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Cover image: Thomas Heeremans (Dutch, ca. 1640–1697), *Winter Scene by a City Wall*, ca. 1660–1697, oil on canvas, museum purchase (73.1)

The painting featured on the journal's cover is from the permanent collection of the University of Missouri's (MU) Museum of Art and Archaeology (MA&A) and is currently on view in its Gallery of European and American Art. Located in Columbia, Mo., in the lower east level of Ellis Library on MU's campus, the MA&A boasts more than 16,000 objects spanning six continents and 6,000 years. Admission to the MA&A is always free. For more information, visit maa.missouri.edu.

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Letter from the Founding Facilitator for Volume 5, Issue 3

Dr. Richard J. Barohn, MD

For this final issue of the calendar year, we open with a eulogy I recently gave at the funeral of Arthur (Art) Dick, MD and his obituary. Art was a professor of neurology at the University of Kansas Medical Center and my colleague for almost 20 years. We worked in the Muscular Dystrophy Clinic side by side for many years. He passed away at the age of 90. In his later years, after he retired, Art was one of the most active reviewers of articles for this journal, for which I am forever grateful. Next, my good friend Dr. Josh Freeman discusses the issue of primary care physicians versus nurse practitioners. We always appreciate Josh's big picture insight into the issues facing health care in America.

In the New Stuff (new discoveries and original research) section, Dr. Moussallem and colleagues performed a multicenter study and concluded they could find no association between the severity of MG and COVID-19 infection. Dr. Robbins and team conducted an interesting study regarding vibration perception in dementia and conclude poor cognition is associated with worsened vibration perception thresholds. In the Clinic Stuff section (case reports), Ensign Loran Grant, a medical student at the Uniformed Services University of the Health Sciences and her physician mentors in the military, report a case of treatment refractory polymyalgia rheumatica that is paraneoplastic, which improved after tumor resection. Dr. Conway, Dr. Bhansali, and our associate editor Dr. Yuebing Li describe a case of an 83-year-old with late onset spinobulbar muscular atrophy (SBMA) who incidentally had a normal creatine kinase. This may be the oldest reported case of SBMA. The last case report is by Dr. Patel and colleagues at the Cleveland Clinic. They report an interesting case of chronic inflammatory demyelinating polyradiculopathy as a paraneoplastic manifestation of metastatic melanoma. In the Looking Back/Looking Forward section (reviews), Suzann Beaupark provides her interesting historical perspective on myasthenia gravis.

The art on the cover I selected again comes from the University of Missouri Museum of Art and Archaeology, with the help of Marie Nau Hunter, the Deputy Director of the museum. It is a wintery scene from Holland in the 1600s by the Dutch painter Thomas Heeremans (1640-1697). The painting is titled *Winter Scene by a City Wall*, and it is on permanent display in the museum in Columbia, Missouri. I thought it was appropriate for a December issue.

Have a Happy Holiday and Happy New Year! Looking forward to 2025 and Volume 6 of the RRNMF Neuromuscular Journal.

Thank you as always for all who make each issue of this journal possible. I am very grateful to you all.

Rick

Eulogy for Dr. Arthur Roland Dick

Dr. Richard J. Barohn, MD

November 16, 2024
Newton, KS

First of all thank you Julie and Jeff and Amy and Steve for allowing me to say a few words about my friend Art Dick. For those of you who do not know me, I am Rick Barohn, and I worked with Art at the University of Kansas Medical Center (KUMC) from 2001 until Art retired in 2019. We all know the Art Dick story and about his family's migration from Canada to the US. And how Art ended up at Bethel College as a student and met Betty and how Art forever more became a Kansan. And we know after Art completed medical school in Maryland and time in the Army as a researcher, he and Betty settled in Prairie Village and Art began his amazing career as a neurologist at the University of Kansas Medical Center where he had a storied 50-year career retiring as a Professor Emeritus.

We know Art was a leader in the field of neurology, especially in the areas of stroke and muscular dystrophy.

And we know he was a pillar of the academic community at KUMC and had many, many important administrative positions over his long career.

And we know what a wonderful physician he was to thousands of grateful patients and what a wonderful teacher he was to thousands of medical students and residents.

But let me tell you all about three things about Art and me you may not know.

First, I met art Dick when I did a neurology rotation at KUMC under him and Dr Ziegler in either 1978 or 1979. I was a University of Missouri Kansas City (UMKC) student and was thinking about a neurology career. The neurology department at KUMC then was really outstanding under the leadership of Dewey Ziegler and Art Dick. I was in awe of both of them. It was here I first witnessed Art's presence as both a leader in the field and for being an amazing physician and teacher. My one-month rotation with Art solidified my intention to pursue neurology as my career.

Second, in 2001 I arrived at KUMC to be the new department chair. The department had been struggling for over a few years and I was brought into bring new energy and ideas. I did a financial evaluation of the department and found the doctors could find ways to improve the department's finances. As a young 45-year-old chair with little experience, I put in Art's annual evaluation something about how he could help, and the next thing I knew he and I were summoned to the Dean's office. The Dean proceeded to give us a lecture on productivity and the only think I could think of was "what have I done!!". This is my hero in neurology and because of my junior chair mistake on what I put in his annual evaluation. Art was called to the principal's office! But Art never said a word about it to me. He and I continued as partners in the department for almost 20 years, working side by side in the Muscular Dystrophy Clinic. I of course never brought it up either, but it was one of the early administrative mistakes I made. And I learned from that mistake and always kept in mind the proper way to treat our senior physicians with respect-both for their sake and because one day you will be a senior physician! I had planned to reminisce with Art about this during my planned visit with him in October but that visit never happened. I did talk to Art on the phone about a week before I was to come to Newton. We were so looking forward to catching up. He wanted to meet me to meet all of his friends in the men's social club. He told me this group of men solved all of the problems of the world every Thursday morning and I was looking forward to meeting them. I am glad I am getting to say hello to many in that group today who are here.

The third story is how Art and I have stayed connected since he moved to Newton and I moved to Columbia, Missouri. When I left KUMC in 2020 I had just started a new neurology journal called Rick's Real Neuromuscular Friends Neuromuscular Journal. I asked Art if he would be willing to be a reviewer of articles and he said "yes". Art became my most reliable reviewer. I could always count on him to be the nice reviewer who could give the young authors constructive and solid advice on how to make the article better. I was still sending Art articles in just the last couple of months, and we talked about this during our call in October. I would hear from Julie how much he enjoyed it when I sent him an article to review, and he would get help from the local librarian at the local medical center to pull the relevant new articles on whatever the submission was about so he would be knowledgeable about the topic. I believe Julie would help him with the on-line submission portal which he learned how to negotiate but he wanted to make sure his comments got back to me without glitches. Art really cared that he did a productive, valuable review and that it got turned in on time and they always were.

Well, those are my three anecdotes about my beloved friend Arthur Dick. Art we all miss you so much already, but I know I and thousands and thousands of medical colleagues, students, residents, patients and their families feel so very privileged that we had you in our lives. God bless you, Arthur Roland Dick.

Dr. Dick and the neuromuscular team from the University of Kansas Medical Center at the annual Carell-Krusen Neuromusucular Symposium in Dallas, Texas. The KUMC group made an annual pilgrimage to Dallas for this great meeting. One of the highlights was eating contraband tacos from Taco Cabana from my rental car's trunk. The hospital would not let me bring in food from the outside, so every year we improvised and had our own breakfast in the parking lot before the meeting started. Dr. Dick loved this ritual.

Dr. Dick, myself, and Dr. John Redford on television for the old-fashioned annual MDA telethons for muscular dystrophy in the early 2000s.

Not enough primary physicians OR Nurse Practitioners: It's the money, stupid!

Joshua Freeman, MD

Originally published in Dr. Freeman's blog "Medicine and Social Justice." https://medicinesocialjustice.blogspot.com/

"Like doctors, more nurse practitioners are heading into specialty care" is the title of a recent article in the Washington Post (June 17, 2024) by Michelle Andrews, a contributing writer for KFF News, and McKenzie Beard. It makes the point that

> Nurse practitioners have long been a reliable backstop for the primary-care-physician shortfall, which is estimated at nearly 21,000 doctors this year and projected to get worse. But easy access to NPs could be tested in coming years. Even though nearly 90 percent of nurse practitioners are certified to work in primary care, only about a third choose the field, according to a recent study.

That study, called 'No One Can See You Now: Five Reasons Why Access to Primary Care Is Getting Worse (and What Needs to Change)' was published by the Millbank Memorial Fund, and goes on at length to explain those reasons, and what needs to change.

> Spoiler Alert: Like physicians, primary care nurse practitioners make less money, often for more work, and far less restricted scope of practice. Or, borrowing from an old political mantra, "It's the money, stupid!" Or, as the WaPo article quotes Candice Chen, an associate professor of health policy and management at George Washington University, "We get what we pay for."

It is, of course, more than just the raw amount of money. It is also how much NPs – and physicians – are paid for the amount of work that they do. This work is undervalued for primary care, based upon the notion that, somehow, being expert in a narrow specialty and knowing a lot about a little, is worth more than having a broad knowledge and being able to help a lot of people, most people, a great deal. Thus, subspecialists dramatically limit their practices to what they feel most expert at and expect the primary care clinician to do everything else. This often includes preparing people for a procedure and following them up after, which are both completely the responsibility of the person doing the procedure. Subspecialists particularly like to send paperwork back to primary care. "Your primary care doctor (or NP) will have to take care of this." Implication: 'Unlike primary care clinicians, I do important things.'

I would argue that managing people's health is doing important things. Which is what the primary care clinician (family physician, general internist, general pediatrician, or the NPs that work in these fields) does. Managing the actual person, you, not just one of your diseases, or one aspect of one of your diseases; being knowledgeable about you, your life, and the interactions of all your conditions and the impact that they have on the rest of your life.

How might this manifest? Let's say you have knee pain. You go to your family physician, who examines it, and decides that you need an x-ray. They review the x-ray and the report, and decide that you might benefit from seeing an orthopedist. They fill out the referral. Then, after the consultation and recommendation from the orthopedist, they review it, and decide how to implement the treatment. That is a lot of work. The orthopedist was done in a few minutes. Guess who gets paid, altogether, more?

Like the physicians that employ them, NPs are often very expert in their limited area (say, heart failure management), but often do not know how to manage that problem in the context of a person whose other diseases or medications may complicate that. This is where the (underpaid) primary care clinician, physician or NP, has to come in. It is a lot of responsibility, a lot of work, and often a lot of extra hours. One NP profiled in the WaPo article is taking training to become a dermatological NP. This is one of the medical fields with the highest pay/work ratios. Most of its work is not emergent and can conveniently be scheduled during the day during the week, and is less likely than many other specialties' work to interfere with treatment for other conditions. And it is very highly reimbursed.

Should people be paid based upon the amount and difficulty of their work? If we did, people doing the most difficult work that everyone agrees needs to be done but that most people do not want to do (e.g., picking up the garbage, doing farm work in the hot sun) would be paid more than those who get fancy offices and lots of perks and boss folks around (e.g., CEOs). But difficult can have other definitions; this is really a separate discussion. In health care, for physicians (and now NPs) it should be how they contribute to the system. Currently the usual measure is money, that is, how much a given practitioner brings into the practice, or more commonly now, to their employer (often a health system), which is based on how much payors (insurers) pay for different things. That amount is not God-given, but a matter of policies that could be changed. Two mechanisms through which the amount of reimbursement is set are the RUC and the facility fee. The RUC is a group of non-governmental physicians appointed by the AMA that makes recommendations on how Medicare money should be divided up between specialists – like "one gallbladder removal is worth 6 complete examinations", or whatever. Medicare is not required to accept their recommendations, but they usually do. And – surprise – the RUC is mostly made up of subspecialists, not primary care clinicians!

The facility fee is an amount that Medicare (and other insurers, see below) tack on to the physician fee if the practice is owned by a health system rather than a physician,

and is often several times the fee for the procedure. To be clear, this means that if I receive a procedure today from a physician in his office and you get the same procedure in the same office by the same physician next week, but in the interim that practice has been acquired by a health system, the charge will be MUCH more. Medicare or your insurance may pay it, or most of it, but your co-pay will be much higher, and all of our premiums go up. This practice is hardly ever made apparent or explained in advance to patients ("Hi, thanks for calling. Just to let you know, Dr. Smith's practice was just acquired by the MuchProfit Health System, so you will be charged three times as much for your procedure as you would have been last week.") This is so insidious (not to say evil, but it is evil) that even doctors are often surprised, as revealed in the essay by Dr. Danielle Ofri in the New York Times (June 17, 2024) 'Even Doctors Like Me Are Falling Into This Medical Bill Trap' and the follow-up letters and comments from other physicians.

The fact that facility fees and the RUC are about Medicare does not mean that they do not affect the fees, cost, and reimbursement from other insurers. Almost all insurers payment rates are set as multiples of Medicare. That is, if Medicare pays $100 for something, they may pay $150 or $200 (and, more recently, those multiples are lower, with patient responsibility higher). Changing these two factors, facility fees and RUC allocations, for Medicare will affect all insurers and make a real difference in income (which is why most subspecialists and hospitals oppose them).

Should primary care clinicians be paid more, or subspecialists less, or somewhere in between? Whichever, by decreasing the difference more clinicians are likely to enter primary care specialties. And, whichever, the raking off of facility fees to increase the wealth of hospitals, not to mention the pocketing of huge profits by insurers, has to stop.

Lack of Relationship Between Myasthenia Gravis and COVID-19 Severity

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Introduction

Myasthenia gravis (MG) is the most common autoimmune neuromuscular junction disorder.[1,2,3] The course of MG is punctuated by exacerbations or frank crises leading to respiratory failure. MG patients are often immunosuppressed by immune modifying pharmacotherapy. As a result, it is conjectured that MG patients may be highly vulnerable to COVID-19 infection and its complications,[4] including respiratory involvement. Although MG is a rare disease with a prevalence of 36,000 to 60,000 cases in the United States,[5] the wide-spread nature and infectivity of SARS-CoV-2 mandate a greater understanding of the relationship between COVID-19 and MG. It is important to correlate the severity of MG with COVID-19 infection and to look at the impact of immunosuppression on MG severity.

As COVID-19 spread worldwide at a very high rate and capacity for mutations, there has been scant research on the relationship between viral infection and MG. A large study of 3,558 registered MG patients in France suggested a limited effect of COVID-19 on MG patients, although it did not use a MG severity measurement but instead relied on Myasthenia Gravis Foundation of America (MGFA) classification.[3] In contrast, Jakubíková, et al.[7] found that 38% of infected patients developed severe pneumonia and 11% died in a cohort of 93 MG patients in Czech Republic. Another study of CARE-MG registry identified a death rate of 24% of 91 MG patients due to COVID-19 without severity assessment of MG prior to COVID-19.[8] A study done by Ozlem, et al.[16] concluded that having well-controlled MG before infection and absence of comorbidities likely affected the course of the infection favorably and that immunosuppression did not influence the progression. Furthermore, a Brazilian study with 15 hospitalized MG patients showed that 73% needed mechanical ventilator support during MG, limiting the study to hospitalized patients and potentially obscuring general population representation.[9]

Our main objective is to study whether the baseline MG severity predicts complicated COVID-19 disease course and assess if immunosuppressive medications and MG severity are contributing factors.

Methods

Data Collection and Participants

This study is an IRB approved observational multicenter study done at seven neuromuscular centers within the United States of America (Table 1). MG patients with positive SARS-CoV-2 PCR virus testing were included. MG diagnosis was confirmed by immunological or neurophysiological testing. Immunological testing was considered positive if the patient had a positive acetylcholine receptor or MUSK serum antibody. Neurophysiological diagnosis of MG was based on >10% decrement on repetitive nerve stimulation study. Each subject was assigned a numerical identifier before being surveyed. The personal data of subjects was confidential and only accessible by the principal investigator and the study coordinator. All data was saved in the research center terminals with security firewall and password protection. Review of the deceased medical record was also confidential and accessible to only authorized personnel from the available electronic medical records. All subjects had signed a privacy practices acknowledgement and requested restrictions form. Before research conduction, all involved research personnel underwent a training session on handling private medical and personal information. A verbal informed consent was obtained from subjects by the surveyors. A detailed explanation of the purpose, design, and use of information was discussed with the subjects, as well as their ability to withdraw their responses from the research at any time. Patients were asked to respond to a questionnaire by phone calls or asked by surveyors to fill online forms of the questionnaire. The questionnaire is included in the appendix section and was performed after developing COVID-19 infection. The time duration between positive SARS-CoV-2 PCR testing and questionnaire administration was not limited or specified as the interviews were conducted in early 2022, but the time ranged from one month to two years. The aim of the questionnaire was to assess the severity of COVID-19 infection and MG status four weeks before testing positive for COVID-19. It included introduction, demographic data, vaccination status, COVID-19 symptoms, MG weakness type, immunosuppressive treatments received, and the MG-QOL15r questionnaire. MG severity was assessed based on the well validated MG-QOL15r questionnaire, which requires little time to administer and is easy to interpret. This questionnaire comprises 15 questions on

how disease symptoms affect the patient's mood, ADLs, work, and social activities.[15] MG-QOL15r score of 0-9 is considered mild MG, 10-19 moderate MG, and 20-30 severe MG.

Questionnaire

Patient data was collected including patient's gender, age, date of myasthenia gravis diagnosis, SARS-CoV-2 virus PCR positive testing and SARS-CoV-2 vaccination status. Symptoms of COVID-19 infection were categorized as:

- No symptoms or mild category (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, and loss of taste and/or smell);
- Moderate category includes patients with pneumonia discovered during clinical assessment or chest imaging; or
- Severe category if patients were admitted to ICU, had SpO_2 <94% on room air at sea level, or were put on a ventilator (NIV included).

During the four weeks before COVID-19 infection, the severity of MG was assessed as:

- Mild severity defined as weakness affecting the eye muscles (e.g., double vision or droopy eyelids);
- Moderate severity with weakness affecting the speech and swallowing muscles (e.g., choking or speech difficulty); or
- Severe severity by weakness affecting other parts of the body (e.g., breathing difficulty, severe leg and/or arm weakness, or death).

MG immunotherapeutic type and dose of medications during this period included steroids, non-steroidal immunosuppressive medications (azathioprine, mycophenolate, tacrolimus, cyclosporine, or methotrexate), rituximab, eculizumab, IVIG, plasma exchange, or none. The steroids dose was further classified as either low dose, considered to be equal to or less than 20 mg by mouth every other day, or high dose steroids, being greater than 20 mg by mouth every other day. The MG-QOL15r questionnaire included items that reflect physical, psychological, and social domains of patient well-being based on the impact MG has had on their quality of life over the four weeks prior to COVID-19 infection. Scoring as 0 if no symptoms, 1 if somewhat had symptoms and 2 if patients had a lot of symptoms in an item affecting QOL. The highest/worse total score was 75.[14]

Data Analysis

Baseline characteristics including age, sex, SARS-CoV-2 vaccination status of each participant were described in all seven centers based on the severity of COVID-19 infection and MG disease severity. For analyses, patients were grouped into four categories based on COVID-19 infection severity (mild, moderate, severe, and death) and MG disease severity was categorized as either mild, moderate, or severe. To evaluate variables that could affect the severity of COVID-19, a univariate logistic regression model analyses was performed with severity of COVID-19 as the dependent variable and the following factors as independent variables: risk factors for COVID-19 including age (≤65 years vs >65 years), sex, COVID-19 vaccination status, MG severity, MG weakness type (generalized vs ocular), MG medications, and high dose steroids groups (2 groups, yes or no). A multivariate ordinal model, wherein a p-value of <0.05 was considered statistically significant studied association between COVID-19 high severity and independent variables including age, sex, COVID-19 vaccination status, and MG severity. A subgroup analysis was done to study association between COVID-19 high infection severity and MG high disease severity in each group of MG weakness type (generalized or ocular), MG medication and high dose steroids (yes or no) based on logistic regression model.

Results

- Patients' Baseline Characteristics

A total of 90 patients from seven neuromuscular centers in the United States were included in this study between December 2021 and August 2023. The mean age of patients was 59.8 (+/- 17.2). Of the total patients included, 48 had an age >65 years and 42 patients had an age ≤65 years. There were more males recruited at four centers, whereas an equal sex distribution was observed in the remaining three centers. Overall, 52 patients were male patients and 38 were female patients (Table 1). Moreover, due to the limited number of participants in the COVID-19 partially vaccinated group number (n=2), we combined partially, and fully vaccinated groups as an ever-vaccinated group. There were 28 patients not vaccinated, and 62 patients were considered in ever vaccinated group. Six out of seven centers had higher percentage of patients who were ever vaccinated.

- COVID-19 Infection and MG severity

The severity of COVID-19 infection and concurrent myasthenia gravis disease severity was assessed as shown in Table 2. COVID-19 infection severity was considered either Mild (n=67 patients), Moderate (n=8), Severe (n=8), or "Death" (n=7). MG severity was categorized into mild, moderate, or severe. The highest percentage of patients was found under the mild categories of both COVID-19 infection and MG severity (49 patients).

Due to the limited number of participants in some COVID-19 severity groups, mild and moderate severity groups were combined as the "Low severity" group and severe and death severity groups as the "High severity" group. A total of 75 and 15 patients were considered to belong to "Low severity" and "High severity" COVID-19 infection groups, respectively. Likewise, due to the limited number of participants in some MG severity groups, moderate and severe groups were combined as a "High severity" group. Mild severity is defined as the "Low severity" group (Table 3). Upon cross tabulation of patients with COVID-19 infection severity and myasthenia gravis

severity, we found low MG severity to be comparable in frequency in the low severity (73.33%) and high severity (66.67%) COVID infection patient groups.

- Factors associated with COVID-19 severity

We studied factors associated with COVID-19 high severity using the univariate logistic regression model (Table 4). In the COVID-19 high severity group, 11 patients (73.33%) were older than 65 years of age and four patients (26.67%) were 65 years or younger, whereas an almost equal proportion of each age group was distributed among patients with COVID-19 low severity. Age as a continuous variable was not shown to be significantly associated with COVID-19 infection severity (p=0.098). Similarly, no significant association was found between sex and COVID-19 severity (p=0.703). Ever being vaccinated against COVID-19 showed an association with low severity COVID-19 infection (p=0.003) as 57 patients (76%) were ever vaccinated and had low severity COVID-19 infection and 10 patients (66.67%) were never vaccinated against COVID-19 and had high severity COVID-19 infection.

The majority of both high (n=10 or 66.67%) and low (n=55 or 73.33%) severity COVID-19 infection groups had low MG severity. There was no significant association (p=0.569) between COVID-19 high/low infection severity and MG high/low disease severity. Similarly, we found no association between COVID-19 severity and MG weakness type (generalized vs ocular) and whether high dose of MG medication was taken or not (p=0.199 and 0.475, respectively).

After controlling for potential confounding variables, including age [≤65 vs. >65], sex, and vaccination status, there was no association (p=0.691) between COVID-19 high infection severity [Severe and Death] and MG high disease severity (Table 5). A subgroup analysis using the logistic regression model with adjustment for sex, age, and COVID-19 vaccination status showed no association between the COVID-19 infection severity and MG disease severity for all patients and each of the two subgroups: MG weakness type [generalized vs ocular] and MG high dose medication (Table 6).

Discussion

This is one of the largest multicenter studies aiming to investigate the association between COVID-19 infection severity, MG disease severity, and MG immunosuppressive medications. Except for an association of vaccination with low severity COVID-19 infection and of older age with severe COVID-19 outcomes (Table 5), we could not identify any association between COVID-19 infection severity and that of MG or its treatment.

A prior smaller study of 15 patients reported that all patients who did not require mechanical ventilation were using prednisone and a second immunosuppressant drug, suggesting a favorable course and a protective role in patients using MG drugs at baseline.[9] In the current study however, we could not replicate this finding as dose of MG medications was not associated with COVID-19 severity. Also, a French cohort[6] showed that immunosuppressants are associated with poor COVID-19 outcomes on univariate analysis but not on multivariate analysis. Univariate analysis in the French study only identified immunosuppressants use and severe MG at COVID-19 onset as risk factors, not age.[6]

These data are not contradictory and can be explained based on the results of the RECOVERY,[18] study. In it, dexamethasone was an effective treatment for severe COVID-19 and ARDS but did not benefit patients who did not require ventilatory support.[3] In our study, COVID-19 vaccination status and age were the only risk factors associated with COVID-19 disease course severity.

We could not identify an association of MG severity or its treatment with COVID-19 severity. One study concluded that clinical course and outcomes in patients with MG and COVID-19 are highly variable.[9] Another study, which might be biased towards reporting poorer outcomes, showed that MG patients with COVID-19 severe acute respiratory syndrome were frequently admitted to hospital, had disease exacerbations, and had a higher mortality than the general population with COVID-19.[5] In an International Neuromuscular COVID-19 Registry including 315 patients from 13 countries, 18% (56) of these neuromuscular cases had MG. In these 56 MG cases, 33 did not require hospitalization. Of the remaining 23 cases, 3 were hospitalized but did not require ventilation/oxygenation, 13 needed ventilation/oxygenation and survived, and 7 died. They did not find MG to be associated with higher odds of severe COVID-19.[13]

Our study has several limitations. The study design allowed for an investigation of association but not causation. A control group would have permitted us to directly compare COVID-19 patients with and without MG. Furthermore, no data analysis was performed to compare immunosuppressant dosing in MG patients who didn't develop COVID-19 with those who did develop COVID-19 infection. In a future study, this comparison would be helpful to relate the possible effect of immunosuppressant dose treatment and COVID-19 infection development. Also, given MG rarity and the limited number of study sites, our study population sample size was midsize. We relied on the MG-QOL15r questionnaire to gauge MG severity. Since it is patient-reported and has subjectivity, it might have introduced some bias. Also, the time duration between positive SARS-CoV-2 virus PCR testing and questionnaire administration was not limited or specified, and may have limited patients' ability to recall the specific details of the sickness event and to correctly answer the questionnaires, raising possible recall bias. In addition, other covariate parameters, such as hypertension or diabetes, were not studied as cofounders for high risk COVID-19 infection or MG severity. Collecting patients' comorbidities and their effects would be helpful to conclude true association

between both severities. One study showed that elderly patients with diabetes are more likely to suffer from severe COVID-19 illness, however there was no evidence of association between diabetes and COVID-19 severity.[17] Moreover, our dose cutoff value for prednisone high dose may have been too low. Despite these limitations, this study informs future design into this complex interaction between MG and COVID-19 infection.

Conclusion

Though there has been a general concern that COVID-19 infection-associated respiratory failure may trigger MG worsening and thus producing severe MG, the relationship between severity of COVID-19 infection and that of MG disease remains unknown. We could not confirm an association between severity of MG and that of COVID-19. We suspect the relationship between both diseases, if any, to be complex and multifactorial. Data from larger worldwide longitudinal studies using objective outcome measures assessed before and after emergent infection are ideally suited to provide better insight into the complex interaction between COVID-19 infection and MG clinical course.

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Appendix:

The questionnaire is previewed below:

Hello, my name is _____. I am contacting you to ask several questions as a part of a study being conducted by our center in order to understand the relationship between: the severity of COVID-19 infection and the severity of myasthenia gravis (MG) disease, the degree of immunosuppression, and prior COVID-19 vaccination. Your contribution will help us understand the effect of COVID-19 infection on patients suffering from MG. The questionnaire will only take few minutes of your time.

All your personal information is confidential, and your replies will be handled and analyzed strictly by authorized research staff.

Do you agree to participate in this study?

Yes (Subject accepted to participate verbally)

No (Subject refused to participate)

Patient died from COVID19. Date of death:

Interviewer initials:

Date of interview: / / (Month/Day/Year)

Center:

ID#:

Subject's Initials:

DOB: / / (Month/Day/Year)

Gender: Male Female Other

1- When were you diagnosed with MG? / (Month/Year)

2- Have you ever tested positive for COVID19?
   a. Yes, Date: / (Month/Year)
   b. No

3- COVID-19 vaccination status:
   a- Fully vaccinated
   b-Partially vaccinated
   b- Not Vaccinated

4- If you have tested positive for COVID-19, which of the following applies to you (*if negative, skip to question 5*)
   a. I had no symptoms or mild symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell)
   b. I had Pneumonia discovered during clinical assessment or chest imaging)
   c. I was admitted to the ICU, had SpO_2 <94% on room air at sea level or I was put on a ventilator (NIV included)..

5- During the four weeks before COVID19 infection, what type of weakness did you have from myasthenia gravis? And if you did not have COVID-19, what level of weaknesses have you had in the last 4 weeks?
   a. My weakness was mainly affected the eye muscles (double vision, droopy eyelids, etc.)
   b. My weakness affected the speech and swallowing muscles (choking, speech difficulty, etc.)
   c. My weakness affected other parts of the body (leg or arm weakness, breathing difficulty, etc.)

6- During the four weeks before COVID-19 infection, what immunotherapeutic medications were you taking for MG? And if you did not have COVID-19, what medications have you been taking in the last 4 weeks?
   a. Low dose steroid (equal to or less than 20mg by mouth every other day)
   b. High dose steroid (more than 20 mg by mouth every other day) and/or non-steroid immunosuppressive medications (Azathioprine (Imuran), Mycophenolate (Cellcept), Tacrolimus (Prograf), Cyclosporine, Methotrexate, etc.)
   c. Rituximab
   d. Eculizumab
   e. IVIG or plasma exchange
   f. I was not on any immunotherapeutic medications

7- MG-QOL15r

Please complete the following quality of life survey, grading your myasthenia gravis during the 4 weeks before COVID19 infection or 4 weeks from now if you did not get COVID-19 infection	Not at all 0	Somewhat 1	Very much 2
1. I was frustrated by my MG			
2. I had trouble with my eyes because of my MG (e.g., double vision)			
3. I had trouble eating because of MG			
4. I had limited social activity because of my MG			
5. My MG limited my ability to enjoy hobbies and fun activities			
6. I had trouble meeting the needs of my family because of my MG			
7. I had to make plans around my MG.			
8. I was bothered by limitations in performing my work (including work at home) because of my MG.			
9. I had difficulty speaking due to MG			
10. I had lost some personal independence because of my MG (e.g., driving, shopping, running errands)			
11. I was depressed about my MG			
12. I had trouble walking due to MG			
13. I had trouble getting around public places because of my MG			
14. I felt overwhelmed by my MG			
15. I had trouble performing my personal grooming needs due to MG			
Total Score:			

Vibrotactile perception depends on cognition not just peripheral nerve integrity: a cross-sectional study

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ABSTRACT

Background: Vibration perception is often considered a peripheral nerve and dorsal column function, without considering the role of cognition. The current study tested cognition's role in vibrotactile perception thresholds (VPT).

Methods: We recruited cases with mild-moderate dementia or mild cognitive impairment thought to reflect probable Alzheimer's pathology (AD/MCI group), and controls without memory concerns (all participants >50 years). Polyneuropathy, B12 deficiency, diabetes, or other conditions associated with cognitive impairment were exclusionary criteria. Participants underwent cognitive evaluation with the Self-Administered Gerocognitive Examination (SAGE), standardized nerve conduction studies, and quantitative VPT testing. Demographic and medical history were obtained through interviews and chart review. We constructed linear regression models to test whether poor cognition correlates with VPT.

Results: Nineteen AD/MCI participants (age 71.5±8.9, 47.4% female) and fourteen controls (age 67.4±9.3, 78.6% female) did not differ in age or gender. Univariate predictors of poor/increased mean VPT (all p-values <0.10) were age, AD/MCI, SAGE score, sural sensory nerve action potential (SNAP) amplitude <5 microvolts, yearly income <$50,000, history of vascular disease, and peroneal motor and sural conduction velocity (CV). SAGE score (standardized β=-0.38, p<0.01); sural SNAP amplitude (β=0.51, p<0.001); peroneal motor CV (β=-0.37, p<0.01), history of vascular disease (β=0.27, p=0.03), and female gender (β=0.22, p=0.10) remained independently associated with VPT in multivariable linear regression analysis (backward modeling; removal criteria p>0.10; model adjusted R^2=0.66; p<0.001).

Conclusions: Poor cognition is associated with worsened VPT. Neurologists should consider cognition when using sensory perception to assess peripheral nerve integrity, both for research and during a traditional neurologic examination.

Introduction

The assessment of vibrotactile perception (VP) is a canonical component of the neurological examination, used to interrogate the dorsal column-medial lemniscus (DCML) afferent pathway. Impaired VP results from interruption anywhere along the DCML's caudal-rostral extent, including "disease of multiple peripheral nerves, [the DCML], and thalamus."[1] The role of cortical function in VP is less widely appreciated. It is conceptually obvious that conscious stimulus detection must be perceived in the cortex, but few studies have formally tested cognition's role in somatosensation. Deficits in other senses have been linked to poor cognition. Poorer olfactory discrimination has long been recognized as a risk factor for cognitive impairment in both Parkinson's disease and Alzheimer's disease.[2] Poorer somatosensory and auditory perception have also been preliminarily linked to cognitive decline,[3] though this has not been well-studied. If deficient VP can be linked to poor cognition, VP testing could be used to identify those at risk of future cognitive decline or as a biomarker to track progression. In addition, since VP testing (as part of the neurological exam) is widely used for clinical localization, understanding cognition's role is crucial to correctly interpreting the exam.

In this cross-sectional pilot study, we tested the hypothesis that cognition is associated with VP thresholds (VPT).

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Dartmouth Committee for the Protection of Human Participants (STUDY#00029795). All participants provided written informed consent prior to participation.

From March 2017 to May 2019 we recruited a convenience sample from the Dartmouth-Hitchcock Neurology clinic. Cases were referred by their primary cognitive/behavioral neurologists if they were age ≥50; diagnosed with amnestic mild cognitive impairment, mild-to-moderate dementia, or major neurocognitive disorder; and Alzheimer's pathology was considered the most probable etiology. "AD/MCI" cases required glucose and B12 screening within 3 months and native English proficiency (for cognitive testing). Excluded were participants with B12 deficiency or diabetes; cognitive impairment from another condition (e.g. vascular dementia, epilepsy, Parkinson's disease); or known neuropathy. Controls were spouses of cases or members of our department. Controls were excluded for diagnoses of neuropathy; cognitive impairment or subjective concerns; B12 deficiency; or diabetes.

We calculated *a priori* that 32 total participants (16 cases and 16 controls) would be required to achieve adequate power, based on a clinically significant difference between groups in mean VPT of 25% (100 units versus 75 units), sampling ratio of 1, standard deviation of 40 units, $\beta = 0.20$ and $\alpha = 0.05$.

All participants underwent structured interviews abstracting information regarding demographics; clinical history (e.g. vascular risks, axial or sciatic-type pain; sensory symptoms; chemotherapy exposure); family history (e.g. neuropathy, dementia); Geriatric Depression Score[4]; and the Self-Administered Gerocognitive Examination (SAGE).[5] SAGE assesses multiple cognitive domains; correlates highly with neuropsychologic testing; and is both sensitive and specific for diagnosing MCI and early dementia.[5] Scores range from 0-22, with SAGE≥17 considered normal.

After limb warming to ≥30.0° Celsius, participants underwent nerve conduction studies (NCS) with our lab's trained technicians using a Natus® Nicolet VikingQuest system according to the techniques described by Preston and Shapiro,[6] including the right sural, peroneal motor, tibial motor, radial sensory, and ulnar motor nerves. Care was taken to ensure supramaximal stimulation and optimization of response according to defined landmarks and measured distances. Norms were derived from the Dartmouth-Hitchcock EMG clinical laboratory. Quantitative VPT was tested using a Vibratron II system (Physitemp Instruments, Inc., Clifton, NJ). After instructions, participants did a practice trial with finger perception. Then, seated participants placed the plantar surface of the bare right great toe (warmed >30.0°C) on the device's vibrating surface. Vibration intensity was slowly increased from 0 vibration units (VU) in 0.4 VU increments until participant's reported perception. After two practice trials, 5 additional trials were conducted, and results were averaged ("mean VPT") for final analysis. If the inter-trial variance was >20%, the procedure was repeated. Participants who did not detect even the most perceptible stimulus (210 VU) were assigned a VPT of 230 VU.

Clinical record forms were entered into a secure REDCap database. SPSS v25.0 (IBM Corp., Armonk, NY) was used for all analyses. We first compared independent variables with VPT using Pearson's *r* for continuous data, and a student's *t*-test for binary variables. We then constructed multivariable linear regression models with VPT as the outcome, entering all variables associated with VPT in bivariate analysis along with gender. We employed "backward" regression modeling (removal criteria $p>0.10$), which eliminated collinearity (e.g. between AD/MCI diagnosis and SAGE score) and produced normally distributed residuals.

Data Availability

Anonymized data is maintained securely and sharable for 10 years to qualified investigators with ethics approval.

Results

19 cases and 14 controls were enrolled. All participants completed the study. Characteristics of the sample are shown in *Table 1*. AD/MCI diagnosis closely mirrored low SAGE: 16/17 participants with SAGE≤16 had clinical AD/MCI, versus 3/16 participants with SAGE≥17 ($p<0.001$, Fisher's Exact). Although all participants saw a doctor regularly without a neuropathy diagnosis, 17/33 participants (51.5%) had at least one abnormally low amplitude SNAP or CMAP (sural <5 microvolts; distal peroneal <2.5 millivolts; distal tibial <3.5 millivolts). Age, AD/MCI diagnosis, lower SAGE, history of vascular disease, income (<$50,000/year), low sural amplitude, sural conduction velocity (CV), and peroneal motor CV were all associated with VPT ($p<0.10$): *Table 1* contains results from univariate analysis showing factors associated with VPT.

Starting with gender and all factors related to VPT in univariate analysis (except income; see below), age, AD/MCI diagnosis, and sural CV were all removed from the final regression equation. The following variables were independently associated with VPT and retained in the final model ($F(5,26)=13.1$; R^2(adjusted)=0.66, $p<0.001$): SAGE; low sural amplitude; female gender; vascular disease history; and peroneal CV (*Table 2*). In sensitivity analysis, substituting individual visuospatially-oriented SAGE questions (i.e. 7 and 8) for total SAGE produced similar results.

One participant had missing income data, so we conducted sensitivity analyses to ensure the data's fidelity: excluding that participant, including that participant with imputed income, and excluding income. Income dropped out of all models so was omitted in the final analysis (above). The analysis was repeated after logarithmically transforming VPT due to a slight right skew and ceiling. SAGE remained independently correlated [β(standardized)= -0.28; $p=0.02$;($F(3,28)=13.8$; R^2(adjusted)=0.55, $p<0.001$)].

Table 1. Characteristics of the sample and results from univariate analysis showing factors associated with Vibrotactile Perception Threshold (VPT), n = 33

Variable	median (IQR)[a], or n (%)	Difference in VPT mean*, or correlation (Pearson's r)	*p-value*
Age	68.0 (63.0-76.5)	(0.44)	0.01
Female gender	20 (60.6)	0.16	0.46
Highest educational attainment ≤ high school	12 (36.4)	0.88	0.72
Yearly income less than $50,000[b]	14 (43.8)	4.20	0.08
Diagnosis of probable AD or aMCI[c] (case)	19 (57.6)	4.56	0.02
Medical conditions			
history of vascular disease[d]	8 (24.2)	4.12	0.09
hypertension[e]	9 (27.3)	- 0.93	0.72
dyslipidemia[e]	12 (36.4)	- 0.89	0.70
self-reported history of tobacco use	16 (48.5)	- 0.01	1.00
self-reported history of back pain	18 (54.5)	- 0.60	1.00
self-reported history of radicular back pain	5 (15.2)	- 1.51	0.48
self-reported history of neck pain	7 (21.2)	- 0.15	0.95
self-reported history of numb feet	6 (18.2)	3.34	0.34
self-reported family history of neuropathy	4 (12.1)	2.10	0.67
self-reported family history of dementia	15 (45.5)	1.33	0.55
Average VPT (VPT units)	6.7 (3.7-11.7)	-	-
Geriatric Depression Score	1 (0-2)	(0.21)	0.24
Self-Administered Gerocognitive Examination (SAGE) score	16 (12-21)	-(0.50)	< 0.01
Low SAGE score (≤ 16)	17 (51.5)	4.38	0.04
Nerve conduction results[f]			
Low distal tibial CMAP (< 3.5 millivolts)	7 (21.2)	5.09	0.18
Low distal peroneal CMAP (< 2.5 millivolts)	7 (21.2)	3.45	0.29
Low sural SNAP (< 5 microvolts)	12 (36.4)	7.18	< 0.01
Absent sural SNAP	4 (12.1)	6.28	0.16
Sural SNAP amplitude (microvolts)	6.5 (4.7-9.25)	(- 0.27)	0.13
Sural SNAP conduction velocity (m/s)	47.1 (41.4-51.2)	(- 0.52)	< 0.01
Distal peroneal CMAP amplitude (millivolts)	4.2 (2.8-6.2)	(- 0.26)	0.14
Distal tibial CMAP amplitude (millivolts)	8.1 (5.6-11.1)	(- 0.14)	0.43
Peroneal conduction velocity (m/s)	44.1 (42.2-46.6)	(- 0.33)	0.06

[a] IQR = interquartile range; SNAP = sensory nerve action potential amplitude; CMAP = compound motor action potential;

* Difference in means, two-tailed t-test for Equality of Means, equal variances not assumed; [b] n = 32

[c] Cases were all diagnosed by their primary neurologist with cognitive impairment or dementia, thought to be due to Alzheimer's pathology

[d] Vascular diseases include cardiovascular, cerebrovascular, or peripheral vascular disease

[e] Hypertension and dyslipidemia = those who identified this by history, or were on medications aimed at treating these conditions

Table 2. Factors independently associated with increasing vibrotactile perception threshold (VPT)*

Variable	*p-value*	Standardized Beta*
SAGE score	< 0.01	- 0.38
Sural SNAP amplitude < 5 microvolts	< 0.001	0.51
Peroneal motor conduction velocity in the leg (m/s)	< 0.01	- 0.37
History of vascular disease	0.03	0.27
Female gender	0.10	0.22

*results from backwards linear regression (criteria for removal $p > 0.10$); n=33, with the following factors entered for consideration: diagnosis of probable Alzheimer's disease or mild cognitive impairment thought like to be due to Alzheimer's disease (AD/MCI diagnosis); sural lower leg conduction velocity (CV); female gender; age; history of vascular disease (cerebrovascular, cardiovascular, or peripheral vascular); peroneal motor CV stimulating below the fibular head and recording from extensor digitorum brevis; sural sensory nerve action potential amplitude < 5 microvolts; total Self-Administered Gerocognitive Exam (SAGE) score

**increase in VPT (vibration units) with either a) the presence of the variable (binary variables), or b) one unit increase of the variable (continuous variables)

Discussion

This study's central finding is that cognition is independently and robustly associated with vibrotactile perception, adjusting for age, gender, and peripheral nerve parameters (i.e. axonal integrity, CV). Several important corollaries follow. First, the clinical use of VP to test peripheral nerves must be filtered through the understanding that deficits localize anywhere along the DCML, and even as rostral as the cortex. Normal VP may suggest normal cognition, while impaired VP may warrant investigation. In the absence of peripheral neuropathy, lumbosacral radiculopathy, or cervical myelopathy, poor VP on neurologic exam may warrant further cognitive evaluation. Second, these results underscore that VP testing is not sufficient to establish nerve fiber loss. In other words, impaired VP has a wider differential than peripheral nerve fiber loss, and research studies that equate poor VPT with peripheral nerve dysfunction make an unwarranted assumption.[3,7] Impaired VPT can reflect peripheral neuropathy and afferent failure, but cognition and spinal conduction also influence perception. The common practice of interpreting poor tuning fork perception as a demonstration of large fiber afferent or DCML damage may be too simplistic. Similarly, the subtly decreased vibratory perception sometimes observed in the elderly may reflect cognitive impairment, not subclinical neuropathy or cervical spondylitic myelopathy. Further study is warranted.

This study has several strengths. This is the first study to examine the relationship between cognition and VPT utilizing comprehensive NCS and a multi-domain cognitive assessment. Prior studies either did not test sensory nerves[3] or used a limited cognitive battery.[8] We also screened out individuals with neuropathy or risk factors (e.g. diabetes) and adjusted for peripheral nerve health (i.e. axonal integrity, CV). This design strengthens the conclusion that increased VPT is due to higher-order deficits, not subclinical neuropathy, and parallels findings from other studies suggesting poor sensory perception is a cognitive deficit.[2,3]

There are also limitations. The cross-sectional design precludes causative attribution; while cognitive impairment may contribute to poor VP, this association may reflect an unmeasured shared risk factor. In that case, VPT might still prove to be a useful biomarker for predicting or tracking AD/MCI; future studies should test this. Second, this pilot study was small and nonrandom. Replication using age and sex-matched controls and a large sample, or a prospective design, is warranted. However, the effect magnitude supports the conclusions. Third, AD/MCI diagnosis relied on expert opinion, not pathology, and AD and MCI were conflated. However, the finding that VP associates with cognitive impairment does not depend on the pathologic etiology and merely reflects poor sensory perceptive integration.

Conclusions

In summary, poor cognition is associated with impaired VPT. Clinicians and researchers should consider cognition's role when using sensory perception to assess peripheral nerve integrity.

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content is solely the responsibility of the author(s) and does not necessarily represent the official views of the NIH. The funders were not involved in the study. In addition, study data were collected and managed using REDCap electronic data capture tools hosted at Dartmouth.

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Disclosures
Drs. Robbins, Bujarski, Stark, Stommel, and Lawson report no disclosures relevant to the manuscript.
Mr. Palladino, Ms. Bursey, and Mr. Mason report no disclosures relevant to the manuscript.

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Appendix 1.

Author	Location	Contribution
Nathaniel M. Robbins MD	Geisel School of Medicine at Dartmouth-Hitchcock Hanover, NH	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Kris A. Bujarski MD	Geisel School of Medicine at Dartmouth-Hitchcock Hanover, NH	Interpreted the data; contributed study participants; revised the manuscript for intellectual content
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Stephen P. Mason	Geisel School of Medicine at Dartmouth-Hitchcock Hanover, NH	Major role in the acquisition of data
Elijah W. Stommel MD, PhD	Geisel School of Medicine at Dartmouth-Hitchcock Hanover, NH	Revised the manuscript for intellectual content
Victoria H. Lawson MD	Geisel School of Medicine at Dartmouth-Hitchcock Hanover, NH	Design and conceptualized study; interpreted the data; revised the manuscript for intellectual content

A case of treatment-refractory paraneoplastic polymyalgia rheumatica that improved after tumor resection: Paraneoplastic polymyalgia rheumatica and papillary thyroid carcinoma

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ABSTRACT

We present a case of a 53-year-old man whose clinical history, examination, and laboratory markers were deemed consistent with the diagnosis of polymyalgia rheumatica (PMR). His symptoms were initially relieved by oral steroids but unexpectedly returned with repeated attempts to taper the steroid dose slowly over time. Among the extensive evaluations for his symptoms, magnetic resonance imaging (MRI) of the cervical spine was performed and demonstrated an incidental thyroid mass. This was eventually diagnosed as papillary thyroid carcinoma and a total thyroidectomy was performed 6 months after his PMR symptom onset. The patient's refractory PMR symptoms resolved shortly thereafter, and he was successfully weaned from oral steroids. This remission following tumor resection posed an interesting question of a paraneoplastic process, which will be explored here.

Key Words: polymyalgia rheumatica; papillary thyroid carcinoma; paraneoplastic syndrome; proximal weakness; myalgias; case report

Introduction

PMR without giant cell arteritis is an inflammatory rheumatological syndrome most commonly seen in people over the age of 50 with clinical symptoms of pain and stiffness in the neck, bilateral hips, and shoulder girdle. There is no clear diagnostic test for this condition, but severely elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as well as morning stiffness are proposed diagnostic criteria.[1] Previous reports suggest an association between PMR and malignancies especially in cases with younger age, mild inflammatory marker levels, or partial corticosteroid response.[2,3] Occasionally, the PMR symptoms may be the first clinical expressions of disseminated cancer.[4]

Case Presentation

A 53-year-old male with hyperlipidemia presented with a 2-month history of gradual progressive pain and subjective weakness in his shoulders and hips. The patient's symptoms evolved to include diffuse myalgias and arthralgias. Notably, his upper extremities were more affected than his lower as he ultimately became unable to lift his arms above his head. Intermittent fevers that exacerbated his symptoms were reported by the patient. He had no rashes or dermatological conditions, and denied jaw claudication, temple pain, headaches, or visual changes. There were no family members with known autoimmune or neuromuscular disorders, though there was a first-degree relative with thyroid cancer.

On clinical examination, he had normal muscle tone and bulk without atrophy, but he endorsed tenderness to mild pressure over his deltoid, trapezius, and bicep muscles bilaterally. He exhibited nearly full motor strength on initial resistance but this seemingly gave way to pain in his deltoids, triceps, left wrist extension, finger spread, and hip flexion. Otherwise, his strength was preserved. It was strongly speculated that his strength was impaired by pain, but this was difficult to distinguish with true muscular weakness on multiple examinations with varying clinicians and their interpretations. His sensory exam showed subtle sensory loss to pinprick and temperature in his bilateral lower extremities in a length-dependent fashion. His deep tendon reflexes were normal in the upper and lower extremities.

On initial evaluation, the patient presented with subacute progressive myalgias, arthralgias and pain-confounding motor impairment in the setting of fevers without antecedent infection. Polymyalgia rheumatica was a likely differential, but the subacute progression of severe symptoms prompted a rule-out of mimickers. With motor symptoms far exceeding sensory (and preserved reflexes), a myopathy was in the differential diagnosis, especially an autoimmune, inflammatory or necrotic variant. Certain myopathies can present with asymmetric deficits, such as inclusion-body myositis; however, the timing of his symptom-onset argues against such chronic processes. The patient's upper extremities were far more affected than his lower, so multiple cervical radiculopathies were also considered particularly in the context of worsening chronic neck pain. Other non-neurologic processes can also present with such symptoms including rheumatoid arthritis and fibromyalgia among others.

A negative drug history ruled out drug-induced myalgia and the patient's creatine kinase, complete blood count, and comprehensive metabolic panel were normal. The ESR and CRP were elevated at 42 mm/hr (normal range: 0-15) and 1.59 mg/dL (normal range: <0.50), respectively, initiating the consideration of inflammatory processes. A serum autoimmune screening panel

consisting of rheumatoid factor, cyclic citrulline peptide IgG/IgA, antinucleotide antibody, ribonucleoprotein extractable nuclear antibody, anti-Smith extractable nuclear antibody, SCL-70 extractable nuclear antibody, and Sjogren's syndrome antibody titers was unremarkable. A nerve conduction study and needle electromyogram were performed with consequent normal results. A MRI C-spine was obtained prior to neurologic evaluation due to earlier concerns of a symptomatic radiculopathy. The results were unremarkable, except for an incidental discovery of a complex nodule of the right thyroid lobe.

The patient's ESR and CRP values were only modestly elevated relative to what is often seen in PMR patients. However, given his symptoms and exclusion of other diagnoses, a presumptive diagnosis of PMR was made.

The patient was treated with a 5-day course of daily 40 mg tablets of oral prednisone with plans to taper to 20 mg over four weeks. His repeat ESR and CRP had normalized within the week of starting his steroid therapy at 13 mm/hr and 0.150 mg/dL, respectively. His symptoms and proximal pains with motor impairment were significantly relieved. In the months that followed, attempts to taper the oral steroids below the 20 mg dosage were met with a return of symptoms, ensuing the patient continue to take 20 mg daily for several months.

During this time, the patient was also being evaluated for the incidental thyroid mass seen on the MRI C-spine. Pathology determined the mass to be papillary thyroid cancer. The patient opted for a complete thyroidectomy due to his family history of thyroid cancer. Follow-up ultrasound was negative for residual thyroid tissue, and no pathologic lymph nodes, masses, or nodules were visualized.

Following his thyroidectomy, the patient's arthralgias and myalgias resolved within weeks. Thereafter, his prednisone was decreased to 10 mg and later 5 mg without the return of symptoms. He remained active and reported being able to routinely lift heavier weights while exercising. Since that time, the patient stopped taking prednisone and has not returned to the neurology clinic.

Discussion

Cancer risk and autoimmune rheumatic diseases may have a bidirectional relationship as chronic inflammation could initiate tumorigenesis or anti-tumor immune responses could result in autoimmunity.[5] Although there is only scant evidence that PMR is a true paraneoplastic disease, there are several reports supporting this relationship with malignancies. Additional studies have shown that PMR symptoms subside following tumor excision and cancer remission.[6-8] PMR and the coincidental finding of papillary thyroid carcinoma has been reported once previously. The case considers a patient with thyroid cancer and accompanying PMR whose symptoms resolved following a thyroidectomy with continual taper of steroid therapy.[8]

In our clinical case, the patient presented with clinical features and laboratory findings consistent with PMR. The patient was greater than 50 years of age and presented with bilateral shoulder and pelvic girdle pain limiting movement for >1 month in the setting of elevated inflammatory markers with a robust steroid response. According to the recommended EULAR/ACR classification, this patient's presentation meets the core inclusion criteria accruing a maximum score of 6.[1] There were no findings on history or workup to suggest another systemic inflammatory or neurologic disorder. His initial workup for PMR had led to an incidental discovery and subsequent identification of papillary thyroid carcinoma of his right lobe. When his refractory PMR symptoms finally resolved after the resection of this tumor, it prompted the inquiry of a potential causal association between his rheumatologic disorder and thyroid cancer.

Prior investigations have suggested that such a causal relationship could exist, indicating that PMR may present as a paraneoplastic process related to neoplasms of the colon, breast, and lung with some limited evidence for lymphoma, prostate and hematologic malignancy.[2,3,7,9] Prior studies have shown there may be an association between PMR and immunologic markers to help classify patients with PMR. HLA-DR genotyping and evaluating the subclassifications of T cells and cytokines may be useful indicators.[10,11] Theoretically, excessive T-cell response and downstream effects may arise from the release of tumor-associated antigens underlying a paraneoplastic mechanism not yet proven. This case report accentuates the careful consideration of a possible paraneoplastic form of PMR in patients such as ours, who present with symptoms consistent with PMR but are relatively younger, have only modest elevations of inflammatory markers and cannot be successfully weaned from steroids.

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A case of very late onset spinobulbar muscular atrophy with normal creatine kinase

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Introduction

Spinobulbar muscular atrophy (Kennedy disease) was initially clinically characterized in 1968 as a slowly progressive form of X-linked spinal and bulbar muscular atrophy (SBMA).[1] Its etiology lies in the expansion of tandem CAG repeats in the first exon of the androgen receptor (AR) gene. The disorder typically manifests as a slowly progressive lower motor neuron (LMN) disease affecting primarily proximal extremity and bulbar muscles. Other manifestations include peri-oral fasciculations, postural tremor, and symptoms of mild androgen insensitivity such as gynecomastia (GM). Certain serum laboratory abnormalities, such as elevated creatine kinase (CK), can help distinguish SBMA from other motor neuron diseases such as amyotrophic lateral sclerosis (ALS).[2] The age of neurologic symptom onset is typically between 30-50 years of life.[3] While larger retrospective case studies have postulated the possibility of symptom onset in adolescence for SBMA,[4] there is significant heterogeneity in clinical presentation. Previous case series suggest that approximately 60% of this heterogeneity can be attributed to variation in CAG repeat length, with higher repeat numbers correlating with a younger age of onset and increased severity.[1] Other components contributing to variability may include environmental, genetic, or epigenetic factors.[2] In this report, we describe a case of SBMA with several atypical features: symptom onset in the 8th decade of life, normal serum CK level, and absence of signs of androgen insensitivity.

Case Description

An 83-year-old, right-handed Caucasian man with a past medical history notable for smoking, chronic obstructive pulmonary disease, and remote heavy alcohol consumption presented in the Spring of 2022 for evaluation of progressive dysphagia and weakness and atrophy in the muscles of all four extremities over the previous five years. His symptoms started initially with dysphagia, and he endorsed 40 lbs weight loss over a two-year period. He reported difficulty in gripping, using buttons and zippers, and recent difficulty holding his head up. In the year prior to presentation he developed progressive dysarthria, gait instability requiring use of a cane, diffuse muscle twitching and muscle atrophy in the bilateral arms, legs, and face.

His neurological exam had several notable findings such as tongue weakness and atrophy without fasciculations, diffuse muscle atrophy in the bilateral arms, legs, and face, and fasciculations in the perioral region and all four extremities. He had mild (4 to 4- on the Medical Research Council Scale) neck flexor weakness, symmetric proximal and distal upper extremity muscle weakness, and mild right more than left weakness in the proximal and distal muscles of the lower extremity (MRC 4/5 to 4-/5). All deep tendon reflexes were absent, and there were no pathological reflexes or frontal release signs elicited. No sensory or coordination abnormalities were appreciated aside from impaired tandem gait. Of note, there was no evidence of gynecomastia or reduced facial hair and he had no history of testicular atrophy or infertility.

Blood work including thyroid stimulating hormone, vitamin B12, folate, hemoglobin A1c, serum immunofixation, kappa/lambda free light chain assay, CK, complete blood count and comprehensive metabolic panel were unremarkable. MR imaging of the brain and cervical spine with contrast was largely unremarkable. On nerve conduction study sensory nerve action potentials (SNAPs) were diffusely absent in the left upper and lower extremities. Needle electromyography showed evidence of active denervation in the thoracic and sacral paraspinal muscles as well as in the distal upper and lower extremity muscles. Diffuse chronic neurogenic changes were observed in the cranio-bulbar, cervical, thoracic, lumbar and sacral regions. These findings were felt to be consistent with combinatorial diagnoses of a motor neuron disease (MND) such as ALS and a concurrent sensory or sensorimotor polyneuropathy secondary to excessive alcohol intake. The diagnosis of ALS was later called into question when his exam remained largely stable on a follow up visit several months later. He ultimately underwent genetic testing for androgen receptor (AR) repeat expansion, which returned positive for 40 repeat expansions of the AR gene consistent with a diagnosis of SBMA. [3]

Discussion

This patient presented with a slowly progressive LMN pattern weakness without significant sensory deficits on physical examination, but with findings on EMG suggestive of MND and concurrent sensory polyneuropathy. The differential diagnosis considered during his initial workup included slowly progressive LMN-predominant MND such as primary muscular atrophy (PMA), ALS, SBMA and chronic neurotoxic effects from remote heavy alcohol consumption. The patient's history of slowly progressive weakness and atrophy affecting facial, bulbar and limb muscles, LMN involvement with fasciculations, absent SNAPs on nerve conductions studies, and positive genetic

testing for 40 repeat expansions of the AR gene (normal number of repeats is 34 or fewer) were consistent with a diagnosis of SBMA.

SBMA is a genetic condition caused by a pathogenic repeat expansion of CAG nucleotides in exon 1 of the AR gene on chromosome Xq11-12.[4] Repeats of 38 or more follow complete penetrance.[5] The AR gene is a ligand-activated transcription factor with a steroid receptor structure. It mediates the physiological action of androgens in male sexual differentiation and spermatogenesis. Dysfunction of the AR receptor causes features of androgen insensitivity in males. Patients with SBMA frequently exhibit characteristics of partial androgen insensitivity, such as oligospermia/azoospermia and testicular atrophy, leading to infertility, gynecomastia, and/or reduced facial hair.[3] Female carriers of SBMA are usually asymptomatic due to low levels of circulating androgen though some may develop mild symptoms of intermittent muscle cramps or twitching.[1]

While the pathogenic mechanism remains incompletely understood, it is widely believed that accumulation of toxic expanded AR in the nucleus leads to degeneration of LMNs in brainstem nuclei and the spinal cord.[1,4] Symptoms of this condition include muscle weakness and atrophy, muscle cramping, gait impairment, fasciculations, dysphagia and dysarthria, and mild-to-moderate sensory abnormalities in the distal extremities.[5] Symptoms of SBMA tend to progress slowly over time, however patients with larger numbers or repeat expansions have been shown to progress more rapidly.[6]

This case of SBMA was atypical in four distinct ways: age at symptom onset being much later than typically occurring; lack of appreciable symptoms or examination findings of androgen insensitivity; and normal CK level. Symptoms of SBMA typically begin in adulthood (average onset of symptoms between 30-50 yo), but one case report of two Japanese twin brothers reported ages of onset as old as 66 and 78 years old. [7] The age of neurological symptom onset is inversely correlated with the number of AR repeat expansions, in that individuals with fewer repeat expansions may not develop symptoms until later in life.[1] The delayed onset in this case could be explained by his lower CAG repeat length.

On electrodiagnostic studies, KD often shows finding of diffuse axonal loss changes. In addition, SNAPs are often diffused reduced or absent, without a length-dependent pattern. Absent or diffusely low SNAP amplitudes without physical examination findings of significant sensory abnormalities is characteristic of the disease.[15]

CK level has been shown to be a valuable biomarker for SBMA for several reasons: elevated CK is seen in 84-94% of patients.[8,9] CK elevations are often at least 3 times the upper limit of normal.[12] CK levels are significantly higher in SBMA compared to healthy controls and ALS patients.[2] CK elevations are seen in SBMA due to muscle degeneration secondary to denervation as well as a primary myopathic process. [10,11]CK levels have been correlated with disease severity and have been shown to decrease in patients experiencing improved muscle symptoms while receiving treatment[11]However the value of CK as a marker of disease progression and stage is less clear.[3]

The management of SBMA is largely supportive. Patients benefit from multidisciplinary care involving occupational and physical therapy, speech and feeding therapies, and psychosocial support services for the patient as well as their caregivers. Consistent follow up is needed with specialists in neurology, cardiology, pulmonology, and endocrinology to monitor progression and potential complications of the disease. Consultation with genetics is helpful not only in confirming the diagnosis, but to counsel the patient and their family members regarding the implications of this genetic mutation. Many therapies aimed at reducing levels of toxic AR protein are being investigated for future use.

In summary, neurologists should suspect SBMA in male patients with LMN-pattern muscle weakness, areflexia, elevated serum CK levels, and signs of androgen insensitivity. However, this case provides further evidence of the clinical heterogeneity and potential difficulty in diagnosing this disease; onset of neurologic symptoms may occur much later in life than initially described, CK levels may be normal, and there may be an absence of androgen insensitivity signs. Furthermore, EMG findings may lead one to suspect ALS or other forms of MND and may be confounded by a clinical history suggestive of sensory polyneuropathy.

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Chronic inflammatory demyelinating polyradiculopathy as a paraneoplastic manifestation of metastatic melanoma

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Introduction

Chronic inflammatory demyelinating polyradiculopathy (CIDP) is an acquired autoimmune neuropathy typically characterized by progressive diffuse limb weakness, sensory loss and hyporeflexia with a disease course of 2 months or greater. The underlying pathology is usually due to increased inflammatory T-cell and macrophage activity. It typically follows a relapsing course with many patients requiring regularly scheduled immunotherapy such as corticosteroids and/or immunoglobulins [1]. Many cases are sporadic without an underlying causative or associated disease process. However, there have been multiple reports that suggest an association with malignancy. The most common associations are hematologic malignancies such as lymphoma and leukemia [2]. Solid tumor malignancies are also known to be implicated. There have been several reported cases and series evaluating the association between CIDP with melanoma [2-10]. Despite the increasing number of reports over the years, this association is still not widely known, which can lead to diagnostic delay. In this article, we report a case of a patient with a known remote history of resected early-stage cutaneous melanoma, who presented with severe refractory CIDP. During his diagnostic evaluation, he was found to have recurrent metastatic malignant melanoma. Treatment of both diseases resulted in marked, sustained clinical improvement. This case highlights the importance of the identification and treatment of melanoma in CIDP patients.

Case

A 50-year-old male with a remote history of resected cutaneous melanoma that was removed 6 years prior presented with weakness of all limbs and associated back and neck pain. His initial examination demonstrated predominantly proximal upper and lower extremity weakness with intact sensation and reflexes. Magnetic resonance imaging (MRI) of his brain and cervical spine were unrevealing. Initial nerve conduction studies at 2 months demonstrated normal sural and median sensory responses, normal median compound muscle action potential (CMAP) with a normal F-wave latency and reduced peroneal motor CMAP recording at the extensor digitorum brevis. Electromyography (EMG) examination showed the presence of long duration motor unit potentials with neurogenic recruitment pattern in the C5-8 and L3-4 nerve root innervated muscles without active denervation. Electrodiagnosis at that time was thought to be most consistent with cervical (C5-8) and lumbar (L3-4) radiculopathies. Physical therapy was recommended.

His weakness progressed to the point that he could not ambulate, and he was hospitalized 10 days after the initial EMG. Examination showed proximal and distal upper and lower extremity weakness bilaterally but intact reflexes and sensation. MRI of the lumbar spine with contrast showed the presence of nerve root enhancement of the cauda equina. Cerebrospinal fluid (CSF) testing revealed the following: protein of 128 mg/dL, glucose of 76 mg/dL and 1 nucleated cell/μL. Cytology was negative for malignant cells. He was treated with a course of intravenous immunoglobulin (IVIG) at 2.0 grams per kilogram of body weight for a presumed diagnosis of CIDP, which led to significant improvement and regaining independent ambulation.

Approximately 1 month later, he was readmitted to the hospital and was found to have significant proximal arm and leg weakness again. Another course of IVIG was given, which led to improvement, and he was also started on prednisone of 30 mg daily. Repeat electrodiagnostic testing after that hospitalization (approximately 6 weeks from the initial electrodiagnostic study) re-demonstrated absent peroneal motor response at the extensor digitorum brevis but also showed interval prolongation of the median motor response latency. Additional motor nerve conduction studies of the ulnar nerve revealed the presence of a partial conduction block, temporal dispersion, reduced conduction velocity and a prolonged F wave latency. Needle electrode examination showed more widespread and a more significant presence of long duration motor unit potentials with neurogenic recruitment in the left C5-T1 and L3-S1 nerve root innervated muscles without active denervation—indicating a worsening polyradiculopathy. He relapsed again approximately 6 weeks later and received 5 sessions of plasmapheresis. Plasmapheresis led to quick improvement, and prednisone was increased to 60mg daily. Hhowever, his weakness relapsed 1 week later which led to readmission. Repeat MRI of the spine revealed the presence of contrast enhancement of thoracic and lumbosacral nerve roots. Repeat CSF testing revealed the following: protein of 196 mg/dL, glucose of 110 mg/dL and 1 nucleated cell/μL with negative cytology. A whole-body positron emission tomography (PET) scan showed multiple hypermetabolic lymph nodes in the right axilla. Further excisional biopsy of the lymph nodes revealed the presence of BRAF

positive metastatic melanoma. He was subsequently treated with complete surgical resection, adjuvant local radiation therapy, encorafenib and binimetinib. For his refractory CIDP, he was treated with 2 doses of rituximab at 1000mg each, mycophenolate mofetil and maintenance plasmapheresis once every 2 weeks for a total of 4 months. This combinatorial treatment of melanoma and CIDP led to significant and persistent improvement of his muscle strength. Repeat electrodiagnostic testing performed 3 months after his last hospitalization (6 months from the second electrodiagnostic study) showed recovery of median and ulnar F responses as well as improvement in motor response amplitudes, latencies and conduction velocities. Repeat PET scan revealed a reduction of hypermetabolic activity in the right axilla without identification of additional hypermetabolic foci. At his last evaluation (1 year from the initial onset), his physical examination showed normal muscle strength, intact deep tendon reflexes and normal sensation while on oral mycophenolate mofetil for CIDP and continuing targeted chemotherapy (encorafenib and binimetinib) for melanoma.

Discussion

This case highlights the importance of the awareness of the association of melanoma with CIDP. A proposed pathologic mechanism for this association is molecular mimicry due to similar surface antigens on melanocytes and peripheral nerves [4].

Table 1 provides a summary of this patient and other reported cases of polyneuropathy associated with melanoma to date. CIDP has also been reported as a complication of immunotherapy for melanoma [11, 12]. Because it is difficult to distinguish whether the neuropathy was secondary to melanoma or a complication of treatment, these cases are not included in the table.

Comparing the characteristics of these cases highlights certain pitfalls in identifying melanoma in CIDP patients. Despite the increasing number of case reports in the literature, this association is still not widely known. Identification of melanoma can be challenging for the neurologist as typical melanoma skin findings may not be present at the time of CIDP and patients with melanoma may rarely report constitutional symptoms. The diagnosis of melanoma in these cases required extensive imaging and verification via biopsy. Testing for malignancy through serum markers, computed tomography, and PET scans are also not standard components in the evaluation of CIDP [1]. Lastly, there is wide variability in the delay between the development of melanoma and the onset of neuropathy. At times, the interval could be many years.

Our patient's clinical course suggests that clinical improvement for these patients relies on treating both the neuropathy and underlying malignancy. His initial course relapsed frequently despite the use of corticosteroids, IVIG and PLEX prior to the recognition of underlying melanoma. These treatment modalities resulted in quick but non-sustained clinical improvement prior to the initiation of anti-melanoma therapy. Sustained clinical improvement occurred when he was receiving treatment for both CIDP and melanoma. This rationale is congruent with the proposed mechanism of molecular mimicry between these 2 entities. Our case highlights the need for recognizing that CIDP can be a paraneoplastic manifestation of melanoma and the importance of treating such patients with combined therapies to achieve an optimal outcome.

Table 1. A list of published cases describing CIDP in association with melanoma

Reference	Age	Sex	Time of melanoma diagnosis before or after CIDP onset	Clinical features	EMG features	Melanoma site	CIDP treatment	Melanoma treatment
Bird et al. [3]	62	M	4 months after	Ascending paresthesias, proximal>distal limb weakness, areflexia	Demyelinating	Axillary lymph node	Plasmapheresis, prednisone	Resection
Bird et al. [3]	43	M	6 months after	Ascending numbness, distal limb weakness, areflexia	Demyelinating	Axillary lymph node	Prednisone	Resection
Bird et al. [3]	49	M	12 months before	Intermittent distal lower extremity paresthesias and weakness, areflexia	Demyelinating	Skin	Declined treatment	Radiation
Weiss et al. [4]	73	F	3 years before	Ascending paresthesias, proximal limb weakness, areflexia	Demyelinating	Not stated	Not stated	Not stated
Antoine et al. [5]	64	M	10 years after	Paresthesias and weakness, diffuse hyporeflexia	Demyelinating	Not stated	Not stated	Not stated
Kloos et al. [6]	68	F	17 years before (skin) 3 months before (lymphadenopathy)	Diplopia, proximal weakness, hyporeflexia	Axonal	Iliac lymph node	IVIG, dexamethasone, plasmapheresis for 1 relapse	Immunotherapy clinical trial
Rousseau et al. [7]	32	M	5 months before	Proximal limb weakness, distal lower extremity areflexia	Demyelinating	Skin	IVIG	Resection
Palma et al. [8]	66	M	14 months before	Proximal limb weakness and areflexia	Demyelinating	Lung	IVIG	Chemotherapy
Dbouk et al. [9]	52	M	6 years before (skin) 3 years before (liver metastasis)	Distal paresthesias, proximal limb and facial weakness, dyspnea	Demyelinating	Skin, liver	Plasmapheresis, prednisone	1st: Resection, chemotherapy 2nd: Chemotherapy
Dbouk et al. [9]	58	F	Concurrent	Distal paresthesias, gait impairment	Demyelinating	Para-aortic lymph node	Plasmapheresis, prednisone	Chemotherapy
Chau et al. [10]	67	M	1 month before	Distal paresthesias, Proximal limb weakness, diffuse hyporeflexia	Demyelinating	Skin, axillary lymph node, spleen	IVIG, intravenous methylpredniso-lone	Not stated
Present case	50	M	6 years before	Back pain, proximal limb weakness	Demyelinating	Axillary lymph node	IVIG, plasmapheresis, prednisone	Chemotherapy, radiation

Abbreviations: CIDP: chronic inflammatory demyelinating polyradiculopathy; EMG: electromyography and nerve conduction study; IVIG: intravenous immunoglobulin

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Myasthenia Gravis Misunderstood: Identifying the Historical Misinterpretations, Miscommunication, and Misconceptions

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ABSTRACT

Myasthenia Gravis (MG) is a serious disease and can present clinically with very severe symptoms in many patients; however, the *fluctuating* severity of MG results in the disease being commonly misdiagnosed as other conditions, including conversion disorder. The earliest recorded literature on MG provides evidence of the variability of signs and symptoms, including many patients who appeared to have mild symptoms initially but died suddenly and unexpectedly from MG. Often, these patients were initially believed to be suffering from hysteria.

This review analyzes some of the most prominent MG literature still cited today. It found that many communication errors have led to today's misunderstandings and have continued to cause difficulties in diagnosis and difficulty in understanding the MG patients' lived experiences. These errors include the intended meaning for 'gravis' being misinterpreted as 'severe' instead of the intended meaning of 'a painful weight in the limbs', the false belief that 'gravis' is Latin for 'grave' and how the miscommunication of the early 1900's MG autopsy studies added to this confusion, where MG continued to be referred to as a 'grave' condition. The continued omission of the sensory symptoms associated with MG from the literature has also been miscommunicated for decades, however such symptoms are now becoming recognized as a result of increasing patient led research.

Myasthenia Gravis should continue to be regarded as a serious disease, due to the devastating effect on quality of life for many people, and the unpredictability of the myasthenic crisis potentially occurring in *all* people living with MG, including those who are undiagnosed. The dismissing of mild symptoms results in many MG patients remaining undiagnosed. The possibility that individuals in this group go on to become victims of Sudden Adult Unexplained Death (SUD) is yet to be investigated, and there is a need for research in this area.

Miscommunication also includes omitting 'old knowledge,' not listening to the patient's lived experience, and failing to integrate relevant interdisciplinary knowledge. Good examples of these are The Mary Walker Effect, and combining patient lived experience with ocular anatomy and physiology knowledge to develop new MG-specific ocular motility clinical tests. A new test is presented for evaluating MG eye signs utilizing knowledge of the 'Safety Factor,' and is referred to as The SLOWLY Test (Significant Level Of Weakness, Loci in Y Axis).

Awareness of the historical misinterpretations, miscommunications, and misconceptions is crucial to preventing delay in diagnosis in MG patients, developing new clinical tests, rehabilitation interventions, and helping doctors and others understand the lived experience of MG patients.

Keywords: myasthenia gravis, conversion disorder, neuromuscular junction, misdiagnosis, The Mary Walker Effect

Introduction

Acquired Autoimmune Myasthenia Gravis (MG) is a potentially fatal, chronic neuromuscular disease affecting the post-synaptic neuromuscular junction (NMJ). The most well-known symptoms of MG include *fluctuating* fatigue and *variable* weakness of the voluntary muscles affecting limbs, trunk, neck, face, eyes, breathing, and swallowing.[1] The eye muscles are the most susceptible muscle group to an autoimmune-mediated attack on the NMJ, and, therefore, accurate ophthalmic examination is vital to aid in an early diagnosis.[2] MG eye signs (MGES) can help to diagnose MG; however, when eye signs are subtle or latent, diagnosis can be difficult. A study of ocular myasthenia gravis (OMG) patients in 1997 found 64% of uncertain cases of OMG converted to generalized MG within 2 to 4 years, whereas only 12% of those treated with immunosuppression converted to generalized MG within 2 to 4 years,[3] hence early diagnosis through eye signs is crucial.

Even though today there is the knowledge that MG is variable, there remains a common misconception where many physicians only diagnose MG at the point where weakness is obvious or 'severe enough.' This misconception can be traced back to miscommunication and misinterpretation of early MG literature. A review of historical etymology literature and German to English translation of medical terms of the late 1800's shows that the intended meaning for 'gravis' was misinterpreted as 'severe' instead of the intended meaning of 'painful heavy limbs.'[4] Case studies from the earliest diagnosed MG patients, 124 years ago, show that even some patients with mild MG signs died suddenly, yet others with more severe symptoms lived for years. Those earlier reports also documented the variable nature of MG known today. This information should provide insight into the dangers for undiagnosed MG patients today and highlight the importance of diagnosing MG earlier in patients who show milder or more subtle signs.

The increase in MG survival rate today is due to improved treatments for diagnosed MG patients; however, myasthenic crisis still occurs in 20% of MG patients and

may be triggered by events such as infection, severe MG exacerbation, certain medications, and anesthesia.[5] In recent years, Takotsubo Cardiomyopathy (TC) has also been reported in MG associated with myasthenic crisis (MC) along with MC in previously undiagnosed MG.[6] Undiagnosed MG patients should be of concern, as their mortality rate is a higher risk due to lack of treatment for their MG, and the risk of inadvertently being exposed to conditions or drugs that can exacerbate MG and place them at risk of MC, TC or choking. As with any disease, awareness leads to knowledge for patients, allowing them to mitigate risk factors that may worsen the disease. This concern about the undiagnosed MG patients in our communities has not previously been reported, and research in this area is essential.

Discussion of Historical Misinterpretations, Miscommunication, and Misconceptions.

This article highlights six issues that have led to today's misunderstandings about MG, which have continued to cause difficulties in diagnosis and poor understanding of MG patients' lived experiences. They include: 1) Misinterpretation of the intended meaning for 'gravis' as being 'severe' instead of the intended meaning of 'a painful weight in the limbs,'[4] through incorrect translation of the intended meaning of the word 'gravis'; 2) misinterpretation of meaning of 'gravis,' through miscommunication of MG severity that led to the incorrect use of the word 'grave' to describe MG; 3) misinterpreting a prominent MG case series paper by Campbell & Bramwell led to the incorrect belief that sensory symptoms are not associated with MG and continued miscommunication about sensory symptoms in MG; 4) miscommunication by omission of 'old knowledge'; 5) not listening to patient lived experience to further understand MG; and 6) failing to communicate and integrate relevant interdisciplinary knowledge to increase knowledge of MG.

1. Incorrect translation of the intended meaning of the word 'gravis'

The term Myasthenia Gravis Pseudo-paralytica was first introduced by the German physician Friedrich Jolly in 1895. In November, 1899, 124 years ago, the Berlin Society of Psychiatry and Neurology accepted the name Myasthenia Gravis and is still used today.[7] Another physician at the time, Leopold Laquer, had also suggested 'Allgemeine schwere myasthenia,' which translated to 'general heavy myasthenia.'[8]

'Schwere' refers to painful weight in the limbs. 'Gravis' means heavy

A review of the meaning and translation of the word 'schwere' was performed, including Latin, German, and English etymology textbooks between 1821 and 2003, first looking at the usage of the words 'schwere' and 'schwer' in the late 1800s within the German language. An 1890 *German-English Dictionary of Medical Terms*[9] lists 'schwer' as an adjective meaning heavy, difficult, serious, severe, dangerous and 'schwere' as meaning heaviness weight when describing the difficulty of movement.

The word 'schwere' was used when discussing the medical condition Myxoedema by William Ord in 1877 to describe an illness in which there was '...Schwere in den Gliedern,' translating to 'Heaviness in the limbs.'[10] An 1891 text, 'Encyclopaedic German-English and English-German Dictionary,' lists the German word 'schwere' as meaning heavy, weighty, and more specifically when discussing pathology, 'schwere' meaning 'a painful weight in the limbs.'[4] This is the first evidence that the Latin word 'gravis' appears to have been chosen by the German physician Friedrich Jolly in 1895 to represent the symptoms of painful heavy muscles. However, changes in the meaning of translation in later years caused an incorrect understanding of the meaning. It is important to note that in medical textbooks, 'schwere' continues to be used for 'heavy,' for example, 'schwere beine' when describing heavy legs from a 2017 German medical textbook.[11]

In a German medical text from 1898, 'Die Im Zusammenhang Mit Anderen Krankheiten,' translated to English as 'In connection with other diseases,"[10] the words *schwere* and *schwer* are seemingly interchangeable, meaning heavy, severe, or hard. This interchangeability of *schwere* and *schwer* is present even today.

Understanding the intended meaning of 'a painful weight in the limbs'[4] is essential for understanding the patient's lived experience and for ensuring that the patient's symptoms aren't dismissed if they don't appear 'severe enough' and they display the symptom of painful heavy muscles.

2. Misinterpretation of the meaning of 'gravis' and miscommunication of MG severity

'Gravis' is not 'Grave'

The word 'grave' originates from the Latin word 'gravis,' meaning heavy or weighty,[12] *and* the French meaning 'serious.'[13] Today, the incorrect statement is that Gravis originates from Grave, such as the common phrase that 'Gravis is Latin meaning grave.' This has led to the common belief that MG is a disease that presents with severe symptoms and causes patients who display less severe symptoms during medical consultation very often to be dismissed. A 1961 Lecture titled *The History of Myasthenia Gravis* by Sir Geoffrey Keynes from the University of Durham, UK refers to 'gravis' as severe but discusses how the name is inappropriate, as "there are many times when the symptoms of MG patients are not severe," questioning whether the name MG should be changed.[14] By this time, people believed that Jolly had named MG using the Latin word 'gravis' due to the severity of the disease; however, as discussed by choosing the Latin word 'gravis,' it is evident that Jolly was referring to painful heavy muscles.[4]

Historical Misinterpretation and Miscommunication of MG Severity

For over a century, many authors have noted that the diagnosis of MG was frequently dismissed in the early stages, as the disease is characterized by daily fluctuations and partial or complete remissions, sometimes for long periods.[1, 15-19]

MG presentation, even in the late 1800s, varied between mild to severe, with the potential of escalating suddenly to death as a result of choking or respiratory failure. In 1893, Samuel Goldflam published an article in German describing three patients with fluctuating weakness of the extra ocular muscles (EOMs), limbs, and breathing difficulties.[20] The article's title translates to "about a seemingly curable bulbar paralytic symptom complex with the participation of extremities."[20] In 1900, Campbell and Bramwell noted that "a characteristic feature of the disease is its tendency to fluctuate in severity from day to day, or from week to week, or even to disappear for months or years, to reappear."[15]

The textbook *The Principles and Practice of Medicine: designed for the Use of Practitioners and Students of Medicine (1901)*, by prominent physician William Osler (1849–1919), provides further evidence that MG was considered a variable disease with many patients initially presenting with mild signs and symptoms. Osler is "generally regarded as one of the greatest and most admired physicians in the history of medicine, [and his text] became the most popular and widely read treatise on medicine in the world."[21] In it, Osler discussed MG's variability, stating there are "...remarkable variations in intensity..." and "...the patient may live for many years; recovery may take place." Of the 180 collected cases, 72 (40%) proved fatal.[22] Many subsequent authors described this variability in severity.[1, 8, 15, 17-19] The mortality rate that can be ascertained in Osler 1901 of 40% is less than the estimate of 75% that has been reported by other authors.[23] Noting this discrepancy from different studies reporting on the same period raises concerns. Further research to find a more accurate mortality rate of the early 1900s would help to understand the true risk of undiagnosed MG patients today since they are untreated and could inadvertently be subjected to substances and situations that are known to cause the risk of death in MG. Is the 40% mortality rate close to the mortality rate for the undiagnosed today? Research to find the answer could include analyzing SUD cases by looking at old photos of the person during their life and looking for MGES, e.g., ptosis and lid retraction, which is variable between photos, or even consistent ptosis or lid retraction that is unexplained by the victim's medical history could indicate undiagnosed MG during their life. The other figure of 75% is likely to be high due to skewing from including the autopsy studies of the time. Further research in this area is important as it will improve knowledge of the importance of early diagnosis and treatment in MG.

Autopsy Studies Led to the Misconception That Nearly All MG Patients Died of MG.

As the cause of MG was unknown at the time, some reports in the early 1900s investigating the cause of MG focused on the autopsies of positive cases; these reports were presented as a case series of MG patients who died suddenly from respiratory failure or choking. One such autopsy report series was documented by Dr. Charles Myers in 1902,[24] where he presented a review of 22 cases provided by several prominent physicians. This report was presented as his thesis for his MD Degree. It included many patients, including one of his own, who were initially misdiagnosed with hysteria and died suddenly and unexpectedly from respiratory failure. Charles Myers is remembered as a respected physician; in later years, he became the president of the British Psychological Society and later president of the Psychology Section of the British Association for the Advancement of Science and editor of the Journal of Psychology. In his thesis, he noted

> So far, I have been speaking of the disease as if it were invariably fatal. But although I intend to confine my remarks mainly to those cases in which necropsy has been performed with negative (or practically negative) results I ought to insist at once that, as our knowledge of the disease has increased, numerous cases have been published in which the patient appears to have quite recovered.[24]

It appears that some authors of the day had a misconception regarding the severity and prognosis of MG that originated from the misinterpretation of these types of MG autopsy reports. In 1903, the first textbook that appeared to have based MG prognosis on autopsy papers stated the "prognosis is grave."[25] The text was *Savill's System of Clinical Medicine Dealing with the Diagnosis, Prognosis, and Treatment of Disease for Students and Practitioners.* This misconception was repeated in subsequent texts,[25, 26] with the statement "the outcome is usually fatal" in the 1923 edition.[27]

Historical Similarities to MG Today

In 1911, Oppenheim discusses that "suffering reveals its insidious, treacherous nature, because not only can relapses occur at any time, but in many cases, death occurs just then, as a patient at a stage, of complete or relative well-being left out of treatment and was no longer thought to be serious or even lethal."[8] These statements are still relevant today, as around 20% of MG patients suffer a MC involving sudden severe respiratory symptoms requiring intervention and may result in death.[5] Even today, many undiagnosed MG patients are also at risk of death, as they are not undergoing appropriate treatment for their MG and may unwittingly be subjected to substances or situations that trigger MC, TC or choking.

A clinical review of 87 cases observed between 1915 and the early part of 1932, described an MG mortality rate

of 39%.[28] Out of the 34 documented deaths, MG had been present for a variable time ranging between six months to 22 years, with an average of four and a half years. Symptoms were noted to be variable, with most cases taking two to four years to diagnose after the initial symptoms, ranging between one month and 25 years. At times, patients complained of weakness for years without any objective symptoms, and many of these patients were believed to be "neurotics."[28] As no treatment was available at the time, this study is a good indication of mortality rates in untreated disease. Today, many undiagnosed MG patients are misdiagnosed as having a conversion disorder and are at risk of dying from sudden MC, TC or choking.

A prominent textbook written by Robert Bing in 1921, who was considered one of Europe's most "illustrious neurologists" of his time,[29] titled "A Textbook of nervous disease for Students and Practicing Physicians; in thirty lectures," describes MG as a disease that:

> Has a great tendency to intermissions, in when the patients for weeks, months and years can be entirely free from trouble; termination in recovery is, on the other hand, rare, and the prognosis is on this account unfavourable since the harmless initial stage of the disease can stretch over an exceedingly long period characterized by long intermissions and short exacerbations, (In one case mentioned [of Cushman's], twenty-two years). Once the myasthenia has reached its full development, however, the situation is exceedingly dangerous. The pseudo-paralysis is constantly more permanent; the muscles recover almost not at all.[17]

He also discussed the importance of rest: "during the exacerbations of the disease, rest in bed; during the intermissions, long periods of entire rest are introduced into the regime of the day."[17] This text provides evidence that milder early signs of MG were documented even in the early 1900s before effective treatments were discovered. Most importantly, it acknowledges that even in the early stages of remission, the MG patient is still in danger of recurrence of potentially dangerous symptoms.

The Dangers of Misconception of MG Severity Today

There is a common misconception today that a patient is required to present with severe muscle weakness to be diagnosed with MG. The reality, as already discussed, is that a patient may have mild or moderate symptoms that can escalate to sudden MG, TC or choking. Too often, a wait-and-see-if-symptoms-worsen approach is undertaken, leaving many patients suffering for years with poor quality of life. Literature often states that MG is not as 'grave' as it had been in the early days; it appears that the clinical course of the mild cases reported from the earlier case reports have been forgotten. It is true that the mortality rate gradually fell associated with the improvements in the medical treatment of MG; however, such statements have resulted in the misconception that MG always presents with severe muscle weakness, and mild symptoms were no longer considered serious. The historical miscommunication of MG is a result of authors continuing to reprint incorrect statements about MG. This misconception persists today in many popular medical textbooks, MG research, and MG information websites.

3. Sensory symptoms miscommunicated as being absent in MG

Interestingly, sensory changes, including ocular pain, headache, paresthesia, and the sensation of heaviness, have been reported throughout literature since the 1800s, including the Campbell & Bramwell report from 1900.[15] However, this well-known report still cited in recent literature had a crucial contradictory remark. The paper stated on the second page of the review that "there are no sensory changes"[15] associated with MG; however, reading the 63 case studies listed in the report, there *are* many sensory symptoms reported, including heaviness, headaches, tenderness, and aching limbs mentioned in detail. This is a significant historical error of interpretation that has been constantly restated in literature even today, resulting in difficulty in diagnosing MG and poor understanding by doctors of the patient's lived experience.

Sensory Symptoms in MG have been Documented Since the Earliest Cases

Even though today MG is commonly believed to be purely a motor disease, there is a long history of recorded sensory symptoms, such as heaviness, ocular pain, muscle pain, headache, and numbness associated with MG. In 1901, Oppenheim described patients reporting sensations such as "heaviness in arms and legs; heavy and unwholesome legs and arms; dizziness, pain in shoulders and neck; paresthesias in legs; paresthesia in the left cheek and severe dizziness and headache."[16] Buzzard, in 1906, recorded the following symptoms in a patient: "He noticed a feeling of heaviness in the right leg, which became easily tired,[30] In 1927, Hart noted in another patient that "she complained at this time of a sensation of heaviness and general exhaustibility, increased by a moderate amount of exertion."[31]

Sensory symptoms have also been documented across other prominent MG literature. A 1908 peer-reviewed textbook titled 'Diseases of the Nervous System' by Dr. Herbert Thomson. Dr. Thomson was a respected physician and vice-president of the Section of Neurology and Psychological Medicine at the Annual Meeting of the British Medical Association, held at Aberdeen in 1914. In his text, he discussed MG, stating, "while the main symptoms are motor, there are occasionally some sensory changes to be noted."[32, 33] He also noted that "transient ocular symptoms are sometimes associated with migraine."[32, 33] Bain, in 1904, reported patients complaining of "premonition, consisting of headache, pain in the neck and back, photophobia, and giddiness have occasionally been noted."[34]

This association of sensory symptoms as a premonition of MG was discussed 40 years later by Dr. Abner McGehee Harvey, who was appointed Chairman of John Hopkins Hospital at age 34. "That sensory disturbances may precede or accompany the first manifestations of weakness is not generally realized. Headache, pain in the eye, numbness and tingling in various regions, and other sensory manifestations were described often enough to deserve some consideration."[35]

Subsequent miscommunication caused by ignoring this knowledge of sensory symptoms has led to the misconception that persists that MG is purely a motor disease. More recent research is acknowledging that "sensory anomalies have been overlooked for decades in myasthenia gravis,"[36] with pain and headaches now recognized by some authors as common symptoms in patients with MG.[37] This knowledge is yet to be communicated to general consulting physicians and in the general MG information that is readily available, contributing to delayed diagnosis and misdiagnosis of the sensory symptoms as being another condition or being "all in the patient's head." This failure to disseminate this important knowledge needs to be urgently remedied.

4. Miscommunication Includes Omitting Information from 'Old Knowledge'

An excellent example of the importance of remembering 'old knowledge' is the clinical sign known as 'The Mary Walker effect,' identified in 1938. Mary Walker, a Scottish physician, observed that exhaustion of one group of voluntary muscles through repetitive use in a patient with MG induced weakness in other groups of muscles that had not been engaged.[38]

The Relevance of The Mary Walker Effect Today

a. Developing new clinical tests

A recently published Case Presentation that introduced the SLOW Test (Simultaneous Lip and Ocular Weakness), by this author showed how knowledge of the Mary Walker Effect could be utilized to develop clinical tests that demonstrate muscle fatigability in MG.[38] The Mary Walker Effect highlights the fact that all eye muscle testing methods that increase fatigability should be performed carefully so as not to overfatigue the MG patient. Further research is recommended as MG is variable among patients and within the same person throughout the day, so testing should be tailored to the individual's level of fatigability at the time of testing.

An alternative test to the SLOW Test[38] could be used and could be called 'The Mary Walker Ball Test', based on Mary Walker's experiment demonstrating the Mary Walker Effect.[38] The patient could squeeze a ball to fatigue the hand and forearm muscles while simultaneously testing for MGES, stopping at the first sign of an MGES. This test was successfully trialed by the author, as an MG patient, eliciting MGES within 5 to 10 seconds, e.g., ptosis in upgaze. Research should be trialed on MG patients to assess the effects of fatiguing other muscles simultaneously, and to analyze the efficiency of the test on all MG subgroups.

b. Rehabilitation Strategies

Understanding The Mary Walker Effect is essential for MG patients in their daily life, to help prevent exacerbations escalating when MG medications, combined with a vigilant balance of rest and appropriate activity levels fail to control symptoms adequately, e.g., an MG patient who has an exacerbation of eye muscle restrictions when looking down needs to understand that continuing to fatigue her eye muscle when looking down while cutting vegetables or attempting to eat from a dinner plate at table height, could potentially result in swallowing difficulties and cause choking. The author, who lives with MG, has found that at times of severe exacerbation of downgaze eye restrictions, a useful rehabilitation strategy is raising the dinner plate by around 20 cm to reduce the use of the eye muscles in the direction that they are the most symptomatic. This patient also benefits from routinely performing reading activities at eye level rather than looking down, as it helps to prevent exacerbations of her eye muscle restrictions, and as per The Mary Walker Effect, helps prevent exacerbation of her other MG symptoms. Also, a comfortable chair supporting other muscles like the arm and neck muscles helps prevent exacerbation of her MG symptoms.

c. Understanding Patient-Lived Experience

In the above example, the patient noted that during periods of poor MG control, preparing dinner has caused MG exacerbation of her bulbar muscles, putting her at risk of choking. This knowledge helps her to seek assistance from others with certain chores or find strategies to do things differently. This is an area of knowledge that should be further developed through patient-led research.

5. Miscommunication also includes not listening to the patient's lived experience.

The value of patient experiential expertise in research has increased in recent years, and future studies involving patients at all levels of research is vital to advancing knowledge in MG. Listening to patients describe their condition has excellent potential to increase understanding of MG. The author is an orthoptist living with generalized MG, and the test below was developed by combining lived experience, professional orthoptic knowledge and experience, with interdisciplinary knowledge.

6. Miscommunication also includes failing to communicate and integrate relevant interdisciplinary knowledge.

A good example of this is how anatomy and physiology knowledge may help to develop new disease-specific ocular motility clinical tests to diagnose latent MGES.

Background of The Neuromuscular Junction 'Safety Factor,' EOM Physiology and Anatomy

Neurotransmission in a normal NMJ is a result of the presence of adequate acetylcholine receptors (AChRs) and Na+ channels (NaChs), including a necessary reserve of supply. The safety factor is a measure of excess or reserve of the NaCh and AChR in the NMJ. It has been shown that in MG, the eye muscle fibers that have a lower safety factor are affected earlier in the fatigue process as there is a loss of Na+ channels and AchRs from the endplate, which reduces the safety factor for neuromuscular transmission.[39]

The eyes are the most susceptible muscle group to an autoimmune-mediated attack on the NMJ.[2] Five of the six identified types of fibers in the orbital and global layers of the EOM have a lower safety factor, increasing the likelihood of the extra-ocular muscles (EOM) suffering from fatigable weakness in MG.[40] Recent studies in human EOMs show that they are much more complex than previously thought.[41] Currently, they have been divided into six types: orbital singly innervated, orbital multiply innervated, global red singly innervated, global intermediate singly innervated, global pale singly innervated, and global multiply innervated fibers.[42] It is now known that all extraocular muscle fibers except pale globe fibers have a lower safety factor, which explains why saccades remain fast in MG patients who exhibit restriction of ocular motility.[43] Electromyographic studies of the extraocular muscles indicate that global fibers are less active than orbital layers during eccentric gaze-holding.[44]

Developing the SLOWLY Test

During ocular motility testing, variable EOM fiber types are engaged depending on factors like the starting point, speed, and direction of the eye movement. Advances in knowledge of the anatomy of the oculomotor system, including fibromuscular pulleys, have provided insight into how specific movements influence which EOM fibers are engaged. The clinical implications are still not fully understood; however, for this report, the knowledge that a weak lateral rectus muscle affects the positions of pulleys, which, in turn, influences the pulling directions of muscles with predominantly vertical actions, was considered as part of the design of the new test describe.[43] This test was named the SLOWLY Test, and excludes saccadic movements, instead including only slow, small vertical pursuit in the mid-lateral field of vision.

A Novel Test - The SLOWLY Test – 'Significant Level of Weakness in the Lateral Y axis mid gaze'

Ocular motility testing in an MG patient has not previously been described in terms of extraocular muscle physiology, including the 'Safety Factor' of each extraocular muscle (EOM) while combined with patient experiential knowledge. This new method involves identifying fixation areas with a 'significant level of weakness in the lateral Y-axis mid-gaze zone.' This area is given the acronym 'SLOWLY' to emphasize the importance of a slow testing speed for MG assessment. The SLOWLY Test induces objective fatigable muscle weakness by utilizing the action of the EOM fibers with the lowest neuromuscular junction (NMJ) 'Safety Factor.' The design for the SLOWLY Test includes testing extra slow, small vertical pursuit eye movements, performed in a manner similar to plotting a blind spot on a confrontation visual field test, alternating with static gaze holding while excluding saccadic movement.

The SLOWLY Test Method

This method is not simply gaze holding but involves small, slow movements not currently tested in standard OM examinations in a zone that is not tested routinely. It consists of asking the patient to follow a target in slow vertical pursuit movements in mid-lateral gaze, with intermittent gaze holding. The procedure involves slowly following a target in this unique pattern to disclose the MGES without initiating saccadic movements. During the SLOWLY Test, as with any OM testing, it is quite easy for patients to become distracted and perform a saccadic movement to regain eye contact with the examiner or at some other target. The examiner must explain to the patient that they should refrain from using fast eye movement and maintain fixation on the target.

It was noted that the patient in this report displayed fatigable weakness associated with a positive SLOWLY Test occurring immediately once a SLOWLY was identified, and remained while the patient maintained their gaze holding in the SLOWLY. However, the MGES disappeared with a change in fixation, a saccadic movement, or a decrease in 'effort' to maintain fixation by the patient. This patient's most significant MGES with a SLOWLY were in right lateral mid-gaze mid-elevation, where she displayed a complete ptosis of the right eyelid and a total left ptosis was identified in left lateral mid-gaze mid-elevation. These MGES were sustained on maintaining fixation in the specific loci. Other MGES, including OM restriction and lid hopping, were also noted in left lateral gaze in other identified loci. These MGES were also more obvious than other traditional methods of testing for MGES previously performed.

The SLOWLY Test is potentially particularly valuable for disclosing latent signs in MG patients, who, due to the variable nature of their disease, may have less obvious signs of objective fatigability at the time of consultation. These patients are often missed with current testing regimes. Further research on groups of the subtypes of MG patients should be undertaken to see if there is a difference in response to the tests between subgroups of MG.

Slow speed for testing for MGES (The SLOW and SLOWLY Test)

Another test designed to elicit latent MGES, the 'SLOW Test,' which is based on the Mary Walker Effect, and examines simultaneous lip and ocular weakness, has also

been previously described by this author.[38] The SLOWLY Test continues with the 'slow' theme, highlighting the importance of a slow-moving target when testing for MGES during ocular motility examination. The SLOWLY Test stands for Significant Level Of Weakness, Loci in the Y axis.

The SLOWLY Test helps explain the fleeting and variable nature of MG eye signs that may occur in some MG patients during ophthalmic clinical assessment. The importance of slowing down the pace of OM testing in MG is explained through a deeper understanding of neuromuscular junction, muscle fiber anatomy, and physiology. This concept also highlights the need for further interdisciplinary studies in OM to develop more effective diagnostic tests for MG, due to the complexity of damage to the NMJ affecting the 'safety factor' in MG and its effect on ocular motility.

Myasthenia Gravis Misunderstood – Conclusion

The historical communication errors regarding MG outlined in this review have contributed to today's misunderstandings of the disease and have continued to cause difficulties in diagnosis and difficulty in understanding MG patients' lived experiences. Myasthenia gravis should continue to be regarded as a serious disease due to the devastating effect on quality of life for many people, and the unpredictability of MC, TC, or choking potentially occurring in *all* people living with MG, including those who are undiagnosed.

Acknowledging the symptom of 'painful heavy muscles' should help with diagnosis and understanding the patient's experience. Patient-led research recording MG patients describe how their muscles feel are vital, and should be compared with the descriptions of painful heavy muscles that been recorded since the early 1900's.[16, 30] This is an important area for future research to document and emphasize Jolly's intended meaning of Myasthenia Gravis as 'weak, painful heavy muscles.'

The dismissing of mild symptoms results in many MG patients remaining undiagnosed, or having a delayed diagnosis, resulting in poorer outcomes for quality of life. The possibility that individuals in the undiagnosed group go on to become victims of Sudden Adult Unexplained Death (SUD) is yet to be investigated, and research should be performed in this area. Awareness that clinical symptoms may be mild and fluctuating, not necessarily severe at the time of clinical assessment and that sensory symptoms are often associated, is crucial to prevent further misdiagnosis. Awareness that clinical tests of fatigability can cause exacerbation of the other muscles that are not engaged is essential for the clinician to not overfatigue the patient and to understand the patient's lived experience. Awareness that interdisciplinary knowledge, such as the physiological and anatomical features of the eye muscles is crucial to further develop accurate clinical assessments to disclose latent and fleeting eye signs in MG.

Awareness of the issues addressed in this paper will directly positively impact patients' lives through earlier diagnoses, initiation of earlier treatment and understanding lived experiences by their doctors, loved ones, and the community. This knowledge will lead to further research to find methods for earlier diagnosis, development of rehabilitation interventions, and improved knowledge to update the incorrect information prominent in the MG field.

Summary

Historical miscommunication and misinterpretations have resulted in misconceptions and MG being a misunderstood disease. This article highlights six issues that have led to today's misunderstandings of MG. These have continued to cause difficulties in diagnosis and difficulty in understanding the MG patients' lived experiences; they include:

1. Misinterpretation of the intended meaning for 'gravis' being misinterpreted as 'severe' instead of the intended meaning of 'a painful weight in the limbs.'[4]

2. Misinterpretation that led to the incorrect use of the word 'grave' to describe MG in a popular 1903 medical textbook, and has been repeated in many subsequent medical texts even today.

3. Misinterpreting a prominent MG case series paper by Campbell & Bramwell led to the incorrect belief that sensory symptoms are not associated with MG. Even though MG patients have reported having sensory symptoms for over 124 years, including in the above-mentioned MG case series paper by Campbell & Bramwell.[15]

4. Miscommunication that occurs when important 'old knowledge' like The Mary Walker Effect is forgotten. Remembering that 'wearing out one muscle group causes exhaustion and weakness in the other muscle groups that have not been stimulated' in MG will help in many ways, like developing new clinical tests,[38] developing new rehabilitation strategies, and helping understand the patient's lived experience. Examples of the latter are described in this paper.

5. Miscommunication involving not listening to the patient's lived experience. Patient experiential knowledge can help develop further understanding in many aspects of MG, including understanding Jolly's intended meaning of weak painful heavy muscles, developing new clinical tests, like the Mary Walker Effect Tests (The SLOW Test and the Mary Walker Ball Test) and the new test named the 'SLOWLY Test;' the latter 2 tests are described in this paper.

6. Miscommunication involving failing to communicate and integrate relevant interdisciplinary knowledge. A good example is how anatomy and physiology knowledge may help develop new ocular motility clinical tests specific to MG. The SLOWLY Test described in this paper was developed in this way.

Future Directions

Patient-led research recording MG patients describe how their muscles 'feel' during periods of exacerbation is an important area for future research to clearly document and emphasize Jolly's intended meaning of Myasthenia Gravis as 'weak, painful heavy muscles.'

Further research utilizing the Mary Walker Effect is recommended to develop new tests, and improve understanding of Patient Lived Experience by doctors. The research should involve patients at every stage.

Interdisciplinary knowledge, such as the physiological and anatomical features of the eye muscles is crucial to the further develop accurate clinical assessments to disclose latent and fleeting eye signs in MG. This area could be further developed with patient-led research.

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