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FACILITATORS

Cover Image: Top: "Smile for Grandma" by Jessica Wohl.
Bottom: "Erwin at the Buffet Table" by Jessica Wohl.

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MEETING STUFF

What's In This Issue?

Letter from the Founding Facilitator for Volume 2, Issue 5

Richard J. Barohn, MD

This is the final issue of Volume 2 for the year 2021. To open Issue 5/Volume 2 we have three additional pieces (in addition to this founding facilitator introduction) in the "What's on Your Mind?" section. The first is from a woman with ALS named Marcie Gibson. Marcie has been a patient of mine since 1994 when I diagnosed her with ALS at age 23. I asked her to write an article about her journey with ALS. Her journey has been remarkable, and she provided a wonderful piece of writing. Next is another terrific article from Dr. Josh Freeman's blog. From the view of a family medicine doctor, Dr. Freeman discusses the controversial FDA approval of the new drug for Alzheimer's disease, which was made over the objection of the FDA advisory panel. Next, I wrote my recollections of how the practice parameter on thymectomy for myasthenia gravis (MG) was developed. This was prompted by an email from a neuromuscular fellow, Nicholas Brennecke at Case Western University in Cleveland in which he asked me to provide the "backstory" about the practice parameter. I don't know how he knew I had a backstory, but I did! Thanks for asking me, Nic. I have located my original proposal to do a thymectomy study that I wrote in 1993 with Carlayne Jackson MD, and I have included this and the MG scales we developed in the "Proposed Stuff – Old Stuff" section.

In the New Stuff category Dr. Li and his group in Cleveland report their positive experience using methotrexate for MG. This case series made me smile since we failed to show the superiority of oral methotrexate over placebo for MG in a randomized controlled trial. The Cleveland experience adds to other anecdotal reports about the benefit of methotrexate in MG. Dr. Mamatha Pasnoor and I are not prepared to give up on proving this benefit and we recently submitted a federal grant to use subcutaneous methotrexate for MG. Wish us luck. We realize we are in an amazing age in the treatment of MG in which we have complement inhibitors and soon we may have neonatal Fc receptor blocking drugs for MG. These options are, amazing breakthrough drugs but they are extremely expensive, and it will be great if we can show an inexpensive drug can be effective in MG patients who are still symptomatic when they are on prednisone. Also in the New Stuff section is a nice manuscript by Dr. Bril and other MG experts along with their partners at Argenx in which they surveyed neurologists in the United States about practice patterns for approaching MG. This information was presented in September at the MSG meeting. The third New Stuff paper is really old stuff and describes the results of static fatigue testing in a group of MG patients. I say this is old stuff as it is data we collected at UT Southwestern in the 1990s when Dr. Wolfe, Laura Herbelin, myself and others were all partners in the MG clinic. This is data we never published but as a collector/hoarder that never throws out anything, I had saved all of the data and Dr. Wolfe had one of his sharp residents, Dr. Lail, put this paper together. So, the New Stuff section in Issue 5 is all MG.

The Clinic Stuff contains three articles. One is a case of acute motor and sensory axonal neuropathy (AMSAN) in the setting of immune thrombocytopenic purpura and Hemophilus influenzae by Drs. Satyasi, Ahmed and Farheen. Another is an interesting case of an adult with Becker muscular dystrophy who also had Covid-19, reported by a group at University of Missouri, Columbia. Finally, there is a case report from the University of Kansas Medical Center group of necrotizing myopathy with a rash following Covid-19 infection and vaccination.

In the "Other Good Stuff- Art Stuff" section is a wonderful poem by Thomas Trevor and Dr. Hani Kushlaf written from the perspective of a patient with inclusion body myositis (IBM). Thomas has IBM and Dr. Kushlaf is a neuromuscular physician. The other piece are lyrics to a song that Walter Anderson wrote called "AINT NO SENSE PROJECT (BOY IN THE BACK SEAT)" that was inspired by Dwight Jones who was recently released from prison in California after serving 21 years of a life sentence for a crime he did not commit. Walter's daughter, Adrian, is a newly minted attorney who works for the Loyola Project For the Innocent who was instrumental in obtaining his release from prison.

Finally, in December we held the annual Kansas City Consortium on Musculoskeletal Disorders (KCMD) at the University of Missouri-Kansas City (UMKC) campus. This annual event is sponsored by four universities: UMKC; University of Missouri-Columbia; University of Kansas Medical Center; and Kansas City University (the region's osteopathic medical school). It is a lively meeting in which science is presented from the neuromuscular and musculoskeletal fields. This year we once again had a number of interesting presentations, many by students. KCMD has a pilot grant program for investigators from these institutions who want to collaborate across university lines on research and several of the presentations were a result of these projects. I am pleased to be able to publish the abstracts from this meeting.

Our cover this month is again from the wonderful artist Jessica Wohl. We had a painting of hers on Vol 2; Issue 4 that is in my collection and on this issue are two more. The

pink painting is called "Smile for Grandma" and the blue painting is called "Erwin at the Buffet Table". I saw these in the early 2000s at a gallery event in the Crossroads area of Kansas City on a First Friday event. I initially purchased the grandma painting from Jessica because the woman reminded me of my grandmother (I think she looks like many grandmas!) Jessica told me she painted a series of paintings inspired from a 1960s wedding photo album in her family. The "Erwin" painting was from that series as well. Later I purchased the "Raymond" painting at a Village Shalom art auction that was on the cover of Vol 2, issue 4. All are up on the walls in our house in Columbia, Missouri now and they have been great favorites of folks viewing the collection. I have one or two more of Jessica's I may put on the journal's cover with her permission.

As we close 2021, I want to thank the authors and facilitators who have supported the journal. I also want to thank our outstanding medical student editors Breanna Tuhlei and JiJi Oufattole, our undergraduate journal assistant Lauren Peck, and of course our outstanding KU digital press team of Marianne Reed and Eric Bader. I appreciate all of you so very much. Happy Holidays and Happy New Year.

Rick

Living on Borrowed Time

Marcie Gibson

I don't remember the date I was diagnosed with ALS. It was a regular, clear, sunny Texas day in January of 1994. I have intentionally forgotten that date; I don't want a dreaded yearly anniversary. That day I walked into Dr. Barohn's office with a full life ahead of me and walked out with virtually no future at all. I didn't ask why me, I asked why not me. The human body is so complex, I don't know how any of us are walking around seemingly healthy. I was 23, in my last semester of college, had just gotten engaged, was about to pursue some plans I had set in place since elementary school, and was looking forward to starting a life with my soon-to-be husband. All that seemed so frivolous when faced with mortality. I had waited too long to start my so-called adult life; now it was too late. Death was the farthest thing from my mind. I wrongly thought I had time. Naively, I thought I would have chance after chance of opportunities. That was a hard lesson learned. I wouldn't have hesitated as much as I did if I could have a do-over. My life had changed with just a few words. So, what do I do now?

I lived in a fog for the first six months, and I don't remember much. I numbly went through the routine of going to school and going to work. I decided to adopt the recovering addicts' philosophy of living pretty early on: one day at a time. When I woke up in the morning, I would focus only on getting through that day. If I started to think about six months or a year into the future, I would be overwhelmed with the difficulties that were to come. I still live this way today. I have a hard time thinking about even two days from now.

In February of 1996 my first nephew was born. I remember saying to myself that I would never see this baby graduate from high school. Not only have I seen him graduate from high school and college, I also saw him get married and grow into a funny, intelligent, confident young man. I have experienced friends getting married, having kids, more nephews and a niece, concerts, SEC college band practice, and other "normal" life occurrences. Sitting in Dr. Barohn's office that terrible day, I didn't see normal life occurrences in my future. I have been given more time than I ever imagined. There are two approaches to life, one as a participant and the other as a spectator. I have lived both. In my pre-ALS life I was very involved in gymnastics, cheerleading, and dance. Now, I am on the sidelines. I prefer being in the middle of things which makes this life, my second life, much tougher.

I had a feeding tube inserted in the summer of 2004. There's something liberating about not eating by mouth. I don't have to think about what I want to eat, I don't have to make it, eat it, or clean up the mess. It frees up a lot of time and energy. Additionally, I get nutrient-dense food without concern for taste. I rarely crave food. I think the connection between my stomach and my brain has been severed. Is that even possible? I take it as a blessing. I can't, however, say it's liberating to lose the ability to breathe. On my 36th birthday my lungs finally gave out. I took the hard path, I chose life. It can be stressful depending on a machine to breathe. There's a tiny part of my brain that's continuously monitoring the vent. First, I ask myself: "am I breathing, vents do fail without warning, was my inhale the right depth, was that a complete exhale, was the timing between breaths as it should be." That part of my brain is constantly on overload. It can get exhausting.

It has been 27 years since I first thought I only had a few years left to live. How have I navigated through this unceasing reminder of death without going insane? One word. . . Faith. I am a Christian. I believe life has meaning; life has purpose. Because of my Biblical worldview I don't believe we are grown-up sea sponges; I don't believe we are no different than ants. My life has value, no matter how small of a life I live. If I didn't believe this I would have ended my life the day I was diagnosed. Why face a life of round-the-clock struggle if life has no purpose and meaning? Hope goes along with Faith. I have to believe that something better may be around the corner. I have to believe that I may see a treatment for ALS and get a second chance with a strong body. If I didn't have hope I would fall into a destructive cycle of depression and despair. None of us can live without hope. My life isn't easy; I have dark days, but I have a lot of joyful days too. Kind of sounds like all of us. I do wonder why I didn't get to be a wife and a mom like 100% of my circle of friends. Why out of all the diseases, did I contract ALS? These are questions I probably won't get answered until I'm standing in the presence of the Creator. And then, will I even care?

Today, I still live in Texas in the house I grew up in. Fortunately, my parents are healthy enough to care for me. This November 2021 I will be 51; I never thought I would see 25. To the world, I am living in that place beyond borrowed time. As a Christian, I know my life will end on the exact day and exact minute that was planned before I was born. What I'm going through isn't a surprise to God. For some reason it took a terminal disease to get me to open my eyes to reality. I was a little blinded. I see my sister and brother's families at least weekly. I have a few friends who have stuck by me throughout this whole illness that I also see. My family and friends are the brave ones. They have chosen to look suffering in the face year after year. Most people rightfully cringe and retreat at the sight of suffering.

Not those committed to me, especially my mom and dad who haven't once threatened to put me in a nursing home, even on the worst of days when all they really want to do is throw me out the window. The fiancee? You already know the answer; he ran. Wouldn't you? If I had been given the choice, I would have run for my life away from ALS too. But there's something positive about a terminal disease, it burns away the useless insecurities that get in the way of seeing what's true. Like family, friends, peace, contentment, humility, gratitude, and maybe a little happiness. I have a strange wish: that everyone be misdiagnosed with a terminal disease. The mistake must be concealed for a least one year. A month or two isn't long enough to realize the blessings mentioned above resulting in positive impacts to yourself and those around you without actually losing your life. Hopefully, anyone reading this article has realized this idea for yourself from interactions with your chronic/terminally ill patients. Live life knowing that good health is a gift not everyone receives.

FDA approves Alzheimer's drug against the recommendation of its scientific panel. Be very concerned.

Joshua Freeman, MD

Originally published in the *Medicine and Social Justice* blog, https://medicinesocialjustice.blogspot.com/2021/06/fda-approves-alzheimers-drug-against.html

Early in June, an article in the *NY Times* discussed the possible approval of aducanumab, a recombinant DNA (the "-ab" is always clue!) drug intended to treat Alzheimer's disease. The FDA approved the drug a few days later, going against the recommendations of its advisory committee of scientific experts, and generating this "Quotation of the Day" in the *Times* from one of its members, G. Caleb Alexander: "There's no way to recover the opportunity to understand whether or not the product really works in the post-approval setting." Almost immediately, three members of the advisory committee, Joel Perlmutter of Mayo, David Knopman of Washington University in St. Louis, and Aaron Kesselheim of Harvard, resigned in protest of the decision. Dr. Kesselman, along with his colleague, Dr. Jerry Avorn, presents a strong indictment of the FDA in an Op-Ed guest essay in the *Times*, and they are not alone. Most neurologists, including those who I know are experts on and leading researchers in Alzheimer's, echo these concerns.

This is pretty unusual. Not just the resignations, but the reason for them – the decision by the FDA to approve a new drug based on evidence of effectiveness so weak that the scientific advisory panel recommended against it. It raises a number of questions, the foremost one of which is "why?" Also: Is this a precedent, and will it happen again, or more regularly? What was the reason that the advisory committee recommended against approval? Who were the people at the FDA who overruled them, and what were *their* reasons?

First let's start with *cui bono?* – who benefits. This is certainly Biogen, the company that developed aducanumab and will market it, under the tradename Aduhelm. It is estimated that it will cost $56,000 a year. This is not a record; there are other recombinant DNA drugs – including several for neurologic conditions – that cost even more. In fact, as indicated in a recent study by the American Academy of Neurology, "Medicare paid 50% more for neurology drugs over 5 years while claims rose only 8%". Still, it is a tidy chunk of change, and since Alzheimer's is a far more common disease than most of the rare ones that are ostensibly treated by more expensive drugs, Biogen expects to make a bundle. And, because only the very very rich could afford this much, most of it will be paid by you. That is, by insurance companies that collect your premiums, and especially by Medicare, the insurer for the majority of Alzheimer's patients, which is funded by your tax dollars. This is described in another article, with the subhead: *'Despite scant evidence that it works, the drug, Aduhelm, is predicted to generate billions of dollars in revenue, much of it from Medicare.'* If people are not insured, or rich, they can forget it. Which, in this case, might be just as well.

Making a lot of money, as much as they possibly can wring out of patients and insurers, is the core business of pharmaceutical companies (and most companies, although pharmaceutical companies have been particularly good at making outrageous profits, always ranking as the #1 industry for profit). It is not, despite their ads, (and they spend much more on marketing than on research and development) about improving your health. You are just the coincident vehicle for generating their profits. Their drugs do not have to actually help you get better; as long as they don't harm you too much – and, of course, as long as the FDA approves them – they are golden. This is why they spend so much on marketing, and lobbying, and specifically lobbying the FDA. Indeed, the "golden parachute" of many FDA staffers is to retire from the agency and get a job lobbying for a drug company. Sigh. So that one is obvious. Corrupt and despicable, yes, worthy of complete anger and condemnation, yes. But obvious. Not, heretofore, however, predictable.

There is another stakeholder group involved, Alzheimer's advocacy groups. The FDA still has an acting chief, Janet Woodcock, and another article notes these groups supported her becoming permanent. It says, *"Woodcock's nomination back in February when the application for the drug, aducanumab by Biogen, was pending, its approval was a sign that they backed the right candidate."* Wow. Shouldn't we be paying them attention? After all, they are not the drug manufacturers who will be making a mint. And Alzheimer's is a terrible disease, and we need effective treatments, right?

Not so fast. Yes, Alzheimer's is a terrible disease. Those who have it suffer greatly, at least until it is so advanced they no longer recognize what is going on. And their loved ones continue to suffer, more and more. A drug that would cure it, or mitigate it, or make it progress more slowly would be wonderful (although it shouldn't cost $56,000 a year!). But

is aducanumab that drug? Not according to the scientific panel, who know. But the advocacy groups are pushing for it anyway. Why? Well, they make not be making most of the money, but they have to justify their existence. And they almost certainly are getting donations from those drug makers. And maybe, even, they care so deeply about the disease that their hope and optimism overcomes appropriate caution. It wouldn't be the first time that this has happened (e.g., the continued promotion by breast cancer advocacy groups for decreasing the age and increasing the frequency of screening even when science showed the opposite).

It also wouldn't be the first time that those advocating for victims of terrible disease pushed strongly for approval before studies were completed. One meaningful and important example is the efforts of groups such as ACT-UP to get early approval for anti-retroviral drugs, as people were dying in droves from AIDS. But there are differences. One is the disease; Alzheimer's is not killing people quickly as did AIDS, and no one is claiming that aducanumab or any other drug will change its eventual downhill course. Another is health equity. In the political and social landscape of the 1980s, AIDS was a disease primarily affecting gay men and IV drug users, definitely not the mainstream. Leaders such as Ronald Reagan refused to offer support. And, perhaps most importantly, the anti-retrovirals were showing a definite positive effect in studies, and the calls were to speed up the approval process. In the current case, the trials are complete and the evidence showing a positive effect is not sufficient.

This is in no small part due to the fact that the "positive effect" studies show involves changes in biomarkers, not changes in people's lives. That is, they look at lab tests rather than whether people die less soon or suffer less. Yes, there is evidence, as there is evidence in many diseases, that these intermediate markers are related to long-term outcomes, but the problem is that the further out they get the more it becomes like a game of "telephone" (well, our drug affects A, and A is related to B, and B may be related to long-term outcomes). We need studies that look at *patient-oriented* not *disease-oriented* or *laboratory-test-oriented* effects.

Sometimes an intermediate marker improves but the patient does not, or gets worse. It could be from a side effect of the drug (drug safety) but it can also be from the desired positive effect of the drug! For a time, diabetes groups pushed to lower the target hemoglobin A1c (HbA1c) -- a measure of long-term glucose level, to be 5 rather than 6, because people with diabetes with lower HbA1c levels had lower levels of diabetes complications. Makes sense. But when the *average* blood sugar over several months is lower, it increases the risk of significant hypoglycemia (low blood sugar), which can be more dangerous than higher sugar. Indeed, if you pass out from low blood sugar, fall and break your hip, and die, the lower rate of complications from your diabetes in the long term is irrelevant. There is an old medical joke about Harvard doctors being very insistent that their residents keep patients' lab values in the normal range, so that even when the patient died, they died in "perfect Harvard balance".

This is not what we want. We want diseases to be cured or ameliorated; for lives to be lengthened and improved in quality. We certainly do not want drug companies to make billions off of people's suffering. When the FDA approves a drug over the recommendations of its scientific panel, it should be of great concern to all of us.

Don't forget *cui bono?*

How the Thymectomy for Myasthenia Gravis Practice Parameter was Developed

Richard J. Barohn, MD

Recently, Dr. Nicholas Brennecke, a neuromuscular fellow at Case Western in Cleveland asked me if I could give him some background information on how the thymectomy practice parameter was developed.[1] He was preparing a talk on thymectomy in myasthenia gravis (MG) and he asked if I "could give me a 'front row seat' on your experience during these years." This prompted me to write him the following story.

I first had the idea to do a randomized thymectomy study in the late 1980s when I was at UTHSC-San Antonio. I presented the idea at the yearly MGA conference to a group of senior doctors in Chicago on a cold December day. I called the presentation MY GRANTs: Myasthenia GRavis RaNdomized Thymectomy study. They were very skeptical and said, "Young man, there is no need for the study, and you should focus your time on something worthwhile and more productive."

I did not give up. I continued to try to put together a group of doctors in the USA in the 90s who wanted to do a randomized thymectomy study. I wrote a protocol and developed a new classification system for MG and I also developed the first version of the Myasthenia Gravis-Activities of Daily Living (MG-ADL) scale for the thymectomy project.[2] We found the original protocol I wrote with Dr. Carlayne Jackson who was my first neuromuscular fellow at UTHSC (San Antonio.) The protocol is dated 4-15-93. I am including it in this issue immediately after these comments in the "proposed stuff – old stuff" category. In this version, we had developed the initial version of the MG-ADL (later modified by Gil Wolfe and Laura Herbelin and I at UTSW.) This protocol also included our attempts at coming up with a new MG grading scale to replace the old osserman scale. I liked this scale, but it did not catch on and instead a committee of the MG Foundation of America through a consensus conference I was on developed the MGFA-MG grading scale which is widely accepted.[3] I had meetings at several American Academy of Neurology (AAN) annual meetings with interested neurologists to discuss the protocol. But I could never get it off the ground very far. I moved to University of Texas – Southwestern (UTSW) in Dallas in 1993 and I took the "advice" from the senior neurologists I originally pitched the idea to: work on something I could accomplish. I began working on an intravenous immune globulin (IVIG)-randomized MG study.[4] Gil Wolfe had just arrived at UTSW in 1994 and he worked with me on the IVIG-MG project. We got an FDA-OPD grant and an MDA grant to fund that study, which was ultimately aborted early due to a nationwide IVIG shortage.

In the late 90s, two things happened. Dr. John Newsom-Davis contacted me from Oxford, England and said he wanted to put together such a study on an international level. He was a senior myastheniologist and I had the feeling he could pull it off where I could not. He asked me to help. I was very busy doing other things at UTSW, and I had just become interim chair of the Department of Neurology. I told him to work with my partner Gil Wolfe instead as his U.S. partner and he did. Around the same time I was asked to put together a practice parameter on MG by the AAN. This was in the very early stages of practice parameter development. They did not tell me which topic in MG to tackle. So, I decided to tackle the thymectomy issue. I did not know how to write a practice parameter. But my close colleague from my U.S. Air Force days was Dr. Gary Gronseth who was then the chair of neurology at Wilford Hall U.S. Air Force Medical Center in San Antonio. This was where I had served on active duty in the military and I was still in the USAF reserved and did my reserve training and time there. Gary was on the ground floor of teaching doctors how to write practice parameters, and since were already friends and colleagues, I was able to work closely with him to pull it off. I gathered all the literature up to the late 1990s. I sat down with Gary in his office at Wilford Hall and we went through each one. He showed me how to classify them as Class 1, 2, 3, etc. All the literature were retrospective reviews. We found the ones that did comparisons of groups that had thymectomy and ones that did not. We found about 25 articles out of hundreds of thymectomy reports. We gathered the outcomes data from these papers and made our best guess as to what the outcomes were. Of course, there was no standardized definition of MG outcomes at this time. Each report had their own definition of remission, improvement, etc. But we did the best we could. At the end of the analysis, it did look like perhaps the thymectomy group did a bit better. But there were many confounders which made us conclude that we needed a true prospective randomized controlled trial. Fortunately, Dr. Newsom-Davis was already putting together an international team to write the NIH grant to fund such a study. Also, at the same time that the thymectomy practice parameter came out, I had been asked to serve on a committee to come up with a new classification of MG (to replace outdated versions) and to come up with recommendations for assessing MG outcomes. This paper came out in the same year (perhaps in the same issue) of Neurology. So the ground work was laid for the thymectomy study.

I was always a skeptic regarding the effect of thymectomy in MG. My mentor Dr. Jerry Mendell first instilled this

skepticism into me as a young fellow in 1986-87. He had presented a talk at the AAN in the mid-1980s raising the question of "Does thymectomy work for MG?" He was not the first to raise this question. Dr. Michael McQuillen when at the University of Kentucky wrote a paper in Neurology called "A Treatment Carol: Thymectomy Revisited" when he reviewed data from prior published trials raising the possibility that we did not have sufficient data to advocate for thymectomy in MG. This was in 1977.[5] One of his protégés Dr. Doug Lanska wrote a similar editorial in Neurology in the early 90s.[6]

Based on this background, I was not convinced thymectomy for MG was an effective procedure based on all the retrospective data that had been reported. And we all had patients in our clinics who had thymectomies but were still very symptomatic on therapy. Then the international community led by Dr. Newsom-Davis did the study and you know the rest of the story. It was spectacularly positive showing thymectomy definitely benefits patients with MG. I became a believer and I now recommend it to most of my generalized MG patients who are acetylcholine receptor-antibody positive. It took ten years to do the thymectomy trial and a great deal of persistence. I was not on the leadership team of the trial but was a participating site at the University of Kansas, and I watched with anticipation as the trial unfolded. All of the investigators met at the time the data was unveiled. I attended the meeting in Oxford, England when Drs. Wolfe, Kaminski, and Cutter revealed the findings of the study and it was clearly positive in favor of thymectomy.[7] I was glad to be proven wrong. With the positive study results, and long-term 5-year follow-up results of subjects on the trial[8], we were able to update the practice parameter.[9]

This shows the power of remaining skeptical on treatments that some consider established with poor data to support their conclusions and it shows the power of an academic and international community to tackle the toughest problems that many seem unsolvable. I am proud to be a part of this story.

Dr. Newsom-Davis died tragically in a car accident in Europe when he was driving to a site in Romania to get them up and started in the thymectomy trial. Drs. Wolfe, Kaminski (neurologists), Dr. Cutter (statistician) and Dr. Fred Jaretski (cardiothoracic surgeon at Columbia in NYC) led the study to its completion. Dr. Jaretski also passed away of natural causes before the study results were unveiled.

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Carlayne E. Jackson, M.D.
Richard J. Barohn, M.D.

A RANDOMIZED CLINICAL TRIAL OF THYMECTOMY FOR THE TREATMENT OF MYASTHENIA GRAVIS

1. Specific Aims:

A. To determine whether thymectomy added to best medical management has an effect on the rate of complete remission in patients with myasthenia gravis (MG) in a randomized, prospective study.

B. To determine whether thymectomy added to best medical management has an effect on the rate of pharmacologic remission or on clinical improvement in patients with MG in a randomized, prospective study.

C. To determine whether there are specific subsets of MG patients such as age, sex, acetylcholine receptor antibody titer, or severity of disease which predict a better response to thymectomy.

2. Background and Significance:

In 1939, Blalock (1) reported the remission of generalized MG in a 21 y/o women following removal of the cystic remains of a necrotic thymic tumor. Since then thymectomy, with or without the presence of thymoma, has gained widespread acceptance as a form of treatment for MG. Thus, thymectomy was the first attempt at "immunotherapy" for MG and continues to be one of the most frequently utilized attempts at treatment. However, all studies on the possible effectiveness of thymectomy are based on retrospective or case control studies. A randomized study has yet to be done despite calls for such a trial by experts in the neuromuscular community (2). Since medical management of MG and respiratory intensive care has now so dramatically shifted the curve of morbidity and mortality, it would seem more necessary than ever to re-examine the potential benefit of thymectomy in a scientifically sound manner.

The role of the thymus gland in the pathogenesis of myasthenia gravis remains highly controversial. Up to 80% of patients with MG have thymus abnormalities, with 10-15% being thymus tumors and the remainder consisting of lymphoid hyperplasia (3). Lymphocytes in the thymus and peripheral blood appear to be sensitized to muscle in MG patients, and recent evidence indicates that thymus tissue from MG patients with and without thymoma are enriched in AchR-reactive T cells (4). On the other hand, Tindall (5) reported that thymectomy resulted in either no early change in acetylcholine receptor antibody levels or a slow and gradual fall requiring a much longer follow-up. Similar results were reported by Kornfeld et al (6) and Roses et al (7).

In experimental autoimmune myasthenia gravis (EAMG) it is the chronic phase that most closely resembles the human disease (8), yet neither thymectomy nor early treatment with antithymocyte serum alters this phase of EAMG (9). Thymectomy in EAMG has not been shown to have any effect on circulating lymphocyte subpopulations (10).

The problems that exist in analyzing prior retrospective studies on the efficacy of thymectomy have been well identified (11). One difficulty is that a determination of the status of remission and improvement by a retrospective unblinded chart analysis is potentially fraught with error. In addition, while most authors agree that "remission" refers to a patient who is asymptomatic off no medications, the category of "improvement" is very subjective and arbitrary. Some authors have defined

improvement to be a mean reduction in the dosage of anticholinesterase medication (12,13,14). These studies relied frequently on quality of life questionnaires rather than on actual neurologic examinations. Indeed, identifying patients who are in remission in a prospective study will be challenging, as outlined below.

McQuillen and Leone (11) compared the remission rates between patients receiving medical and surgical management reported in several large series performed, with one exception, prior to 1965. This date was chosen because treatment with corticosteroids for myasthenia gravis began the following year. They could find no significant differences between the two treatment groups. Abstracted is the key information from their review:

REMISSION RATE: NONSURGICAL THERAPY		
Author	*n*	*Percent*
Kennedy and Moersch (17)	87	31
Grob (18)	202	23
Simpson (12)	99	16
Oosterhuis (19)	180	31
Perlo and associates (15)	417	24
OVERALL	985	24

REMISSION RATE: SURGICAL THERAPY		
Author	*n*	*Percent*
Simpson (12)	258	21
Perlo and associates (15)	267	34
Mulder and associates (13)	73	36
Emeryk and Strugalska (14)	112	23
Patatestas and associates (16)	111	25
OVERALL	821	28

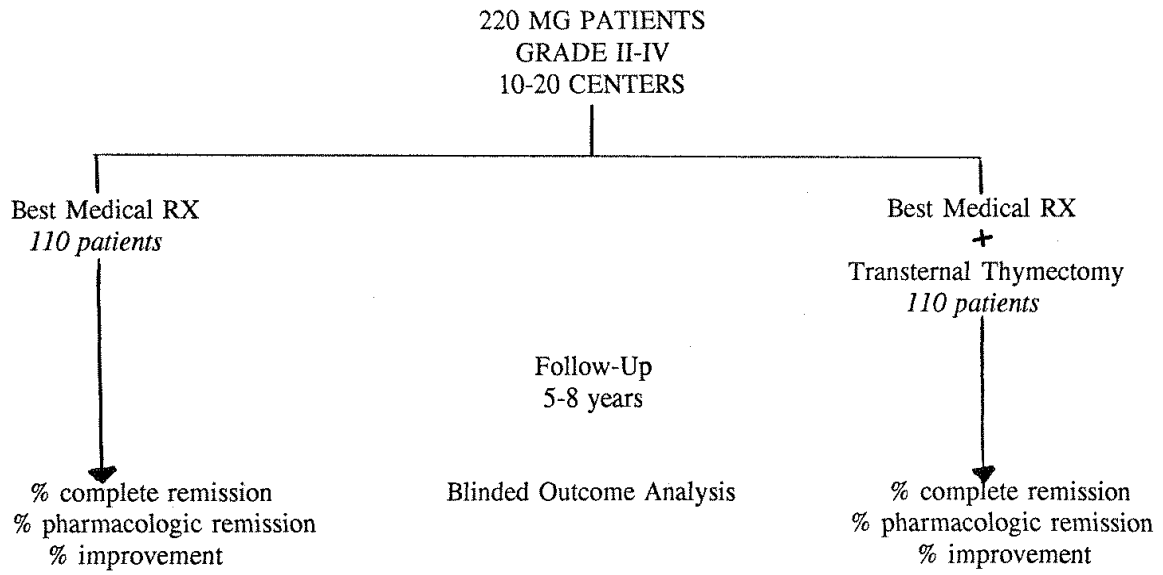
Considering that this early era in the treatment of MG would bias the results against medical therapy, it is even more impressive that there seems to be little difference.

Other methodologic problems with these early studies include treatment groups that were not comparable in terms of age, sex, or severity of disease. When these variables were considered, some authors showed that remission rates did not appear to depend on age (20), although others observed a much greater benefit in those younger than 40 (12,21). Women reportedly have a 14-23% better benefit from thymectomy; yet several series did not show a difference in benefit between sexes (12,14,15,22). In some reports, there is a suggestion that the more severe the MG grade before thymectomy, the more likely the patient is to improve (15); other series report the opposite (13) while some were unable to show any significant difference between groups based on disease severity (14,21). One of the largest retrospective studies published was that of Perlo (15) who reported the results of 267 patients. Complete remission post-thymectomy occurred in 35%, with an additional 41% showing improvement defined as the control of symptoms on medications. However, the response to thymectomy was not immediate. Of the 92 patients that ultimately achieved a complete remission over a 10 year period, only 25% remitted the first year, 40% the second year and 55% in three years. Complete remission in the medical group was only 17% with an additional 11% showing improvement.

A more recent retrospective report by Fujii et al (23) also enthusiastically endorses thymectomy. In this retrospective study, the authors examined the course of 50 patients who underwent transternal thymectomy and showed a 32% complete remission rate and concluded that preoperative clinical stage, duration of disease and serum acetylcholine receptor antibody titer did not affect the post-operative prognosis. However, they also suggested that women and patients <40 years of age showed more benefit than other patients. The authors were also able to demonstrate significant increases in CD3+ cells, HLADR+ cells and B cells in the thymus of patients who had a poor post-operative course. On the other hand, Beghi et al (21) retrospectively analyzed the courses of 844 patients, of whom 63% had thymectomy, and found that thymectomized subjects had only a slightly increased chance of complete remission compared to non-surgical patients, and this was considered to be of borderline significance. They felt that younger age and shorter duration of disease may have contributed to an increased likelihood of remission. However, they recommended that a prospective randomized study be performed to resolve these issues.

The controversy surrounding thymectomy will undoubtedly continue until a proper randomized, clinical trial is performed in a population homogeneous for variables presumed to be predictive of response, i.e., age, sex, and severity of disease. A randomized trial to clearly define the role of thymectomy is long overdue due to the invasive nature of this procedure.

3. **Experimental design and methods:**



A. ***Diagnosis:*** All patients admitted to the study must have a diagnosis of MG. The diagnosis of MG will be made by the unblinded clinical investigators at each facility. The diagnosis will be based on:

1) An elevated acetylcholine receptor antibody
2) Ocular, facial, bulbar, or extremity weakness and fatigability without other neurologic etiology.

Other supportive evidence for myasthenia gravis includes a positive Tensilon test and abnormal repetitive stimulation or single-fiber EMG, but these are not mandatory for the study.

B. Classification: All MG patients will be classified according to the severity of their disease using a modified Osserman classification that was developed and currently is used at the University of Texas Health Science Center of San Antonio. The classification is as follows:

Grade 1: Ocular involvement alone (ptosis, diplopia, orbicularis oculi weakness in the absence of other bulbar, neck or limb weakness is allowable in this group).

Grade 2: Mild generalized MG; normal activities of daily living are preserved with only mild symptoms of weakness or fatiguability. Includes patients with subjective complaints of only ocular weakness but who on exam show evidence of limb/neck weakness. Symptoms necessitate initiation of treatment with Mestinon therapy alone (no immunosuppressive drugs needed).

Grade 2b: Mild restricted MG; normal activities of daily living are preserved with only mild weakness restricted to bulbar involvement without subjective limb weakness(may have subjective/objective neck weakness; the only allowable objective limb weakness would be of the hip flexors, which can be no worse than MRC grade 4; may also have ocular involvement). Symptoms necessitate treatment with Mestinon therapy alone (no immunosuppressive drugs needed).

Grade 3: Moderate generalized MG; normal activities of daily living are interrupted because of weakness and fatigue. Symptoms require initiation of treatment with immunosuppressive therapy.

Grade 3b: Moderate restricted MG; restricted to bulbar and /or respiratory (diaphragmatic) involvement without subjective limb weakness (may have subjective/objective neck weakness; the only allowable objective limb weakness would be of the hip flexors, which can be no worse than MRC grade 4; may also have ocular involvement); no impending respiratory failure or inability to swallow requiring mechanical feeding. Immunosuppressive therapy is required for treatment.

Grade 4: Severe generalized MG (myasthenic crisis); profound weakness in the extremities requiring confinement to bed and hospitalization; established respiratory failure requiring mechanical ventilation or bulbar weakness requiring mechanical feeding.

Grade 4b: Severe restricted MG (myasthenic crisis); restricted to bulbar and/or respiratory muscles with no subjective limb weakness (may have neck weakness and hip flexor weakness on exam no worse than MRC grade 4; may have ocular involvement); requires mechanical feeding or mechanical ventilation.

Grade 0 (remission): This stage will not be used at the time of entry into the study, but will be used at follow-up evaluations. Patients in clinical remission can include the following groups.

Grade 0a: No objective cranial nerve or extremity weakness. Off all medications.

Grade 0b: No objective cranial nerve or extremity weakness. Remains on Mestinon.

Grade 0c: No objective cranial nerve or extremity weakness. Remains on immunosuppressive drugs.

Grade 0a+, 0b+, 0c+: Any of the above 0 grades, but the patient may still have slight orbicularis oculi or hip flexor weakness (grade 4+ or 5-), despite the absence of any subjective symptoms of ocular/bulbar or extremity weakness.

C. ***Inclusion Criteria:*** Patient selection will be based on a clinical diagnosis of myasthenia gravis, with all of the following specific criteria:

1) Patients between the ages of 18 and 50 who demonstrate evidence of ocular, facial, bulbar, or extremity weakness based on neurologic examination and history. Entry must be within 6 months of initial diagnosis. Ocular weakness alone will not be acceptable for the purposes of this study (ie. patients must be grade 2-4). Patients with grade 1 disease will be followed monthly, and should generalized symptoms or signs develop, they can then be randomized. Patients must be entered within 6 months of onset of generalized symptoms. Patients will not be excluded if standard medical therapy has already been initiated (Mestinon, prednisone, Imuran, IVIG, plasmapheresis).
2) A definite diagnosis of MG must be accompanied by the presence of an elevated acetylcholine receptor antibody titer.
3) The patient's signs and symptoms should not be able to be better explained by some other disease process.
4) Patients must be physically healthy for their age and diagnosis without a history of another major chronic or debilitating illness.
5) Patients must be properly motivated, willing to cooperate in not unbinding the study, and willing to return for the follow-up visits during the study.
6) Patients must give written informed consent before participating in this study. A copy of the witnessed consent must be noted in the Investigator's medical records.

D. ***Exclusion Criteria:***

1) Patients who cannot undergo thymectomy due to other medical conditions.
2) Patients suspected of having a thymus tumor based upon abnormal chest CT or MRI.
3) Patients with altered levels of consciousness, dementia, or abnormal mental status.
4) Patients with a history of neurologic, chronic degenerative or psychiatric disorders other than MG.
5) Females who are pregnant or lactating.

E. Study Entry/Randomization: At the initial presentation of the patient, the investigator at each center will perform a clinical evaluation which will determine the patient's eligibility for participation in the study. All patients will undergo the following studies prior to enrollment: 1) acetylcholine receptor antibody level, 2) chest CT or MRI. Patients who do not meet the inclusion criteria or who have exclusion criteria will not be entered into the study.

For those patients who do meet the criteria, the investigator will perform a baseline evaluation which will include: manual muscle testing of 34 muscle groups using a MRC (25) scale (Appendix A), hand grip strength (in kg) using a Jamar dynamometer, forced vital capacity (in liters) using a pulmonary function monitor, a battery of quantitative functional tasks (Appendix B) and a questionnaire indicating the patient's level of disability in terms of activities of daily living (ADLs) (Appendix C). Protocol eligibility and admission information consisting of demographic data,

summary of history, examination findings, and results of diagnostic studies on each patient will be entered into patient booklets and the data forwarded to the Project Clinical Coordinator promptly after patient enrollment (Appendix D).

All patients will then be randomized to the following treatment groups:

1) Medical treatment alone

2) Thymectomy: patients in the thymectomy group may also be placed on medical therapy as necessitated by the severity of the disease. All thymectomies should be done through a trans-sternal surgical approach. Thymectomies will be done within 6 weeks of randomization.

Registration and randomization will be performed through the Patient Registration Office at the University of Texas Health Science Center in San Antonio by calling (210)567-4750 during the hours of 9AM to 4PM Central time, Monday through Friday. Since this is a multi-center trial, randomization will be accomplished using dynamic allocation to ensure that the number of patients are balanced over centers with regards to treatment group, age (<40 versus >40), and grade of disease (grade 2 versus grade 3).

F. Follow-up and Data Collection: Patients will be entered over a three year period, and the study will be continued until all patients have been followed at least 5 years. Patients will have follow-up examinations by a physician who will not have prior knowledge with regard to whether or not the patient had a thymectomy, i.e., the "Blinded Investigator" (BI). The BI will be a co-investigator from the nearest study center who will travel to the same study center every 6 months. The first follow-up evaluation will be performed within 6 months after randomization and then at 6 month intervals. Training sessions for all of the participating BI's will be required to ensure consistency with performing the testing outlined below and filling out the case report forms. During these BI evaluations, patients will be required to wear turtlenecks or shirts buttoned at the collar in order to conceal any surgical scars and will be reminded not to offer any information which could potentially unblind the study. The BI will not have access to the patient's clinic or hospital records nor to the results of the patient's prior study evaluations.

The BI will be responsible for completing the following battery of testing:

1. Manual Muscle Testing
2. Handgrip strength (in kg) using a Jamar dynamometer
3. Forced vital capacity
4. MG Quantitative Functional Scale

If patients are on Mestinon, examinations should be done 2 to 6 hours after the last Mestinon dose (in order to assess if the patient is in pharmacologic remission).

At each evaluation, patients will also be asked to complete a MG Quantitative ADL Scale as well as a progress report asking whether the patient subjectively feels they are currently in remission (either on or off medications).

Based upon the results of the BI's clinical evaluation, each patient will subsequently be assigned an MG grade by the BI (Appendix E). The BI will be responsible for completing all the appropriate case report forms and sending them to the coordinating center of this study for computer entry.

Patients will be routinely followed by the investigator at each center (ie. the "unblinded investigator") between visits by the BI as needed for assessment of medication needs/adjustments and monitoring of immunosuppressive drug side effects. In the event that the unblinded investigator feels that the patient has had a significant relapse, the investigator will complete a "relapse form" (Appendix F) and send it to the coordinating center. A significant relapse will be defined as any symptomatic worsening necessitating a change in medications or a change in MG grade. Other than notification of relapses, only the data obtained during the BI examinations, however, will be utilized for this study.

At the conclusion of the 5 year follow-up evaluation or upon withdrawal from the study, an acetylcholine receptor antibody level will be drawn.

G. End-Points: The primary endpoint for this study will be the number of patients at the end of the follow-up period who are in complete remission off all medications for at least 6 months. Secondary endpoints will be: 1) the number of patients at the end of the follow-up period who are in pharmacologic remission, 2) MG grade(indicating disease severity) at the end of the study period, 3) average manual muscle test score at the end of the study period, 4)MG quantitative functional score at the end of the study period, 5)MG quantitative ADL score at the end of the study period, 6)average dose of medications. The number of relapses over the study period will also be compared between the two groups.

4. Monitoring:

A monitoring committee consisting of 3-4 neurologists and a biostatistician with experience in treating MG patients and clinical trials who are not investigators enrolling patients in the study will review all the case report forms and relapse forms in order to confirm designations of MG grade and criteria for relapse. The committee will meet at a minimum of once a year. In addition, the committee will review the interim statistical analyses.

5. Sample Size and Statistical Analysis:

The primary objective of this study is to determine whether thymectomy added to best medical management has an effect on the remission rate. Based upon the published retrospective series previously referenced, we estimate that after 5 years of follow-up, 15% of patients under best medical management will have achieved complete remission, and 40% will achieve pharmacologic remission. In order for thymectomy to be considered effective therapy, we will require that the complete and pharmacologic remission rates improve to 30% and 70% respectively. The required difference in complete remission rates is equivalent to a hazard ratio of 2.2, that is, at any point in time, patients undergoing thymectomy are 2.2 times as likely undergo remission. We will require a total of 220 patients (110 in each arm), followed for a minimum of 5 years, in order to detect this difference at the 0.05 level of significance (two-tailed) with 80% power. Although not the primary focus of the study, this sample size will be more than sufficient to detect the anticipated differences in pharmacologic remissions and will, in fact, allow the inclusion of concomitant variables in the analysis models and the separate analysis of grade or age subgroups, in order to examine the possibility that some types of patients benefit more than others. A study of this size will necessitate the involvement of at least 10 centers, however enrollment would proceed much more quickly with 20 centers.

Interim analyses will be performed to allow nonthymectomized patients to crossover to the thymcetomy arm as soon as possible if there is clear evidence of a beneficial effect. If 220 patients are accured more or less uniformly over 3 years, and the study is continued until all patients have been followed at least 5 years (8 years duration), then, after accounting for the requirement of a 6 month duration of remission, we expect to accrue about 1260 person-years of evaluable follow-up. 25% of thi experience should be completed by 3.5 years, 50% will be completed by 5 years and 75% will be completed by 6.5 years. Interim and final analyses of time to durable remission will be conducted usin O'Brian-Fleming boundaries (26), at the p=0.00004, 0.004, 0.02, and 0.041 levels of significance, respectively. This will ensure an overall experiment-wise
level of 0.05.

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4-15-93

Principal Investigator_____

A RANDOMIZED CLINICAL TRIAL OF THYMECTOMY FOR THE TREATMENT OF MYASTHENIA GRAVIS

MANUAL MUSCLE STRENGTH SCORING FORM

Center/Patient #_____ Patient Initials _____

Date of Visit___/___/___

Position 1: Sitting	Right	Left
Shoulder abduction (< 15° from horizontal)	____	____
Elbow flexion	____	____
Wrist flexion	____	____
Wrist extension	____	____
Thumb abduction	____	____

	Right	Left
Knee extension (may be 10° below horizontal	____	____
Ankle dorsiflexion	____	____
Ankle eversion	____	____
Ankle inversion	____	____
Hip flexion (> 30° from horizontal)	____	____

Position 2: Prone	Right	Left
Neck extension	____	____
Ankle plantar flexion	____	____

	Right	Left
Knee flexion	____	____
Hip extension	____	____

Position 3: Side lying	Right	Left
Hip abduction	____	____

Position 4: Supine	Right	Left
Elbow extension	____	____
Neck flexion	____	____

Facial Strength	Right	Left
(eyelid closure)	____	____

Handgrip dynamometry (kg):

RIGHT	____	____	____
LEFT	____	____	____

Forced vital capacity (liters): _____ _____ _____

Appendix A

Principal Investigator _____

A RANDOMIZED CLINICAL TRIAL OF THYMECTOMY FOR THE TREATMENT OF MYASTHENIA GRAVIS
QUANTITATIVE FUNCTIONAL SCORING SYSTEM

Center/Patient # _____ Patient Initials _____

Date of Visit ____/____/____

TEST ITEMS WEAKNESS	*NONE*	*MILD*	*MODERATE*	*SEVERE*	*PATIENT SCORE*
Grade	**0**	**1**	**2**	**3**	
Double vision (lateral gaze) Sec.	>60	>10-60	>1-10	Spontaneous Heterotropia	
Ptosis (upward gaze) Sec.	>60	>10-60	>1-10	Spontaneous	
Head, lifted (45°, supine) Sec.	>120	>30-120	>0-30	0	
Right arm outstretched (90° standing) Sec.	>240	>90-240	>10-90	≥10	
Speech following counting aloud from 1-100 (onset of dysarthria)	>100	>75-100	>15-74	<25	
Right leg outstretched (45°, supine) Sec.	>100	>30-100	>0-30	0	
Vital capacity (l) male female	 >3.5 >2.5	 >2.5-3.5 >1.8-2.5	 >1.5-2.5 >1.2-1.8	 <1.5 <1.2	
Dominant hand grip (KgW) male female	 >45 >31	 >15-45 >10-30	 5-15 5-10	 <5 <5	

TOTAL SCORE _____

Appendix B

Principal Investigator_____

A RANDOMIZED CLINICAL TRIAL OF THYMECTOMY FOR THE TREATMENT OF MYASTHENIA GRAVIS

MYASTHENIA GRAVIS QUANTITATIVE ADL SCORING SYSTEM

Center/Patient #_____ Patient Initials _____

Date of Visit___/___/___

GRADE	*0*	*1*	*2*	*3*	*PATIENT SCORE*
Chewing	Normal	Fatigue with solid foods	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Mild shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
Impairment of ability to brush teeth or comb hair	None	Mild	Moderate	Severe	
Impairment of ability to arise from a chair	None	Mild	Moderate, must use arms	Severe, require assistance	
Impairment of ability to see due to double vision	None	Mild	Moderate	Severe	
TOTAL SCORE					

CONTROLLED STUDY OF THYMECTOMY IN MYASTHENIA GRAVIS
MG PATIENT PROGRESS

1. On the medications you are taking (if any), do you feel that your myasthenia gravis is currently in remission? _____Yes _____No

2. If you are not in remission, do you feel your symptoms have improved since your last evaluation? _____Yes _____No

Appendix C

Principal Investigator_____

A RANDOMIZED CLINICAL TRIAL OF THYMECTOMY FOR THE TREATMENT OF MYASTHENIA GRAVIS

CLINICAL/LABORATORY DATA SHEET

Center/Patient#_____ Patient Initials_____

Date of Visit___/___/___

Results of tensilon test and date performed _____

Results and date of rep stim (Include recording sites)_____

Results and date of single fiber (Include muscles tested)_____

Results and date obtained Acetylcholine Receptor AB assay _____

Results and date of chest CT _____

Results and date of anti-striated muscle antibody levels _____

Patients MG Classification:

Most severe grade _____ Date _____
Grade at onset of symptoms _____ Date _____
Grade at most recent eval _____ Date _____

Treatment of MG (briefly state what Rx patient has had and what current meds are)

_____

_____

_____

_____

Appendix D1

Principal Investigator _____

A RANDOMIZED CLINICAL TRIAL OF THYMECTOMY FOR THE TREATMENT OF MYASTHENIA GRAVIS

CLINICAL/LABORATORY DATA SHEET

Center/Patient # _____ Patient Initials _____

Date of Visit ___/___/___

DEMOGRAPHIC DATA AND HISTORY

Date of Birth ___/___/___ Age (years) _____
Ethnic Original: __Caucasian __Black __Hispanic __Oriental _____Other

	MONTH	YEAR
Estimated onset of symptoms	_____	_____
Date of diagnosis	_____	_____

Initial symptoms _____

_____

Past medical history: __Yes __No If yes, list below:

1. _____ 2. _____

3. _____ 4. _____

Past surgical history: __Yes __No If yes, list below:

1. _____ 2. _____

3. _____ 4. _____

Allergies: __Yes __No If yes, list below:

1. _____ 2. _____

3. _____ 4. _____

Medications:

1. _____ 2. _____

3. _____ 4. _____

Appendix D2

Principal Investigator_____

A RANDOMIZED CLINICAL TRIAL OF THYMECTOMY FOR THE TREATMENT OF MYASTHENIA GRAVIS

BLINDED INVESTIGATOR'S PROGRESS ASSESSMENT

Center/Patient #_____ Patient Initials _____

Date of Visit___/___/___

---

1. Patient's current MG classification:

Grade 1 ___	Grade Oa ___
Grade 2 ___	Grade Ob ___
Grade 2B ___	Grade Oc ___
Grade 3 ___	Grade Oa*___
Grade 3B ___	Grade Ob*___
Grade 4 ___	Grade Oc*___
Grade 4B ___	

2. MG quantitative functional score _____ (0-24)

3. MG quantitative ADL score _____ (0-18)

4. Average muscle score _____
(To be calculated by statistical center)

5. Medications patient is currently taking for myasthenia gravis. (Please give doses.)

Mestinon_____ Cyclosporine_____

Prednisone_____ IVIG_____

Imuran_____ Other_____

Methotrexate_____

Cyclophosphamide_____

Appendix E

Principal Investigator_____

A RANDOMIZED CLINICAL TRIAL OF THYMECTOMY FOR THE TREATMENT OF MYASTHENIA GRAVIS

RELAPSE FORM

Center/Patient #_____ Patient Initials _____

Date of Visit___/___/___

---

1. Current MG classification:

2. Previous MG classification:

3. Current MG medication dosages:

Mestinon_____	Cyclophosphamide_____
Prednisone_____	Cyclosporine_____
Imuran_____	IVIG_____
Methotrexate_____	Other_____

4. Previous MG medication dosages:

Mestinon_____	Cyclophosphamide_____
Prednisone_____	Cyclosporine_____
Imuran_____	IVIG_____
Methotrexate_____	Other_____

Appendix F

TABLE 1

CLINICAL CLASSIFICATION FOR GRADING MG SEVERITY

Grade 0 (remission): No symptoms or signs of disease. Patients in clinical remission can include the following groups.

Grade 0a: No objective cranial nerve or extremity weakness. Off all medications.

Grade 0b: No objective cranial nerve or extremity weakness. Remains on Mestinon.

Grade 0c: No objective cranial nerve or extremity weakness. Remains on immunosuppressive drugs.

Grade 0a+, 0b+, 0c+: Any of the above 0 stages, but the patient may still have slight orbicularis oculi or hip flexor weakness (grade 4+ or 5-), despite the absence of any subjective symptoms of ocular/bulbar or extremity weakness.

Grade 1: Ocular involvement alone (ptosis, diplopia, orbicularis oculi weakness in the absence of other bulbar, neck or limb weakness is allowable in this group).

Grade 2: Mild generalized MG; normal activities of daily living are preserved with only mild symptoms of weakness or fatiguability. Symptoms are mild enough so that they can be managed with Mestinon therapy alone (no immunosuppressive drugs needed). Includes ocular patients with evidence of limb/neck weakness on exam (but no subjective extremity weakness).

Grade 2B: Mild restricted MG; restricted to bulbar involvement without subjective limb weakness (may have subjective/objective neck weakness; the only allowable objective limb weakness would be of the hip flexors, which can be no worse than grade 4; may also have ocular involvement). Symptoms controlled with Mestinon alone; immunosuppressive therapy not required.

Grade 3: Moderate generalized MG; normal activities of daily living are interrupted because of weakness and fatigue to the extent that symptoms require initiation of treatment with immunosuppressive therapy.

Grade 3B: Moderate restricted MG; restricted to bulbar and/or respiratory (diaphragmatic) involvement without subjective limb weakness (may have subjective/objective neck weakness; the only allowable objective limb weakness would be of the hip flexors, which can be no worse than grade 4; may also have ocular involvement); no respiratory failure or inability to swallow requiring mechanical ventilation or feeding. Immunosuppressive therapy is required for treatment.

Grade 4: Severe generalized MG; profound weakness in the extremities requiring confinement to bed and hospitalization; associated with respiratory failure requiring mechanical ventilation or bulbar weakness requiring mechanical feeding (nasogastric or gastric tubes).

Grade 4B: Severe restricted MG; restricted to bulbar and/or respiratory muscles with no subjective limb weakness (may have subjective/objective neck weakness; the only allowable objective limb weakness would be of the hip flexors, which can be no worse than grade 4; may also have ocular involvement); requires mechanical feeding (nasogastric or gastric tubes) or mechanical ventilation.

Methotrexate Use in Generalized Autoimmune Myasthenia Gravis: A Case Series

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ABSTRACT

Methotrexate (MTX) is an inexpensive and well-tolerated immunosuppressive medication that is used anecdotally in autoimmune myasthenia gravis (MG). However, the efficacy in MG is unclear at this time. This retrospective analysis describes six patients with acetylcholine receptor antibody-positive MG who were treated with MTX and corticosteroids. The efficacy of MTX was measured by steroid-sparing effect and the Myasthenia Gravis Foundation of America (MGFA) classification. MTX initiation was associated with a reduction in prednisone dosage in all patients. Minimal manifestation status was reached at an average duration of 10 months in 5 patients. No patients were hospitalized for myasthenia gravis exacerbations. There were no major side effects experienced with MTX use. This retrospective analysis suggests that MTX is safe and probably efficacious as a corticosteroid-sparing agent in the management of MG.

Keywords: *Myasthenia gravis, Methotrexate, Immunosuppression, Corticosteroid, Acetylcholine receptor antibody*

Introduction

Autoimmune myasthenia gravis (MG) is a disorder of neuromuscular junction transmission characterized by T-cell mediated destruction of the post-synaptic membrane acetylcholine receptor. Treatment often necessitates the use of immunosuppressant medications including corticosteroids and corticosteroid-sparing agents.[1] Azathioprine (AZA) and mycophenolate are the two most common medications used in the United States for this purpose and are considered first-line corticosteroid-sparing agents.[2-3] Choices after these two medications are unclear and may include eculizumab, cyclosporine, tacrolimus, or methotrexate (MTX). MTX has been used for over 50 years in various clinical indications with anecdotal evidence of positive efficacy in MG. However, studies on its efficacy in MG have generated conflicting results.[4-6] The objective of this study is to describe our experience of using MTX in a small group of patients with generalized MG.

Methods

This retrospective analysis includes six patients with acetylcholine receptor (AChR) antibody-positive MG who were treated with oral MTX and prednisone at the Cleveland Clinic Neuromuscular Center between May 2006 and July 2020. Patients were selected from the myasthenia gravis database curated at the Cleveland Clinic Neuromuscular Center. Outcomes assessed included daily prednisone dosage, MTX dosage, Myasthenia Gravis Foundation of America (MGFA) classification[7] at 6-month intervals, intravenous immune globulin (IVIG) or plasmapheresis usage, hospitalizations for MG exacerbation or crisis, earliest time to reach minimal manifestation status, and earliest time to cessation of prednisone. MTX dosing and any side effects documented are recorded. The study was approved by our institutional review board.

Results

Six MG patients, four females and two males, were included (Table 1). All patients were positive for AChR antibodies. The average age of onset of MG was 57 years (range: 32 to 87 years). In three patients, MTX was started following an average disease duration of 7 years (range: 2 to 16 years). In two patients, MTX was started at the time of MG diagnosis. In the remaining patient, MTX was started for rheumatoid arthritis and was continued after MG diagnosis was made 7 years later. Two patients underwent thymectomy. Four patients received prior immunosuppression (prednisone, tacrolimus, azathioprine, mycophenolate, and cyclosporine). Coexisting autoimmune conditions were present prior to MG diagnosis in four patients (systemic lupus erythematosus, rheumatoid arthritis, psoriasis). The average duration of follow-up was 65 months from MTX initiation. Four patients were on MTX for coexisting autoimmune conditions (Table 1).

Minimal manifestation status (MMS) was achieved in five patients. The time from MTX initiation to reach minimal manifestation status was 9.6 months (range: 1-26 months). The remaining patient was classified as MGFA 2b throughout the study. One patient was given monthly IVIG concurrently with the first three months of MTX use. Following MTX initiation, no hospitalizations for MG exacerbation occurred in any patient. A mild exacerbation occurred in one patient that required a brief reintroduction of prednisone from months 19-24 at 10mg with successful taper to 2.5 mg daily over the subsequent 2 years. In four patients, prednisone was discontinued with the average

Table 1. Demographics and immunosuppressant usage

Patient	Sex	MG Onset age (years)	MGFA Classification at initiation of MTX	Prednisone dose (mg/d) at initiation of MTX	Maximal MTX dose (mg)	Final MTX dose (mg)	Thymectomy	Immunosuppressant usage prior to MTX	Coexisting autoimmune conditions
1	F	32	IIb	7	22.5	20	Yes	P, C	SLE
2	F	44	IIb	0	25	25	No	T, A, MM, P	None
3	M	67	I	20	20	20	Yes	MM, A, C	RA
4	M	87	IIa	40	15	15	No	None	Psoriasis
5	F	51	IIa	20	12.5	12.5	No	None	RA, Celiac
6	F	72	I	30	19	10	No	A, MM	None

Abbreviations: A, azathioprine; C, cyclosporine; F, female; M, male; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MM, mycophenolate mofetil; MTX, methotrexate; P, prednisone; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T, tacrolimus

time to cessation being 10.8 months (range 9-12 months). In one patient, prednisone daily dosage was less than 7.5 mg throughout the study and the remaining patient was placed on MTX monotherapy. The prednisone daily dosage was <7.5mg by month 7 following MTX initiation in all patients (Figure 1). The average MTX dose at the final visit was 17mg weekly (range 10-25mg). All patients tolerated MTX well and the only side effects noted in two patients included mild transaminitis and diarrhea, without the need of adjusting MTX dosage.

Discussion

In this small retrospective study, the efficacy and corticosteroid sparing effects of MTX were noted without significant side effects. The prednisone daily dosage was <7.5mg by month 7 following MTX initiation in all patients, representing an efficient dosage reduction. In a similar fashion, minimal manifestation status was achieved in 9.6 months in 5 of 6 patients which is a major clinical milestone to attain. Four patients were on MTX for other autoimmune conditions prior to their MG diagnosis, representing a clinical situation that is not uncommon. Furthermore, patients did not require hospitalization or rescue IVIG/plasmapheresis despite having a typical MG severity prior to treatment. Our experience indicates that MTX can likely be continued together with low dose prednisone or as monotherapy with good control of MG symptoms.

The use of MTX in the treatment of MG was initially reported in 1969,[8] but is now regaining interest with positive anecdotal evidence. Our findings are consistent with several

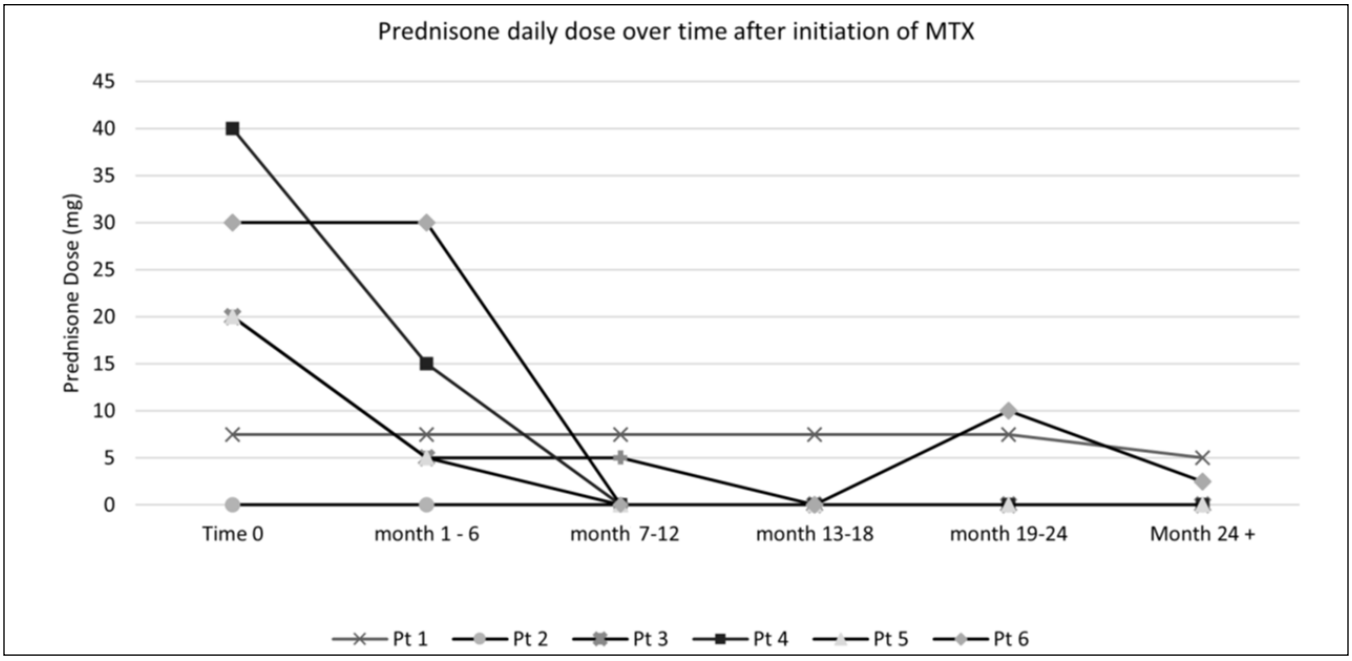

Figure 1. Change of prednisone daily dose over time following MTX initiation

small studies. For example, Karaahmet *et al.* described improvement in 3 patients with MG and rheumatoid arthritis after MTX treatment.[4] In a larger single-blinded trial, Heckmann *et al.* randomized 24 generalized MG patients to receive azathioprine or MTX in addition to prednisone for 24 months.[5] This included predominantly newly-diagnosed patients with MGFA class II-V (86% MGFA III-V) disease. The average prednisone dosage was reduced by more than 50% in both groups with no significant difference in the frequency of relapse and remission. This study suggested MTX and AZA are similarly effective in the treatment of generalized MG.

Pasnoor *et al.* completed a randomized, placebo-controlled trial of 50 generalized MG patients who were on stable doses of prednisone with a median dose of 20mg per day.[6] In contrast to the study by Heckmann *et al.*,[5] they found that the addition of MTX for 12 months versus placebo resulted in no difference in the average daily prednisone dose between the two groups from months 4 to 12. However, the study may have been limited by the inclusion of patients with mild severity (MGFA II and III) and a short study duration.

The major limitations of this single center case series primarily relates to the small sample size and retrospective design. The lack of any prospective data collection or control group limits the generalizability of our conclusions. Nevertheless, our data seem to support that MTX can be used in special situations as a corticosteroid sparing agent in the management of MG, especially for those who have coexisting rheumatological conditions. Future controlled prospective studies would help clarify whether MTX can serve as an effective steroid-sparing agent by employing a larger study group over longer study period.

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Practice Patterns in the Management of Myasthenia Gravis: A Cross-Sectional Survey of Neurologists in the United States

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ABSTRACT

Background: Management of myasthenia gravis (MG), a rare immunoglobulin G autoantibody–mediated neuromuscular junction disorder, is driven by physician experience. To gain insight into current practices and physician needs, neurologists' use of guidelines and disease activity evaluations to manage MG was assessed.

Methods: In November and December of 2020, a quantitative, cross-sectional, 51-item, online survey–based study was used to collect data from 100 community neurologists, from 31 US states, who treat MG. Differences across ratio variables were analyzed via Chi-square and *t* tests, at a significance level of $P<0.05$.

Results: Of respondents, 76% reported using clinical judgment rather than guidelines to inform treatment decisions, and only 29% reported awareness of the updated 2020 International Consensus Guidance for Management of Myasthenia Gravis. Treatment patterns reported include use of prednisone-equivalent corticosteroid doses ≤10 mg/day for ≥6 months (76% of respondents). When corticosteroids are contraindicated or after failure of an initial nonsteroidal immunosuppressant therapy (NSIST), immunoglobulin therapy is the respondents' preferred initial treatment in patients with acetylcholine receptor antibody–positive generalized MG (vs a second NSIST). Respondents expressed interest in more guidance on crisis management, initiating/titrating maintenance medications, and managing patients with comorbidities.

Conclusions: Respondents to this survey reported varied approaches to MG management and, in some clinical settings, heavier reliance on clinical judgment than on available consensus-based guidance. Also observed was potential underutilization of NSISTs in patients for whom corticosteroids are contraindicated, with reliance, instead, on immunoglobulin.

Keywords: *cross-sectional survey, myasthenia gravis, clinical practice guideline, clinical practice patterns, disease management*

Introduction

Myasthenia gravis (MG) is a rare acquired autoimmune disease, characterized by fluctuating muscle weakness (1, 2) frequently affecting facial, bulbar, neck, respiratory, and limb muscles (2). MG results from abnormal binding of pathogenic autoantibodies to components of the neuromuscular junction (NMJ), disrupting normal neuromuscular transmission and leading to variable muscle weakness that typically worsens with exertion (1). MG pathophysiology is primarily centered on acetylcholine receptors (AChRs). Up to 85% of patients with generalized MG (gMG) have immunoglobulin G (IgG) autoantibodies (3), which have a direct effect on skeletal AChRs, inducing muscle weakness (1). A small proportion of patients have MG involving antibodies to muscle-specific tyrosine kinase (MuSK) or lipoprotein receptor–related protein 4 (LRP4) (1). MG is the most common acquired NMJ disorder, according to data published from 1990 to 2014, with an annual international prevalence ranging from 5.35 to 35 per 100,000 persons and an annual international incidence ranging from 0.3 to 2.8 per 100,000 persons (1, 4).

There are broadly accepted therapies for MG, although often with low levels of evidence to support their use (5) and, until recently, there were no international recommendations to guide care for MG. As treatment options continued to expand, improved strategies for managing this heterogeneous disease became necessary (6). Accordingly, a 15-member international task force was convened in 2013 by the Myasthenia Gravis Foundation of America (MGFA) to address this unmet need. The task force published its International Consensus Guidance for Management of Myasthenia Gravis in 2016 (7), covering symptomatic and immunosuppressive treatment, therapeutic plasma exchange (TPE) and intravenous

immunoglobulin (IVIg), management of myasthenic crisis, thymectomy, juvenile MG, MuSK MG, and MG in pregnancy (7). The panel was reconvened in 2019, adding a new member representing South America, to review and update the 2016 recommendations and guidance. The revised International Consensus Guidance was published in November 2020, with new recommendations for use of rituximab, eculizumab, and methotrexate; management of immune checkpoint inhibitor (ICI)–induced MG; and early immunosuppression in ocular MG (8).

Management of MG focuses on reducing symptoms with an acetylcholinesterase inhibitor (AChEi) or modulating the immune system (9). Pyridostigmine is the preferred first-line AChEi for MG (2). In early or mild MG, pyridostigmine can provide rapid and substantial improvement in muscle strength; however, treatment-related adverse effects (AEs) are common and therapeutic benefit is often limited (2). Most patients with MG will require immunomodulatory treatment to achieve treatment goals and restore physical activity (1, 2). Oral corticosteroids are the primary immunomodulatory therapy for maintenance management of MG (2). Clinical benefit is relatively fast, with most patients experiencing improvement within weeks (10). At high doses or with long-term use, however, corticosteroids can cause significant AEs, including steroid-induced diabetes, hypertension, cataracts, glaucoma, and neuropsychiatric disturbances (9, 10).

Azathioprine is a nonsteroidal immunosuppressive therapy (NSIST) for MG, with a relatively long latency to clinical effectiveness, estimated as 6 to 18 months (10). Use of an NSIST in gMG can increase risk for serious infection and slightly increases incidence of some cancers, including squamous cell carcinoma and lymphoma (9). TPE and IVIg are rapid and effective immunomodulating treatments often used for acute myasthenic exacerbation or crisis; however, treatment effect is not durable beyond a matter of weeks (10) and this option is not available to some patients because of treatment cost or lack of necessary equipment. New and emerging classes of pharmacologic agents being used in MG target B cells, T cells, complement, and the neonatal FC receptor (9). There is hope that newer therapies will better address unmet needs in the management of MG.

While often effective, older immunosuppressive therapies can require trials of up to 12 months to determine efficacy. The increase in therapeutic options, particularly progress in targeted immunotherapies, holds promise for safer, faster, and more sustained benefit in patients with MG (11) and for patients whose disease is refractory to or who are intolerant of standard therapies (12, 13). However, randomized clinical trial data that guide MG management remain limited and often cannot be applied across the various subpopulations of MG because of restrictive trial entry criteria. Consensus-driven treatment recommendations that are updated to reflect therapeutic advances are helpful in this environment, but their dissemination and adoption among MG health care providers has not been studied.

This quantitative cross-sectional online survey was designed to gain a better understanding of US community neurologists' standard treatment practices in MG and the extent of formal treatment guidance utilization. We assessed how community neurologists use available treatment guidance and survey instruments to measure disease activity to manage patients with MG. We also investigated whether the 2020 International Consensus Guidance had yet impacted clinical practice, examined potential barriers preventing its use, and explored areas where additional, targeted, education may be indicated.

Materials and Methods

The study was quantitative and utilized a cross-sectional design to collect survey-based data from community neurologists in the United States. The 10-minute online survey was constructed to investigate patient assessment methods, as well as treatment decision-making, among neurologists who manage patients with MG. All survey questions were developed by and finalized via discussion-based input from all authors. Prior to online study launch, pilot testing of 2 community neurologists was used to validate appropriate wording of questions, comprehensiveness of response sets, and inclusion of clinically salient topics/questions. The pilot test participants self-administered the online survey while concurrently participating in a telephone interview with the study project lead. Responses from pilot testing were not included in final survey data analyses.

The 51-item, self-administered questionnaire (**Appendix A**) was designed to elicit information from practicing community neurologists on a variety of MG-related topics, including familiarity with and usage of the International Consensus Guidance for clinical decision-making; treatment goals (full treatment goal definitions are in **Appendix B**); clinical features and evaluations or measures commonly used to diagnose, track patient progress, or guide clinical decisions; typical induction and maintenance corticosteroid dosages; outcome measures used to determine response to therapy; and physician approaches to patient education, especially regarding thymectomy and expectations for treatment.

The quantitative survey data were collected between November 19, 2020, and December 3, 2020. A multifaceted approach to ensure the quality of data and collection

Table 1. Demographic information for online survey respondents (community neurologists)

Respondent characteristics	N=100
Number of patients with MG treated per year	
Mean (SD)	66 (104.6)
Median	28
Range	3-500[a]
Primary practice setting, %	
Not university affiliated	51
University affiliated	49
Board certifications (may be ≥1 per respondent), %	
Neurology	89
Electrodiagnostic medicine	37
Neuromuscular medicine	37
Pediatric neurology	11
Primary practice type, %	
Solo	17
Single-specialty partnership or group (≥2 physicians)	28
Multi-specialty partnership or group (≥2 physicians)	55
Number of years since residency/training	
Mean (SD)	16 (9.9)
Median	15
Range	3-59

Abbreviations: MG, myasthenia gravis; SD, standard deviation.
[a] Of respondents, 1 reported seeing 300 patients; 3 reported seeing 400 patients; 1 reported seeing 450 patients; and 2 reported seeing 500 patients.

methods was used. A random sample of 1300 confirmed community neurologists were recruited from e-Rewards, a Dynata, LLC (Shelton, Connecticut) subsidiary performing health care market research; panel members who met eligibility criteria and completed the survey were compensated for their time and opinions. Prospective US-based survey respondents were already members of the Dynata physician panel, having completed the registration and enrollment process, including provision of medical education number to confirm physician status. Dynata monitors its panel pool to ensure members do not claim different specialties for different surveys and that only members of the targeted specialty are included in the email invitations, which also minimizes screen failures. Second-level verification for potential fraudulent responders was accomplished via checks for duplicate participants, using variables such as IP address, matching across demographic data points, and checks of device-related data via third-party digital fingerprint technology.

Qualifications for survey participation included specialization in neurology, having been in practice for at least 2 years since residency completion, treating or consulting on at least 2 patients with MG per year, and practicing in the United States (physicians practicing in the state of Vermont were excluded due to legal restrictions regarding online survey participation). The email invitation provided a general description of the survey topic (ie, "neurology patient management") and a link to the online survey. To prevent respondents from taking the survey more than once, each email invitation was linked to a unique identifier. Survey respondents remained anonymous to the study sponsor and the authors of this manuscript. No patient data were obtained and no questions were asked of physician respondents that would allow identification of any patients. For these reasons, this study was exempt from institutional review board (IRB) approval under United States Code of Federal Regulations Title 45 Part 46.101(b)(2); the study received a formal letter of exemption from the Copernicus Group IRB (Cary, North Carolina).

Data quality was monitored using a variety of strategies. Final data were reviewed to ensure that answers were given consideration and were not simply randomly generated responses. Logic checks, which were built into the survey script, were used to monitor and detect responses that were potentially illogical or inconsistent. Participants (n=2) whose data indicated overuse of non-responses (ie, "NA") were removed from the sample before final analysis, as was 1 participant who completed all responses in less than 30% of the median duration to complete the survey. Each respondent's route through the survey was checked to

ensure the respondent did not bypass any significant section. Descriptive statistics were performed using Chi-square and *t* tests to evaluate differences across ratio variables, including board certification subgroup, practice setting, and years in practice. Statistical significance was assessed at the alpha level of $P<0.05$. Descriptive analyses were performed using SPSS Statistics 26.0 (IBM; Armonk, New York), and data analysis was performed by study author PN.

Results

Demographics for the 100 community neurologists who satisfied selection criteria and successfully completed the survey are described in **Table 1**. Thirty-one of the 50 US states were represented in the survey sample (**Figure 1**). Of respondents, 51% are affiliated with a university. The majority (89%) are board certified (BC) in neurology, 37% in electrodiagnostic medicine/clinical neurophysiology, 37% in neuromuscular medicine (NM), and 11% in pediatric neurology. University-affiliated neurologists were significantly more likely to report being BC in other domains, particularly in NM. The greatest differences in practice patterns were observed between neurologists who are board certified in neuromuscular medicine (NMBC) and neurologists who are non-NMBC. Importantly, there was a large difference between these 2 groups in reported awareness of the 2020 International Consensus Guidance: only 19% of the 63 non-NMBC respondents were aware of the newly released International Consensus Guidance vs almost half (46%) of the 37 NMBC respondents.

Overall, most respondents (76%) reported using clinical judgment rather than treatment guidelines to make MG treatment decisions (**Figure 2A**). Decision-making processes were most often reported as guided by assessments of patient strength, activities of daily living (ADLs), and tolerance of treatment rather than by any single recommended goal, such as the 2016 International Consensus Guidance treatment goal of minimal manifestation status (MMS). Only 44% of respondents reported using MMS. The majority (64%) of respondents reported not using any specific guideline for MG treatment decisions.

Of respondents who did report use of a guideline to manage treatment (n=36; **Figure 3A**), more than half reported using "American Academy of Neurology" (AAN); others reported "MGFA guidelines" or "other." Respondents were asked to select any clinical treatment guidelines they use for clinical management of patients with MG; those data, as well as verbatim responses for "other" clinical tools, are in **Figure 3B**.

In response to a survey question inquiring whether they would offer thymectomy to patients with purely ocular MG, 68% of NMBC neurologists replied affirmatively compared to 43% of non-NMBC neurologists. For patients with gMG with a positive AChR antibody status, 95% of both NMBC and non-NMBC neurologists indicated that they would offer thymectomy. In contrast, only 62% of NMBC neurologists would offer thymectomy to patients with a positive MuSK antibody status, compared to 78% of non-NMBC neurologists.

The diagnostic tests reported as most frequently used by all survey respondents (both NMBC and non-NMBC) to confirm diagnosis of MG were AChR antibody panel (87%), MuSK antibodies (77%), and repetitive nerve stimulation (RNS; 75%). Single-fiber electromyography (SFEMG) was reported by 46% and AChEi challenge and LRP4 antibody by 37%; however, LRP4 antibodies are also used in some cases to support diagnosis. Other diagnostic tests included ice pack, which was reported as being used by 31%, and "other," by 1%. In seronegative patients, respondents said they confirm MG by RNS (78%), SFEMG (63%), AChEi challenge (45%), and "other" (3%). Approximately a third (31%) of all respondents reported monitoring autoantibody levels to evaluate response to therapy. Those reporting use of autoantibody levels to assess treatment response did not differ by practice setting or BC status. Of respondents who reported using autoantibody testing, the type utilized most often is AChR serologies. Further measures used to track MG disease status are summarized in **Figure 2B**.

The majority (74%) of respondents reported targeting a prednisone-equivalent corticosteroid dose ≤10 mg/day for chronic use (≥6-month periods); however, when asked the percentage of patients with gMG in whom the respondents avoided corticosteroids, the mean percentage was 27% for

Figure 1. Number of Survey Respondents, by State
Map of the United States, with number of survey respondents from each state listed as n value. The survey email invitation provided only a general description of the survey topic (i.e., "Neurology Patient Management") and a link to access the online survey. N=100.

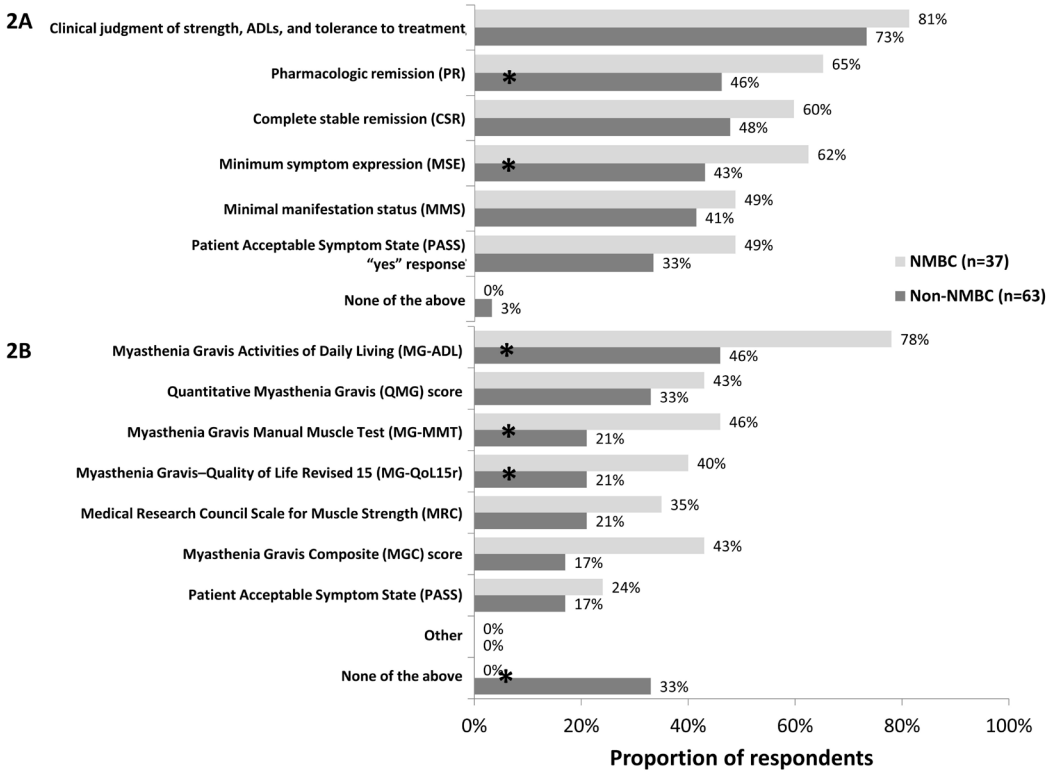

Figure 2. Goals and Assessment Measures Used for MG Treatment Decisions
Abbreviations: ADL, activity of daily living; gMG, generalized myasthenia gravis; MG, myasthenia gravis; NMBC, neuromuscular medicine board certified.
This survey focused on gMG unless otherwise specified. Data allowed selection of more than 1 measure where applicable, so percentages sum >100%.
Survey question 2A: "Which disease-specific measures do you use routinely in your clinic to track MG status?"; 2B: "Which of the following treatment goal(s) do you use to guide MG treatment decisions?". (N=100).
* Indicates difference was statistically significant ($P<0.05$).

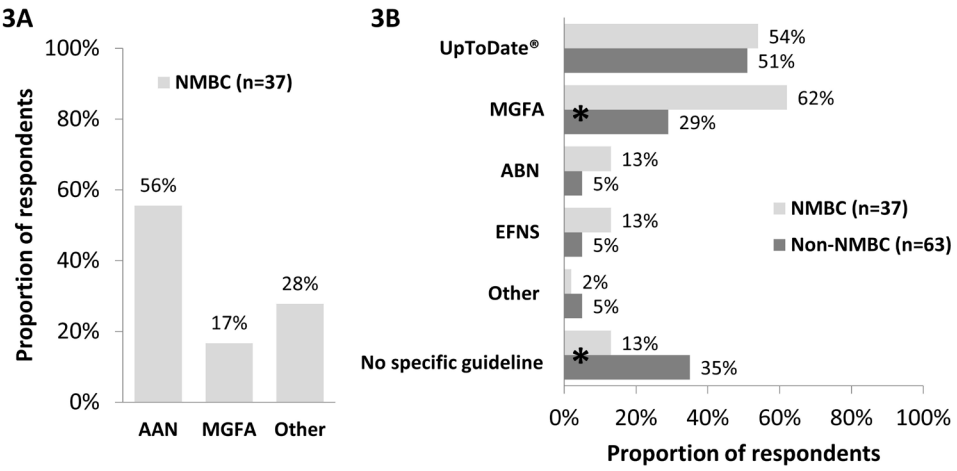

Figure 3. Use of Treatment Guidelines in MG Management
Abbreviations: AAN, American Academy of Neurology; ABN, Association of British Neurologists; EFNS, European Federation of the Neurological Societies; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; NMBC, neuromuscular medicine board certified.
Survey question 3A: "What specific guideline do you use for making treatment decisions for MG patients?" (open-ended question/unaided response; n=36); 3B: "Which of the following clinical treatment guidelines, if any, is the most useful to you in guiding your clinical management of MG patients? (Select all that apply)".
(N=100).
"Other" (verbatim open-text responses from participants) included UpToDate; clinical judgment; neuromuscular society guidelines; lab tests, Tensilon, and nerve stimulation; symptomatic and immunosuppressant; International Consensus Guidance (2016); closely watched pulmonary function tests; safety, need for thymectomy, and minimal immune suppression; weakening neurological system, activities of daily living (ADLs), and new onset of limitations.
* Indicates difference was statistically significant ($P<0.05$).

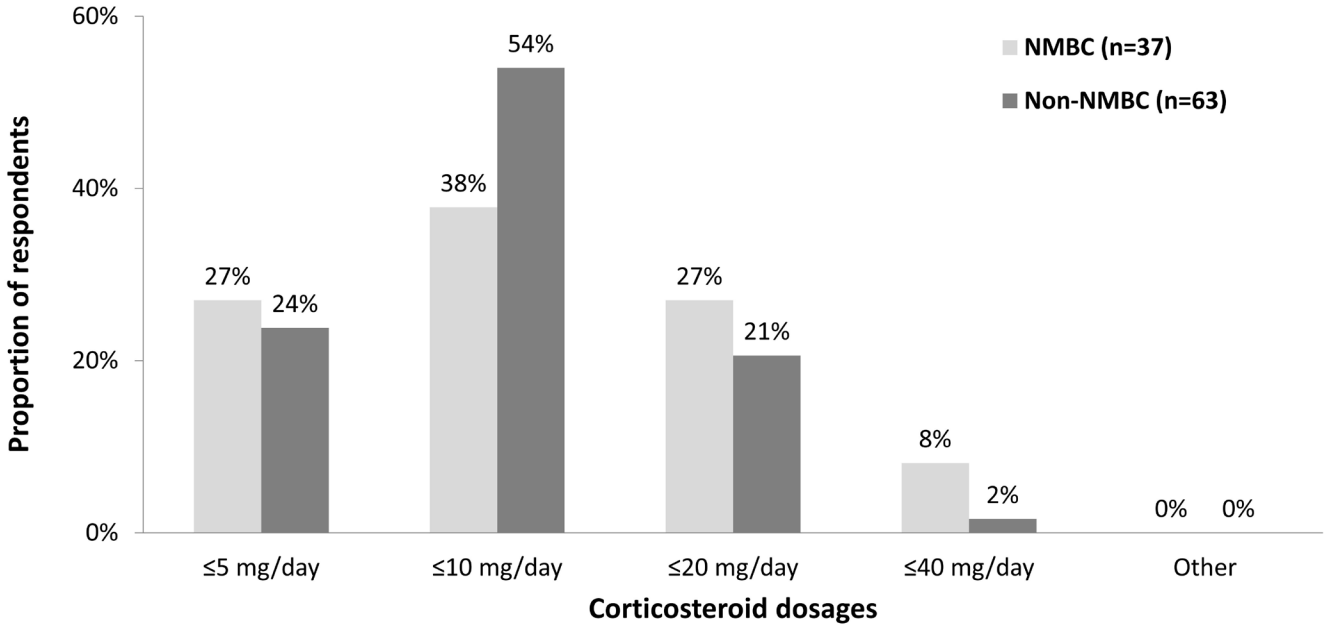

Figure 4: Corticosteroid Dosages Considered Safe
Abbreviations: gMG, generalized myasthenia gravis; NMBC, neuromuscular medicine board certified.
This survey focused on gMG unless otherwise specified.
Survey question: "What chronic, long-term (≥6 mo) prednisone-equivalent steroid dose do you consider safe (ie, to minimize adverse events for long-term use)?".
N=100.

both NMBC and non-NMBC clinicians. Overall, 23% of respondents said they consider a prednisone-equivalent dose ≤20 mg/day safe for ≥6 months' use, with only 4% reporting doses ≤40 mg/day safe for that duration (**Figure 4**). More NMBC than non-NMBC respondents endorsed higher corticosteroid dosages as safe. To track disease and therapeutic progress, more than 70% of respondents reported using change in Myasthenia Gravis Activities of Daily Living (MG-ADL) score to help decide when to adjust therapy in a patient with gMG: 30% reported using a 2-point change, 41%, a 3-point change. Another 29% reported not using MG-ADL scores for decisions regarding treatment adjustments.

For newly diagnosed patients seropositive for AChR antibodies for whom corticosteroids are contraindicated, responses revealed a preference for IVIg or subcutaneous immunoglobulin (SCIg) over slower-acting NSISTs as the initial treatment choice (**Figure 5A**). A similar preference was seen with respect to patients with AChR antibody–positive gMG after failure of a first NSIST: 42% of all respondents said they would use IVIg or SCIg next in such patients rather than another NSIST (**Figure 5B**). Eculizumab was the next most common treatment. It was selected by 32% of non-NMBC respondents and 18% of NMBC respondents, despite its high cost, for patients with AChR antibody–positive gMG in whom a first-choice NSIST had failed to control symptoms, followed by a second NSIST, rituximab, and TPE. **Figure 5C** illustrates the various therapeutic approaches used by respondents for newly diagnosed patients with AChR antibody–positive gMG contraindicated for corticosteroids.

Referral practices were also assessed. Statistically significantly more NMBC than non-NMBC respondents (70% vs 48%, respectively) reported receiving referrals for a second opinion on diagnosis or management of patients with MG. There was also a statistically significant between-group difference for making referrals, with only 11% of NMBC respondents vs 24% of non-NMBC respondents referring patients to other providers.

Finally, specific topics respondents said they would like to see targeted in MG treatment guidelines included acute MG crisis management (43%), followed by initiating/titrating maintenance medications in chronic MG (29%) and managing populations of special interest, including pregnancy, pediatric, and ICI-induced MG (23%). Another 20% wanted further information on how to treat pure ocular MG, define treatment goals, and track improvement using disease measures. In addition, respondents said they would like to see MG treatment guidelines address management of comorbidities such as diabetes; heart disease; lupus, thyroiditis, and other autoimmune diseases; renal disease; and osteoporosis, in descending order (**Figure 6**).

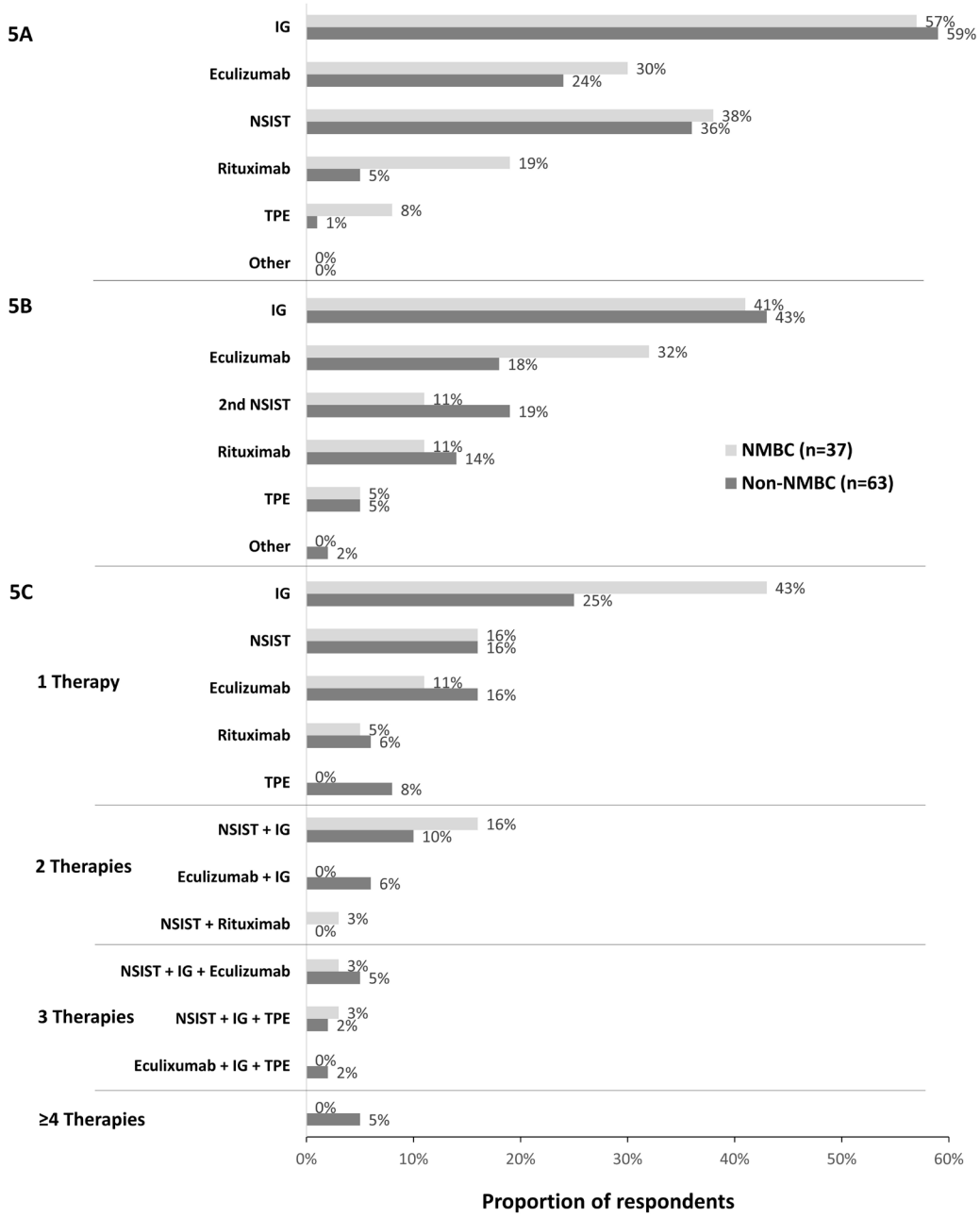

Figure 5. Initial, Second-Line, and Combinatorial Therapeutic Strategies for AChR Antibody–Positive Patients Contraindicated for Steroids

Abbreviations: AChR, acetylcholine receptor; gMG, generalized myasthenia gravis; IG, immunoglobulin (IVIg or SCIg); IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living; NMBC, neuromuscular medicine board certified; NSIST, nonsteroidal immunosuppressive therapy; SCIg, subcutaneous immunoglobulin; TPE, therapeutic plasma exchange.

Combination therapies were permitted (5C), so percentages may sum >100%.

Survey question 5A: "In newly diagnosed AChR$^+$ gMG patients contraindicated for steroids and with moderate functional impairment (MG-ADL >8; moderate severity), what initial therapeutic approach best describes your typical clinical practice?"; 5B: "If the first choice for nonsteroidal immunosuppressant therapy (NSIST) fails to control symptoms, what therapy do you go to next for AChR$^+$ patients with gMG?"; 5C: "In newly diagnosed AChR$^+$ gMG patients contraindicated for steroids and with moderate functional impairment (MG-ADL >8; moderate severity), what initial therapeutic approach best describes your typical clinical practice? (Select all agents initiated concurrently)".

(N=100).

* Indicates difference was statistically significant ($P<0.05$).

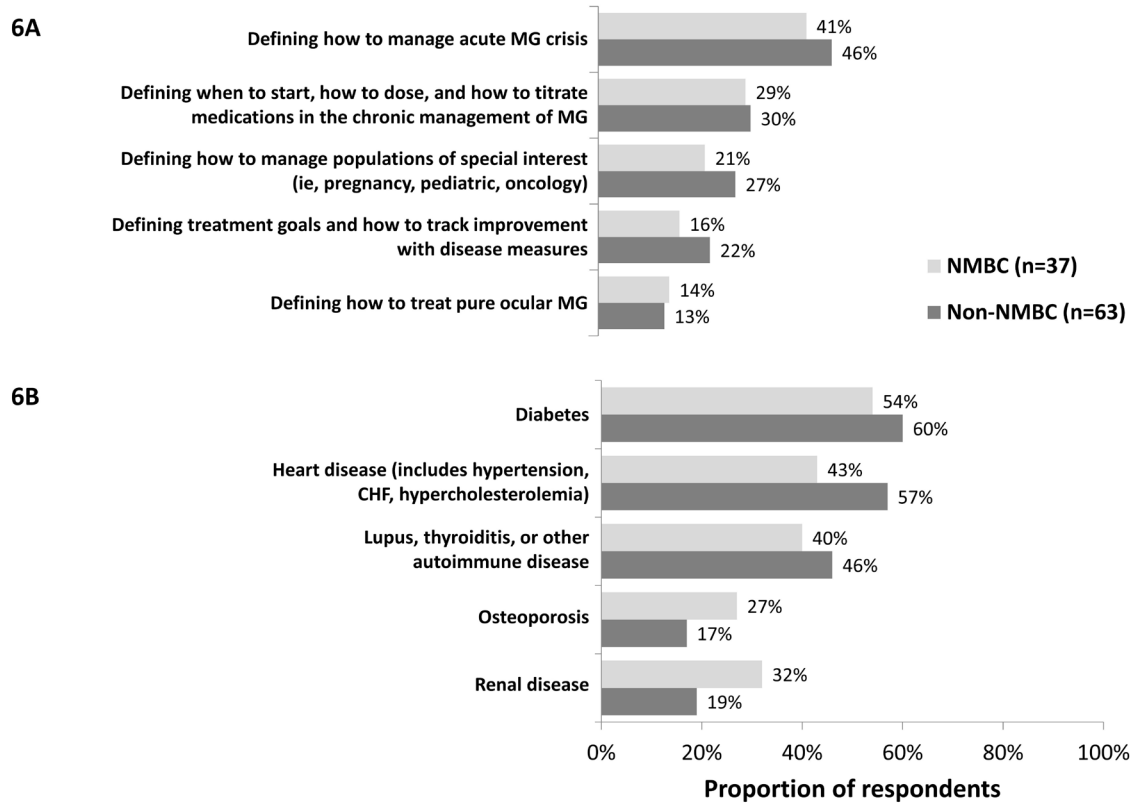

Figure 6. Topics and Comorbidities Chosen as Most Important in Management of MG
Abbreviations: CHF, congestive heart failure; MG, myasthenia gravis; NMBC, neuromuscular medicine board certified.
More than 1 topic could be rated "extremely important," so percentages sum >100%.
Survey question 6A: "Please rate the following topics in terms of their importance for inclusion in MG treatment guidelines" (5-point Likert scale: not important, minimum importance, important, very important, extremely important); 6B: "Of the comorbidities below, which would you like to see in upcoming guidelines to inform MG treatment decision-making? Please click to indicate the order of importance".
(N=100).

Discussion

The relatively low overall percentage of respondents who reported awareness of the 2020 International Consensus Guidance highlights a critical need both for educational outreach to enhance awareness and understanding of guideline recommendations and for their increased dissemination. Awareness was particularly low among non–university-affiliated neurologists, although this is potentially the group for whom the International Consensus Guidance would be most useful. Only 18% of non–university-affiliated neurologists said they were aware of the 2020 International Consensus Guidance vs 38% of neurologists who work in university-affiliated settings. It is likely that clinical neurologists working in small practices are faced with difficult treatment decisions but lack the benefit of colleagues who are highly experienced neurologists with whom to discuss challenging cases (14).

The majority of respondents reported not using a specific treatment guideline in making MG treatment decisions. Of the 36 respondents who did report use of guidelines, 56% reported using "AAN guidelines," although the AAN itself has not issued specific guidelines for the treatment of MG. The 2016 International Consensus Guidance was published in *Neurology*, the journal of the AAN, and can be accessed from the AAN website (15). Likewise, the MGFA website has a link to the International Consensus Guidance, which may have driven responses regarding use of "MGFA guidelines"(7).

Despite availability of links to the published consensus-based guidance recommendations on various neurology-associated websites, aspects of the International Consensus Guidance have not been widely implemented. The 2016 International Consensus Guidance recommended MMS as the goal for treatment of MG (7); however, less than half of the surveyed neurologists use MMS to guide MG treatment decisions. Thirty-seven percent of respondents reported routine use of the Quantitative Myasthenia Gravis (QMG) score to track MG clinically, although this measure requires a spirometer to assess percentage of vital capacity and a dynamometer to assess handgrip strength (17). It is possible that at least some of these respondents do not perform the entire assessment but do utilize some of the strength

assessments. Similarly, 30% of respondents reported routinely using Myasthenia Gravis-Manual Muscle Testing (MG-MMT), which is based on routine neurological examination and has the advantage of ease of use.

Managing corticosteroid therapy in MG has been reported as a substantial challenge for some physicians in primary and secondary care settings (2). This ongoing challenge may also indicate a gap in education on, and clinical confidence in, determining a dosage regimen that is high enough to provide clinical benefit but low enough to avoid serious AEs. The majority of neurologists surveyed stated they consider a prednisone-equivalent dose ≤10 mg/day safe for ≥6 months' use; only 4% endorsed doses up to 40 mg per day as safe. Similarly, rheumatology guidelines have defined prednisone-equivalent doses ≤5 mg/day as an acceptable maintenance dosage for most patients (16). Guidance on optimal pharmacologic management of MG, including initial and maintenance doses for the most commonly used therapeutics, was included in the supplementary materials of the 2016 International Consensus Guidance (7). The supplementary materials do not seem to have been as well disseminated as the primary document, based on the number of respondents who indicated a need for guidance on this topic.

Cost and availability often factor into clinical treatment decisions. Insurance coverage and formulary issues may have influenced neurologists' reported choices of tests and treatments. Because the range of treatment options for MG is broadening, it is likely that cost will become an even larger factor in treatment decisions (5). Survey results showed that current treatment decision-making often results in a higher cost burden for the patient and health care system: IVIg/SCIg was the most commonly reported second-line therapy for patients with AChR antibody–positive gMG after an NSIST failed to control their symptoms. Surprisingly, IVIg was also the initial therapy of choice, rather than an NSIST, of most respondents to treat newly diagnosed AChR antibody–positive gMG when corticosteroids are contraindicated. Eculizumab, despite its high cost, was the second-most common therapy chosen for such patients. Ease of use and rapidity of onset, compared to other corticosteroid-sparing agents, may be contributory factors to the high reported usage of IVIg and eculizumab.

The International Consensus Guidance recommends referral to a physician or center that specializes in MG care for patients with refractory MG. A majority of NMBC respondents reported receiving referrals from other doctors, in accordance with the published guideline. Still, respondents in this survey reported referring only a mean of 19% of patients with possible MG for a second opinion.

This survey revealed additional topics that should be better addressed, including management of MG populations of special interest, notably ICI-induced MG and ocular MG. Survey respondents requested treatment guidance for rituximab, methotrexate, and eculizumab, all of which were covered in the 2020 update. Survey results also raised educational gaps in management of common comorbidities, including steroid-induced diabetes and cardiac-related issues, as well as lupus, thyroiditis, and other autoimmune diseases.

Limitations

This study did not address all pertinent issues in the optimal management of patients with MG, and insights and feedback are representative of opinions and practices in the United States only. The focus was primarily on patterns of assessment and therapeutic use of corticosteroids, NSISTs, and autoantibody levels. The survey was designed to determine current levels of knowledge and implementation of existing treatment guidelines. Challenges in managing specific populations or subtypes of MG were not addressed, although they remain important topics for physician education.

Conclusions

Community neurologists employ various approaches to MG treatment decision-making, mostly independent of practice guidelines. The majority of respondents were not aware of the updated 2020 International Consensus Guidance; this guidance publication may not be the optimal approach for disseminating to the larger community information regarding consensus-based recommendations for managing MG.

Disclosures

- This study was funded by argenx, the manufacturer of efgartigimod. Efgartigimod is an investigational agent that is not currently approved for use by any regulatory agency.

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Appendix A: Survey Measure

MG Guidelines Study
Quantitative Survey Instrument
10-minute online survey (N=100)

Main survey
Treatment Questions:

[PREVIOUS Q9]

1) This survey focuses on generalized myasthenia gravis (MG) unless otherwise specified. Which of the following treatment goal(s) do you use to guide MG treatment decisions?

   a. Minimum Symptom Expression (MSE) – MG-ADL Score of 0 or 1; regardless of taking MG therapy or not.
   b. Complete Stable Remission (CSR) – The patient has had no symptoms or signs of MG for at least 1 year and has received no therapy for MG during that time. There is no weakness of any muscle on careful examination by someone skilled in the evaluation of neuromuscular disease. Isolated weakness of eyelid closure is accepted.
   c. Pharmacological Remission (PR) – Same as CSR, but the patient is still receiving some form of pharmacologic therapy for MG. Patients taking AChEi are excluded from this category because their use suggests the presence of weakness.
   d. Minimal Manifestation Status (MMS) – The patient has no symptoms or functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of CSR or PR do have weakness that is only detectable by careful examination.
   e. Patient Acceptable Symptom State (PASS) Question – 'Yes' Response as the Goal to the following question: Considering all the ways you are affected by Myasthenia, if you had to stay in your current state for the next few months, would you say that your current disease status is satisfactory?
   f. Clinical judgement of patient strength, lifestyle activities, and tolerance to treatment.
   g. None of the above [EXCLUSIVE]

[PREVIOUS Q8]

2) Which disease specific measures do you use routinely in your clinic to track MG status? Select all that apply.

   1. Myasthenia Gravis Activities of Daily Living (MG-ADL)
   2. Quantitative Myasthenia Gravis Score (QMG)
   3. Myasthenia Gravis Composite Score (MGC)
   4. Myasthenia Gravis Quality of Life revised 15 (MG-QoL15r)
   5. Myasthenia Gravis-Manual Muscle Testing (MG-MMT)
   6. Medical Research Council Scale for Muscle Strength (MRC)
   7. Patient Acceptable Symptom State (PASS)
   8. Other [SPECIFY]
   9. None of these [EXCLUSIVE]

10) Deleted

11) Would you offer thymectomy to patients with **purely ocular** MG (MGFA Class 1)?
   1. Yes
   2. No

12) Please indicate whether you offer thymectomy in **generalized MG** patients with the following antibody status.

	Yes	No
1. AChR$^+$		
2. MuSK$^+$		
3. LRP4$^+$		
4. Agrin		
5. Seronegative		

13) With what percent of your AChR Ab$^+$ patients **do you discuss** thymectomy?
[RANGE 0 – 100]
|_|_|_| percent of AChR Ab$^+$ patients under 65 with whom you **<u>discuss</u>** thymectomy

14) What percentage of your AChR Ab$^+$ patients **<u>undergo</u>** thymectomy?
[RANGE 0 – 100]
|_|_|_| percent of AChR Ab$^+$ patients under 65 **<u>undergo</u>** thymectomy

15) DELETED

[IF ANY PATIENTS UNDERGO THYMECTOMY (Q14>1), ASK QUESTION]

16) Among your patients who undergo thymectomy, what percent undergo each of the following procedures?
[RANGE:0-100]
   1. Minimally invasive |_|_|_| percent
   2. Trans-sternal |_|_|_| percent

[SHOW RUNNING TOTAL; MUST SUM TO 100%]

17) When initiating steroids on an outpatient basis in a newly diagnosed generalized MG patient, what prednisone equivalent dose do you start?
[RANGE: 0-100.00]
|_|_|_| mg/d

18) What is the maximum steroid dose you would use to achieve disease control?
[RANGE: 0-100.00]
|_|_|_| mg/kg/d

19) Do you initiate with daily steroid dosing or every-other-day steroid dosing?
   1. Daily (QD)
   2. Every Other Day (QOD)

20) Upon initiation of steroids, on average, how long does it generally take to reach a minimally effective dose and then begin tapering steroids?
    1. 1 month
    2. 3 months
    3. 6 months
    4. 12 months
    5. 18 months
    6. 24 months
    7. >24 months

21) What **chronic, long-term** (≥6 mo) prednisone-equivalent steroid dose do you consider safe (ie, to minimize AEs for long-term use)?
    a. ≤5 mg per day
    b. ≤10 mg per day
    c. ≤20 mg per day
    d. ≤40 mg per day
    e. Other

22) When assessing a generalized MG patient, what change in MG-ADL score would cause you to make a change in the patient's MG treatment?
    a. 2-point change in MG-ADL
    b. 3-point change in MG-ADL
    c. I do not make treatment decisions based on MG-ADL

23) In general, from the time of starting a steroid, how long do you wait for a clinical response to steroids before determining the need to add a nonsteroidal immunosuppressant therapy (NSIST)?
    a. I do not wait; I start an NSIST and steroid at the same time
    b. 1 month
    c. 3 months
    d. 6 months
    e. >6 months

23b) How long does it take for you to begin to wean?
    a. 1 month
    b. 3 months
    c. 6 months
    d. >6 months

24) Which nonsteroidal below do you prefer as 1st line after steroid initiation? Select one response only. [RANDOMIZE]
    a. Azathioprine (Azasan®, Imuran®)
    b. Cyclosporine (Gengraf®, Neoral®, Sandimmune®)
    c. Mycophenolate (CellCept®, Myfortic®)
    d. Methotrexate (Rheumatrex®, Trexall®)
    e. Tacrolimus (Astagraf XL®, Envarsus XR®, Prograf®)
    f. Cyclophosphamide (Cytoxan®)
    g. Other [SPECIFY]

25) Please briefly describe why [NSIST FROM Q24] is your 1st line preferred NSIST after steroid initiation.

26) With what [NSIST FROM Q24] dose do you initiate as a starting dose? [RANGE: 0-999]

[IF Q24=A (Azathioprine), SHOW OPTIONS]
|_|_|_| mg/day by mouth

[IF Q24=B (Cyclosporine), SHOW OPTIONS]
|_|_|_| mg/kg/day by mouth

[IF Q24=C (Mycophenolate), SHOW OPTIONS. ALLOW ONE OPTION TO BE BLANK.]
|_|_|_| mg/day by mouth
|_|_|_| mg/day by IV infusion

[IF Q24=D (Methotrexate), SHOW OPTIONS]
|_|_|_| mg/week

[IF Q24=E (Tacrolimus), SHOW OPTIONS]
|_|_|_| mg/kg/day by mouth

[IF Q24=F (Cyclophosphamide), SHOW OPTIONS. ALLOW ONE OPTION TO BE BLANK]
|_|_|_| mg/kg/day by mouth
|_|_|_| mg/kg/day by IV infusion

[IF Q24=G (Other), SHOW OPTIONS.]
[TEXT BOX]

27) How high of a/an [INSERT NSID FROM Q24] dose do you use? [RANGE: 0-9999]
[IF Q24=A (Azathioprine), SHOW OPTIONS]
|_|_|_| mg/day by mouth

[IF Q24=B (Cyclosporine), SHOW OPTIONS]
|_|_|_| mg/kg/day by mouth

[IF Q24=C (Mycophenolate), SHOW OPTIONS. ALLOW ONE OPTION TO BE BLANK]
|_|_|_| mg/day by mouth
|_|_|_| mg/day by IV infusion

[IF Q24=D (Methotrexate), SHOW OPTIONS]
|_|_|_| mg/week

[IF Q24=E (Tacrolimus), SHOW OPTIONS]
|_|_|_| mg/kg/day by mouth

[IF Q24=F (Cyclophosphamide), SHOW OPTIONS. ALLOW ONE OPTION TO BE BLANK]
|_|_|_| mg/kg/day by mouth
|_|_|_| mg/kg/day by IV infusion

[IF Q24=G (Other), SHOW OPTIONS.]
[TEXT BOX]

28) What duration of [INSERT NSIST FROM Q24], do you allow before determining lack of efficacy?
    a. 1 month
    b. 3 months
    c. 6 months
    d. 6-12 months
    e. 12-18 months
    f. >18 months

29) In a typical MG patient, if symptoms are controlled, how long do you typically wait before attempting to taper nonsteroidal immunosuppressants (NSIST) *after* disease control is attained?
    a. 0 to 3 months
    b. 4 to 6 months
    c. 6 to 12 months
    d. 12 to 24 months
    e. >24 months
    f. I do not taper

30) If the 1st choice for nonsteroidal immunosuppressant therapy (NSIST) fails to control symptoms, what therapy do you go to next for AChR-Ab^{+} patients with generalized MG?
    a. A second nonsteroidal immunosuppressive therapy (NSIST)
    b. Immune Globulin (IVIg or SCIg)
    c. Eculizumab
    d. Rituximab
    e. Therapeutic Plasma Exchange
    f. Other

31) In newly diagnosed AChR-Ab+ generalized MG patients **contraindicated for steroids**, and with moderate functional impairment (MG-ADL >8; moderate severity), what initial therapeutic approach best describes your typical clinical practice? Please select multiple agents ONLY if you initiate more than one agent at the same time. [MULTIPLE RESPONSE]
    a. A nonsteroidal immunosuppressive therapy (NSIST)
    b. Immune Globulin (IVIg or SCIg)
    c. Eculizumab
    d. Rituximab
    e. Therapeutic Plasma Exchange
    f. Other

32) In what percentage of generalized MG patients do you avoid steroids?
[RANGE 0 – 100]
|_|_|_| percent

33) Which clinical labs do you routinely monitor in an MG patient? Please specify any additional monitoring for your choice of nonsteroidal immunosuppressant therapy (NSIST)?

34) Do you monitor autoantibody levels in an MG patient to evaluate response to therapy?
    a. Yes
    b. No

[IF Q34=1 (Yes), ASK Q35]

35) Which of the following autoantibody levels do you use to **<u>evaluate response</u>** of an MG patient to therapy? Check all that apply.
    a. None [ANCHOR]
    b. AChR+
    c. MuSK+
    d. LRP4+
    e. Agrin
    f. Other [TEXT BOX]

36) Which of the following treatments would you consider using in treating a MuSK+ patient? Check all that apply.
    a. AChEi
    b. Steroids
    c. Rituximab
    d. NSIST
    e. IVIg and/or SCIg
    f. Eculizumab
    g. Plasma exchange

37) Do you recommend vaccine boosters to your MG patients?
    a. Yes
    b. No
    c. Conditional recommendation; please specify [SPECIFY]

38) Which vaccines do you typically recommend? Select all that apply.
    a. Pneumococcal
    b. Influenza
    c. Varicella zoster
    d. Tetanus
    e. Meningococcal
    f. Other [SPECIFY]
    g. None, due to concern of exacerbating MG [EXCLUSIVE]

39) What is your preferred treatment for managing MG crisis?
    a. IVIg
    b. PLEX
    c. High-dose steroids
    d. Other

General Guideline Questions:

40) When you are making a treatment decision for a patient diagnosed with myasthenia gravis (MG) do you use specific clinical treatment guidelines to make treatment decisions for your patients?
    a. Yes
    b. No, I do not use a specific guideline

    [ASK Q41 IF USE SPECIFIC GUIDELINE (Q40=YES)]

41) What specific guideline do you use for making treatment decisions for MG patients?

42) Which of the following clinical treatment guidelines, if any, is the most useful to you in guiding your clinical management of MG patients? Select all that apply.
    [RANDOMIZE]
    a. Association of British Neurology (ABN) Myasthenia Gravis Management Guidelines
    b. European Federation of Neurological Societies (EFNS) Guidelines for the Treatment of Autoimmune Neuromuscular Transmission Disorders
    c. International Consensus Guidance for the management of myasthenia gravis (MG Foundation of America [MGFA]-appointed Task Force guidelines)
    d. UpToDate® (Wolters Kluwer UpToDate, Inc.)
    e. Other [SPECIFY] [ANCHOR]
    f. I do not use a specific guideline

43) Please rate the following topics in terms of their importance for inclusion in MG treatment guidelines.

[RANDOMIZE]	Not important	Minimum importance	Important	Very important	Extremely important
Defining treatment goals and how to track improvement with disease measures					
Defining when to start, how to dose and how to titrate medications in the chronic management of MG					
Defining how to manage populations of special interest (i.e., pregnancy, children, cancer patients)					
Defining how to manage acute MG crisis					
Defining how to treat pure ocular patients					

44) Of the comorbidities below, which would you like to see in upcoming guidelines to inform MG treatment decision making? Please click to indicate the order of importance.
[SORTING TASK]
   a. Diabetes
   b. Lupus, thyroiditis or other autoimmune disease
   c. Heart disease (including hypertension, CHF, hypercholesterolemia)
   d. Osteoporosis
   e. Renal disease
   f. Other [SPECIFY]

45) Which diagnostic test(s) do you regularly perform to confirm MG? Select all that apply.
   a. AChEi challenge
   b. Repetitive nerve stimulation
   c. Single-fiber EMG
   d. AChR antibody panel
   e. MuSK antibody
   f. LRP4 antibody
   g. Ice pack test
   h. Other [SPECIFY]

46) How do you confirm MG diagnosis in a seronegative patient?
[ALLOW MULTIPLE RESPONSE]
   a. AChEi challenge
   b. Repetitive nerve stimulation
   c. Single-fiber EMG
   d. Other [SPECIFY]

47) Do other neurologists refer patients to you for a second opinion on the diagnosis/management of MG?
    a. Yes
    b. No

48) What percentage of possible MG patients do you refer for a second opinion? [RANGE: 0-100]
    |_|_|_| percent of possible MG patients referred for a second opinion

49) Are you currently aware of the newly released 2020 International Consensus Guidelines developed with conjunction with the MGFA Task Force?
    a. Yes
    b. No

50) Do you use rituximab in AChR^{+} MG patients?
    a. Yes
    b. No

51) Do you use eculizumab in non-refractory MG patients?
    a. Yes
    b. No

52) Do you use eculizumab in seronegative MG patients?
    a. Yes
    b. No

53) Have you treated patients with immune checkpoint inhibitor–induced MG?
    a. Yes
    b. No

54) What is your treatment of choice for immune checkpoint inhibitor–induced MG? Select all that apply.
    a. Steroids
    b. Plasma exchange
    c. IVIg
    d. Other [SPECIFY]

[END OF SURVEY]

Appendix B. Treatment goals as defined in survey

Minimum symptom expression (MSE)	MG-ADL score of 0 or 1, regardless whether taking MG therapy or not.
Complete stable remission (CSR)	Patient has had no symptoms or signs of MG for ≤1 year, with no therapy for MG during that time. There is no weakness of any muscle on careful examination by someone skilled in the evaluation of neuromuscular disease. Isolated weakness of eyelid closure is accepted.
Pharmacologic remission (PR)	Same as CSR, but the patient is still receiving some form of pharmacologic therapy for MG. Patients taking AChEi are excluded from this category because their use suggests the presence of weakness.
Minimal manifestation status (MMS)	The patient has no symptoms or functional limitation from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of CSR or PR do have weakness that is only detectable by careful examination.
Patient Acceptable Symptom State (PASS) question	Positive (ie, "yes") response to the following question: Considering all the ways you are affected by MG, if you had to stay in your current state for the next few months, would you say that your current disease status is satisfactory?
Clinical judgment	Judgment of patient strength, ADLs, and tolerance to treatment.

Abbreviations: AChEi, acetylcholinesterase inhibitor; ADL, activity of daily living; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living.

The Correlation Between Static Fatigue Testing and the Quantitative Myasthenia Gravis Score and Activities of Daily Living Profile

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ABSTRACT

Fatigue is a common symptom in myasthenia gravis (MG), but both objective and subjective measures of fatigue are poorly studied in the disease. We conducted a pilot study of static fatigue testing (SFT) in a group of MG patients, using an isometric quantified muscle analysis computer system. Results from sustained isometric contraction of 5 muscle groups in 77 patients were correlated to the Quantitative MG Score (QMG) and the Activities of Daily Living Profile (MG-ADL), two commonly used outcome measures. Pearson correlation coefficients for the SFT were highest (0.33) for hand grip for both the QMG and MG-ADL. Correlations were quite poor for the proximal muscle groups and ankle dorsiflexion. More work is needed to develop objective and subjective measures of fatigue in MG.

Keywords: *myasthenia gravis, fatigue, disease outcomes*

Introduction

Fatigue is a clinical manifestation of skeletal muscle weakness in myasthenia gravis (MG). Quantification of the fatigue in MG during isometric exercise has not been carefully studied and may be a useful measurement in clinical research trials. Interestingly, fatigue measurements have been reported in amyotrophic lateral sclerosis[1] and multiple scleriosis[2] but not in MG patients. Our goal was to study static fatigue testing (SFT) in MG patients using an isometric quantified muscle analysis (QMA) computer system. As such, we analyzed a physiological measure of fatigue, that may or may not relate to actual muscle weakness and that differs from subjective assessments of fatigue such as the Fatigue Severity Scale.[3] We compared the results of the SFT to the Quantitative Myasthenia Gravis Score (QMG)[4] and the Activities of Daily Living Profile (MG-ADL).[5]

Methods

Seventy-seven MG patients were evaluated, using the SFT, QMG[4] and MG-ADL.[5] SFT was performed on the dominant side (side of handwriting) on handgrip, elbow flexion, elbow extension, knee extension, and foot dorsiflexion. The isometric muscle testing was performed using standardized techniques developed in amyotrophic lateral sclerosis trials.[6,7] The hardware for isometric muscle testing and computer software for fatigue analysis were developed by Jim Fielding (the Computer Source, Gainesville, GA).

Patients were placed in gravity-eliminated positions with the limbs stabilized by the examiner (Table 1). They pulled against a standardized strap attached to a strain gauge that was connected to the computer system. For each SFT measurement, the patient performed maximum muscle contraction for 30 seconds. Isometric strength (kgs of force) was measured for 30 seconds and analyzed in 5 epochs. The 5 epochs were W1: 0-5 secs, W2: 2-7 secs, W3: 4-9 secs, W4: 25-30 secs, and W5: 0-30 secs. SFT results were assessed by comparing the maximum force generated in the 2-7 second epoch (W2) with the 25-30 second epoch (W4) (Figure 1). The W2 and W4 epochs were chosen for comparison to allow for the subject to build up to a full force in the first two seconds and then compare that value to the

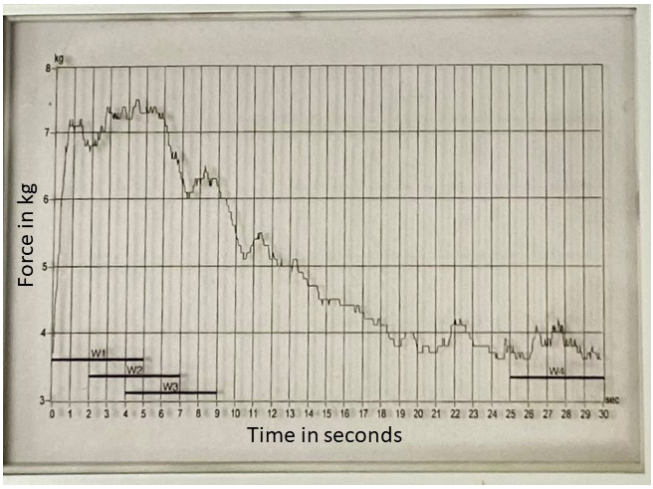

Figure 1. Static fatigue testing in a single MG subject demonstrating the decline in isometric strength across time epochs. Epochs W1 through W4 are noted by bars on the x-axis.

Table 1. Static fatigue testing procedures by muscle group

Muscle group	Test position	Limb stabilization
Hand grip	Sitting; elbow bent to 90 degrees	Support under forearm and under dynamometer[6]
Elbow flexion	Supine; elbow at 90 degrees with maximum contraction, forearm in neutral	Stabilizing at the shoulder and at the elbow (ulnar groove)
Elbow extension	Supine; elbow at 90 degrees with maximum contraction, forearm in neutral	Stabilizing at shoulder and over the biceps
Knee extension	Sitting over the edge of the bed; knee at 90 degrees with maximum contraction, towel under distal thigh to level femur	Pushing down on the shoulders
Foot dorsiflexion	Supine; ankle at 90 degrees dorsiflexion with maximum contraction	Pushing down distal to the knee

final five seconds of the 30-second contraction interval. Statistical analysis comparing SFT to the QMG and MG-ADL was performed using a Pearson correlation coefficient.

Results

The Pearson correlation coefficient between the SFT and QMG was 0.33 for hand grip, 0.23 for elbow extension, 0.10 for elbow flexion, 0.15 for ankle dorsiflexion, and 0.16 for knee extension. The coefficient between the SFT and MG-ADL was 0.33 for hand grip, 0.06 for elbow extension, 0.03 for elbow flexion, 0.15 for ankle dorsiflexion, and 0.19 for knee extension.

Discussion

Overall, correlation coefficients were low between SFT and two validated and commonly utilized measures of clinical status in MG. SFT measurements for hand grip demonstrated the best correlation with the QMG and MG-ADL. Possible explanations for the overall poor correlations include the fact that SFT assesses fatigue in only one muscle group at a time, whereas both the QMG and MG-ADL provide a more global picture of MG clinical status. Quantitative outcome measures in MG are often effort-dependent, and a subject's receptiveness to encouragement by the examiner can vary. In addition, the time epochs chosen to generate the SFT value may not have been optimized for the correlation. Perhaps comparison of the slope of the decline in isometric contraction at different time points would provide a stronger correlation with existing measures.

Even without a strong correlation to established outcome measures, SFT may capture other information of value in MG. Ten percent of the variance of both QMG and MG-ADL was accounted for by SFT. This indicates that the SFT is providing some additional information regarding overall MG clinical status to that provided by the QMG and MG-ADL. Further study would be needed to see if SFT or a related strategy that objectively measures fatigue would provide a sensitive and reliable endpoint for interventional studies in MG.

Subjective measures of fatigue have been developed, most notably the Fatigue Severity Scale (FSS). The FSS has been applied to multiple sclerosis[8] and Parkinson disease[3] with variable correlation to established measures of disease severity, similar to our findings with SFT in MG. In neuromuscular conditions, the FSS demonstrated fair psychometric properties in congenital myopathies, but had little value in spinal muscular atrophy type 2.[9] The FSS has not been subjected to rigorous study in MG. Among existing subjective measures developed for MG, the chewing item in the MG-ADL does query subjects on their experience of fatigue with solid or soft food, but by no means provides a broad assessment of muscle fatigue.[5] Although some items in the MG Quality of Life 15 Score could be impacted by fatigue, the term "fatigue" does not actually appear on the questionnaire.[10] A recent study of a subjective fatigue measure in 779 Danish MG patients examined the association between the self-reported Multidimensional Fatigue Inventory (MFI-20) and a physical activity survey.[11] Of the five MFI-20 domains, general fatigue, physical fatigue, and reduced activity were most prominently impacted. Those MG subjects able to tolerate higher levels of physical activity reported lower levels of fatigue on the MFI-20 and also had more favorable MG-ADL scores, with correlation values in the 0.4 range.[11]

Objectively measuring for fatigue in MG or other disease states presents a considerable challenge. Further studies that include established clinical and electrophysiological measures in MG could determine how useful SFT or a related approach would be in MG clinical trials.

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Acute Motor and Sensory Axonal Neuropathy (AMSAN) and Immune Thrombocytopenic Purpura (ITP) Related to Hemophilus Influenzae

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ABSTRACT

We describe a rare case presenting with signs of acute motor and sensory axonal neuropathy (AMSAN) and immune thrombocytopenic purpura (ITP) possibly triggered by *Hemophilus influenzae*. Guillain-Barre syndrome (GBS) is an autoimmune disorder purported to be due to molecular mimicry, often with a preceding infection, leading to myelin sheath or even axonal damage, in the peripheral nervous system. There have been rare occasions of concurrent GBS and ITP, but even rarer is the presence of both AMSAN and ITP, which requires quick recognition and evaluation. This case highlights the need for a thorough initial history taking and a general physical exam, in addition to unique management decisions and strategies in patients with suspected GBS as there may be signs of other associated disorders that require immediate attention.

Keywords: *GBS, AMSAN, ITP*

Case Report

A 42-year-old man with a past medical history of nephrolithiasis and mitral valve prolapse had been experiencing sinus congestion and pressure that he had been treating with Nyquil for a week prior to presentation. He stated that his symptoms had been improving until 2 days prior when he began to experience progressive upper and lower extremity, distal greater than proximal, numbness and tingling that eventually progressed to his elbows and his ankles. He was stumbling as he attempted to walk and presented to the emergency department (ED). In the ED, there was concern for posterior circulation stroke, but NIH stroke scale was zero without any extremity ataxia. CT scan of the brain showed no hemorrhage or ischemic stroke. Vital signs were stable and he was afebrile. Neurological examination revealed no mental status, cranial nerve, motor, sensory, or coordination deficits, but he was completely areflexic. General examination showed oropharyngeal wet purpura with glossal and palatal lesions, raising concern for coagulopathy. Complete blood count revealed a low platelet level of 3000/mcL with an otherwise normal white blood cell and hemoglobin level.

Hematology recommended immediate platelet transfusion of four units and starting IVIG for suspected ITP. Given the high index suspicion for Guillain-Barre syndrome, we determined that IVIG would be the best option in treating both conditions. Initially, there was no respiratory distress (initial negative inspiratory force was at -40 cm H2O, vital capacity was 2.2L). However, his vital capacity decreased to 1.7L and on the third day of hospitalization he was promptly intubated given further declining vital capacity (0.61L). A respiratory viral panel revealed *Haemophilus influenzae* positivity and he was started on a seven-day course of Azithromycin. Nerve conduction studies are summarized in Table 1. Needle examination revealed increased insertional activity and fibrillations in only the right tibialis anterior muscle. Motor unit potentials showed reduced recruitment with normal duration, amplitude in most of the tested muscles.

Over the course of the next two days, he completed a course of IVIG at 2g/kg, and an improvement in platelet count was noted, however he continued to decline neurologically with significant quadriparesis (motor strength 1/5 in each extremity). Sensory examination was notable at this time for diminished light touch sensation in bilateral lower extremities. Given his continuing decline, he was started on plasmapheresis for 5 sessions with partial improvement in strength with exam notable for 4/5 strength in most upper extremity muscle groups and 3/5 for most lower extremity muscle groups. Tracheostomy was performed initially; however, gradually he was weaned off the ventilator. Given his significant dysphagia, a PEG was placed.

After 3 weeks, he was discharged to a local rehabilitation facility and he continued to improve in his strength, dysphagia, respiratory function. The tracheostomy tube was decannulated and PEG tube removed. He was able to eat a regular diet in 2 weeks and ambulate without assistance for several minutes at a time, needing periods of rest due to fatigue.

At 12-month follow up, patient was able to work full time, had mild fatigue and some paresthesias, however neurological examination revealed normal strength and sensation. He had no further recurrence of presenting symptoms and recovered reasonably well.

Table 1. Nerve conduction studies in a patient with AMSAN at 3 weeks from symptom onset

Nerve	Sensory Peak Latency (ms)	Sensory Distal Amplitude (MicroV)	Motor Distal Latency (ms)	Motor Distal Amplitude (mV)	Motor Conduction Velocity (m/s)	F Wave Latency (ms)
Median*	3.39(<3.7)	6.6 (>20)	3.54 (<4.4)	7.1 (>4.0)	51.3 (>49.0)	NR (<31)
Ulnar*	3.28 (<3.5)	7.0 (>10.0)	2.24 (<3.8)	6.5 (>6.0)	52 (>49.0)	NR (<32)
Radial**	2.4 (<2.9)	6.7 (>15)				
Tibial^^			5.21 (<6.1)	1.8 (>3)	48.3 (>41)	NR
Peroneal^			6.41 (<6.1)	0.9 (>5.0)	42.5 (>44)	
Sural	2.97 (<4.2)	4.2 (>6.0)				
Superficial Peroneal	NR	NR				

NR = no response. Normal values in parentheses.
*Stimulating wrist, recording digits 2 or 5 (sensory) or recording abductor pollicis brevis or abductor digiti minimi muscle (motor).
**Stimulating forearm, recording anatomical snuff box.
^Stimulating ankle, recording extensor digitorum brevis muscle.
^^Stimulating ankle, recording abductor hallucis muscle.

Discussion

Gullian-Barre syndrome (GBS) is a disease in which there is typically damage to myelin surrounding peripheral nerves and typically presents as the classic ascending weakness, paresthesias, and numbness, all potentially in the setting of a preceding infection; this pattern is particularly associated with the GBS-subtype of Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP)[1,2]. There are several other variants of GBS, one of which is Acute Motor and Sensory Axonal Neuropathy (AMSAN), which carries a worse prognosis and causes axonal injury rather than pure demyelination[1, 3]. Compared to AIDP, AMSAN patients tend to progress much more quickly, have a higher chance of becoming debilitated and quadriparetic and have a longer time for recovery. AIDP tends to be a predominantly T-cell mediated disorder, whereas AMSAN is typically more B-cell mediated; however, it still responds to the same recommended initial treatments for GBS, such as intravenous immunoglobulin (IVIg) and plasmapheresis[3].

ITP is characterized by depletion of platelets due to an auto-antibody mediated process targeting surface glycoproteins, specifically GpIIb-IIIa. There is thus far, no known common receptor or process that has linked both GBS and ITP. However, as molecular mimicry is the underlying mechanism for both these diseases, there is a chance for both these entities to co-occur in the same patient as was the case with our patient and a few other patients in the literature [1,4].

In our patient, IVIG was used to treat both ITP and suspected GBS. While his ITP resolved fairly quickly with the treatment within a span of a week, his presentation of AMSAN continued to progress to respiratory distress and quadriparesis which only began to improve 3 weeks after initial presentation after 5 sessions of plasmapheresis.

In our patient, *Haemophilus influenzae* was detected. There have been cases of both GBS and ITP associated with this bacteria, as well as a case reported with both GBS and ITP[5]. Mori *et al.* investigated the link between *H. influenzae* and GBS and suspected that recovery was actually improved if GBS was associated with antecedent respiratory infection with this bacterium, and that EMG in these cases actually showed increased rate of axonal variants [6], such as was observed in our case.

Our patient did not have significant cranial nerve involvement and did in fact have recovery to the point of functioning independently close to 12 months after initial presentation. Additionally, out of all the previous cases, the patient reported by Ward *et al.* is the only other patient who was treated with plasmapheresis [1]. This illustrates the heterogeneity of presentation and treatment even in patients with AMSAN. There have been at least a few cases of various different subtypes of GBS and ITP suggesting that while it is a rare occurrence, there does seem to be some underlying process that increases the risk of an additional autoimmune reaction in a patient already suffering from one [1,7,8,9,10,11,12,13,14,15]. Finally, this case does highlight the unique management and diagnostic decision-making in a patient with both ITP and AMSAN.

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A Case Report of COVID-19 Positive Becker Muscular Dystrophy

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ABSTRACT

Background: Becker and Duchenne muscular dystrophies constitute the most common inherited dystrophinopathies. The chronic steroid treatment predisposes them to any infection, hence, we sought to determine the current COVID-19 infection in them. We conducted an analysis on a real-world database to identify the effect of COVID-19 infection and identified a case of Becker muscular dystrophy who tested positive for COVID-19. For our analysis, we utilized Cerner Real-World Data™ that was provided through Cerner's HealtheDataLab research tool.

Case report: A 63-year-old Caucasian male with Becker muscular dystrophy, hyperlipidemia, and atrial fibrillation, was hospitalized with COVID-19 infection. Our search revealed June 22, 2020, as the patient's COVID-19 service date when tested positive. The patient received antibiotics and supportive therapy during hospitalization. Intricate details like oxygen requirement, blood gas analysis, and mechanical ventilation could not be retrieved if used. The patient developed complications like sepsis, pneumonia, acute respiratory failure that resulted in prolonged hospitalization. Our data reported that the patient was alive during discharge.

Conclusion: Although patient developed complications during hospitalization, no death from the COVID-19 infection was observed in our analysis.

Keywords: *Becker Muscular Dystrophy, COVID-19 infection, Muscular dystrophy.*

Background

Becker and Duchenne muscular dystrophies constitute the most common inherited dystrophinopathies. Becker muscular dystrophy (BMD) is an X-linked recessive disorder characterized by progressive muscle weakness, secondary to the truncated dystrophin gene's low levels. This gene encodes for a protein called dystrophin-4, and the incidence is one-third as frequent as Duchenne muscular dystrophy (DMD), which is a severe form.[1, 5] They present with progressive muscle weakness, and the chronic steroid treatment predisposes them to any infection.[1, 2] The current global pandemic COVID-19 infection presents with a dry cough, fever, headache, shortness of breath, and reduced sensation of smell. In severe cases, it results in pneumonia, acute respiratory failure, myocardial injury, and death.[2] COVID-19 infection has several implications on the course of various neuromuscular diseases. We conducted an analysis on a real-world database to identify the effect of COVID-19 infection on BMD/DMD patients.

Case Report

For our analysis, we utilized Cerner Real-World Data™ that was provided through Cerner's HealtheDataLab research tool.[4] The COVID-19 dataset in HealtheDataLab contains de-identified patient data of one hundred and seventeen thousand patients from 62 contributing health systems. The dataset contained all patients tested for COVID-19 at some point during their visits to one of the 62 health centers. All patients with the DMD/BMD tested for COVID-19 were identified using ICD-10-CM code (G71.01) and SNOMED-CT code (76670001). This yielded a total of 5 patients that were tested either positive or negative for COVID-19. Out of them, two patients were aged 17 (DMD), and the other three (BMD) ranged from 38-63. One of the five patients tested positive for COVID-19 infection on June 22, 2020 and was hospitalized. Our Institutional Review Board waived the consent form as we utilized de-identified patient data.

The patient identified was a 63-year-old Caucasian male, and comorbidities identified were hyperlipidemia and atrial fibrillation. The duration of hospitalization in the patient was 28 days. The patient received antibiotics and supportive therapy during hospitalization. Intricate details like oxygen requirement, blood gas analysis, and mechanical ventilation could not be retrieved if used. The complications identified during the hospital stay were pneumonia, atrial fibrillation, sepsis, and respiratory failure. The data reported that the patient was alive during discharge; however, the discharge disposition could not be retrieved as it was listed as an empty value in the database.

Discussion

Note that BMD patients are prone to develop COVID-19 infection and complications. The immunocompromised state in these BMD patients secondary to steroid treatments predisposes them to infections and complications.[1, 2, 3] As per a consensus recommendation, there are no significant changes in the standard of care for BMD patients.[2, 3] They also reported providing appropriate care must be targeted to prevent the adrenal crisis in these patients when they fall ill. Higher doses of corticosteroids are recommended in those scenarios.[2]

The common cause of death in BMD patients is cardiac dysfunction/cardiomyopathy.[5] In our case the patient developed sepsis and acute respiratory failure from the COVID-19, which resulted in prolonged hospitalization of almost a month.

Although the patient developed complications during hospitalization, no death from the COVID-19 infection was observed in our analysis.

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Dermatomyositis-like Rash Associated with Anti-3-hydroxy-3-methylglutaryl-coenzyme A Reductase Autoantibody Necrotizing Myopathy Following COVID-19 Infection and Vaccination

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Introduction

The clinical presentation of immune-mediated necrotizing myopathies (IMNM) includes the acute or subacute onset of severe, symmetric proximal weakness with potential for facial weakness and/or dysphagia, elevated creatinine kinase (CK), predominant myofiber necrosis with minimal inflammation on muscle biopsy, and minimal or no extramuscular manifestations. [1-3] Recently, there have been rare case reports of patients presenting with a characteristic dermatomyositis (DM)-type rash, including a heliotrope rash or Gottron's papules, who were subsequently found to have serologic evidence of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibodies and muscle biopsies most consistent with IMNM as opposed to perifascicular atrophy and predominant perivascular perimysial inflammation.[2,4-6] Here we present an additional case of a 62-year-old female who presented with a characteristic heliotrope and bimalar rash who was subsequently found to have HMGCR-associated necrotizing myopathy temporally associated with her 2nd mRNA COVID-19 vaccination and remote history of statin exposure.

Case Report

A 62-year-old female with a history of diabetes mellitus type II and hypertension presented for consultation regarding 3 months of progressive weakness in her bilateral upper and lower extremities. She reported a history of a mild SARS-CoV-2 infection 10 months prior to initial consultation during which she noted diffuse muscle aches and difficulty standing for long periods of time for a 3-week period, however, returned to her baseline level of function following recovery. She did not require any hospitalization.

She first noted recurrence of her muscle aches and difficulties standing for prolonged periods of time approximately 2 weeks following her second mRNA COVID-19 vaccination 3 months prior to consultation. As opposed to her prior SARS-CoV-2 infection experience, the onset of her symptoms was more subacute per the patient's report, and she initially attributed them to side effects from her vaccination. Unfortunately, the patient's symptoms failed to improve over the subsequent 3 weeks and she began to notice difficulty getting in and out of a chair without using her hands. She could not brush her hair without resting and needed to rest her arm against the shower wall in order to wash her hair. Symptoms continued to progress to the point where she required assistance from two people to stand up out of a vehicle and could no longer walk without the use of a cane for short distances and required a wheelchair when out of the home. She denied any swallowing difficulties but did notice some dyspnea with exertion. She denied any diplopia or sensory changes. She noticed a new-onset bimalar erythematous rash one month prior to consultation but denied any rash on her trunk or hands.

Given the progressive weakness, she was initially referred to an outside neurologist who obtained an EMG which demonstrated myopathic findings with membrane irritability in the right deltoid, biceps, triceps, flexor carpi radialis, vastus medialis, and iliopsoas, consistent with a myopathy with muscle membrane irritability, as well as a mild to moderate axonal sensorimotor polyneuropathy based on absent sural and superficial peroneal sensory responses and borderline low or low peroneal and tibial motor study amplitudes. Imaging obtained included a cervical spine MRI which was within normal limits, brain MRI which demonstrated some mild age-related involutional changes but was otherwise unremarkable, and lumbar spine MRI which demonstrated facet hypertrophy with moderate central canal narrowing and moderate to severe left L5-S1 neuroforaminal stenosis. Her CK was found to be elevated at 6,892 U/L and she was referred to the neuromuscular clinic for further evaluation.

Initial examination 2 weeks after her initial outside neurology consultation demonstrated mild neck flexor (MRC 4/5) and extensor (4+/5) weakness with proximal weakness noted in the shoulder abductors (4-/5), shoulder external rotation (4/5), and forearm pronation (4/5) bilaterally. Elbow flexion was 4+/5 bilaterally. Lower extremity strength demonstrated moderate hip flexion weakness (3-/5) and hip abduction/adduction weakness (4-/5) bilaterally with mild knee extension/flexion (4/5) weakness and preserved ankle dorsiflexion/plantarflexion. Sensation was grossly intact to pinprick without a length-dependent gradient with some vibratory loss in the left

lower extremity at the ankle attributed to local edema. Reflexes were preserved (2/4) with the exception of the Achilles' reflexes (0/4) and the patient had a waddling gait which required the assistance of a single point cane. She was noted to have a bimalar erythematous rash (Figure 1) but no other skin abnormalities. She was not currently taking statin medications but noted she was on atorvastatin for 1 month (stopped due to myalgias) over 5 years prior to presentation.

Given her presentation, the patient was referred for a left biceps muscle biopsy the following day which demonstrated mild fiber size variability with predominant necrosis and regeneration without perifascicular changes or predominant perivascular perimysial inflammation most consistent with a necrotizing myopathy (Figure 1). Laboratory results which returned following the results of the biopsy demonstrated an elevated HMGCR antibody of greater than 200 units (normal 0-19). A myositis-specific antibody panel demonstrated negative Jo-1, PL-7, PL-12, EJ, OJ, SRP Mi-2, U3 RNP, MDA-5, NXP-2, TIF-1 Gamma, Anti-PM/Scl-100, US snRNP, U1-RNP, KU, SSA, SSB, and SAE antibodies. Her ANA titer was positive at 1:320.

Malignancy screening including CT of the chest, abdomen, and pelvis, mammogram, and serum immunofixation and kappa/lambda light chain ratios was negative except for likely reactive pelvic lymph nodes with recommendation for repeat pelvic CT in 3-4 months. The patient was started on a regimen of oral prednisone as well as weekly oral methotrexate and has noted some functional improvements despite only being on therapy for 3 weeks. She has also noted improved swelling around her orbits but continues to note some erythema. Given her temporal course related to her mRNA COVID-19 vaccination, she has also been referred for enrollment in an NIH study evaluating the association of myositis with COVID-19 vaccines.

Discussion

Immune-mediated necrotizing myopathies account for approximately 20% of autoimmune myopathies with anti-HMGCR antibodies representing the most frequently associated antibody, ranging from 22 to 61% of cases, with anti-SRP representing the next most frequently associated autoantibody.[1,3,7] The frequency of anti-HMGCR antibodies is highest in older patients with prior statin exposure. However, since its discovery in 2010 it has been associated with statin naïve patients as well as those with an underlying malignancy.[1,8,9] In addition, while rare, anti-

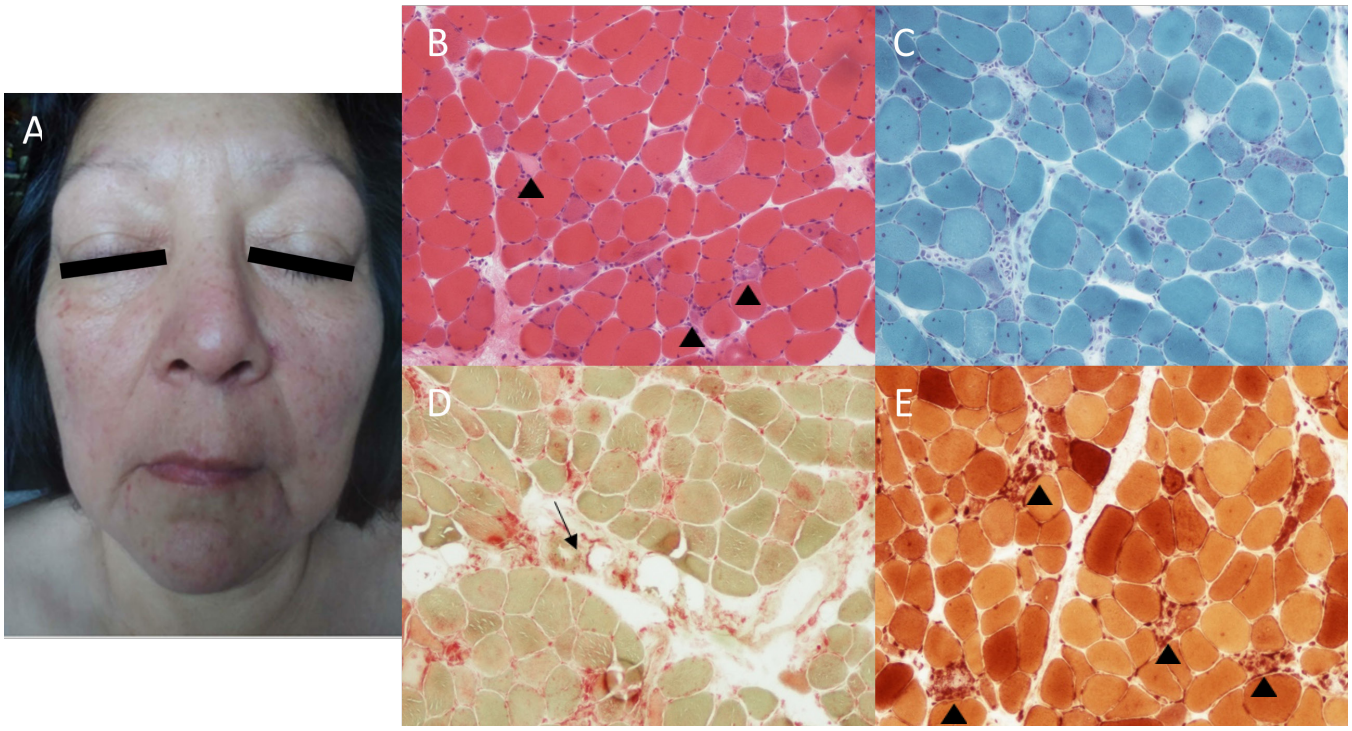

Figure 1. Erythematous heliotrope and bimalar rash (A) noted on initial examination. Left biceps muscle biopsy. H&E (B) and Gomori Trichrome (C): mild fiber size variability with many necrotic fibers and several undergoing myophagocytosis (arrowheads) with scant inflammation. Acid Phosphatase (D) with many necrotic fibers and a single focus of perivascular inflammation (arrow). Non-specific esterase (E) with several fibers undergoing myophagocytosis (arrowheads). No perifascicular atrophy or prominent perivascular perimysial inflammation was noted on any of the stains.

HMGCR antibodies have been reported in other idiopathic inflammatory myopathies (IIM) and connective tissue diseases, including 1.9% of adult-onset DM cases, 6.7% of juvenile DM cases, and 1.2% of primary Sjögren's syndrome cases.[2,9-11]

The typical presentation of IMNM associated with anti-HMGCR antibodies is associated with a mean age of onset of 55 with a female predominance of acute to subacute onset of progressive proximal extremity weakness, more pronounced in the lower extremities. CK is elevated at least 10 times the upper limit of normal and remains elevated despite stopping statin therapy if the patient was previously exposed.[1,3,7] Typical biopsy findings include predominant myofiber necrosis with myophagocytosis and regeneration with scant inflammation. MAC and MHC-1 expression on the sarcolemma of non-necrotic fibers as well as MAC deposition on small blood vessels has also been described.[1,3,12] While bulbar and respiratory involvement is rare, some case series have noted dysphagia.[1,7,8]

Skin involvement has been noted in 15-44% of anti-HMGCR-positive patients, however, specific findings for dermatomyositis such as Gottron's papules, Gottron's sign, or heliotrope rash, were uncommon.[7,12-15] To our knowledge, there are only four additional case reports of biopsy proven statin-associated anti-HMGCR with a specific DM skin rash (i.e. Gottron's papules, Gottron's sign, or heliotrope rash).[2,4-6,10] This clinical entity has been recognized in the most recent 2018 ENMC dermatomyositis classification criteria as "anti-HMGCR myopathy with a DM-like rash" with a single case series comparing these patients against those with HMGCR antibodies without a DM-like rash and noting those with DM-like rashes had a younger age of onset and shorter disease duration at time of diagnosis.[13,16]

In addition to the unique skin findings, the significance of the temporal relation to the patient's second COVID-19 vaccination and her prior COVID-19 infection remains uncertain. While the most common presentation of the SARS-CoV-2 infection includes fever and upper and lower respiratory symptoms, generalized myalgias have been seen in up to 50% of cases.[17,18] Progression to myopathy or myositis has only been rarely reported with only a few case reports of rhabdomyolysis which was acute and concurrent with SARS-CoV-2-related pneumonia as well as flaccid quadriplegia after intensive care management.[19-21] While necrotizing autoimmune myopathy is typically idiopathic, triggers outside of statin exposure or underlying malignancy also may include post-viral autoimmune antibodies.[22] There is a single case report of SARS-CoV-2 IgG positive autoimmune necrotizing myopathy with negative HMGCR and SRP antibodies one month following an initial COVID-19 infection which responded to immunotherapy.[19] To date there have been no clear cases of autoimmune myopathy related to COVID-19 vaccination with only a single case report of a self-limited vaccine related myositis which resolved spontaneously 6 weeks after onset of symptoms without intervention.[23]

Anti-HMGCR myopathy with a DM-like rash appears to be a unique clinical entity with a younger age of onset and shorter duration of symptoms as compared to HMGCR antibody-positive IMNM without typical DM-like skin manifestations. This case outlines the importance of muscle biopsy and complete serologic testing for myositis-associated antibodies in securing the correct diagnosis, even in the setting of specific skin manifestations for dermatomyositis. As anti-HMGCR antibodies are not on routine myositis panels, these antibodies should be considered in addition to routine myositis-specific antibodies in those patients with a significant CK elevation with or without prior statin exposure even in the setting of a DM-like rash, as this may have therapy implications given the often-inadequate response to corticosteroid monotherapy in IMNM. Finally, while we cannot rule out a causal relationship between onset of her HMGCR-positive IMNM and her COVID-19 infection and/or vaccination, this relationship will require further exploration by means of enrollment in larger patient databases to better understand whether there is a true relationship between COVID-19 vaccination and/or infection and subsequent development of IMNM or other IIM.

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Steps in Inclusion Body Myositis

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I used to reach for the sky.
But now wonder why
I can't raise my arm to reach
for food,
or fodder for my rants,

Has their word been codified
to have me ostracized?
Who are they to decide
I should be cast aside
sit in a wheelchair,
or be denied
my place
or pride?

Every muscle screaming at me.
To what end?
What have I done to offend
those cells on which I depend
each time I ascend
a stair or reach despair
in futile prayer?

They refuse to cooperate
without debate
as if I were an ingrate
who doesn't appreciate
the pain that continues without abate.

With each step I consume
a portion of the bloom,
that portion of life
that fades
as down its path
I resist until
that last step,
that small step,
drops into my tomb

AINT NO SENSE PROJECT (BOY IN THE BACK SEAT)

Walter Anderson

Three kids out driving in a car
Not doin much, not going far
Couple of shots blast out of nowhere
Blue lights flashing and sirens blare

Boy in the backseat barely a teen
Two in front three years older
Cops force 'em off on to the shoulder
But can't find a weapon on the scene

Big brain detectives can't figure it out
Covered by an eclipse of doubt
District Attorney does the lazy and lame
Boy in backseat gets the blame

Snap your fingers fast as that
The Boy gets sentenced to the max
Didn't matter what were the facts
Here's your bunk complete with rats

Driver and shotgun they just lied
Signed document DA supplied
Boy in backseat completes the picture
Case is closed and made a fixture

Five years then into his sentence
A little bigger a little stronger
Just must say it can't be wronger
Stolen was his adolescence

Ten years pass and boy is a man
Sometimes dreams of Yucatan
He does not smoke he does no dope
Outside friends smuggle in some hope

Year fifteen he still keeps steady
Reading law books makes him heady
Somehow his story gets attention
On NPR his name they mention

Now it's been twenty since life was wrecked
But case is now an Innocence Project
Their noble cause needs our support
It's Boy in the Backseat's last resort

Kansas City Musculoskeletal Diseases Consortium
6th Annual Symposium on Musculoskeletal and Neuromuscular Diseases
UMKC – Pierson Auditorium, 5000 Holmes, Kansas City, MO
Friday, December 3, 2021
10:00 a.m. – 2:00 p.m.

10:00 am	**Welcome and Introduction of Keynote Speaker:** **Edward R. O'Connor,** PhD, MBA, FACHE, Executive Director, KCMD Consortium, Provost and Executive Vice President for Academic, Research and Student Affairs, Kansas City University
10:10 am	**Keynote Speaker: Richard J. Barohn**, MD, Executive Vice Chancellor for Health Affairs, University of Missouri - Columbia, "A Tale of 4 CIITies …. Clinical Investigator Initiated Trials"
11:00 am	**2019 and 2020 KCMD Award Winner Research Updates** Moderated by **Dr. O'Connor**
11:05 am	Abdulbaki Agbas, KCU, *"Serum Exosomal-based Biomarker Development in Canine model of ALS TDP-43 Assessment: An Update"*
11:20 am	John Stanford, KUMC, *"Unilateral Forelimb Resistance Training in an Ovariectomized Rat Model of Osteoporosis: An Update"*
11:35 am	Charlotte Phillips, MU, *"Osteogenesis imperfecta; skeletal muscle weakness, mitochondrial dysfunction, and cardiomyopathy: An Update"*
11:50 am	**Group Q&A –** Dr. O'Connor, Moderator
12:00 pm	**Lunch**
12:30 pm	**POSTER PRESENTATIONS** Elizabeth Bryda, MU, *"Rat Resource and Research Center"* Daniel Davis, MU, *"University of Missouri - Animal Modeling Core (AMC)"* Claire Houchen, UMKC, *"Jaw Bone Length is Altered by Pharmacological Inhibition of Matrix Metalloproteinase-9"*

RRNMF Neuromuscular Journal 2021;2(5):64-77

Qwynton Johnson and Alpha Bah, KCU, "*The Profile of Post-Translational Modifications of TDP-43 in Neurodegenerative Diseases: A Blood-Based Biomarker Development"*

Kevin Middleton, MU, *"Bayesian Modelling to Address the Challenges of Estimating Craniofacial Growth Patterns"*

Rose Schauffler, MU, *"Evaluation of Tibiofemoral Motion in ACL Deficient Populations"*

Colt Solberg and Bradley Thornton, KCU, *"Identification of the Human Retinal Dystrophin Promoter: Target for Treatment of Duchenne Muscular Dystrophy"*

Jacob Thomas, MU, *"Comparison of Azure Kinect and Vicon Motion Capture System for Kinematic and Spatiotemporal Evaluation of Sit-to-Stand"*

Bradley Thornton and Colt Solberg, KCU, *"Impact of Human Retinal Dystrophin Expression on Cardiomyopathy in DMD Model Mice"*

Batool Alkhamis and Wen Liu, KUMC, *"Benefits of interval walking in older people with knee osteoarthritis"*

Sara Ricardez Hernandez, MU, *"Investigating the respiratory defects in a novel patient-based spinal muscular atrophy with respiratory distress type 1 (SMARD1)"*

1:45 pm **Group Q&A –** Dr. O'Connor, Moderator

2:00 pm **Closing Remarks: Dr. O'Connor**

RRNMF Neuromuscular Journal 2021;2(5):64-77

Exosomal TAR DNA binding protein 43 profile in canine model of amyotrophic lateral sclerosis: A preliminary study in developing blood-based biomarker for neurodegenerative diseases.

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ABSTRACT

Objective: Blood-based biomarkers provide a crucial information in progress of neurodegenerative diseases with minimally invasive sampling method. Validated blood-based biomarker application in people with amyotrophic lateral sclerosis would derive numerous benefits. Canine degenerative myelopathy is a naturally occurring animal disease model to study the biology of human amyotrophic lateral sclerosis. Serum derived exosomes are potential carriers for cell-specific cargoes making them ideal venue to study biomarkers for a variety of diseases and biological processes. This study assessed the exosomal proteins that may be assigned as surrogate biomarker that may reflect biochemical changes in central nervous system.

Methods: Exomes were isolated from canine serum using commercial exosome isolation reagents. Exosomes target proteins contents were analysed by Western blotting method.

Results: The profiles of potential biomarker candidates in spinal cord homogenate and that of serum-derived exosomes were found elevated in dogs with degenerative myelopathy as compare to control subjects.

Conclusions: Serum-derived exosomal biomolecules can serve as surrogate biomarkers in neuro degenerative diseases.

Rat Resource and Research Center

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The Rat Resource and Research Center (RRRC) was established in 2001 with funding from the National Institutes of Health (NIH). The goals of the RRRC are to 1) shift the burden for maintaining and distributing rat models from individual investigators to a centralized repository, and 2) provide the biomedical community with ready access to valuable rat strains/stocks and other related services that enhance the use of rats in research. Currently, the RRRC has over 540 rat lines received through active recruitment of important rat models and donations from investigators. Upon importation of strains/stocks into the RRRC, sperm and embryos are cryopreserved to ensure against future loss of the model. The RRRC distributes live animals, cryopreserved sperm and embryos as well as rat embryonic stem (ES) cell lines. Quality control measures for all materials include extensive genetic validation and health monitoring. The RRRC has unique capabilities not readily found elsewhere including, in conjunction with the MU Animal Modeling Core, the ability to make genetically engineered rat models using a variety of state-of-the-art technologies including genome editing (i.e. CRISPR/Cas9) as well as traditional methods such as random transgenesis and modified embryonic stem cell microinjection into blastocysts. Due to high success rates with intra-cytoplasmic sperm injection, the RRRC uses sperm cryopreservation as a cost-effective method for banking large collections of single gene mutations and ensuring reliable recovery when models are requested. The RRRC has expertise in rat reproductive biology, colony management, health monitoring, genetic assay development/optimization, and isolation of germline competent ES cell lines from transgenic rats; our staff and researchers are readily available for consultation and collaborations. The RRRC has a number of fee-for-service capabilities such as a wide variety of genetic analyses, cytogenetic characterization including spectral karyotype analysis, strain rederivation, strain creation, spermatozoa cryopreservation, isolation of specific rat tissues and microbiota characterization. Our website (www.rrrc.us) allows user-friendly navigation and provides information about all strains/stocks, cell lines, model donation procedures, on-line ordering, lists of services, and protocols. Current research efforts include generation and characterization of a variety of new rat models using CRISPR/Cas9 technology, refinement of models, characterization of the rat microbiota and its influence on model phenotypes, and improvements to rat in vitro fertilization. In addition to the RRRC, the University of Missouri is home to two other NIH-funded animal resources: the MU Mutant Mouse Resource and Research Center (MMRRC) and the National Swine Resource and Research Center (NSRRC) as well as the MU Metagenomics Center (MUMC) and MU Animal Modeling Core (AMC). Together, these highly collaborative groups provide a variety of animal model-related services across species to facilitate biomedical research.

MU Animal Modeling Core (AMC)

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Genome editing in animal models allows scientists to study how genes function by helping them to better understand animal and human diseases caused by specific DNA mutations or defective proteins. Genetically modified animals have been widely used in developing new treatments for conditions ranging from cancer, neurological diseases, and immune disorders to extremely rare diseases found around the world. The Animal Modeling Core (AMC) offers a wide variety of services associated with creating and characterizing genetically modified animal models. Along with traditional approaches such as random transgenesis and targeting embryonic stem cells, the AMC utilizes cutting-edge genetic modification tools such as the CRISPR/Cas system when generating animal models. CRISPR/Cas technology can be used in virtually any species and is completely customizable in regards to what genetic alterations to make. The AMC has established an efficient pipeline to create personalized human variant single nucleotide polymorphism (SNP) animal models to recapitulate specific human diseases. This pipeline includes zygote electroporation of CRISPR/Cas reagents along with a single-stranded DNA template containing the desired human variant SNP. Recently, the AMC has generated an array of personalized mouse lines modeling Spinal Muscular Atrophy with Respiratory Distress Type-1 (SMARD1). These models were generated by introducing specific human variant alleles to mimic the human disease linked to specific SNPs. These models represent the first SMARD1 mouse models that include an associated respiratory phenotype more closely recapitulating the human SMARD1 disease than past models. In conjunction with generating the SMARD1 mouse models, the AMC has created several other personalized mouse and rat models with human variant SNP alleles using this same pipeline. These types of services will further facilitate personalized medicine aspects of biomedical research.

Jaw Bone Length is Altered by Pharmacological Inhibition of Matrix Metalloproteinase-9

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Defects in craniofacial bone are one of the most common birth defects; among these are defects in jaw length (micro- and macrognathia). Micro- and macrognathia negatively affect quality of life by interfering with mastication and breathing, but the only available treatment option is multiple invasive surgeries, making ameliorative pharmacological interventions highly desirable. Lower jaw bone modeling and remodeling during development is complex and not fully understood, but previous data from our lab demonstrated a role for bone-resorbing osteoclasts in establishing lower jaw length. Matrix metalloproteinase-9 (MMP9) is a proteolytic enzyme secreted by osteoclasts during bone resorption. Aligning with known increases in osteoclast activity over the course of jaw bone development, qPCR analysis of MMP9 expression in embryonic Japanese quail (*Coturnix japonica*) lower jaws increases 34-fold from the developmental stage just prior to onset of bone resorption to the developmental stage when the facial skeleton is largely calcified ($n=7$/group, $p<0.0005$). We tested the effect of inhibiting MMP9 by delivering a single dose of a pharmacological inhibitor of MMP9 (iMMP9; 5mg/kg) to quail embryos *in ovo* over this same window of development. Morphologically normal quail have a premaxilla that extends beyond the distal tip of the lower jaw, and 90% of embryos given control saline had the normal lower jaw to premaxilla alignment ($n=16$). In contrast, 20% of iMMP9-treated quail had a lower jaw that was equal in alignment to the premaxilla and an additional 25% of iMMP9-treated quail had a lower jaw that protruded past the premaxilla ($n=20$). Control and iMMP9-treated quail skulls were scanned via microcomputed tomography and analyzed using Drishti software. iMMP9-treated quail had a significantly longer lower jaw bone than control quail, as well as a significantly higher lower to upper jaw ratio than control quail ($n=5$-6/group, $p<0.05$). Our data suggest manipulating bone resorption through pharmacological modulation of MMP9 activity is a potential option for altering lower jaw length developmentally.
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The Profile of Post-Translational Modifications of TDP-43 in Neurodegenerative Diseases: A Blood-Based Biomarker Development

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ABSTRACT

Objective: To develop a blood-based biomarker for neurodegenerative diseases is a much needed tool for clinicians. Well-developed and validated blood-based biomarker will serve in early diagnosis for neurodegenerative diseases and screening purposes for patient recruitment in clinical trials. In our research, we will attempt to establish a portfolio of post-translationally modified TAR-DNA/RNA binding protein (TDP-43), a regulator of nuclear transcription factor, in platelet lysate obtained from patients with Amyotrophic Lateral Sclerosis (ALS) and agematched healthy subjects. Our aim is to identify the most prominent post-translationally modified TDP-43 derivatives as an ALS-specific biomarker and to demonstrate that such assessment can be performed in peripheral tissue such as blood. These studies will pave the road to identify disease specific TDP-43 derivative(s) that can be a potential biomarker.

Methods: Samples of ALS cytosol and age-matched controls were provided by an ALS clinic at University of Kansas Medical Center. Some platelet samples were obtained from local community blood banks for optimization studies. High-Performance Immunoprecipitation (HPIP) was utilized to enrich TDP-43 from platelet cytosol samples. The concentrated TDP-43 samples were analyzed by Western blot analysis then probed against specific antibodies including phosphorylation, ubiquitination, acetylation, cysteine oxidation, and SUMOylation. LiCor imagining and wavelength analyzing software was used to determine the level of signal intensity.

Results: The TDP-43 derived from the ALS positive sample resulted in weaker signal intensity in SUMOlyation, ubiquination, and cysteine oxidation. However, acetylation and phosphorylation of TDP-43 in the platelet cytosol obtained from patients with ALS displayed a strong signal intensity compared to the control.

Conclusion: Select post-translational modifications of TDP-43 may be used as a potential biomarker. Further validation studies and analysis must be conducted to develop potential biomarkers of ALS in the future.

Bayesian Modelling to Address the Challenges of Estimating Craniofacial Growth Patterns

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Objectives: Modelling the predicted patterns of growth in the craniofacial skeleton, both for a population and a single individual, allows estimation of peak growth velocity (PGV) and age at peak growth velocity (aPGV). Although commonly used polynomial models are flexible, they suffer from the absence of an asymptote at growth cessation. The double logistic growth model is preferred from a biological standpoint but is sensitive to its starting values, often leading to convergence failures. This study developed Bayesian multilevel double logistic growth models for linear metrics of craniofacial growth.
Methods: We studied longitudinal growth using multilevel double logistic models of 12 linear measurements using 14,891 lateral cephalograms from the Craniofacial Growth Consortium Study in females and males across ages 2.5 to 28 years (870 individuals per sex; median 9 cephalograms per individual). This model included six parameters, including an asymptotic maximum at growth cessation. Peak growth velocity (PGV) and age at peak growth velocity (aPGV) were determined via differentiation. Models were estimated using the stan programming language (ver. 2.19) in R (ver. 3.6.1), yielding posterior parameter and derived quantities of PGV and aPGV.
Results: Longitudinal growth in all measurements was successfully estimated using Bayesian inference. Across all traits, estimates of PGV and aPGV differed between females and males, with female aPGV occurring on average 2.8 years earlier and male PGV 35% faster. Population-level size at growth cessation was most variable among traits, highlighting some of the challenges of multilevel non-linear models.
Conclusions: Bayesian multilevel modelling addresses many challenges of craniofacial growth estimation using polynomials. Priors inherent to the Bayesian framework loosely constrain parameters, resulting in excellent model performance and both population- and individual-level predictions that may be used to assess growth potential and inform the timing of orthodontic treatment.

Evaluation of Tibiofemoral Motion in ACL Deficient Populations

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INTRODUCTION: Anterior cruciate ligament (ACL) injuries are one of the most common disorders of the knee with over 200,000 injuries occurring annually in the US[1]. An understanding of the normal range of tibiofemoral motion in a healthy population is necessary for identification of abnormal motions linked to ACL injury risk and pathology. Proper treatment of ACL injuries can help prevent further degenerative changes such as osteoarthritis[2]. Measurement of bone motion during dynamic activity for healthy and ACL deficient populations can differentiate pathological knee motion related to injury. While there are several technologies available to investigate tibiofemoral motion in three planes, many are limited by cost, skin artifact, and portability. This study used electromagnetic motion sensors and custom clamps to efficiently measure tibiofemoral motion in the clinic in both healthy and ACL deficient populations.
METHODS: Electromagnetic sensors were attached to 3D printed custom pieces fixated to the bony landmarks of the distal femur and proximal tibia. The femoral clamp provided a compressive fit across the condyles, while the tibial clamp was fixated immediately inferior to the tibial tuberosity on the anterior crest. A series of calibration steps and computational algorithms determined the knee axis of rotation and anatomical axes. Relative motion of the two sensors was then translated into anatomically relevant coordinates to acquire flexion-extension, varus-valgus, and internal-external rotation angles. Three cycles from each participant were used for analysis of lateral step-down and step-up and over tasks.
RESULTS: Following Institutional Review Board approval, the device was used to evaluate knee motion during functional tasks for healthy control (n=20, 14 female, 25.6 ± 5.0 years) and ACL deficient populations (n=20, 8 female, 31.3 ± 10.5 years). Comparison of cycle normalized ensemble averages showed statistically significant differences in internal-external rotation between ACL deficient and healthy populations for 90% of the cycle during step-up and over tasks and 100% of the cycle for lateral step-down tasks.
DISCUSSION: Tibiofemoral motion data was efficiently and accurately collected for both normative and pathological patients in a clinical setting. The ACL deficient group showed more external rotation during both tasks. This aligns with previous data[3]. Bilateral differences in control data may be due to inherent morphological differences[4] or task learning. Such real time data may be useful as an early screening and diagnostic tool for clinicians including physical therapists, athletic trainers, and orthopedic specialists when treating, operating on, and evaluating patients with ACL injuries.
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Identification of the Human Retinal Dystrophin Promoter: A Potential Pharmaceutical Target for Duchenne Muscular Dystrophy

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ABSTRACT

Duchenne muscular dystrophy (DMD) is an X-linked genetic disorder that affects 1/3,500 males. Clinically, DMD presents with progressive muscle degeneration, scoliosis, loss of ambulation at twelve years of age, in addition to respiratory and cardiac complications. Death usually occurs around age twenty due to pulmonary and/or cardiac failure. Mutations that cause DMD lead to a lack of dystrophin. Currently, glucocorticoids are used to improve the patient's quality of life. There is no current cure for DMD. The goal of our research is to develop a novel pharmaceutical treatment for DMD, utilizing an isoform of human dystrophin, called retinal dystrophin (Dp260; dystrophin protein 260 kDa), that was discovered by our lab. This isoform of dystrophin contains the same functional domains as skeletal muscle dystrophin, but is smaller in size as compared to the 427 kDa muscle dystrophin and is primarily expressed in retina but not in muscle. Our lab showed that, expression of a human retinal dystrophin transgene in muscle of a DMD model mice provides health benefits with rescue of kyphosis, significantly improved cardiac and skeletal muscle, along with normal lifespan. Currently, the long range goal is to identify and characterize the promoter region driving expression of Dp260 in a cell line (that does not produce retinal dystrophin) stably transfected with an expression vector plasmid containing the promoter. This cell line will be used for high throughput screening with thousands of drugs/biological compounds to identify those that induce expression of retinal dystrophin in the muscle tissue of DMD patients.

Comparison of Azure Kinect and Optical Retroreflective Motion Capture for Kinematic and Spatiotemporal Evaluation of the Sit-to-Stand Test

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Background: The sit-to-stand test (STS) is commonly used to evaluate functional capabilities within a variety of clinical populations. Traditionally STS is a timed test, limiting the depth of information which can be gained from its evaluation. The Azure Kinect depth camera has the potential to add in-depth analysis to STS. Despite these potential benefits, the recently released (2019) Azure Kinect has yet to be evaluated for its ability to accurately assess STS.
Research Question: Purposes of this work were to compare data captured during STS using both a 12-camera Vicon motion capture system and the Azure Kinect; and to calculate kinematic and spatiotemporal variables related to the four phases of the STS cycle.
Methods: Spatiotemporal and kinematic measures for STS were simultaneously collected by both devices for 15 participants (24.15±2.32yrs., 1739.3±97.35mm). Cycle waveforms were compared for right and left hip and knee flexion/extension angular displacement, right and left hip and knee flexion/extension angular velocity, and knee-to-ankle separation ratio. Evaluated discrete outcome variables included: phase time points (the timepoints at which phases began and ended), maximum knee extension velocity from phases 3-4, medial-lateral pelvic sway range, and total time to completion. Waveform summary data were compared using R, R^2, and RMSE. Discrete variables were analyzed using Spearman's Rank correlation coefficient.
Results: R and R^2 values between the two systems indicated high levels of correlation (all R values >0.711, all R^2 values >0.660). Although there was an overall high level of agreement between waveform shapes, high RMSE values indicated some minor tracking errors for Kinect within the STS cycle. Spearman's Rank correlation coefficient indicated high levels of correlation between the systems for discrete variables (all R values >0.89), with the exception of medial-lateral pelvic sway range.
Significance: The Azure Kinect provides valuable insight into STS movement strategies allowing for improved precision in clinical decision making across multiple clinical populations.
Acknowledgements: This study was funded in part by the University of Missouri Coulter Biomedical Accelerator.
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Impact of Human Retinal Dystrophin Expression on Cardiomyopathy in DMD Model Mice

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ABSTRACT

Duchenne Muscular Dystrophy (DMD) is one of the most common degenerative muscle diseases that impacts approximately 1/3,500 boys. This disease results in death of the patient in the third decade of life. There is currently no cure for DMD, but therapies do exist that attempt to improve the quality of life in DMD patients. Although these therapies have some success in mitigating the disease progression, all encounter immunogenicity effects because a protein that is not endogenous is produced. To combat these challenges, our lab is studying a potential novel therapy of expressing retinal dystrophin (Dp260; Dystrophin Protein 260 kDa) in muscle as a curative treatment. A human Dp260 transgene was generated to assess the effects of expressing retinal dystrophin in muscle tissue of DMD model mice. We showed the presence of the transgene in DMD mice had significant results when comparing to DMD mice without the transgene. DMD mice exhibit scoliosis (severe curvature of the spine), cardiomyopathy, and experience a shortened lifespan (4-5 months for DMD vs. one year or more for normal mice). DMD mice that express the Dp260 Tg are rescued from almost all harmful pathological defects. Dp260 expression alters DMD mice from a lethal, severe myopathy into a mild, viable myopathy. DMD Tg mice also exhibit a normal lifespan when compared to normal control mice. The focus of my research is to collect more data on the presence of cardiomyopathy in DMD model mice and compare the cardiac tissue to DMD mice that possess the transgene. This, along with functional studies, should yield imperative data on the extent of Dp260 expression on improving the cardiomyopathy phenotype of this disease.

Interval walking effect on people with knee osteoarthritis

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ABSTRACT

People with knee osteoarthritis (KOA) often complain the increased pain after physical exercise such as walking. A past study indicated that interval walking may reduce pain level compared to the continuous walking in people with KOA, but their intervention was only one exercise session. In this pilot randomized clinical trial, we examined the effect of interval walking (IW), and continues walking (CW) exercise for 6 weeks on the pain and fitness level of the subjects with KOA.

Sixteen participants with KOA were randomly assigned to either an IW group (n=8), or CW (n=8) group. They all completed an exercise program with 30 minutes of walking exercise, 3 times/week over a period of 6 weeks. The participants in the IW group were asked to complete the 30 minutes in 2 bouts (15 minutes each) and have 30-40 minutes resting period between the 2 bouts. The participants in the CW group were asked to walk for 30 minutes in one continuous bout. Pain level using the visual analogue scale and fitness level using the 6-minute walk test were assessed at baseline and at the end of the exercise program.

There was significant decrease ($p<0.05$) in pain level within both groups post intervention compared to baseline. There was significant difference in the change of pain score pre- to post- intervention between groups ($p<0.05$) favoring the IW group. In addition, there was significant improvement in fitness level in the IW ($p<0.01$) but not in the CW ($p=0.095$) group pre- and post-intervention. However, there was no significant between groups differences in the change of fitness level at the end of the study.

The results of our pilot trial show that walking exercise in separate interval bouts might be more effective in reduce pain and improve fitness, as compared to walking exercise in one continuous bout in people with KOA.

Investigating the respiratory defects in a novel patient-based spinal muscular atrophy with respiratory distress type 1 (SMARD1) mouse model

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Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is an infantile motor neuron disease characterized by respiratory impairment and distal muscle atrophy that results in death within 13 months of age. SMARD1 is caused by mutations in the *Immunoglobulin-m-DNA Binding Protein 2 (IGHMBP2)* gene. To better understand SMARD1 disease progression, we generated a novel mouse model *Ighmbp2*$^{D564N/D564N}$ based on the patient mutation D565N. This mutation lies within the helicase domain of IGHMBP2 and has been demonstrated to maintain the nucleic acid binding and ATPase function, but lacks helicase activity (Guenther et al., 2009). Structural studies suggest that this mutation is defective in translocating along the RNA (Lim et al., 2012).

Respiratory defects are a defining clinical symptom of SMARD1 and has not been identified in SMARD1 animal models. We assessed whether *Ighmbp2*$^{D564N/D564N}$ mice demonstrated respiratory deficiencies by conducting quantitative whole-body plethysmography on postnatal day 12 mice. Analyses were performed under normoxia and hypoxia with hypercapnia (challenge) conditions. *Ighmbp2*$^{D564N/D564N}$ mice displayed deficits in respiratory rate under both conditions, including apneas and erratic breathing, while demonstrating a higher tidal volume compared to wildtype controls. To further correlate the respiratory deficits to cellular pathology, the cervical spinal cord motor neurons were analyzed. Additionally, diaphragm neuromuscular junctions and muscle fiber size were also quantified. Currently, we are determining the extent to which the deficits exist within the respiratory pathways. By further understanding what causes the respiratory dysfunction in *Ighmbp2*$^{D564N/D564N}$ mice we can evaluate which therapeutic approaches are necessary to modify respiratory dysfunction.

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