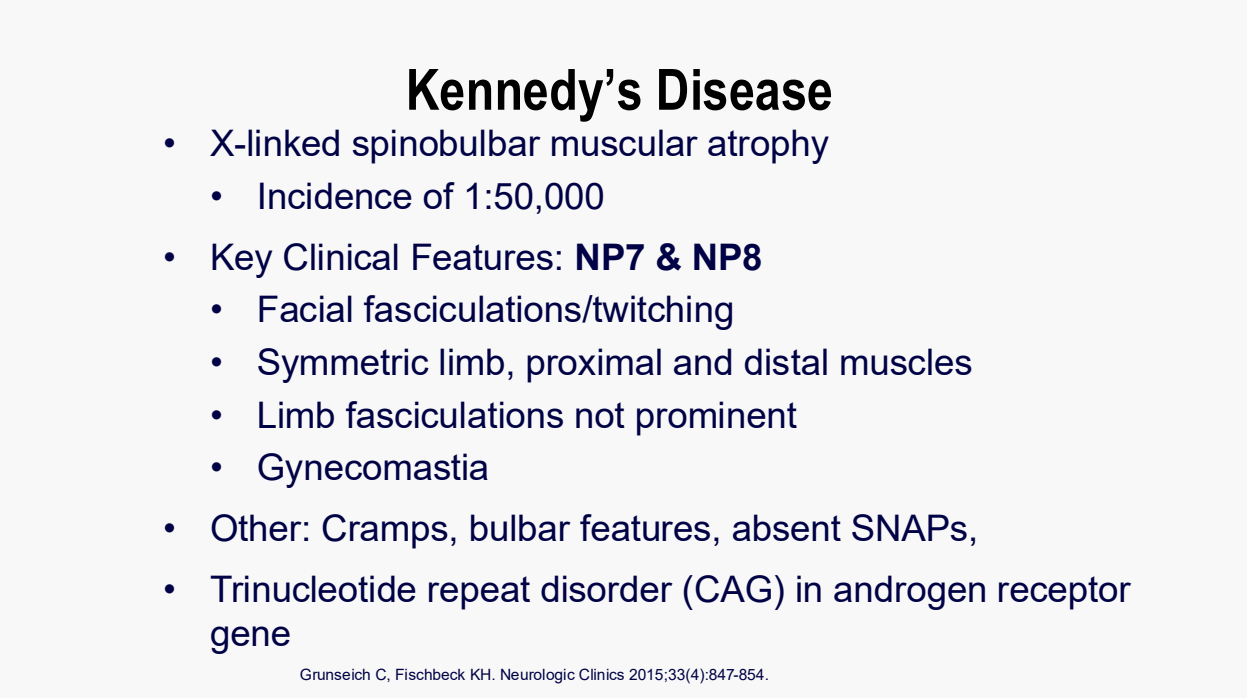
The first breakthrough therapy for SMA was an antisense oligonucleotide drug called nusinersen (Finkel et al., 2016). Nusinersen promotes increased protein production by modifying SMN-2 gene splicing, increasing functional SMN protein levels. This therapy works by converting a severe phenotype into a more benign one.

Figure 4



Nusinersen is administered intrathecally. Subsequently, an oral therapy that modifies SMN-2 messenger RNA and increases functional SMN protein production was FDA-approved. This drug is called evrysdi (Risdiplam). Antisense therapy was followed by gene replacement therapy, onasemnogene abeparvovec (Zolgensma), which was approved by the FDA in 2019 (Mendell et al., 2017).

Kennedy's Disease
Figure 5

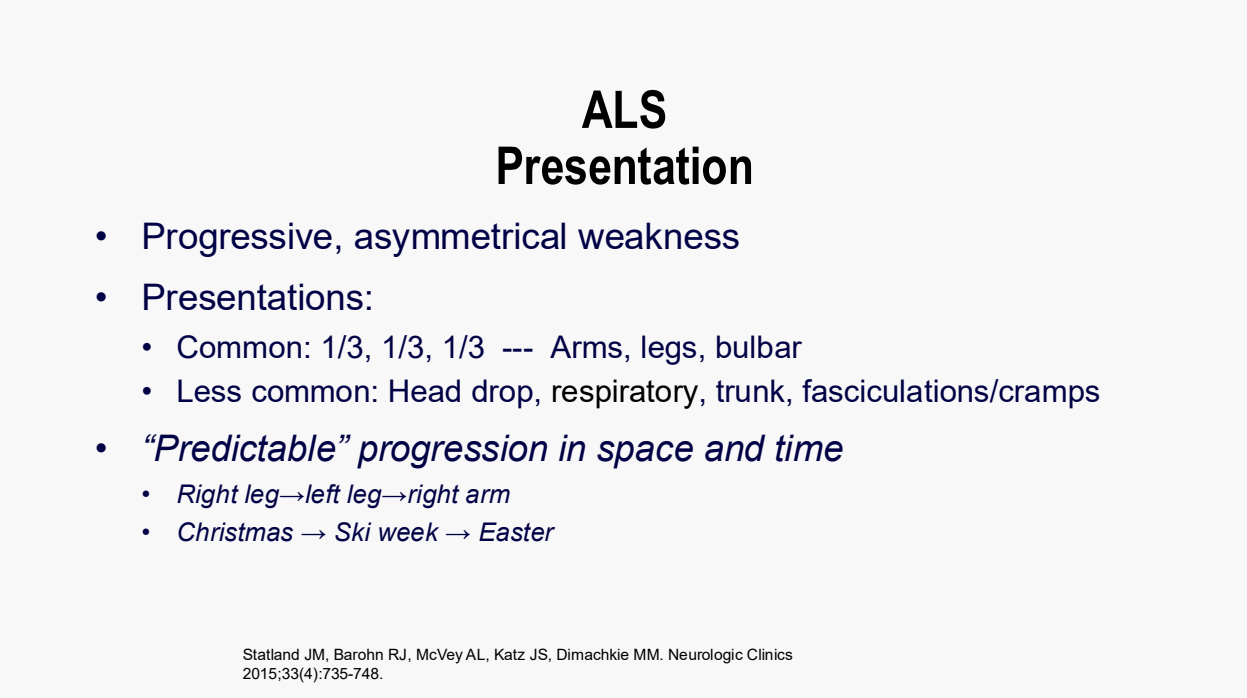


Kennedy's disease is an adult-onset spinal muscular atrophy that affects only men because the affected gene is located on the X chromosome (Grunseich & Fischbeck, 2015; La Spada et al., 1991). It is also referred to as spinal bulbar muscular atrophy, although the severity of bulbar involvement is variable. Kennedy's disease is rare, with an estimated prevalence of 1 in 50,000. It presents with proximal and distal pure motor weakness along with some degree of bulbar involvement, usually consisting of tongue or facial muscle atrophy, fasciculations, and dysarthria. Because of the combination of extremity and bulbar involvement, this condition falls into both the NP7 and NP8 categories.

Kennedy's disease is slowly progressive. Patients often do not know the exact date of onset owing to the extremely insidious progression. They typically present to clinic after gradual worsening begins to affect daily activities and function. The disease is frequently diagnosed when a patient presents with symmetric extremity weakness and additional features such as perioral muscle twitching or gynecomastia is identified. This constellation of findings should prompt the clinician to order genetic testing for Kennedy's disease.

These patients may also complain of muscle cramps and symptoms of laryngospasm. Interestingly, although they have no sensory symptoms or signs, they can have absent sensory nerve action potentials (SNAPs). The underlying mutation is an increased number of trinucleotide repeats in the androgen receptor gene. At this time there is no FDA-approved therapy for Kennedy's disease.

Amyotrophic Lateral Sclerosis
Diagnosis of ALS
Figure 6



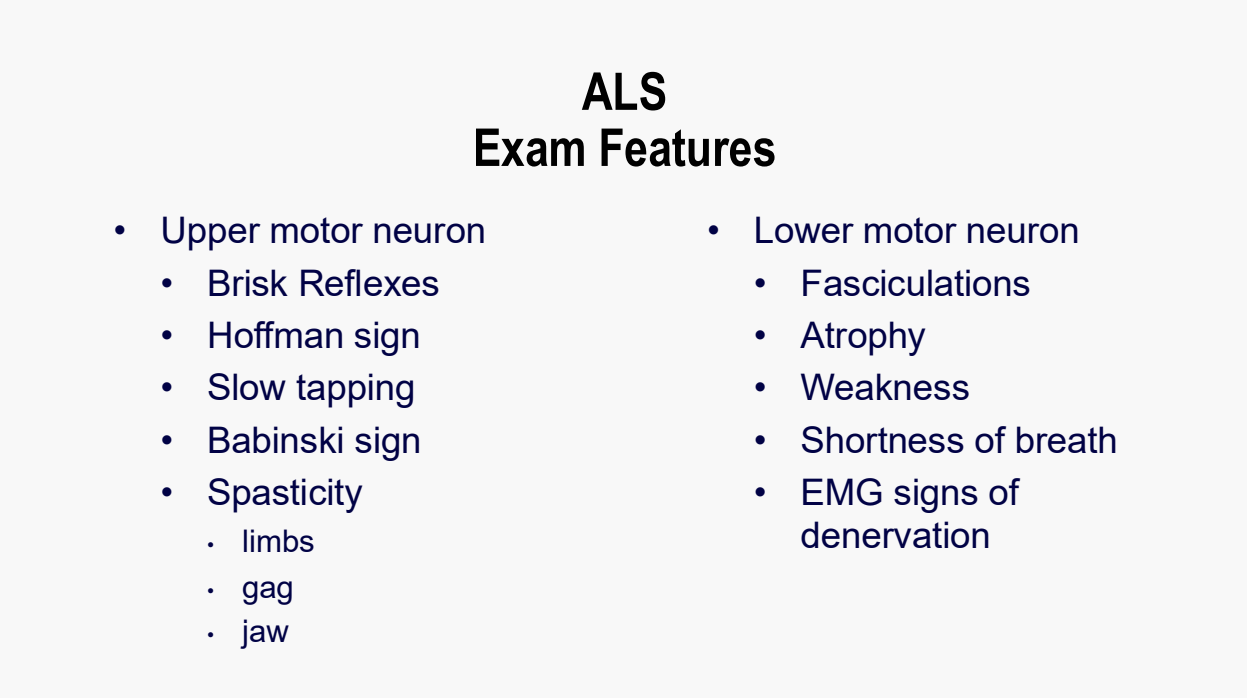
Amyotrophic lateral sclerosis (ALS) is usually an easy diagnosis for a neurologist to make clinically, based on history and exam. Diagnostic consideration frequently begins while listening to the history of progressive weakness that spreads in a predictable pattern. The approximate date and location of onset are the first two key questions to ask. In general, approximately one-third of cases begin in the arms, one-third in the legs, and one-third in the bulbar region. A smaller percentage of cases presents with head drop, respiratory symptoms and signs, or trunk weakness. Only rarely do patients initially present with fasciculations.

The spread of ALS is characteristically predictable. For example, if symptoms begin in the right leg, weakness will almost always appear next in the left leg. When such a case spreads to the arms, the right arm will usually be affected first. Recognizing this predictable pattern of progression increases diagnostic suspicion, and the neurologic examination should be directed toward identifying weakness in regions suggested by the history.

The primary lower motor neuron signs include weakness, atrophy, and fasciculations (Figure 7). Fasciculations may be the most important diagnostic clue, and patients should be undressed and examined in a hospital gown to allow inspection of proximal muscles. Fasciculations frequently occur in proximal arm and leg muscles and may be missed without appropriate examination. Fasciculations are present in nearly all cases of ALS, but their detection requires focused observation.

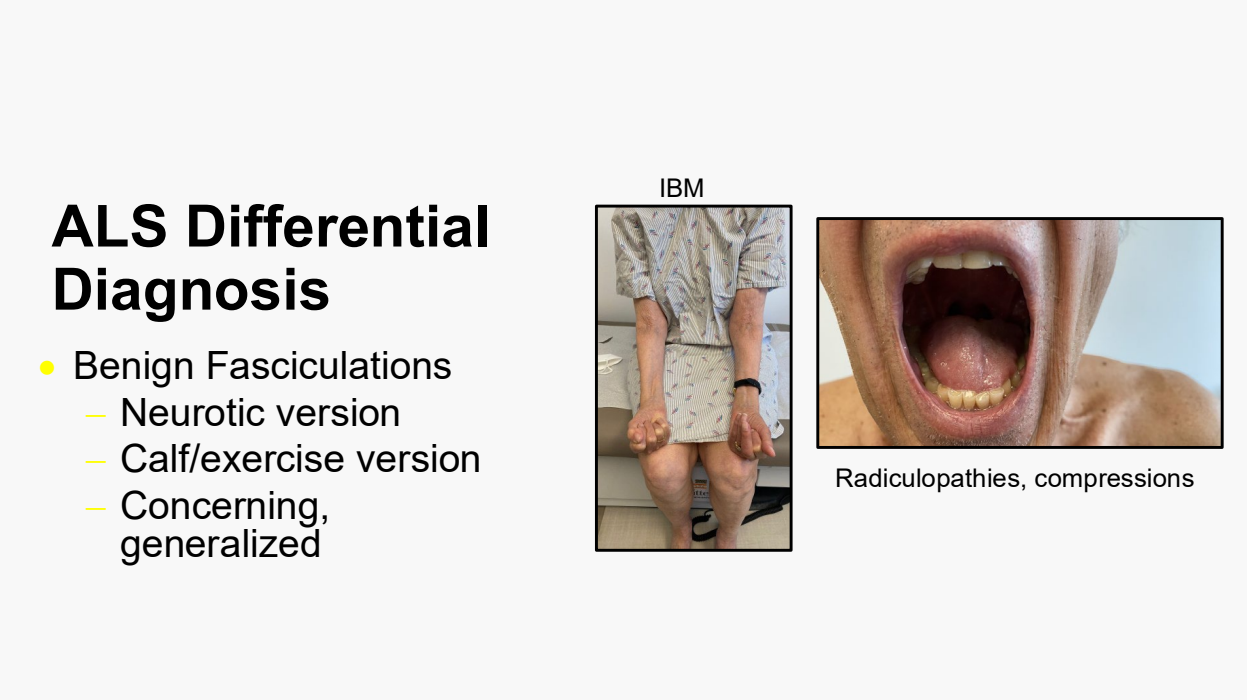
In ALS, upper motor neuron signs are often more subtle than those seen in stroke, multiple sclerosis, or other disorders with predominant corticospinal tract involvement.

Figure 7



Increased tone and Babinski signs are usually absent early in the disease and may never develop in some patients. In contrast, subtle and typically asymmetric findings—such as Hoffman signs, crossed adductor responses or other examples of reflex spread—are often present, making it important for the clinician to actively search for these signs. Asymmetric slowing of finger or foot tapping are other useful indicators of upper or lower motor neuron involvement. Side-to-side comparison of limbs is essential to identify subtle differences.

Differential Diagnosis
Figure 8



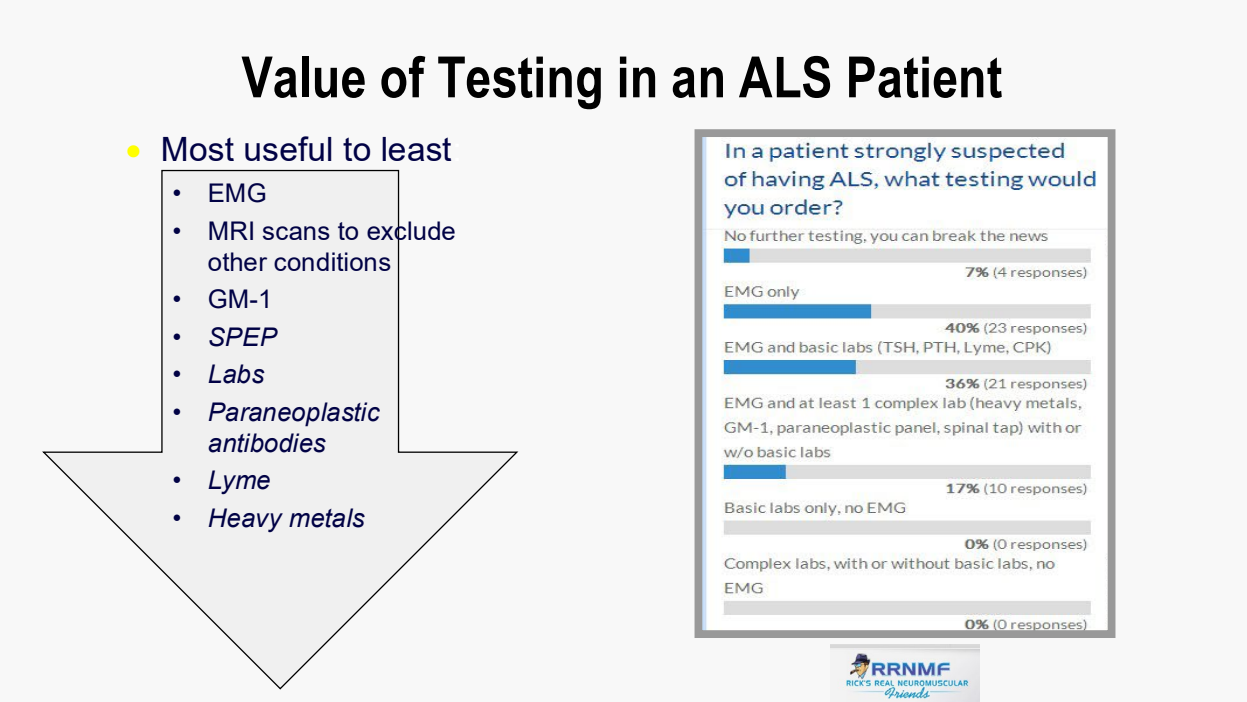
Benign fasciculations are an extremely common complaint and can cause significant anxiety. We recognize three distinct benign fasciculations syndromes. The first involves patients who experience random twitches in facial or extremity muscles. They often become anxious after searching the internet. In these cases, it is important to address anxiety and reassure patients that they do not have an underlying neuromuscular disease. The second category includes patients who experience fasciculations after exercise, most commonly affecting the calf muscles. The third category includes patients with intense, generalized fasciculations that resemble those seen in ALS, but who lack other features of the disease, including weakness or upper motor neuron signs. Although a small number of these patients may later develop ALS, most do not. In such cases, alternative diagnoses such as Isaacs' syndrome should be considered, though a specific cause is often not identified. These patients may require follow-up examinations every few months for a year or longer to ensure that ALS is not evolving.

One condition that can present with focal pure motor weakness and fasciculations is radiation-induced neuropathy. This may involve limb muscles or the tongue. A history of cancer treated with radiation therapy, lack of progression to other regions, and absence of upper motor neuron signs distinguish this condition from ALS.

Myelopathy due to spinal cord compression or other causes can also rarely produce fasciculations that may be mistaken for ALS. Conversely, with limb-onset ALS, patients are often referred to a spine surgeon before seeing a neurologist. As a result, many undergo multiple MRI scans and sometimes surgical

procedures before the correct diagnosis is made. In these cases, symptoms typically progress following surgery, indicating the need to reconsider the original diagnosis.

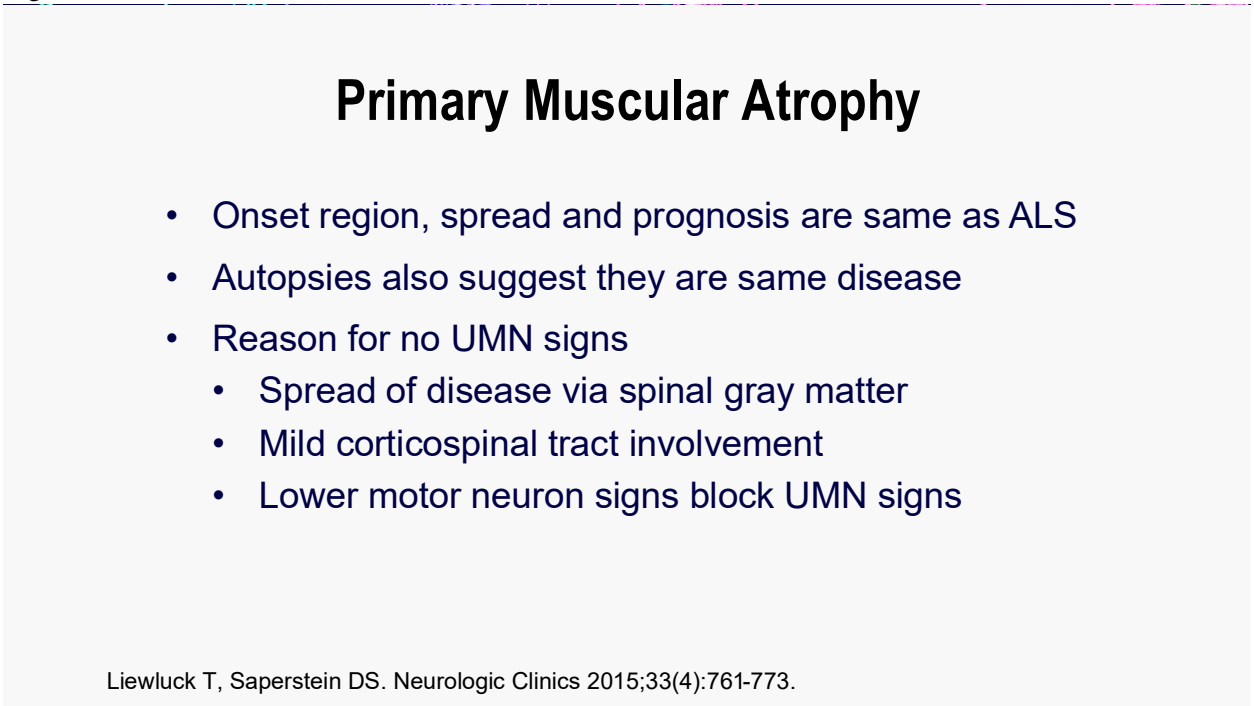
The Value of Testing in ALS
Figure 9



In our experience, clinicians can often be confident in the diagnosis of ALS without electromyography (EMG); however, this rarely occurs in current neurology practice. Laboratory testing is likely to have limited value once the physician recognizes ALS from the history and physical examination. Many patients with ALS have a mildly elevated creatine kinase (CK), but this is non-specific. We believe there is an over-reliance on EMG to make the diagnosis of ALS. EMG is done in most patients during the evaluation, but the diagnosis should be clear from the history and physical examination. In a small number of cases, demonstrating denervation in limb muscles that are not weak can help the clinician increase their diagnostic confidence about the diagnosis of ALS. If weakness in a muscle is detected on examination, demonstrating denervation potentials—fibrillations and often fasciculations—actually adds little to the diagnosis. On the other hand, EMG can also be useful for identifying denervation in thoracic paraspinous muscles, which cannot be examined for weakness in the same way as limb muscles. Very few other conditions produce denervation in thoracic paraspinous muscles.

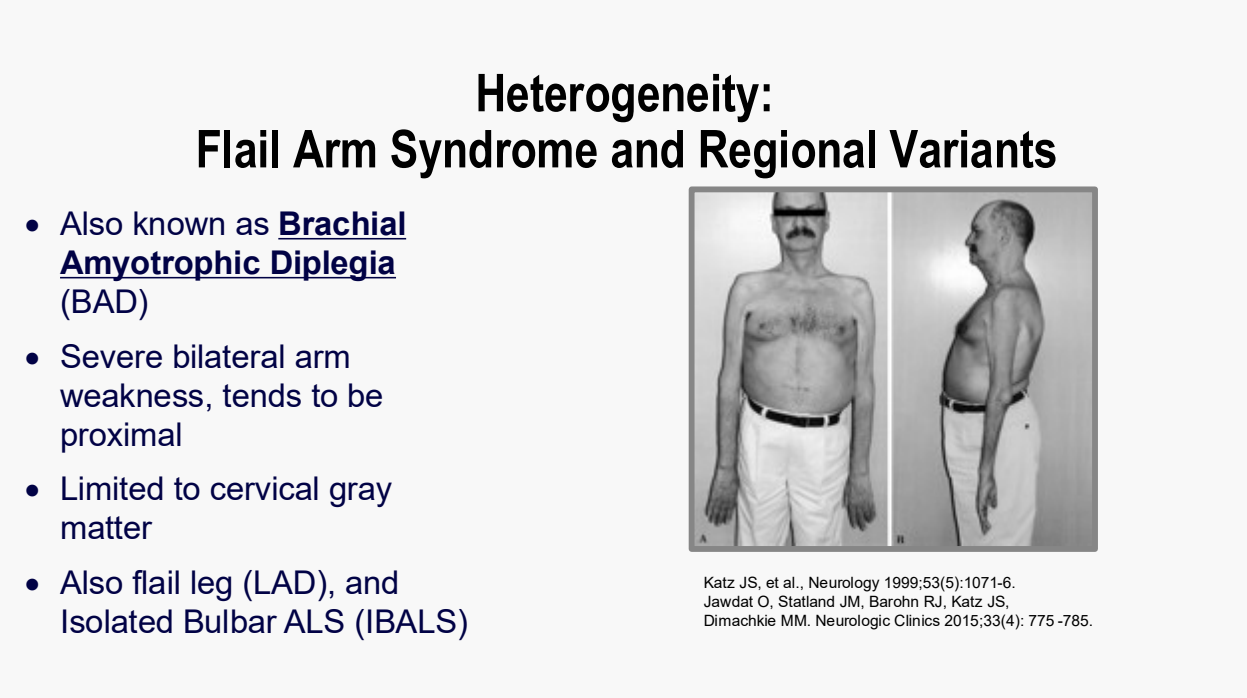
Similar to EMG, we believe magnetic resonance imaging (MRI) is over-utilized in typical cases of ALS. MRI is not necessary when ALS affects multiple regions (bulbar and limb) but can be useful when the clinical findings have a specific localization. For example, if a patient has a focal anatomical pattern such as lower motor neuron signs in the arms and upper motor neuron findings in the legs, without bulbar symptoms or signs, a cervical spine MRI may be helpful.

Figure 10



Primary muscular atrophy (PMA) is the lower motor neuron variant of ALS. We consider PMA to be essentially the same disease as ALS, but without upper motor neuron findings on physical examination. The regions of onset (one-third arm, one-third leg, one-third bulbar) and the pattern of spread are identical to those seen in typical ALS. Although the implication of a PMA diagnosis is that only gray matter is pathologically involved, autopsy studies often reveal abnormalities in the corticospinal and corticobulbar upper motor neuron tracts. Potential explanations that may account for the absence of upper motor neuron signs on examination include that upper motor neuron tracts are not degenerating rapidly or severely enough to produce clinical signs. Additionally, if lower motor neuron involvement occurs first and is marked by significant atrophy, weakness, and reduced movement, upper motor neuron signs may be difficult or impossible to detect on examination.

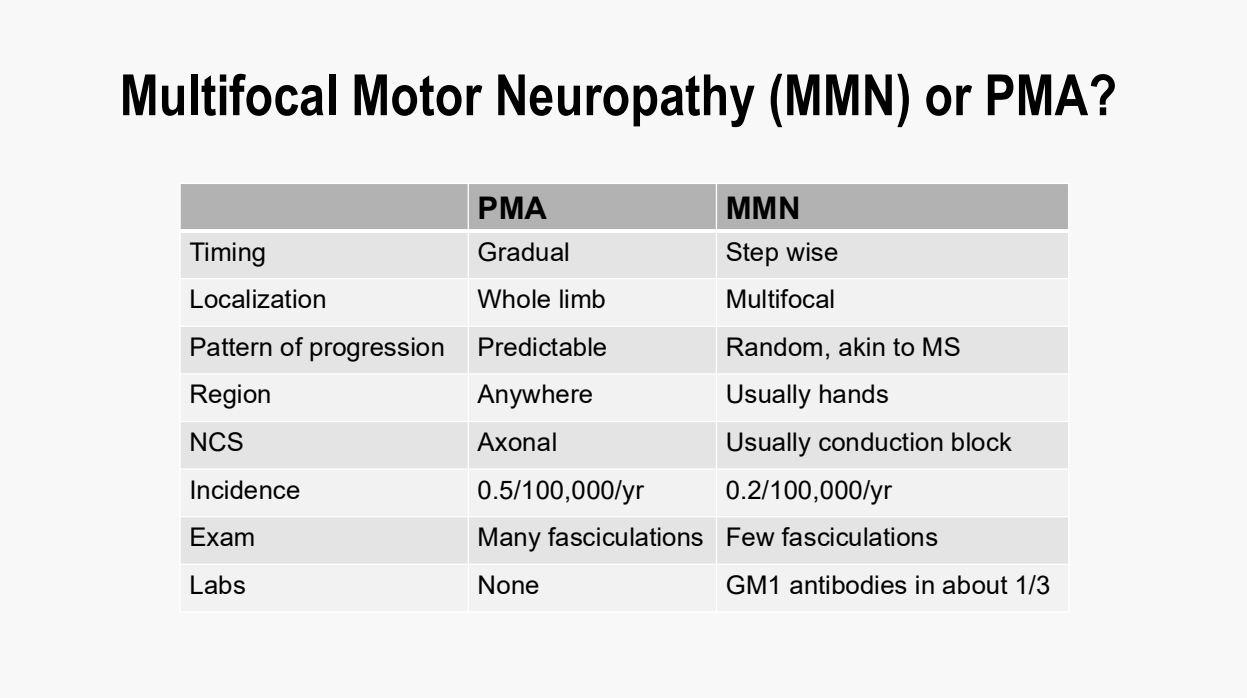
Regional Lower Motor Neuron Variants of PMA
Figure 11



A subset of patients have pure lower motor neuron involvement that begins in one arm and spreads to the contralateral arm without involvement of the legs, neck, or bulbar muscles. We have termed this condition brachial amyotrophic diplegia (BAD), while a British group has referred to it as flail arm syndrome. The general consensus is that a patient can be categorized as having BAD only after there has been no progression to the legs or bulbar muscles for at least two years, at which point the prognosis may be more favorable than that of typical PMA or ALS. Most patients with BAD eventually do show involvement in other regions. Overall survival can be five to ten years, or even longer.

We have also described a comparable regional variant that remains confined to the legs for at least two years, which we have termed leg amyotrophic diplegia (LAD); this is referred to as flail leg syndrome by British authors (Dimachkie et al., 2013; Jawdat et al., 2015). Rarely, we have observed patients in whom the disease remains confined to the arms or legs for decades without spreading to other regions.

Differentiating PMA from Multifocal Motor Neuropathy (MMN)
Figure 12



In contrast to ALS, PMA must be distinguished from multifocal motor neuropathy (MMN) due to the shared features of weakness and lack of upper motor neuron signs. PMA tends to demonstrate a very predictable and gradual pattern of spread, as discussed above. In contrast, MMN often progresses in a stepwise fashion, involving distal extremity muscles, in which a particular muscle group may become affected relatively quickly without further weakness developing in the remainder of the limb (Dimachkie et al., 2013; Saperstein et al., 1999; Stino et al., 2025). MMN also shows a degree of randomness in its involvement of nerves and the muscles they innervate. For example, left hand weakness may be followed by right foot weakness. A discerning clinician may note selective muscle sparing in MMN, such as ulnar nerve involvement without median nerve involvement in the same limb. MMN almost always affects the hands initially, may never progress to the legs, and does not involve bulbar muscles. Finally, PMA is far more common than MMN.

Nerve conduction studies should also differentiate these two conditions. MMN typically demonstrates demyelinating features on motor nerve conduction studies, which may include partial conduction block, temporal dispersion, or slowed conduction velocities. In rare cases, a very proximal lesion in MMN may result in only downstream axonal damage being evident, making electrophysiologic evidence of demyelination difficult to identify. We have referred to cases with no clear evidence of focal demyelination—many of which ultimately respond to immunoglobulin therapy—as multifocal acquired motor axonopathy (MAMA).

Respiratory Presentation of ALS
Figure 13

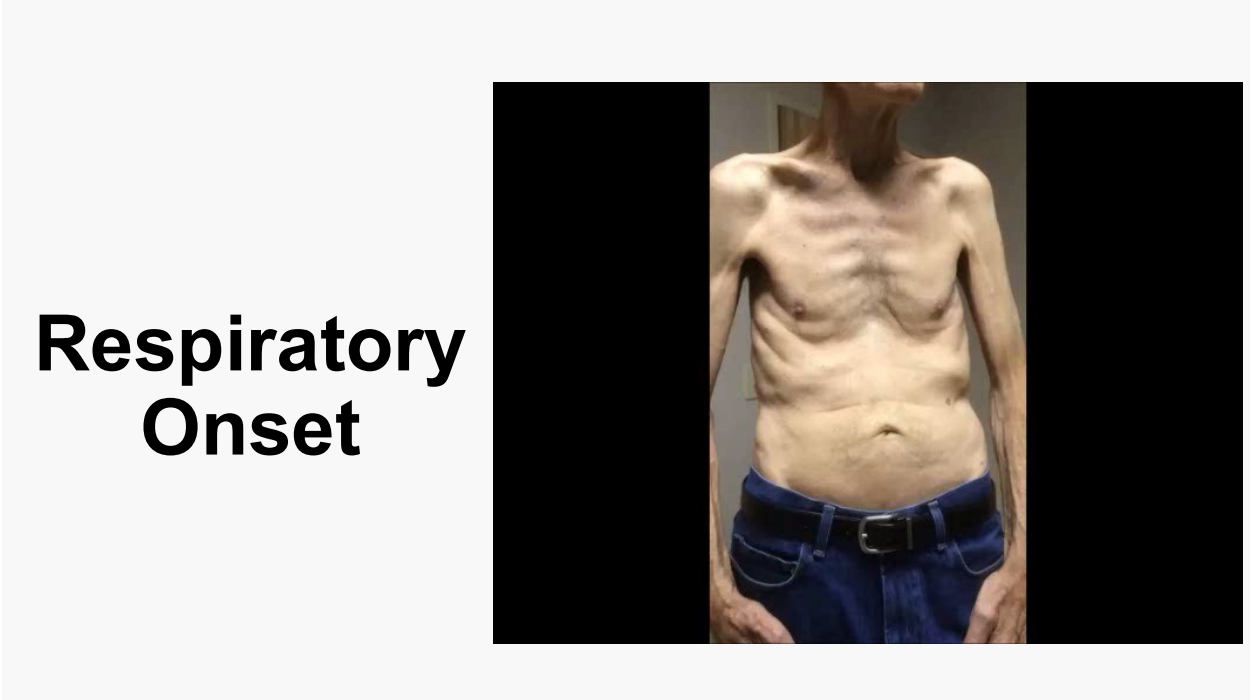
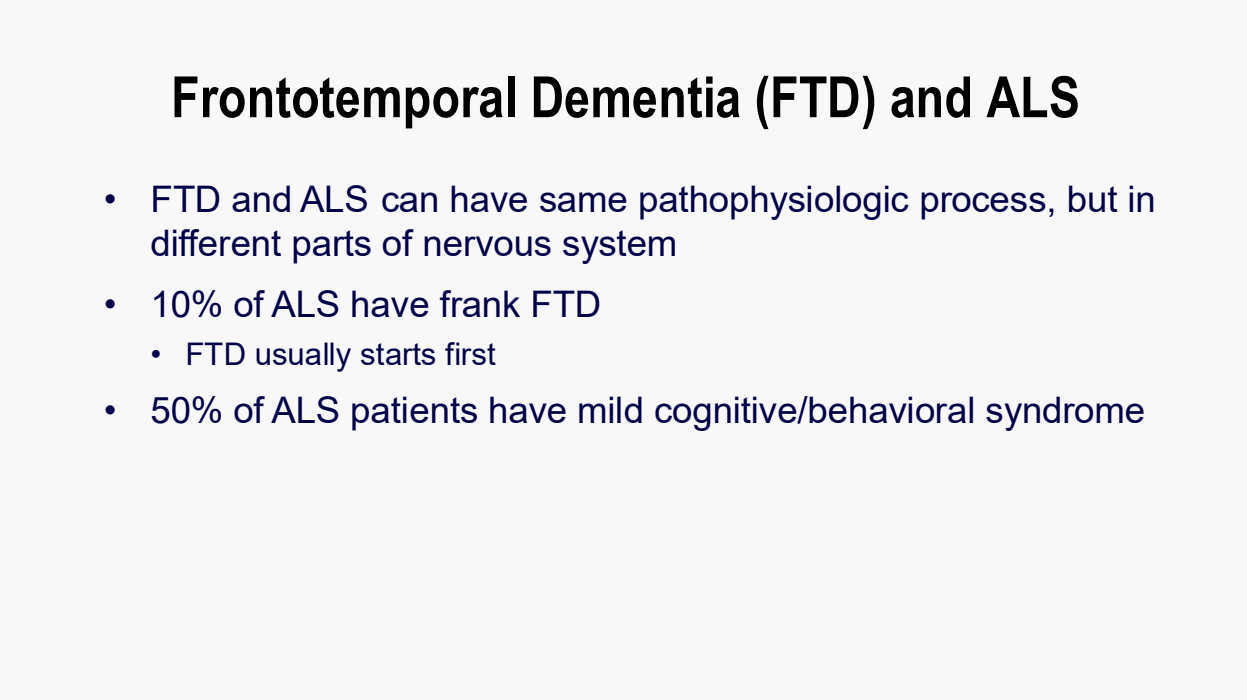


Figure 13 illustrates respiratory-onset ALS, showing atrophied intercostal muscles with relative sparing of the limbs. The respiratory presentation also indicates that there is diaphragmatic muscle weakness. Fasciculations are evident in the chest wall but not in the arms. These patients have a characteristic clinical presentation that often does not initially include neurological complaints. The first symptom is usually weight loss, likely due to inefficient breathing and loss of appetite. Because patients often present to their physicians for evaluation of weight loss, they may undergo extensive cancer and malnutrition workups before it is recognized that they have a respiratory problem. Weight loss and decreased appetite frequently begin before the forced vital capacity (FVC) has declined substantially.

Other symptoms may include frequent nighttime awakenings related to respiratory compromise from the combination of diaphragmatic weakness and REM sleep, during which accessory breathing muscles become paralyzed. Patients sometimes think they are awakening due to urinary frequency, which mistakenly raises the question of urologic problems. The variability of these symptoms can result in multiple referrals over several months before the patient is evaluated by a neurologist. Not surprisingly, some patients progress to advanced respiratory failure and admission to intensive care units before ALS is recognized.

ALS with Cognition Changes
Figure 14



Frontotemporal dementia (FTD) and ALS represent the same disease process affecting different regions of the nervous system (Woolley & Strong, 2015). Both disorders have pathology with misfolded aggregated TDP-43 protein in neurons and glia. Approximately 10% of ALS patients have frank FTD. FTD may begin in the right hemisphere with behavioral abnormalities or in the left hemisphere with aphasia. A key historical clue is that the spouse does most of the talking while the patient appears inattentive due to disinhibition or language problems. The patient may frequently stand up, walk around the room, or behave inappropriately. Other times, it may appear that the patient does not understand what is being said, and in some cases, the patient is frankly aphasic.

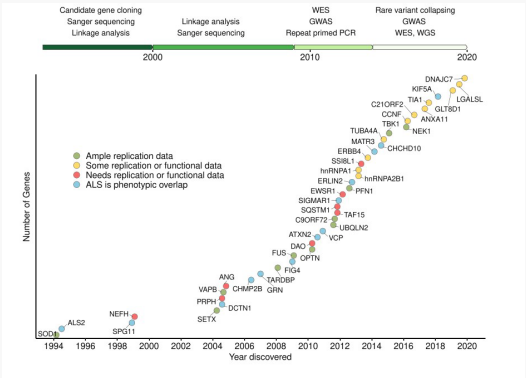
ALS patients with FTD may also develop apraxia of the mouth and oral musculature and be unable to speak, even though facial and tongue strength appear normal on examination. In addition, another 40% of ALS patients have some degree of cognitive impairment that can be diagnosed by neuropsychological testing but do not have any overt cognitive symptoms. Recognizing FTD in ALS patients is critical because it is associated with a poor prognosis and significantly alters how spouses and caregivers must manage the disease.

Genetics of ALS

Figure 15

ALS Genetics

- More than 40 associated genes today
  - Risk factor for developing sporadic ALS
  - Direct cause of pathology
  - Modifier of disease course
- FUS
  - Early onset, severe
  - Antisense proving beneficial
- TARDBP
  - Produces TDP-43 protein aggregates



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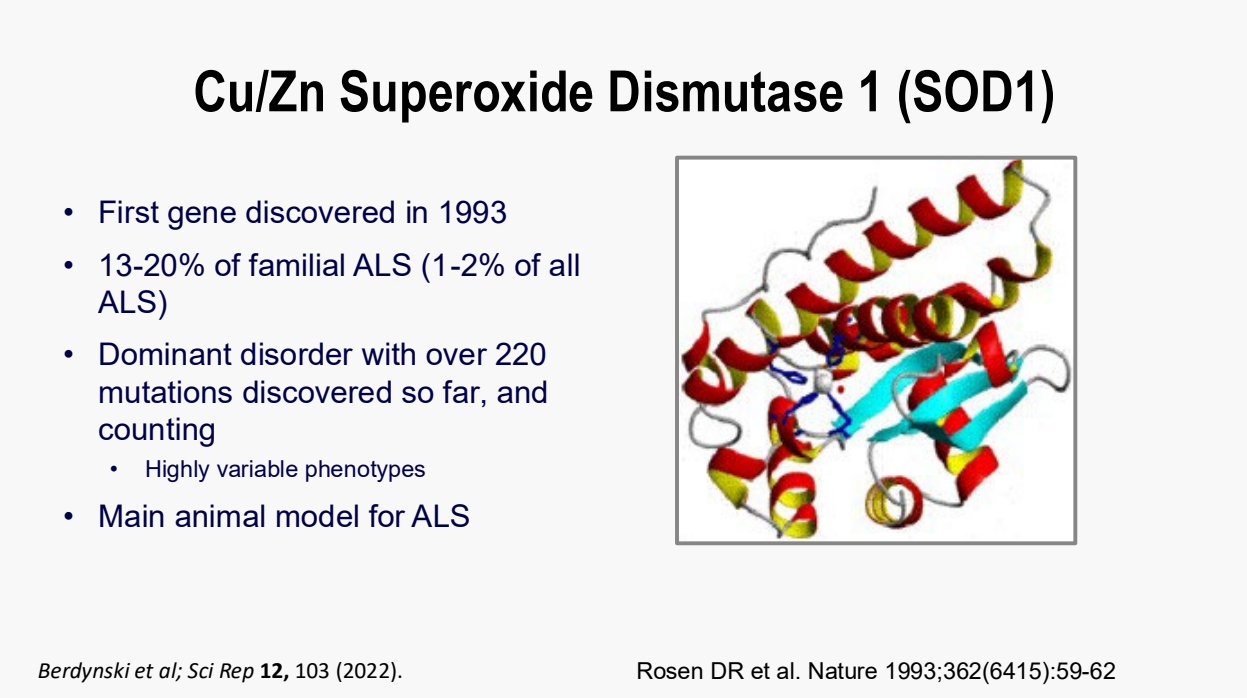
Approximately 30-40 causal or risk-modifying gene mutations have been identified in ALS. The two most common mutations are in the SOD1 gene and the C9ORF72 gene SOD1 mutations account for the majority of familial autosomal dominant ALS cases (Boylan, 2015; DeJesus-Hernandez et al., 2011; Rosen et al., 1993).

Figure 16



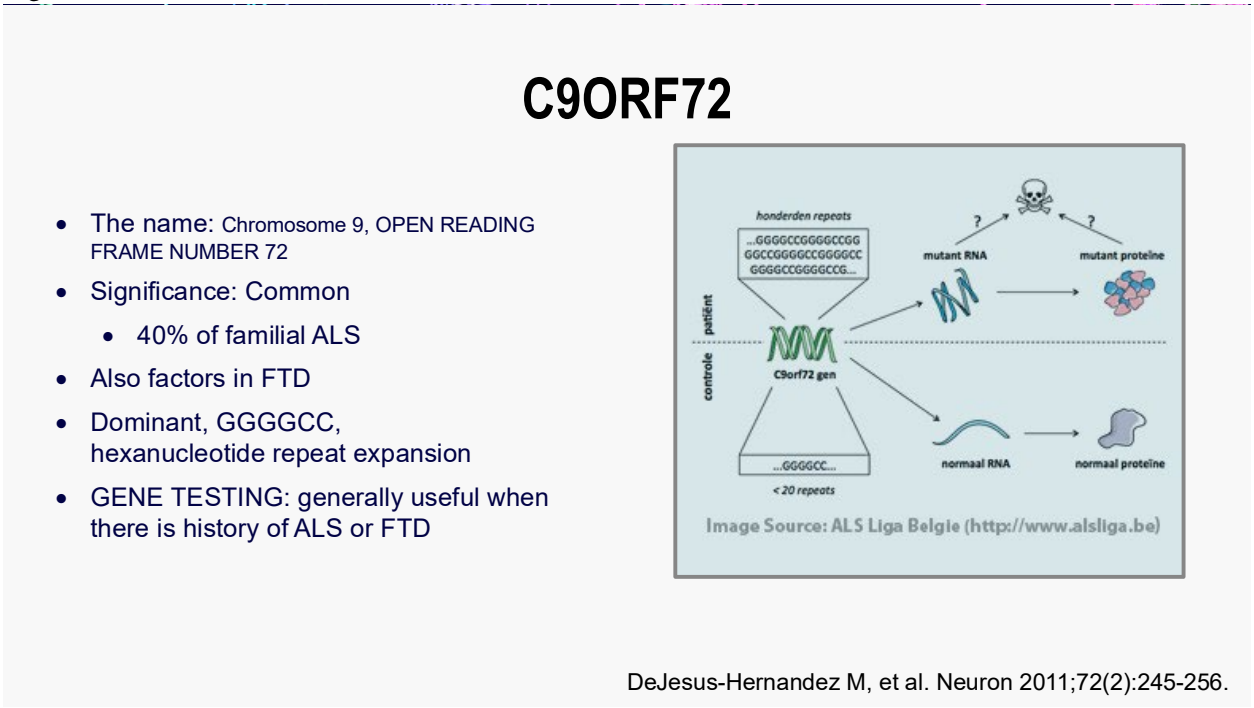
Approximately 10% of all ALS patients have familial autosomal dominant disease and up to 20% of these patients have SOD1 mutations. Therefore roughly 2% of all ALS patients harbor a SOD1 mutation.

SOD1 mutations were the first genetic abnormalities identified in ALS in 1993 (Rosen et al., 1993). More than 200 mutations in the SOD1 gene have been described, most of which are missense variants. Some mutations are associated with aggressive disease, while others produce a relatively mild phenotype. The A4V mutation is notable for being both common and associated with a rapidly progressive form of ALS.

The principal animal model used in ALS research is based on SOD1 mutations. However, patients with SOD1 mutations develop misfolded SOD1 protein aggregates, whereas other genetic and sporadic forms of ALS typically demonstrate aggregates of TDP-43. Notably, many therapeutic agents that have shown efficacy in SOD1 mouse models have not been effective in human ALS. An exception is the drug tofersen (See below). This discrepancy suggests that the SOD1 mouse model may not be an ideal preclinical model for studying potential treatments for human ALS.

Another gene of major importance is the C9ORF72 gene, located on chromosome 9 (chromosome 9 open reading frame 72).

Figure 17



DeJesus-Hernandez M, et al. Neuron 2011;72(2):245-256.

This mutation represents the most common genetic cause of ALS, occurring in approximately 50% of familial ALS cases and about 7% of all ALS cases. The disorder is caused by a hexanucleotide repeat expansion on chromosome 9. Frontotemporal dementia (FTD) is also caused by mutations in the same gene, and both degenerative disorders share TDP-43 pathology.

Families in which some members have FTD and others have ALS are highly likely to harbor a C9ORF72 mutation. For example, we have observed identical twin brothers where one presented with FTD and the other with ALS within the same year.

Caring for the Patient with ALS
Figure 18

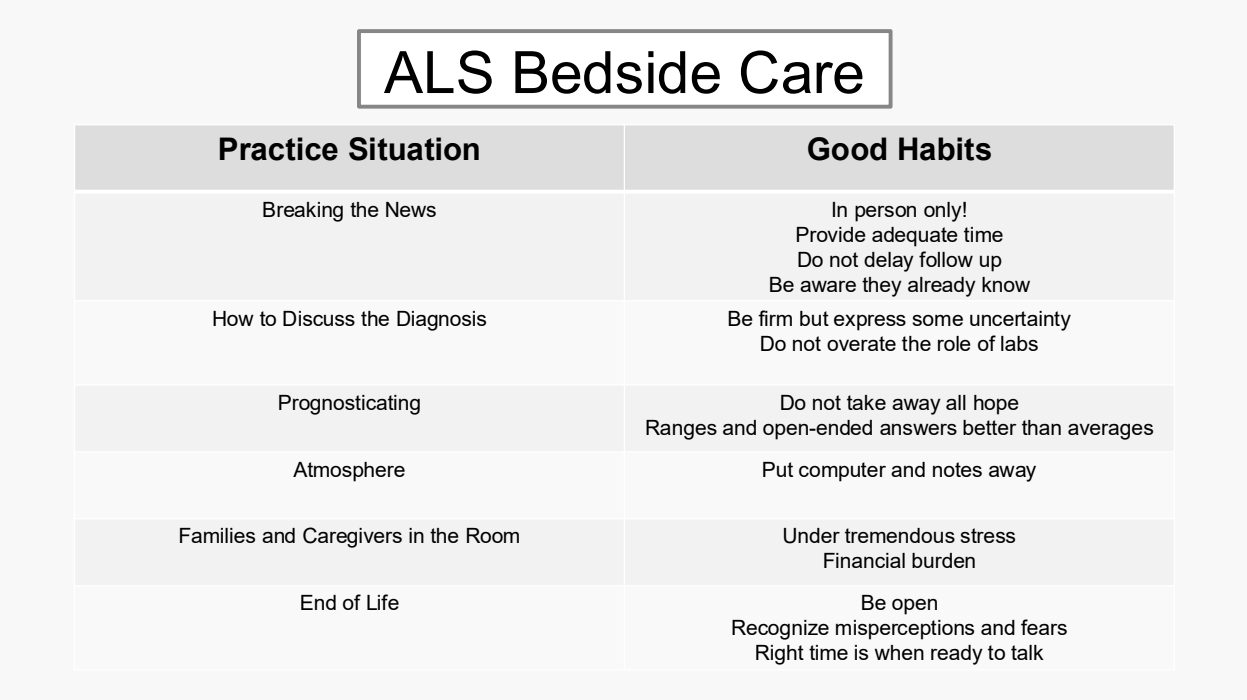


Figure 18 highlights practical considerations regarding communication with patients and families at the time of an ALS diagnosis. It is important that sufficient time is allocated when first informing the patient and family of the diagnosis. The clinician should clearly explain why ALS is the correct diagnosis and avoid overemphasizing the role of prior or future laboratory testing. Instead, patients and families should understand that the diagnosis is based predominantly on symptoms and physical examination findings, and that only ALS produces this specific constellation of features.

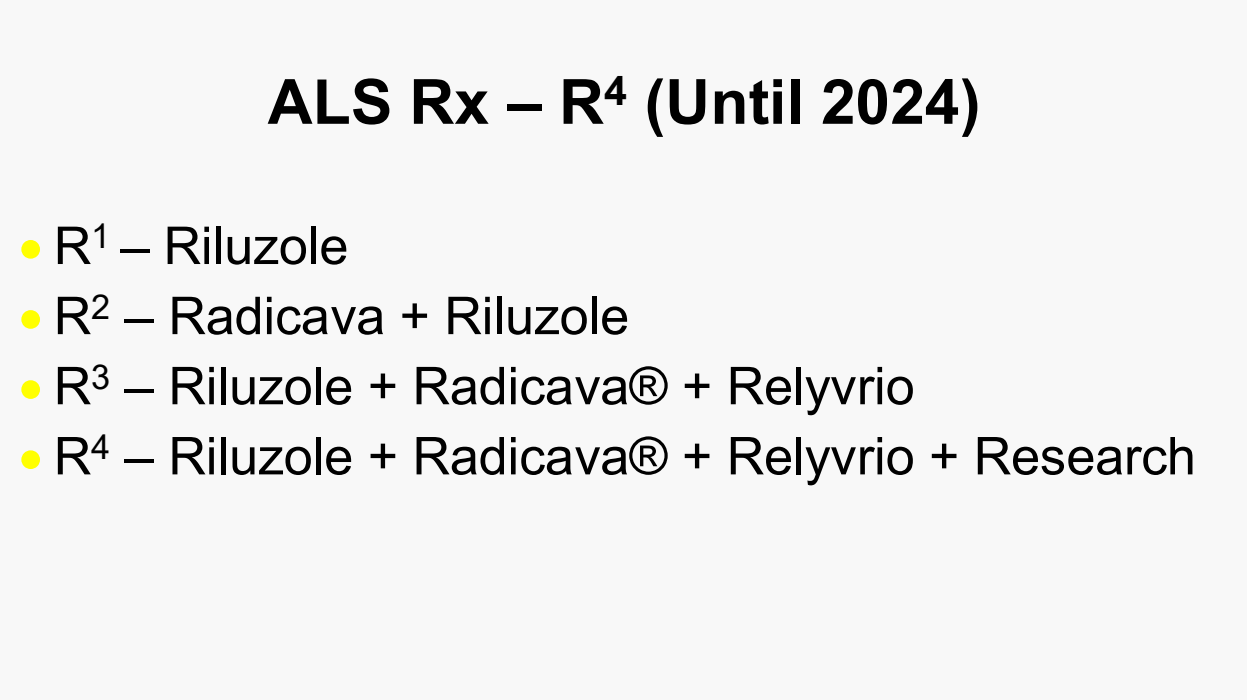
With regard to prognosis, we explain that although approximately half of patients die from the disease within three to five years, some will live longer and a few will live much longer. We stress that the prognosis in an individual patient cannot be determined at the time of diagnosis and often requires an additional six to twelve months of follow-up. Thus, while receiving the diagnosis of ALS is ominous for the patient and family, they can benefit from having hope that perhaps they will have a slower-than-typical course. The multidisciplinary teams that make up ALS clinics often serve to support patients and families as they gradually come to terms with the implication of the diagnosis.

Although it is ultimately important to discuss end-of-life issues, including advance directives and decisions regarding do-not-resuscitate and do-not-intubate orders, these topics should not be addressed during the initial visits. However, it is the responsibility of the ALS physician to ensure that these discussions occur at the appropriate time as the disease progresses, which in some cases may be years after the initial diagnosis (Jackson et al., 2015).

Approach to the Management and Treatment of ALS

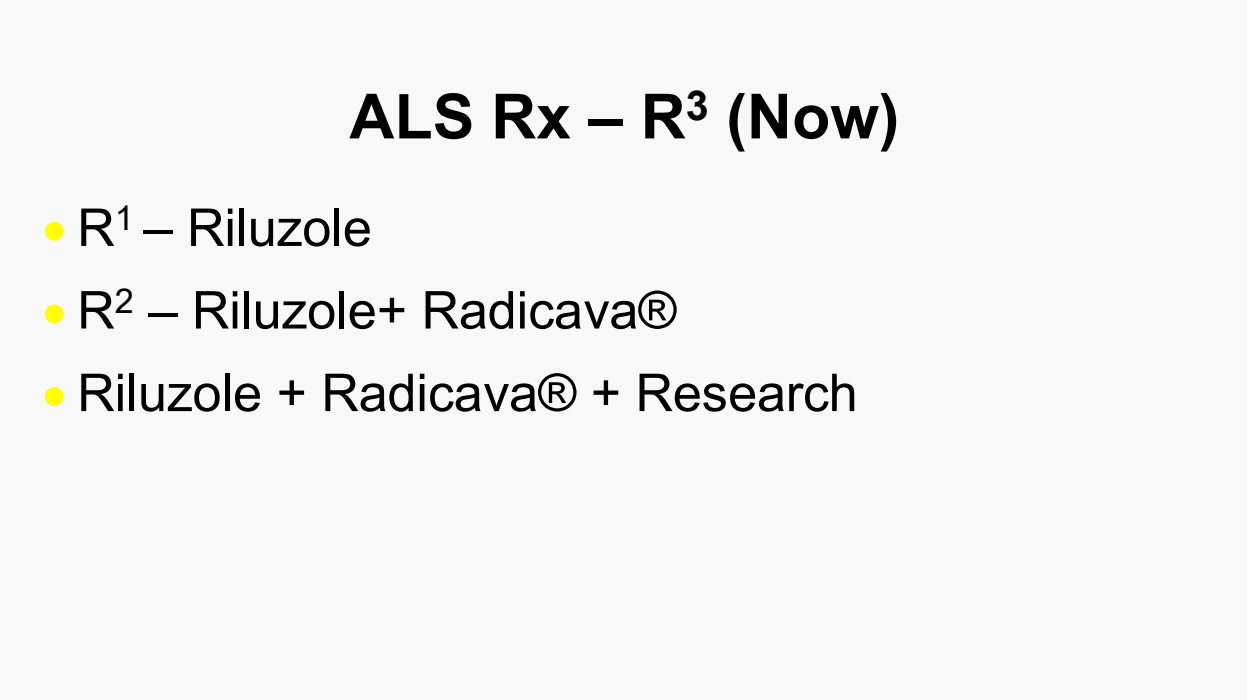
Until 2024, we used the R^4 approach to ALS management. This stands for Riluzole, Radicava, Relyvrio, and Research (Figure 19).

Figure 19



However, in 2024, the FDA withdrew its approval of Relyvrio, and we have since returned to the R^3 approach (Figure 20). The Relyvrio story will be discussed near the end of this treatment section.

Figure 20



Riluzole (trade name Rilutek), a glutamate inhibitor, was the first medication approved for the treatment of ALS (Figure 21) (Lacomblez et al., 1996). It received FDA approval in the 1990s after studies demonstrated that patients taking riluzole had longer survival compared with those receiving placebo. Riluzole is taken twice daily and, very rarely, can affect liver enzyme levels.

Figure 21

Riluzole
Effect on Survival

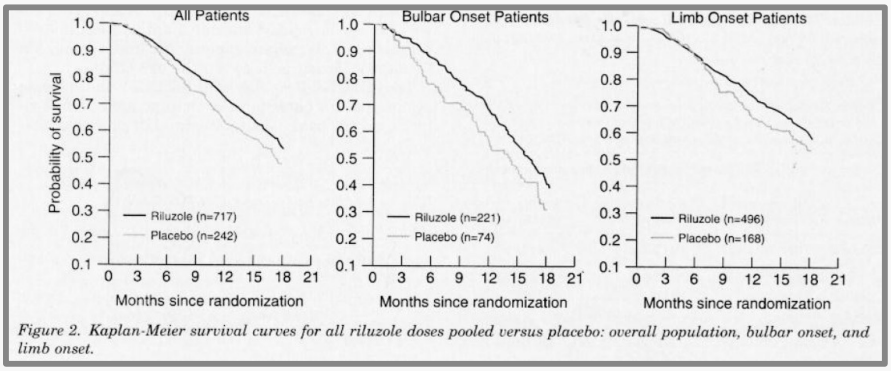


Figure 2. Kaplan-Meier survival curves for all riluzole doses pooled versus placebo: overall population, bulbar onset, and limb onset.

Lacomblez L et al, Lancet 1996 May 25;347(9013):1425-31

Radicava was the next drug approved for ALS (Figure 22) (Writing Group on Behalf of the Edaravone ALS 19 Study Group, 2017). The generic name for Radicava is edaravone.

Figure 22

Radicava® (edaravone)

- A free radical scavenger used in stroke since early 2000s
  - IV infusion: 10 of 14 days on/ 14 days off
- Two trials:
  - Initial trial found trends of efficacy over six months
    - Result was not significant due to slow progressors
  - Pivotal trial in more than 130 patients using very specific criteria found significant result

Edaravone is a free radical scavenger that has been used intravenously in Japan for many years in the treatment of acute ischemic stroke. The initial trial of edaravone in ALS showed a trend toward efficacy but did not reach statistical significance. Based on a subgroup analysis, the investigators hypothesized that the study had failed because it included too many slow progressors for a six-month trial duration. A second trial was designed using very specific inclusion criteria to exclude slow progressors and found that edaravone reduced the rate of functional decline by approximately 33% compared with placebo (Figure 23). The FDA approved edaravone for the treatment of ALS based on the results of the second trial (Figure 24). Notably, this is believed to be the first instance in which the FDA approved a drug without any trial participants from the United States.

Figure 23

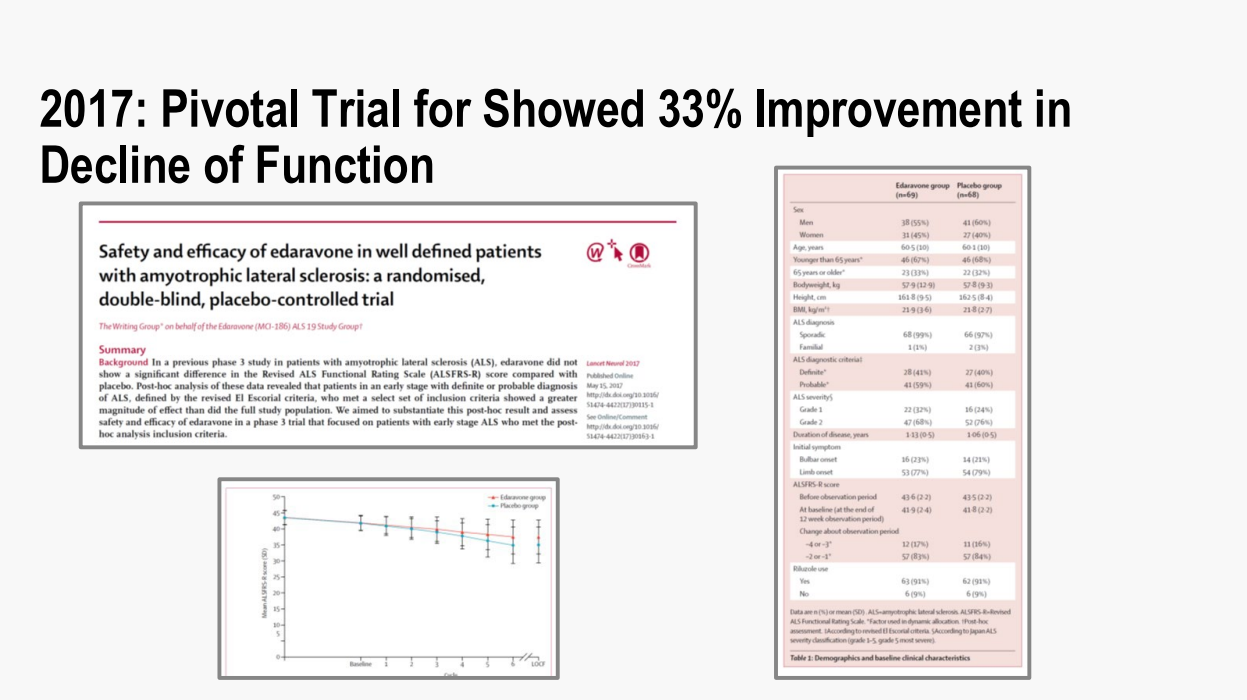
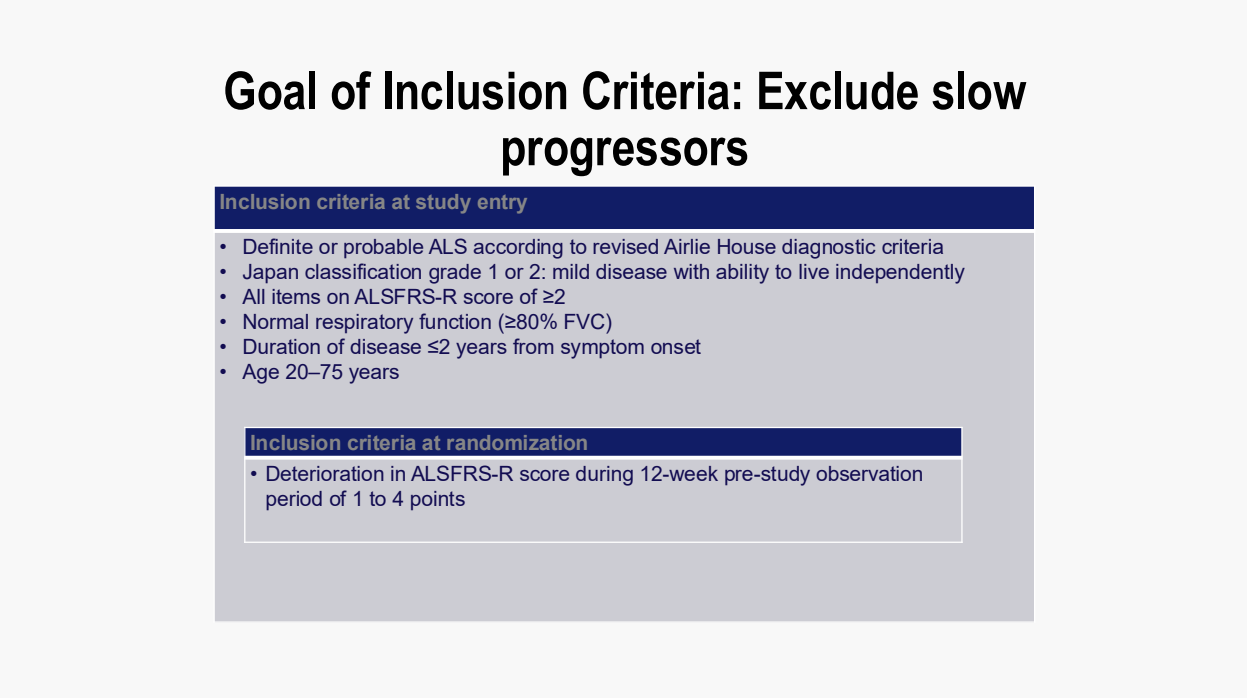


Figure 24



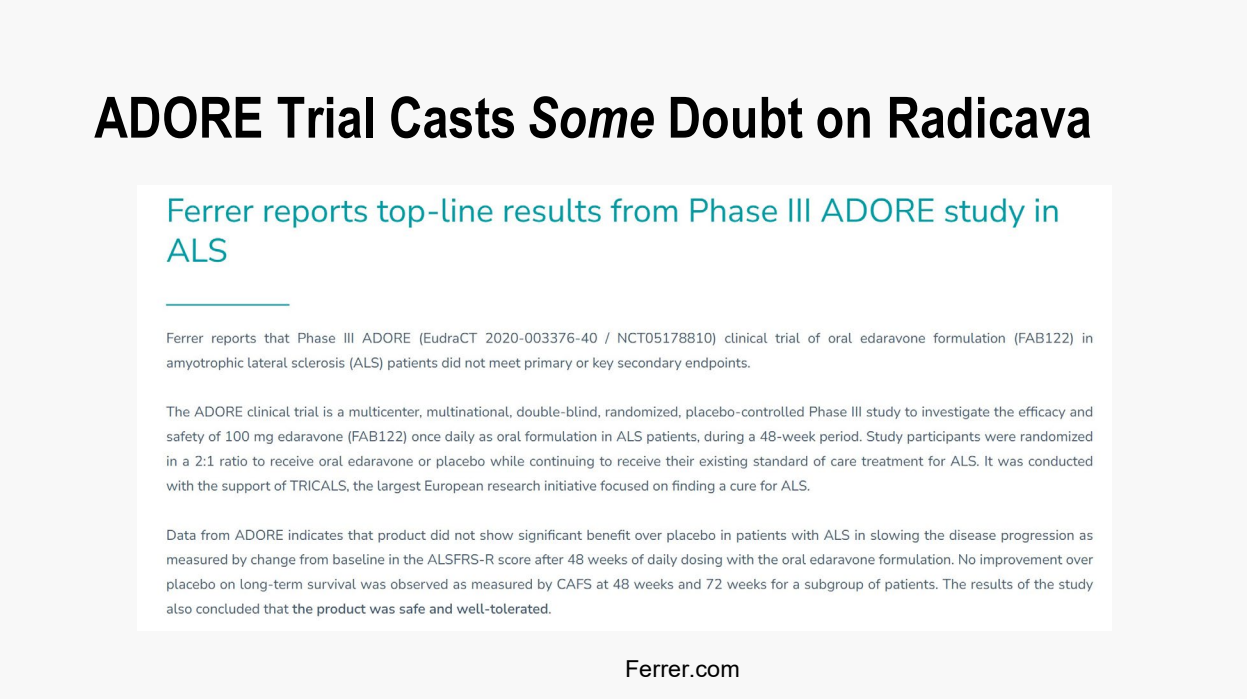
Patients enrolled in the edaravone trials were already receiving riluzole, suggesting that the benefit of edaravone may be additive when used in combination with riluzole. The original trials used an intravenous formulation. Subsequently, the manufacturer developed an oral formulation and demonstrated that the oral preparation had pharmacodynamic properties similar to the intravenous formulation. As a result, edaravone is now administered as an oral suspension, taken 10 out of every 28 days, following the same dosing schedule as the original intravenous trials.

The definitive edaravone study focused on a very narrow population of ALS patients in their effort to exclude slow progressors. The goal was to enroll patients who were likely to demonstrate measurable progression over a six-month period. To accomplish this, investigators designed entry criteria to avoid both floor and ceiling effects (Figure 24). To avoid floor effects, patients were required to retain a significant degree of function across all muscle groups as defined by changes on the ALS Functional Rating Scale (ALSFRS). To avoid ceiling effects, patients had to demonstrate involvement in at least three or four regions according to the El Escorial criteria for ALS.

While this approach allowed for a successful clinical trial, it had the unintended consequence of insurance companies later using these narrow criteria to deny coverage to patients who did not meet them. We believe that although restrictive criteria were necessary to demonstrate drug efficacy in a clinical trial setting, they should not be used to exclude patients in real-world practice who may have progressed beyond the narrow enrollment window or who have not yet developed significant weakness.

Subsequent to the FDA approval, some doubt has been raised regarding the effectiveness of edaravone (Figure 25). The ADORE clinical trial was a multicenter, international, randomized, double-blind, placebo-controlled phase III study (Ferrer, 2024; Maia, 2024). This trial, which was conducted after edaravone had already received FDA approval, did not demonstrate superiority of edaravone over placebo when ALSFRS decline or survival were used as endpoints. However, this study did not apply the same narrow inclusion criteria and employed a different dosing protocol with daily administration. Interestingly, this study has not been published.

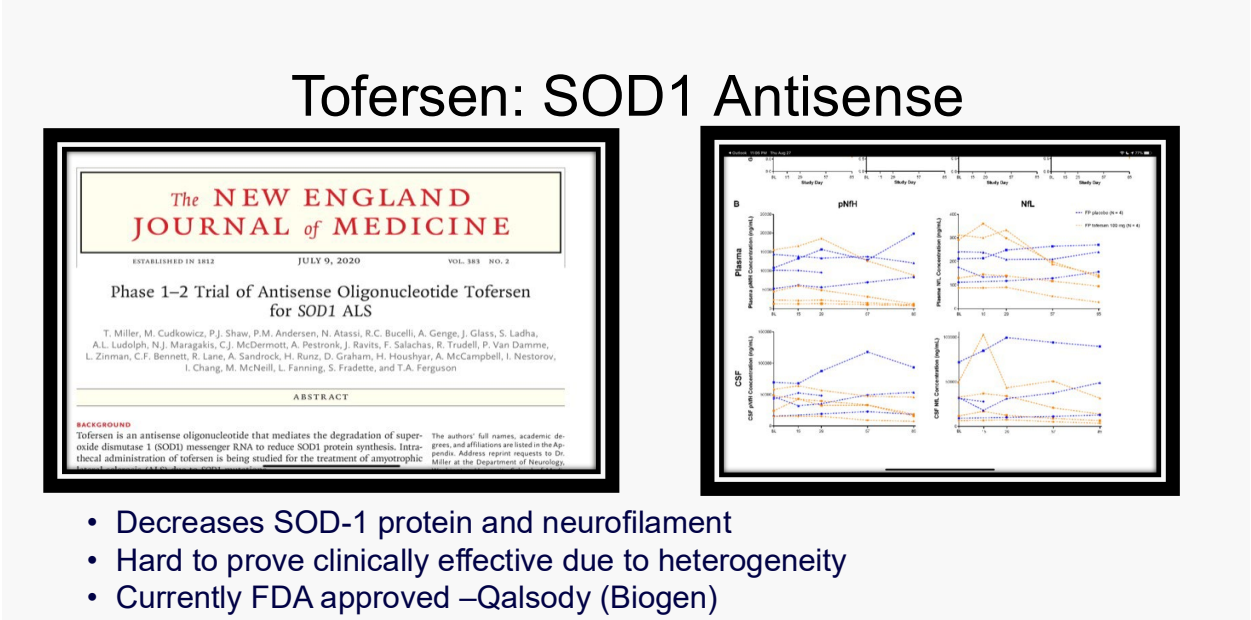
Figure 25



The most recent drug approved for the treatment of ALS is tofersen (named after former Biogen employee Toby Ferguson), an antisense oligonucleotide administered intrathecally that blocks the synthesis of SOD1 protein. This treatment is used in patients with SOD1 mutations and lowers levels of both mutant and wild-type SOD1 protein, theoretically preventing the protein aggregation that contributes to disease pathogenesis.

Initial studies demonstrated that tofersen reduced SOD1 and neurofilament levels but did not show that patients receiving the drug experienced a slowing of disease progression. Nevertheless, the FDA approved treatment for patients with autosomal dominant ALS associated with SOD1 mutations. Subsequent studies show that tofersen extends survival and slows disease progression, particularly when administered early in the disease course (Miller et al., 2025).

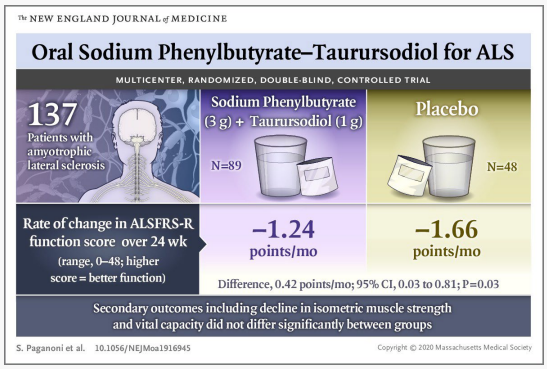
Figure 26



A company called Amylyx conducted a study of a combination therapy consisting of tauroursodeoxycholic acid (TUDCA) and phenylbutyrate. In 2020, a phase II trial demonstrated improved survival and slower disease progression compared with placebo (Paganoni et al., 2020, 2021). Based on these results, the FDA approved the drug but required that a planned phase III trial be completed. The drug was marketed as Relyvrio. Part of the rationale for approval after a phase II study was pressure from patient advocacy groups, who felt it was unfair to deny patients access to the drug while awaiting results from the pivotal phase III trial.

Figure 27

Recent Developments

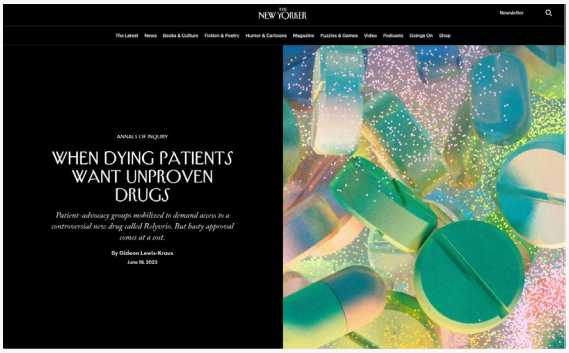


- Amylyx
  - Sodium phenylbutyrate is a histone deacetylase inhibitor
  - Taurursodiol
  - First trial completed in 2019
    - Improved function and survival
  - FDA approved as of September 2022

After Relyvrio entered the market and was widely used by ALS patients in the United States, results from the phase III trial demonstrated that the drug was not superior to placebo (Johnson, 2024). Despite several publications showing positive results from the phase II trial, the negative findings in the phase III trial, termed “The Phoenix Trial”, were never formally published. Consequently, Relyvrio was withdrawn from the market and is no longer a treatment option for ALS. The pressure placed on the FDA to approve the drug early prompted discussion in the lay press regarding the risks and benefits of approving therapies based on early-stage studies (Figure 28).

Figure 28

Relyvrio (2024 – Ineffective in Larger Trial)



- Autopsy suggests:
  - First trial relatively small
  - Tested limits of what FDA allowed for registration
  - Pressures from various groups

BrainStorm funded and conducted a stem cell trial for ALS in which stem cells were harvested from patients' own bone marrow, modified by the company, and then reintroduced via intrathecal injection into the cerebrospinal fluid.

Figure 29

Stem Cells

- BrainStorm
  - Trial of about 200 patients
  - Stem cells from own bone marrow
    - Altered and then returned to CSF
  - Earlier work suggested some patients improved transiently, but not seen in trial
  - Trial shows interesting results, but not significant
    - Still under FDA review

Clinicaltrials.gov

The BrainStorm trial did not demonstrate a statistically significant slowing of disease progression in the treatment group compared with placebo, although trends toward benefit were reported in patients earlier in the disease course (Figure 30) (Cudkowicz et al., 2022). One potential limitation of the study was that baseline ALS Functional Rating Scale (ALSFRS) scores were lower than those in prior ALS trials due to the specific enrollment criteria used (Figure 31) (Lindborg et al., 2024). This raised the possibility that the trial failed because of floor effects in patients with more advanced disease.

Figure 30

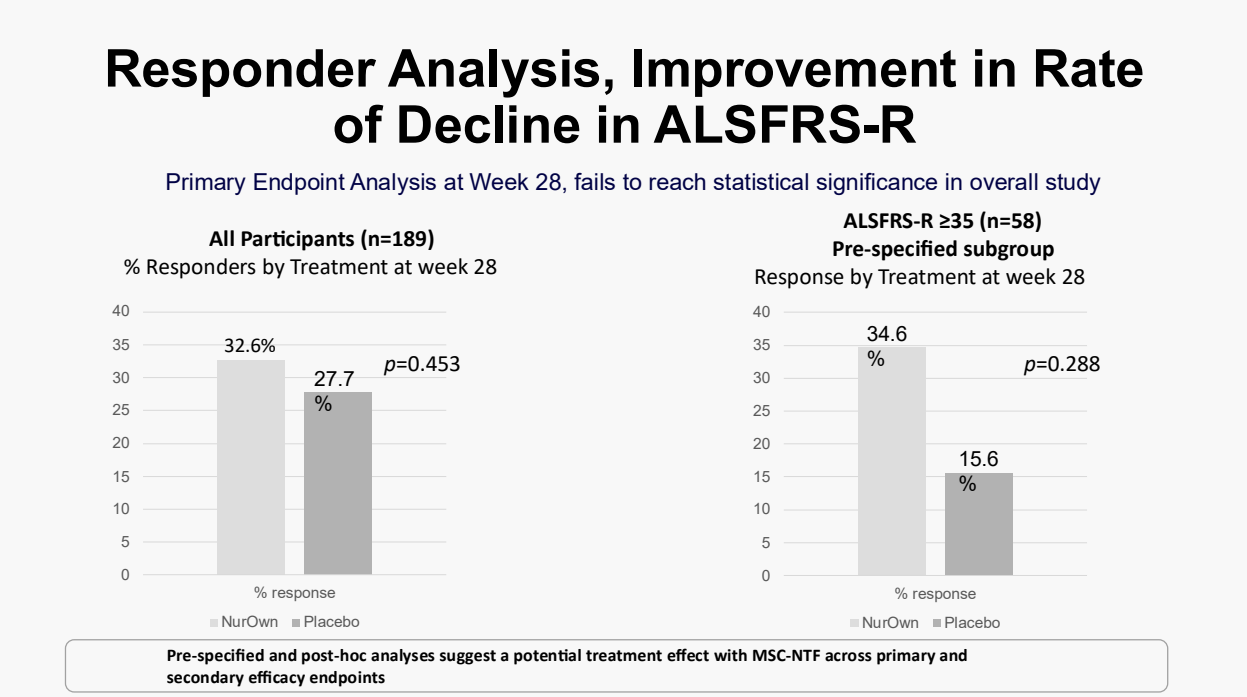
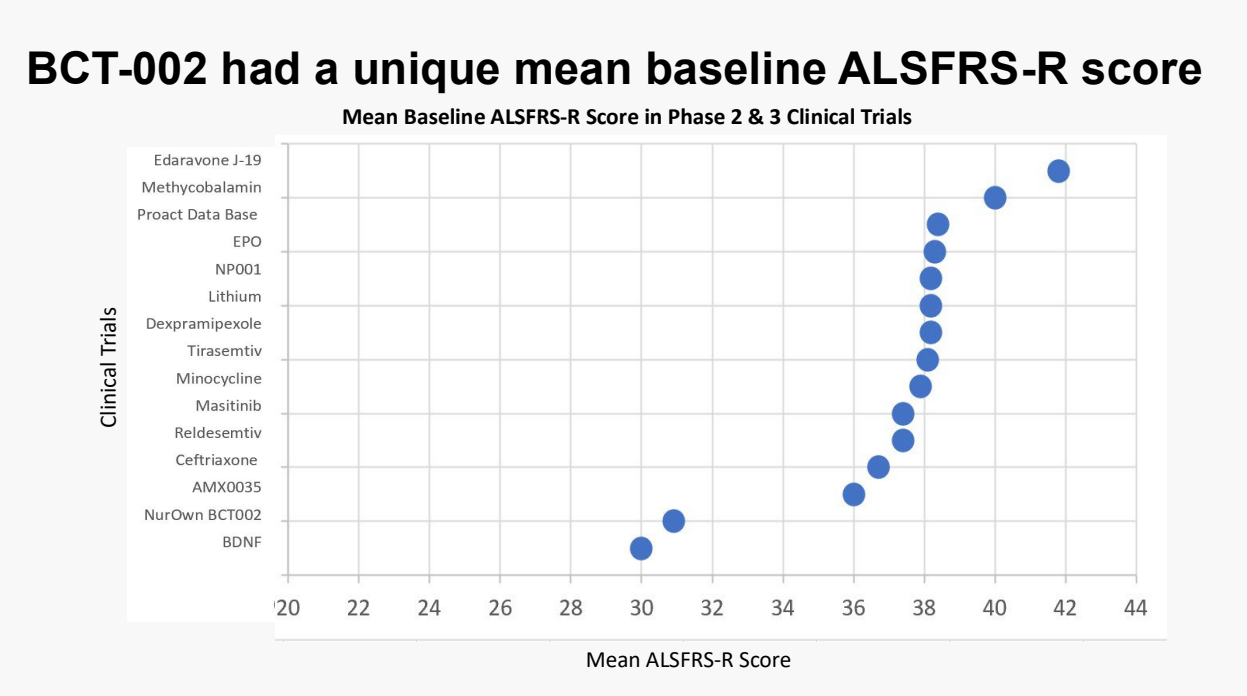


Figure 31



There have been numerous ALS clinical trials since the BrainStorm and Relyvrio development programs in which investigational drugs have failed to demonstrate clinical efficacy. It is common for sponsors to search for signals of benefit within patient subgroups after results from relatively small trials are reported. As a result, the field continues to face a dilemma regarding which therapies should advance to large phase III trials. It remains unclear whether these failures reflect shortcomings in trial design or whether ALS is an inherently complex disease with pathophysiology that is still poorly understood, limiting our ability to develop effective therapies.

The Platform Trial is a study based at Massachusetts General Hospital. In a platform trial, multiple drugs are evaluated simultaneously using a single shared placebo group. This design reduces the number of patients assigned to placebo while allowing randomization across several active treatment arms. The advantages include improved efficiency, shared protocols and infrastructure, a single institutional review board, and reduced overall costs. This approach creates an economy of scale and allows sponsors to de-risk financial investments by identifying potentially effective therapies before committing to large and expensive phase III trials.

Figure 32

Platform Trial and a Word on ALS Trial Philosophy

- Platform Trial (MGH)
  - Many drugs in pipeline, human data
  - Study several drugs at same time
  - Now on Protocol G
  - Five ineffective trials thus far
- Creative Destruction
  - Study a lot of drugs
  - Don't miss a winner
  - Don't push ineffective treatments

VIEWPOINT

The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

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The drug development enterprise is struggling. The development of new therapies is limited by high costs, slow progress, and a high failure rate, even in the late stages of development. Clinical trials are most commonly based on a "one population, one drug, one disease" strategy, in which the clinical trial infrastructure is created to test a single treatment in a homogeneous population.

This approach has been largely unsuccessful for multiple diseases, including sepsis, dementia, and stroke. Despite promising preclinical and early human trials, there have been numerous negative phase 3 trials of treatments for Alzheimer disease[1] and more than 40 negative phase 3 trials of neuroprotectants for stroke.[2] Effective treatments for such diseases will likely require combining treatments to affect multiple targets in complex cellular pathways and, perhaps, tailoring treatments to subgroups defined by genetic, proteomic, metabolomic, or other markers.[3]

There has been increasing interest in efficient trial strategies designed to evaluate multiple treatments and combinations of treatments, in heterogeneous patient populations, with the capability to add new treatments

benefits when evaluating potentially synergistic combination treatments (eg, treatment A, treatment B, treatment C, and all combinations) if the starting point is the testing of each treatment in isolation.

What Is a Platform Trial?

A platform trial is defined by the broad goal of finding the best treatment for a disease by simultaneously investigating multiple treatments, using specialized statistical tools for allocating patients and analyzing results. The focus is on the disease rather than any particular experimental therapy. A platform trial is often intended to continue beyond the evaluation of the initial treatments and to investigate treatment combinations, to quantify differences in treatment effects in subgroups, and to treat patients as effectively as possible within the trial. Although some of the statistical tools used in platform trials are frequently used in other settings and some less so, it is the integrated application of multiple tools that allows a platform trial to address its multiple goals. The **Table** summarizes the general differences between a traditional clinical trial and a platform trial.

During a platform trial, accumulating outcome data

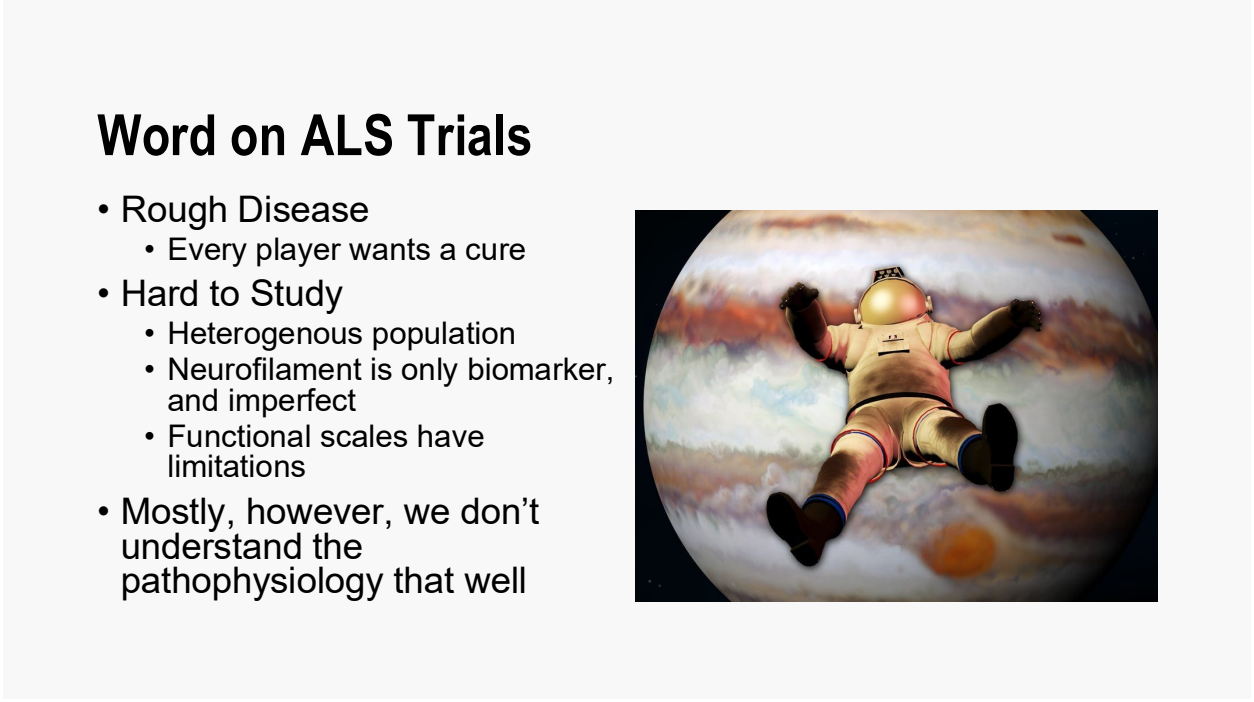
JAMA Published online March 23, 2015 Opinion
Berry, et al. JAMA. 2015;313(16):1619-1620.

In reality, ALS remains an exceptionally challenging disease in which it is difficult to achieve meaningful progress through clinical trials. Figure 33 depicts a man attempting to reach Jupiter. We are often asked why, if humans can land on the moon, we cannot find an effective treatment for ALS. One answer is that developing a treatment for ALS is far more complex than landing on the moon and may be more comparable to placing a human on Mars—or even Jupiter.

The ALS clinical trial population is highly heterogeneous, with patients enrolling at different stages of disease and exhibiting widely variable rates of progression. This heterogeneity necessitates large sample sizes to minimize random effects that can lead to misleadingly positive or negative outcomes. Current biomarkers for ALS include serum and cerebrospinal fluid neurofilament light chains; however, reliance on these markers remains somewhat theoretical, as there have been too few successful trials to validate their predictive value fully.

Ultimately, the major challenge in ALS clinical trials is our incomplete understanding of disease pathophysiology. Until significant advances are made in elucidating the underlying mechanisms of ALS, it will remain difficult to make rational decisions about which therapeutic targets to pursue. Nonetheless, these trials are conducted with the understanding that scientific knowledge continues to advance and with the hope that we will eventually cross a threshold leading to clearly effective treatments in the near future. Of course, a little luck would also help.

Figure 33



References

1. Barohn RJ, Wolfe GI, Saperstein DS, Dimachkie MM, Katz JS. Pattern recognition of neuropathy and neuronopathy. RRNMF Neuromuscul J. 2024;5(1):44–74.
2. Barohn RJ, Wolfe GI, Saperstein DS, Dimachkie MM. Pattern recognition approach to neuropathy and neuronopathy. Neurol Clin. 2025;43(4):617–635.
3. Berdyński M, Miszta P, Safranow K, Andersen PM, Morita M, Filipek S, Żekanowski C, Kuźma-Kozakiewicz M. SOD1 mutations associated with amyotrophic lateral sclerosis: analysis of variant severity. Sci Rep. 2022;12:103.
4. Berry SM, Connor JT, Lewis RJ. The platform trial: an efficient strategy for evaluating multiple treatments. JAMA. 2015;313(16):1619–1620.
5. Boylan K. Familial amyotrophic lateral sclerosis. Neurol Clin. 2015;33(4):807–830.
6. BrainStorm Cell Therapeutics Inc. BrainStorm announces new survival data from expanded access program cohort: 90% of ALS patients survived over 5 years with NurOwn®. Press release. New York: BrainStorm Cell Therapeutics; 2025.
7. Cudkowicz ME, Lindborg SR, Goyal NA, Miller RG, Burford MJ, Berry JD, et al. A randomized placebo-controlled phase 3 study of mesenchymal stem cells induced to secrete high levels of neurotrophic factors in amyotrophic lateral sclerosis. Muscle Nerve. 2022;65(3):291–302.

8. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, et al. Expanded GGGGCC hexanucleotide repeat in C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron. 2011;72(2):245–256.
9. Dimachkie MM, Barohn RJ, Katz JS. Multifocal motor neuropathy, multifocal acquired demyelinating sensory and motor neuropathy, and other chronic acquired demyelinating polyneuropathy variants. Neurol Clin. 2013;31(2):533–555.
10. Ferrer. Ferrer reports top-line results from phase III ADORE study in ALS. Press release. Spain: Ferrer Internacional; 2024.
11. Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Lancet. 2016;388(10063):3017–3026.
12. Goutman SA, Hardiman O, Al-Chalabi A, Chio A, Savelieff MG, Kiernan MC, et al. Amyotrophic lateral sclerosis. Lancet Neurol. 2022;21(5):480–493.
13. Gregory J, Fagegaltier D, Phatnani HP, Harms MB. Genetics of amyotrophic lateral sclerosis. Curr Genet Med Rep. 2020;8:121–131.
14. Grunseich C, Fischbeck KH. Spinal and bulbar muscular atrophy. Neurol Clin. 2015;33(4):847–854.
15. Jackson CE, McVey AL, Rudnicki S, Dimachkie MM, Barohn RJ. Symptom management and end-of-life care in amyotrophic lateral sclerosis. Neurol Clin. 2015;33(4):889–908.
16. Jawdat O, Statland JM, Barohn RJ, Katz JS, Dimachkie MM. Amyotrophic lateral sclerosis regional variants. Neurol Clin. 2015;33(4):775–785.
17. Johnson A. Forbes [Internet]. Forbes Media LLC; 2024. Here's why ALS drugs removed from market-and what that means for patients. Available from: https://www.forbes.com/sites/ariannajohnson/2024/04/04/heres-why-als-drug-relyvrio-is-being-removed-from-market-and-what-that-means-for-patients/
18. Katz JS, Wolfe GI, Andersson PB, Saperstein DS, Elliott JL, Nations SP, et al. Lower motor neuron syndromes: clinical features and diagnosis. Neurology. 1999;53(5):1071–1076.
19. Katz JS, Wolfe GI, Bryan WW, Jackson CE, Amato AA, Barohn RJ. Electrophysiologic findings in multifocal motor neuropathy. Neurology. 1997;48:700–707.
20. Kolb SJ, Kissel JT. Spinal muscular atrophy. Neurol Clin. 2015;33(4):831–846.
21. Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Lancet. 1996;347(9013):1425–1431.
22. La Spada AR, Wilson EM, Lubahn DB, Harding AE, Fischbeck KH. Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. Nature. 1991;352:77–79.
23. Lefebvre S, Bürglen L, Reboullet S, Clermont O, Burlet P, Viollet L, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell. 1995;80(1):155–165.
24. Lewis-Kraus G. The New Yorker [Internet]. The New Yorker; 2023. When dying patients want unproven drugs. Available from: https://www.newyorker.com/magazine/2023/06/26/relyvrio-als-fda-approval
25. Liewluck T, Saperstein DS. Progressive muscular atrophy. Neurol Clin. 2015;33(4):761–773.
26. Lindborg SR, Goyal NA, Katz JS, et al. Debamestrocel multimodal effects on biomarker pathways in amyotrophic lateral sclerosis are linked to clinical outcomes. Muscle Nerve. 2024;69:719–729.

27. Maia M. ALS News Today: a bionews community [Internet]. Bionews, Inc. 2024. Endaravone formulation FAB122 fails to slow ALS progression. Available from: https://alsnewstoday.com/news/als-progression-fails-slow-with-edaravone-formulation-fab-122/
28. Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. N Engl J Med. 2017;377(19):1713–1722.
29. Miller T, Cudkowicz M, Shaw PJ, Andersen PM, Atassi N, Bucelli RC, et al. Phase 1–2 trial of antisense oligonucleotide tofersen for SOD1 ALS. N Engl J Med. 2020;383(2):109–119.
30. Miller TM, Cudkowicz ME, Shaw PJ, Genge A, Sobue G, Bucelli RC, et al. Long-term tofersen in SOD1 amyotrophic lateral sclerosis. JAMA Neurol. 2025. Epub ahead of print.
31. Paganoni S, Macklin EA, Hendrix S, et al. Long-term survival of participants in the CENTAUR trial of sodium phenylbutyrate–taurursodiol in amyotrophic lateral sclerosis. N Engl J Med. 2021;384:915–923.
32. Paganoni S, Macklin EA, Hendrix S, et al. Trial of sodium phenylbutyrate–taurursodiol for amyotrophic lateral sclerosis. N Engl J Med. 2020;383:919–930.
33. Rosen DR, Siddique T, Patterson D, Figlewicz DA, Sapp P, Hentati A, et al. Mutations in Cu/Zn superoxide dismutase gene are associated with familial ALS. Nature. 1993;362(6415):59–62.
34. Saperstein DS, Amato AA, Wolfe GI, Katz JS, Nations SP, Jackson CE, et al. Multifocal acquired demyelinating sensory and motor neuropathy: the Lewis–Sumner syndrome. Muscle Nerve. 1999;22(5):560–566.
35. Statland JM, Barohn RJ, McVey AL, Katz JS, Dimachkie MM. Patterns of weakness, classification of motor neuron disease, and clinical diagnosis of sporadic amyotrophic lateral sclerosis. Neurol Clin. 2015;33(4):735–748.
36. Stino A, Dimachkie MM, Katz JS. Immune-mediated neuropathies other than typical CIDP. Neurol Clin. 2025;43:781–797.
37. Woolley SC, Strong MJ. Frontotemporal dysfunction and dementia in amyotrophic lateral sclerosis. Neurol Clin. 2015;33(4):787–805.
38. Writing Group on Behalf of the Edaravone ALS 19 Study Group. Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis. Lancet Neurol. 2017;16(7):505–512.

Borrowed Time

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University of Kansas Medical Center

This morning after dropping my son off to school I was walking to my car while he and his class were walking from chapel back to class. I kept waving each time I passed a parked car in the parking lot and it almost became a game as he started to look for me and I started to look for him after each car. Our smiles and laughs increased each time we passed a car. I knew that at some point I would reach my car and no longer see him. And without warning, it happened, I didn't see him. I got into my car and thought about this some more. We raise our kids and there are hard days and easy days and in between days, and sometimes we want these more challenging times to fast forward. But before you know it, they leave the nest. They and you will walk past the last car and poof they are adults and maybe starting their own families.

I am writing this to remind myself and others that this time we have is borrowed. In my profession I see people die of acute neurologic diseases. Without a warning a family has lost a loved one…a parent, a grandparent, a sibling, uncommonly a child. I see it in their eyes and faces, they yearn for just one more day where they can be with their loved one, and talk to them, and LIVE with them. But that time unfortunately is gone.

Remember to give an extra hug and kiss to those you love and say one more 'I love you'.

History of Neurology: 'Sparkling Italians' – Giovanni Morgagni, Alessandro Volta, and Luigi Galvani

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University of Missouri School of Medicine

A live recording of this lecture can be viewed here:
RRNMF – Early, Early Neurology History Sparkling Italians

This History of Neurology segment discusses early Italian neuroscience research, subtitled "Sparkling Italians."

The first Italian physician and scientist to discuss is Giovanni Morgagni, who was the father of modern anatomic pathology. He was educated in Bologna, the first true Western university, founded in 1088 (Oxford University, by comparison, was founded in 1096). He taught at another historic university, the University of Padua, founded in 1222, for 56 years (The University of Padua was also where Andreas Vesalius taught and published *De Humani Corporis Fabrica* in 1543).[1] Morgagni wrote the book On the Seats and Causes of Diseases,[2] in which he recorded dissections or autopsies in 646 patients and correlated them with their clinical symptoms and course. He emphasized the importance of basing diagnosis, prognosis, and treatment on pathologic anatomy. This work was originally published in five books in large folios, but later English translations compiled it into three volumes.[3] One important neurologic discovery from these autopsies was that the site of the lesion in apoplexy, or stroke, was in the brain on the opposite side of the involved body parts—a major finding.

Let us now discuss the 'Sparkling' Italians who were the early leaders in the development and the concept of the use of electricity. The term "electricity" was first coined by William Gilbert in the 1600s, the famous scientist in England who published the landmark book *On the Loadstone of Magnetic*

Figure 1

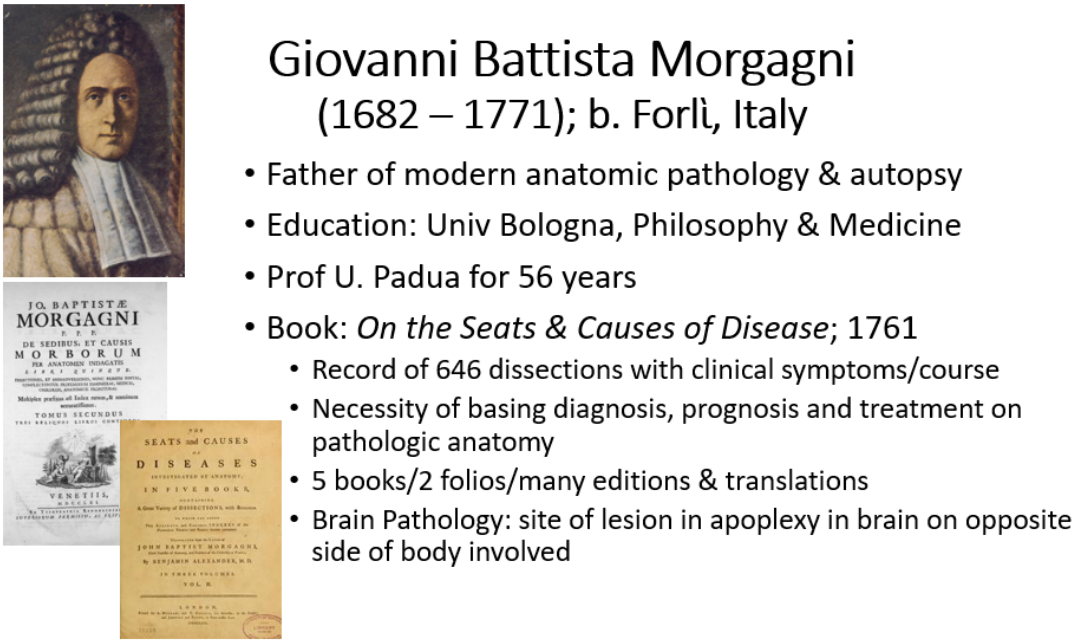
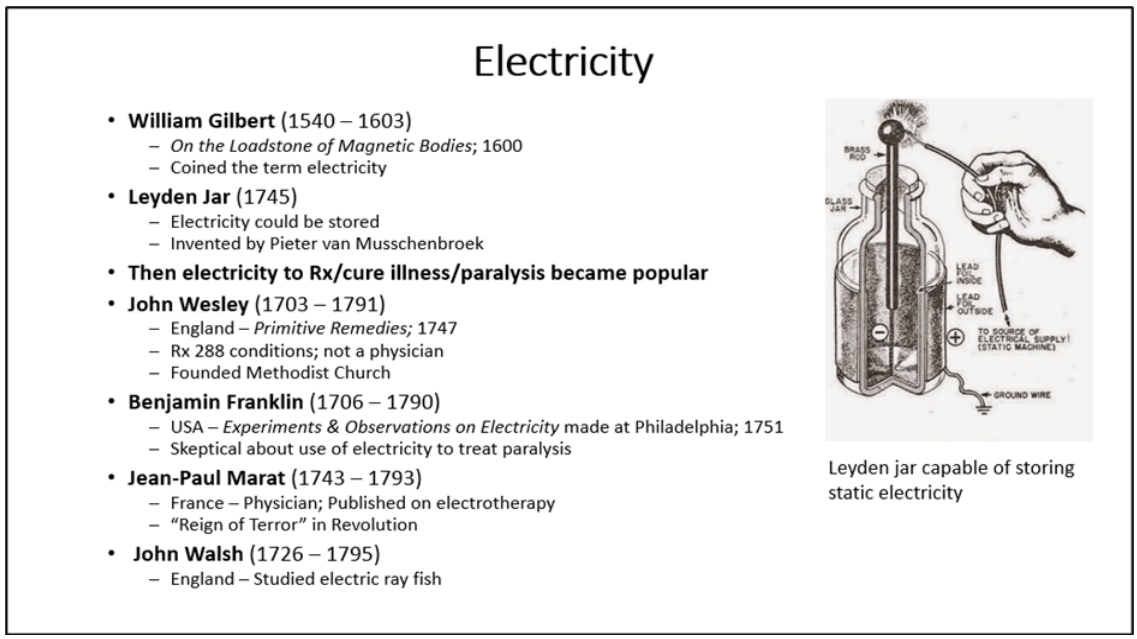
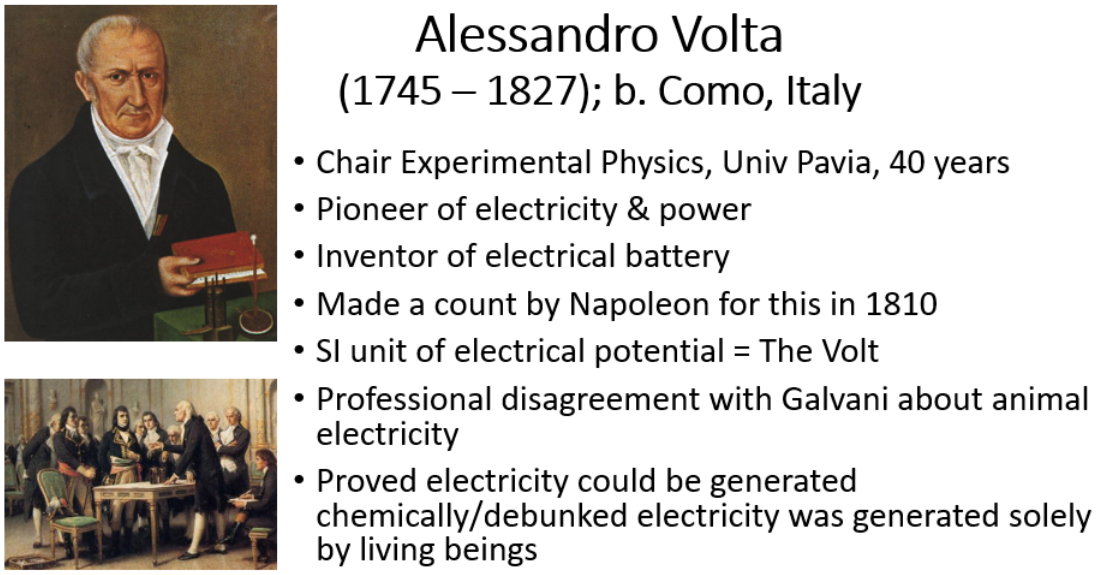


Figure 2



Leyden jar capable of storing static electricity

Figure 3



Bodies in 1600.[4] About a hundred years later, the Leyden jar was invented, allowing electricity to be stored. Soon afterward, electricity began to be used to treat patients with paralysis and other illnesses. This became very popular through the writings of John Wesley—who was not a physician but wrote several books on this treatment[5]—and who also founded the Methodist Church. Another figure, Jean-Paul Marat, a French physician and one of the leaders of the Reign of Terror during the French Revolution, also wrote extensively on electrotherapy. Benjamin Franklin,[6] who was a leader in electricity, was more reserved in his enthusiasm for using it to treat neurologic disorders. John Walsh, a scientist in English and fellow of the Royal Society, performed numerous studies on the electrical properties of torpedo fish.

Alessandro Volta and Luigi Galvani made their scientific contributions shortly after these early discoveries in electricity. Alessandro Volta was a professor of physics at the University of Pavia for 40 years. He was considered the inventor of the electrical battery and was made a count by Napoleon in 1810. An English translation of a letter by Volta describing the battery to a member of the Royal Society of London was published the *Society's Transactions* after his death in 1832 (Figure 4).[7] The volt, the standard international unit for electrical potential, is named after him. Volta had a long

Figure 4

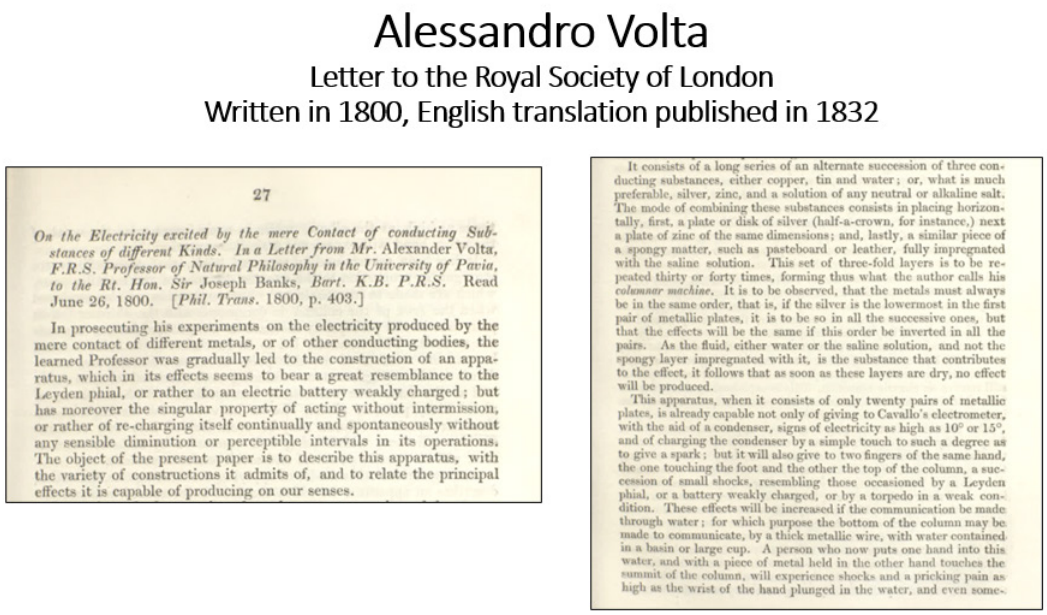
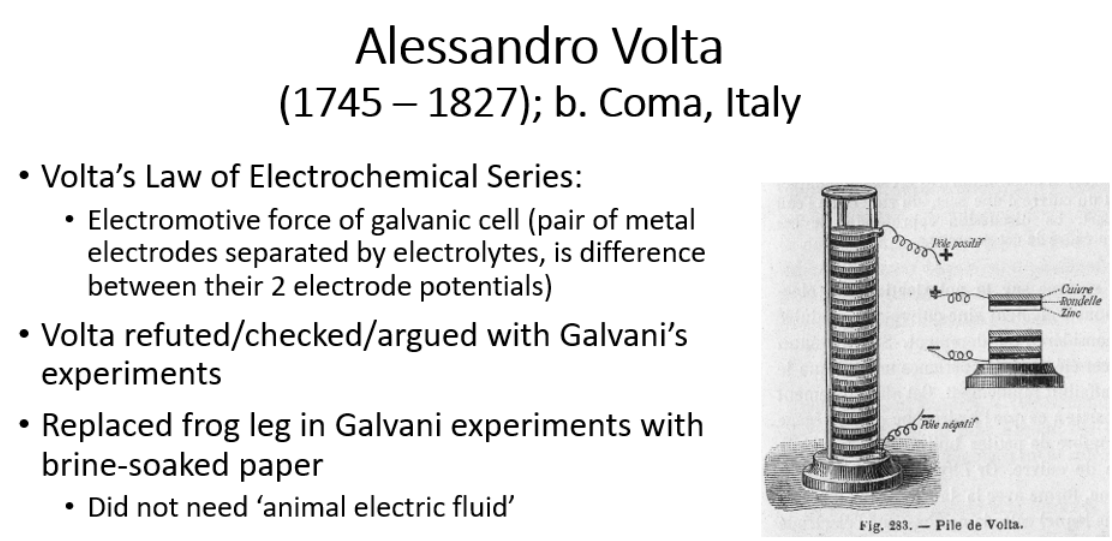


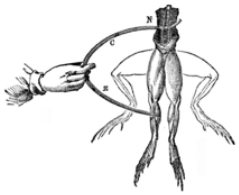
Figure 5



disagreement with Luigi Galvani (Figure 5) about whether there was such a thing as animal electricity. Galvani thought there was; Volta thought there was not. Volta proved that electricity was generated chemically and did not need to be produced by living beings.

He used his invention, known as Volta's pile or Volta's battery, to refute Galvani's ideas about "animal electric fluid. Volta carefully repeated Galvani's experiments and devised new methods to perform them—an impressive scientific approach. He even replaced the frog legs used in Galvani's experiments with brine-soaked paper, showing that the muscle tissue itself was not necessary to produce an electrical effect.

Figure 6

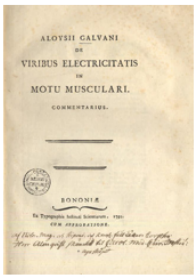


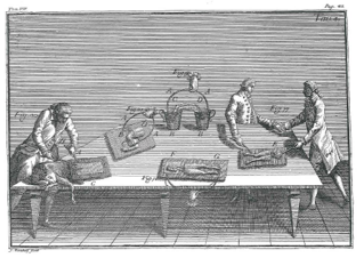
Electrodes touch a frog, and the legs twitch into the upward position

Luigi Galvani
(1737 – 1798); b. Bologna, Italy

- Physician, physicist, biologist & philosopher
- Education: Univ. of Bologna & faculty there his whole career
- Discoverer of bioelectricity and the father of electrophysiology
- 1780; muscles of dead frog legs twitched when struck by electric spark
  - Made muscle nerve preps
  - Therefore, Father of concept we can study electric patterns & signals from tissues
- "Animal Electricity" – term to define the force that activates the muscles of his specimens
- Believed conductions were due to electricity intrinsic to animal body parts

Figure 7





Galvani 1791 – Research Team

Luigi Galvani
(1737 – 1798); b. Bologna, Italy

- Volta disagreed and made 1st chemical battery to displace Galvani's theory – Volt's "pile"
  - But Volta coined term *Galvanism* for a direct current of electricity produced by chemical action
- While Volta was correct, Galvani was active pioneer in muscle & nerve research & neurophysiology
- He is the original EMG-er!
- Galvonometer – Instrument for detecting & measuring electrical current
- Book: *Commentary on the Effects of Artificial Electricity on Muscle Motion* (1791)
  - Describes detailed planning, execution & interpretation of experiments with illustrations – very popular / landmark treatise

Luigi Galvani was a physician, physicist, and biologist. Like Morgagni, he was educated in Bologna. Unlike Morgagni, he remained at the University of Bologna and taught there his entire career. He is considered the discoverer of bioelectricity and the father of electrophysiology. In 1780, he showed that applying an electric spark to a dead frog's leg muscle caused it to twitch. He performed numerous experiments using muscle and nerve preparations and is rightly considered the originator of the concept that we can study electrical patterns and signals from biological tissues. He believed there was an "animal electricity" or a force within the muscle that generated this electrical activity—a concept Volta rejected. In Figure 6, you not only see his portrait but also examples of his experiments, where electrodes were used to stimulate frog muscles.

His research team worked extensively with muscle and nerve preparations from frogs and other animals. Galvani published his findings in Commentary on the Effects of Artificial Electricity on Muscle Motion, originally published in Latin in 1791.[8,9] The book contained amazing illustrations, including long fold-out diagrams of muscle and nerve experiments (Figures 7–10). These are the experiments Volta later replicated, most of which he successfully repeated. The term galvanometer, an instrument for detecting and measuring electrical current, is of course named after Galvani.

Figure 8

Galvani 1791 – Muscle Stimulation Demonstration for the Public!

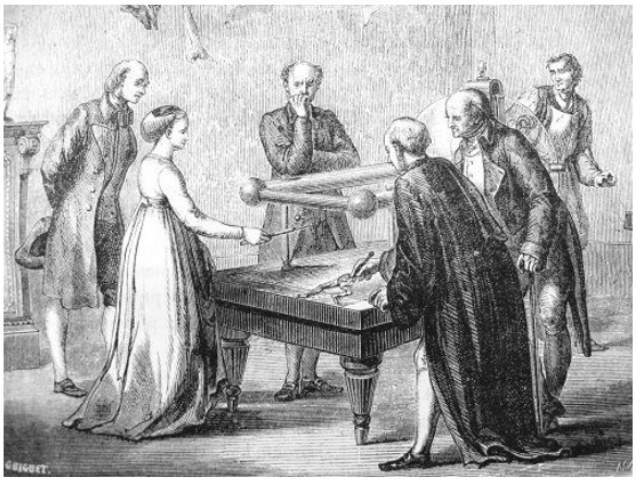


Figure 9

Galvani 1791 – The Lab!

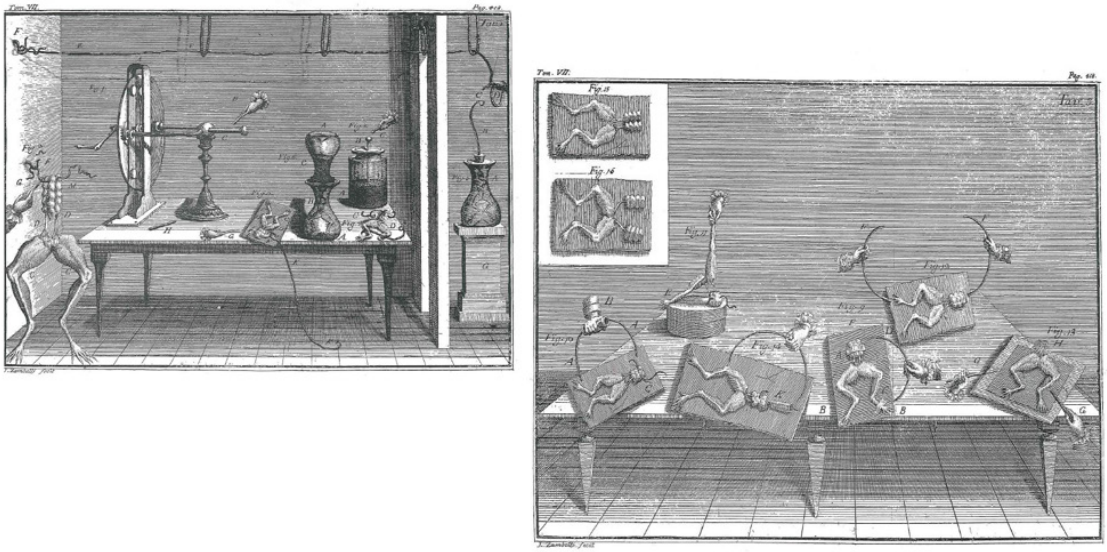
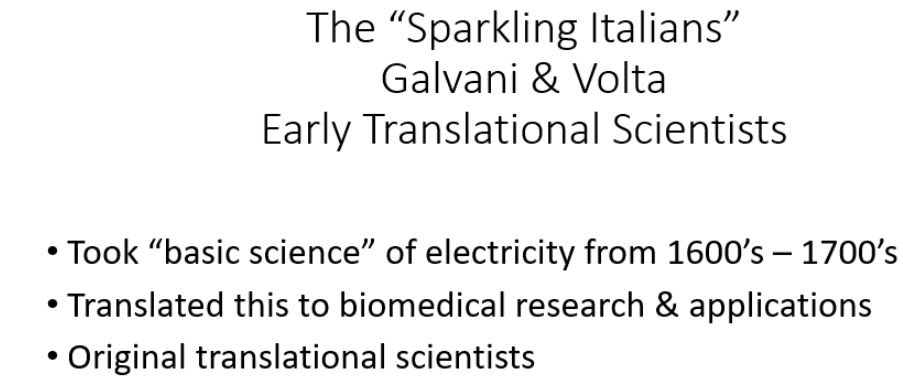


Figure 10

Figure 11



Galvani also gave public demonstrations of muscle stimulation to lay audiences, including politicians and investors (Figure 8). His laboratory featured both indoor and outdoor experiments—famously, he even conducted tests on his patio, connecting frog legs to metal wires during thunderstorms to capture lightning as a power source (Figures 9 &10). In a way, you could call him the first "Bill Gates," doing experiments in his own version of a garage.

The "Sparkling Italians," Galvani and Volta, took basic science concepts of electricity from the 1600s and 1700s and translated them into biomedical research and applications. They truly deserve to be considered among the original translational scientists. Galvani can also be considered the original electromyographer, or the first practitioner of EMG.

References

1. Vesalius A. *De humani corporis fabrica.* 1555.
2. Morgagni GB. *De sedibus et causis morborum per anatomen indagatis libri quinque*. Venetiis: ex Thypographia. 1761.
3. Morgagni GB. The seats and causes of diseases investigated by anatomy; in five books, ... Translated by Benjamin Alexander, MD, from the Latin of John (Giovanni) Baptist Morgagni. 1769;1.
4. Gilbert W. On the Loadstone of Magnetic Bodies. 1600.
5. Wesley J. Primitive Remedies. 1747.
6. Franklin B. Experiments & Observations on Electricity. 1751.

7. Volta A. On the Electricity excited by the mere Contact of conducting Substances of different Kinds. Proc. R. Soc. 1832;(1):27.
8. Galvani L. *De Viribus Electricitatis in Motu Musculari Commentarius*. 1791.
9. Galvani L. Commentary on the effects of electricity on muscular motion, Translated into English by Margaret Glover Foley, with notes and critical introduction by I. Bernard Cohen, Norwalk (Conn.), Burndy Library, 1953.

History of Neurology: Charles-Édouard Brown-Séquard - The Original International Neurologist

Richard J. Barohn, MD

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

A live recording of this lecture can be viewed here: RRNMF - Charles-Édouard Brown-Séquard

This History of Neurology article is about Charles-Édouard Brown-Séquard, who I consider the first original international neurologist. I'll explain why I think that as I go through his story.

Brown-Séquard was born in the Mauritius Islands off the coast of Africa (Figure 1). Interestingly, his father, Brown, was an American sea captain who died at sea before Brown-Séquard was born. His mother, Charlotte Séquard, was French, although she herself was born in Port Louis in the Mauritius Islands. He grew up very poor and was also poorly educated early in life. In 1838, his mother took him to Paris, where he began to receive some formal education.

At first, he wanted to be a poet and wrote a great deal of poetry. Eventually, he decided that poetry was not for him and he burned all of his manuscripts. He then enrolled in medical school and changed his name to the French form by which we now know him, Charles-Édouard Brown-Séquard. In 1846, he graduated from the Faculty of Medicine in Paris. His medical thesis focused on experimental research on the physiology of the spinal cord, which marked the beginning of his lifelong study of this subject.[1]

Just a few years later, he published his classic experiments in which he sectioned the spinal cord and demonstrated that pain and temperature pathways were crossed, while the corticospinal tracts remained ipsilateral.[2] This work produced what became known as Brown-Séquard syndrome. These experiments made him famous and led to his success throughout his career.[3-7]

Around this time, his mother died, and he had very little income. He continued performing spinal cord experiments in animals and seeing patients, but he was very depressed and experienced many psychosomatic symptoms even at that time. I will return to this later. This period marked the beginning of his transatlantic life, as he moved back and forth between Europe and America in various clinical and academic positions (Figure 2).

In 1852, he moved to the United States. At that point, he did not speak English, but he learned it and began seeing

Figure 1

Charles-Édouard Brown-Séquard MD
1817-1894

- B - Port Louis, Mauritius
- American father, French mother, born British
- Edward Brown sea captain, lost at sea before Édouard's birth
- Charlotte Séquard, born Port Louis (French)
- Grew up poor, poorly educated
- 1838; 1st Paris visit with his mother
  - Wanted to be a poet! Burned his manuscripts but enrolled at Faculty Medicine of Paris
- Changes name to Édouard Brown-Séquard
- 1846; Graduated/Thesis: Researches and Experiments on the Physiology of Spinal Cord
- 1850; Demonstrated crossed sensory paths when cut cord in animals - Brown-Séquard Syndrome
- Mother died 1848, very poor; just did research and saw patients
  - Depressed/psychosomatic symptoms

Figure 2

Éduoard Brown-Séquard MD – America and England

- 1852 – Moved to American and learned English
    - Saw patients, delivered babies, co-wrote Obstetrics book
        - Letters of introduction by Broca and others
    - Lectured and experimental demonstrations in NY, Boston, Philadelphia
- 1853 – Married Ellen Fletcher (American), returned to Paris/Mauritius
- 1854 – Professor of Physiology at New Medical College of Virginia in Richmond
    - Bored and disillusioned
- 1855 – Returned to Paris, visited London/Cambridge
- 1856 – Son born,back to USA to see family and lecture – Boston, NY, Baltimore, Charleston,
- 1857 – Returned NY to lecture
- 1858 – London lectures, Royal Society
- 1859 – Edinburgh, Glasgow, London, Dublin
- 1860 – Queen Square, National Hospital for Nervous Diseases – Brown-Séquard one of 2 founding physicians
    - Friends with Darwin, Huxley, Jackson
- 1860 – Published: *Course Lectures on the Physiology and Pathology of the Central Nervous System*

patients. He engaged in a wide range of medical practice, including delivering babies, and he co-wrote an obstetrics book while in America. He carried letters of introduction from famous French neurologists such as Broca, and his spinal cord experiments had already established his reputation. As a result, he was invited to lecture and perform experimental demonstrations in New York, Boston, and Philadelphia.

He married an American woman and later returned to Paris and the Mauritius Islands for a period of time. In 1854, he returned to the United States and accepted his first academic position as a professor of physiology at a new medical college in Richmond, Virginia. Even today, the medical school in Richmond still refers to Brown-Séquard as one of its original neurology faculty members. However, after only a year he became bored and disillusioned in Virginia and returned to Paris in 1855.

During this period, he visited London and Cambridge for the first time. Shortly afterward, he had a son. Because his wife was American, they returned to the United States to visit her family and introduce the baby. While there, he delivered a series of lectures in Boston, New York, Baltimore, and Charleston and then published a book based on the lectures.[5] In 1858, he was invited to give a series of lectures at the Royal College of Surgeons in England. While in England, he also lectured in Edinburgh, Glasgow, and Dublin.

In 1860, he was named one of the founding neurologists at the National Hospital for Nervous Diseases at Queen Square in London. This was a significant appointment. His College of Surgeons lectures were later published in a book titled Course of Lectures on the Physiology and Pathology of the Nervous System (Figures 3 and 4).[6]

Figure 3

Course Lectures on the Physiology and Pathology of the Central Nervous System (1860) delivered at the Royal Society, London

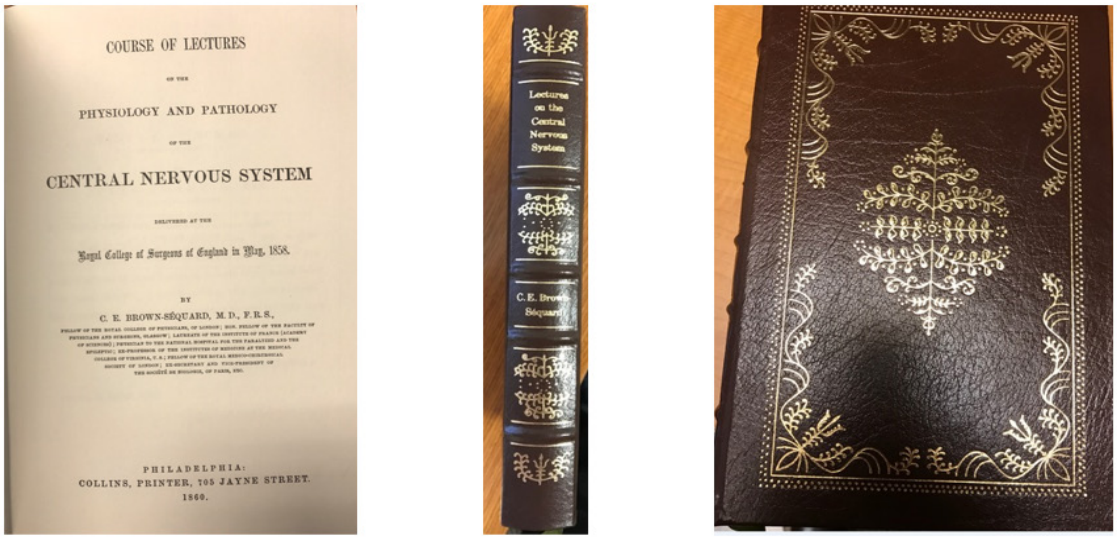


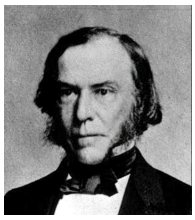
Figure 4

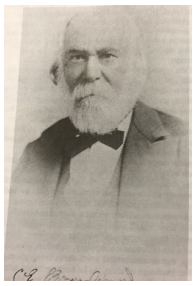
Course Lectures on the Physiology and Pathology of the Central Nervous System (1860)

Figure 5

Éduoard Brown-Séquard, MD – Back to America and France

- 1864 – Harvard; Professor Physiology and Pathology of the Nervous System; wife dies
  - Resigns 3 times, meets Weir Mitchell
- 1867 – Returned to Paris – with Charcot
- 1871 – to NY due to Franco-Prussian War
  - Remarried (woman 30 yrs younger) Maria
- 1873 – Boston, lectured with Agassiz, OW Holmes, Putnam in audience
  - Clinical practice in NYC
  - With Edward Sequin (Columbia) started Archives of Scientific and Practical Medicine
- 1874 – 2nd wife dies, post partum
- 1876 – returned to Paris
- 1877 – 3rd marriage; lectured Cambridge, NYC
- 1878 – Claude Bernard dies and Edward Brown-Séquard assumes Professor and Chair of Medicine College de France (Magendie old chair) and his lab
  - Close to L. Pasteur, Gustave Eiffel
- 1894 – 3rd Wife Dies, Emma
  - Edward Brown-Séquard dies several months later, age 77
- 577 publications
  - First in 1846 – Doctoral Thesis; 6 in 1894





The book became well known in the medical and neurological communities and firmly established his international reputation. The volume also included beautiful illustrations.

He continued traveling extensively (Figure 5). After his time in London, he returned to the United States and became a professor of physiology and pathology of the nervous system at Harvard, the first chair of its kind in the United States. During this period, his first wife died. He attempted to resign from Harvard three times but was persuaded to stay. He became friends with Weir Mitchell but eventually returned to Paris, where he interacted with Charcot, who was then in charge of the Salpêtrière. Brown-Séquard was appointed chair of comparative and experimental pathology at the Museum of Natural History. This was a controversial appointment. There was opposition by a number of prominent scientists, possibly including Claude Bernard, who expressed concerns about the rigor of Brown-Séquard's scientific method.[7] This distinguished academic chair had previously been held by Claude Bernard, a scientific pioneer who wrote a classic book about the experimental method in 1865.[8] Interestingly, Brown-Séquard had previously confirmed and elaborated on Bernard's groundbreaking studies on the sympathetic control of the vasomotor mechanism. Claude Bernard had shown that destruction of the cervical sympathetic ganglion caused dilation of blood vessels, which produced erythema and increased temperature on that side of the face and especially the ear. Brown-Séquard subsequently demonstrated electrical stimulation of the cervical sympathetic ganglia caused vasoconstriction, blanching, and decreased temperature of the rabbit's ear.[9] He also spent a great deal of effort studying epilepsy, searching for both the cause of epilepsy and potential treatments, and he was among the first to suggest the use of bromides for seizures.[10,11] By the 1860s, he was a recognized authority on all disorders of the nervous system.

Because of fears surrounding the Franco-Prussian War, which France ultimately lost, he left Paris and returned to New York. He remarried, this time to a woman named Maria, who was thirty years younger than him. He resumed lecturing in Boston, met prominent figures such as Oliver Wendell Holmes and Charles Pickering Putnam, and began practicing medicine in New York City. He founded a new journal, Archives of Scientific and Practical Medicine, one of many journals he established throughout his life.

In 1874, his second wife died postpartum. He returned to Paris, married again, and once more traveled to the United States to lecture in New York City. Before that, he lectured in Cambridge, England. In 1878, he was invited back to Paris following the death of Claude Bernard. Brown-Séquard assumed Bernard's position as professor and chair of medicine at the Collège de France, a highly prestigious role. While in France, he became friends with Louis Pasteur and Gustave Eiffel.

In 1894, his third wife died, meaning he outlived all three of his wives. Shortly thereafter, he himself died at the age of seventy-seven. He was extraordinarily prolific, producing a total of 577 publications. His first publication was his 1846 doctoral thesis on spinal cord experiments,[1] and in the year of his death, he published six papers.

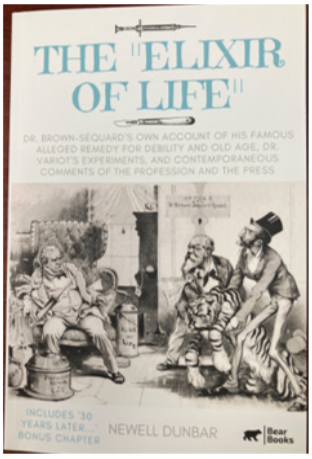
Figure 6

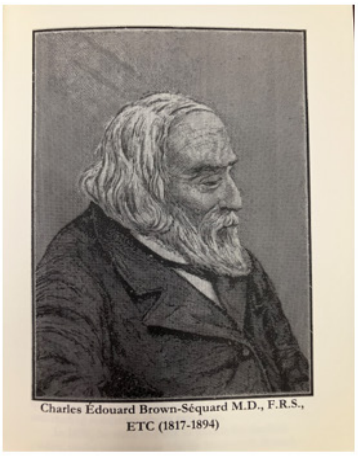
Éduoard Brown-Séquard, MD & Endocrinology

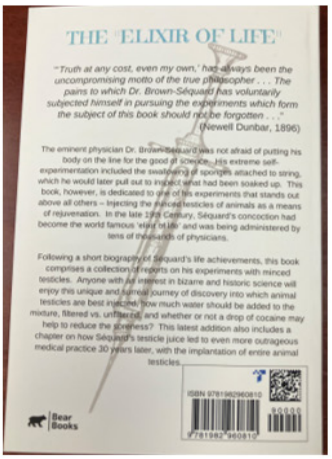
- 1855 – Addison reported disease of the adrenal glands caused anemia, weakness, bronzing of skin and other changes
- 1856 – Brown-Séquard reported excision of both adrenal glands in cats, dogs guinea pigs, rabbits and mice led to death within 24 hours
- Many initially disputed Addison and Brown-Séquard
  - Their experiments and observations initiated modern endocrinology
- Age 72 - Brown-Séquard noticed decline of strength, concentration, fatigue, increase of insomnia, worsening constipation
  - Created solution of testicular blood, seminal fluid and testicular extract from healthy dogs and guinea pigs and injected in himself 10 X over 3 weeks.
  - Reported his observation to Société de Biologie
  - Noticed increased mental concentration, physical endurance, stream of urine, bowel habits and increased power in his forearm by 5-6 kgs
- Very controversial but many including W Hammond confirmed findings
- Brown-Séquard used adrenal extracts for Addison's Disease and others used thyroid extracts for myxedema
  - Generally no benefit until fat solvents used in 1930, but Brown-Séquard started the field of hormone replacement

Figure 7

The "Elixir of Life"; Brown-Séquard's own account of his famous alleged remedy for debility and old age, Dr. Variot's experiments, and contemporaneous comments of the profession and the press




Charles Édouard Brown-Séquard M.D., F.R.S., ETC (1817-1894)



Beyond neurology, Brown-Séquard had many innovative ideas. He was among the first endocrinologists (Figure 6). After Addison described what is now called Addison's disease, Brown-Séquard conducted animal experiments in 1856 to confirm these findings by removing adrenal glands from cats, dogs, guinea pigs, rabbits, and mice, which resulted in death.[12,13] Although the findings of both Addison and Brown-Séquard were initially disputed, they were both ultimately proven correct.

At age seventy-two, Brown-Séquard, who had long experienced psychosomatic symptoms, complained of declining strength, poor concentration, fatigue, insomnia, and worsening constipation. While this may have reflected normal aging, he devised a solution made from testicular blood, seminal fluid, and extracts from the testicles of healthy dogs and guinea pigs. He injected himself ten times over three weeks and believed that his condition improved. He reported these findings to a French scientific society and even measured his strength and stamina in what would now be considered an open-label, single-subject experiment (Figure 7).[14]

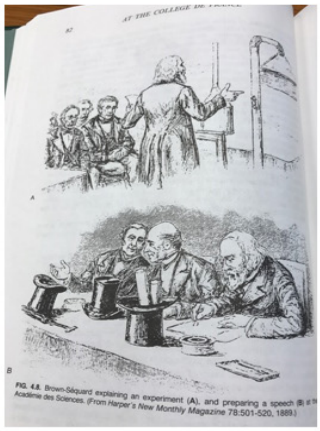
Although controversial, his ideas attracted attention. In the United States, Dr. William Hammond, surgeon general of the US Army during the civil war, close friend of Dr. Weir Mitchell, and author of the first textbook of neurology published in the United States, believed Brown-Séquard might be on the right track.[15] His extracts were eventually commercialized and sold publicly. Brown-Séquard also used adrenal extracts to treat Addison's disease and thyroid extracts to treat myxedema. These treatments failed, but this was due to limitations in known chemistry at that time. Later, when the field of chemistry improved and better compounds could be extracted and modified appropriately and administered to patients with success, Brown-Séquard's hypotheses were proven correct.

Brown-Séquard was truly an extraordinary individual. Throughout his career, he remained a dedicated teacher. He was even caricatured in French literature, where his life-extension extracts were mocked. Today, a bust of Brown-Séquard still exists in Port Louis in the Mauritius Islands (Figure 8).

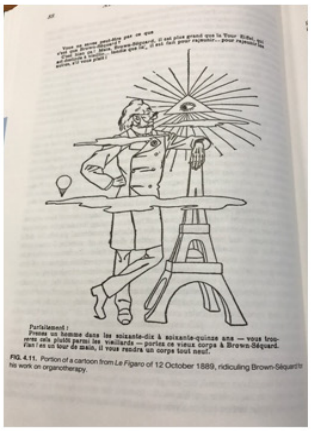
A biography of Brown-Séquard was published in 1946 by J. M. D. Olmstead.[16] More recently, two excellent books have been written about Brown-Séquard by Professor Michael J. Aminoff, University of California-San Francisco (Figure 9).[17,18] The first was published in 1992 and the second in 2011.

Figure 8

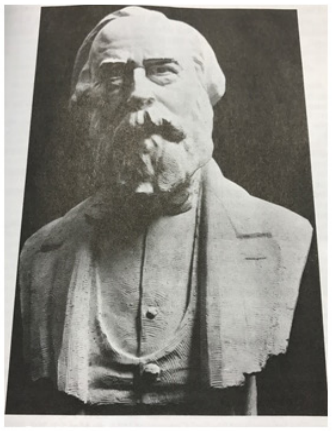
Éduoard Brown-Séquard, MD



Teaching



"Elixir of Life"

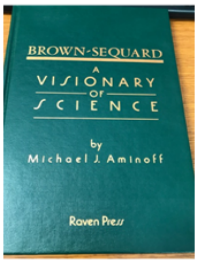


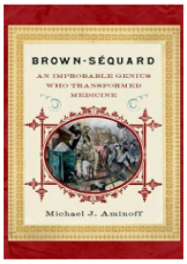
Bust in Port Louis, Mauritius

Figure 9

Biographies of Charles Éduoard Brown-Séquard in English

- Olmstead JMD. Charles Edouard Brown-Séquard, A Nineteenth Century Neurologist and Endocrinologist. Baltimore: Johns Hopkins Press. 1946.
- Aminoff MJ. Brown-Séquard: A Visionary of Science. Raven Press. 1993.
- Aminoff MJ. Brown-Séquard: An Improbable Genius Who Transformed Medicine. New York, NY, Oxford University Press. 2011.





References

1. Brown-Séquard CE. Recherches et experiences sur la physiologie de la moelle épinière. Thèse de Paris. 1846.
2. Brown-Séquard M. De la transmission des impressions sensitives pas la moelle épinière. C R Soc Biol. 1849;1:192-194. English translation in: Wilkins RH, Brody IA, editors. Neurological classics. New York (NY): Johnson Reprint Corp; 1973. p. 49-50.
3. Brown-Séquard CE. Explication de l'hémiplégie croisée du sentiment. C R Soc Biol (Paris). 1850;2:70, 134, 195.
4. Brown-Séquard CE. Experimental researches applied to physiology and pathology. 1853. H. Bailliere, New York, NY and London and Paris. p. 63-68, 95-98. Originally published in: Med Exam (Philadelphia). 1852-1853.
5. Brown-Séquard CE. Experimental and clinical researches on the physiology and pathology of the spinal cord. Printed by Colin and Nowlan, Richmond, Virginia, 1855. Also published in the Virginia Medical Surgical Journal. 1855;4:177, 283.
6. Brown-Séquard CE. Course lectures on the physiology and pathology of the central nervous system. 1860. Republished as part of Landmark Library of Neurology and Neurosurgery series, Burmingham (AL): Gryphon Publications; 1995.
7. Schiller J. Claude Bernard and Brown-Séquard: the chair of general physiology and the experimental method. J Hist Med Allied Sci. 1966;21:260-270.
8. Bernard C. An introduction to the study of experimental medicine. Originally published in French, 1865. First English translation 1827, New York, McMillan Company. Dover Publications Reprint; 1957.
9. Brown-Séquard CE. Researches on the influence of the nervous system upon the functions of organic life. Med Exam (Philadelphia). 1852;8:481; and in Experimental researches applied to physiology and pathology. 1853. H. Baillere, New York (NY) and London and Paris. pp 6-12.
10. Brown-Séquard CE. Recherches expérimentales sur la production d'une affection convulsive épileptiforme, a la suite de lésions de la moelle épinière. Arch Gen Med (5 Ser). 1856;7:143.
11. Brown-Séquard CE. In: Researches on epilepsy: its artificial production in animals and its etiology, nature, and treatment in man. Boston: Clapp. 1857. Originally published in individual articles in Boston Med Surg J; 1857.
12. Brown-Séquard CE. Researches experimentales sur la physiologie et la pathologie des capsules surrenales. C. R. Acad Sci 1856;43:422-425.
13. Brown-Séquard CE. Nouvelles researches sur les capsules surrenales. C. R. Acad Sci, 1857;44:246-248.
14. Dunbar N. The "Elixir of Life"; Brown-Séquard's own account of his famous alleged remedy for debility and old age, Dr. Variot's experiments, and contemporaneous comments of the profession and the press. First published in 1889 by C. J. Cupples Company, Boston, USA. Republished 2018, Bear Books, Leicestershire, UK.
15. Ibid, pages 63, 64.
16. Olmstead JMD. Charles Edouard Brown-Séquard, A nineteenth century neurologist and endocrinologist. Baltimore: Johns Hopkins Press; 1946.
17. Aminoff MJ. Brown-Séquard: a visionary of science. Raven Press. 1993.
18. Aminoff MJ. Brown-Séquard: an improbable genius who transformed medicine. New York (NY): Oxford University Press; 2011.

Two American Civil War Neurologists: The Civilian & The General

Richard J. Barohn, MD

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

A live recording of this lecture can be viewed here:
RAF5 - Two Civil War Neurologists The Civilian & The General

This is another installment in the History of Neurology lecture series. This lecture is on Two Civil War Neurologists, the Civilian and the General.

The civilian is Silas Weir Mitchell. Dr. Mitchell was born in Philadelphia. He attended the University of Pennsylvania and then went to Jefferson Medical College. He traveled to Paris, where he studied under Claude Bernard and Pierre Rayer. Afterward, he returned to America to start a private practice. He also conducted research in toxicology using snake venom, and it was during this time that he began working with Dr. William Hammond, who became a general. Drs. Mitchell and Hammond published numerous papers before the Civil War broke out.

When the war began, Mitchell was assigned to the new neurology hospital called Turner Lane Hospital in Philadelphia. This neurology hospital was established by General Dr. Hammond, who placed Dr. Mitchell in charge, along with Dr. Morehouse and Dr. Keen, a surgeon. The hospital received many soldiers who had injuries from the Civil War. At the time of the Battle of Gettysburg, Dr. Mitchell actually went out to the battlefield and brought soldiers back to Philadelphia for care.

He, Dr. Morehouse, and Dr. Keen became acutely aware of nerve injuries caused by Minié balls, which were the ammunition used in firearms at the time of the Civil War. Minié balls and the Minié rifle were designed by Claude-Étienne Minié in 1846. Wounds inflicted by the conical Minié ball were different from those caused by the round balls from smoothbore muskets, since the conical ball had a higher muzzle velocity and greater mass, and easily penetrated the human body.[1] Mitchell described the term causalgia to refer to severe pain, color change, temperature change, and skin changes that occurred in patients with nerve injuries from these Minié ball wounds.

They published their experiences during the Civil War in a landmark book titled Gunshot Wounds and Other Nerve Injuries.[2] He also published another book during the war called Reflex Paralysis with the same co-authors.[3] After the Civil War, Dr. Mitchell published his most famous book, Injuries of Nerves and Their Consequences, in 1872.[4] This was the first comprehensive book on nerve injuries.

Figure 1

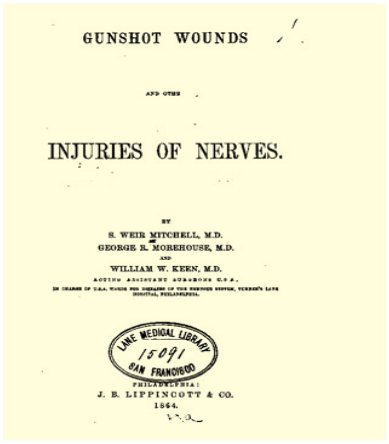
Figure 2

Silas Weir Mitchell (1829-1914)

- Erythromelalgia: known as "Weir Mitchell disease."
- One of the first to use reflexes as part of Neurology exams.
  - Described sensory reinforcement of reflexes
- Rest cure for neurasthenia
  - Isolation, confinement to bed, diet, electrotherapy, and massage
- Published books on Rest Cure for public and medical audiences.
  - Wear and Tear (1871)
  - Fat and Blood and How to Make Them (1877)
  - Rest in the Treatment of Nerves Disease (1875)
  - The Treatment of Certain Forms of Neurasthenia and Hysteria (1877)
- A founder of American Neurological Association (1875)
  - President 1908-09
- Never had an academic appointment.
- In and out patient work at Orthopedic Hospital and Infirmary for Nerve Disease.

Figure 3

Silas Weir Mitchell (1829-1914)


GUNSHOT WOUNDS

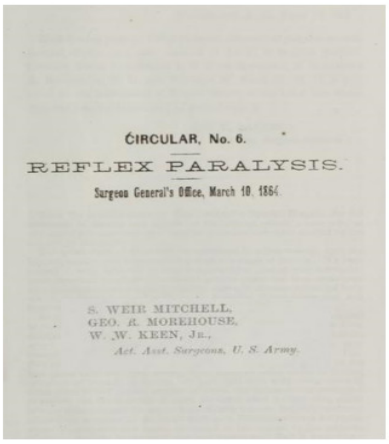
AND OTHER

INJURIES OF NERVES.

BY

S. WEIR MITCHELL, M.D.
GEORGE R. MOREHOUSE, M.D.
AND
WILLIAM W. KEEN, M.D.

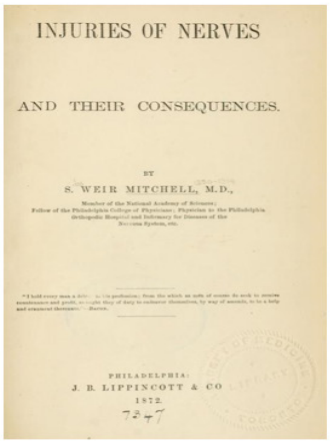
PHILADELPHIA:
J. B. LIPPINCOTT & CO.
1864.


CIRCULAR, No. 6.

REFLEX PARALYSIS.

Surgeon General's Office, March 10, 1864.

S. WEIR MITCHELL,
GEO. R. MOREHOUSE,
W. W. KEEN, Jr.,
Act. Asst. Surgeons, U. S. Army.


INJURIES OF NERVES

AND THEIR CONSEQUENCES.

BY

S. WEIR MITCHELL, M.D.,

PHILADELPHIA:
J. B. LIPPINCOTT & CO.
1872.

After the war, Dr. Mitchell became known for several other contributions. He first described erythromelalgia, a term we still use in our clinics to describe patients with burning, dysesthesia, and discoloration of the feet bilaterally. He was among the first to incorporate reflex testing as part of the routine neurological exam. In photographs, such as in Figure 3, you can see him holding a reflex hammer while examining a patient. The hammer that Dr. Mitchell is using in this picture was designed specifically for him by Dr. J. Madison Taylor, also from Philadelphia. The muscle stretch reflex was first described by Heinrich Erb and Carl Westphal in 1875. Physicians began using their fingers to elicit muscle stretch reflexes. Drs. Taylor and Mitchell believed that an instrument was necessary to test muscle stretch reflexes easily. The head of the hammer was made of rubber which is still the material used for reflex hammers today. Therefore, Dr. Mitchell was one of the first to use a reflex hammer in his practice.[5]

Mitchell also developed the "rest cure" for neurasthenia. Neurasthenia was a term that Mitchell and others used for patients with a number of non-organic somatic complaints. The rest cure consisted of isolation and confinement, diet, electrotherapy, and time in rest homes for several weeks to recover from neurasthenic symptoms. He wrote several books about this, both for the lay public and the medical profession.

He was one of the founders of the American Neurological Association and served as its president in the early 1900s. Interestingly, he never held an academic appointment. He always worked in both inpatient and outpatient settings at the

Figure 4

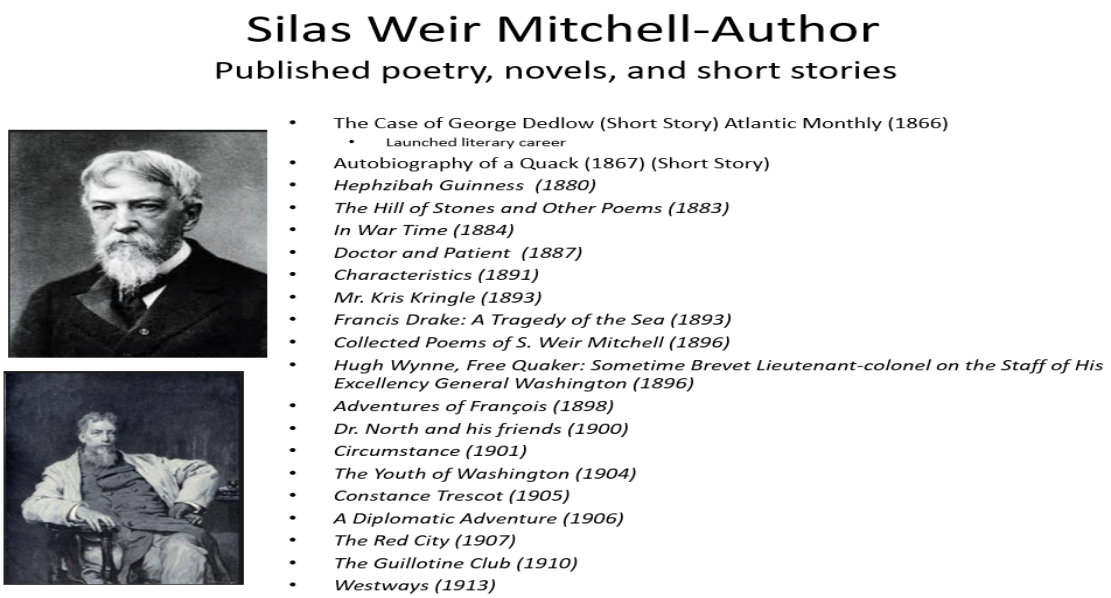


Figure 5

Orthopedic Hospital and Infirmary for Nervous Diseases in Philadelphia.

Mitchell was also famous for pursuits outside of medicine. He was an author of novels and poetry. His novels were extremely popular and sold very well at the time, and some are still in print today. Figure 5 shows a screenshot from a recent search I did on Weir Mitchell's books that, surprisingly, are still being republished. I say that I am surprised by this because I have collected and tried to read the early editions of his novels and have found that they do not translate well to the modern era. Nevertheless, he was indeed a very successful author.

As an aside, I think that the young Weir Mitchell, as shown in Figure 6, has a striking resemblance to the modern actor Donald Sutherland (M*A*S*H, Animal House, A Time to Kill, The Hunger Games) when he was a young man!

The general was Dr. William Hammond. He was Weir Mitchell's friend, and as I mentioned earlier, they conducted research together on snake venoms. Dr. Hammond was a US Army physician who served tours in New Mexico, Kansas, and Florida, and he was stationed at West Point for a time. He was involved in the Sioux Indian Wars and briefly chaired Anatomy and Physiology at the University of Maryland after his initial army service.

When the Civil War broke out, President Lincoln appointed him Surgeon General at a very young age. General Hammond assigned Dr. Mitchell to lead the neurological hospital at Turner's Lane. Dr. Hammond also founded the Army Medical Museum, which later became known as the AFIP (Armed Forces Institute of Pathology). He improved sanitation in wartime hospitals and developed the pavilion system for Army hospitals, which was used for generations.

Figure 6

Figure 7

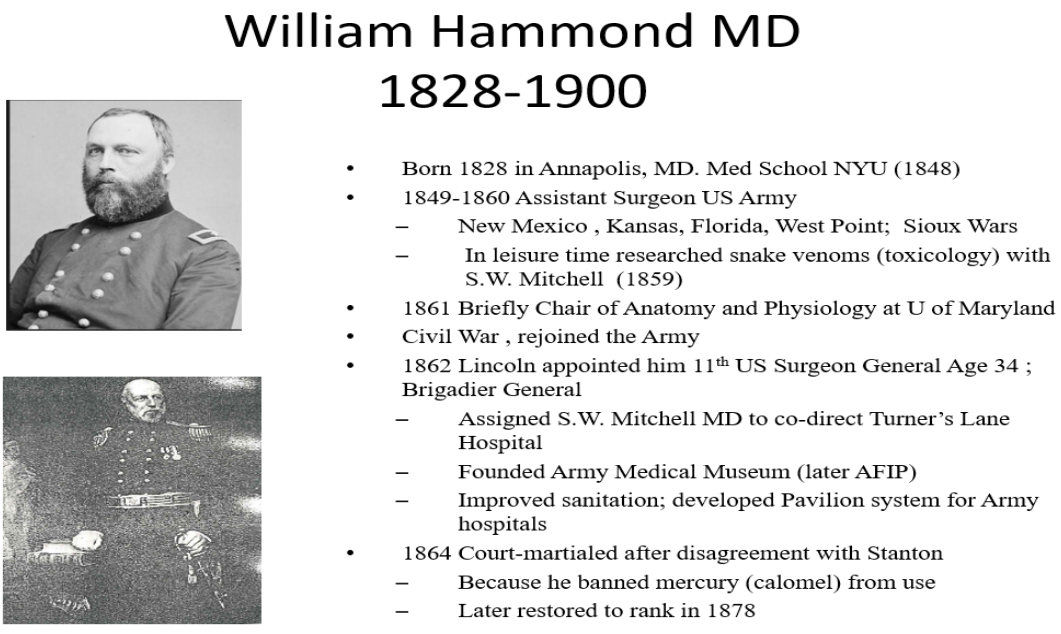
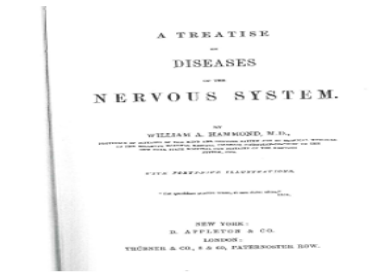
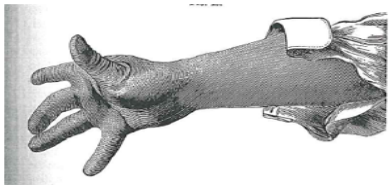
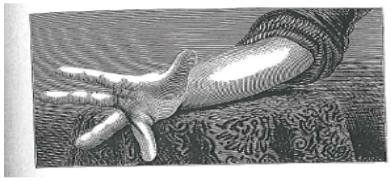


Figure 8


A TREATISE
ON
DISEASES
OF THE
NERVOUS SYSTEM.
BY
WILLIAM A. HAMMOND, M.D.,
NEW YORK:
D. APPLETON & CO.
LONDON:
TRÜBNER & CO., 8 & 60, PATERNOSTER ROW.





William Hammond MD
1828-1900

- 1867 Prof of Nervous and Mental Diseases at Bellevue Hospital NYU; lectured in neurology, Columbia.
  - Later on faculty at U of Vermont, Burlington (1871)
- Practice limited to nervous or mental diseases. (first in the USA)
- 1871 *Treatise on Diseases of the Nervous System*
  - First real neurology text book in the USA
- Described athetosis (Hammond's Disease)
  - Speculated lesion was in corpus striatum.
- Research on lithium for mania
- Co-founder with S.W. Mitchell and others of the ANA (1874)
  - President 1882
- Critic of Spiritualism. *The Physics and Physiology of Spiritualism* (1871) and *Spiritualism and Allied Causes and Conditions of Nervous Derangement* (1876)
- Wrote 7 novels (1868-1887)

However, Hammond eventually came into conflict with Secretary of War Edwin Stanton and was court-martialed. His rank was later restored in 1878. A well-known photo shows Dr. Hammond putting on his uniform late in life after being reinstated as a general.

After the war, Hammond set up a private practice in New York devoted to nervous and mental diseases. This was the first practice of its kind, and he can therefore be justly described as the first neurologist in the United States. He joined the staff at Bellevue Hospital, lectured at Columbia, and later joined the faculty at the University of Vermont. He wrote what is considered the first major American textbook on diseases of the nervous system, titled A Treatise on Diseases of the Nervous System.[6] It is an impressive and well-illustrated volume. Reproductions of this volume are still easily obtainable.

Hammond coined the term athetosis and correctly speculated that its cause lay in the basal ganglia, or corpus striatum. The condition was known as "Hammond's disease" for many years. He also conducted research on lithium for mania, which is remarkable since it remains one of our main treatments today. Along with Weir Mitchell, he co-founded the American Neurological Association.

Hammond was also a vocal critic of spiritualism, which was fashionable in the late 1800s. He wrote books debunking spiritualism as pseudoscience. He wrote seven novels, not as many as Weir Mitchell, but still a notable number for a neurologist.

So, not only were Drs. Mitchell and Hammond great physicians, but they were also prolific novelists whose books were widely read at the time.

This concludes the History of Neurology lecture on Two Civil War Neurologists, the General and the Civilian.

References

1. Keegan J. The American Civil War: A Military History. 1st ed. Alfred A. Knopf; 2009.
2. Mitchell SW, Keen WW, Morehouse GR. Gunshot Wounds and Other Injuries of Nerves. Philadelphia: J.B. Lippincott. 1864.
3. Mitchell SW, Keen WW, Morehouse GR. Reflex Paralysis. Washington, D.C. 1864.
4. Mitchell SW. Injuries of Nerves and Their Consequences. Philadelphia: J.B. Lippincott. 1872.
5. Lanska, DJ. The History of Reflex Hammers. Neurology. 1989;39(11):1542.
6. Hammond WA. A Treatise on Diseases of the Nervous System. New York, D. Appleton and company. 1871.

About the Cover

Marie Nau Hunter

Interim Director
Museum of Art and Archaeology,
University of Missouri

Cover image: Albert Bierstadt (American, born Germany, 1830–1902), *North Italian Landscape*, ca. 1856–57, oil on canvas, museum purchase (77.203)

While not of Stresa, Italy, where the September 2025 NMSG meeting was held, the *Northern Italian Landscape* painted by renowned German-American artist Albert Bierstadt and featured on this journal's cover might remind conference goers of the beauty of the Italian landscapes witnessed in between neuromuscular study sessions and reports on related drug trials.

Bierstadt is best known for his large oil paintings of the American West. He first traveled westward from his home and studio in New York City in 1859 with a federal land surveyor, sketching along the way as he gathered inspiration for eventual works. The resulting views were almost always lavishly painted, evoking what might be considered romanticized depictions of the locations chosen by the artist.

The size of Bierstadt's *Northern Italian Landscape* that hangs in our Gallery of European and American Art is much less than the monumental paintings the artist is best known for. But it is no less impressive in showcasing the Bierstadt's ability to paint sweeping views of the outdoors. Our files note that the scene is likely one he chose to paint while staying in Rome in 1856 and 1957.

The expanded label in our gallery, written by the museum's curator of European and American Art, Rima Girnius, PhD, reads as follows:

> German-born artist Albert Bierstadt became famous for his expansive views celebrating the majesty of America's western mountain ranges. However, like many of his contemporaries, he refined his technique and established his credibility as an artist when he lived in Europe from 1853 to 1857. This painting is based on sketches executed during one of his excursions through the mountains of Germany and Italy. Although small in scale, it is grand in conception and anticipates his later work. Glowing under warm twilight, this tranquil scene celebrates humankind's harmony with nature. Two figures meet on a country road in the foreground while Italianate buildings sit nestled in the trees on the left.

Museums undertake all varieties of special events and tricks of the trade to entice visitors in to enjoy the art. In our case, the busiest three-day weekend of the year is the annual Art in Bloom. The event has become a perennial favorite of mid Missourians, having first been presented in 2005. We bill it as a pairing of fine art and flowers. How lucky we are to partner on it with a multitude of generous and creative florists, professional and student, to undertake the big weekend.

The basics are that florists each select a work of art that most interests them and then design florals for delivery at a prescribed time. The arrangements – 18 of them this past April – are installed in our galleries near the works that serve as the inspiration for each. They are first revealed to museum members at an evening event called Flowers After Hours.

Over the next two days, we offer expanded public viewing hours and related special events like a floral themed Family Day at the Museum. In all, more than 1,300 came through our doors to enjoy Art in Bloom 2026, a record for us.

Bierstadt's *North Italian Landscape* was selected this year by Columbia, Mo.-based Kent's Floral Gallery as their inspiration for Art in Bloom. Floral designer Brittani Williams offered this when asked what drew her to the painting:

> "The colors caught my eye first thing. They are inviting and made me want to stop to take a closer look. The more I look at it, the more I want to be in the painting, taking it all in. I love designing in a way that can highlight natural lines and curves and add structure to emphasize the beauty that is already there."

Art in Bloom 2026 floral arrangement created by Kent's Floral Gallery, Columbia, Mo., as a pairing to Albert Bierstadt's *North Italian Landscape*, a painting in the permanent collection of the University of Missouri's Museum of Art and Archaeology.

All weekend of Art in Bloom, the public is invited to vote on the arrangements as they stroll the galleries. Awards are announced Sunday afternoon, a few hours before the close of Art in Bloom. For her work, Brittani was awarded Best Use of Color (professional category). Please enjoy this photograph of her floral creation as it was in our European and American Art Gallery, on a pedestal within view of the Bierstadt painting.

Photos of all 18 of the Art in Bloom 2026 submissions can be viewed on our website. The images are accompanied by descriptors from each florist about their selections.

If you are reading this from a screen in central Missouri, please visit the museum to see Bierstadt's *North Italian Landscape* in person, as works of art are best viewed. If you live and work further away, I hope you'll plan a trip to Columbia.

As I have written in past columns, please ask for me at the museum's visitors services desk if you stop in during regular work hours. I will tour you though our galleries with a special stop to admire Bierstadt's painting.

The Museum of Art and Archaeology (MA&A) is located in the lower east side of Ellis Library, with entrances off Hitt Street, Lowry Mall, and from within Ellis. Regular hours during the week are 10 a.m. to 4 p.m. Tuesday through Friday, and noon to 4 p.m. on Saturdays and Sundays. Admission to the museum is always free.

For more information about the MA&A, in general, including a calendar of events and a searchable database of the museum's permanent collection of more than 16,000 objects, visit maa.missouri.edu. If you want to experience the beauty and fun of Art in Bloom, mark your calendar now for April 24-25, 2027.

The 2027 Next Generation Research Grant in Neuromuscular Disease

Advancing early-career research for innovative treatments.

will open for applications in mid-June. This early-career research grant consists of a commitment of $150,000 over two years, and is awarded in partnership between the NMSG and the American Brain Foundation. For additional details and to apply, visit https://www.americanbrainfoundation.org/for-researchers/#ngrg.

KEY DEADLINES:

- **Applications Open:** Mid-June 2026
- **Applications Due:** October 1, 2026
- **Review Process:** October - December 2026
- **Recipient Selection:** Mid-January 2027
- **Fellowship Term Begins:** July 1, 2027