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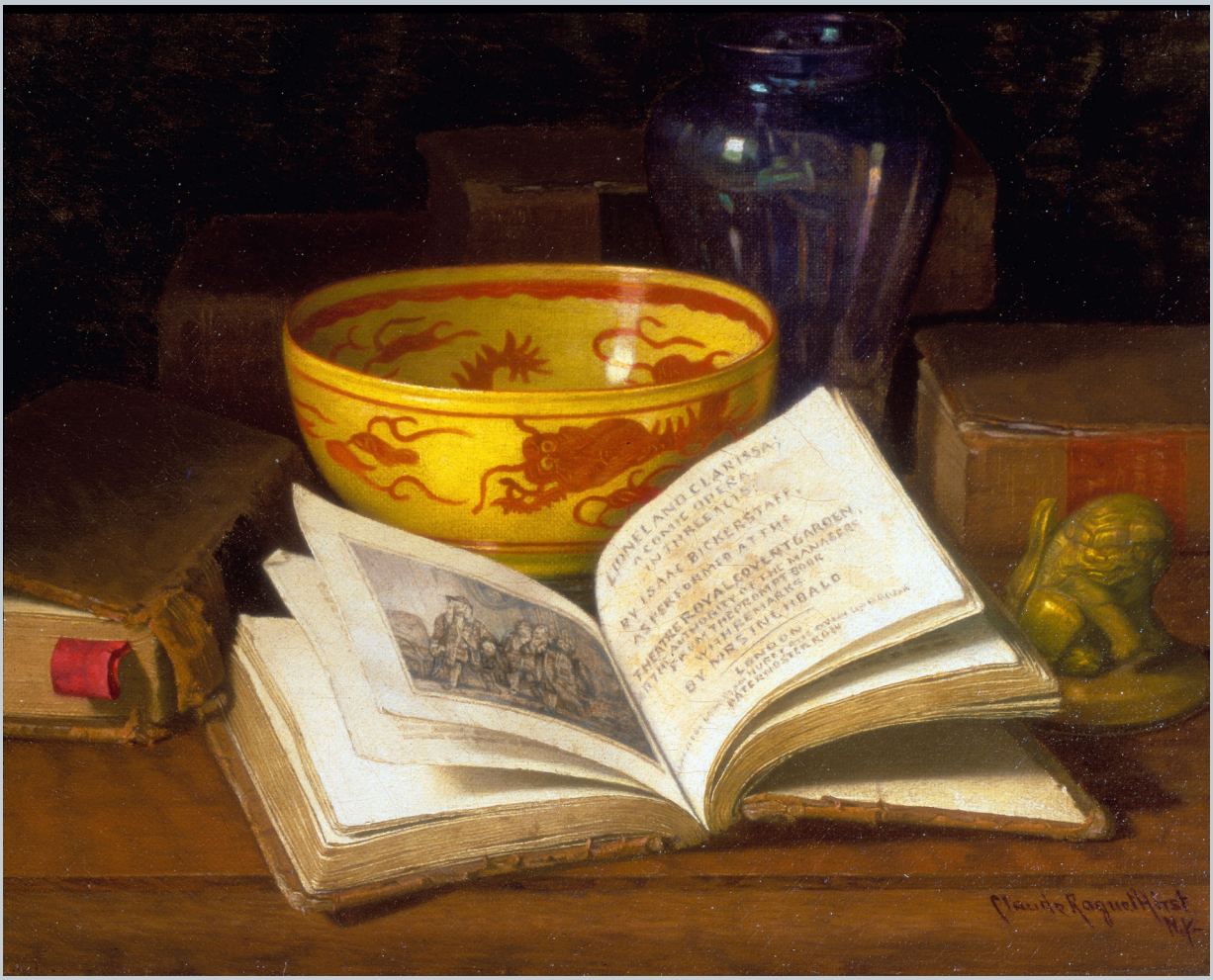

The Official Journal of:

EDITORS

Cover image: Claude Raguet Hirst (American, 1855–1942), *Still Life with Bowl (Lionel and Clarissa—A Comic Opera)*, 1922, oil on canvas, Gilbreath-McLorn Museum Fund and Gift of Museum Associates (91.280)

For more information, see "About the cover," p.100.
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Letter from the Founding Editor for Volume 6, Issue 1

Richard J. Barohn, MD

Welcome to Volume 6, Issue 1 of the RRNMF NMJ, our first issue of 2025. In this issue you will find the following:

We have editorials from both Dr. Josh Freeman and Dr. Don Frey, who are both retired chairs of family medicine and they continue to provide inciteful views on medicine and life both in the USA and beyond.

In our new original papers, Dr. Mandeville and colleagues in Massachusetts describe findings of near fiber EMG in a cohort of myasthenia gravis patients. Drs. Mahmood, McKee and Yuebing Li describe their experience of detecting a lymphoproliferative disorder in twenty patients with motor neuron disease. Grace Li and colleagues report on their database search on articles describing stem cell therapy for myasthenia gravis.

In the Case Reports section, Dr. Ortiz-Guerrero describes the challenges of a case of MRI negative myelitis associated with myelin oligodendrocyte glycoprotein (MOG) antibodies. And the teams at the University of Missouri, of which I am a member, have two case reports. One led by Dr. Ketabforoush and colleagues about a case of facioscapulohumeral dystrophy (FSH) and myasthenia gravis (MG) and a review of the literature of similar cases with co-existent diseases. And the other first authored by Janie Bruce and a number of colleagues describing a patient with inclusion body myositis who lost their finger prints, also known as acquired adermatoglyphia. In the review article section, we again publish a transcript from the neuromuscular course I and a number of colleagues have put on around the country for over a decade. This transcript with power point slides is the lecture on the neuromuscular junction and covers MG and the Lambert-Eaton myasthenic syndrome (LEMS).

Finally, the cover art for this issue again comes from the University of Missouri Museum of Art and Archeology. It is a wonderful still life by the American artist Claude Raguet Hirst. It is on permanent display in the museum and I have become a big fan of not only the museum but of this painting in particular showing an arrangement of antique books and a bowl, vase, and little figurine. I am very glad that Deputy Museum director Marie Nau Hunter has provided a more detailed description of the work and was able to once again get permission for us to highlight a work from the museum. In her piece she also describes the museum at Mizzou and welcomes all who come to campus to visit. It is a gem right in the middle of campus.

We are also very pleased to add a new associate editor, Dr. Dipika Aggarwal. Dr. Aggarwal is a neurologist at the University of Kansas Medical Center and was once one of my residents and fellows. We are glad to have her on board the team. We also have added a University of Missouri medical student as a copyeditor, Alana Labaschin. Another new member is Michaela Duran who is serving as our Undergraduate Editor. She replaces Lauren Peck who graduated and is about to start PA school. Thank you Dr. Aggarwal, Alana and Michaela, and Lauren. We will be adding additional medical students in the near future as some of our current student editors will near graduation.

The NMSG 26th Annual Scientific Meeting will be held in Stresa, Italy, September 26-28. The abstract submission portal is open and will close on June 1. Travel funds are available for the highest scored non-industry abstracts. More information can be found here.

Finally, we would like to thank our reviewers who kindly helped us in doing reviews of submitted manuscripts in 2024. A list of the reviewers is listed on the following page.

Rick

Thank You to our 2024 Reviewers!

Justin Abbatemarco
Dipika Aggarwal
Carolina Bennett
Jonathan Bresner
Vera Bril
Banjamin Claytor
Andres De Leon
Ericka Greene
Saiju Jacob
Chafic Karam
Yuebing Li
Alexis Lizarraga
Michael Pulley
Vernon Rowe
Nirav Sanghani
David Saperstein
Matthew Varon
Gil Wolfe

Dark times for public health and healthcare: Will the insurance industry fix itself?

Joshua Freeman, MD

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

It's an exciting time for both health care and public health! Anything is possible, and if it isn't yet, it soon will be! On the public health front, President-elect Trump has nominated Robert Kennedy Jr. for the position of Secretary of Health and Human Services. Kennedy has long been what is generously called a "vaccine skeptic" and his lawyer, Aaron Siri, has sued the Food and Drug Administration to revoke the approval of the polio vaccine. Although the *NY Times* article says 'Like Mr. Kennedy, Mr. Siri insists he does not want to take vaccines away from anyone who wants them. "You want to get the vaccine — it's America, a free country,"' this is disingenuous. If the FDA approval is revoked, *nobody* will be able to get it.

I have written recently about the importance of vaccines, especially polio and measles, in preventing disease and death (Raw milk, vaccines, and RFK, Jr: Some dates worth remembering, Nov 15, 2024). A series of letters to the *Times* in response to this article make the risk clear. Read them; they address the science, the controlled trials of polio vaccine, the experience of those who were doctors and children during previous polio epidemics, and touchingly, the experience for dancer Tanaquil LeClerq, wife of choreographer George Balanchine (short answer: no vaccine, polio, and paralysis). In regard to other vaccines, we can read in the *Times* 'Tiny Coffins: Measles Is Killing Thousands of Children in Congo' and imagine it happening in the US as a result of Kennedy's anti-vaccine actions. Kennedy calls his movement "health freedom" and says that he will give infectious diseases a "break" (whatever that means), but in fact, as described by Gregg Gonsalves in *The Nation,* RFK Jr. Is Giving Infectious Diseases a Promotional Tour.

I posted on Facebook that I have heard people say "kids get too many shots", and asked "then which preventable disease do you want your child to die of?" One comment I got from a colleague was that the problem was not that kids get too many shots, but that too many kids *get shot*! The most recent killings, in a Christian school in Madison, WI (15-Year-Old Girl Identified as the Shooter in a Wisconsin School) were at least the 323rd this year in the United States! *This* is an epidemic; the extent of which people in most other countries cannot imagine, and, like many of us, wonder what will be done about it. Sadly, the answer is going to be very little, if anything. We may be closing out the statistics for deaths from school shootings in 2024, but nothing suggests that 2025 will be any better.

On the healthcare front, things are not getting better. The anger at the health insurance industry exposed by the shooting of UnitedHealthcare CEO Brian Thompson was deep, broad and well-justified, as I wrote in Murder of a Health Insurance CEO: People HATE the companies and the people who run them (Dec 8, 2024). Study after study continues to appear providing evidence that more and more people that have inadequate, unaffordable, or no health insurance. The *Commonwealth Fund* recently published a report that shows Hispanic/Latino Adults Lack Adequate, Affordable Health Insurance Coverage, and that this led to their existent trouble accessing health care, but the breadth of this concern goes far beyond Latinos.

Maybe we can come up with a solution! I think I have already indicated several – mainly instituting a single-payer universal national health insurance program or, until we do, capping the amount of out-of-pocket costs a person can have to a reasonable number ($1000?). Another potential solution could be limiting the profits of health insurers, as well as the ways in which health care providers (e.g., hospitals, nursing homes, doctors, etc.) generate revenue—whether for-profit or nonprofit—at the expense of people's health.

Others have entered this discussion. In a remarkable Op-Ed essay in the *NY Times* on Dec 13, UnitedHealth Group's CEO Andrew Witty (Brian Thompson's boss, who makes more than $20M a year) wrote The Health Care System Is Flawed. Let's Fix It. Remarkably, the Times chose to publish it despite offering no meaningful solutions for fixing the issue—certainly none that would threaten UnitedHealth's profits. It mostly displays the *Times'* complicity in an effort to focus *away* from the righteous fury of the American people with the health insurance industry.

USA Today reports on Seven reasons why Americans pay more for health care than any other nation, and it gets most of them right: Reason 1: Lack of price limits, Reason 2: Hospitals and doctors get paid for services, not outcomes, Reason 3: Specialists get paid much more—and want to keep it that way, Reason 4: Administrative costs inflate health spending, Reason 5: Health care pricing is a mystery, Reason 6: Americans pay far more for prescription drugs than people in other wealthy nations, Reason 7: Private equity. There are a few others, but it is a good list. Despite that, however, it doesn't come up with a meaningful, comprehensive solution to any of the matters. Indeed, it ends up quoting the Witty piece referenced above, "*We know the health system does not work as well as it should, and we understand people's frustrations with it,*" rather than having any kind of answer. For instance, no mention of universal non-profit health insurance, limits on hospital system (and physician) incomes, or banning private equity and other for-profit players from the health system!

Maybe it is asking a lot for insurance companies, largely the perpetrators of this massive scam that is bleeding the entire US economy, to come up with a "solution". But *USA Today, Commonwealth Fund,* and others do such a good job of identifying the problem, they should be able to take the simple next step to recommending the fix. In what I consider to be an amazingly open (if entirely disgusting and reprehensible) acknowledgment of their agenda, CNBC reported back in April 2018 that Goldman Sachs, the huge investment bank (led by CEO Jamie Dimon), raised the question, while discussing biotech research, 'Is curing patients a sustainable business model?'.

Actually, it is a good question. Maybe the answer is "no". Most ethical physicians I know (and it is the vast majority who are ethical) have always said something like "I look forward to the day when we can put ourselves out of business". Investment banks and other forms of private equity, as well as the insurance companies like UnitedHealth and the providers that they control, do not see this as a positive. Maybe it is refreshing to see such a stark portrayal of the problem? Or not.

But I, along with what I believe to be most Americans, would prefer to see diseases and the people suffering from them cured. We would be glad to see the profits of these crooks, profiteers and privateers, along with the extravagant salaries of their C-suite executives and boards, disappear.

Wandering among the ghosts in Dresden, searching for the letter "L"

Donald R. Frey, MD

This article originally appeared in Dr. Frey's blog, "A Family Doctor Looks at the World." https://afamilydoctorlooksattheworld.com/

"I envy you lads," the Englishman said. "You lads are leaving this afternoon for Dresden—a beautiful city, so I'm told. . .you needn't worry about bombs, by the way. Dresden is an open city. It is undefended, and contains no war industries or troop concentrations of any sort."— Kurt Vonnegut, Slaughterhouse Five, 1969.

"There were so many corpses, that German soldiers gave up burying them and simply burned them on the spot with flame-throwers."—Kurt Vonnegut (1922-2007), recalling the aftermath of the bombing of Dresden that he witnessed as a prisoner of war (POW), February 15, 1945.

Visit Dresden on an overcast winter day and the ghosts will be sure to find you. Amidst some of the most formidable gothic structures in the world, buildings that once gave the city the title "Florence of the Elbe River," you can almost feel Dresden groan under the strain of its history.

The massive Cathedrals and public buildings stood for decades. Then came February 13, 1945.

Throughout the war, the sophistication of bombing techniques had been evolving for both the Allies and Nazis--bigger planes, more bombs, and greater casualties. In Europe, it reached its peak that winter day on the Elbe.

Years before I set foot in Dresden, I'd visited Coventry, England. Located in the industrial north, it was best known for its local heroine, Lady Godiva, who supposedly rode through town in her birthday suit to protest high taxes. The story also goes that an unlucky young chap (as the Brits would say) named Tom, 'peeped' at the naked figure too long, and either went blind or was struck dead, depending on who you want to believe. His name has been associated with voyeurism ever since.

Coventry later became known as the Detroit of England, manufacturing the nation's automobiles. By 1940 it had been converted to wartime production. The Nazis, who had been ruthlessly bombing London for months, were determined to take out Coventry's capacity. On the night of November 14, 1940, they launched *Mondscheinsonate,* Operation Moonlight Sonata.

515 German bombers crushed the city, leaving even the Cathedral of St. Michael in ruins. Nearly seven hundred people perished, the number kept low only because thousands were able to hunker down in underground shelters.

The bombing was so complete, so utterly devastating, that the Nazi propaganda machine invented a new verb to describe it--*"koventrieren,"* or in English 'to coventrate', meaning "to annihilate or reduce to rubble".

Up to this point, the British had bombed primarily military targets. But now the gloves came off for both sides. Massive bombing, without regard to civilian populations, became the order of the day.

This brings us to Dresden.

From a military perspective, Dresden was neither a troop center nor a manufacturing hub. Arguably, it was railroad crossroads at best, far removed from British or American fighting. Most Germans thought it was the last place they'd experience a concentrated bombing.

Of course, they were wrong. On the night of February 13, 1945, the first wave of British Lancaster bombers struck, over 700 in all. By morning, the city was in flames. Then came the Americans.

Over 316 B-17 bombers hit the city on the 14th. They returned on the 15th. By now Dresden was in ruins.

Over 4,000 tons of bombs struck the city. Most German air defenses had been transferred elsewhere, and to say the city was a sitting duck would be an understatement.

No one knows how many were killed. Estimates range from 20,000 to 100,000. More than Coventry. Probably fewer than Tokyo. The city was packed with refugees. The Russians were pushing rapidly from the east, and those fleeing the advance were pouring into the city. Just how many is impossible to say.

Why Dresden? Some say it was because of the city's railroad access. Others claim intelligence indicated the Germans were going to establish a defensive bulwark in the city, and that the bombing could aid the Russian advance to the east.

Still others claim it was also meant to impress, and maybe even intimidate the Russians. One Royal Air Force (RAF) memo issued to its airmen included in its justification for the bombing "...incidentally to show the Russians when they arrive what Bomber Command can do."

The bombing created what is commonly called a "firestorm." Flames so hot, so all consuming, they suck every oxygen molecule into the inferno. Those who aren't burned to death suffocate from breathing the dead air.

The heat was so intense that bomber crews 16,000 feet above the city were drenched in sweat as their planes were tossed about by the updrafts.

The firebombing of Dresden remains controversial to this day. Some called it a war crime. Some said it was justified. It was war. These things happen.

Walking around the city, I tried to ask the ghosts, but they weren't talking.

Which brings us to Kurt Vonnegut.

A 22-year-old Army scout, Private Vonnegut was captured at the Battle of the Bulge, and ultimately sent to Dresden to labor as a POW. He and his fellow captees were

housed in a damp underground cavern that had previously been used to store butchered beef.

Schlacthof Funf, it was called. Slaughterhouse Five. The prisoners were confined there when the bombing started. They didn't emerge until the 15th, and suddenly confronted the aftermath. Vonnegut would later recall the landscape looked like the surface of the moon—except there were bodies everywhere.

Vonnegut, of course, later became a celebrated author, but it took him nearly twenty-five years and multiple shredded drafts to tell the story of Dresden. For those who haven't read it, it's a disjointed, dizzying story of Vonnegut's alter ego, Billy Pilgram, who also survives the bombing of Dresden, only to become "unstuck in time," moving backward and forward, even reliving his own death years later.

There's also flying saucers and alien abductions, but I won't spoil it for you. In short, it's exactly the kind of book you'd expect from a gifted science fiction author, who almost certainly suffered from undiagnosed post-traumatic stress disorder (PTSD).

Today, Coventry and Dresden consider themselves to be sister cities. Both have been rebuilt. Stone by stone. Brick by brick. And they share the same pain.

But neither will ever be the same.

Which brings us to the Drake Equation. And the letter "L."

Like most American kids, Frank Drake was fascinated with the thought of life on other planets. Later, as an astrophysicist, he decided to try to calculate the odds that such planets existed, and whether they could ever communicate with us.

It became known as the Drake Equation. For the benefit of any math geeks, you can find it at the bottom of this post. The equation didn't deal with UFOs or little green men, but rather with the likelihood that radio waves or some form of communication could reach us here on earth.

The equation took all sorts of factors into consideration. How many planets are out there? How many can support life? And what fraction of those go on to develop civilizations capable of transmitting messages into space?

Then Drake added one final question to the puzzle—what is the average **length of time** a civilization can actually transmit such messages (the letter "L" in his equation). Is it forever? Is it a million years?

Or does a civilization that reaches such a point only flourish for the blink of an eye before it destroys itself?

With radio telescopes and deep space probes that can map the known universe, we are just beginning to define most of variables in the Drake Equation.

All except one. What is L? We don't have a clue.

An English veteran of the First World War once said that the only redeeming aspect of his time in the War was knowing that it had been so terrible, so utterly horrifying, that such a war could never happen again. Of course it did.

The weapons of the Second World War put those of the First to shame. High altitude bombing. Massive tank warfare. And of course, the atom bomb.

The war also saw the world's most highly sophisticated effort on the part of one group of people to exterminate another group of people from the face of the earth.

Since the war's end, our civilization has seen many advances: miraculous medical discoveries, the internet, global travel.

We've also developed intercontinental ballistic missiles (ICBMs), hypersonic missiles, nerve gas, and biological weapons. And of course, the hydrogen bomb.

In Rwanda and elsewhere, the determination of one group of people to utterly destroy another group purely for the sake of who those people are, continues to play itself out. We've even given it a name: genocide.

This brings us back to Dresden.

As 2025 looms, countries are again posturing, threatening, and arming themselves to the hilt. Leaders are demonizing those within their own borders and beyond. Nationalism of all stripes, with its 'us against you' extremism, is rapidly growing throughout the world.

How many of those extraterrestrial civilizations reached precisely this point before blowing themselves up? How many reached this point, only to step back at the brink and move away from their destruction?

What direction will we take? What will be the L variable in our own equation?

Who knows? But these are the kinds of things a 73-year-old Midwesterner thinks about as he wanders the streets of Dresden. Listening for the voices of ghosts.

So it goes.

And (as promised) The Drake equation:

$N = R_* \times f_p \times n_e \times f_l \times f_i \times f_c \times L$ N=R∗·fp·ne·fl·fi·fc·L

Where

N = the number of civilizations in the Milky Way galaxy with which communication might be possible

and

R_* = the average rate of star formation in our Galaxy.

f_p = the fraction of those stars that have planets.

n_e = the average number of planets that can potentially support life per star that has planets.

f_l = the fraction of planets that could support life that actually develop life at some point.

f_i = the fraction of planets with life that go on to develop intelligent life (civilizations).

f_c = the fraction of civilizations that develop a technology that releases detectable signs of their existence into space.

L = the length of time for which such civilizations release detectable signals into space.[6][7]

Happy New Year, everyone. Please be safe.

Near Fiber Electromyography in the Diagnosis of Myasthenia Gravis

Ross Mandeville, MD[1], Adam Patterson, MD[1], Justin Luk[2], Art Eleanore[3], Oscar Garnés-Camarena, MD[4], Dan Stashuk, PhD[5]

[1] Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
[2] Department of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[3] Department of Neurological Surgery, Beth Israel Lahey Hospital and Medical Center, Tufts University School of Medicine, Burlington, Massachusetts, USA
[4] Department of Clinical Neurophysiology, Jiménez Díaz Foundation University Hospital, Madrid Spain
[5] Department of Systems Design Engineering, University of Waterloo, Waterloo Ontario, Canada

Abstract

Background:
Near fiber EMG (NFEMG) focuses on the activity of muscle fibers close to the electrode and offers the ability to semi-automatically assess neuromuscular junction instability using measures conceptually similar to single fiber EMG (SFEMG) jitter. As such, compared to SFEMG, NFEMG measures of instability can be obtained significantly faster, with minimal training and manual editing and no marker positioning. The objective of this retrospective study was to compare the accuracy of using NFEMG and SFEMG measures of instability in diagnosing myasthenia gravis (MG).

Methods:
NFEMG was blindly applied to recordings from 50 patients SFEMG-tested at Surgery, Beth Israel Lahey Hospital and Medical Center (BIDMC) in the prior 18 months (12 with MG, 38 without). Excluding the myopathic and neurogenic patients, diagnosis based on NFEMG and SFEMG results were compared to the clinical diagnosis using cross-validation that involved 10 randomly selected training sets and their corresponding testing sets.

Results:
In patients free of myopathy or neuropathy, NFEMG sensitivity was 100% while specificity ranged from 89% to 95% (mean of 90%). When testing on the entire cohort of patients free of other neuromuscular conditions, NFEMG sensitivity and specificity were 100% and 94%, respectively, while SFEMG sensitivity and specificity were 94% and 97%, respectively.

Conclusion:
NFEMG is a rapid technique, requiring minimal training, which is accessible to any physician trained in basic EMG. The results of this study support its promise as an exciting and practical alternative to SFEMG in diagnosing MG, but prospective studies are needed.

Introduction

Myasthenia Gravis (MG) is an autoimmune neuromuscular disease that is underdiagnosed and likely affects more than 70 thousand people in the United States alone[1,2]. The impact on quality of life can be profound and, beyond the life-threatening nature of the condition. The disease can affect many activities of daily living such as vision, breathing, and swallowing, and it is often associated with significant depression and anxiety[3]. The diagnosis of MG classically relies on a combination of clinical findings, presence of autoantibodies, and neuroelectrophysiological studies including repetitive nerve stimulation (RNS) and SFEMG[4]. Although antibodies can be detected in most patients with MG[5], a subset is seronegative, especially ocular MG[6,7]. This requires neuroelectrophysiologic testing to confirm MG and avoid the significant risks associated with overdiagnosis, including years of unnecessary immune therapy and invasive thymectomy or the risks and quality of life implications of underdiagnosis[8–10]. The potential for seronegative MG leads to its inclusion in the differential diagnosis for many patients with weakness of unclear etiology. At most centers, by far the majority of patients undergoing SFEMG do not have MG[13]. However, without confirmation, this large population of patients is at risk of exposure to unnecessary immune therapies. While smaller in size, an important population of seronegative patients are at risk of undertreatment. This results in a high demand for the limited resource of SFEMG, with a healthcare impact far wider in reach than suggested by the relatively small number of seronegative MG patients. Ever more important is the plethora of therapies now available and in the research pipeline that require high performance, efficient, and practical biomarkers of therapeutic response both clinically and in research.

SFEMG assesses electrophysiological temporal dispersion variability between pairs of muscle fibers belonging to the same motor unit (MU) using high pass filtered potentials recorded using single fiber or concentric needle electrodes, and has been shown highly sensitive and specific in the diagnosis of MG[14,15]; however, sensitivity and specificity varies significantly depending on the level of training and population studied[10,16]. In addition to requiring significant training and time to perform, its poor availability in rural and underserved areas in the United States and worldwide[17] likely results in a consequential healthcare disparity for those suspected of having MG, although this has not been directly quantified to date.

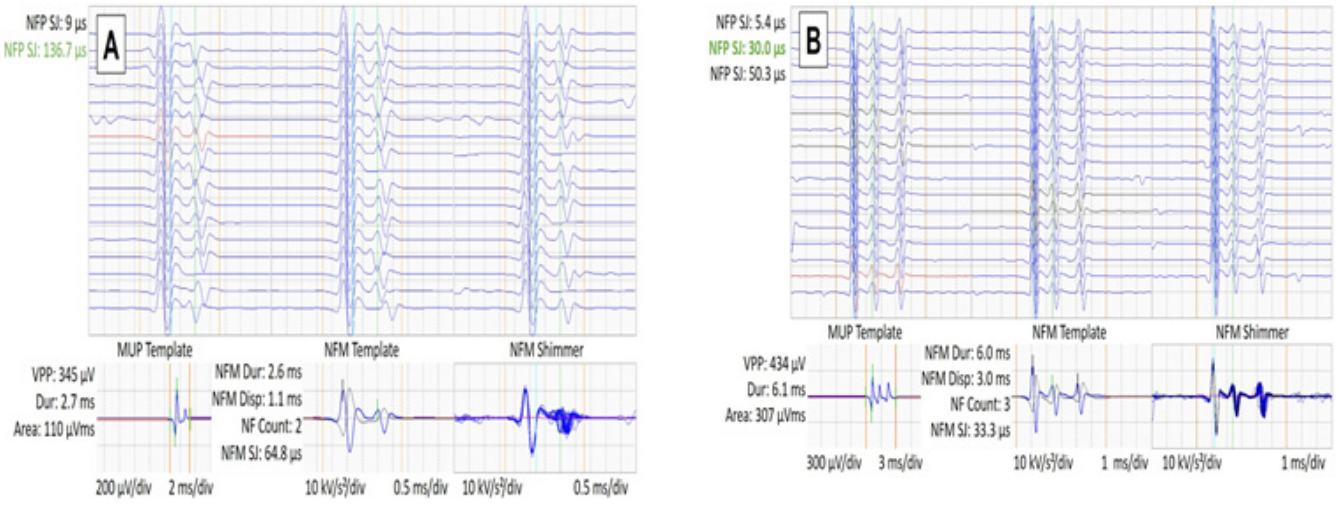

Figure 1. Exemplary NFEMG. The lower panel in each figure shows a raster of NFMs, aligned to the cyan lines, containing 2 NFPks (A) and 3 NFPks (B), respectively. To the left of each raster are the NFPk SJ values associated with each NFPk; these are conceptually similar to SFEMG fiber-pair jitter values. In the lower panels of each figure section, from left to right: a MUP and NFM template and NFM shimmer (overlapped single NFM traces). NFM and MUP feature values are shown: the orange lines demarcate NFM duration. Each short vertical line on the NFM template corresponds to a NFPk. The time interval between the first and last NFPk is the NFM dispersion. NFPk count is the total number of NFPks in the NFM template. NFM duration, dispersion and NFPk count inform about electrophysiological temporal dispersion. NFM SJ and NFPk SJ inform about global and local electrophysiological temporal dispersion variability, respectively.

NFEMG is the study of near fiber MU potentials (NFMs)[18–20], which are motor unit potentials (MUPs) that have been filtered using a low-pass-double differentiation filter. Each symmetric-shaped peak in an NFM, or NF peak (NFPk), represents the contribution of an individual fiber, or a small group of fibers, close to the recording electrode. To assess electrophysiological temporal dispersion variability, NFEMG uses segment jitter (SJ) values based on offset times between matched segments of consecutive NFMs and calculated in a fashion similar to mean consecutive difference (MCD) values. Global NFM instability can be assessed using NFM SJ values based on all NFM segments within the NFM duration. Local NFM instability can be assessed using NFPk SJ values based on the segments of individual NFPks. Example NFEMG data from two MUs are shown in Fig.1. In comparison, SFEMG uses fiber-pair jitter statistic values based on times between individual threshold crossings of pairs of MU fiber potentials. The primary NFEMG parameter of interest in this study is NFPk SJ.

NFEMG is a semi-automated process, requiring significantly less time to perform than SFEMG. Potential benefits of NFEMG over SFEMG stem from: a) there being no need to focus/trigger on a specific fiber-pair, saving significant time in searching for a fiber-pair inherent in standard SFEMG and requiring significant training, b) multiple fiber-pairs are extracted for each contraction, in contrast to SFEMG that triggers on a single fiber-pair, c) a significant degree of post-processing/signal cleaning is automated, reducing time spent selecting signals to include in the jitter analysis, d) multiple other metrics are obtained simultaneously, including MU characteristics, that may aid in diagnosis and improve specificity. The training requirement for NFEMG compared to SFEMG is minimal and includes basic signal cleaning, likely requiring less than an hour of training (from our experience); although further development and automation promises to minimize this aspect further still.

A complementary and important feature of NFEMG is the additional information provided. This includes a wide range of additional quantitative morphological and firing frequency metrics that have the potential to improve diagnostic accuracy beyond just a measure of electrophysiological temporal dispersion variability; this may especially be of significance to specificity.

In an initial study into the diagnostic potential of NFEMG for MG[19], NFPk SJ values were directly compared to the jitter value of the exact corresponding fiber-pair as measured by conventional SFEMG to assess correlation and diagnostic concordance between the two techniques when measuring the jitter from the same fiber pair. Correlation (Spearman) between SFEMG and NFPk jitter values was 0.76. The mean difference between SFEMG and NFPk jitter values was 16 µs, without a trend towards over or underestimation. Using a dichotomous classifier, only 12.8% of SFEMG fiber-pairs with increased jitter values showed normal NFPk SJ values (false negative indications), and 9.6% of SFEMG fiber-pairs with normal jitter showed increased NFPk SJ (false positive indications). SFEMG thresholds used for classification were obtained from a multicenter study using concentric needles[21] whereas NFEMG thresholds were obtained

applying the extrapolated reference values procedure[22]. This study formed the basis for the current study and the decision to evaluate SFEMG versus NFEMG decisions at the muscle level.

Given the conceptual similarity between information provided by SFEMG and NFEMG, coupled with the outcomes of initial investigations, this current study was designed to further evaluate the potential utility of NFEMG in the diagnosis of MG by assessing its performance in a setting that reflects its clinical application, i.e. the population with diagnostic uncertainty that comprises those referred for SFEMG testing. The objective of this single-center, retrospective observational study was to assess the performance of NFEMG in diagnosing MG through comparison to both a patient's clinical diagnosis and to SFEMG. NFEMG can be applied with minimal training in a fraction of the time taken to perform SFEMG, reducing patient discomfort, increasing reliability due to minimizing user variability through automation, and potentially addressing an important health service gap.

Methods

NFEMG was applied to EMG signals recorded under a SFEMG protocol from 50 adult patient studies completed over an 18-month interval. IRB approval was acquired and requirement for informed consent was waived. A patient study was included if raw (i.e. 10Hz-10kHz bandpass filtered, removing the SFEMG high-pass filter) EMG signals were available, the study was performed to assess for MG, and the study contributed to a formal clinical diagnosis. Studies were excluded if the EMG signals were corrupted or contaminated with significant artifacts, fewer than nine contractions were obtained, or the diagnosis remained unconfirmed at the time of data analysis. The raw EMG signals were recorded for a minimum of 5 s using Natus Synergy EDX systems and 30-gauge disposable CNE electrodes (Natus Teca Elite; uptake area of 0.03 mm^2) and filtered with a 1–10 kHz bandpass filter for SFEMG analysis (exported with standard CNE filter settings of 10Hz-10KHz). Recordings were conducted by five different but experienced and fellowship trained electromyographers.

The raw EMG signals were exported and reformatted for DQEMG[23,24], which automatically extracted one or more MUPTs per contraction and performed the NFEMG analysis. One experienced electromyographer (RM) reviewed extracted MUPTs in all recordings using the DQEMG interface, with secondary review performed on several recordings to ensure consistency (DS) (both reviewers were blinded to the diagnosis). MUPTs were excluded if there was significant artifact or needle movement in the recordings that could not be rapidly accounted for using manual editing, in a similar fashion to cleaning of SFEMG traces. NFPk SJ values less than 10 µS and those associated with a NFM with only one NFPk were excluded.

Numerous different approaches on varying patient populations have been taken for determining thresholds for SFEMG jitter over the years[21,25,26]. All of these involve defining a threshold value for a specific SFEMG jitter statistic (i.e. mean or number of individual outliers) calculated using a control-data training set. A positive indication of MG is provided if the SFEMG jitter statistic, calculated using values sampled from an examined muscle, exceeds the defined threshold. To define similar diagnostic criteria to be applied to NFPk SJ values, threshold values for specific NFPk SJ statistics (i.e. mean or number of individual outliers) calculated using a control-data training set were defined. Two NFPk SJ statistics were considered: mean-NFPk SJ and percentage of high-NFPk SJ values.

The mean-NFPk SJ is simply the mean of the NFPk SJ values measured in a muscle/patient. A high-NFPk SJ value is above a high-NFPk SJ threshold and is not expected to be measured frequently in a control muscle/patient. A high-NFPk SJ value suggests some level of abnormality (a possibility of disease). The high-NFPk SJ threshold value was set as 2 standard deviations above the mean of all individual NFPk SJ values across all the 34 control studies considered. The percentage of high-NFPk SJ values is the percentage of high-NFPk SJ values measured in a muscle/patient.

A control-data training set included 15 healthy controls, randomly selected from the total pool of 34 controls (i.e. patients without MG, neuropathy, or myopathy). Given a specific randomly selected control-data training set, the corresponding 31-member test set contained the remaining 19 unselected controls and the 12 MG patients (and excluding 4 cases with myopathy and/or neuropathy). Using the threshold defined for each statistic, two diagnostic criteria were applied to the data in the corresponding test set and evaluated. For the mean-NFPk SJ and percentage of high-NFPk SJ values statistics, a positive indication of MG was assumed if the corresponding NFPk SJ statistic, calculated using values from a muscle/patient in the test set, exceeded the defined threshold associated with the corresponding NFPk SJ statistic.

Ten-fold cross validation was completed to assess the generalizability of each of these diagnostic criteria (i.e. to provide a range for sensitivity and specificity). Across the ten selected training sets, for each training set, the mean of the mean-NFPk SJ values was calculated, and this mean plus 2 SD of the mean-NFPk SJ training set values was calculated as a training set mean-NFPk SJ threshold. The mean of the ten mean-NFPk SJ thresholds was then used as the mean-NFPk SJ threshold for all testing sets. The threshold value for the percentage of high-NFPk SJ values used for all testing sets was empirically determined as the value that provided the highest sensitivity-specificity performance across the testing sets, with a bias toward sensitivity given the potential for NFEMG to act as a screening test prior to SFEMG. The calculated mean-NFPk SJ threshold and determined percentage of high-NFPk SJ

values threshold criteria were then applied to the entire cohort of patients free of other neuromuscular conditions.

SFEMG jitter values were reported as the mean absolute value of consecutive differences (MCD). Diagnosis, age, gender, and presence of a condition that might affect jitter results, as well as mean jitter and percentage of individual pairs above published age-adjusted SFE thresholds[27] were recorded. Internal parameters of the automatic DQEMG technique were set to the same values as described in prior articles[28]. We report descriptive statistics, including mean and standard deviations, and 95% confidence intervals. We created two-by-two tables to assess the occurrence of abnormal jitter values in patients with and without MG. From these tables, we calculated sensitivity and specificity for NFEMG and SFEMG. All P values were two-sided with a significance of 0.05. Results were analyzed using SPSS version 26.

Results

Clinical diagnosis of MG was confirmed in 12 out of 50 patients based on clinician judgement following CNE SFEMG (Table 1). Four patients had alternative neuromuscular conditions. Ages ranged from 25 to 86 years (mean 60.7 years), with 57% male and 43% female. For the NFEMG analysis, the mean number of NFPk SJ values included per subject was 61. For the SFEMG analysis the mean number of SFEMG jitter values included per subject was 16. The mean of mean-NFPk SJ and mean-SFEMG jitter values were slightly different for the 34 healthy patients (25.53 µs vs 28.57 µs, p=0.032). The mean of the meanNFPk SJ values for the 12 MG patients was lower compared to the mean of the mean-SFEMG jitter values for MG patients (47.42 µs vs 64.83 µs, P<0.14). Looking at NFPk SJ values in aggregate, without regard for patient association, the mean NFPk SJ value of those under 60 years old was significantly different to those over 60 years old (25.3 µs and 29.5 µs, respectively; p<0.001).

Table 1. Sample size, gender distribution, and mean NFPk SJ and SFEMG jitter values for MG and healthy patients. **Excluding 4 patients with myopathy or neuropathy.*

	Count (%)	Mean (Range) (µs)	SD (Var) (µs)
Age	50 (100%)	60.7 (25-86)	16.27 (265.0)
Males	29 (58%)	-	-
Females	21 (42%)	-	-
mean-NFPk SJ (healthy)*	34 (68%)	25.5 (17.8-34.2)	3.77 (14.2)
mean-NFPk SJ (MG)	12 (24%)	47.4 (33.7-81.5)	15.38 (236.5)
mean-SFEMG Jitter (healthy)*	34 (68%)	28.6 (15.0-42.0)	6.58 (43.4)
mean-SFEMG Jitter (MG)	12 (24%)	64.8 (35.0-146.0)	36.73 (1349)

Correlation statistics between mean SFEMG jitter and mean NFPk SJ for all patients are plotted in Figure 2. All three statistics demonstrate strong correlation between the two metrics, including the intraclass correlation coefficient (ICC).

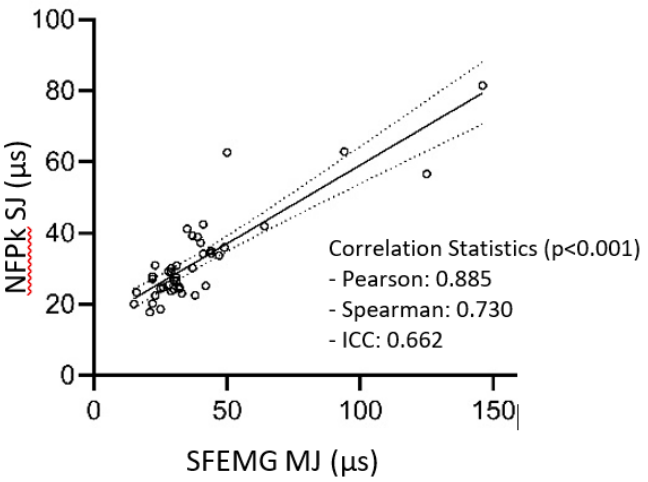

Figure 2: Correlation between patient mean NFPk-SJ and SFEMG jitter across all patients. ICC: intraclass correlation coefficient.

Across the ten-fold cross-validation completed, the mean-NFPk SJ threshold value was calculated to be 33.3 µs. Table 2 (columns 2 and 3) displays the sensitivity and specificity results across the 10 test sets and for the entire cohort using the mean-NFPk SJ statistic and a mean-NFPk SJ threshold value of 33 µs. Across the 10 testing sets, sensitivity ranged from 75%-100% with a mean of 98%, while specificity ranged from 75%-87% with a mean of 82%. For the entire cohort of patients free of other neuromuscular conditions, sensitivity and specificity were 100% and 88%, respectively.

The high NFPk SJ value threshold calculated across the 34 control studies was 60.3 µs. A high NFPk SJ value threshold of 60 µs was applied to each training set and the mean percentage plus 2 SD of high-NFPk SJ values was determined for each training set. The range of the percentage of high-NFPk SJ values across the 10 training sets (3.2%-9.2%) was then used as the range over which the percentage of high-NFPk SJ values threshold was varied to search for the best sensitivity-specificity performance across the 10 testing sets which resulted in a selected percentage of high-NFPk SJ values threshold value of 8% (threshold values in the 7-9% range provided similar results). The percentage of high-NFPk SJ values statistic and this selected percentage of high-NFPk SJ values threshold value was then applied to the 10 test sets (to estimate a range for sensitivity and specificity) as well as to the entire cohort of patients free of other neuromuscular conditions (Table 2, columns 4 and 5). Across the 10 testing sets, sensitivity was consistently

Table 2: Results using a mean-NFPk SJ threshold of 33 μs for each testing set as well as the entire cohort (columns 2 and 3). Columns 4 and 5 show results when using the combination of a high-NFPk SJ threshold of 60 μs with a percentage of high-NFPk SJ values threshold of 8% for each testing set as well as the entire cohort.

	Mean > 33 μs		**8% > 60 μs**	
Testing Set	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
1	100%	85%	100%	90%
2	100%	-85%	100%	90%
3	100%	84%	100%	89%
4	100%	84%	100%	95%
5	100%	87%	100%	93%
6	100%	75%	100%	90%
7	100%	78%	100%	89%
8	75%	84%	100%	89%
9	100%	83%	100%	89%
10	100%	78%	100%	89%
Mean	**98%**	**82%**	**100%**	**90%**
Min	75%	75%	100%	89%
Max	100%	87%	100%	95%
Entire Cohort	**100%**	**88%**	**100%**	**94%**

100%, while specificity ranged from 89%-95% with a mean of 90%. For the entire cohort of patients free of other neuromuscular conditions, sensitivity and specificity were 100% and 94%, respectively.

When the mean-NFPk SJ threshold and the percentage of high-NFPk-SJ values threshold were used in combination, the results did not surpass the performance achieved by using the percentage of high-NFPk SJ values threshold alone (sensitivity and specificity of 100% and 94%, respectively).

We separately re-analyzed the diagnostic performance of NFMEG using a protocol that more closely matched the intended application of NFEMG, i.e., within the context of a standard EMG protocol. As such, we only included the first 20 NFPk SJ values, which usually occurred within the first 5 or 6 contractions (exported SFEMG recordings). Reassuringly, the performance of NFEMG remained high in the face of this reduced amount of data (sensitivity 92%, specificity 88%).

Across the entire cohort of patients free of other neuromuscular conditions, the SFEMG sensitivity and specificity were 94% and 97 respectively.

Discussion

SFEMG is the most accurate neurophysiological test for assessing the neuromuscular junction instability that occurs in MG, and the most widespread application of this method during the last two decades has been using concentric needle electrodes (CNE). This method requires extensive training, time, and patient tolerance to complete. The low availability outside of major academic centers in many countries potentially exposes seronegative MG patients to the risks of undertreatment and likely far more to overtreatment[8–10]. The significant variability in the application of SFEMG between centers will also likely result in substantial variable diagnostic performance. Using NFPk SJ values has the potential to overcome many of the issues associated with SFEMG including, the time burden of the study, patient discomfort, variability due to user, and significant training requirements. The results of this preliminary investigation into the diagnostic accuracy of using NFEMG, specifically, NFPk SJ values, in MG suggest they perform similarly to SFEMG jitter values.

Although this study is only an initial assessment of the ability of using NFPk SJ values for diagnosing MG, based on the relatively modest retrospective sample, the sensitivity and specificity of using the combination of a high-NFPk SJ value threshold in conjunction with a percentage of high-NFPk SJ values threshold (100% and 89-95%, respectively, across all 10 testing sets, and 100% and 94% for the entire cohort of patients free of other neuromuscular conditions) for the diagnosis of MG compared well with using SFEMG jitter values (94% and 97% for the entire cohort of patients free of other neuromuscular conditions). In most of the patients that were determined falsely positive using NFPk

SJ values, SFEMG jitter values were also high but did not meet the associated SFEMG lab thresholds or levels of clinical suspicion for a diagnosis. Given the characteristics of the tests and sampling error, it is inevitable that discrepancies will occur in borderline cases between tests (concordance) and, indeed, in the same test at different time-points (reliability). In borderline cases such as these, whether just above or just below a given threshold, numbers should not be relied upon concretely but rather the clinical picture and additional clinical data will always dictate the eventual diagnosis[29]. A borderline range may be clinically more useful than concrete thresholds with a dichotomous result. Whether a lab uses SFE thresholds for SFEMG or one of the newer CNE based thresholds may impact the precise sensitivity and specificity of the test (as do many other factors related to testing, patient characteristics, pretest probabilities, and clinical context) but should not alter clinical management because borderline results are only an indicator of post-test probability, similar to any other clinical data point, and should be used as such within the paradigm of inductive reasoning applied in clinical diagnosis.

SFEMG was used as a secondary comparator in this study, with clinical diagnosis being used for the primary comparison. It is important to note that SFE thresholds[30] were used to determine normal and abnormal SFEMG jitter results in this study, as opposed to the increasingly used CNE thresholds[21] published more recently. As mentioned, using higher thresholds (SFE thresholds) likely reduces false positives. However, this has not necessarily been borne out in studies using CNE to date, which have suggested little effect on diagnostic results between using SFE or CNE electrode thresholds in the few studies to have examined this directly. Several groups have compared CNE to SFE SFEMG jitter values[15,16,21,25,31,31–37]. Erta et al.[38] found no significant difference between CNE and SFE mean jitter values, number of abnormal pairs, or ability to identify patients with unstable neuromuscular junctions when recorded in the same patients. In a slightly later study, Farrugia et al.[36] similarly found no significant difference between mean CNE and SFE jitter values, while Papathanasiou and Zamba-Papanicolaou[39] noted no significant difference when applied to stimulation SFEMG. However, although most studies initially seemed to report no difference in jitter values when directly comparing recording techniques, suggested thresholds for CNE are frequently lower than those published for SFE[21,30], and usually without accounting for age. Kouyoumdjian[35] surmise that summated signal jitter may be more or less than that measured from individual fiber potentials, depending on which analysis method is used (earliest part of the signal or signal peak).

Kokubun et al.[26] report numerous potential cut-off values for voluntary Frontalis CNE SFEMG jitter values; possible thresholds reported for mean jitter values were between 27.7 µs and 53.4 µs, and for individual pair values between 43.8 µs and 56.8 µs. The multicenter study with perhaps the strictest criteria to date[21] recommends mean MCD jitter thresholds (based on 2 SDs above the mean of the mean MCD jitter values) of 31 µs for Orbicularis oculi and 28 µs for Frontalis, with individual jitter value thresholds at 45 µs and 38 µs respectively (using 2 SDs above the mean value of a patient's 18th highest individual jitter value), which is similar among the majority of CNE SFEMG studies. As with any test, effectiveness is dependent on its application in practice, and the level of adherence to published guidelines is dependent on numerous factors, including availability and application of published guidelines[15], quality and quantity of training, patient population, and physician characteristics among others[25]. Few if any studies have assessed the diagnostic accuracy of SFEMG jitter values as generally practiced, where less strict and varied criteria are usually applied. An ability to standardize a diagnostic test as much as possible is essential, and removing examiner and threshold variability through automation is one such way to improve applicability and minimize disparities in testing as widely applied in clinical settings. NFEMG represents one such way to achieve this.

CNE SFEMG Jitter values of patients referred for SFEMG but free of neuromuscular conditions in this study ("healthy controls") were similar to Kokubun et al.[26], but higher than most other studies. This may in part be due to the retrospective nature of the study, the variety of examiners, a non-research-based setting, and the age and other characteristics of the participants. The "healthy controls" were not specifically selected, were symptomatic (referred for SFEMG and thereby representative of the target population for the diagnostic), and may have had underlying conditions resulting in increased jitter that were not documented and may also have skewed the values. Furthermore, if reference values are used that have a higher cut-off, there may be a tendency to cut short the cleaning of data once the study is deemed negative and accept lower signal quality, which may artificially inflate the mean jitter values reported.

Although original SFE reference values are based on age brackets[27,30], some studies have reported little difference in mean jitter with age[21], while most reports have noted a trend, perhaps depending on the numbers of elderly included in the studies and muscles tested (limb versus cranial). In this study, the mean-NFPk SJ values of healthy controls over and under 60 years of age differed significantly (25.3 µs vs 29.5 µs; $p<0.05$; see Fig. 5).

There are a number of additional investigations required to fully explore the potential of using NFPk SJ values for the diagnosis of MG. Large prospective studies across centers would allow for, 1) rigorous interrogation of the reliability of the values across the breadth of relevant practitioner characteristics, 2) assessment of

the benefit of the additional quantitative data provided by NFEMG including, NFM duration, NFM dispersion and NFPk count as well as MU firing rates, which may aid substantially in test specificity and patient care[13], and 3) further improvement to algorithms and incorporation of the technique into current workflows and machines.

Limitations

In addition to a relatively small sample size, the retrospective and observational nature of this study was a main limitation. As such, recordings were not obtained or cleaned for SFEMG in as controlled a manner as can be achieved during a prospective study. In addition, in this study the NFEMG analyzed signals were recorded during SFEMG (i.e. using SFEMG needle positioning techniques but with standard EMG filter settings). In general, signals acquired for NFEMG analysis are expected to be acquired during standard needle EMG examinations and as such may not be as "focused" as SFEMG recordings. It is unclear if this will have an impact on the diagnostic performance or efficiency of NFEMG but the majority of NFPk SJ values were not based on the fiber pair targeted by SFEMG, therefore the impact of how the NFEMG analyzed signals were recorded is likely to be minimal. As such, it is anticipated that NFEMG results would likely not differ significantly when standard CNE EMG recordings are used.

Incorporation bias is often present in studies assessing the diagnostic accuracy of SFEMG in MG[40]. This bias is avoided in the primary aim of this study because the diagnostic accuracy of using NFPk SJ values was the main objective, and the results of using NFPk SJ values were not utilized in diagnostic decision making. However, when comparing the performance of NFPk SJ values to SFEMG jitter values, incorporation bias needs to be considered, although this would favor the performance of using SFEMG jitter values over NFPk SJ values. Spectrum bias[40] was also reduced in this study (MG was not confirmed in any patient prior to testing), although pretest probabilities for a diagnosis of MG varied greatly between included patients.

This retrospective observational study was primarily designed to provide preliminary data on the feasibility of using NFEMG to detect and diagnose MG. Increased numbers of MG and control patients need to be studied across multiple sites and users. In addition, whether patients are in clinical remission, the severity of their MG or MGFA class, distinction between ocular and generalized, the AChR antibody titer, presence of prior myasthenic crises, thymoma or thymectomy, or medications should also be considered.

Conclusion

This initial study suggests that NFEMG could be effectively used to diagnose MG with similar accuracy but in a more practical manner compared to SFEMG. However, prospective studies are needed. Characteristics including greater yield of jitter values per recording, significantly reduced acquisition time, minimal training requirement compared to SFEMG, and potential to apply the technique to signals acquired during routine EMG suggest NFEMG may be able to serve as an efficient screen prior to referring for SFEMG or as an effective alternative diagnostic test. The low threshold to widespread clinical uptake offers the potential to cost-effectively address a significant national and global healthcare disparity for the large population of patients with weakness and the potential for seronegative MG.

References

1. Melzer N, Ruck T, Fuhr P, et al. Clinical features, pathogenesis, and treatment of myasthenia gravis: a supplement to the Guidelines of the German Neurological Society. *J Neurol*. 2016;263(8):1473-1494. doi:10.1007/s00415-016-8045-z
2. Carr AS, Cardwell CR, McCarron PO, McConville J. A systematic review of population based epidemiological studies in Myasthenia Gravis. *BMC neurology*. 2010;10:1-9.
3. Dewilde S, Philips G, Paci S, et al. Patient-reported burden of myasthenia gravis: baseline results of the international prospective, observational, longitudinal real-world digital study MyRealWorld-MG. *BMJ Open*. 2023;13(1):e066445. doi:10.1136/bmjopen-2022-066445
4. Selvan VA. Single-fiber EMG: A review. *Annals of Indian Academy of Neurology*. 2011;14(1):64. doi:10.4103/0972-2327.78058
5. Lazaridis K, Tzartos SJ. Autoantibody Specificities in Myasthenia Gravis; Implications for Improved Diagnostics and Therapeutics. *Front Immunol*. 2020;11:212. doi:10.3389/fimmu.2020.00212
6. Valls J. Single Fiber EMG, third ed., Erik V. Stålberg, Joze Trontelj, Donald B. Sanders. Edshagen Publishing House, Fiskebäkskil, Sweden (2010). ISBN: 978-91-633-6509-6. *Clinical Neurophysiology*. Published online December 31, 2011. doi:10.1016/j.clinph.2011.05.022
7. Chan KH, Lachance DH, Harper CM, Lennon VA. Frequency of seronegativity in adult-acquired generalized myasthenia gravis. *Muscle Nerve*. 2007;36(5):651-658. doi:10.1002/mus.20854
8. Al-Asmi A, Nandhagopal R, Jacob PC, Gujjar A. Misdiagnosis of Myasthenia Gravis and Subsequent Clinical Implication. *Sultan Qaboos Univ Med J*. 2012;12(1):103-108.
9. Harrison P, Barton J, Winkel A. Chronic mimics of myasthenia gravis: a retrospective case series. *Neuromuscular Disorders*. 2023;33(3):250-256. doi:10.1016/j.nmd.2023.01.006

10. Andrapalliyal N, Claytor B, Li Y. Incidence and causes of overdiagnosis of myasthenia gravis. *Muscle and Nerve*. 2023;67(6):464-468. doi:10.1002/mus.27774
11. Gilhus NE, Tzartos S, Evoli A, Palace J, Burns TM, Verschuuren JJGM. Myasthenia gravis. *Nat Rev Dis Primers*. 2019;5(1):30. doi:10.1038/s41572-019-0079-y
12. Farmakidis C, Pasnoor M, Dimachkie MM, Barohn RJ. Treatment of Myasthenia Gravis. *Neurologic Clinics*. 2018;36(2):311-337. doi:10.1016/j.ncl.2018.01.011
13. Khoo A, Hay Mar H, Borghi MV, Catania S. Electrophysiologic evaluation of myasthenia gravis and its mimics: real-world experience with single-fiber electromyography. *Hospital Practice*. 2022;50(5):373-378. doi:10.1080/21548331.2022.2125706
14. Stålberg E. Single fiber electromyography for motor unit study in man. In: Shahani, Manik, ed. *Motor System: Neurophysiology and Muscle Mechanisms*. Elsevier Science Ltd; 1976.
15. Sanders DB, Arimura K, Cui L, et al. Guidelines for single fiber EMG. *Clinical Neurophysiology*. 2019;130(8):1417-1439. doi:10.1016/j.clinph.2019.04.005
16. Nadeem AS, AL-Salmi KS, AL-Salti AM. The Utility of Concentric Needle Single Fiber Electromyography in Diagnosing Myasthenia Gravis. *OAJNN*. 2021;13(5):044-056. doi:10.19080/OAJNN.2021.15.555907
17. Cherian A, Baheti NN, Iype T. Electrophysiological study in neuromuscular junction disorders. *Annals of Indian Academy of Neurology*. 2013;16(1):34. doi:10.4103/0972-2327.107690
18. Mandeville R, Patterson A, Garnés-Camarena O, Stashuk D. Near Fiber Segment Jitter in the Diagnosis of Myasthenia Gravis. In: *MGFA Scientific Session at AANEM Annual Meeting.* ; 2023.
19. Garnés-Camarena O, Mandeville R, Stashuk D. Comparison of near fiber segment jitter and single fiber pair jitter values in myasthenia gravis. In: *MGFA Scientific Session at AANEM Annual Meeting.* ; 2023.
20. Piasecki M, Garnés-Camarena O, Stashuk DW. Near-fiber electromyography. *Clinical Neurophysiology*. 2021;132(5):1089-1104.
21. Stålberg E, Sanders DB, Ali S, et al. Reference values for jitter recorded by concentric needle electrodes in healthy controls: A multicenter study. *Muscle & nerve*. 2016;53(3):351-362.
22. Lee I, Sanders DB, Nandedkar SD, Kazamel M. Single-institutional reference values for concentric needle jitter analysis using the extrapolated reference values procedure: Comparison to published reference values. *Muscle Nerve*. 2021;63(1):113-116. doi:10.1002/mus.27092
23. Doherty TJ, Stashuk DW. Decomposition-based quantitative electromyography: Methods and initial normative data in five muscles. *Muscle Nerve*. 2003;28(2):204-211. doi:10.1002/mus.10427
24. Stashuk DW. Detecting single fiber contributions to motor unit action potentials. *Muscle Nerve*. 1999;22(2):218-229. doi:10.1002/(SICI)1097-4598(199902)22:2<218::AID-MUS10>3.0.CO;2-S
25. Benatar M, Hammad M, Doss-Riney H. Concentric-needle single-fiber electromyography for the diagnosis of myasthenia gravis. *Muscle Nerve*. 2006;34(2):163-168. doi:10.1002/mus.20568
26. Kokubun N, Sonoo M, Imai T, et al. Reference values for voluntary and stimulated single-fibre EMG using concentric needle electrodes: A multicentre prospective study. *Clinical Neurophysiology*. 2012;123(3):613-620. doi:10.1016/j.clinph.2011.07.044
27. Bromberg MB, Scott DM. Single fiber EMG reference values: reformatted in tabular form. Published online 1994.
28. Malanda A, Stashuk DW, Navallas J, et al. Automatic jitter measurement in needle-detected motor unit potential trains. *Comput Biol Med*. 2022;149:105973. doi:10.1016/j.compbiomed.2022.105973
29. Morren JA, Levin KH, Shields RW. Diagnostic Accuracy of Single Fiber Electromyography for Myasthenia Gravis in Patients Followed Longitudinally: *Journal of Clinical Neurophysiology*. 2016;33(5):469-474. doi:10.1097/WNP.0000000000000285
30. Gilchrist JM. Single fiber EMG reference values: A collaborative effort. *Muscle Nerve*. 1992;15(2):151-161. doi:10.1002/mus.880150205
31. Sarrigiannis PG, Kennett RP, Read S, Farrugia ME. Single-fiber EMG with a concentric needle electrode: Validation in myasthenia gravis. *Muscle & Nerve*. 2006;33(1):61-65. doi:10.1002/mus.20435
32. Kouyoumdjian JA, Stålberg EV. Reference jitter values for concentric needle electrodes in voluntarily activated extensor digitorum communis and orbicularis oculi muscles. *Muscle & Nerve*. 2008;37(6):694-699. doi:10.1002/mus.21043
33. C.N. Machado F, A. Kouyoumdjian J, E. Marchiori P. Diagnostic accuracy of concentric needle jitter in myasthenia: Prospective study: CNEMG Jitter in MG. *Muscle Nerve*. 2017;55(2):190-194. doi:10.1002/mus.25229
34. Stålberg EV, Sanders DB. Jitter recordings with concentric needle electrodes. *Muscle & Nerve*. 2009;40(3):331-339. doi:10.1002/mus.21424
35. Kouyoumdjian JA, Paiva GP, Stålberg E. Concentric Needle Jitter in 97 Myasthenia Gravis Patients. *Front Neurol*. 2020;11:600680. doi:10.3389/fneur.2020.600680
36. Farrugia ME, Weir AI, Cleary M, Cooper S, Metcalfe R, Mallik A. Concentric and single fiber needle electrodes yield comparable jitter results in myasthenia gravis. *Muscle Nerve*. 2009;39(5):579-585. doi:10.1002/mus.21151

37. Cattaneo L, Cucurachi L, Pavesi G. Concentric needle recording of neuromuscular jitter in the temporalis muscle. *Neurophysiologie Clinique/Clinical Neurophysiology*. 2007;37(1):50-51. doi:10.1016/j.neucli.2007.02.001
38. Ertas M, Baslo MB, Yildiz N, Yazici J, Ge AE. Concentric needle electrode for neuromuscular jitter analysis. *Muscle Nerve*. 2000;23(5):715-719. doi:10.1002/(SICI)1097-4598(200005)23:5<715::AID-MUS8>3.0.CO;2-V
39. Papathanasiou ES, Zamba-Papanicolaou E. A comparisonbetweendisposableandreusablesinglefiber needle electrodes in relation to stimulated single fiber studies. *Clinical Neurophysiology*. 2012;123(7):1437-1439. doi:10.1016/j.clinph.2011.10.046
40. Benatar M. A systematic review of diagnostic studies in myasthenia gravis. *Neuromuscular Disorders*. 2006;16(7):459-467. doi:10.1016/j.nmd.2006.05.006

Coexistence of amyotrophic lateral sclerosis and lymphoproliferative disorders – Analysis from a tertiary center

Selina Mahmood MD[1], Zachary McKee MD[2], Yuebing Li MD PhD[2]

[1] Department of Neurology, Jacobs School of Medicine and Biomedical Sciences at University at Buffalo, Buffalo, NY, USA
[2] Department of Neurology, Cleveland Clinic, Cleveland, USA

Abstract

Background: The coexistence of motor neuron diseases (MNDs) and lymphoproliferative disorders (LPDs) has been documented historically in a few small retrospective studies but an update is lacking.

Objective: The goal of this study is to expand the database of patients with these coexisting diseases, and to describe the natural history and overall outcomes including presumed or identified cause of mortality (neurologic versus oncologic).

Materials and methods: A retrospective analysis of all patients within the Cleveland Clinic diagnosed with one or more LPDs between January 1, 2012 and June 30, 2021, was performed to identify patients with a diagnosis of MND.

Results: A total of 20 patients with one MND diagnosis and one coexisting LPD were included in the final analysis. Their clinical features are characterized. In 17 patients, the diagnosis of LPD was made prior to the MND diagnosis. Eighteen patients passed away with a mean survival of 49.1 (range: 6 to 128) months from the MND onset. In 16 patients, the cause of death was MND related. The incidence rates of MNDs and myasthenia gravis were examined in a group of 6,169 patients with LPDs. The incidence rate of MNDs in LPDs seems to be higher than those of the general population, appeared over-represented when comparing to the occurrence of myasthenia gravis in LPDs.

Conclusion: Coexisting MND and LPD continue to occur. There seems to be an over representation of MND in patients with LPDs.

Introduction

The association between neuromuscular diseases and malignant neoplastic disease has been reported since the 1960's.[1] Specifically, the coexistence of motor neuron diseases (MNDs) including amyotrophic lateral sclerosis (ALS), primary lateral sclerosis (PLS), progressive muscular atrophy (PMA) and those of lymphoproliferative disorders (LPDs), including various subtypes of lymphoma, leukemia, multiple myeloma and Waldenström's macroglobulinemia, was described in a few small studies prior to the 20th century.[1-6] Gordon et al. reported the frequency of LPDs in patients with MND patients may range from 2% to 5%, depending on the methods of evaluation.[6] It remains unclear whether a potential association exists between MNDs and LPDs. Furthermore, significant updates on the epidemiology, clinical characteristics, or outcomes of patients with coexisting MNDs and LPDs have not been published since the late 1990s. In this study, we aim to analyze a group of patients who possesses both MND and LPDs in our tertiary center.

Materials and Methods

The following two in-house databases at our institution were reviewed: a database of 1,266 patients with MNDs (familial or sporadic ALS, PMA, PLS), and a hematology/oncology database of 6,169 patients diagnosed with LPDs (Hodgkin lymphoma, follicular lymphoma, non-follicular lymphoma including large B cell lymphoma and Burkitt lymphoma, T and natural killer cell lymphoma, Waldenström macroglobulinemia, multiple myeloma, lymphoid leukemia, myeloid leukemia, and monocytic leukemia). These two databases included selected patients seen in our institution between January 1, 2012 and June 30, 2024. A group of patients carrying simultaneous diagnoses of MNDs and LPDs were identified, based on the final conclusion of treating neuromuscular and hematological physicians. Only adult patients who age 18 years or greater were included. Detailed information regarding the neurologic diagnoses, oncologic diagnoses, presenting symptoms and neurologic exam features, electrodiagnostic findings, and survival were collected and summarized.

Results

A total of 20 patients were included in the final analysis. Their demographic information, diagnoses and selected clinical features are outlined in Table 1. Twelve (60.0%) were male and the average onset age of MND was 65.9 (range: 45 to 82) years.

The following MND diagnoses were encountered: ALS (N=17), PLS (N=2), and PMA (N=1). Onset regions of MND were as follows: lumbosacral (N=10), cervical (N=7) and craniobulbar (N=3). The following LPDs were encountered: lymphoma such as follicular lymphoma, diffuse large B cell lymphoma, marginal zone B cell lymphoma, Hodgkin's lymphoma and non-Hodgkin lymphoma (N=10), chronic lymphocytic leukemia (N=5), multiple myeloma (N=3), Waldenström's macroglobulinemia (N=1) and T cell large granular lymphocytic leukemia (N=1). In 17 (85.0%) patients, the diagnosis of LPD was established prior to the MND diagnosis. In the remaining 3 patients, the MND diagnosis was made earlier. The average interval between MND and LPD diagnoses were 63.0 (range: 0.5 to 189)

Table 1. Clinical features of 20 patients with coexisting motor neuron diseases and lymphoproliferative disorder

patient	Sex	MND diagnosis	MND onset age (years)	MND onset region	LPD diagnosis	First diagnosis	Interval between MND and LPD diagnosing (months)	Survival from MND onset (months)	Cause of death
1	M	ALS	70	cervical	lymphoplasmacytic lymphoma	LPD	2	77	unclear
2	M	ALS	76	craniobulbar	chronic lymphocytic leukemia	MND	0.5	14	MND related
3	M	ALS	63	craniobulbar	Hodgkin lymphoma	LPD	189	89	MND related
4	M	ALS	51	lumbosacral	chronic lymphocytic leukemia	MND	75	128	MND related
5	F	ALS	74	lumbosacral	extranodal marginal zone B-cell lymphoma	LPD	129	19	MND related
6	F	PMA	82	cervical	follicular lymphoma	LPD	66	6	MND related
7	F	ALS	54	lumbosacral	Waldenström macroglobulinemia	LPD	72	41	MND related
8	M	ALS	75	cervical	Chronic lymphocytic leukemia	MND	3	13	MND related
9	F	ALS	70	lumbosacral	Diffuse large B cell lymphoma	LPD	70	97	MND related
10	F	ALS	78	lumbosacral	follicular lymphoma	LPD	121	39	MND related
11	M	ALS	75	cervical	non-Hodgkin's lymphoma	LPD	29	65	MND related
12	M	ALS	66	lumbosacral	follicular lymphoma	LPD	2	19	MND related
13	M	PLS	63	lumbosacral	lymphoplasmacytic lymphoma	LPD	2	72	unclear
14	M	ALS	62	cervical	diffuse large B-cell lymphoma	LPD	79	29	MND related
15	M	ALS	65	lumbosacral	chronic lymphocytic leukemia	LPD	70	62	MND related
16	M	ALS	58	cervical	chronic lymphocytic leukemia	LPD	116	59	MND related
17	F	ALS	55	likely bulbar	multiple myeloma	LPD	100	24	MND related
18	F	ALS	72	lumbosacral	multiple myeloma	LPD	9	30	MND related
19	F	PLS	64	lumbosacral	T cell large granular lymphocytic leukemia	LPD	76	>197	alive
20	M	ALS	45	cervical	multiple myeloma	LPD	49	>110	alive

months.

Eight (40.0%) patients had cerebrospinal fluid (CSF) studies as a part of their workup. Of these, 5 (62.5%) patients had elevated CSF protein (mean 80 mg/dl, range: 51-109 mg/dl) and 1 patient had a unique oligoclonal band present in the CSF.

At the conclusion of this study, 18 (90%) of the included patients deceased, with an average survival from the onset of MND being 49.1 (range: 6 to 128) months. Two patients (one with ALS and multiple myeloma, the other with PLS and T cell large granular lymphocytic leukemia) remain alive following an MND course of 110 and 197 months respectively (Table 1). In 16 (88.9%) of 18 patients, the cause of mortality was MND related. In the remaining 2 patients, the cause of death was unknown.

We made a comparison of the incidence rates of various notable neuromuscular disorders based on patients exclusively from the hematology/oncology database of 6,169 patients. The following neuromuscular disorders were encountered: MND (N=6) and myasthenia gravis (N=6).

Discussion

The reported frequency of LPDs in patients with MND was 2-5%.[5,6] Louis et al. performed bone marrow examination in each of 161 patients MNDs, and found 4 (2.5%) cases of LPDs.[5] In the current study of 1,266 patients with MND, a total of 20 (1.6%) patients with coexisting LPDs were identified. Our incidence rate matches well with those of Louis et al., considering that bone marrow biopsy was not one of the inclusion criteria in our study. Mandatory bone marrow biopsy in all MND patients would certainly increase the diagnostic yield of LPDs.[5]

There has been no case control study to determine whether the frequency of MND in patients with LPDs is disproportionately greater, thus their coexistence remains possibly incidental. However, our current analysis seems to suggest that an association may exist between MNDs and LPDs. While the prevalence of MNDs in the United States is reported to be 11.8 per 100,000, this retrospective study identified 6 (97.3 per 100,000) out of 6,169 patients with LPDs carried a diagnosis of MND.[9] In comparison to MNDs, the prevalence rate of myasthenia gravis is higher at 37 per 100, 000 in the general US population, even a few fold higher in patients aged 50 years or older, an age hood when MND and LPD typically occurs.[8] However, we found an equal number of MG (N=6) and MND (N=6) in this large group of 6,169 patients with LPDs, implying a likely relative over-representation of MNDs.

In patients with coexisting LPDs and MNDs, the initial symptoms could belong to MND or LPD.[6] In 17 of 20 patients included in the current study, LPD diagnosis was made earlier than MND, raising the possibility that LPD or subsequent treatment could trigger the occurrence of MND secondary to neurotoxicity mediated by LPD or treatment. It has been suggested that lymphoma cells may result in a paraneoplastic mechanism by producing autoantibodies that binds to motor neurons resulting in neuronal dysfunction.[9] Alternatively, MND and LPD could share a common cause that can be neurotropic and oncogenic, and the onset of each syndrome is determined by a number of genetic and environmental factors that are unique to each individual. Increased frequency of paraproteinemia has been documented in patients with MND.[10] It was also previously shown that the presence of monoclonal paraproteinemia in MNDs increases the likelihood of LPDs.[2]

It is well known that MNDs associated with LPD is primarily of the lower motor neuron. However, MNDs associated with LPDs is not restricted to lower motor neuron. In one study, 88% of patients with MNDs and LPDs qualified for the diagnosis of ALS.[6] Cases of coexisting PLS and LPDs were described previously, as well as 2 patients from this study.[5] It was previously described that MNDs were responsible for death in all such cases and treatment such as radiation or immunosuppressive therapy had no effect on the progression of MND.[6,11] Observations from our study seem to be consistent with prior observations. In our study, the mean survival was approximately 4 years from the MND onset, and the majority of our patients died of MND related events.

The limitations to this study include the small sample size and the retrospective nature, which may have led to incomplete data analysis.

Conclusions

The overlap between MND sand LPDs has been historically reported. This retrospective study lends support that this overlap persists and may not be coincidental. Further studies should include population or case control studies to look for a causal relationship between these two categories of disorders. The clinical association between MNDs and LPDs has implications about elucidating possible disease pathology and major implications for management and treatment.

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References:

1. Rowland, L. P., & Schneck, S. A. (1963). Neuromuscular Disorders Associated with Malignant Neoplastic Disease. *Journal of chronic diseases*, *16*, 777–795
2. Younger, D. S., Rowland, L. P., Latov, N., Hays, A. P., Lange, D. J., Sherman, W., Inghirami, G., Pesce, M. A., Knowles, D. M., & Powers, J. (1991). Lymphoma, motor neuron diseases, and amyotrophic

lateral sclerosis. *Annals of neurology*, *29*(1), 78–86.
3. Sanders, K. A., Rowland, L. P., Murphy, P. L., Younger, D. S., Latov, N., Sherman, W. H., Pesce, M., & Lange, D. J. (1993). Motor neuron diseases and amyotrophic lateral sclerosis: GM1 antibodies and paraproteinemia. *Neurology*, *43*(2), 418–420.
4. Rowland, L. P., Sherman, W. L., Hays, A. P., Lange, D. J., Latov, N., Trojaborg, W., & Younger, D. S. (1995). Autopsy-proven amyotrophic lateral sclerosis, Waldenström's macroglobulinemia, and antibodies to sulfated glucuronic acid paraglycoside. *Neurology*, *45*(4), 827–829.
5. Louis, E. D., Hanley, A. E., Brannagan, T. H., Sherman, W., Murphy, P., Lange, D. J., Trojaborg, W., Younger, D. S., Lovelace, R. E., Latov, N., & Rowland, L. P. (1996). Motor neuron disease, lymphoproliferative disease, and bone marrow biopsy. *Muscle & nerve*, *19*(10), 1334–1337.
6. Gordon, P. H., Rowland, L. P., Younger, D. S., Sherman, W. H., Hays, A. P., Louis, E. D., Lange, D. J., Trojaborg, W., Lovelace, R. E., Murphy, P. L., & Latov, N. (1997). Lymphoproliferative disorders and motor neuron disease: an update. *Neurology*, *48*(6), 1671–1678.
7. Wolfson C, Gauvin DE, Ishola F, Oskoui M. Global Prevalence and Incidence of Amyotrophic Lateral Sclerosis: A Systematic Review. Neurology. 2023;101(6):e613-e623.
8. Rodrigues E, Umeh E, Aishwarya, Navaratnarajah N, Cole A, Moy K. Incidence and prevalence of myasthenia gravis in the United States: A claims-based analysis. Muscle Nerve. 2024;69(2):166-171.
9. Mélé N, Berzero G, Maisonobe T, Salachas F, Nicolas G, Weiss N, Beaudonnet G, Ducray F, Psimaras D, Lenglet T. Motor neuron disease of paraneoplastic origin: a rare but treatable condition. J Neurol. 2018;265(7):1590-1599.
10. Tavolato B. ALS and paraproteinemia. Neurology. 1991;41(2 (Pt 1)):331-332.
11. Rowland L. P., Gordon, P. H., Younger D.S., Sherman, W. H., Hays A. P., Louis E. D., Lunge D. J., Trojaborg J. W., Lovelace, R. E., Murphy, P. L., and N. Latov, N.. Lymphoproliferative disorders and motor neuron disease, Neurology. 1998; 50 (2):576.

Abbreviations: MND, motor neuron disease; LPD, lymphoproliferative disorder; M, male; ALS, amyotrophic lateral sclerosis; F, female; PMA, progressive muscular atrophy; PLS, primary lateral sclerosis

An updated review on the utility of hematopoietic stem cell transplant in the treatment of refractory myasthenia gravis

Grace Li BA[1];
Morgan Heber MD[1]; Tiffany Pike-Lee MD[1];

[1] Wright State University Boonshoft School of Medicine
[2] Department of Neurology, Neurologic Institute, Cleveland Clinic
[3] Department of Neurology, Walter Reed National Military Medical Center

Abstract

INTRODUCTION: Hematopoietic stem cell transplantation (HSCT) has been shown to be an effective treatment in many severe autoimmune diseases. There have been a number of reported cases of successful HSCT in severe, refractory myasthenia gravis (MG).

OBJECTIVE: To review and summarize the current literature on the role of HSCT in the management of refractory MG.

METHODS: Databases including PubMed, clinical trials.gov, and Cochrane Reviews were searched for research articles containing "hematopoietic stem cell transplantation," "stem cell," and "myasthenia gravis." Articles were excluded if they were not written in English.

RESULTS: A total of 16 patients across 8 publications were identified as having undergone HSCT in the setting of MG. Following HSCT, all patients had significant improvement in their MG status, with 11 achieving complete stable remission. Common adverse effects were mostly infection-related and included neutropenic fever, cytomegalovirus viremia or reactivation, mucositis, and upper respiratory tract infection.

CONCLUSION: HSCT has the potential to provide sustained benefit for patients with MG who are refractory to conventional treatment. A large-scale prospective study is warranted to better define its role in the treatment of MG.

Introduction

Myasthenia gravis (MG) is an autoimmune neurological disorder that results from impaired transmission at the neuromuscular junction through the binding of antibodies to post-synaptic proteins.[1] Clinical manifestations include fluctuating muscle weakness affecting the ocular, bulbar, limb, and respiratory muscles. Myasthenic crisis is the most severe form of MG, requiring the use of mechanical or non-invasive ventilation. The most common antibodies are directed against the nicotinic acetylcholine receptor (AChR-Ab) or muscle-specific kinase (MuSK-Ab).[1]

The number of patients diagnosed with MG has increased in recent years. In 2021, the incidence and prevalence of MG in the USA were 37 per 100,000 and 3.7 per 100,000, respectively, both of which increased from the 1980s and 2000s.[2] The mainstay of treatment includes pyridostigmine as well as long-term immunosuppression with corticosteroids and corticosteroid-sparing agents such as azathioprine and mycophenolate mofetil. Other agents including complement inhibitors, neonatal fragment crystallizable receptor (FcRn) therapy, and anti-CD20 agents such as rituximab may be used. However, 10-15% of patients with MG continue to be treatment-refractory. Historically, this has been defined as failing to respond to adequate doses of conventional immunosuppression, experiencing side effects or comorbidities that preclude the use of typical agents, requiring excessive doses of potentially risky agents, or needing frequent rescue therapies.[3,4,5] The optimal treatment for this group of MG patients remains poorly defined. Therefore, there is a need to continuously identify alternative treatments for refractory MG patients.

Hematopoietic stem cell transplantation (HSCT)has emerged as a potential treatment modality for patients with refractory MG. Hematopoietic stem cells (HSCs) are collected from the patient or the donor in autologous and allogeneic transplants, respectively. HSCs are preserved with cryotherapy while the patient undergoes chemotherapy to ablate their innate immune system. The previously collected HSCs are then infused into the patient, leading to immune system reconstitution and recovery.[6] Studies have compared the effectiveness of autologous and allogenic transplants. For instance, between 1997 and 2014, European Society for Blood and Marrow Transplantation (EBMT) registry reported that most patients received autologous transplants, compared to fewer than 20 patients who had received allogenic transplants.[7] Since it has a better side effect profile, autologous HSCT has been preferred over allogeneic HSCT.

HSCT has been utilized in cases of refractory, autoimmune conditions including multiple sclerosis (MS), with good results.[8,9] There is mounting evidence supporting the safety and efficacy of HSCT in refractory MS, especially in cases of relapsing-remitting disease.[10,11] However, there is a paucity of data summarizing the use of HSCT in MG. This review aims to provide a summary of the reported cases of HSCT in patients with MG and the current evidence for using HSCT in this patient population.

Methods

Databases including PubMed, clinical trials.gov, and Cochrane Reviews were searched for research articles describing the safety and effectiveness of HSCT in the treatment of MG. The search was completed using the terms "hematopoietic stem cell transplantation," "stem cell,"

and "myasthenia gravis." Articles not written in English were excluded. Patient characteristics included age, sex, disease duration, antibody status, prior MG treatments, and Myasthenia Gravis Foundation of America (MGFA) classification. Additional data collected included number of patients, comorbidities, HSCT type, MG outcomes, and reported side effects.

Results

A total of 16 patients (12 females and 4 males) from 8 publications were identified as having undergone HSCT for MG (Table 1). At the time of transplant, comorbid conditions included follicular lymphoma, familial Mediterranean fever, polymyositis, and aplastic anemia.[13,15,16] At the time of HSCT, MG disease duration ranged from 1 to 38 years (median 6 years). Patient ages ranged from 17 to 64 years (median 46 years). Fifteen patients underwent autologous HSCT while one underwent allogenic HSCT.[19]

Ten patients (62.5%) patients tested positive for AChR-Ab and 4 patients (25%) tested positive for MuSK-Ab. The remaining two patients tested negative for AChR-Ab, but they did not receive testing for MuSK-Ab.[13] Based on the MGFA classification, MG status was classified as follows: class IIIb in 2 patients (12.5%), IVa in 1 (6.3%), IVb in 5 (31.3%), and V in 6 (37.5%). MGFA status in 2 patients with generalized myasthenia gravis was unknown.[16,19] Before HSCT, all patients underwent various and numerous treatments for MG. The most common were prednisone in 14 patients (87.5%), plasmapheresis in 14 (87.5%), pyridostigmine in 13 (81.3%), intravenous immunoglobulin (IVIG) in 13 (81.3%), mycophenolate mofetil in 9 (56.3%), azathioprine in 8 (50%), rituximab in 8 (50%), and thymectomy in 8 (50%).

Follow-up duration ranged from 2 to 149 months post-transplant (median 38 months). All patients showed symptomatic improvement, with onset of improvement ranging from 2 weeks to 1 year after transplant (median 7 weeks). Fourteen patients (87.5%) were able to discontinue all MG medications. Eleven patients (68.8%) achieved a status of complete stable remission Of the patients who did not achieve complete stable remission, two had significant clinical improvement with minimal ocular symptoms and reduced AChR-Ab levels at their final follow-ups.[14,19] One patient originally classified as MGFA Class V prior to HSCT improved to Class IIa with discontinuation of all MG therapies.[12] One patient with coincident familial Mediterranean fever had to continue immunosuppression, but she experienced less frequent MG exacerbation after HSCT.[15] One patient with coexisting polymyositis and aplastic anemia showed improvement in muscle strength with some residual muscle weakness.[16]

Adverse effects related to HSCT included neutropenic fever in 7 patients (43.84%), cytomegalovirus viremia or reactivation in 5 (31.3%), mucositis in 4 (25%), upper respiratory tract infection in 2 (12.5%), oral herpetic infection in 2 (12.5%), bacteremia in 2 (12.5%), and rash in 2 (12.5%). One (6.3%) patient developed a secondary autoimmune disease of amegakaryocytic thrombocytopenia.[13] Three (18.8%) patients did not experience any notable adverse effects related to HSCT.[12,13,16] However, the patient with comorbid follicular lymphoma experienced a relapse of the lymphoma 12 months after HSCT and died 17 months later.[13] The authors of the study felt these complications were not related to HSCT.

Discussion

Literature supports an expanded usage of HSCT as an emerging therapy for various autoimmune neurological disorders such as multiple sclerosis, neuromyelitis optica, and chronic inflammatory demyelinating polyneuropathy.[20,21]

The treatment of refractory MG cases has remained a significant challenge for clinicians. These patients do not typically respond to many traditional immunotherapies such as corticosteroids, azathioprine, mycophenolate mofetil, IVIG, or plasmapheresis. While the newer generation therapies such as complement inhibitors or FcRn therapy may provide benefits in a portion of patients, such treatments do not lead to disease remission. Our above summary of the current literature suggests that HSCT could has provide significant and sustained benefits in a selection of refractory MG cases. All patients who underwent HSCT responded positively. Fourteen (87.5%) of 16 patients were able to stop all MG medications and eleven (68.8%) achieved complete stable remission. Our summary seems to suggest that HSCT is equally effective for both AChR-Ab and MuSK-Ab positive MG patients. For patients refractory to traditional MG treatments, HSCT appears to be an effective option.

However, HSCT is different from traditional immunotherapy in that it requires hospital admission. Its associated temporary but profound immunosuppression may have both short-term and long-term implications on the body's immune system. So far the most notable side effects of HSCT are infections or infection related events including neutropenic fever, CMV viremia or reactivation, mucositis, and upper respiratory tract infection. In addition to HSCT side effects, HSCT also requires a conditioning regimen to provide sufficient immunoablation to reduce the risk of rejection and graft-versus-host-disease (GVHD) prior to HSCT which can also lead to further immune system weakening, rendering patients to risk of infections, new autoimmunity and malignancy in the long term. With an increased use of HSCT, there will be a better understanding of its indications, efficacy, and complications.

Our review had some limitations. The included studies were all retrospective, either case reports or case series. Retrospective studies are prone to bias in data collection, patient recall, and patient reporting. Even though HSCT

has been a promising treatment for the refractory MG cases we investigated, the sample size is relatively small, and the patients may not be representative of all patients with refractory disease. The case series in our review with the greatest number of MG patients had seven, which was the largest case series of MG patients known to date.[13] To better understand the role of HSCT in MG treatment, a randomized prospective study of a larger sample size is needed.

Conclusion

HSCT has been shown to provide sustained benefit in a small sample of cases of refractory MG. Large-scale, prospective studies are needed to further investigate the role of HSCT in the treatment of MG.

References

1. Gwathmey KG, Burns TM. Myasthenia Gravis. *Semin Neurol*. 2015;35(4):327-339. doi:10.1055/s-0035-1558975.
2. Rodrigues E, Umeh E, Aishwarya, Navaratnarajah N, Cole A, Moy K. Incidence and prevalence of myasthenia gravis in the United States: A claims-based analysis. *Muscle Nerve*. 2024;69(2):166-171. doi:10.1002/MUS.28006.
3. Suh J, Goldstein JM, Nowak RJ. Clinical characteristics of refractory myasthenia gravis patients. *Yale J Biol Med*. 2013 Jun 13;86(2):255-260.
4. Silvestri NJ, Wolfe GI. Treatment-Refractory Myasthenia Gravis. *J Clin Neuromuscul Dis*. 2014;15(4):167-178. doi:10.1097/CND.0000000000000034.
5. Drachman DB, Adams RN, Hu R, Jones RJ, Brodsky RA. Rebooting the immune system with high-dose cyclophosphamide for treatment of refractory myasthenia gravis. *Ann N Y Acad Sci*. 2008;1132:305-314. doi:10.1196/annals.1405.033.
6. Mariottini A, Bulgarini G, Cornacchini S, Damato V, Saccardi R, Massacesi L. Hematopoietic Stem Cell Transplantation for the Treatment of Autoimmune Neurological Diseases: An Update. *Bioengineering (Basel)*. 2023;10(2):176. doi:10.3390/BIOENGINEERING10020176.
7. Greco R, Labopin M, Badoglio M, Veys P, Silva JMF, Abinun M, Gualandi F, Bornhauser M, Ciceri F, Saccardi R, Lankester A, Alexander T, Gennery AR, Bader P, Farge D, Snowden JA. Allogeneic HSCT for Autoimmune Diseases: A Retrospective Study From the EBMT ADWP, IEWP, and PDWP Working Parties. *Front Immunol*. 2009;10. doi:10.3389/FIMMU.2019.01570.
8. Muraro PA, Pasquini M, Atkins HL, Bowen JD, Farge D, Fassas A, Freedman MS, Georges GE, Gualandi F, Hamerschlak N, Havrdova E, Kimiskidis VK, Kozak T, Mancardi GL, Massacesi L, Moraes DA, Nash RA, Pavletic S, Ouyang J, ... Saccardi R. Long-term Outcomes After Autologous Hematopoietic Stem Cell Transplantation for Multiple Sclerosis. *JAMA Neurol*. 2017;74(4): 459-469. doi:10.1001/JAMANEUROL.2016.5867.
9. Sormani MP, Muraro PA, Schiavetti I, Signori A, Laroni A, Saccardi R, Mancardi GL, Capello E, Uccelli A, Bagigalupo F, Repice AM, Portaccio E, Barillaro A, Russo C, de Luca G, Farina D, Tartaro A, Blanco Y, Berenguer J, ... Zonari P. Autologous hematopoietic stem cell transplantation in multiple sclerosis: A meta-analysis. *Neurology*. 2017;88(22):2115-2122. doi:10.1212/WNL.0000000000003987.
10. Boffa G, Massacesi L, Inglese M, Mariottini A, Capobianco M, Moiola L, Amato MP, Cottone S, Gualandi F, de Gobbi M, Greco R, Scimè R, Frau J, Zimatore GB, Bertolotto A, Comi G, Uccelli A, Signori A, Angelucci E, ... Mancardi G. Long-term Clinical Outcomes of Hematopoietic Stem Cell Transplantation in Multiple Sclerosis. *Neurology*. 2021;96(8): E1215–E1226. doi: 10.1212/WNL.0000000000011461.
11. Nash RA, Hutton GJ, Racke MK, Popat U, Devine SM, Steinmiller KC, Griffith LM, Muraro PA, Openshaw H, Sayre PH, Stuve O, Arnold DL, Wener MH, Georges GE, Wundes A, Kraft GH, Bowen JD. High-dose immunosuppressive therapy and autologous HCT for relapsing-remitting MS. *Neurology*. 2017;88(9):842-852. doi:10.1212/WNL.0000000000003660.
12. Beland B, Hahn C, Jamani K, Chhibber S, White C, Atkins H, Storek, J. Autologous hematopoietic stem cell transplant for the treatment of refractory myasthenia gravis with anti-muscle specific kinase antibodies. *Muscle Nerve*. 2023;67(2):154-157. doi:10.1002/MUS.27772.
13. Bryant A, Atkins H, Pringle CE, Allan D, Anstee G, Bence-Bruckler I, Hamelin L, Hodgins M, Hopkins H, Huebsch L, McDiarmid S, Sabloff M, Sheppard D, Tay J, Bredeson C. Myasthenia Gravis Treated With Autologous Hematopoietic Stem Cell Transplantation. *JAMA Neurol*. 2016;73(6):652-658. doi:0.1001/JAMANEUROL.2016.0113.
14. Håkansson I, Sandstedt A, Lundin F, Askmark H, Pirskanen R, Carlson K, Piehl F, Hägglund H. Successful autologous haematopoietic stem cell transplantation for refractory myasthenia gravis – a case report. *Neuromuscul Disord*. 2017;27(1):90-93. doi:10.1016/j.nmd.2016.09.020.
15. Inan B, Bekircan-Kurt CE, Demiroğlu H, Göker H, Erdem-Özdamar S, Tan E. Autologous stem cell transplantation in a patient with refractory anti-MuSK-Positive myasthenia gravis and familial mediterranean fever. *Neurol. Sci. Neurophysiol*. 2022;39(2):115-118. doi:10.4103/NSN.NSN_197_21.
16. Mitsumune S, Manabe Y, Yunoki T, Kono S, Aoyama K, Shinno Y, Narai H, Abe K. Autologous Bone Marrow Transplantation for Polymyositis Combined

with Myasthenia Gravis and Aplastic Anemia: A Case Report. *Case Rep Neurol*. 2018;10(1):108-111. doi:10.1159/000488476.

17. Schlatter MI, Yandamuri SS, O'Connor KC, Nowak RJ, Pham MC, Obaid AH, Redman C, Provost M, McSweeney PA, Pearlman ML, Tees MT, Bowen JD, Nash RA, Georges GE. Remission of severe myasthenia gravis after autologous stem cell transplantation. *Ann Clin Transl Neurol*. 2023;10(11):2105-2113. doi:10.1002/ACN3.51898.
18. Sossa Melo CL, Peña AM, Salazar LA, Jiménez SI, Gómez ED, Chalela CM, Ayala-Castillo M, Peña IM. Autologous hematopoietic stem cell transplantation in a patient with refractory seropositive myasthenia gravis: A case report. *Neuromuscul Disord*. 2019;29(2):142-145. doi:10.1016/j.nmd.2018.11.008.
19. Strober J, Cowan MJ, Horn BN. Allogeneic Hematopoietic Cell Transplantation for Refractory Myasthenia Gravis. *Arch Neurol*. 2009;66(5):659-661. doi:10.1001/ARCHNEUROL.2009.28.
20. Burman J, Tolf A, Hägglund H, Askmark H. Autologous haematopoietic stem cell transplantation for neurological diseases. *J Neurol Neurosurg Psychiatry*. 2018;89(2):147-155. doi:10.1136/jnnp-2017-316271.
21. Pasquini MC, Voltarelli J, Atkins HL, Hamerschlak N, Zhong X, Ahn KW, Sullivan KM, Carrum G, Andrey J, Bredeson CN, Cairo M, Gale RP, Hahn T, Storek J, Horowitz MM, McSweeney PA, Griffith LM, Muraro PA, Pavletic SZ, Nash RA. Transplantation for autoimmune diseases in north and South America: a report of the Center for International Blood and Marrow Transplant Research. *Biol Blood Marrow Transplant*. 2012;18(10):1471-1478. doi: 10.1016%2Fj.bbmt.2012.06.003.

Table 1: Summary of Reported Cases of HSCT in Patients with MG

Study	Age at HSCT/ Sex	Disease duration at HSCT (yrs)	MG features (disease type/ worst MGFA class/Ab status)	MG treatment prior to HSCT	HSCT type	HSCT related complications	Follow-up duration and outcome of MG	Notes
Beland et al., 2023[12]								
Patient #1	62/F	4	MGFA class V, MuSK-Ab (+)	Prednisone, methotrexate, rituximab, plasmapheresis	Autologous	URTIs, venous catheter related infection	66 months, MG improved (MGFA class IIa), off all MG medications	Improvement by 3 months
Patient #2	55/F	3	MGFA class IVb, MuSK-Ab (+)	Prednisone, azathioprine, rituximab, plasmapheresis	Autologous	None	42 months, CSR, off all MG medications	Improvement by 4 months
Patient #3	38/F	3	MGFA class IVb, MuSK-Ab (+)	Prednisone, rituximab, plasmapheresis	Autologous	Herpetic stomatitis, bacteremia, URTI, premature menopause	36 months, CSR, off all MG medications	Improvement by 2 months
Bryant et al., 2016[13]								
Patient #1	43/F	5	MGFA class V, AChR-Ab (-)	Pyridostigmine, prednisone, azathioprine, mycophenolate mofetil, cyclosporine, IVIG, plasmapheresis, thymectomy	Autologous	none	149 months, CSR, off all MG medications	Improvement by 7 weeks
Patient #2	55/M	11	MGFA class IIIb, AChR-Ab (+)	Pyridostigmine, prednisone, mycophenolate mofetil, IVIG, plasmapheresis	Autologous	Mucositis, CMV viremia	91 months, CSR, off all MG medications	Improvement by 3 weeks
Patient #3	49/F	14	MGFA class IVb, AChR-Ab (+)	Pyridostigmine, prednisone, azathioprine, IVIG, plasmapheresis, thymectomy	Autologous	Mucositis, VZV dermatitis	40 months, CSR, off all MG medications	Improvement by 6 weeks
Patient #4	24/F	7	MGFA class IIIb, AChR-Ab (+)	Pyridostigmine, prednisone, mycophenolate mofetil, IVIG	Autologous	Neutropenic fever, Mucositis, CMV viremia	33 months, CSR, off all MG medications	Improvement by 4 months
Patient #5	42/F	7	MGFA class IVa, AChR-Ab (-)	Pyridostigmine, prednisone, azathioprine, mycophenolate mofetil, cyclosporine, IVIG, plasmapheresis, thymectomy	Autologous	Neutropenic fever, CMV viremia, BK virus hemorrhagic cystitis, oral HSV	32 months, CSR, off all MG medications	Improvement by 2 weeks

Patient #6	42/F	5	MGFA class IVb, AChR-Ab (+)	Pyridostigmine, prednisone, azathioprine, mycophenolate mofetil, IVIG, plasmapheresis, thymectomy	Autologous	Amegakaryocytic thrombocytopenia	41 months, CSR, off all MG medications	Improvement by 5 weeks
Patient #7	53/F	1	MGFA class V, AChR-Ab (+)	Pyridostigmine, prednisone, IVIG, plasmapheresis	Autologous	Neutropenic fever	29 months, CSR, off all MG medications	HSCT for follicular lymphoma with coincident active MG. MG improvement by 5 weeks
Håkansson et al., 2017[14]	64/F	38	MGFA class V, AChR-Ab (+)	Pyridostigmine, prednisone, methylprednisolone, azathioprine, mycophenolate mofetil, sirolimus, cyclosporine, cyclophosphamide, rituximab, eculizumab, terbutaline, bortezomib, IVIG, plasmapheresis	Autologous	Neutropenic fever, drug-related exanthema	24 months, significantly improved, off all MG medications	Improvement by 3 weeks
Inan et al., 2022[15]	27/F	1	MGFA class V, AChR-Ab (-), MuSK-Ab (+)	Pyridostigmine, methylprednisolone, rituximab, IVIG, plasmapheresis	Autologous	Urinary tract infection, Neutropenic fever, immunoglobulin deficiency	30 months, improved, still requiring intermittent rituximab, plasmapheresis and IVIG	Coexisting familial Mediterranean fever, MG improvement after 4 months
Mitsumune et al., 2018[16]	54/M	27	GMG, AChR-Ab (+)	Pyridostigmine, prednisone, cyclosporine, cyclophosphamide, IVIG, thymectomy	Autologous	none	2 months, improved	Coexisting polymyositis, aplastic anemia, thymoma
Schlatter et al., 2023[17]	33/F	14	MGFA class IVb, AChR-Ab (+)	Pyridostigmine, prednisone, mycophenolate mofetil, cyclophosphamide, rituximab, eculizumab, IVIG, plasmapheresis, thymectomy	Autologous	Neutropenic fever, rash, EBV reactivation	26 months, CSR, off all MG medications	Improvement by 3 weeks

Sossa Melo et al., 2019[18]	60/M	4	MGFA class V, AChR-Ab (+), MuSK-Ab (-)	Pyridostigmine, prednisone, azathioprine, cyclosporine, mycophenolate mofetil, rituximab, IVIG, plasmapheresis, thymectomy	Autologous	Neutropenic fever, CMV reactivation	65 months, CSR, off all MG medications	Improvement by 9 weeks
Strober et al., 2009[19]	17/M	16	GMG, AChR-Ab (+)	Pyridostigmine, corticosteroids, azathioprine, mycophenolate mofetil, cyclophosphamide, rituximab, IVIG, plasmapheresis, thymectomy	Allogeneic	Mucositis, *Staphylococcus epidermidis* bacteremia, CMV reactivation	40 months, improved, off all MG medications	Improvement within first year

Abbreviations: Ab, antibody; AChR, acetylcholine receptor; CMV, cytomegalovirus; CSR, complete stable remission; EBV, Epstein Barr virus; F, female; GMG, generalized myasthenia gravis; HSCT, Hematopoietic stem cell transplantation; HSV, herpes simplex virus; IVIG, intravenous immunoglobulin; M, male; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific kinase; URTI, upper respiratory tract infection; VZV, varicella zoster virus.

Diagnostic and treatment challenges in MRI-negative myelitis associated with MOG antibody: A case report and literature review

Gloria Ortiz-Guerrero MD[1], Daniel Mafla MD[2], Carley Carter MD[2], Arpan Patel MD[2]

[1]Department of Neurology, Mayo Clinic, Rochester, MN, USA
[2]Department of Neurology, The University of Kansas Medical Center, Kansas City, KS, USA

ABSTRACT

Background:
MRI negative cases of MOG associated inflammatory myelopathy, optic neuritis, and encephalitis have been reported in the literature. Negative MRI can lead to diagnostic uncertainties and treatment delay.

Objectives:
We report the case of a patient presenting with a subacute myelopathy and negative spinal MRI who tested positive for serum MOG antibodies and showed improvement with immunotherapy.

Conclusion:
MOGAD may present with atypical patterns or negative MRIs, leading to diagnostic uncertainties. A negative spinal cord MRI in patients with a history and examination consistent with an inflammatory myelopathy should not preclude investigation of MOG antibodies and initiation of early empirical immunotherapy.

Introduction

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a spectrum of autoimmune-mediated syndromes presenting as monophasic or relapsing inflammatory attacks of the CNS. It typically manifests as optic neuritis and/or myelitis in the adult population, but clinical phenotypes also include acute disseminated encephalomyelitis (ADEM); cerebral cortical encephalitis (CCE); and brainstem syndromes.[1,2]

When the spinal cord is affected, as with any myelitis, patients may experience weakness, a sensory level, bladder/bowel dysfunction, and spasticity. A minority can present with an acute flaccid myelitis instead of the more common upper motor neuron syndrome. In contrast to enterovirus D68–associated acute flaccid myelitis, MOG-associated cases often responded well to short-term immunotherapy.[3]

A viral prodrome is more commonly in MOG-associated myelitis than with other CNS demyelinating diseases. Characteristic imaging features can also be suggestive of this condition. MRI may reveal longitudinally extensive lesions (three or more spinal segments) and/or short segment lesions.[1,2] The absence of gadolinium enhancement and the restriction of lesions to gray matter are typical, distinguishing it from multiple sclerosis (MS) or AQP4-positive neuromyelitis optica spectrum disorder (NMOSD).[3] It can affect the spinal cord anywhere from the medulla to the conus medullaris. In fact, involvement of the conus medullaris is more common in MOGAD than in other inflammatory disorders.[3]

Patients who have MOG attacks typically recover well. It is not unusual for a patient with MOGAD to present with complete paralysis due to thoracic myelitis and return to the clinic 3 to 6 months later with the ability to walk again, often without assistance.[1] Nevertheless, among all MOG-associated disorder phenotypes, myelitis is the most likely to cause permanent disability.[3]

Recovery from myelitis often leads to the normalization of the spinal cord, making it difficult to visualize old lesions on subsequent scans. This has led to the notion that MOGAD may be a cause of "MRI negative myelitis".[1,4] However, cases of MOGAD without evidence of signal abnormalities on MRI have also been reported during early stages of this condition, which has led to diagnostic uncertainties and treatment delay.[5,6]

The recommended MOG antibody test is a cell-based assay, and since 2018, its use has become widespread. However, like other techniques for assessing this antibody (e.g., ELISA), it has a high rate of false-positive results. In some laboratories, only IgG1 antibodies to MOG are considered positive, whereas in others, IgG is deemed positive if it exceeds a specific titer, increasing its specificity.[1] More frequently than not, lower MOG antibody levels should prompt consideration of other conditions.

This report describes a patient with a clinical presentation of an inflammatory myelopathy with negative MRI results in the acute and subacute setting, yet positive serology for MOG-IgG antibodies at a low titer, illustrating the diagnostic challenges in MOGAD and the potential for low titers to represent true positives in the right clinical scenario.

Case Report

Written consent was obtained from our patient for this case report. A 47-year-old female with a medical history of thyroid cancer in remission (post resection) and a prior gastric sleeve surgery (2 years prior) presented to our institution with a 10-day history of subacute asymmetric bilateral lower extremity paresthesia and weakness with urinary retention and saddle anesthesia. At another hospital on day 5 of symptoms, MRIs of the **cervical** and **thoracic spine** were reportedly **negative**, and she was treated with 500 mg of IV **methylprednisolone** for three doses, but the steroid course was **terminated early** due to an "inconclusive" workup. She was discharged with a

suspected diagnosis of **functional neurologic disorder (FND).**

Over the next 5 days, her deficits progressively worsened, eventually leading to **flaccid paraplegia.** At presentation to our institution, her physical exam revealed **paraplegia** with **loss of all sensory modalities** below the T11 dermatome and increased reflexes in her lower extremities. The patient had received her first dose of the **Pfizer-BioNTech COVID-19 vaccine 14 days prior** to symptom onset.

Upon admission, her **CSF analysis** showed: **23 WBC/uL** (normal <5), **10,752 RBC/uL** (none), **48 mg/dl protein** (normal 15-45), and **62 mg/dl glucose** (normal 40-75). **Oligoclonal bands (OCBs)** were not tested initially, but a follow-up lumbar puncture (3 months later) showed no elevation of **free kappa light chains** (0.016, range <0.1000).

Extensive **infectious workup** (syphilis, HIV, hepatitis, COVID-19, bacterial and fungal CSF cultures, CSF viral PCR [enterovirus, herpes simplex virus, West Nile]) were all negative. Metabolic labs, including vitamin B12 (1369 pg/ml, normal range 180-914), folate (13.4 ng/ml, normal range >3.9), vitamin E (10 mg/L, normal range 5.5-17), and copper (1.09 mcg/ml, normal range 0.75-1.45) were within normal limits. **Rheumatologic labs** (ANA, anti-SSA/SSB, rheumatoid factor, aquaporin-4 antibodies, etc.) were also negative. Sedimentation rate (5 mm/hr [range 0-20]) and C-reactive protein (0.04 mg/dl [range <1.0]) were not elevated.

The exception to her negative workup was a positive serum MOG IgG antibody (Myelin Oligodendrocyte Glycoprotein (MOG-IgG1) Fluorescence-Activated Cell Sorting (FACS) Assay, Serum, Mayo Clinic Laboratories) with a titer of 1:40 (reference range <1:20).

Initial **MRI of the cervical, thoracic, and lumbar spine** (Day 10 since the onset of symptoms) was **normal. Brain MRI** showed **non-specific FLAIR hyperintensities** in the **bifrontal cortex** (Figure 1). A **spinal angiogram** was normal ruling out a vascular etiology. **Electromyography (EMG)** showed normal motor and sensory peripheral nerve function. A repeat cervicothoracic MRI was unrevealing. She had no previous history consistent with optic neuritis, thus evoked potentials of the optic nerves and optical coherence tomography were not performed. A **second CSF analysis** (Day 16 since the onset of symptoms) showed **1 WBC/uL, 31 mg/dl protein**, and **55 mg/dl glucose.**

Despite the diagnostic uncertainty, the patient was started on **1000 mg IV methylprednisolone** daily for five days. Due to the severity of her symptoms, she also underwent **five cycles of plasmapheresis** with minimal improvement by the time of hospital dismissal to inpatient rehabilitation.

At her two-week outpatient follow-up, she showed **mild improvement** in her motor and sensory deficits. Follow-up MOG-IgG a month later **remained positive** at a titer of 1:20. **Two months later**, the patient developed **left arm weakness** and worsening **left leg weakness**, prompting further treatment with **IV methylprednisolone** and **intravenous immunoglobulin (IVIG).** MRIs of the cervical and thoracic spinal cord were again unrevealing. She was further treated with two doses of rituximab followed by monthly IVIG for maintenance immunotherapy. At the **six-month follow-up**, she was able to walk with a **walker** and had resolved sensory and urinary symptoms. A **one-year follow-up MRI** continued to show no spinal cord lesions.

Fourteen months post-presentation, she was ambulatory without assistance but had mild residual **left leg weakness** (4/5 strength in left knee flexion, dorsiflexion, and plantar flexion). The patient moved out of town and was evaluated at a different institution for a suspected **myelopathy relapse** a month later. A **thoracic spine MRI** reported a **long-segment T2 hyperintensity** spanning **5 levels (T7-T11)** with **questionable patchy enhancement**, though these images were not available for our review.

Discussion

We present a case of MOG antibody-associated myelitis with MRI-negative findings in both the acute and subacute phases, along with a low positive antibody titer, both of which pose significant diagnostic and therapeutic challenges.

While MRI is an essential diagnostic tool in the workup of inflammatory CNS conditions, our case highlights the growing recognition of **MRI-negative MOGAD**, a phenomenon reported in the literature. A retrospective study at Mayo Clinic found that 10% (7 out of 73 patients) of patients with myelitis associated with MOG antibody had normal MRIs within six weeks of symptom onset. Three out of 7 patients developed myelitic lesions when MRIs were repeated after 6 to 26 days. The MOG-IgG titer in these patients ranged from 100-10,000.[4] In our patient, normal MRIs of the spinal cord were seen on follow up scans up to 1 year from her initial presentation and her MOG titers did not exceed 1:40.

The absence of spinal cord abnormalities on MRI in patients who otherwise have a clinical presentation consistent with an inflammatory myelopathy is atypical. The fact that a substantial proportion of patients can have negative CSF findings further complicates this situation, putting this patient population at risk of being misdiagnosed and at risk of treatment delays. This was exemplified by our patient, who, despite the significant deficits, was discharged from an outside facility with a suspected diagnosis of FND. Negative MRIs are also common in patients with other autoimmune conditions such as anti-NMDA receptor autoimmune encephalitis and glutamic acid decarboxylase (GAD) antibody spectrum disorders.[7] Myelopathies with a negative MRI encompass a broad differential diagnosis that should not be ignored (Table 1). Early identification of these etiologies allows a prompt and targeted medical treatment, potentially leading to a better prognosis.

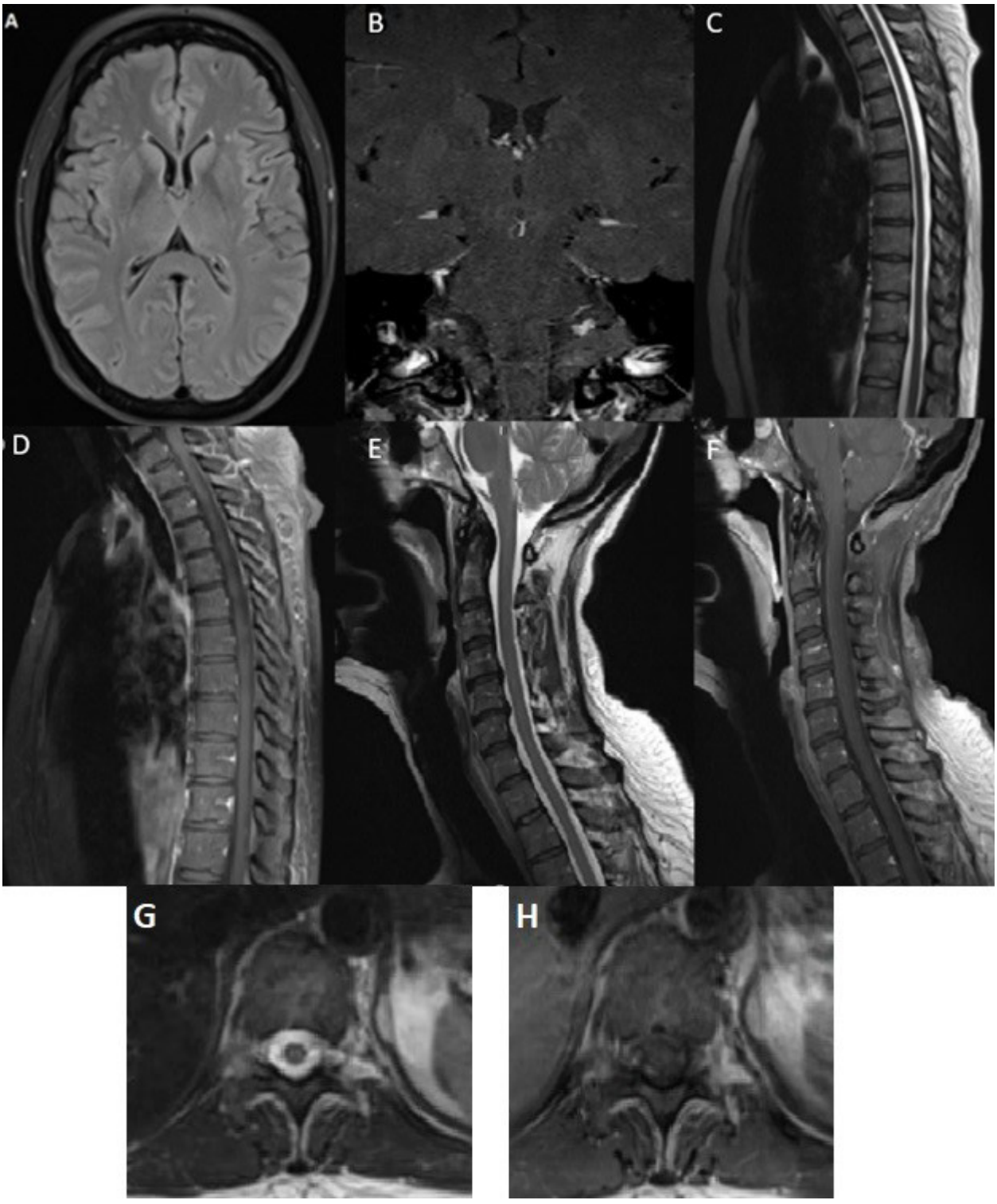

Figure 1. 3T MRIs. A) MRI brain w/wo contrast, T2 FLAIR sequence showing several punctate FLAIR hyperintense subcortical bifrontal white matter foci (blue arrows). B) Coronal T1 post-contrast brain MRI with no enhancing lesions. C and D) (C. Sagittal T2, D. Sagittal T1 post-contrast) MRI of the T-spine without cord signal abnormalities or enhancing lesions. E and F) (E. Sagittal T2 and F. Sagittal T1 post-contrast) MRI of the C-spine without cord signal abnormalities or enhancing lesions. G and H) (G. Axial T2 H. axial T1 post-contrast) Axial MRIs of the T-spine at T11 showing no obvious lesions, corresponding to the sensory level on patient´s neurologic examination.

Table 1. Differential diagnosis in negative-MRI myelopathies.

Myelopathy Subtype
Nutritional
B12 deficiency
Copper deficiency
Vitamin E deficiency
Vascular
Spinal arteriovenous malformation/fistula
Spinal cord infarcts
CNS vasculitis
Infectious
Viral myelitis
Covid-19, Zoster, Epstein-Barr, herpes simplex, cytomegalovirus, adenovirus, enterovirus, coxsackie B virus, AIDS, HIV, HTLV I or II
Fungal Infections
Cryptococcus, aspergillus
Post infectious
Autoimmune
Systemic lupus erythematosus
Sjogren's syndrome
Stiff person syndrome/GAD spectrum disorders
Glial fibrillary acidic protein (GFAP) - related disorders
Anti-glycine receptor-associated myelopathy
MOGAD
Neoplastic
Intravascular B cell lymphoma
Paraneoplastic encephalomyelitis
Anti-hu and anti-CV2/CRMP5
Structural lesions
Parasagittal meningioma
Arnold-Chiari malformation
Tethered Cord

The MOG antibody cell-based assay is highly specific when the titer is greater than 1:100; lower titers may be associated with false positives.[1] As an aside note, the serum sample for the first MOG ab test in our patient was collected after she had completed five daily doses of 1000 mg of methylprednisolone. Although it may have been too soon, it is unclear whether this could have affected the titer result. Nevertheless, the low antibody titer in this case underscores the need for careful consideration of clinical presentation, disease progression, and patient recovery, rather than relying solely on titers or MRI results for diagnosis. In the presence of a phenotype suggestive of MOGAD, even a low positive titer should prompt consideration of steroids, as this approach represents an overall safe form of acute immunotherapy.

Our patient received the first dose of the Pfizer-BioNTech COVID-19 vaccine 14 days prior to the onset of her neurological symptoms. The number of case reports of inflammatory myelitis following COVID-19 infection is similar to that following COVID-19 vaccination.[8,9] While these cases typically show positive MRI findings, at least 7 cases of an MRI-negative myelopathy associated with COVID-19 infection have been reported.[9,10] To date, no cases of MRI negative myelopathies have been reported in association with a COVID-19 vaccine.

For patients with suspected vaccine-related neurologic complications, it is crucial to select candidates for MOG antibody testing carefully. Testing should be reserved for cases presenting with a well-described MOGAD phenotype to minimize the risk of false positives, particularly because the prevalence of low-titer MOG antibodies in the general healthy population is not well established. The temporal profile of our patient's deficits were typical of an inflammatory myelopathy.

Despite the low positive titer in our patient, the clinical features, the natural course of the disease, the particularly good recovery after her initial attack, and the recurrent attacks after 2 and 15 months of her initial presentation, are strongly suggestive of the titer being a true positive result.

In conclusion, a negative spinal cord MRI in a clinical scenario highly suggestive of an inflammatory myelopathy should not discourage physicians from testing for MOG antibodies and considering early empirical immunotherapy, as prompt treatment may improve the chances of a favorable prognosis. This case highlights the need for further research into the significance of low MOG antibody titers and MRI-negative presentations. More studies are needed to establish clear diagnostic thresholds and treatment protocols for these atypical presentations.

Conflict of interest statement

The authors have no conflict of interest to disclose.

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References

1. Levy M. Immune-Mediated Myelopathies. Continuum (Minneap Minn). 2024;30(1):180-98.
2. Deneve M, Biotti D, Patsoura S, Ferrier M, Meluchova Z, Mahieu L, et al. MRI features of demyelinating disease associated with anti-MOG antibodies in adults. J Neuroradiol. 2019;46(5):312-8.
3. Longbrake E. Myelin Oligodendrocyte Glycoprotein-Associated Disorders. Continuum (Minneap Minn). 2022;28(4):1171-93.
4. Sechi E, Krecke KN, Pittock SJ, Dubey D, Lopez-Chiriboga AS, Kunchok A, et al. Frequency and characteristics of MRI-negative myelitis associated with MOG autoantibodies. Mult Scler. 2021;27(2):303-8.
5. Perez CA, Garcia-Tarodo S, Troxell R. MRI-Negative Myelitis Associated With Myelin Oligodendrocyte Glycoprotein Antibody Spectrum Demyelinating Disease. Child Neurol Open. 2019;6:2329048X19830475.
6. Grangeon L, Hebant B, Guillaume M, Ahtoy P, Lefaucheur R. Myelitis with normal spinal cord MRI: don't forget anti-MOG antibodies disease! Acta Neurol Belg. 2020;120(4):945-6.
7. Zhang T, Duan Y, Ye J, Xu W, Shu N, Wang C, et al. Brain MRI Characteristics of Patients with Anti-N-Methyl-D-Aspartate Receptor Encephalitis and Their Associations with 2-Year Clinical Outcome. AJNR Am J Neuroradiol. 2018;39(5):824-9.
8. Naeem FN, Hasan SFS, Ram MD, Waseem S, Ahmed SH, Shaikh TG. The association between SARS-CoV-2 vaccines and transverse myelitis: A review. Ann Med Surg (Lond). 2022;79:103870.
9. Roman GC, Gracia F, Torres A, Palacios A, Gracia K, Harris D. Acute Transverse Myelitis (ATM):Clinical Review of 43 Patients With COVID-19-Associated ATM and 3 Post-Vaccination ATM Serious Adverse Events With the ChAdOx1 nCoV-19 Vaccine (AZD1222). Front Immunol. 2021;12:653786.
10. Memon AB, Al-Hader R, Patel S, Malik S, Megally M, Steijlen KL, et al. Late-onset rapidly progressive MRI-negative-myelitis after COVID-19 illness. Clin Neurol Neurosurg. 2021;202:106513.

When Facioscapulohumeral dystrophy Meets Myasthenia gravis: Case Report and Literature Review

Arsh Ketabforoush MD[1,2*], Ryan Castoro MD[1,2], W. David Arnold MD[1,2,3,4], Richard J. Barohn MD[1,3]

[1] NextGen Precision Health, University of Missouri, Columbia, Missouri , USA
[2] Department of Physical Medicine and Rehabilitation, University of Missouri, Columbia, Missouri , USA
[3] Department of Neurology, University of Missouri, Columbia, Missouri , USA
[4] Department of Medical Pharmacology and Physiology, University of Missouri, Columbia, Missouri , USA

ABSTRACT

Simultaneous occurrences of rare disorders are significant diagnostic and management challenges. In this case report, we describe the initial clinical presentation, diagnosis, and management of a 66-year-old man with a history of concurrent facioscapulohumeral dystrophy (FSHD) and myasthenia gravis (MG). He presented at age of 54 with longstanding symptoms of facial, scapular, and limb weakness which was previously diagnosed at age 23 as limb girdle muscular dystrophy. He also exhibited new symptoms of ptosis, diplopia, and bulbar muscle weakness. Genetic testing and acetylcholine receptor autoantibody testing confirmed the diagnoses of both FSHD and MG. This report discusses the diagnostic obstacles, findings before and after treatment, and reviews previously reported cases of concurrent FSHD and MG. We emphasize the need for clinicians to remain vigilant for the development of symptoms from another rare disease in patients already diagnosed with one, avoiding premature attribution of new symptoms to the baseline condition.

Introduction

Facioscapulohumeral dystrophy (FSHD) is the third most prevalent type of muscular dystrophy, following Duchenne muscular dystrophy and myotonic dystrophy type 1.[1] The pooled prevalence of FSHD across all age groups is 3.95 per 100,000 individuals.[2] FSHD is primarily inherited as an autosomal dominant disorder, though up to 30% of cases occur sporadically due to de novo mutations. Symptoms of FSHD generally manifest in the second decade of life but can appear at any age, ranging from infancy to late adulthood.[3] Clinically, FSHD presents with asymmetric, gradually progressing weakness that initially affects the face, shoulders, and arms. This is followed by the distal lower limbs and pelvic girdle muscles involvement. Bulbar, extraocular, and respiratory muscles are often not affected.[4]

Myasthenia gravis (MG) is an autoimmune neuromuscular junction disorder marked by fatigue and weakness of skeletal muscles with a global prevalence of approximately 12.4 per 100,000.[5,6] In MG, autoantibodies target acetylcholine receptors or associated proteins in the pre- and post -synaptic membranes of the neuromuscular junction or the synaptic space. These autoantibodies cause variable localized or generalized skeletal muscle weakness. The weakness predominantly affects proximal muscles more than distal ones and almost always involves the extraocular muscles, leading to diplopia and ptosis.[5]

The simultaneous occurrence of FSHD and MG is uncommon according to medical literature and poses significant diagnostic and management challenges. Through the presentation of a rare case of concurrent MG and FSHD combined with a review of the literature we outline the complicated clinical presentation and immunomodulation responses for this unique population.

Case Presentation

The patient is a 66-year-old male who was initially seen at 54 years of age. At that time, he presented with chronic symptoms of limb weakness with prominent scapular winging. When he was 19 years old he developed proximal arm weakness and was diagnosed with an unspecified limb-girdle muscular dystrophy after a muscle biopsy at 23 years of age. Similar symptoms were reported in his mother, maternal grandmother, and sister, and he mentioned that his sister had a positive genetic test for "muscular dystrophy" and also had MG. She lives in California, and we are not able to obtain her records. Despite the patient's symptoms, he was active and worked as a police officer. When he was 54 years old, he developed new, variable symptoms of diplopia, ptosis, and worsening difficulty with chewing. Given the insidious onset of his bulbar symptoms, an MG workup was done, and he was diagnosed with the condition. Serologic testing revealed a positive ACh-R antibody (we do not have the level from that time), and genetic testing reveled a contraction of D4Z4 repetitive element on chromosome 4q35 consistent with FSHD type I.

Over the next decade he was been treated with a variety of medications for MG at various times, including pyridostigmine, prednisone, mycophenolate mofetil, and intravenous immunoglobulin (IVIG). Over nine years he had two episodes of exacerbation and was hospitalized for plasmapheresis, with one resulting in temporary mechanical ventilation. Ultimately, chronic monthly IVIG treatment was very effective, and he tapered off prednisone and mycophenolate mofetil. ACh-R antibody titer was 10.4 ng/L four years after diagnosis. Two years ago, his insurance company denied continued IVIG treatment. Since then,

Table 1. Motor examination results are graded from 0 (no contraction) to 5 (normal strength) for both the right and left sides across various muscle groups tested.

Muscle	Right	Left	Muscle	Right	Left
Orbicularis oculi	3	3	Knee Extension	5	5
Orbicularis oris	3	3	Knee Flexion	5	5
Neck Flexion	4		Ankle Dorsiflexion	4	4
Neck Extension	5		Ankle Plantarflexion	5	5
Shoulder Abduction	4+	4+	Ankle Eversion	4+	4+
Elbow Flexion	5-	5-	Ankle Inversion	5	5
Elbow Extension	5-	5-	Hip Flexion	4	4
Wrist Flexion	5	5	Hip Abduction	5-	5-
Wrist Extension	5	5	Hip Adduction	5	5
Finger Abduction	5	5			
Finger Extension	4+	4+			
Thumb Abduction	4	4			

he has been maintained on pyridostigmine, but he has experienced cholinergic side effects, which have limited its use. He has been offered complement inhibitor and Fc blocker medication, but he has declined. He continues to report ongoing symptoms, but he is willing to tolerate his current symptoms without restarting prior medications or starting new medications. At his most recent follow up visit, he reported experiencing occasional ptosis, double vision, and difficulty in chewing and swallowing. The Myasthenia Gravis Activities of Daily Living (MG ADL), with a score of 6, scoring 1 on following parameters: chewing, swallowing, breathing, rising from a chair, double vision, and eye droop.[7] On examination, there was bilateral scapular winging. Extraocular motility was full and there was no ptosis. The right and left eye had a palpebral fissure measurement of 10 mm. The motor examination results are summarized in Table 1. His most recent serum AchR antibody level was 3.56 nm/L.

Discussion

Both FSHD and MG are rare diseases, and their coexistence has seldom been reported. *Table 2* provides a concise summary of cases reporting concurrent occurrences of both MG and FSHD.[8,9] One of the authors (RJB) reported two cases in 2004 with Italian colleagues.[10] Prior to this publication the most recent cases were reported in 2019. Filippeli et al. reported a 69-year-old woman with a 13-year history of FSHD, confirmed by a DNA deletion test, who presented with dysphagia, diffuse limb weakness, and binocular diplopia. The diagnosis of MG was confirmed through a decrement response on repetitive nerve stimulation, increased jitter values in single-fiber electromyography, elevated acetylcholine receptor-binding antibodies, and significant improvement following pyridostigmine and IVIG therapy.[11] Also in 2019, Nauman et al. reported a 77-year-old patient with a confirmed diagnosis of FSHD for 27 years and MG for 4 years, who experienced worsening symptoms such as double vision, ptosis, swallowing difficulties, and exacerbation of previous weaknesses. Following treatment with IVIG, the patient's condition notably improved.[12] The first reported case in the literature was by Sakuma et al. when described a similar case involving a 50-year-old man with a 35-year history of FSHD who developed MG.[13] The primary lesson from these reports is that the onset of bulbar and extraocular symptoms in a patient with established FSHD should raise suspicion for MG and prompt further evaluations such as repetitive nerve stimulation, single-fiber EMG, and antibody titer detection.

Could there be secondary mechanisms which MG and FSHD are related? AChR antibodies have been observed in patients with various other diseases, including myotonic dystrophy, limb-girdle muscular dystrophy, and mitochondrial myopathy and ALS.[14-16] The detection of AChR antibodies indicates a breakdown of immune tolerance to these receptors, likely due to muscle fiber degeneration and subsequent autoinflammation.[15] Minor alterations in the structure of the AChR within skeletal muscle due to degenerative processes could potentially trigger sensitization. This, along with the release of DNA or RNA particles from degenerating muscle tissue, might activate Toll-like receptors (TLRs), responsible for responding to inflammatory signals from both pathogens and internal cellular damage. These modified antigens may then activate CD4 cells and B cells. If the immune system detects significant changes in these antigens, tolerance could be disrupted, leading to the production of autoantibodies.[15]

Moreover, in FSHD as many as 80% of muscle biopsies from patients display some level of infiltration by mononuclear inflammatory cells. However, despite this infiltration, disease progression remains unaffected, and patients do not experience any benefits from prednisone treatment.[9,10] Therefore, in cases where both FSHD and MG occur simultaneously, the detection of AChR antibodies

could be an indication of the immune-mediated process triggered by underlying muscle damage due to muscular dystrophy. Perhaps this could explain why our patient's sister also may had FSHD and MG. Based on the prevalence rates of 3.95 per 100,000 for FSHD and 12.4 per 100,000 for MG and the world population is 8,115,094,06015 (as of 2024) while ignoring the biases of meta-analyses, it is estimated that approximately 40 people worldwide are experiencing both conditions concurrently.

Our patient exhibited symptoms of FSHD approximately 30 years before being diagnosed with MG, similar to the case of Asadollahi et al. the other cases MG developed several years after FSHD diagnosis.[8-13] In a patient with FSHD the following should raise the suspicion of MG: double vision, new asymmetric ptosis, new acute or subacute difficulty with chewing and swallowing, and acute respiratory failure.

Our literature review indicates that most of the reported cases of concurrent FSHD and MG occur in men and diagnosed after the fifth decade of life.[8-10,12,13] In some instances, the FSHD diagnosis was initially missed and only identified later when significant FSHD symptoms, such as foot drop, became evident.[8,9,13] In terms of treatment despite the underlying weakness from FSHD the symptoms of MG responds to standard treatment of MG including pyridostigmine, corticosteroids, and intravenous immunoglobulin (IVIG).[8-13]

Often, physicians may prematurely attribute new symptoms to the baseline rare disease the patient is already experiencing (i.e. Occam's razor). Thus, a lesson of this report is that clinicians should recognize that a patient with one rare disease can develop symptoms of another rare disease. This reinforces the famous quote from Sherlock Holmes: "When you have eliminated the impossible, whatever remains, however improbable, must be the truth".[17]

References

1. Statland JM, Tawil R. Facioscapulohumeral muscular dystrophy. *CONTINUUM: Lifelong Learning in Neurology*. 2016;22(6):1916-1931.
2. Mah JK, Korngut L, Fiest KM, et al. A Systematic Review and Meta-analysis on the Epidemiology of the Muscular Dystrophies. *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques*. 2016;43(1):163-177. doi:10.1017/cjn.2015.311
3. Tawil R, Kissel JT, Heatwole C, Pandya S, Gronseth G, Benatar M. Evidence-based guideline summary: Evaluation, diagnosis, and management of facioscapulohumeral muscular dystrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. *Neurology*. 2015;85(4):357-364.
4. Statland J, Tawil R. Facioscapulohumeral muscular dystrophy. *Neurol Clin*. 2014;32(3):721-728.
5. Pasnoor M, Dimachkie MM, Farmakidis C, Barohn RJ. Diagnosis of myasthenia gravis. *Neurol Clin*. 2018;36(2):261-274.
6. Salari N, Fatahi B, Bartina Y, et al. Global prevalence of myasthenia gravis and the effectiveness of common drugs in its treatment: a systematic review and meta-analysis. *J Transl Med*. 2021/12/20 2021;19(1):516. doi:10.1186/s12967-021-03185-7
7. Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. *Neurology*. Apr 22 1999;52(7):1487-9. doi:10.1212/wnl.52.7.1487
8. Asadollahi M, Rezaiyan B, Amjadi H. A rare case of facioscapulohumeral muscular dystrophy and myasthenia gravis. *Iran J Neurol*. 2012;11(1):28-9.
9. McGonigal A, Thomas AM, Petty RKH. Facioscapulohumeral muscular dystrophy and myasthenia gravis co-existing in the same patient: a case report. *Journal of Neurology*. 2002/02/01 2002;249(2):219-220. doi:10.1007/PL00007868
10. Sansone V, Saperstein D, Barohn R, Meola G. Concurrence of facioscapulohumeral muscular dystrophy and myasthenia gravis. *Muscle & nerve*. 2004;30(5):679-680.
11. Filippelli E, Barone S, Granata A, Nisticò R, Valentino P. A case of facioscapulohumeral muscular dystrophy and myasthenia gravis with positivity of anti-Ach receptor antibody: a fortuitous association? *Neurological Sciences*. 2019/01/01 2019;40(1):195-197. doi:10.1007/s10072-018-3554-4
12. Nauman F, Hussain MFA, Burakgazi AZ. The Development of Myasthenia Gravis in a Patient with Facioscapulohumeral Muscular Dystrophy: Case Report and Literature Review. *Neurol Int*. 2019;11(3):8191.
13. Sakuma H, Shimazaki S, Saito H, Ohuchi M. [A patient with facioscapulohumeral muscular dystrophy accompanied by myasthenia gravis]. *Rinsho Shinkeigaku*. Apr-May 2001;41(4-5):179-83.
14. Avallone AR, Di Stefano V, Bevilacqua L, et al. AChR-seropositive myasthenia gravis in muscular dystrophy: diagnostic pitfalls and clinical management challenges. *Neurological Sciences*. 2024:1-8.
15. Lane RJ, Roncaroli F, Charles P, McGonagle DG, Orrell RW. Acetylcholine receptor antibodies in patients with genetic myopathies: clinical and biological significance. *Neuromuscular disorders*. 2012;22(2):122-128.
16. Zoltowska K, Webster R, Finlayson S, et al. Mutations in GFPT1 that underlie limb-girdle congenital myasthenic syndrome result in reduced cell-surface expression of muscle AChR. *Human molecular genetics*. 2013;22(14):2905-2913.
17. Doyle AC. *The sign of four*. Broadview Press; 2010.

Table 2. Summary of cases reporting concurrent occurrences of both MG and FSHD.

	Cases							
Author	Ketabforoush et al.	Filippelli et al.[11]	Nauman et al.[12]	Asadollahi et al.[8]	Sansone et al.[10]	Sansone et al.[10]	McGonigal et al.[9]	Sakuma et al.[13]
Year	2024	2019	2019	2012	2004	2004	2002	2001
Country	USA	Italy	USA	Iran	Italy-USA	Italy-USA	UK	Japon
Age	66	69	77	70	69	60	56	50
Sex	Male	Female	Male	Male	Male	Male	Male	Male
FSHD manifestation	FSHD symptoms began at age 19. MG symptoms and the FSHD diagnosis occurred at age 54.	diagnosed with FSHD 13 years prior	diagnosed with FSHD at the age of 50 (27 years ago)	50-year history of slowly progressive asymmetrical weakness of proximal upper limb muscles.	clinically diagnosed with FSHD, confirmed by deletion analysis (33 kb) two years prior to admission	For 5-10 years, there has been mild, fluctuating difficulty in raising arms overhead, carrying heavy items, and standing up straight.	nearly 40-year history of foot drop and shoulder girdle weakness	35-year history of FSHD affecting the lower extremities
Family history of FSHD	Sister, mother, and maternal grandmother	two brothers and one nephew						Mother
MG manifestation	diplopia, ptosis, and worsening difficulty with chewing	20 days history of nasal timbre, followed by dysphagia and diffuse limb weakness needing bilateral support for walking, with binocular diplopia on the vertical plane appearing in the last 10 days	Diagnosed with MG at age 74 (3 years ago), his symptoms worsened, including double vision, ptosis, and swallowing issues, along with the deterioration of previous weaknesses.	15 days history of progressively worsening difficulty in chewing and dysarthria	sudden onset of dyspnea, dysphagia, dysarthria, ptosis, and severe limb weakness	fluctuating dysarthria that began 8 months prior	4 months history of left eyelid drooping, varying in severity throughout the day	Difficulty in chewing and swallowing
Anti acetylcholine receptor antibody	10.4 nmol/L	16.01 nmol/l	elevated	markedly elevated	12 pmol/L	4.1 pmol/L	6.71 nmoles/L	97 nmol/L
Repetitive nerve stimulation (RNS)		(− 10.8% at 2 Hz, − 15.6% at 5 Hz) on the orbicularis oculi muscle and (− 14.9% at 2 Hz, − 15.2% at 5 Hz) trapezius		decrement response	decremental response	decremental response	Normal Limits	waning pattern

SFEMG/EMG		Myopathy-increased jitter in the extensor digitorum communis (in 65%of 20 pairs, mean value 55.8 us)		myopathy		short-duration motor unit potentials	SFEMG showed increased jitter (mean 72.3 microseconds)-EMG demonstrated short duration polyphasic motor units with a high frequency recruitment pattern, indicating a myopathic process.	myopathic changes
Edrophonium Test		Neostigmine test was performed. Dysarthria, ptosis, and diplopia showed dramatic improvement, with returning of RNS to normal after 25 min from neostigmine injection (− 9.6% at 5 Hz		dysarthria and chewing difficulty showed dramatic improvement			ptosis improved with edrophonium	decreased waning and the clinical symptoms
Thymoma		not detected	not detected				small thymoma-Thymectomy	thymectomy
creatine kinase		high (414 UI/l)	elevated	normal		1.5-fold elevation		normal
Treatment	Chronic intravenous immunoglobulin (IVIG), pyridostigmine	intravenous immunoglobulin (IVIG) therapy at 0.4 g/kg/day for 5 days and started on pyridostigmine	steroids, pyridostigmine, and mycophenolate mofetil-IVIG treatment at 1g/kg/day for 2 days.	choline-esterase inhibitor agents	dexamethasone (25 mg daily), azathioprine (50 mg daily), and pyridostigmine (270 mg daily)	Pyridostigmine-mycophenolate mofetil (1000 mg twice daily)	pyridostigmine	corticosteroid and choline esterase inhibitor

Acquired adermatoglyphia associated with sporadic inclusion body myositis

Janie L. Bruce B.S,[1]; Benjamin W. Casterline M.D. PhD[2]; Breanna C. Tuhlei MD[3]; Nakul Katyal MD[4]; Dinanath P. Attele DO[5]; Erik R. Ensrud MD[6]; Susan M. Zurowski MD[2]; William D. Arnold MD[7]; Richard J. Barohn MD[6]

[1]University of Missouri School of Medicine,
[2]University of Missouri Department of Dermatology,
[3]University of Missouri Department of Family Medicine,
[4]University of Kentucky Department of Neurology,
[5]University of Utah Department of Neurology,
[6]University of Missouri Department of Neurology,
[7]University of Missouri Department of Physical Medicine & Rehabilitation

Abstract

A 70-year-old male patient with inclusion body myositis presented to dermatology clinic for evaluation of loss of fingerprints. Eight years previously, he had fingerprints taken for a government permit. Inclusion body myositis (IBM) was diagnosed four years later after the patient developed muscle weakness in his left lower extremity and right upper extremity and was confirmed by muscle biopsy. The patient also reported loss of skin lines that gave his fingers a shiny appearance, most prominently on the left hand, in which he had weakness associated with inclusion body myositis. He was unable to renew the government permit due to an inability for the machine to read his fingerprints. Upon exam, the fingers of his hands, most prominently the left 3rd and 4th digits, had a smooth texture and glossy appearance circumferentially, associated with diminution of skin lines and palmar dermatoglyphs. Workup for connective tissue and other autoimmune diseases was negative. This case suggests asymmetric adermatoglyphia may distinguish a subset of patients with IBM.

Key Words: adermatoglyphia, loss of fingerprints, inclusion body myositis, dermatoglyphs

Introduction

Dermatoglyphs are volar skin lines that form complex and individually unique patterns. In contrast to other skin lines, which develop throughout life in association with muscle use and age-related loss of elasticity, fingerprint patterns are established in gestation. Detailed developmental studies have demonstrated that ectodermally derived epidermis forms dermatoglyphs through patterns of epithelial budding dependent on expression of EDAR and FGF20.[1,2] Unlike the hair placode, which requires the same developmental signals in the epidermis, WNT-dependent recruitment of mesenchymal cells does not occur. Subsequently, waves of WNT-driven proliferation of basilar epidermis originating at the apex of distal phalanges leads to the regularly spaced suprabasilar thickening that forms the primary ridges of fingerprints. Although no new primary ridges arise after 17 weeks gestation, secondary ridges arise between primary ridges and the ducts of sweat glands form pores on the surface of ridges.[2,3] A recent genome-wide association study uncovered variants in limb development genes associated with fingerprint type, likely because fingerprint patterns are correlated with hand and finger proportions.[4] The integrity of dermatoglyphs can be affected by acquired conditions such as dyshidrotic eczema, contact dermatitis, scabies, herpetic whitlow, trauma, micro-abrasions, psoriasis, or Steven Johnson Syndrome.[5]

Although rare, dermatoglyphs can also be affected by congenital conditions such as an inherited absence of epidermal ridges and ectodermal dysplasias.[6,7] Isolated autosomal dominant adermatoglyphia has been described in very few families and is also known as the "immigration delay disease" due to patients' difficulties obtaining government documents. A key finding common in these families is an irregular number of sweat gland openings.[6] Ectodermal dysplasias include a range of syndromes with multiple abnormalities of ectodermal structures including hair, nail, teeth, and sweat glands. Basan syndrome and autosomal dominant adermatoglyphia are ectodermal dysplasias caused by mutations in the skin specific isoform of the SMARCAD1 gene. These two syndromes are rare and have been grouped together into SMARCAD Syndrome. This acronym stands for SMARCAD1-associated congenital facial Milia, Adermatoglyphia, Reduced sweating, Contractures, Acral Bullae, and Dystrophy of nails.[7]

Inclusion body myositis (IBM) is the most common myopathy in patients aged 50 years or older.[8,9] IBM classically presents with progressive and asymmetric weakness. Finger flexors and quadricep muscles are predominantly affected.[10] IBM can be classified as either sporadic or hereditary, with the sporadic form being more common. Sporadic IBM has both inflammatory and degenerative features leading to ongoing debate over the primary driver of the pathogenesis.[9] Endomysial and perivascular immune cell infiltration, and circulating autoantibodies support involvement of the immune system, a lack of responsiveness to immunosuppression and immunomodulatory treatments supports degeneration rather than inflammation, and induction of protein aggregates by inflammatory cytokines supports inflammation rather than degeneration.[9,10,12] While other inflammatory myopathies, such as idiopathic inflammatory myopathy and dermatomyositis, have characteristic skin eruptions, IBM is not known to involve the skin.

Case Presentation

A 70-year-old male with a past medical history of inclusion body myositis, coronary artery disease, type II diabetes mellitus, hypertension, gastroesophageal reflux disease, obstructive sleep apnea, and a 60 total pack year smoking history presented to dermatology clinic for evaluation of loss of fingerprints. Although he had previously normal fingerprints (Fig. 1), the patient had recently been unable to renew a permit due to inability to verify identity because the fingerprinting machine could not detect his fingerprints. The patient was aware of the loss of skin lines on his hands, specifically his fingers because his fingers had developed a shiny appearance. The changes were most apparent on the right second, third, and fourth fingers, where his muscle weakness was most severe. Consequently, he attributed these changes to his diagnosis of inclusion body myositis.

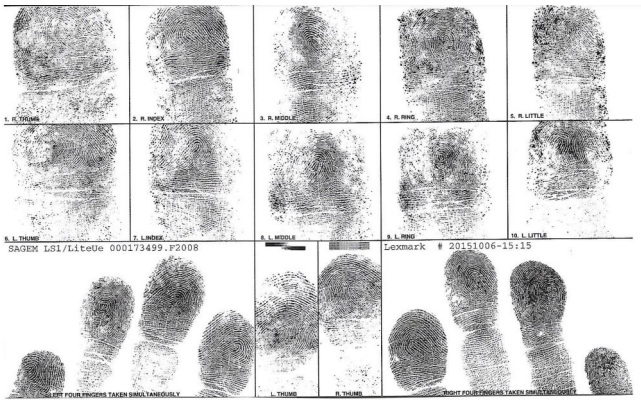


Figure 1. Fingerprints. Patient's normal fingerprints taken three years prior to diagnosis.

At the age of 65 years, the patient presented to his primary care physician with balance difficulty, some weakness of the upper extremities, and occasional trouble swallowing. The patient was referred to neurology, where he was noted to have atrophy of his right arm and forearm with decreased finger flexion on the right side 4/5; decreased dorsiflexion and eversion of the right foot 4+/5; and decreased dorsiflexion, eversion, and inversion of the left foot 4/5. Normal muscle tone and bulk was noted in the left upper extremity and bilateral lower extremities. A modified barium swallow study showed decreased anterior hyoid excursion and decreased laryngeal closure, but swallow was within functional limits. EMG and needle study was performed on the right upper and lower extremities. Myopathic findings were found in the left psoas and right flexor digitorum profundus, with some active denervation potentials seen in the right flexor digitorum profundus, right flexor pollicis longus, right xtensor hallucis longus, right flexor digitorum longus, and left tibialis anterior. MRI of the cervical and lumbosacral spine showed degenerative disc disease but not severe enough to cause his degree of weakness. MRI of the pelvis and left femur showed patchy abnormal signal and enhancement within the rectus femoris, vastus lateralis, and tensor fascia lata muscles. This pattern was most consistent with a myopathy. Based on the asymmetric findings, IBM was suspected. A muscle biopsy of the right rectus femoris muscle using local anesthetic showed endomysial inflammation and rimmed vacuoles, suggestive of IBM. The diagnosis of IBM was confirmed with NT5CIA antibody. A creatine supplement and over the counter taurorsodeoxycholic acid (TUDCA) were started, as well as physical, occupational, and speech therapy for long-term support.

Subsequently, weakness and atrophy in the right upper extremity progressed to the patient being unable to completely close his fist. The patient started having shoulder and hip dislocations due to muscle weakness and first noticed the tips of his fingers were becoming smooth and glossy. He experienced no related pain, sensory issues, redness, discoloration, or Raynaud-like phenomenon. The smoothness and loss of skin lines on his hands increased, and he was referred to the dermatology clinic for evaluation.

On exam, skin atrophy with diminution of flexion creases and dermatoglyphs was noted, with the most profound changes in the distribution of the right flexor digitorum profundus (Fig. 2). Dermoscopy of affected fingers revealed effacement of dermatoglyphs but no other specific features. ANA profile and serologies for autoimmune conditions including autoimmune myositis were ordered. ANA titer was positive to 1:160 with speckled pattern, which was concluded to be nonspecific. Antibodies against SSB, RNP, Sm, SSA Ro52, SSA Ro60, Scl-70, Jo 1, and dsDNA were negative. Additional testing for a panel of antibodies against PL-7, PL-12, EJ, OJ, SRP, Mo-2, TIF-1-gamma, MDA-5, NXP-2, Ku, Scl-100, U1 RNP, U2 RNP, and U3 RNP was also negative.

Eccrine dysfunction is a feature common to genetic adermatoglyphia syndromes. Therefore, eccrine function was assayed by applying iodine to the patient's fingers and pressing the finger pads, once dry, onto plain white paper. This modification of the starch-iodine sweat test technique permits visualization of eccrine secretion to the resolution of individual glands.[13] Results demonstrated fewer secreting eccrine glands from the finger pads, most noticeably on the right hand where the patient's weakness and fingerprint effacement are also the greatest (Figs. 3A-3B).

Discussion

Evidence of muscle involvement in the development or maintenance of dermatoglyphs has not been reported. Congenital absence of fingerprints is a feature of Naegeli-Franceschetti-Jadassohn syndrome and dermatopathia pigmentosa reticularis, which are associated with mutations in keratin 14 and support fingerprints as primarily epithelial structures.[14] A loss of fingerprints from pathological skin thickening is a feature of scleroderma, an autoimmune condition characterized by fibrotic infiltration of the

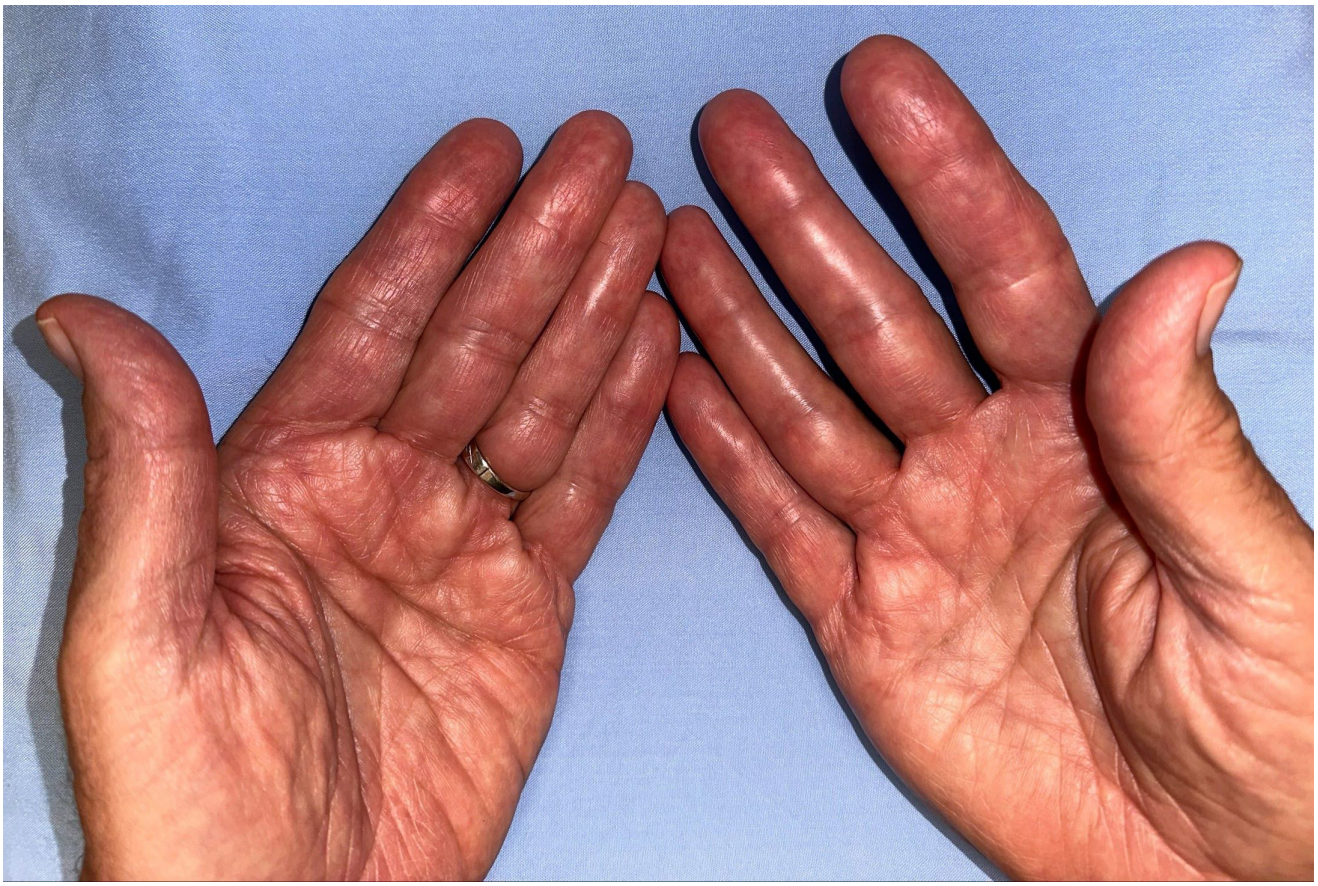


Figure 2. Bilateral palmar hands. Smooth texture and glossy appearance of the fingers of bilateral hands, most prominently the left 3rd and 4th digits. There is absence of skin lines and diminution of palmar dermatoglyphs.

dermis and other organs.[15,16] Overlap between inclusion body myositis and scleroderma has been rarely reported.[17,18] However, fibrosis is not the underlying mechanism for the loss of fingerprints in our patient, whose skin was thin and atrophic rather than fibrotic, and there were no other symptoms nor serological evidence of scleroderma. Similarly, there were no symptoms of dermatitis, accidental trauma, burns, or infection. The patient's history did not support a drug-related cause or other dermatologic condition known to impact fingerprints.

Diminished skin wrinkling of the dorsal fingers has been reported in a series of three patients with IBM who had a loss of wrinkling of the dorsal distal interphalangeal joints in association with flexor weakness of these fingers.[19] Fingerprints were not discussed. In the study of fingerprint analysis, these flexion creases are called white lines and are known to become exaggerated with age, to the point of obscuring dermatoglyphs in some individuals.[20] The authors of the case series suggest flexion creases are maintained by regular skeletal muscle contractions, as in facial rhytides, which can be temporarily relieved by botulinum toxin chemo-denervation of facial musculature.[19] However, chemo-denervation of the palms and soles is not reported to efface dermatoglyphs in patients treated with botulinum toxin for palmar hyperhidrosis. Dermatoglyph effacement is also not described in stroke or other degenerative processes of the central or peripheral nervous system. Therefore, asymmetric absence of fingerprints may be a cardinal feature of some patients with IBM. The associated eccrine dysfunction also matches the patient's distribution of IBM symptoms. Whether this a cause or consequence of acquired adermatoglyphia is uncertain.

Acknowledgment

We are grateful to the patient for his perspicacity, curiosity and patience during this study.

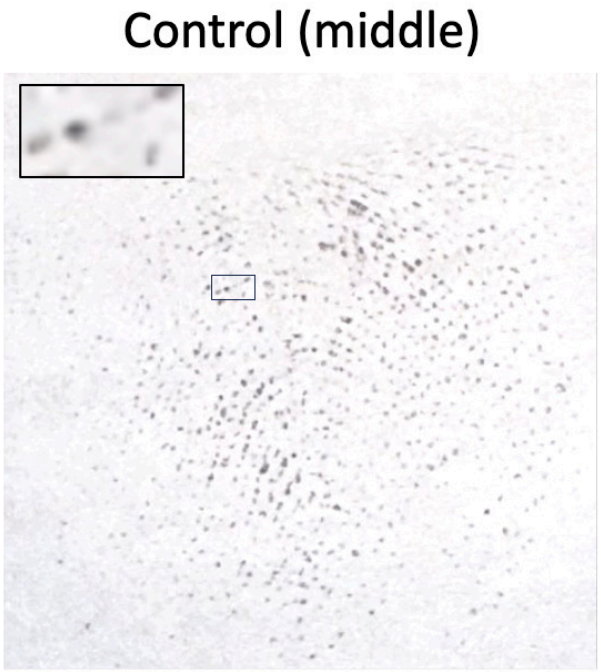
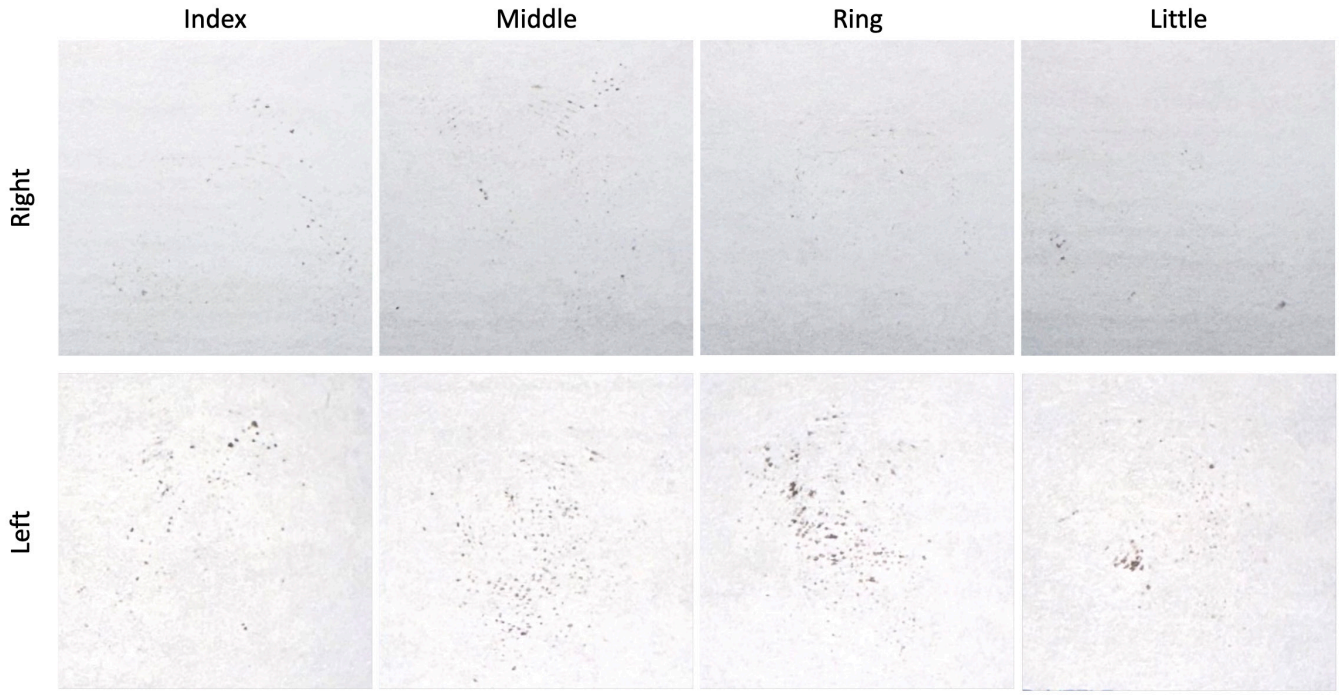


Figure 3A (left). Control. Third finger pad of a control subject. Each dot (magnified in inset) represents the secretory output of an individual eccrine gland.

Figure 3B (below). Patient. Patient finger pads two through four from the right and left hand.



References

1. U.S. Department of Justice. The Fingerprint Sourcebook. National Institute of Justice, 2014 Oct 17. ISBN-10:1502828421. ISBN-13:978-1502828422
2. Glover JD, Sudderick ZR, Shih BBJ, Batho-Samblas C, Charlton L, Krause Andrew, et al. The developmental basis of fingerprint pattern formation and variation. Cell. 2023 Mar 2;186(5):940-956.e20. doi: 10.1016/j.cell.2023.01.015. Epub 2023 Feb 9. PMID: 36764291.
3. Tafazoli M, Shahri NM, Ejtehadi H, Haddad F, Nooghabi HJ, Shahri MM, et al. Biological Variability of Sweat Gland Pores in the Fingerprints of a Fars Iranian Family from Khorasan Razavi Province, Iran. Iranian Society of Anatomical Sciences Journal. 2013 July. Vol 10, No 2. Pages 99-104. doiL10.37506/hxejzd32. CorpusID: 44633546
4. Li J, Glover JD, Zhang H, Peng M, Tan J, Mallick CB, et al. Limb development genes underlie variation in human fingerprint patterns. Cell. 2022 Jan 6;185(1):95-112.e18. 10.1016/j.cell.2021.12.008. PMID: 34995520; PMCID: PMC8740935.
5. Sarfraz N. Adermatoglyphia: Barriers to Biometric Identification and the Need for a Standardized Alternative. Cureus. 2019 Feb; 11(2): e4040. Published online 2019 Feb 8. doi:10.7759/cureus.4040. PMCID: PMC6456356, PMID:31011502
6. Burger B, Fuchs D, Sprecher E, Itin P. The immigration delay disease: adermatoglyphia-inherited absence of epidermal ridges. J Am Acad Dermatol. 2011 May;64(5):974-80. doi: 10.1016/j.jaad.2009.11.013. Epub 2010 Jul 8. PMID: 20619487.
7. Valentin MN, Solomon BD, Richard G, Ferreira CR, Kirkorian AY. Basan gets a new fingerprint: Mutations in the skin-specific isoform of SMARCAD1 cause ectodermal dysplasia syndromes with adermatoglyphia. Am J Med Genet A. 2018 Nov;176(11):2451-2455. doi: 10.1002/ajmg.a.40485. Epub 2018 Oct 5. PMID: 30289605; PMCID: PMC10557913.
8. Hervier B, Rimbert M, Colonna F, Hamidou MA, Audrain M. Clinical significance of anti-Ro/SSA-52 kDa antibodies: a retrospective monocentric study. Rheumatology (Oxford). 2009 Aug;48(8):964-7. doi: 10.1093/rheumatology/kep145. Epub 2009 Jun 16. PMID: 19531627.
9. McGrath ER, Doughty CT, Amato AA. Autoimmune Myopathies: Updates on Evaluation and Treatment. Neurotherapeutics. 2018 Oct;15(4):976-994. doi: 10.1007/s13311-018-00676-2. PMID: 30341597; PMCID: PMC6277300.
10. Naddaf E, Barohn RJ, Dimachkie MM. Inclusion Body Myositis: Update on Pathogenesis and Treatment. Neurotherapeutics. 2018 Oct;15(4):995-1005. doi: 10.1007/s13311-018-0658-8. PMID: 30136253; PMCID: PMC6277289.
11. Clerici AM, Bono G, Delodovici ML, Azan G, Cafasso G, Micieli G. A rare association of early-onset inclusion body myositis, rheumatoid arthritis and autoimmune thyroiditis: a case report and literature review. Funct Neurol. 2013 Apr-May;28(2):127-32. doi: 10.11138/FNeur/2013.28.2.127. PMID: 24125563; PMCID: PMC3812730.
12. Guglielmi V, Cheli M, Tonin P, Vattemi G. Sporadic Inclusion Body Myositis at the Crossroads between Muscle Degeneration, Inflammation, and Aging. Int J Mol Sci. 2024 Feb 27;25(5):2742. doi: 10.3390/ijms25052742. PMID: 38473988; PMCID: PMC10932328.
13. Randall WC. Quantitation and regional distribution of sweat glands in man. J Clin Invest. 1946 Sep;25(5):761-7. doi: 10.1172/JCI101760. PMID: 16695370; PMCID: PMC435616
14. Lugassy J, Itin P, Ishida-Yamamoto A, Holland K, Huson S, Geiger D, et al. Naegeli-Franceschetti-Jadassohn syndrome and dermatopathia pigmentosa reticularis: two allelic ectodermal dysplasias caused by dominant mutations in KRT14. Am J Hum Genet. 2006 Oct;79(4):724-30. doi: 10.1086/507792. Epub 2006 Aug 25. PMID: 16960809; PMCID: PMC1592572.
15. Allanore Y, Simms R, Distler O, Trojanowska M, Pope J, Denton CP, et al. Systemic sclerosis. Nat Rev Dis Primers. 2015 Apr 23;1:15002. doi: 10.1038/nrdp.2015.2. PMID: 27189141.
16. Hosseinialhashemi M, Daneshfard B. Finger Printlessness in Scleroderma. Iran J Public Health. 2016 Jun;45(6):835-6. PMID: 27648435; PMCID: PMC5026847.
17. Derk CT, Vivino FB, Kenyon L, Mandel S. Inclusion body myositis in connective tissue disorders: case report and review of the literature. Clin Rheumatol. 2003 Oct;22(4-5):324-8. doi: 10.1007/s10067-003-0715-4. PMID: 14576992.
18. Giannini M, Ellezam B, Leclair V, Lefebvre F, Troyanov Y, Hudson M, et al. Scleromyositis: A distinct novel entity within the systemic sclerosis and autoimmune myositis spectrum. Implications for care and pathogenesis. Front Immunol. 2023 Jan 26;13:974078. doi: 10.3389/fimmu.2022.974078. PMID: 36776390; PMCID: PMC9910219.
19. Lin AY, Koo B, Wang LH. Diminished distal dorsal finger wrinkling in patients with sporadic inclusion body myositis. J Clin Images Med Case Rep. 2021; 2(4): 1260. doi:10.52768/2766-7820/1260
20. Hicklin RA. Anatomy of Friction Ridge Skin. In: Li SZ, Jain A. (eds) Encyclopedia of Biometrics, Springer, Boston, MA. 2009: 23-28. doi:10.1007/978-0-387-73003-5_48

Bariatric surgery as a potential trigger for worsening hereditary spastic paraparesis: Case report

Rebecca T. Hsu MD[1], Hristelina Ilieva MD PhD[2]

[1]Department of Neurology, University of Pennsylvania, Philadelphia, Pennsylvania;
[2] Department of Neurology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

Introduction

HSP is a heterogeneous group of genetic neurodegenerative disorders characterized by slowly progressive spasticity caused by degeneration of the long tracts of the spinal cord, particularly the corticospinal tract and dorsal columns. HSP is divided into uncomplicated and complicated forms depending on the presence of other neurologic features beyond spastic paraparesis. Uncomplicated HSP describes spastic paraparesis with possible sphincter disturbances while complicated HSP is accompanied by additional features, such as ataxia, optic atrophy, pigmentary retinopathy, intellectual disability, extrapyramidal signs, dementia, deafness, peripheral neuropathy, and epilepsy. We report a patient with c.1246C>T (p.R416C) heterozygous variant on the *ATL1* gene causing a complicated form of hereditary spastic paraparesis (HSP) who had an early age of onset but had non-progressive disease until a rapid decline at age 57 after bariatric surgery. The same mutation on the *ATL1* gene was identified in family members with HSP at a young age. Intriguingly, the mother of the proband carrying the mutation remained asymptomatic.[1] This suggests that environmental factors, modulator genes, or epigenetic factors contribute to the varied presentation of HSP. Our case report suggests that bariatric surgery could be a potential inciting event for clinical worsening in patients with HSP.

Case Report / Presentation:

The patient of interest is a Caucasian man who had symptoms starting at age 5. His weakness first manifested with clumsy walking and difficulty running. He has had poor balance since young. He believes that his weakness first started in his thighs before extending distally. At the age of 7, the patient was evaluated in several hospitals and underwent three myeloencephalograms and electrophysiological studies reported to be without concern for demyelinating disorder. He reports that his motor deficit, notably affecting only his lower extremity muscles diffusely, plateaued at age 10. He did not have any major ambulatory dysfunction until age 57. At age 57, he underwent bariatric surgery and lost approximately 130 pounds. Since then, he has noticed worsening lower extremity strength with decreased ability to ascend and descend the stairs or walk longer distances. He has had no weakness in the upper extremities, trunk, or cranial nerves. His other symptoms include difficulty hearing since age 50 for which he has hearing aids as well as dysphagia secondary to achalasia requiring myotomy. Several months after his bariatric surgery, his neurologic exam demonstrated distal arm weakness, left worse than the right, as well as distal greater than proximal leg weakness, again left worse than right. He had more muscle wasting in his distal compared to proximal leg muscles. His reflexes were 3+ throughout with positive Babinski reflexes. He had diminished pinprick, proprioception, and vibration sense in the toes with a graded reduction in the distal legs up to the shin. His gait showed feet dragging with inverted knees. No one in his family, including his four brothers and two children, had similar symptoms. Normal results were obtained for vitamin B12, folate, thyroid stimulating hormone, and creatinine, including negative serologies for ganglioside antibodies, hepatitis C, and Smith ribonucleoprotein antibodies. His hemoglobin A1C was 5.4%. At this time, electrodiagnostic testing demonstrated length-dependent motor and sensory axonal polyneuropathy. There was also evidence of active and chronic bilateral lower lumbar and upper sacral radiculopathies of mild-to-moderate severity. Magnetic resonance imaging of the spine showed moderate-to-severe central canal stenosis at C5-C6, L2-L3, L4-L5, and L5-S1. He was not deemed to be a candidate for intervention of his spinal stenosis by neurosurgery because his symptoms were thought to be out of proportion to his degree of cervical stenosis . Finally, he underwent genetic testing which demonstrated a c.1246C>T heterozygous variant on the *ATL1* gene consistent with a diagnosis of HSP. By age 61, he could only walk short distances with a walker but mainly relied on a scooter for transport.

Discussion:

More than 80 mutations have been found to cause HSP[2], with some genes discovered to be involved in the axonal transport of macromolecules, organelles, and cargoes.[3-4] Onset for HSP varies from early childhood to 70 years of age, with variability in age of onset seen even among family members with the same genetic mutation.[5] Our patient had features of HSP at a young age but appeared to reach a plateau at age 10. He retained the ability to walk until age 57 when he lost a significant amount of weight after bariatric surgery. His slowly progressive muscle atrophy and weakness, hyperreflexia, electrodiagnostic testing showing length-dependent motor and sensory axonal polyneuropathy, and genetic analysis showing a mutation in the *ATL1* gene were consistent with a diagnosis of HSP. In patients with a pathogenic *ATL1* gene mutation causing HSP, less than 25% required the use of a walking aid or wheelchair after a mean disease duration of 32 years.[6]

His clinical course was unusual because most patients with HSP reach a plateau after a period of continuous worsening. To our knowledge, there have been no other case reports documenting a rapid decline in weakness after patients have reached clinical stability for decades. Our case report suggests that bariatric surgery or its downstream effects may be a factor contributing to this unusual clinical course.

The incidence of developing peripheral neuropathy after bariatric surgery is around 16%.[7] Sural nerve biopsies in these patients showed axonal degeneration with perivascular inflammation.[7] Deficiencies in vitamin B1, vitamin B6, vitamin B12, vitamin E, copper, and niacin were considered the greatest risk factors, although nutritional deficiency was not present in all patients who developed neuropathy after bariatric surgery.[8-10] At the same time, a meta-analysis found that neuropathic symptoms improved in patients with diabetes after bariatric surgery.[11] Although no frank nutritional deficiencies were identified in our patient, micronutrient deficiencies may have contributed to his progressive axonal neuropathy. Furthermore, research into bariatric surgery has shown that obesity-related epigenome is altered after bariatric surgery via different patterns of DNA methylation.[12] The epigenetic reprogramming may have altered the phenotypic expression of this patient's genetic mutation, promoting disease progression. Our patient was likely more vulnerable to nerve injury due to his underlying HSP.

For many years, the range of phenotypic expressions among patients with HSP has puzzled clinicians. Until now, no identifiable stressors have been proposed for the initial presentation or clinical worsening in patients with HSP. Bariatric surgery may have evoked worsening symptoms of neuropathy either by itself due to micronutrient deficiencies or in combination with the genetic abnormality in this susceptible individual who carried an *ATL1* gene mutation.

In conclusion, this report summarizes our experience with an *ALT1* linked case of HSP in an adult patient who experienced an acceleration of his disease post bariatric surgery. Until specific treatments for HSP subtypes become available, careful considerations of underlying neurological condition(s) in addition to typical bariatric pre-surgical clearance evaluations seem necessary in order to mitigate disease and its impact on patient function.

References

1. Dong EL, Wang C, Wu S, et al. Clinical spectrum and genetic landscape for hereditary spastic paraplegias in China. Mol Neurodegener. 2018;13:36. doi:10.1186/s13024-018-0269-1
2. Hedera P. Hereditary spastic paraplegia overview. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews®*. University of Washington, Seattle; 2021. Accessed September 16, 2021. http://www.ncbi.nlm.nih.gov/books/NBK1509/
3. Soderblom C, Blackstone C. Traffic accidents: Molecular genetic insights into the pathogenesis of the hereditary spastic paraplegias. Pharmacol Ther. 2006;109(1):42-56. doi:10.1016/j.pharmthera.2005.06.001
4. Crosby AH, Proukakis C. Is the transportation highway the right road for hereditary spastic paraplegia? Am J Hum Genet. 2002;71(5):1009-1016. doi:10.1086/344206
5. Klebe S, Stevanin G, Depienne C. Clinical and genetic heterogeneity in hereditary spastic paraplegias: From SPG1 to SPG72 and still counting. Rev Neurol. 2015;171(6):505-530. doi:10.1016/j.neurol.2015.02.017
6. Dürr A, Camuzat A, Colin E, et al. Atlastin1 mutations are frequent in young-onset autosomal dominant spastic paraplegia. Arch Neurol. 2004;61(12):1867-1872. doi:10.1001/archneur.61.12.1867
7. Thaisetthawatkul P, Collazo-Clavell ML, Sarr MG, Norell JE, Dyck PJB. A controlled study of peripheral neuropathy after bariatric surgery. Neurology. 2004;63(8):1462-1470. doi:10.1212/01.WNL.0000142038.43946.06
8. Landais A. Neurological complications of bariatric surgery. Obes Surg. 2014;24(10):1800-1807. doi:10.1007/s11695-014-1376-x
9. Koffman BM, Greenfield LJ, Ali II, Pirzada NA. Neurologic complications after surgery for obesity. Muscle & Nerve. 2006;33(2):166-176. doi:10.1002/mus.20394
10. Rudnicki SA. Prevention and treatment of peripheral neuropathy after bariatric surgery. Curr Treat Options Neurol. 2010;12(1):29-36. doi:10.1007/s11940-009-0052-2
11. Aghili R, Malek M, Tanha K, Mottaghi A. The effect of bariatric surgery on peripheral polyneuropathy: a systematic review and meta-analysis. Obes Surg. 2019;29(9):3010-3020. doi:10.1007/s11695-019-04004-1
12. Fraszczyk E, Luijten M, Spijkerman AMW, et al. The effects of bariatric surgery on clinical profile, DNA methylation, and ageing in severely obese patients. Clin Epigenetics. 2020;12(1):14. doi:10.1186/s13148-019-0790-2

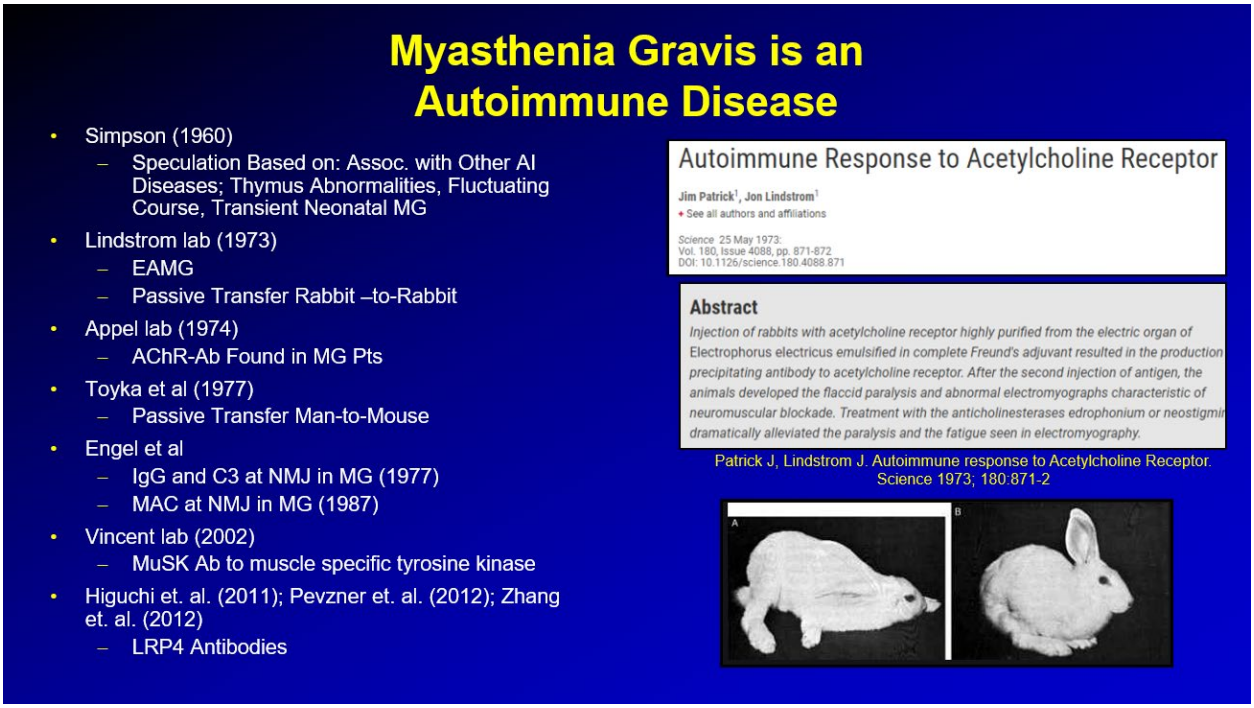
Neuromuscular junction disorders

Richard J. Barohn MD[1], Mamatha Pasnoor MD[2], Gil I. Wolfe MD[3], Todd D. Levine MD[4], David S. Saperstein MD[5], Jonathan S. Katz MD[6], Mazen M. Dimachkie MD[2]

[1]University of Missouri School of Medicine, Columbia Missouri
[2]University of Kansas School of Medicine, Kansas City Kansas
[3]University at Buffalo Jacobs School of Medicine and Biomedical Sciences /SUNY, Buffalo New York
[4]HonorHealth Neurology - Bob Bové Neuroscience Institute
[5]Center for Complex Neurology, EDS and POTS Phoenix Arizona
[6]California Pacific Medical Center

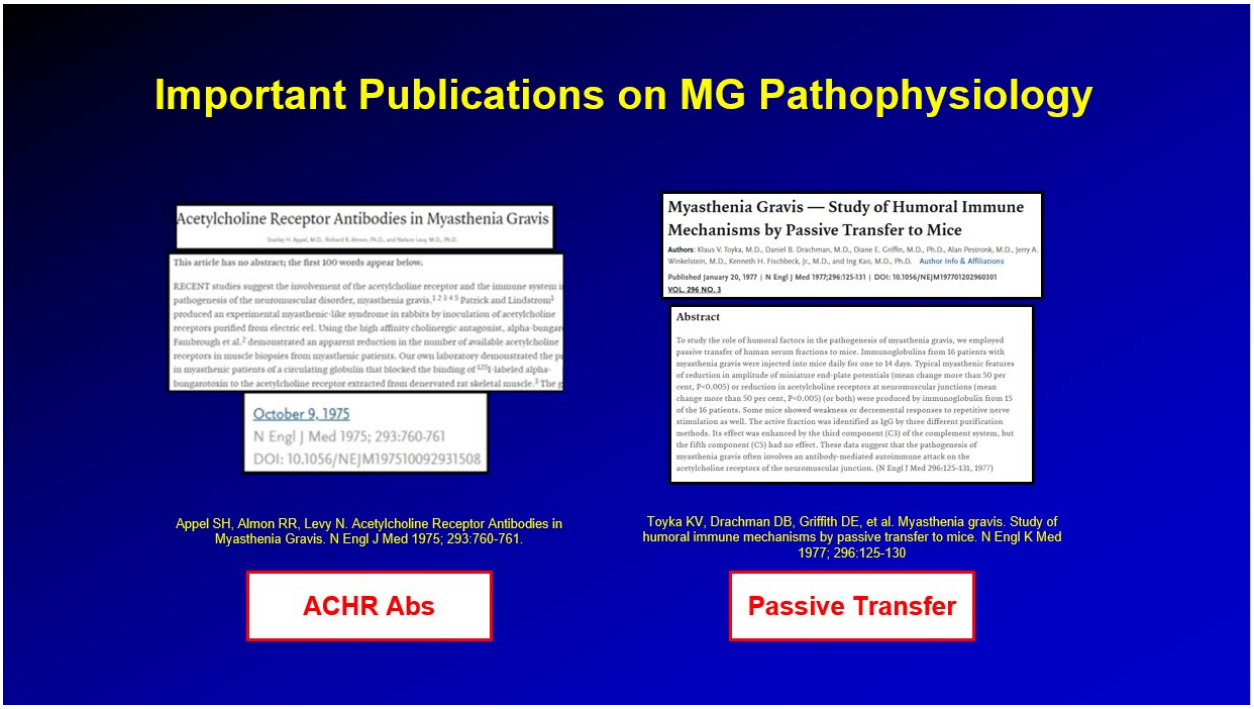
MG is an Autoimmune Disorder

Figure 1



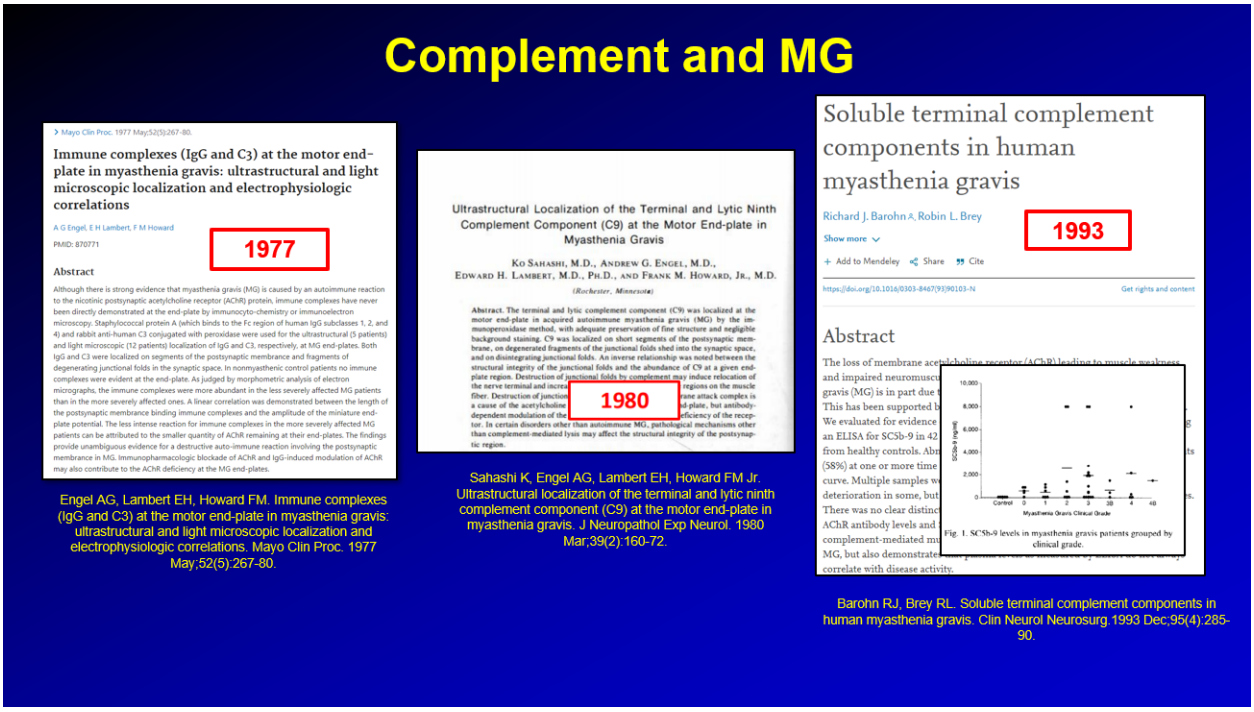
The concept that myasthenia gravis (MG) is autoimmune is relatively recent given how long we have known about the disease. It was speculated that MG was an autoimmune disease in 1960 by Dr. Simpson (Figure 1). His speculation was based on several observations that included the association of MG with other autoimmune diseases, thymus gland abnormalities, fluctuating course, and transient neonatal MG where infants born to MG mothers are weak at birth and then improved gradually. The real proof did not emerge until the early 1970s. In 1973 Dr. Jon Lindstrom, in his laboratory in California, produced the first experimental allergic MG model in rabbits. His group was able to passively transfer myasthenia from rabbit to rabbit. Dr. Stanley Appel was part of the team at Duke in 1974 that was first able to identify acetylcholine receptor antibodies (AChR-Ab) in MG patients. A couple of years later, Dr. Klaus Toyka and his team in Germany were able to passively transfer these antibodies from human to mouse (Figure 2).

Figure 2



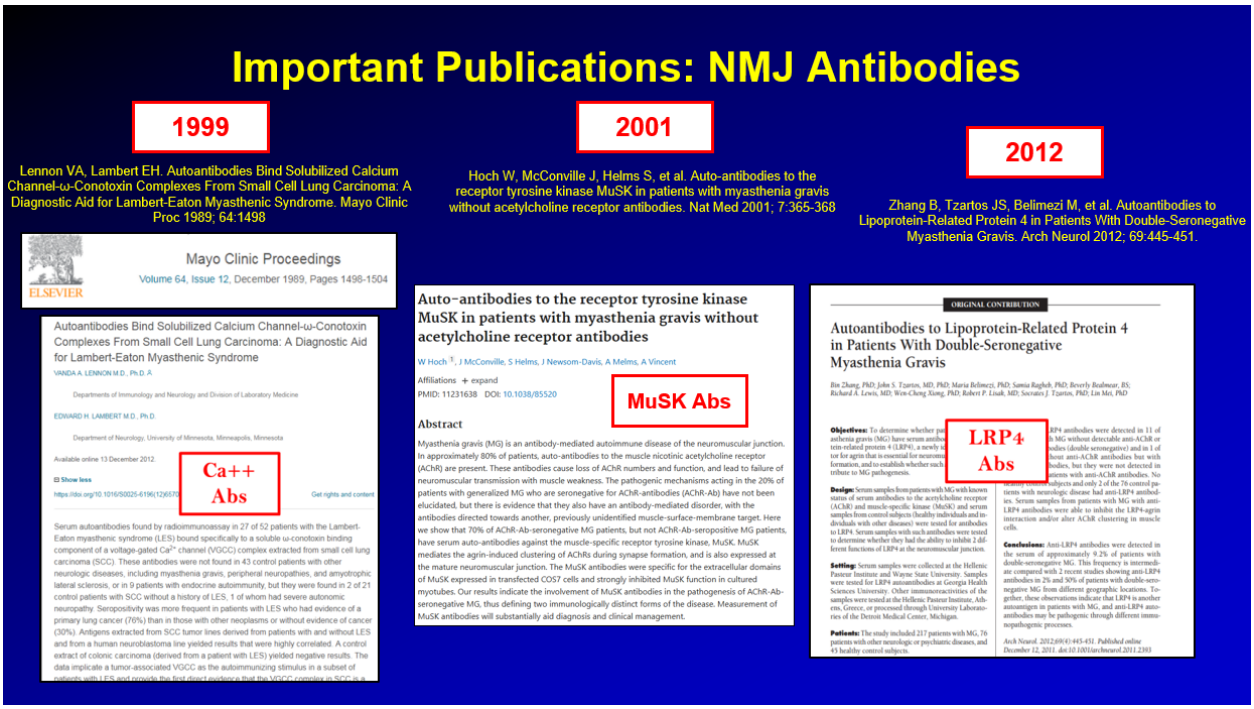
In 1977 at the Mayo Clinic, Dr. Andrew Engel and his team made the initial observations that in addition to the autoimmune antibodies, complement was important in MG pathophysiology at the neuromuscular junction. Our group was able to demonstrate complement elevation in the plasma of MG patients. The complement elevation was higher when the disease was more severe. The finding that complement was important in the development of MG ultimately led to the use of complement inhibitors for the treatment of MG (Figure 3).

Figure 3



The next big scientific breakthrough was in 1999 when Doctors Vanda Lennon and Edward Lambert discovered that the Lambert-Eaton myasthenic syndrome was due to antibodies directed against the presynaptic voltage-gated calcium channels at the neuromuscular junction. In 2001 Dr. Angela Vincent's lab in Oxford, England discovered antibodies directed against the muscle-specific tyrosine kinase (MuSK) at the neuromuscular junction in patients with MG who did not have AChR antibodies. In 2011 and 2012 several labs found low-density lipoprotein receptor-related protein 4 (LRP4) antibodies in a portion of MG patients who were seronegative to both AChR and MuSK. While there are other antibodies that are still being pursued in research labs, these three are now commercially available--AChR, MuSK, and LRP4.

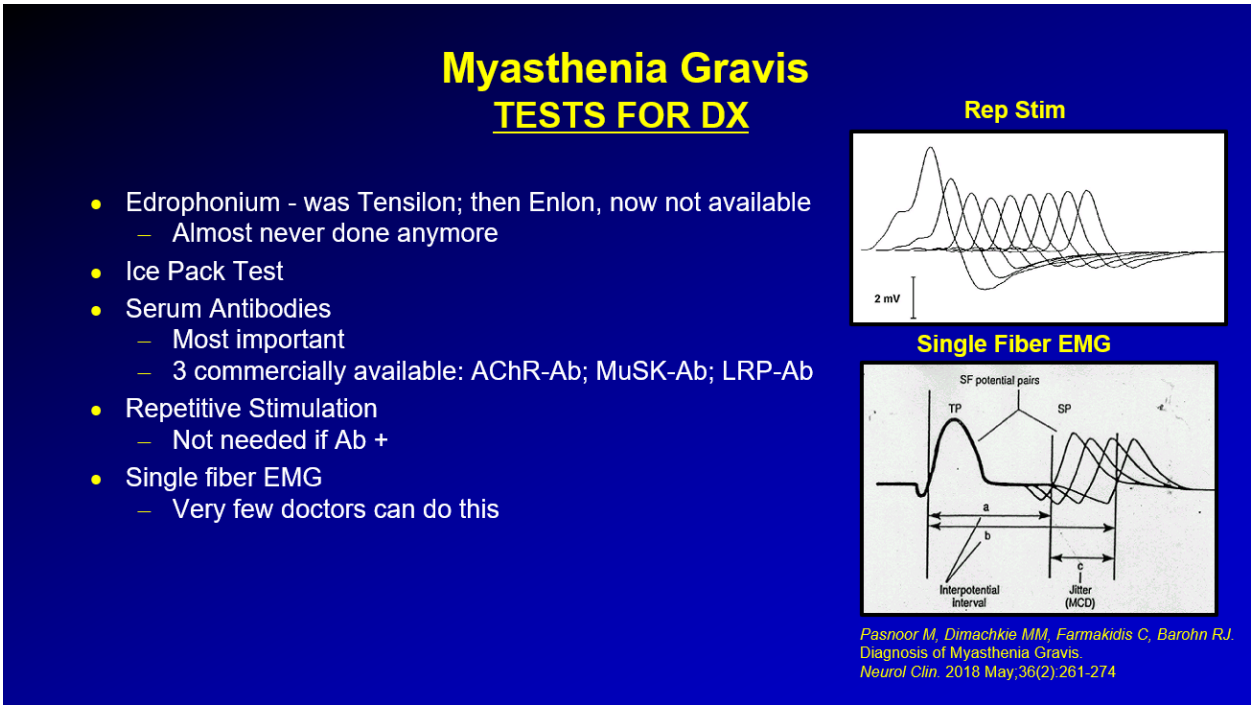
Figure 4



Diagnosis of MG

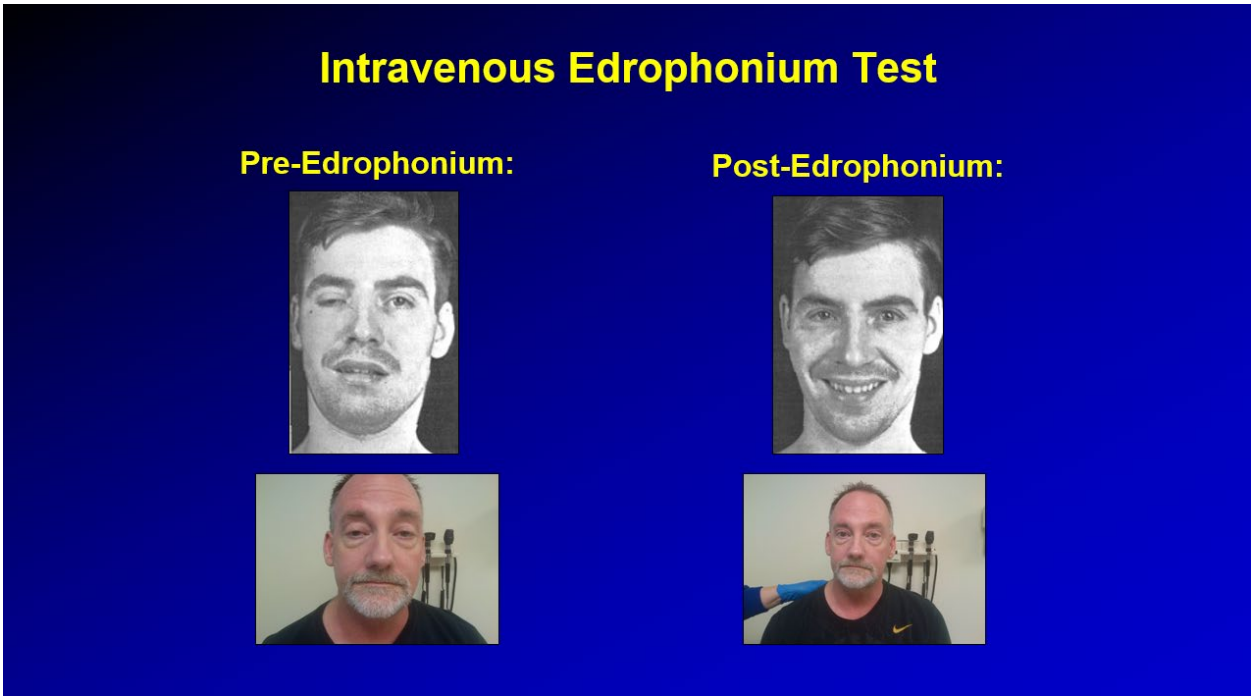
Edrophonium-chloride, previously known by the trade names Tensilon and Enlon, was developed in the mid-1950s to diagnose MG (Figure 5).

Figure 5



By injecting intravenously this acetylcholinesterase inhibitor, some symptoms and signs of MG could be improved or reversed, especially ptosis (Figure 6).

Figure 6



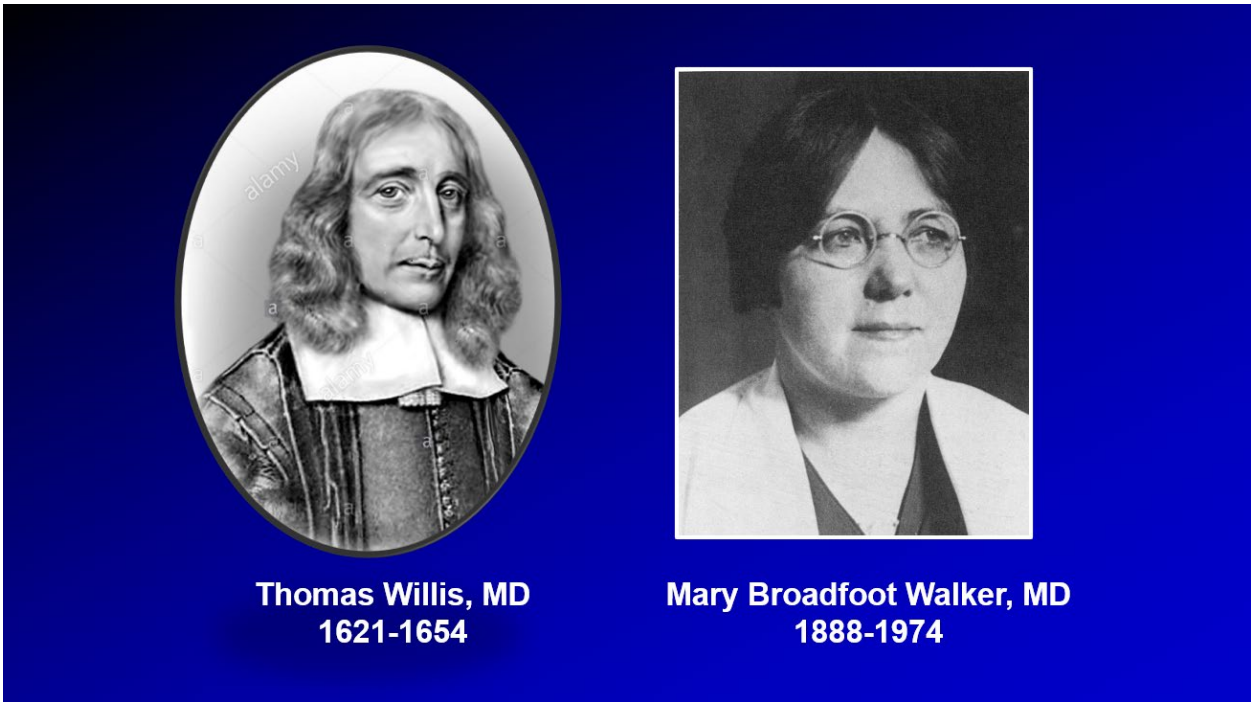
However, since 2018 edrophonium is no longer available in the United States. We hope that one day a drug company will bring edrophonium back on the market because we believe it is useful in the diagnosis of MG in both inpatient and outpatient settings when patients first present with symptoms and signs. In the absence of the ability to do edrophonium tests, an ice pack test can be performed by putting ice wrapped in a plastic bag over a patient's ptotic eye to see if the lid raises. This is not as effective as an edrophonium test. The pharmacologic basis for the ice pack test is that cold temperature slows down the activity of the enzyme acetylcholinesterase thus increasing the availability of the neurotransmitter acetylcholine at the neuromuscular junction to effect neuromuscular transmission. Serum antibodies are the most important diagnostic test and as mentioned above, there are now three commercially available serum antibodies: antibodies to AChR, MuSK, and LRP4. Repetitive stimulation is still a useful test to demonstrate neuromuscular junction pathophysiology. Figure 3 shows an example of an abnormal decremental response of an ulnar-innervated hand muscle when the

ulnar nerve was stimulated at 2 Hertz. In a patient who has the typical presentation of MG symptoms and signs, a positive antibody test to these components of the neuromuscular junction lessens the need to do repetitive stimulation as the diagnosis has already been confirmed.

Single fiber electromyography (EMG) is also a useful test to demonstrate neuromuscular junction dysfunction (Figure 3). It is more sensitive than repetitive stimulation. Single fiber EMG is most often used to document evidence of neuromuscular junction dysfunction in antibody-negative patients. However, single fiber EMG is a difficult test to perform that requires training and special equipment and it is not available at many medical centers.

Two historic figures that led to our understanding and treatment of MG

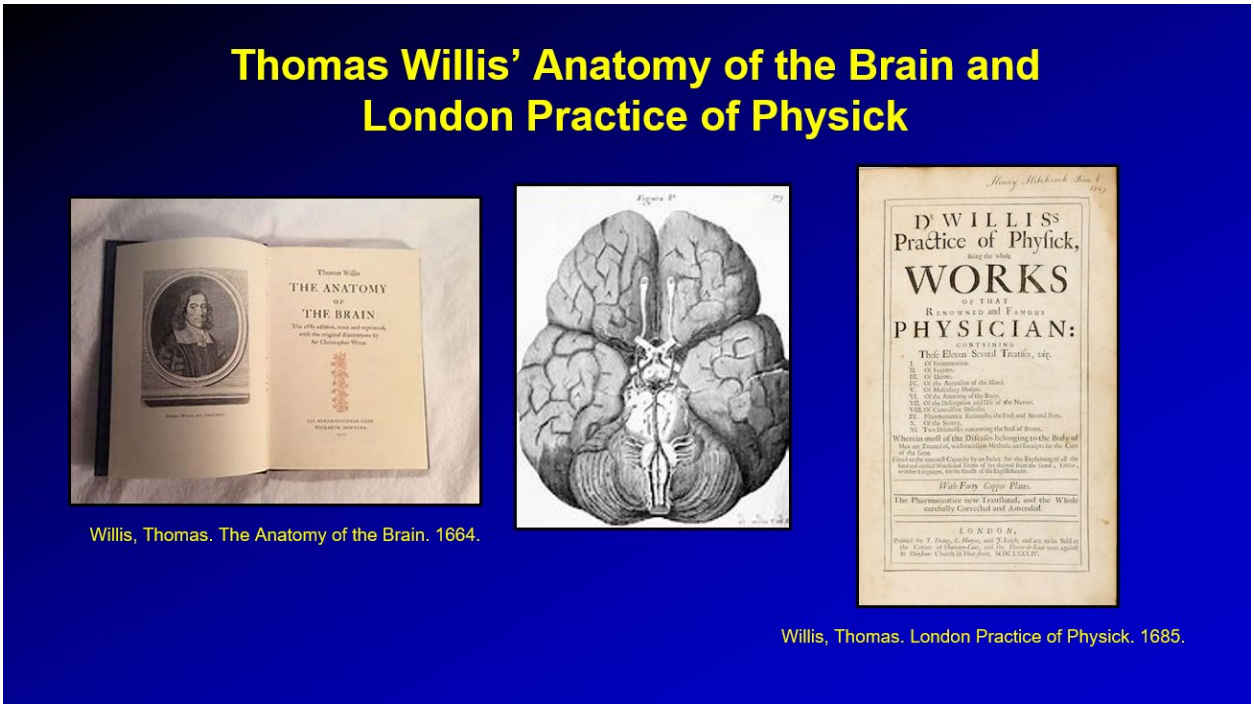
Figure 7



Who are these two individuals in Figure 7? The man on the left is Thomas Willis who was an important physician who practiced in England in the 1600s. He was primarily famous for publishing on the anatomy of the brain and describing the vasculature at its base which we now call the circle of Willis. He also was the first physician to describe the clinical features of MG in one of the many books that he published. 'De Anima Brutorum', published by Willis in London in 1672 and written in Latin, described patients who were well in the morning and fatigued toward noon and were unable to speak for a long time. This book was then translated into English in 1685 under the title 'The London Practice of Physick':

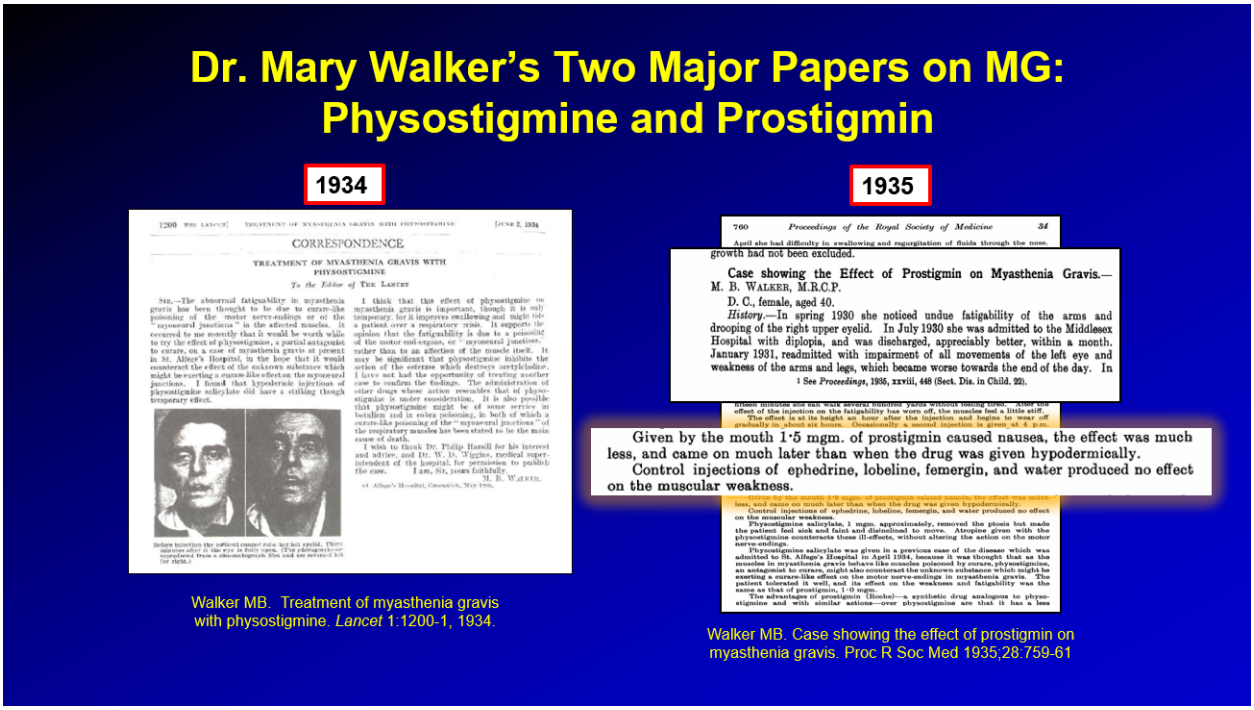
"in the morning [they] are able to walk firmly, to fling about their Arms hither and thither, or to take up any heavy thing, before noon the stock of Spirits being spent, which had flowed into the Muscles, they are scarce able to move Hand or Foot" (Figure 8).

Figure 8



The woman may not be as well known to many of you but she's one of the heroes in MG history and her name is Mary Broadfoot Walker. Dr. Walker first demonstrated that physostigmine and prostigmin were effective in treating MG. She published two papers, one in 1934 and one in 1935, that showed this beneficial effect.

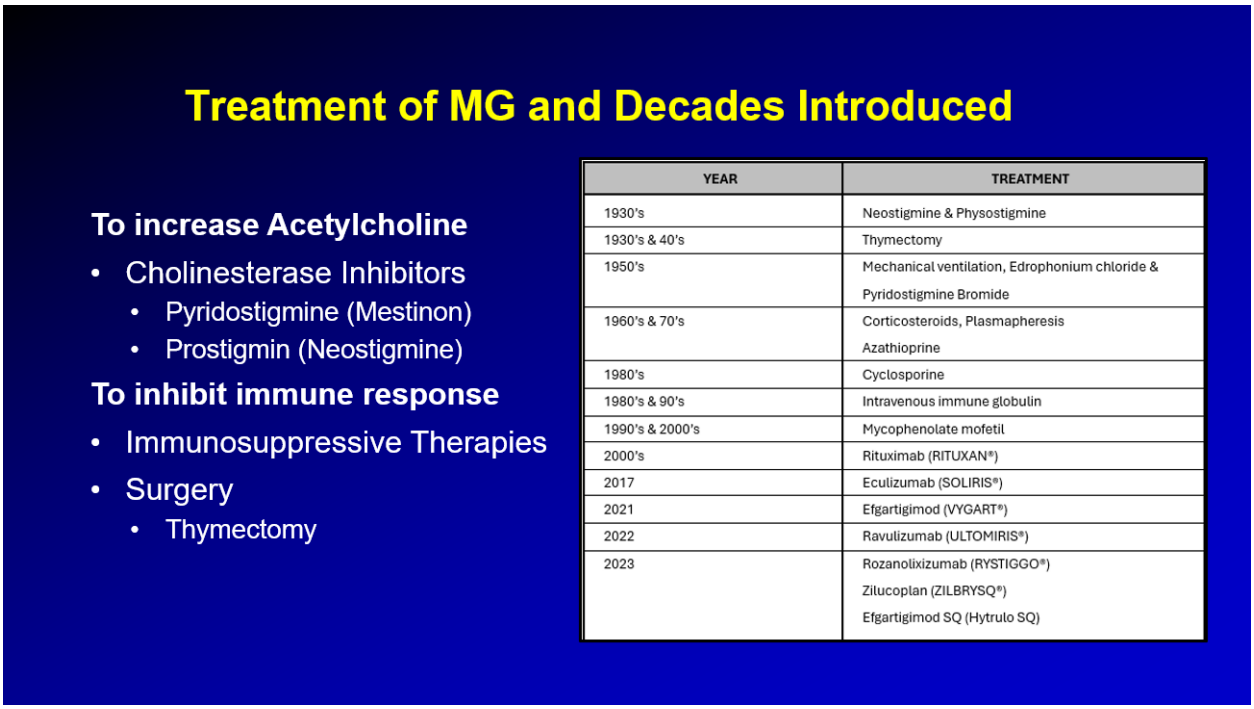
Figure 9



She saw similarities between the symptoms and signs of MG and curare intoxication. Curare poisoning was being treated with physostigmine, and based on this knowledge, she decided to use these drugs to treat MG-and it worked! This was a landmark discovery in the history of medicine. In the 1935 paper, she injected not only prostigmin (also known as neostigmine) but then injected water placebo and showed that the placebo did not work (see highlighted area in Figure 9). The observations of Dr. Walker were the biggest breakthrough in the treatment of MG in the early half of the last century.

The next major observation in the treatment of MG regarded the thymus gland. For years cases of MG had been observed with enlarged thymus glands or thymic tumors. In the 1930s and 40s thymectomy began being used for thymomatous and non-thymomatous MG by Dr. Alfred Blalock and others, and they reported improvement in the status of the patients (Figure 10).

Figure 10



YEAR	TREATMENT
1930's	Neostigmine & Physostigmine
1930's & 40's	Thymectomy
1950's	Mechanical ventilation, Edrophonium chloride & Pyridostigmine Bromide
1960's & 70's	Corticosteroids, Plasmapheresis Azathioprine
1980's	Cyclosporine
1980's & 90's	Intravenous immune globulin
1990's & 2000's	Mycophenolate mofetil
2000's	Rituximab (RITUXAN®)
2017	Eculizumab (SOLIRIS®)
2021	Efgartigimod (VYGART®)
2022	Ravulizumab (ULTOMIRIS®)
2023	Rozanolixizumab (RYSTIGGO®) Zilucoplan (ZILBRYSQ®) Efgartigimod SQ (Hytrulo SQ)

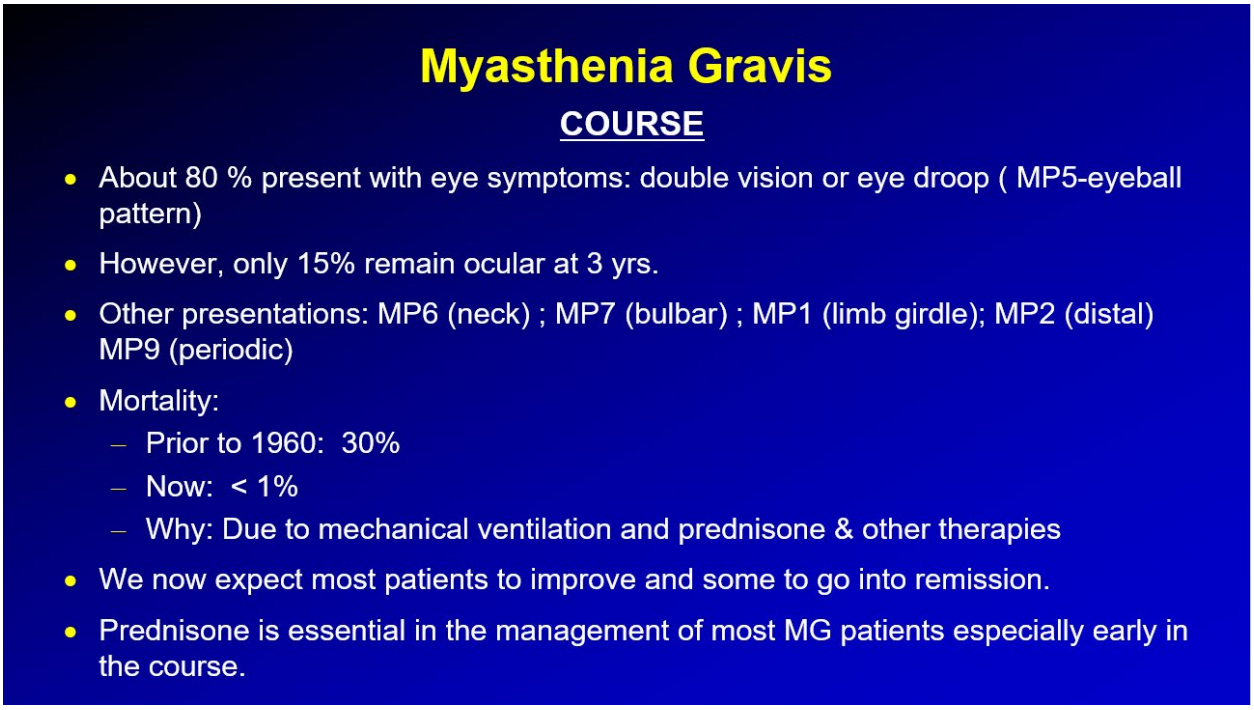
A major advance in the treatment of MG occurred in the 1950s when mechanical ventilators became available. As mentioned, edrophonium chloride became available in the 1950s, and then pyridostigmine bromide, which goes by the trade name of Mestinon, was developed in the mid-1950s and largely replaced the use of prostigmin (Neostigmine) due to fewer side effects. Pyridostigmine (Mestinon) became the first FDA-approved drug for MG in 1955. Corticosteroids and plasmapheresis were introduced in the 1970s. However, there were many reports in which ACTH was used for MG beginning in the 1950s which was really the first attempt of using corticosteroids for MG. The late 1960s and early 1970s ushered in an era of using drugs that were developed to prevent organ transplant rejection in autoimmune diseases such as MG. The first was azathioprine and the next was cyclosporine, and finally mycophenolate mofetil. In the 1980s and 90s, intravenous immune globulin (IVIG) began being used for MG.

Around 20 years ago, rituximab was first introduced as MG therapy. All of the above medications were approved for other disease states and were off label for MG. Finally, in 2017 the first FDA-approved

immunotherapy for MG was introduced-eculizumab--and subsequently several other drugs have been FDA-approved for MG, most notably efgartigimod in 2021.

Course of Disease and Patterns of Presentation

Figure 11



The course of MG is well known. Eighty percent are present with the ocular symptoms of either double vision or a droopy eyelid. This is the MP5 eyeball pattern discussed in the pattern recognition lecture published previously. However, only 15% of patients remain purely ocular at three years of disease duration. Other presentations include the MP6 neck drop pattern, the MP7 bulbar pattern, occasionally the MP1 limb-girdle pattern, and sometimes the MP2 distal pattern. Because many patients state that they get weaker with exercise, the MP9 pattern should be added to this list. Prior to all of the treatments that were just mentioned, MG was indeed a grave disease. The mortality rate prior to 1960 was 30%. However with our current therapies, the mortality rate should be well below 1%. Patients should not die of MG. When this does occur, it is usually due to complications from one or more of the therapies such as an overwhelming infection. The dramatic reduction in the mortality rate

in the 1960s and 1970s was most likely due to the introduction of mechanical ventilation and corticosteroids, but certainly other therapies played a role as well.

Time to Effectiveness of Each Therapeutic Modality

How long does it take these individual therapies to have a clinical effect? First it should be recognized that not all of these therapies will be effective in every patient. If they are effective, the time of onset to the improvement ranges from minutes to months depending on the therapy.

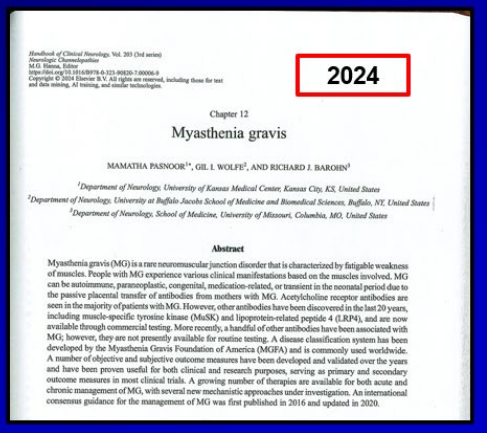
Figure 12

Treatment of Myasthenia Gravis

Typical Time to Clinical Effect After Initiating Therapy

Pasnoor, Wolfe, Barohn. Handbook of Clinical Neurology, 2024;203:185-203.

THERAPY	TIME
Pyridostigmine	Minutes
Plasmapheresis	1-14 days
IVIg	1-14 days
Prednisone Eculizumab Efgartigimod	2-8 weeks 2-8 weeks 2-8 weeks
Cyclosporine	2-6 months
Methotrexate	2-6 months
Mycophenylate	2-6 months
Azathioprine	12-18 months
Rituximab	months
Thymectomy	months to years



2024

Chapter 12

Myasthenia gravis

MAMATHA PASNOOR[1*], GIL I. WOLFE[2], AND RICHARD J. BAROHN[3]

[1]Department of Neurology, University of Kansas Medical Center, Kansas City, KS, United States
[2]Department of Neurology, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, United States
[3]Department of Neurology, School of Medicine, University of Missouri, Columbia, MO, United States

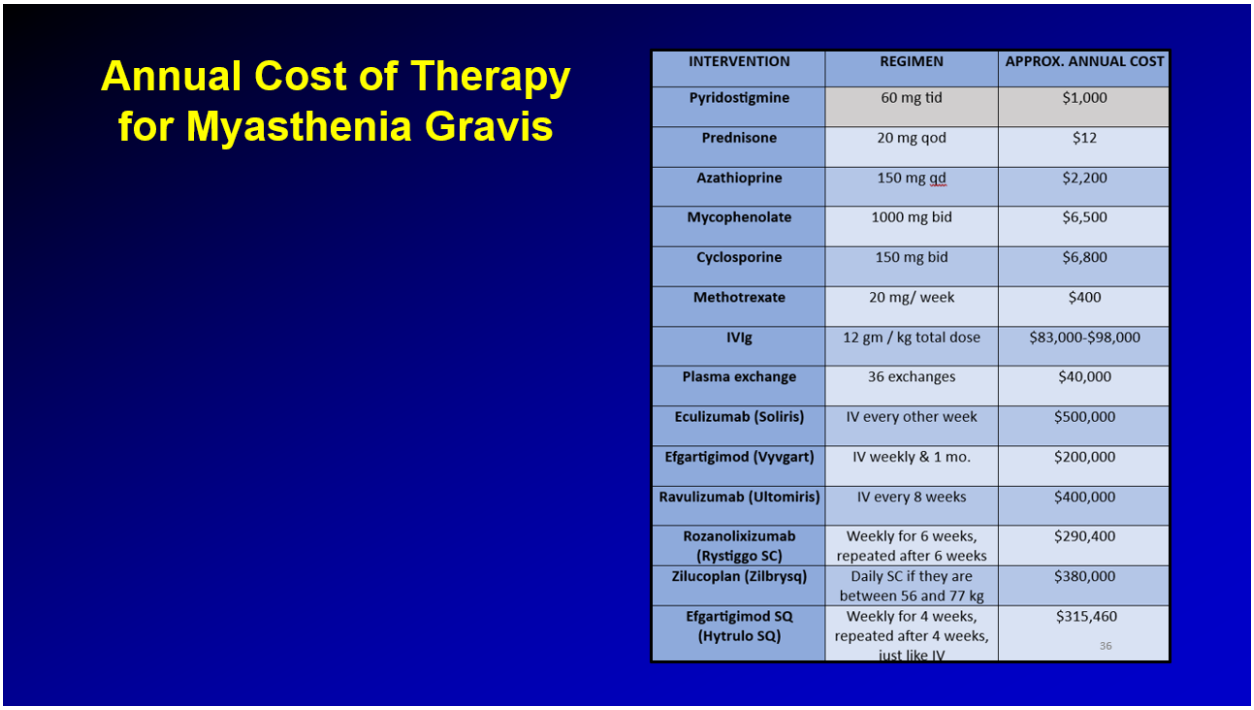
Abstract

Myasthenia gravis (MG) is a rare neuromuscular junction disorder that is characterized by fatigable weakness of muscles. People with MG experience various clinical manifestations based on the muscles involved. MG can be autoimmune, paraneoplastic, congenital, medication-related, or transient in the neonatal period due to the passive placental transfer of antibodies from mothers with MG. Acetylcholine receptor antibodies are seen in the majority of patients with MG. However, other antibodies have been discovered in the last 20 years, including muscle-specific tyrosine kinase (MuSK) and lipoprotein-related peptide 4 (LRP4), and are now available through commercial testing. More recently, a handful of other antibodies have been associated with MG; however, they are not presently available for routine testing. A disease classification system has been developed by the Myasthenia Gravis Foundation of America (MGFA) and is commonly used worldwide. A number of objective and subjective outcome measures have been developed and validated over the years and have been proven useful for both clinical and research purposes, serving as primary and secondary outcome measures in most clinical trials. A growing number of therapies are available for both acute and chronic management of MG, with several new mechanistic approaches under investigation. An international consensus guidance for the management of MG was first published in 2016 and updated in 2020.

Pyridostigmine works in a matter of minutes. Plasmapheresis and IVIG work in days. Prednisone and eculizumab work in 2 to 8 weeks. Cyclosporine, methotrexate, and mycophenolate mofetil, if they are going to have an effect, only start showing benefit after two to six months, sometimes longer. On the other hand, azathioprine, which does have an effect on MG, does not have an effect for 12 to 18 months. Rituximab, if it is effective, may take several months. Thymectomy surprisingly also seems to have an effect within several months.

Annual Cost of Individual Therapies

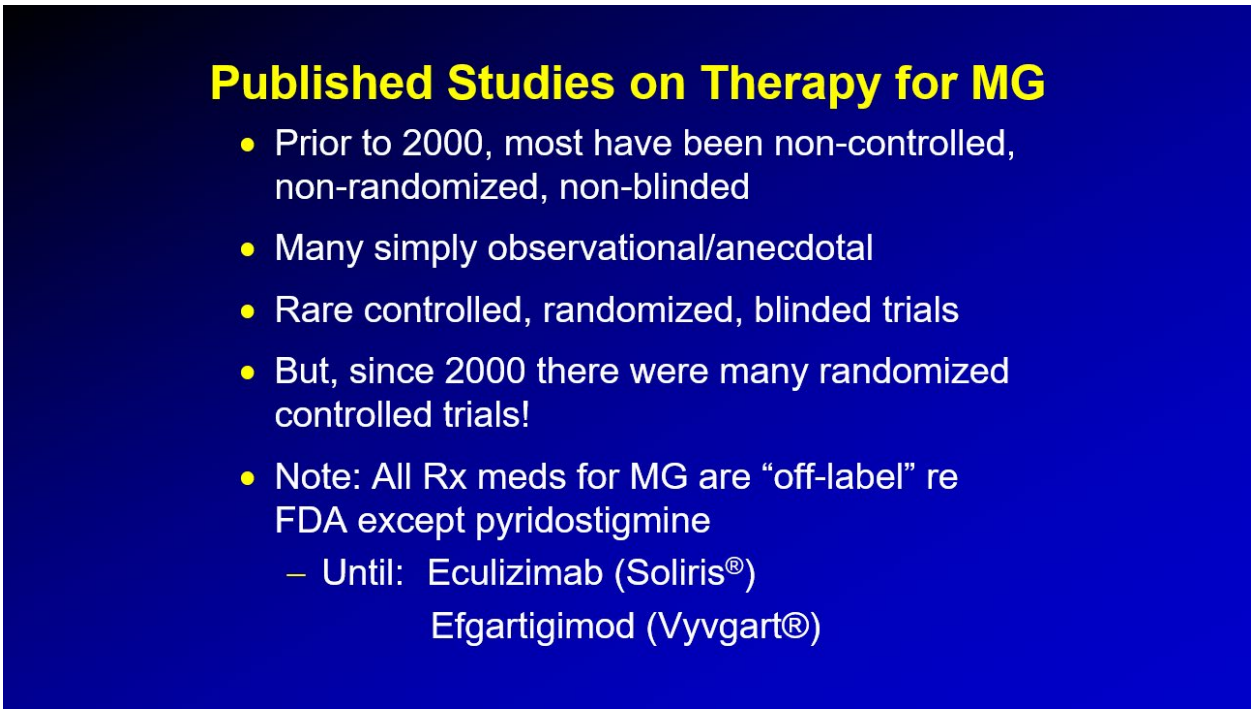
Figure 13



The cost of these drugs ranges from very inexpensive to staggeringly expensive and that is shown in Figure 13. If you can get prednisone for a dollar a month at your local Walmart, then the cost is $12 a year. After that, the drugs get increasingly more expensive. Methotrexate, which has been around since the 1950s, is relatively inexpensive compared to other oral immunosuppressive agents. On the other hand, IVIG and plasmapheresis have a large price tag. But the new biologics that either inhibit complement or Fc receptors are even more costly.

Published Studies on Therapy for MG

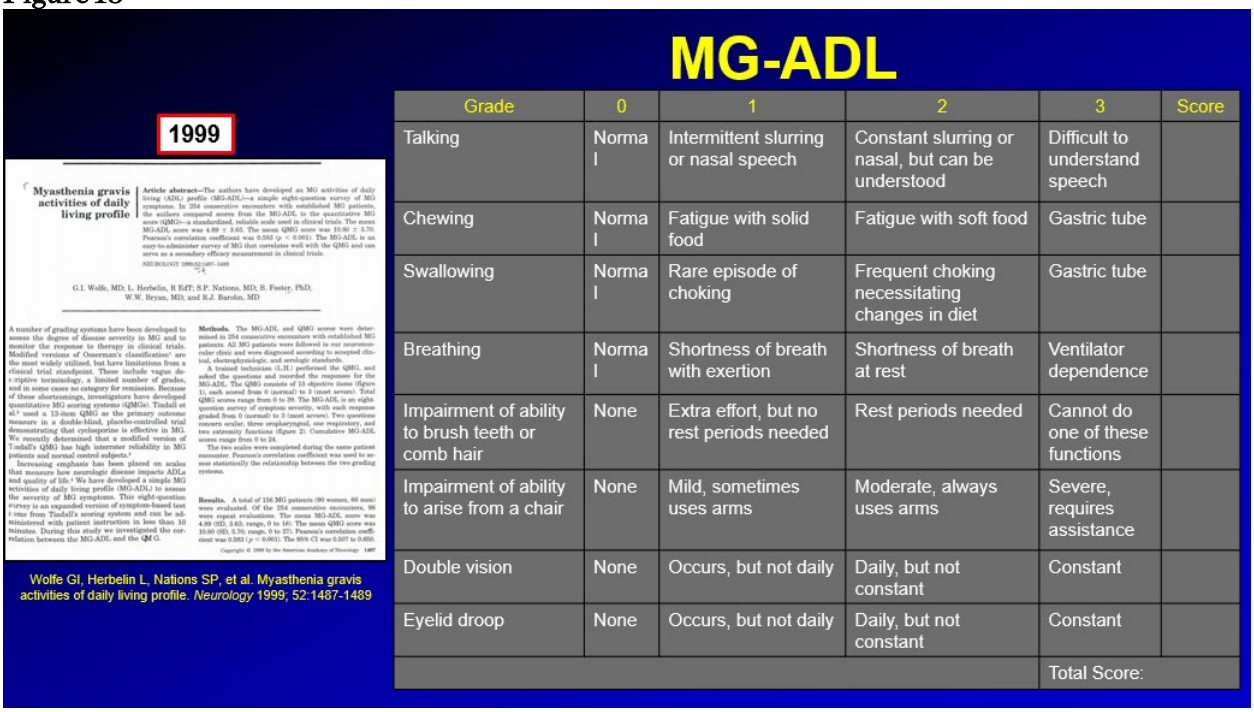
Figure 14



Prior to 2000 most MG studies were uncontrolled, nonrandomized, and unblinded with a few exceptions. There were many observational and anecdotal studies, particularly around thymectomy and prednisone. However, since 2000 there have been many published randomized controlled trials. We are currently in an exciting age of innovation regarding the treatment of MG. The list of FDA approved drugs in the biologic era continues to expand and now includes eculizumab, efgartigimod intravenous (IV), ravulizumab, rozanolixizumab, zilucoplan, and subcutaneous (SQ) efgartigimod.

MG Activities of Daily Living Scale

Figure 15



MG-ADL

Grade	0	1	2	3	Score
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
				Total Score:	

If you are going to be taking care of MG patients, then it is important to know about the MG activities of daily living scale MG-ADL which our team developed at University of Texas Southwestern in the 1990s. This scale was developed for research purposes, but it should now be routinely used to monitor the progress of MG patients. It is a very simple scale to use. A medical assistant can ask the patient the questions or the patient can fill it out on their own. In the office setting when a patient is first put in the waiting or the examination room, the MG-ADL can be completed. Therefore, when the physician walks in the exam room to begin the encounter the MG-ADL scale will have already been completed. The advantage of obtaining an MG-ADL at each clinic visit is that you have a quantitative score of the severity of the MG.

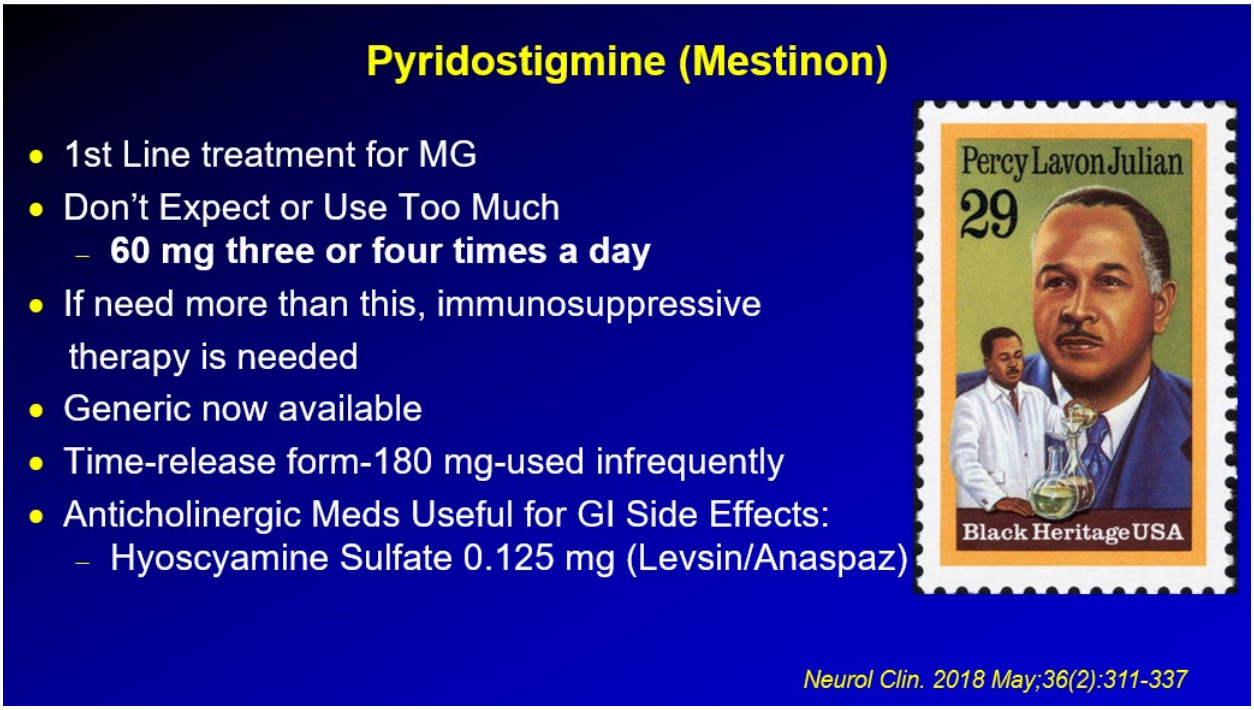
It is strongly encouraged that the MG-ADL be done routinely as a standard of care every time a MG patient is seen whether or not it is in a general neurologist's office or a tertiary care neuromuscular clinic.

Pyridostigmine

Pyridostigmine is the first-line treatment for MG. It also goes by the trade name Mestinon. The most important caveat with pyridostigmine is not expecting from or using it too much. If the patient is on 60mg three or four times a day and they are still symptomatic then it is time to go on to immunosuppressive therapy.

There is no need to increase the dose to 120mg every two or three or four hours. All this will do is cause more side effects such as increased bowel movements and sweating, and it will not improve the MG symptoms or signs any more than the effect of 60mg three or four times a day. Generic pyridostigmine is now available and it is just as effective as the trade drug. It is less expensive.

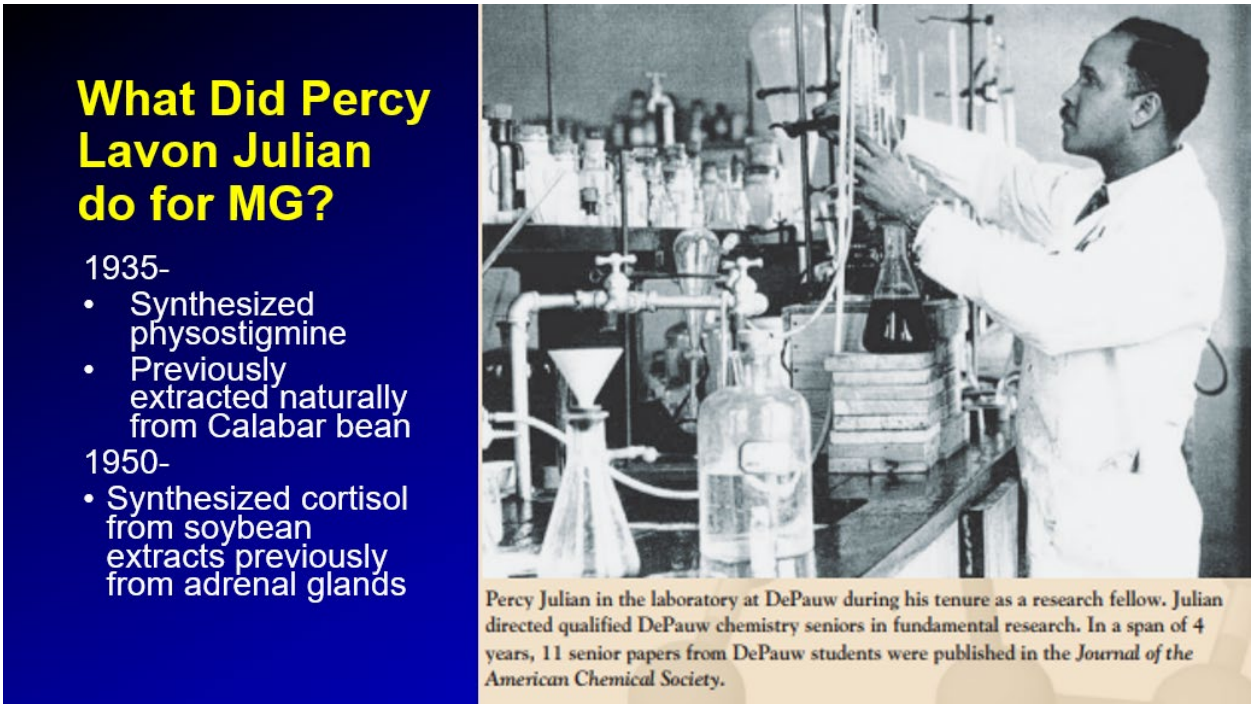
Figure 16



There is also a version called Mestinon Time Span which is a time release formulation. In general, we prefer not to use this formulation, as it gives a large pyridostigmine dose and absorption is erratic. However some patients take the time release tablet at bedtime presumably so they have fewer MG symptoms in the morning. Therefore, if a patient insists on using the time release capsule and believes they are benefiting we will agree with their decision as in these instances the patient is usually correct. If the patient does have loose stools on pyridostigmine, it should be treated with a muscarinic anticholinergic agent such as hyoscine sulfate 0.125mg that is taken with each pyridostigmine dose up to three times a day.

Percy Lavon Julian was a chemist who started his career at DePauw University and he and his team synthesized physostigmine.

Figure 17



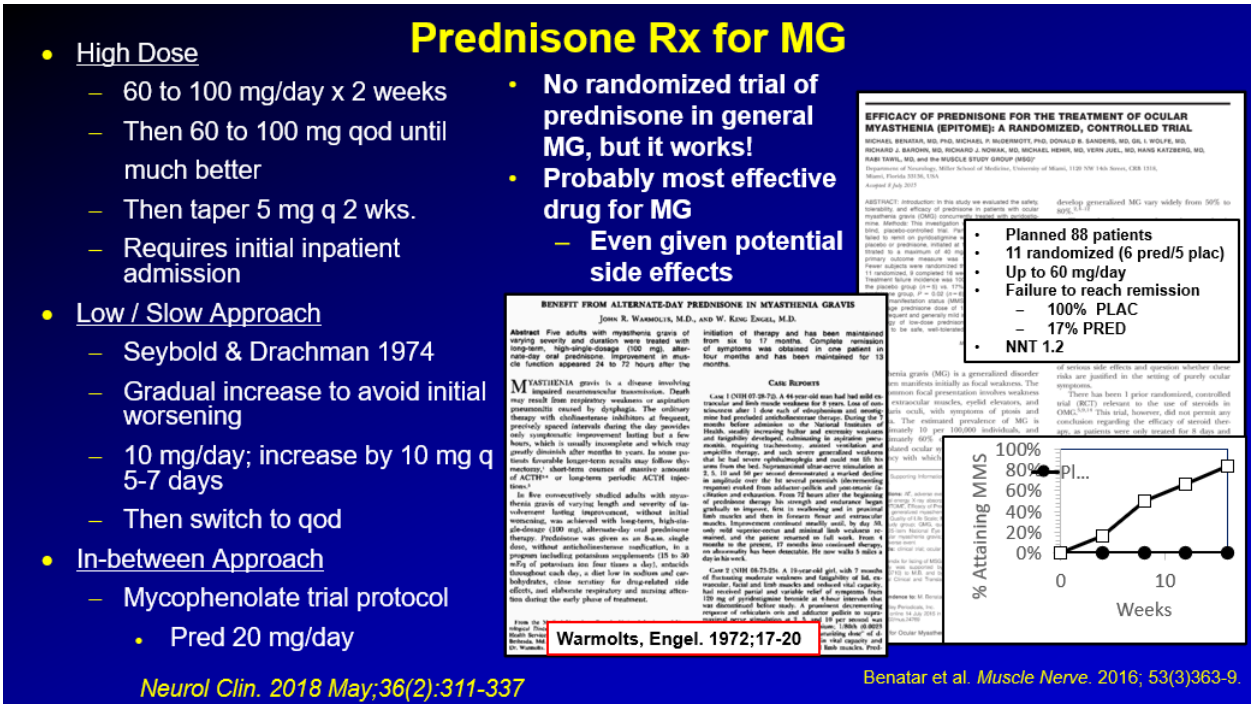
Prior to that, physostigmine had to be extracted naturally from Calabar beans which was the source of the drugs that Mary Walker used.

The use of corticosteroids for MG

The synthesis of acetylcholinesterase inhibitors by Dr. Julian's team was a huge breakthrough in MG. For this reason alone, he should be considered a hero in our understanding and treatment of MG. However, he should perhaps be even better remembered for the discovery in the 1950s in which his team synthesized cortisol from soybean extracts.

Previously cortisol had to be extracted from adrenal glands. His technique revolutionized the use of corticosteroids for many diseases.

Figure 18



While high-dose prednisone therapy is used to treat MG, it has been observed that if you put a generalized MG patient on high-dose prednisone therapy (60 to 100 mg a day), a small percentage of patients will have transient worsening during the first week of therapy.

Therefore, when an MG patient is placed on 60 to 100 mg a day of prednisone this should be done when they are in a hospital setting, and this usually is when they are in crisis on a ventilator or experiencing severe worsening that requires hospitalization. When starting prednisone as an outpatient, what has been used for decades is the go-low and slow escalation approach developed by Drs. Marjorie Seybold and Dan Drachman in the 1970s. In this approach, the patients start on 10 mg a day of prednisone, and every week you increase by 10 mg up to the target dose that you wish to reach. At some point, the patient can be switched to every other day to reduce the side effects. A third approach came out of our experience performing the Muscle Study Group mycophenolate mofetil trial

in MG. During that trial all new MG patients were placed immediately on 20 mg a day of prednisone and either mycophenolate mofetil or placebo.

We learned in this study that a patient can be put immediately on prednisone of 20 mg a day and a benefit could be achieved without increasing the dose in many patients.

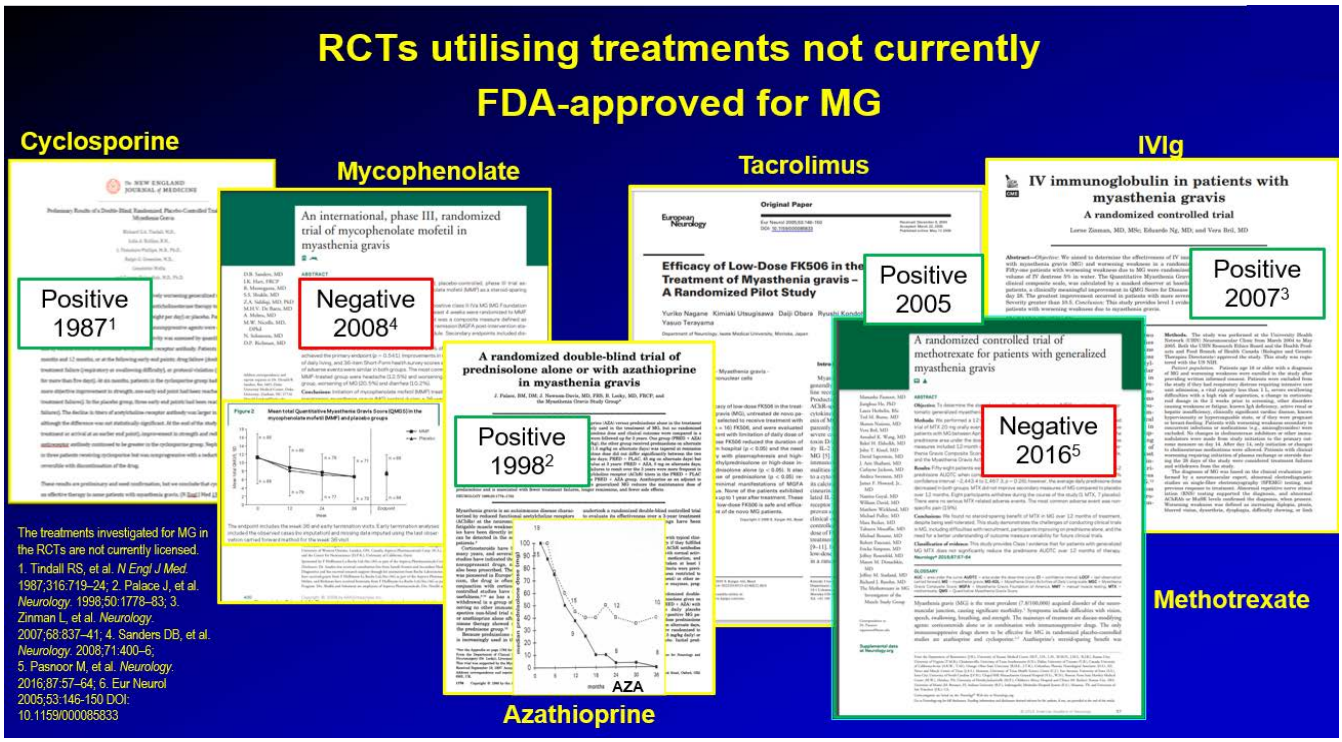
There are no randomized controlled trials of oral prednisone for generalized MG, but we all know from years of using the drug in MG that it is effective. We do have a small randomized controlled trial in ocular MG that was led by Dr. Michael Benatar and showed a dramatic effect of prednisone compared to a placebo in ocular MG patients (Figure 18). Essentially all of the ocular patients on prednisone got better but none of the patients on placebo improved.

The first paper that used high-dose prednisone in MG was authored by Drs. John Warmolts and King Engel at the NIH in 1972, and this was another landmark paper in the history of MG (Figure 18). The MG patients they reported improved dramatically even though this was not a placebo-controlled trial.

Other non-FDA approved immunosuppressive drugs for MG

Between the 1970s until the advent of the new biologic drugs a number of immunosuppressive drugs have been used to treat MG patients with varying degrees of success. A number of randomized control trials with these drugs have been performed and published (Figure 19).

Figure 19



Azathioprine (Imuran)

Azathioprine is effective in MG, but the problem with the drug is that it does not have an effect for at least a year and does not have its maximal effect for 18 months after it is started (Figure 20).

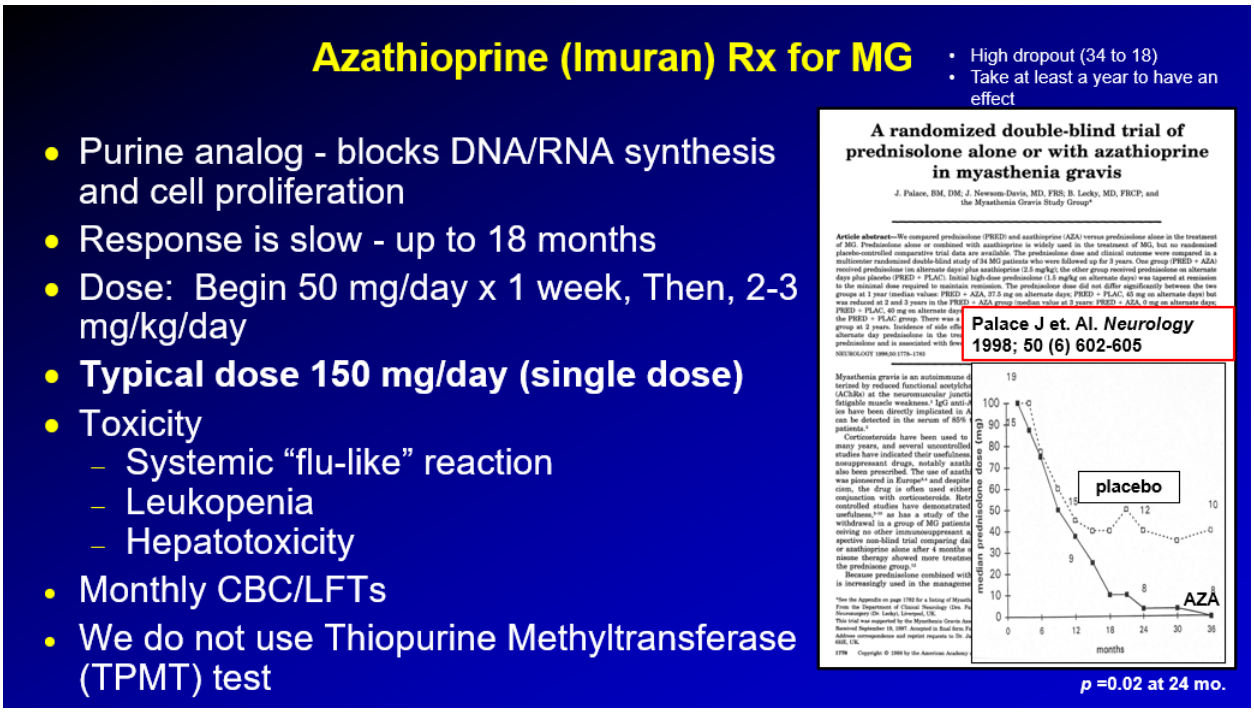
Therefore, it is not a drug that is used to improve MG patient symptoms in the near term.

Azathioprine is used to decrease patient dependency on prednisone in the long term.

In general, we do not believe that a generalized MG patient and also an ocular MG patient can be managed without initially using prednisone. You can occasionally avoid prednisone in a small number of patients but generally, you have to use immunosuppressive therapy in the form of corticosteroids to see an initial improvement in a MG patient. Our view on this may change over time but currently, we use prednisone in all of our generalized MG patients once they get the maximum benefit from pyridostigmine. But we place greater emphasis now on trying to reduce prednisone to lower doses as

quickly and safely as possible with the help of other therapies as part of the goal of limiting corticosteroid-related side effects.

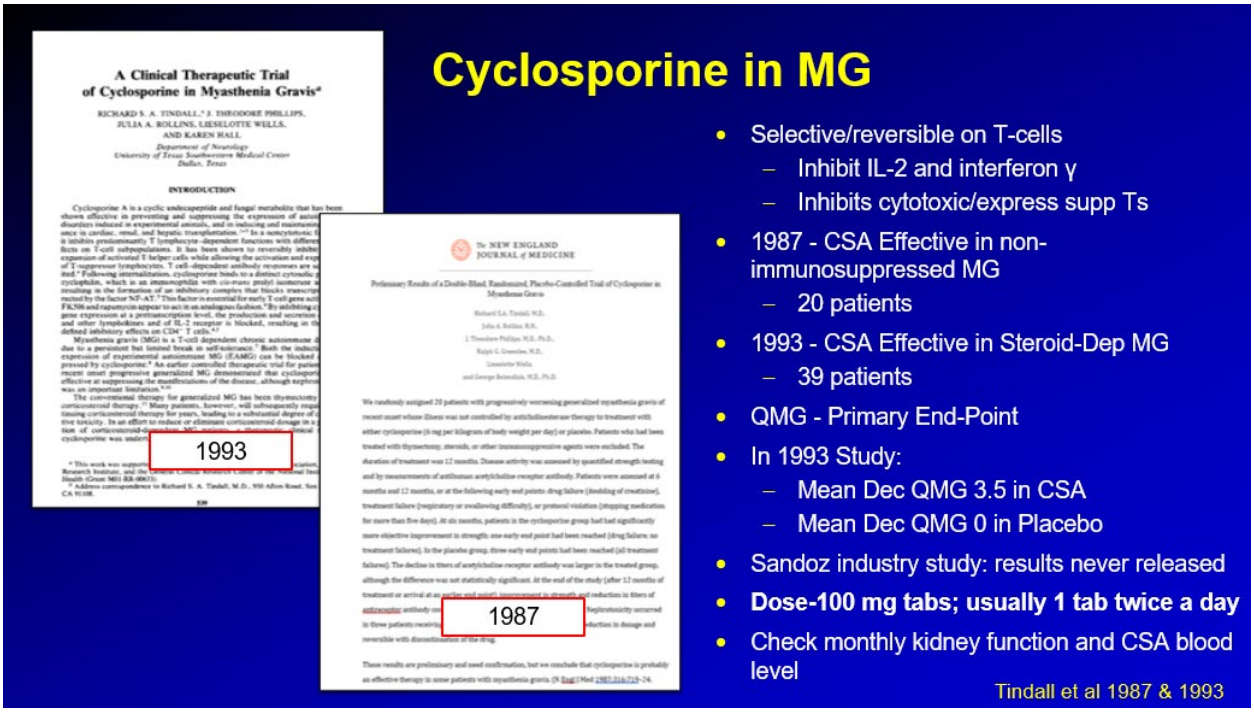
Figure 20



Cyclosporine and tacrolimus

The next drug after azathioprine that we began using as cyclosporine, again off label. Cyclosporine, like azathioprine, was first developed to suppress the immune system on patients undergoing organ transplantation. There were two cyclosporine randomized controlled trials for MG performed at University of Texas Southwestern, showing that cyclosporine was effective in improving patients with MG compared to placebo (Figure 21).

Figure 21

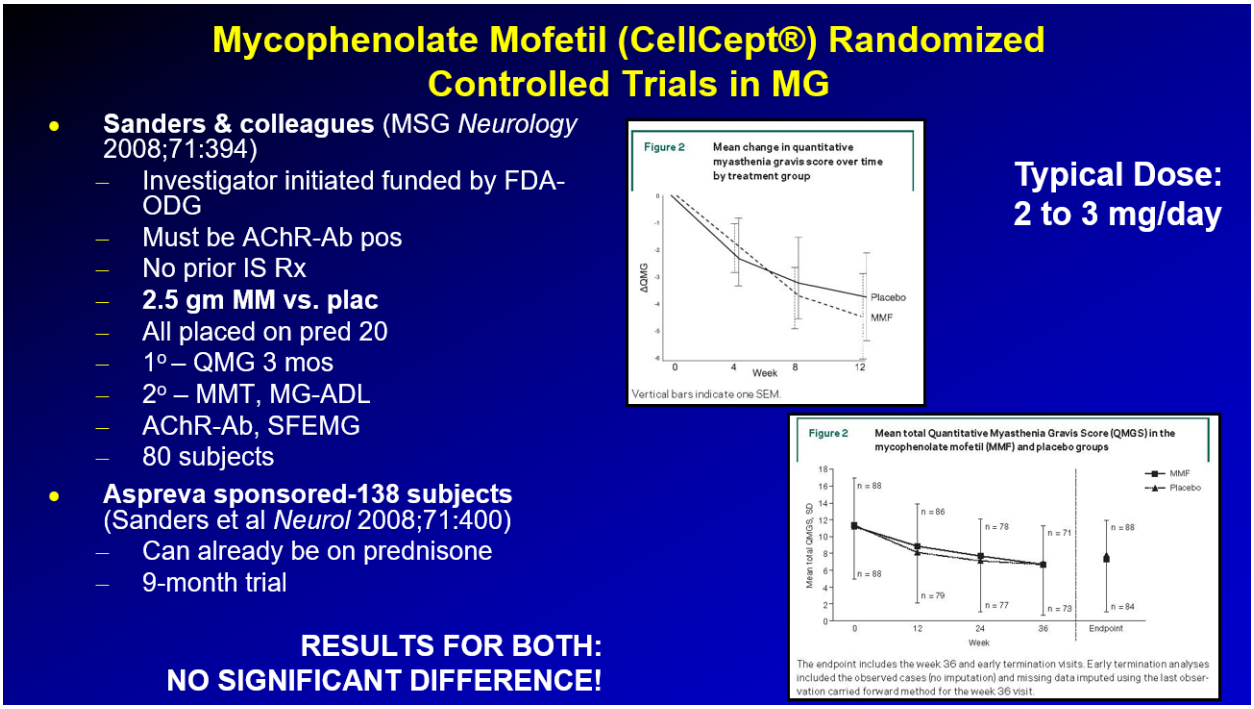


Therefore, in the mid and late 1980s and into the 1990s some of us were using a lot of cyclosporine for our MG patients. When it has an effect, this seems to occur in two to four months. Compared to others, it is a somewhat challenging drug to use because you have to monitor renal side effects, blood pressure and drug interactions very closely.

Mycophenolate Mofetil

Many of us stopped using cyclosporine as often in MG when the drug mycophenolate mofetil (CellCept) became available, primarily because it had fewer side effects and was easier to monitor (Figure 22).

Figure 22

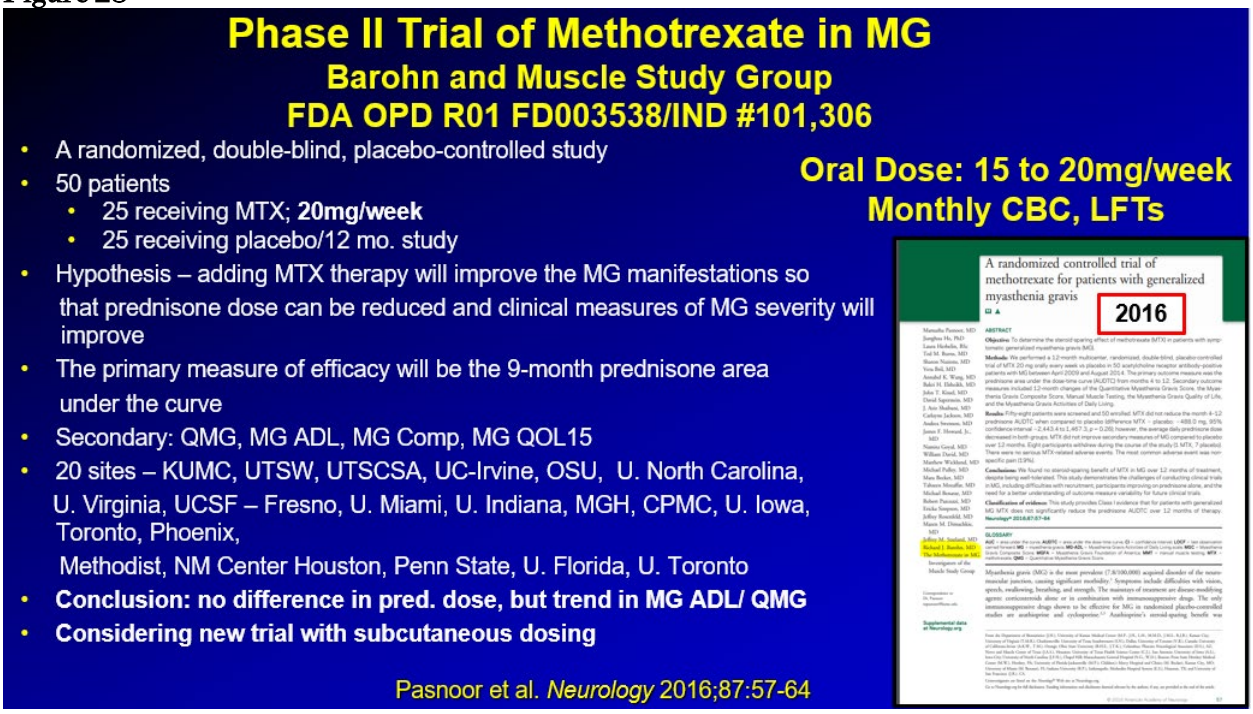


While mycophenolate mofetil is still used by many neurologists to treat MG, there have been two very good randomized controlled trials of mycophenolate mofetil in MG compared to a placebo. Both studies were negative; there was no hint of positivity at all in either study. So while this has dampened our enthusiasm for mycophenolate mofetil, it does not mean that we never use mycophenolate mofetil in MG, but in some clinics, it has lost its placement as a second-line drug for MG.

Methotrexate

When we had the results of the negative mycophenolate mofetil trials we then searched for another oral drug to test in MG, and we turned to the very old compound methotrexate which was originally developed in the 1940s for cancer treatment.

Figure 23



Many of us have been using methotrexate for years for dermatomyositis and polymyositis and we were comfortable using it. We thought that it could be effective in MG. We and others had anecdotal experience of MG patients improving on methotrexate. Our team designed a trial, randomizing patients to methotrexate versus placebo. It was a one-year trial in which patients received methotrexate 20 mg or placebo once a week. In this trial we used oral methotrexate, but subcutaneous methotrexate is also an option and probably produces higher blood levels and may be more effective. In the research trial, we enrolled 50 patients at 20 sites in the US and Canada. We made a decision to use as our primary endpoint the cumulative prednisone dose the patient received during the trial. Our secondary endpoints were the MG-ADL score described earlier and the quantitative MG (QMG) score, an objective measure of strength.

To our disappointment, the study was negative using our primary endpoint of prednisone dose. In other words, patients on methotrexate did not have lower prednisone requirements than those on placebo.

On the other hand, our secondary endpoints were very close to nearing statistical significance. We believe that if we would have chosen the MG-ADL score as our primary endpoint we would have had a better chance of demonstrating that methotrexate was effective in MG. Many of us still believe that methotrexate is effective in some MG patients. In the future we hope to investigate further the use of methotrexate in MG and perhaps to use the subcutaneous delivery method.

Intravenous Immunoglobulin (IVIG)

The MG community began using IVIG for MG in the 1990s. This was about the same time we began using IVIG for Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), and dermatomyositis. IVIG is still not FDA-approved for MG. There has been one well-designed randomized control trial from Canada which showed IVIG was more effective than placebo in MG patients (Figure 24).

Figure 24

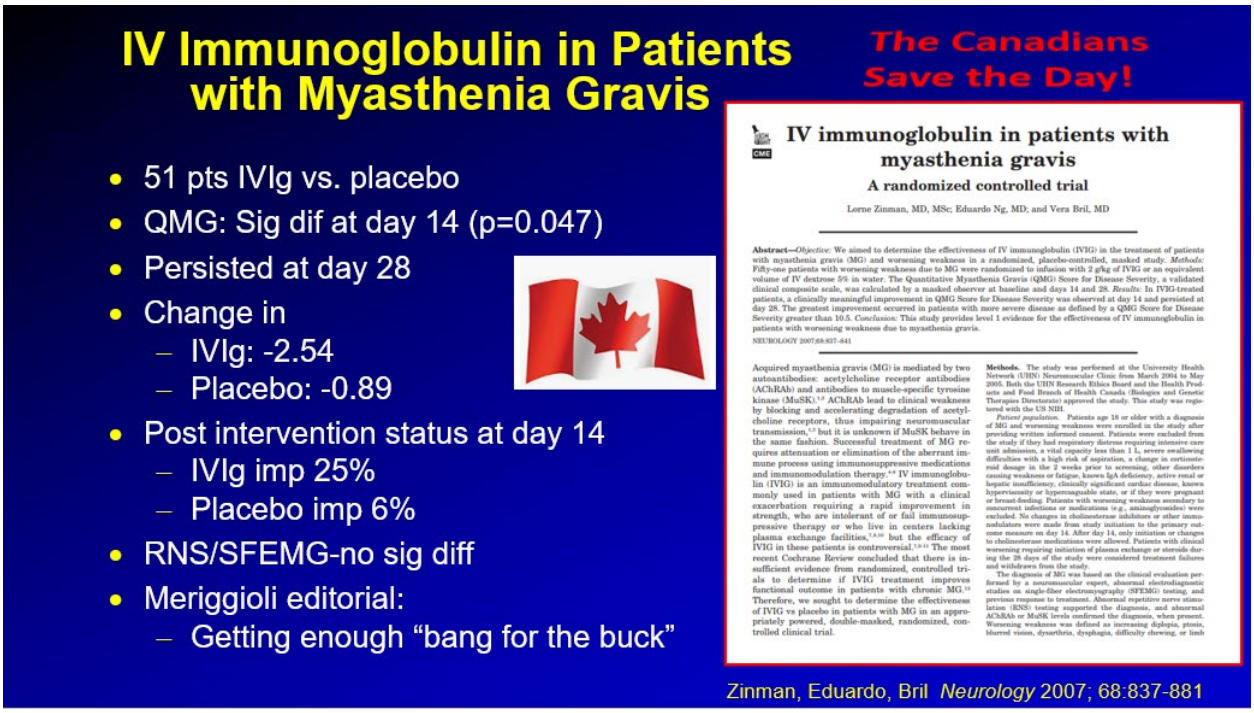
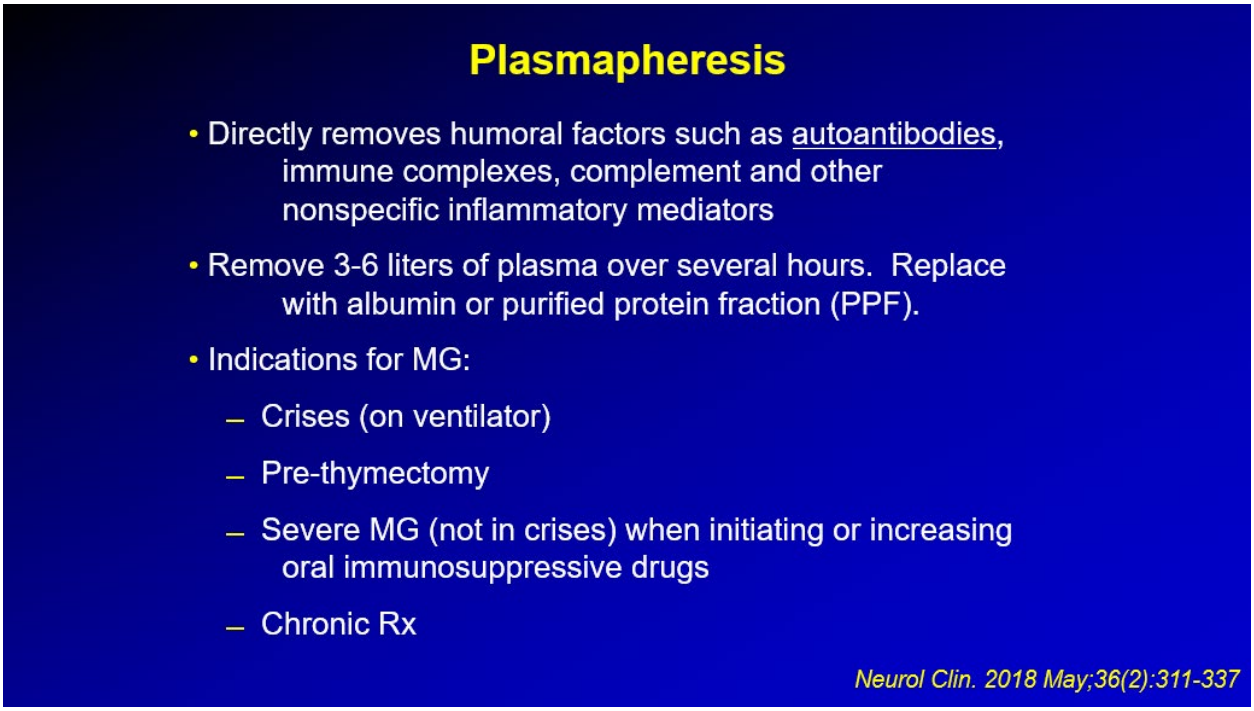


Figure 24 shows a very important article for you to know about. This is the results of the research trials which showed that IVIG is more effective than placebo in a well-designed randomized control trial. It is the best information available to make the case to insurance companies when you are trying to convince them to cover the cost of IVIG in a MG patient. The use of IVIG for MG is similar to the dosing used in CIDP. There is a 2 gram per kilogram loading dose followed by monthly doses of one gram per kilogram. The biggest mistake we have observed by practitioners using IVIG is that they do not continue the chronic maintenance therapy monthly after the loading dose. We recommend monthly maintenance therapy continue for six months and then the patient may be reevaluated to see if the drug has been effective and if it needs to be continued. Usually if the drug has been effective it does need to be continued for even a longer period of time and stopping the drug will often result in a relapse of symptoms.

Plasmapheresis

Plasmapheresis is a technique in which antibodies are removed from the patient's body by removing their plasma. If the patient's plasma contains harmful antibodies such as those directed against the AChR or MuSK causing MG, then removing the antibodies can result in improvement of MG symptoms and signs.

Figure 25

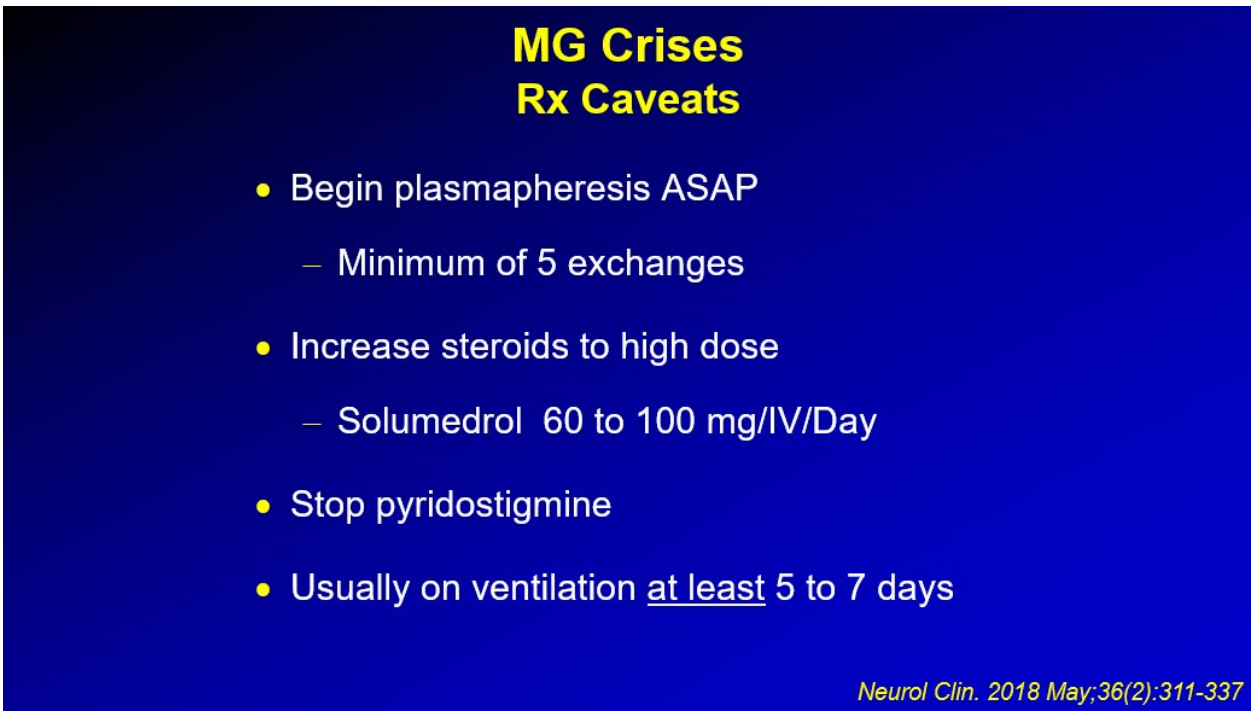


Each plasmapheresis treatment removes 3 to 6 liters of plasma over several hours. Plasmapheresis is most often used in MG when a patient is in crisis and on a ventilator or if the patient is nearly in crisis but not yet on a ventilator, and they are admitted to the hospital for a course of plasmapheresis to avoid further worsening. Occasionally we use plasmapheresis prior to a thymectomy to make the patient stronger in preparation for surgery. However, in the modern era it is less common to use plasmapheresis preoperatively because we try to optimize the patient's status using prednisone and other drugs before the thymectomy.

When we admit the patient for plasmapheresis this generally involves 5 to 10 courses of plasmapheresis over 10 to 20 days. During this time there are other MG medications that are optimized so that when the patient is discharged they will not have to be readmitted when the effect of the plasmapheresis wears off after a few weeks. There are a very small number of patients who require chronic plasmapheresis once or twice a month, particularly MG patients with MuSK antibodies.

We still prefer to use plasmapheresis for our patients in crisis on a ventilator rather than IVIG. We believe plasmapheresis is probably more effective than IVIG in the crisis situation but there is really no comparative effectiveness data on this topic. If your hospital has the ability and experience to use plasmapheresis when an MG patient is in crisis, we would suggest that course of therapy. However, if you are in a hospital that does not have access to plasmapheresis, then loading a patient with IVIG is another option (Figure 26).

Figure 26



A minimum of five plasmapheresis treatments should be performed, but usually if a patient is in crisis they will require more and perhaps up to ten. The plasmaphereses are usually performed every other day to allow time for the patient's clotting factors to reaccumulate between exchanges.

While the patient is on the ventilator, corticosteroids should be given in the form of Solu-Medrol IV up to 60 to 100mg a day. Also, while the patient is on a ventilator, one should stop the pyridostigmine, as it will cause excessive oral secretions and complicate airway management. Pyridostigmine does not have

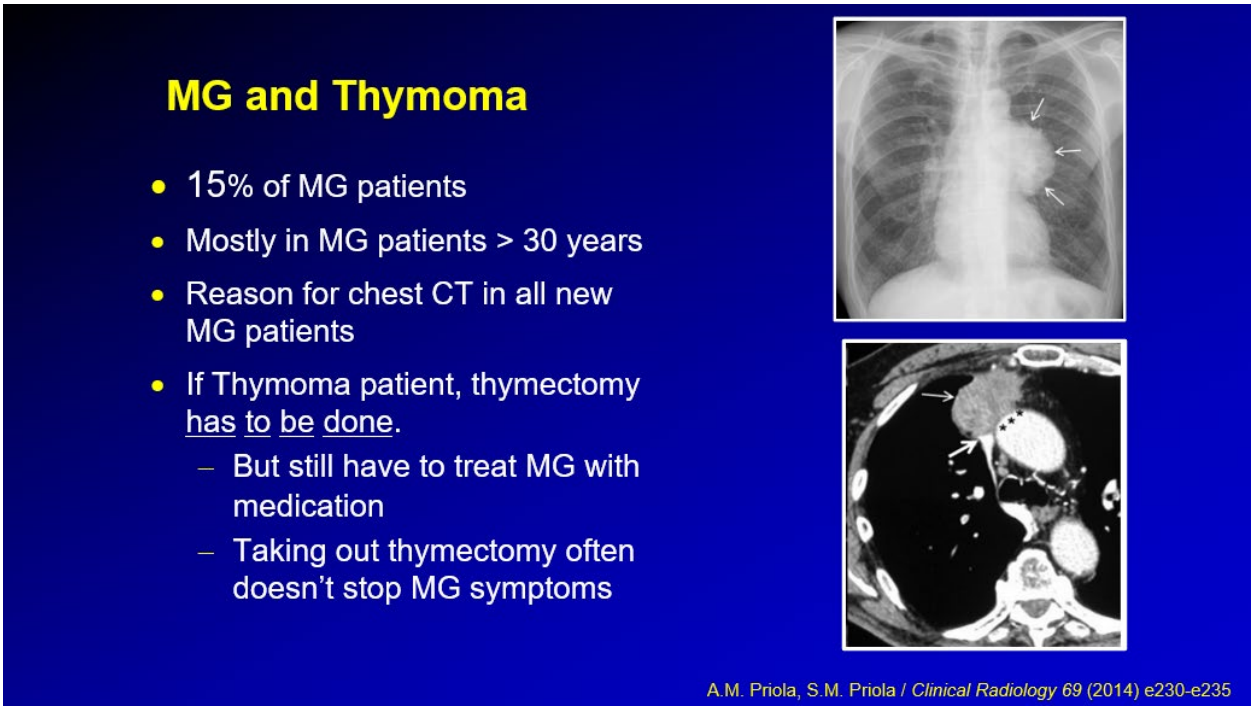
a role in MG crisis. You can restart the pyridostigmine orally when they are extubated and taking oral medications. A myasthenic patient is generally on a ventilator for at least five to seven days in the intensive care unit (ICU).

If the ICU doctors are advocating taking the patient off the ventilator after two to three days when they seem to be improving, there is a need to convince them that the patient needs to be rested on a ventilator for at least five to seven days before attempting extubation.

MG, thymoma, and thymectomy

Thymoma occurs in 15% of MG patients. The reason a chest CT is obtained on all new MG patients, both ocular and generalized, is to search for thymoma. The chest CT is not performed to look for so-called thymic hyperplasia which is a judgement call by the radiologist and can frequently be overinterpreted. The only reason to obtain a chest CT in a MG patient is to look for a thymoma. While a routine chest x-ray can occasionally show a thymoma it is usually only revealed once the thymoma has grown to a large size as shown in Figure 27.

Figure 27



The chest CT is used to demonstrate the presence of a thymoma in its early stages. Figure 27 shows a thymoma visualized on a chest CT. If a thymoma is identified it is mandatory to do a thymectomy as soon as possible. Before the thymectomy is performed the patient should be put on pyridostigmine, and usually they need to also start prednisone and other drugs to improve their status and stabilize them prior to the thymectomy.

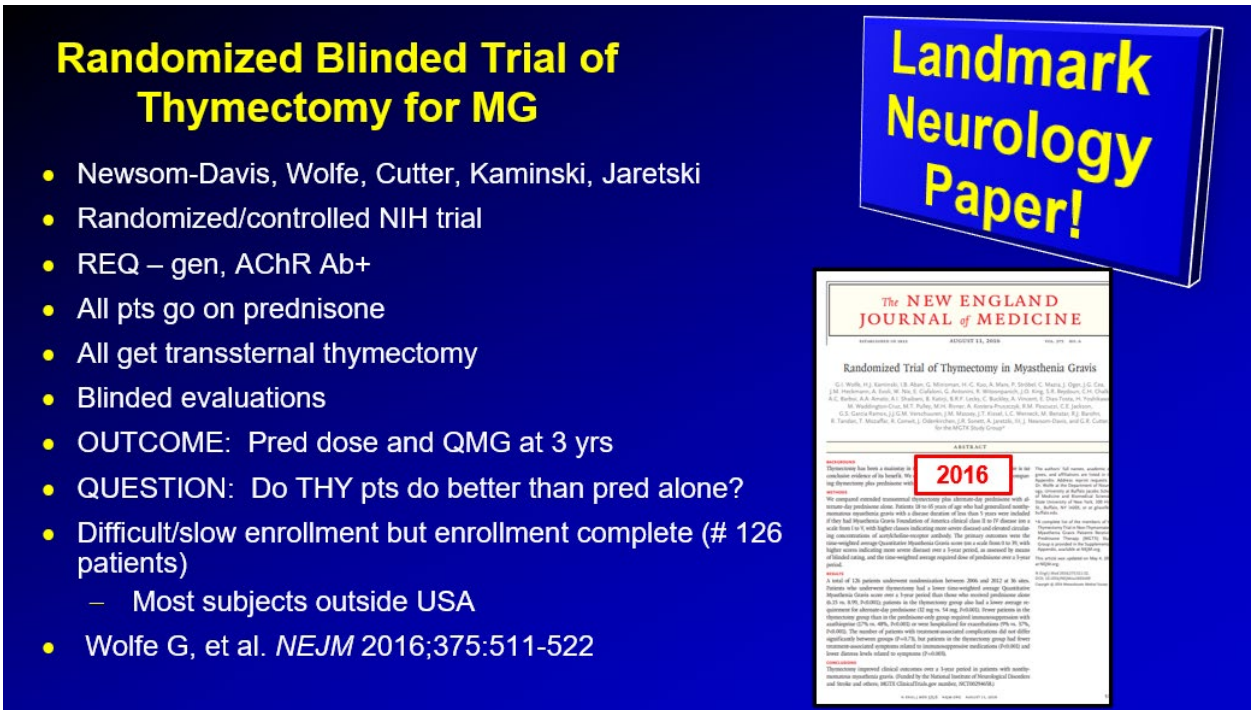
Thymoma is a mandatory reason to have a thymectomy. Thymectomy is also done for MG patients as a form of therapy if they do not have thymoma. This is called non-thymomatous MG and is the most common form of MG. A decision to do a thymectomy is not based on the chest CT in a non-thymomatous patient but based on data discussed below.

Until recently we did not have a randomized controlled trial of thymectomy in MG; now we do.

This is another landmark neurology publication, similar to the initial paper describing plasmapheresis treatment for Guillain-Barré syndrome. We consider both to be landmarks in neuromuscular

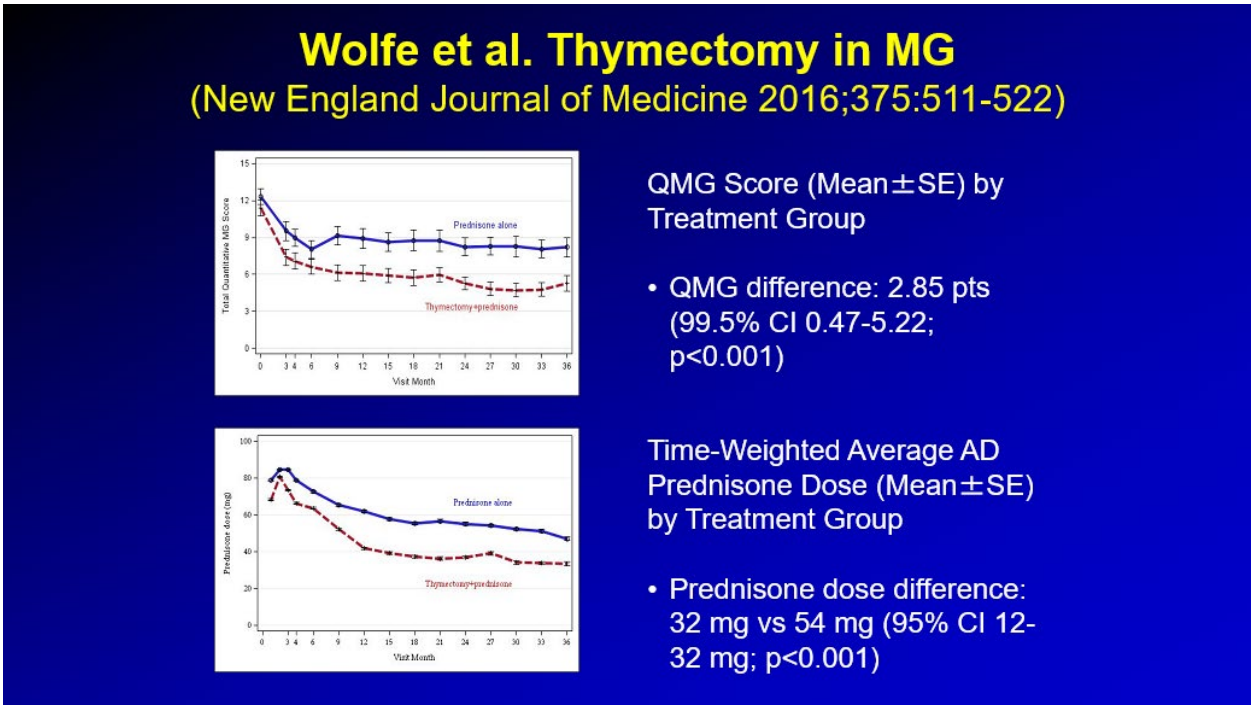
neurology publications as the result of large multicenter trials that led to a consensus and really changed how we managed patients.

Figure 28



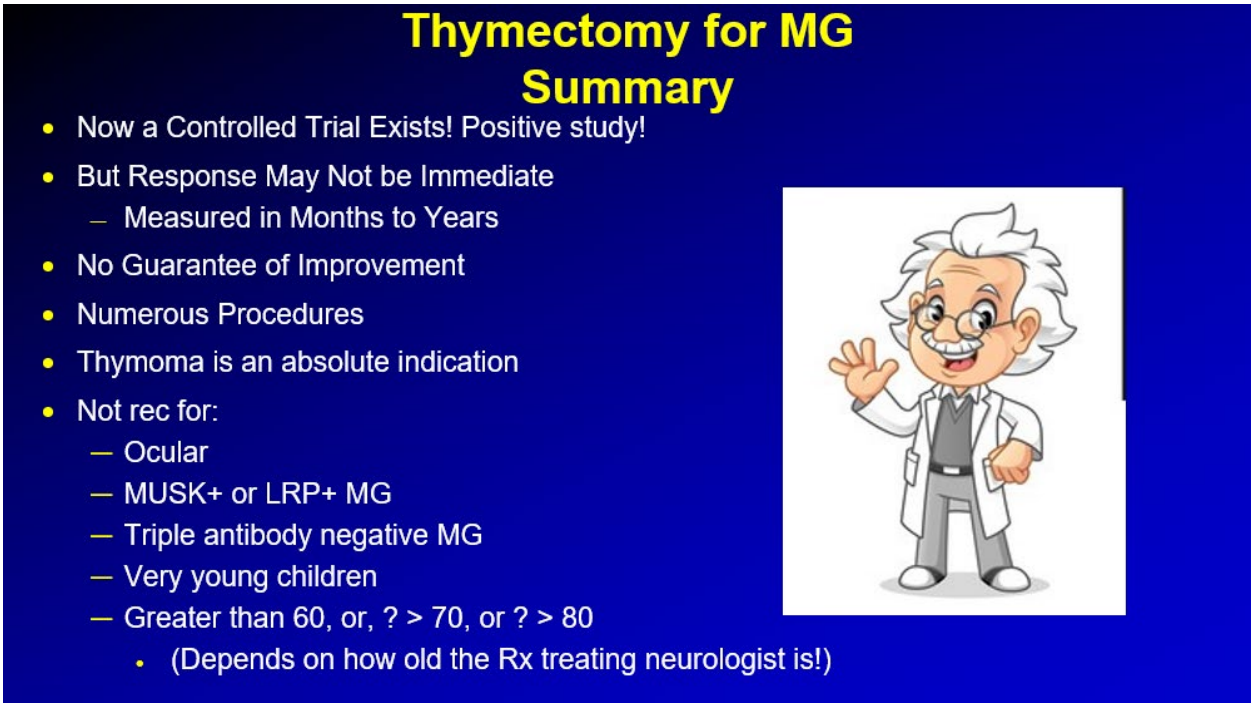
In this international trial, the MG community came together and enrolled over 100 patients and randomized them to either thymectomy or medical treatment. All patients were put on a prednisone-dose protocol and when the patients improved the prednisone was tapered per standardized protocol. What this important study showed was that at four months we can start seeing that patients who receive a thymectomy had a lower prednisone daily dose and also had a lower QMG score indicating improved MG (Figure 29). This data held up in a follow-up study of the same population at five years. Therefore, we now have a controlled trial of thymectomy in MG and to the surprise of many, the study was dramatically positive.

Figure 29



When you advise patients regarding whether or not they want to have a thymectomy, you do need to tell them that the response may not be immediate and that there's no guarantee that the thymectomy will result in an improvement, even though the study showed that overall patients who get a thymectomy are more likely to improve (Figure 30).

Figure 30



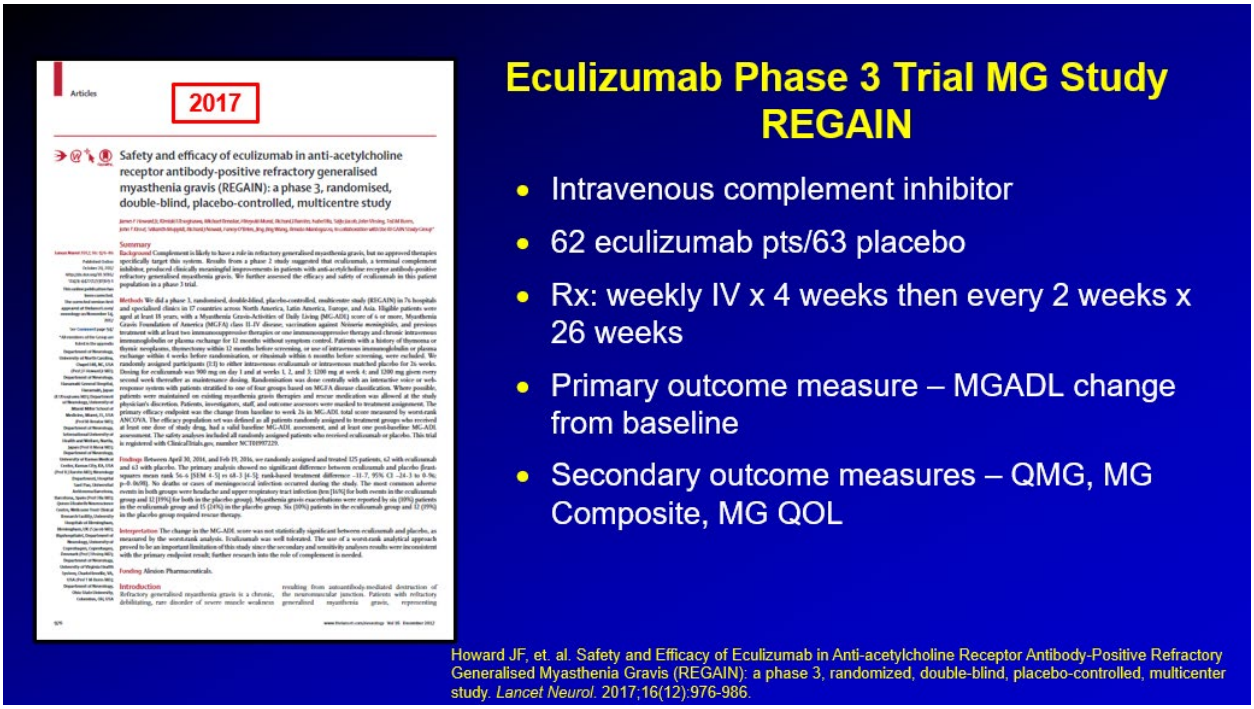
The type of procedure that is done for a thymectomy is variable. In the study that we just referred to all patients received identical extended transsternal thymectomies. However, transsternal thymectomies are not done very often today in the age of robotic surgery, so most patients now receive robotic or minimally invasive thymectomy surgery. We do not believe that there is ever going to be a comparative effectiveness research study comparing the various types of thymectomy.

We do not routinely recommend thymectomy for triple antibody-negative MG, but again this is somewhat debatable. We do not do thymectomies in young children who are under the age of two. Over the years there has been a belief that you should not do thymectomies in someone who is elderly. But the question is what is the upper age at which you would not do a thymectomy and the answer is not known. In the thymectomy study, patients were allowed to be enrolled up to age 65. But if an MG patient is a healthy 73 year-old should they get a thymectomy? We simply do not know the answer based on data and therefore the decision is left to the physician and the patient.

Complement inhibitors in MG

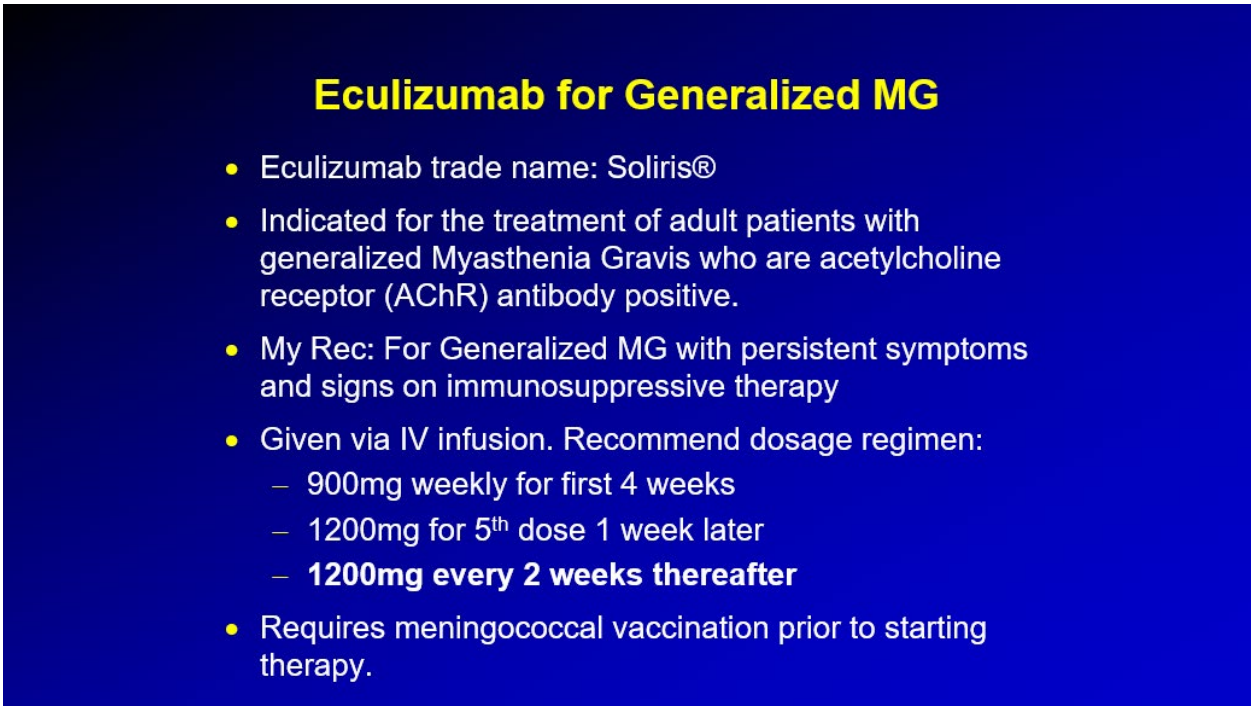
As we mentioned earlier in this presentation, Dr. Andrew Engel and the group at Mayo Clinic first showed how important the role of complement was at the neuromuscular junction in MG (Figure 3). These early pivotal papers were published in the 1970s and 1980s. As mentioned earlier, one of us (Dr. Barohn) performed a study in the 1990s that measured serum terminal complement levels in MG patients and was able to show that not only were they elevated but the magnitude of increase correlated with disease severity. The recognition of the role of complement in MG ultimately led to the pharmaceutical development industry having an interest in trying complement inhibitors as a therapy for MG. Eculizumab had previously been FDA approved for paroxysmal nocturnal hemoglobinuria (PNH) and hemolytic uremic syndrome (HUS). The pharmaceutical company that developed eculizumab for PNH and HUS then performed phase 2 and phase 3 trials for MG.

Figure 31



These trials were successful and showed that patients who received intravenous complement inhibitors had improved MG-ADL scores, and other secondary outcome measures including QMG score. Many believe that the development of complement inhibitors for MG is the biggest breakthrough in MG therapy over the last 50 years. This drug is now FDA-approved under the trade name Soliris. The labeling indication says it is indicated for the treatment of adult patients with AChR antibody positive generalized MG. However, the labeling indication approved by the FDA perhaps may be too wide and currently the neuromuscular community uses eculizumab therapy for generalized MG patients that still have persistent signs on immunosuppressive therapy or when immunosuppressive therapy has previously failed.

Figure 32



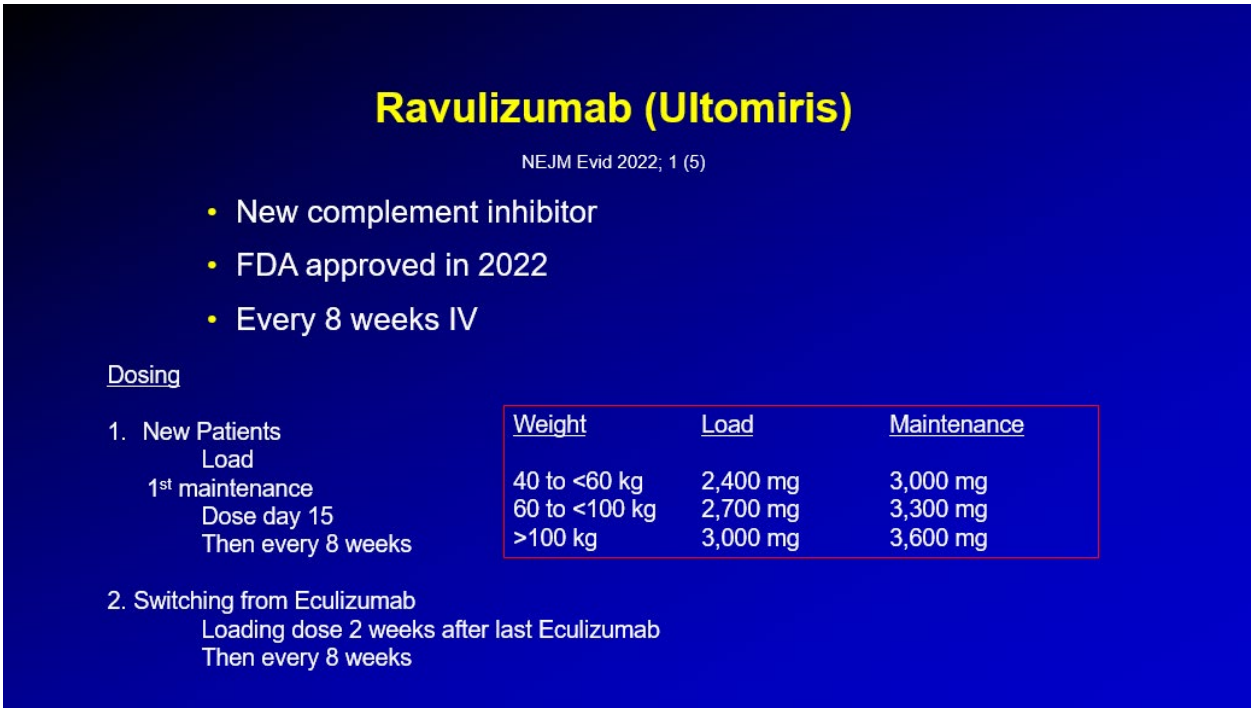
Before a patient receives eculizumab they need to have completed a full meningococcal vaccination regimen.

For the first month, eculizumab is administered weekly and after that, the infusions are given every two weeks. These can be done either in an outpatient hospital setting or at home.

After the release of eculizumab the same pharmaceutical company released ravulizumab (tradename Ultomiris). The major advantage of ravulizumab is that it can be administered every 8 weeks intravenously (Figure 33). Figure 33 shows the recommended loading and maintenance doses for ravulizumab. More recently, zilucoplan (Zilbrysq), another complement inhibitor, was FDA approved (Figure 13). The advantage of zilucoplan is that the drug is self-administered subcutaneously as a quick injection daily. Immunization guidelines for meningococcus have been recently updated by the Advisory Committee on Immunization Practices (ACIP) and should be closely followed for patient safety. In addition to meningococcus vaccination, clinicians should be aware that the late 2024 ACIP

recommendation is not to start complement inhibitors until after a full immunization series with 3 doses of the meningococcus B vaccine which takes 6 months, or in patients who cannot wait for 6 months, they should receive antibiotic prophylaxis. The 2024 ACIP recommendations state: "Persons on complement inhibitor therapy likely remain at substantially increased risk for meningococcal disease, even if they are fully vaccinated or taking antimicrobial prophylaxis...Persons not up to date with meningococcal vaccinations for whom urgent complement inhibitor therapy is indicated should be provided antimicrobial prophylaxis. Few data are available to guide decision-making regarding the optimal duration of antimicrobial prophylaxis; therefore, the duration of prophylaxis should be determined based on clinical judgment. Providers could consider treating patients with antimicrobial prophylaxis for the duration of complement inhibitor treatment."

Figure 33



Rituximab in MG

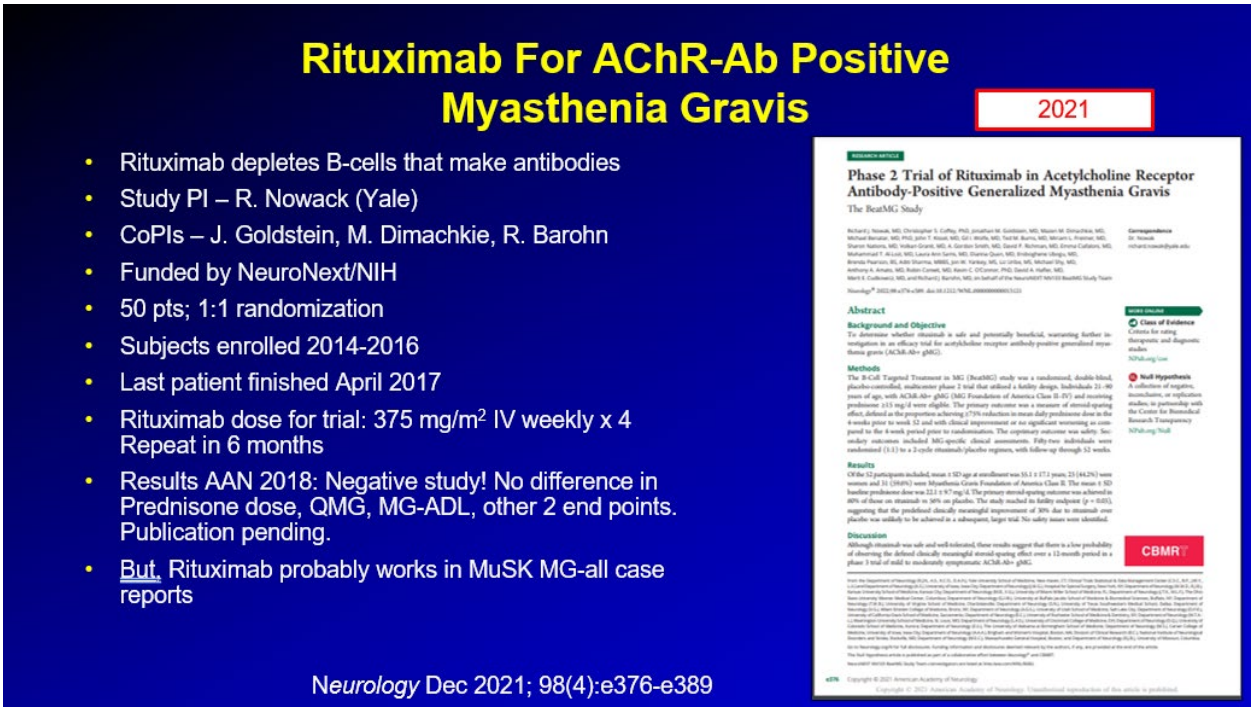
Rituximab was developed as a treatment for hematologic tumors because it eliminates B-lymphocytes. Due to this action, rituximab was applied to MG and other autoimmune diseases. It is generally believed that rituximab is very effective for patients with MUSK MG even though a randomized controlled trial has never been done in this rare patient population.

We all believe rituximab probably works for most MG patients, but MUSK MG is so rare that a randomized controlled trial may never be performed.

Many in the MG community believe that rituximab is effective in AChR-Ab positive MG based on anecdotal experience. This led to a randomized controlled trial in MG with rituximab in MG and generalized AChR antibody MG (Figure 34).

To our disappointment, the study was negative and did not show any steroid sparing effect compared to placebo.

Figure 34



Moore recently, a rituximab study out of Sweden suggested that there might be a benefit in recent onset AChR antibody positive MG.

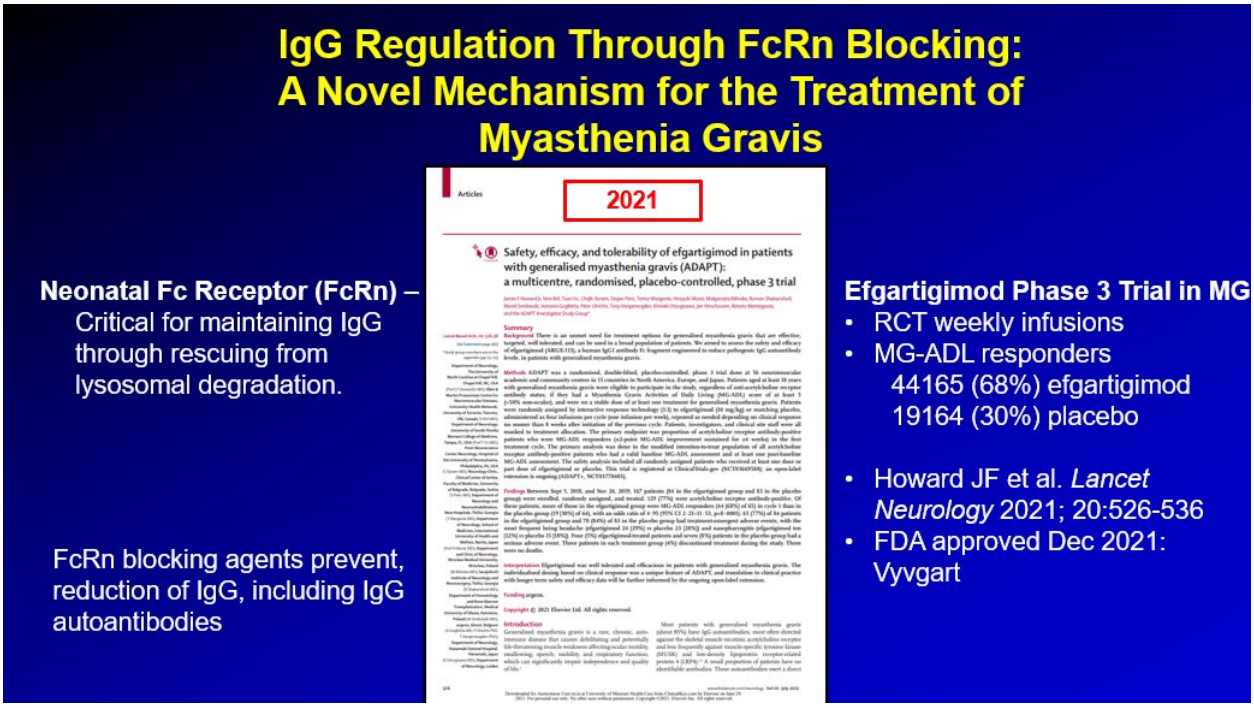
Fc receptor blockers

Another new class of drugs that has shown to be effective in MG is neonatal Fc receptor blockers. Efgartigimod decreases the level of all IgG that a human produces through blocking the FcRn receptor (Figure 35). This novel mechanism of action promotes intracellular lysosomal degradation of IgG. The FcRn is critical for maintaining IgG through rescuing IgG from lysosomal degradation and allowing it to exit the cells after entry as part of normal IgG recycling. Therefore, by blocking the FcRn receptorendogenous IgG levels decrease.

A phase 3 trial with this drug in MG was positive and led to FDA approval. As mentioned above, the generic name for the drug is efgartigimod with the tradename Vyvgart (Figure 13). The intravenous

preparation of this drug is on average given as 4 weekly cycles followed by a break for about 4 weeks, but this is also dependent on the patient's response to therapy. Recently a subcutaneous preparation for this drug has also been FDA approved, efgartigimod SQ, with tradename Vyvgart Hytrulo SQ, as well as another subcutaneous FcRn blocking agent, rozanolixizumab (Rystiggo).

Figure 35



Treatment recommendations for MG

Figure 36

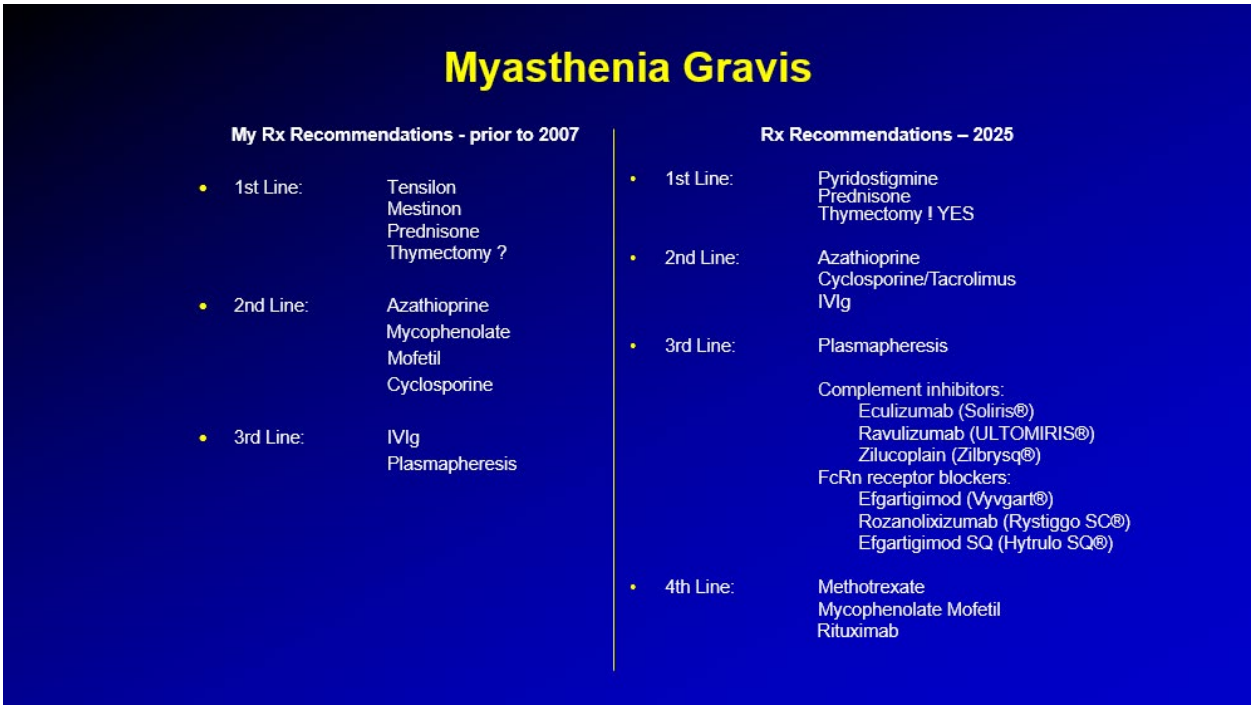


Figure 36 shows what our recommendations for MG were in 2007 compared to what they are now in 2024. This figure shows us how far we have come in the field of MG.

The first line treatment is pyridostigmine and we now have a generic form.

Prednisone is still the first line immunosuppressive treatment. Thymectomy is also a first line treatment, but usually patients are stabilized first on prednisone.

Second line treatment consists of traditional immunosuppressive drugs that have shown to be positive in randomized controlled trials: azathioprine, tacrolimus, and IVIG although all are off label.

Third line treatment is plasmapheresis, and the new class of FDA approved drugs that either suppress complement or the FcRn receptor blockers.

The fourth line category includes drugs that still have not been shown to be effective in randomized controlled trials such as methotrexate, mycophenolate mofetil, and rituximab.

These drugs may work in selected patients, but they are in the fourth line category as the randomized controlled trials with these drugs so far have been negative. Now, there is extensive discussion among the physicians and patients in the MG community whether the complement inhibitor and FcRn receptor blocking drugs can be used as first or second line therapy. In many instances this is now being done but the practice is somewhat restricted because often insurance companies require that at least two traditional immunosuppressive drugs have been used before one of these new classes of drugs can be tried. We suspect that over time as more data accumulates the newer drugs will be used as first and second line therapy.

Emerging Therapies

Chimeric antigen receptors T (CAR-T) cell therapy has revolutionized the care of patients with many advanced malignancies. CAR-T therapies and other related advanced cell therapy approaches are in clinical trials for autoimmune neuromuscular diseases, including MG. The antigenic targets of CAR-T are either the B-cell maturation antigen (BCMA, a marker of plasmablasts and plasma cells) or the CD19 surface cell marker (expressed on plasmablasts and earlier B-cell lineage cells). The goals are to reset the immune system targeting BCMA+ or CD19+ cells, to revert to a naïve B-cell phenotype and to impact pathogenic autoantibody production. Steps in these studies include leukapheresis to remove white blood cells from the patient, cell manufacturing (for T-cell enrichment, followed by virus-based transfection of enriched T cells, then cell expansion), and finally by reinfusion under a controlled setting into the patient. Therefore, this autologous approach requires close collaboration and care coordination between neurology, oncology and cell therapy to manage these complex studies. This is to closely monitor for any adverse event such as cytokine-release syndrome and for immune effector cell-associated neurotoxicity syndrome. The aim from these studies is to assess whether these approaches are safe in MG and ultimately whether patients can reach prolonged drug-free disease remission.

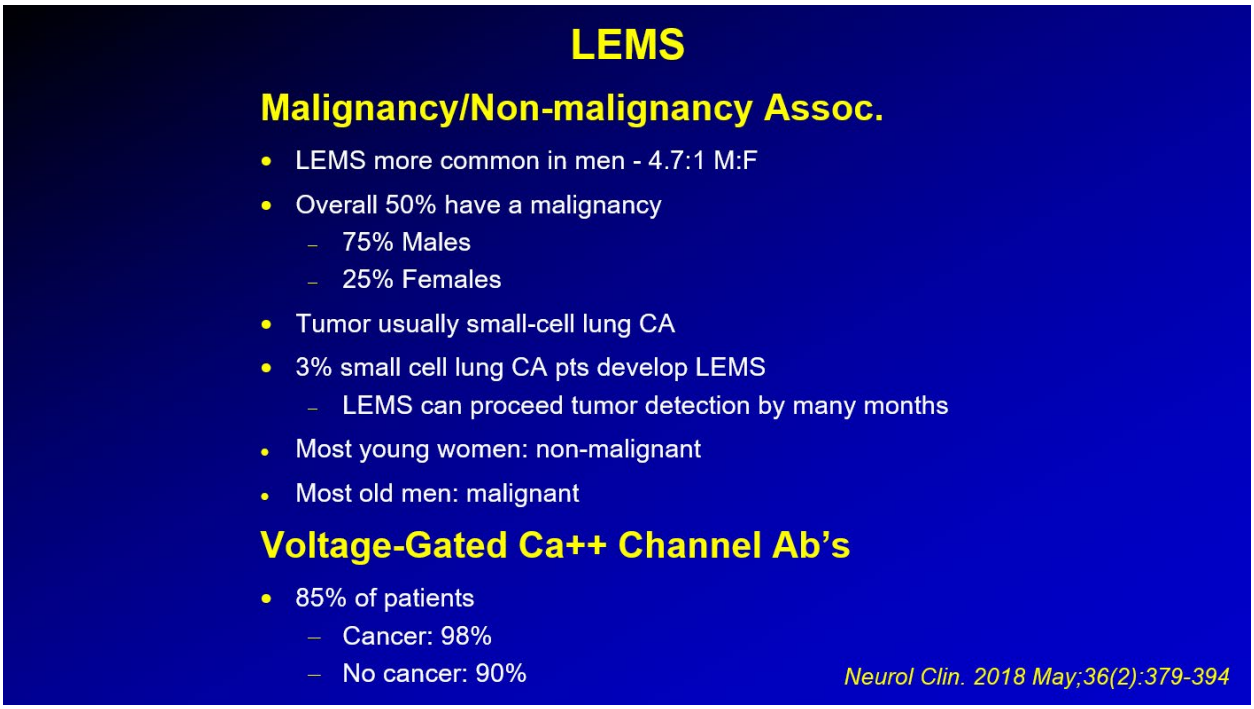
Lambert-Eaton myasthenic syndrome

Lambert-Eaton myasthenic syndrome (LEMS) basically comes in two categories: those patients that have cancer and those who do not have cancer.

The cancer patients are usually older men and the non-cancer patients are generally younger women, although of course there are many exceptions.

Both groups have voltage gated calcium channel antibodies in the blood that are directed against the presynaptic terminals and prohibit the release of acetylcholine into the synaptic cleft. The detection of voltage gated calcium channel antibodies is not specific for LEMS. The diagnosis of LEMS requires electrophysiologic confirmation. This can be done even before the voltage gated calcium channel antibody results are obtained.

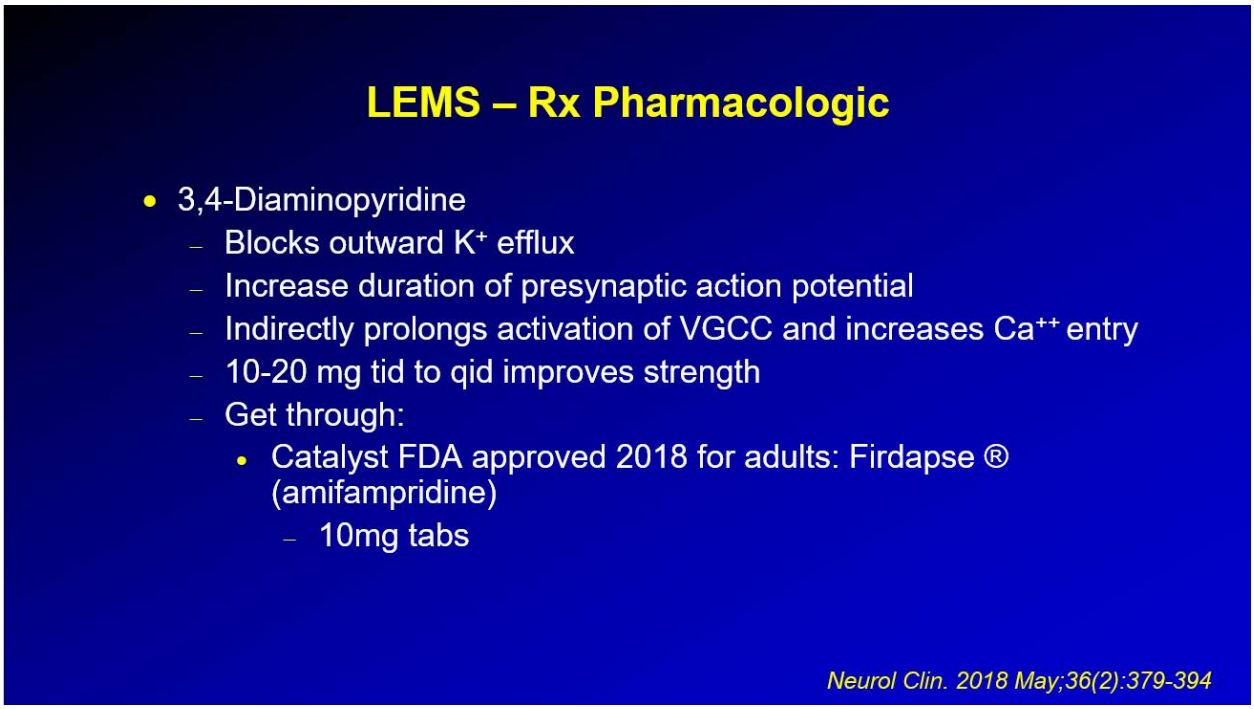
Figure 37



Electrophysiological evidence is obtained via nerve conduction studies when one can show a dramatic increment in the size of the compound muscle action potential either by doing a brief 10 seconds of exercise or by performing 50 Hertz repetitive stimulation.

The treatment of LEMS is twofold: there is symptomatic treatment and there is immunosuppressive treatment. The symptomatic treatment involves giving 3,4 diaminopyridine (Figure 38).

Figure 38



3,4-Diaminopyridine blocks the outward potassium efflux and increases the duration of the presynaptic action potential and thereby indirectly prolongs the activation of voltage gated calcium channels and increases calcium entry.

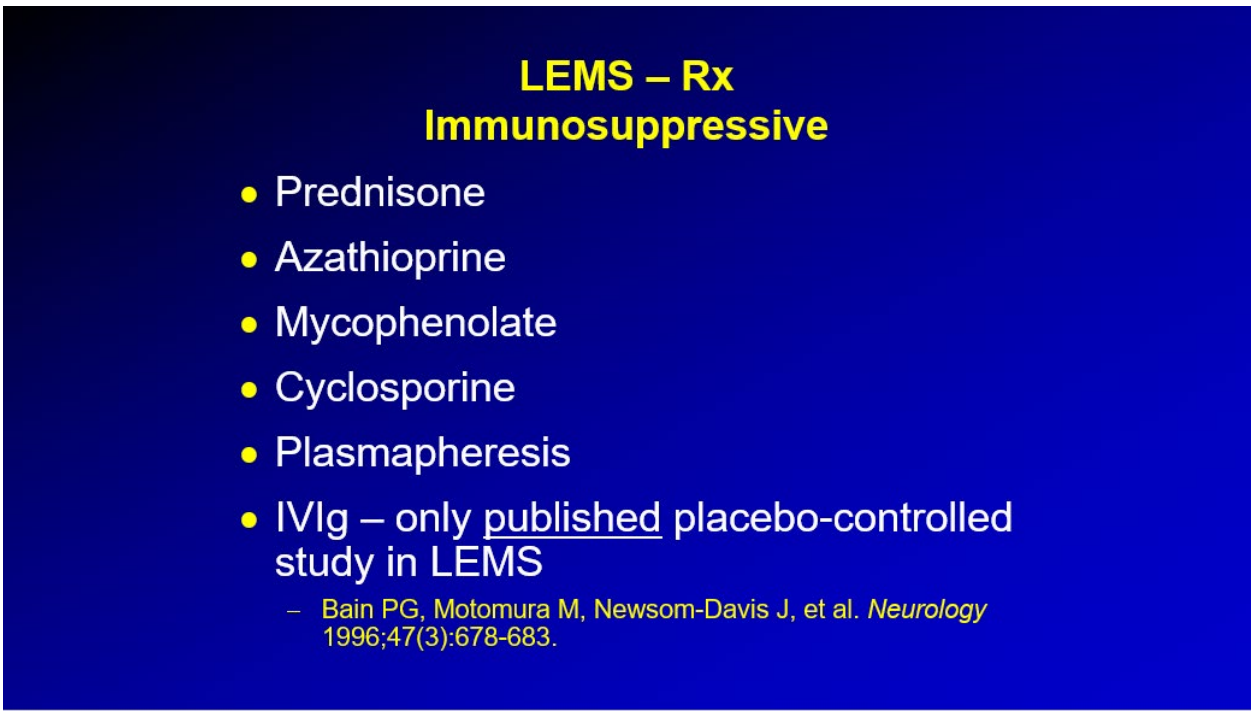
In essence, it increases the presynaptic release of acetylcholine vesicles into the neuromuscular junction.

This is very effective symptomatic treatment for LEMS patients and improves their strength.

The typical dose is 10 to 20 mg three to four times a day.

There were two FDA-approved forms: one is by Catalyst, and it is called Firdapse; the other was made by Jacobus, but that drug is no longer on the market. In the past we could obtain 3,4 diaminopyridine through compounding pharmacy but this is no longer an option now that an FDA-approved drug exists. Even when you put a patient on 3,4-diaminopyridine you usually still have to treat them with immunosuppressive treatment for LEMS and this involves the same traditional drugs that we use in MG (Figure 39).

Figure 39



In general, we do not believe that LEMS can be treated without prednisone. Other traditional immunosuppressive treatments can be used including azathioprine, mycophenolate mofetil and cyclosporine. Plasmapheresis and IVIg are also effective in LEMS.

Amazingly there is a placebo-controlled trial of IVIG in LEMS done by the British in the 1990s which showed a positive benefit of the drug compared to placebo.

Therefore, there are a number of treatment options. The bottom line is even if patients have cancer, you as the treating neurologist have to treat LEMS with 3,4-diaminopydridime because treating the cancer alone will not improve the weakness from LEMS.

Many of the patients who have small cell cancers and LEMS will die in a matter of months. Therefore, the goal of the neurologist is to keep them as strong as possible as long as possible so they can enjoy the remaining days that they have.

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References

Abuzinadah AR, Jabari D, Jawdat O, Pasnoor M, Glenn M, Herbelin L, McVey AL, Barohn RJ, Dimachkie MM. Satisfactory Response With Achieving Maintenance Low-Dose Prednisone in Generalized Myasthenia Gravis. J Clin Neuromuscul Dis. 2018 Dec;20(2):49-59.

Appel SH, Almon RR, Levy N. Acetylcholine receptor antibodies in myasthenia gravis. N Engl J Med. 1975 Oct 9;293(15):760-1.

Muscle Study Group. A trial of mycophenolate mofetil with prednisone as initial immunotherapy in myasthenia gravis. Neurology. 2008 Aug 5;71(6):394-9.

Bain PG, Motomura M, Newsom-Davis J, Misbah SA, Chapel HM, Lee ML, Vincent A, Lang B. Effects of intravenous immunoglobulin on muscle weakness and calcium-channel autoantibodies in the Lambert-Eaton myasthenic syndrome. Neurology. 1996 Sep;47(3):678-83.

Barnett C, Herbelin L, Dimachkie MM, Barohn RJ. Measuring Clinical Treatment Response in Myasthenia Gravis. Neurol Clin. 2018 May;36(2):339-353.

Barohn RJ. Percy Lavon Julian PhD- The Man Who Wouldn't Give Up. RRNMF Neuromuscular Journal. 2021;2.

Barohn RJ, McIntire D, Herbelin L, Wolfe GI, Nations S, Bryan WW. Reliability testing of the quantitative myasthenia gravis score. Ann N Y Acad Sci. 1998 May 13;841:769-72.

Barohn RJ, Brey RL. Soluble terminal complement components in human myasthenia gravis. Clin Neurol Neurosurg. 1993 Dec;95(4):285-90.

Benatar M, McDermott MP, Sanders DB, Wolfe GI, Barohn RJ, Nowak RJ, Hehir M, Juel V, Katzberg H, Tawil R. Efficacy of prednisone for the treatment of ocular myasthenia (EPITOME): A randomized, controlled trial. Muscle Nerve. 2016 Mar;53(3):363-9.

Brittain G, Roldan E, Alexander T, Saccardi R, Snowden JA, Sharrack B, Greco R. The Role of Chimeric Antigen Receptor T-Cell Therapy in Immune-Mediated Neurological Diseases. Ann Neurol. 2024 Sep;96(3):441-452.

Engel AG, Lambert EH, Howard FM. Immune complexes (IgG and C3) at the motor end-plate in myasthenia gravis: ultrastructural and light microscopic localization and electrophysiologic correlations. Mayo Clin Proc. 1977 May;52(5):267-80.

Farmakidis C, Pasnoor M, Dimachkie MM, Barohn RJ. Treatment of Myasthenia Gravis. Neurol Clin. 2018 May;36(2):311-337.

Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A, Vincent A. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. Nat Med. 2001 Mar;7(3):365-8.

Howard JF Jr, Barohn RJ, Cutter GR, Freimer M, Juel VC, Mozaffar T, Mellion ML, Benatar MG, Farrugia ME, Wang JJ, Malhotra SS, Kissel JT. A randomized, double-blind, placebo-controlled phase II study of eculizumab in patients with refractory generalized myasthenia gravis. Muscle Nerve. 2013 Jul;48(1):76-84.

Howard JF Jr, Bril V, Vu T, Karam C, Peric S, Margania T, Murai H, Bilinska M, Shakarishvili R, Smilowski M, Guglietta A, Ulrichts P, Vangeneugden T, Utsugisawa K, Verschuuren J, Mantegazza R. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2021 Jul;20(7):526-536.

Howard JF Jr, Freimer M, O'Brien F, Wang JJ, Collins SR, Kissel JT. QMG and MG-ADL correlations: Study of eculizumab treatment of myasthenia gravis. Muscle Nerve. 2017 Aug;56(2):328-330.

Howard JF Jr, Utsugisawa K, Benatar M, Murai H, Barohn RJ, Illa I, Jacob S, Vissing J, Burns TM, Kissel JT, Muppidi S, Nowak RJ, O'Brien F, Wang JJ, Mantegazza R. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. Lancet Neurol. 2017 Dec;16(12):976-986.

Jaretzki A 3rd, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, Sanders DB. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Ann Thorac Surg. 2000;70(1):327-334.

Kao I. Myasthenia gravis. Study of humoral immune mechanisms by passive transfer to mice. N Engl J Med. 1977;296(3):125-130.

Katz NK, Barohn RJ. The history of acetylcholinesterase inhibitors in the treatment of myasthenia gravis. Neuropharmacology. 2021 Jan;182:108-303.

Kesner VG, Oh SJ, Dimachkie MM, Barohn RJ. Lambert-Eaton Myasthenic Syndrome. Neurol Clin. 2018 May;36(2):379-394.

Leite MI, Jacob S, Viegas S, Cossins J, Clover L, Morgan BP, Beeson D, Willcox N, Vincent A. IgG1 antibodies to acetylcholine receptors in 'seronegative' myasthenia gravis. Brain. 2008 Jul;131(Pt 7):1940-52.

Lennon VA, Lambert EH. Autoantibodies bind solubilized calcium channel-omega-conotoxin complexes from small cell lung carcinoma: a diagnostic aid for Lambert-Eaton myasthenic syndrome. Mayo Clin Proc. 1989 Dec;64(12):1498-504.

Nagane Y, Utsugisawa K, Obara D, Kondoh R, Terayama Y. Efficacy of low-dose FK506 in the treatment of Myasthenia gravis--a randomized pilot study. Eur Neurol. 2005;53(3):146-50.

Nowak RJ, Coffey CS, Goldstein JM, Dimachkie MM, Benatar M, Kissel JT, Wolfe GI, Burns TM, Freimer ML, Nations S, Granit V, Smith AG, Richman DP, Ciafaloni E, Al-Lozi MT, Sams LA, Quan D, Ubogu E, Pearson B, Sharma A, Yankey JW, Uribe L, Shy M, Amato AA, Conwit R, O'Connor KC, Hafler DA, Cudkowicz ME, Barohn RJ. Phase 2 Trial of Rituximab in Acetylcholine Receptor Antibody-Positive Generalized Myasthenia Gravis: The BeatMG Study. Neurology. 2022;98(4):e376-e389.

Oh SJ, Shcherbakova N, Kostera-Pruszczyk A, Alsharabati M, Dimachkie M, Blanco JM, Brannagan T, Lavrnić D, Shieh PB, Vial C, Meisel A, Komoly S, Schoser B, Sivakumar K, So Y. Amifampridine phosphate (Firdapse(®)) is effective and safe in a phase 3 clinical trial in LEMS. Muscle Nerve. 2016 May;53(5):717-25.

Palace J, Newsom-Davis J, Lecky B. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group. Neurology. 1998 Jun;50(6):1778-1783.

Pasnoor M, Dimachkie MM, Farmakidis C, Barohn RJ. Diagnosis of Myasthenia Gravis. Neurol Clin. 2018 May;36(2):261-274, 311-337.

Pasnoor M, He J, Herbelin L, Burns TM, Nations S, Bril V, Wang AK, Elsheikh BH, Kissel JT, Saperstein D, Shaibani JA, Jackson C, Swenson A, Howard JF Jr, Goyal N, David W, Wicklund M, Pulley M, Becker M, Mozaffar T, Benatar M, Pazcuzzi R, Simpson E, Rosenfeld J, Dimachkie MM, Statland JM, Barohn RJ. A randomized controlled trial of methotrexate for patients with generalized myasthenia gravis. Neurology. 2016;87(1):57-64.

Pasnoor M, Heim AJ, Herbelin L, Statland J, Dimachkie MM, Becker M, Barohn RJ. Methotrexate Polyglutamation in a Myasthenia Gravis Clinical Trial. Kans J Med. 2020;13(Suppl 2):10-13.

Pasnoor M, Wolfe GI, Barohn RJ. Myasthenia gravis. Handb Clin Neurol. 2024;203:185-203.

Patrick J, Lindstrom J. Autoimmune response to acetylcholine receptor. Science. 1973;180(4088):871-872.

Priola AM, Priola SM. Imaging of thymus in myasthenia gravis: from thymic hyperplasia to thymic tumor. Clin Radiol. 2014 May;69(5):e230-45.

Rivner MH, Quarles BM, Pan JX, Yu Z, Howard JF Jr, Corse A, Dimachkie MM, Jackson C, Vu T, Small G, Lisak RP, Belsh J, Lee I, Nowak RJ, Baute V, Scelsa S, Fernandes JA, Simmons Z, Swenson A, Barohn R, Sanka RB, Gooch C, Ubogu E, Caress J, Pasnoor M, Xu H, Mei L. Clinical features of LRP4/agrin-antibody-positive myasthenia gravis: A multicenter study. Muscle Nerve. 2020;62(3):333-43.

Sahashi K, Engel AG, Lambert EH, Howard FM Jr. Ultrastructural localization of the terminal and lytic ninth complement component (C9) at the motor end-plate in myasthenia gravis. J Neuropathol Exp Neurol. 1980;39(2):160-72.

Sanders DB, Hart IK, Mantegazza R, Shukla SS, Siddiqi ZA, De Baets MH, Melms A, Nicolle MW, Solomons N, Richman DP. An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. Neurology. 2008;71(6):400-406.

Saperstein DS, Barohn RJ. Management of myasthenia gravis. Semin Neurol. 2004;24(1):41-48.

Schillie S, Loehr J, Chen WH, Moser CA, Cooper G, Isenhour C, McNamara LA. New Dosing Interval and Schedule for the Bexsero MenB-4C Vaccine: Updated Recommendations of the Advisory Committee on Immunization Practices - United States, October 2024. MMWR Morb Mortal Wkly Rep. 2024;73(49):1124-28.

Muppidi S, Benatar M, Murai H, Barohn RJ, Illa I, Jacob S, Vissing J, Burns TM, Kissel JT, Nowak RJ, Andersen H, Casasnovas C, de Bleecker JL, Vu TH, Mantegazza R, O'Brien FL, Jing Jing Wang JJ, Fujita KP, Howard JF Jr; Regain Study Group. A trial of mycophenolate mofetil with prednisone as initial immunotherapy in myasthenia gravis. Neurology. 2008;71(6):394-99.

Tindall RS, Phillips JT, Rollins JA, Wells L, Hall K. A clinical therapeutic trial of cyclosporine in myasthenia gravis. Ann N Y Acad Sci. 1993;681:539-551.

Tindall RS, Rollins JA, Phillips JT, Greenlee RG, Wells L, Belendiuk G. Preliminary results of a double-blind, randomized, placebo-controlled trial of cyclosporine in myasthenia gravis. N Engl J Med. 1987;316(12):719-24.

Toyka KV, Drachman DB, Griffin DE, Pestronk A, Winkelstein JA, Fishbeck KH, Granit V, Benatar M, Kurtoglu M, Miljković MD, Chahin N, Sahagian G, Feinberg MH, Slansky A, Vu T, Jewell CM, Singer MS, Kalayoglu MV, Howard JF Jr, Mozaffar T. Safety and clinical activity of autologous RNA chimeric antigen receptor T-cell therapy in myasthenia gravis (MG-001): a prospective, multicentre, open-label, non-randomised phase 1b/2a study. Lancet Neurol. 2023;22(7):578-90.

Walker MB. Treatment of MG with physostigmine. The Lancet. 223(5779):1200-1201.

Willis T. London Practice of Physick. 1685:432.

Willis T. The Anatomy of the Brain. 1664.

Wolfe GI, Barohn RJ, Sanders DB, McDermott MP. Comparison of outcome measures from a trial of mycophenolate mofetil in myasthenia gravis. Muscle Nerve. 2008;38(5):1429-1433.

Wolfe GI, Barohn RJ, Foster BM, Jackson CE, Kissel JT, Day JW, Thornton CA, Nations SP, Bryan WW, Amato AA, Freimer ML, Parry GJ. Randomized, controlled trial of intravenous immunoglobulin in myasthenia gravis. Muscle Nerve. 2002;26(4):549-52.

Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. Neurology. 1999;52(7):1487-1489.

Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A, Ströbel P, Mazia C, Oger J, Cea JG, Heckmann JM, Evoli A, Nix W, Ciafaloni E, Antonini G, Witoonpanich R, King JO, Beydoun SR, Chalk CH, Barboi AC, Amato AA, Shaibani AI, Katirji B, Lecky BR, Buckley C, Vincent A, Dias-Tosta E, Yoshikawa H, Waddington-Cruz M, Pulley MT, Rivner MH, Kostera-Pruszczyk A, Pascuzzi RM, Jackson CE, Garcia Ramos GS, Verschuuren JJ, Massey JM, Kissel JT, Werneck LC, Benatar M, Barohn RJ, Tandan R, Mozaffar T, Conwit R, Odenkirchen J, Sonett JR, Jaretzki A 3rd, Newsom-Davis J, Cutter GR. Randomized Trial of Thymectomy in Myasthenia Gravis. N Engl J Med. 2016;375(6):511-22.

Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A, Ströbel P, Mazia C, Oger J, Cea JG, Heckmann JM, Evoli A, Nix W, Ciafaloni E, Antonini G, Witoonpanich R, King JO, Beydoun SR, Chalk CH, Barboi AC, Amato AA, Shaibani AI, Katirji B, Lecky BRF, Buckley C, Vincent A, Dias-Tosta E, Yoshikawa H, Waddington-Cruz M, Pulley MT, Rivner MH, Kostera-

Pruszczyk A, Pascuzzi RM, Jackson CE, Verschuuren JJGM, Massey JM, Kissel JT, Werneck LC, Benatar M, Barohn RJ, Tandan R, Mozaffar T, Silvestri NJ, Conwit R, Sonett JR, Jaretzki A 3rd, Newsom-Davis J, Cutter GR. Long-term effect of thymectomy plus prednisone versus prednisone alone in patients with non-thymomatous myasthenia gravis: 2-year extension of the MGTX randomised trial. Lancet Neurol. 2019;18(3):259-268.

Zhang B, Tzartos JS, Belimezi M, Ragheb S, Bealmear B, Lewis RA, Xiong WC, Lisak RP, Tzartos SJ, Mei L. Autoantibodies to lipoprotein-related protein 4 in patients with double-seronegative myasthenia gravis. Arch Neurol. 2012;69(4):445-51.

Zinman L, Ng E, Bril V. IV immunoglobulin in patients with myasthenia gravis: a randomized controlled trial. Neurology. 2007;68(11):837-41.

About the Cover

Marie Nau Hunter

Deputy Director, Museum of Art and Archaeology,
University of Missouri

Cover image: Claude Raguet Hirst (American, 1855–1942), *Still Life with Bowl (Lionel and Clarissa—A Comic Opera)*, 1922, oil on canvas, Gilbreath-McLorn Museum Fund and Gift of Museum Associates (91.280)

We are so pleased to again provide an image for the cover of this publication, this issue being the third such iteration. Collaboration with disciplines outside of the arts is a hallmark for museum professionals. Most importantly (for us), it gets more eyes on art in the Museum of Art and Archaeology's (MA&A) permanent collection and hopefully results in interest in our exhibitions and related programming.

Claude Raguet Hirst's *Still Life with Bowl (Lionel and Clarissa—A Comic Opera)* is currently on view in the museum, greeting visitors as they enter our Gallery of European and American Art. The label accompanying it, written by our very talented Curator of European and American Art, Rima Girnius, PhD, reads as follows:

> Claude (born Claudine) Hirst was one of the few women artists of her era to paint still lifes in a deceptively realistic style known as *trompe l'oeil* (French for "deceives the eye"). Her skill in capturing details of texture and fleeting light with meticulous precision is evident in this assortment of decorative vessels and old, leather-bound volumes. Featured in the immediate foreground is a book open to the title page of Isaac Bickerstaff's *Lionel and Clarissa*. The book is a comedy of manners that features independent women who rebel against their fathers' choices of husbands. Included on the title page is the name of feminist critic, Elizabeth Inchbald, perhaps suggesting Hirst's support of women's rights.

Dr. Girnius has taken a thoughtful approach in her organization of the Gallery of European and American Art. Visitors can tour the space and appreciate the chronology of the art within, but Girnius has provided additional layers of information to give a global perspective. This is in keeping with current museum practices; that it is important to offer more than just art at which to look (though "art for art's sake" is definitely still a thing). Museums need to provide context. Dr. Girnius's introductory panel in the Gallery of European and American Art does exactly that:

> European and American Art from a Global Perspective
> The Gallery of European and American Art offers a selective overview of the principal values, practices, and beliefs underpinning Western art from the 13th through the 19th centuries. The presentation pays particular attention to the cross-cultural exchanges and encounters that fueled the stylistic and technical development of European visual arts.
> Europe's participation in global trade—first stimulated by the military campaigns waged by Christians against Muslims (1050–1300 CE)—witnessed a dramatic expansion in the early modern period (ca. 1450–1700 CE). Maritime and land routes between Europe, Africa, Asia, and the Americas not only transported raw materials and luxury goods but also served as conduits for the movement of people and exchange of ideas. Because of increased commercial networks, artists adopted new motifs, experimented with techniques, and gained access to prized pigments.
> There was, however, a human cost attached to Europe's increased engagement with the wider globe. In their pursuit of new markets and sources of wealth, European kingdoms and states gained control over territories and their inhabitants in distant lands through military conquest. They implemented a system of forced labor to extract the natural resources of colonized lands at low cost, exploiting first the indigenous populations and then enslaved Africans.

The expanded label included with Hirst's *Still Life with Bowl* provides the additional global perspective for the subject matter depicted:[1]

[1] Exhibited in the museum's Gallery of European and American Art just under Hirst's painting is a small stone sculpture, part of our collection of Asian objects. Its identifying label, also written by Dr. Girnius, reads:

> Seal Stone Surmounted by a Lion, China, ca. 18th - 19th century, stone, gift of J. Lionberger Davis (67.5)
> This stone sculpture is a Chinese seal used to stamp and validate important personal documents, contracts, and works of art. Mounted on its square base is a crouching lion, a creature traditionally used as a symbol of good luck and protector of truth. A Fu dog, as it is known, is among the items on display in Claude Hirst's *Still Life with Bowl*.

This approach also provides an important opportunity to bring works out of storage that would not otherwise be on display (Dr. Girnius does so in one other example in

Collecting East Asian Art in America

A yellow-glazed ceramic bowl, possibly from Jingdezhen in southern China, occupies a central position in Hirst's composition. Its presence, as well as the addition of the Fu dog, reflects America's fascination with East Asian art during the late 19th and early 20th centuries. This taste for "exotic" luxury goods was fueled by the success of large international exhibitions held in American cities from 1876 onwards. Designed to bring together the technological and artistic achievements of nations around the globe, the so-called World's Fairs exposed a large segment of America's population to Chinese culture. Dealers and collectors took advantage of the political and economic instability in China during this time, buying or looting art and antiquities with relative ease.

If you are reading this from a screen in central Missouri, you have little excuse for not visiting Hirst's painting in person, as works of art are best viewed. It is a lovely work of art. If you live and work further away, I hope you'll plan a trip to Columbia. The city and the University of Missouri's (MU) campus both have so much to offer, including the museum.

Please ask for me at the museum's visitors' services desk if you stop in during regular work hours. It would be my pleasure to give you a tour of our galleries and to admire together Hirst's painting and her in skill as an artist. If you are really lucky on the day you come by, you might encounter Dr. Girnius walking the galleries, checking on the art, and considering next projects for the museum's spaces that host temporary exhibitions and displays.

In case I cannot meet you during your visit, I'll share with you here a basic timeline of the museum which is, unfortunately, a hidden gem of MU's flagship campus.

The museum's history is a storied one, starting in the late nineteenth century when a teaching collection was established by professors Walter Miller and John Pickard for students matriculating in MU's department of classical archaeology and history of art. Miller and Pickard acquired photographs, plaster cast reproductions of well-known Greek and Roman sculptures, and original works of art. A letter written by Professor Pickard on January 1, 1895, to MU President Richard Jesse (for whom Jesse Hall is named), asked for $10,000 to purchase objects and furniture. That same year, MU's catalog included a mention of a museum in Academic Hall. More than 100 works acquired in those early years remain in the MA&A's collection today.

Professors Miller and Pickard both retired from MU during the Great Depression. In 1935, the university disbanded its department of classical archaeology and history of art, though the study collections were maintained.

The arrival to campus of professors Saul S. Weinberg in 1948 and Homer L. Thomas in 1950 revived the study of art history and archaeology at MU. And with the support of MU President Elmer Ellis, the study collections became an official project of the university, complete with a modest budget for the purchase of seventeen objects.

Professor Weinberg served as the museum's first director. His wife Gladys, an accomplished archaeologist in her own right and an internationally recognized expert in ancient glass, was the museum's first curator of ancient art and eventually became assistant director. Gladys founded the museum's peer-reviewed journal, *MUSE*, still published today.

A formative gift of Old Master works was received from the Samuel H. Kress Foundation in 1961, essentially launching a museum of art and archaeology and its designated gallery space in Ellis Library. In 1976, the MA&A moved into its first permanent location on campus, in Pickard Hall, immediately north of the Chancellor's Residence, allowing the MA&A to significantly expand public programming.

An abrupt move of the museum in 2013 occurred when radiation was discovered in Pickard Hall (the building had once housed the university's chemistry department including a contemporary of Dr. Marie Curie). That move landed the collection in an off-campus location for nearly ten years. While exhibitions continued to change and new educational programs were offered, MU student and faculty attendance plummeted. The time needed for transportation to and from the museum's location on Columbia's business loop made it prohibitive for most university classes to meet in our galleries and storage areas.

As with so many other industries, MA&A operations grinded to a halt with the onset of the global COVID-19 pandemic in March 2020. After an initial shut-down, the museum re-opened for a brief period before closure for its eventual move back to campus in 2022 to the lower level of Ellis Library. Once all 16,000 objects were carefully packed and transported across town (again), the museum remained closed for nearly four years as renovation of our current space was undertaken. Along the way, several important staff changes occurred, including the hiring of a new director, curator of European and American Art, deputy director, registrar, and educator.

Less than a year ago, on May 3, 2024, the museum finally reopened in the heart of MU's flagship campus. We offer five gallery spaces, two of which are permanently installed: the Saul S. and the Gladys D. Weinberg Gallery of Antiquities, named in honor of the museum's founders,

the European and American Art Gallery, with an ancient Mesoamerican). In this case, it is doubly important since we do not have a dedicated gallery for Asian art as previous museum locations did. And while it is just one small work, it allows us to discuss an important cross-cultural trend that might not otherwise be a topic in this exhibition space.

and the Gallery of European and American Art. The latter includes Claude Raguet Hirst's *Still Life with Bowl*, featured as this issue's cover image.

Many other paintings, drawings, and prints are displayed in our galleries, of course, as well as sculpture, textiles, and mixed media objects. Our permanent collection spans six continents and 6,000 years, with ancient works to contemporary art. This spring semester, three new exhibitions will open in addition to the ongoing permanently installed displays, two of them organized by Dr. Girnius, the other by Curator of Antiquities, Benton Kidd, PhD.

The Museum of Art and Archaeology 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, including a calendar of events and a searchable database of the museum's permanent collection, visit maa.missouri.edu.