RRNMF
Neuromuscular
Journal
vol. 4:2 June 2023

The Official Journal of:

Neuromuscular Study Group

RRNMF
RICK'S REAL NEUROMUSCULAR Friends

Cover Image: *Woman Holding a Balance* by Johannes Vermeer, c. 1664.
National Gallery of Art, Washington, DC

CONTENTS

ART AND OTHER GOOD STUFF

Letter from the Founding Facilitator for Volume 4, Issue 2

Richard J. Barohn, MD
Department of Neurology, University of Missouri, Columbia, MO

Welcome to the latest issue of the RRNMF Neuromuscular Journal, in which we have many interesting publications for you to read and enjoy.

In our What's on Your Mind? section, Josh Freeman provides us with another analysis of the inequities of access to healthcare and pleads for more primary care and no financial barriers for anyone. I really enjoy that Josh allows us to publish his pieces in a super-specialized neuromuscular journal! Josh is, of course, a family medicine physician, and over our decades of friendship we have had many discussions on how we both see health care from different perspectives: He from primary care and me as a super specialist. I think it is good for us specialists to always be cognizant of the primary care physicians' viewpoint on what we do.

We also have two pieces that I first wrote for my "Executive Vice Chancellor for Health Affairs/Dean messages," which I send to all the faculty and employees at the University of Missouri School of Medicine and the University of Missouri Healthcare system twice a month. I adapted them for publication in this journal. I wrote the first one for Black History month, and it is about Dr. Louis Tompkins Wright, a surgeon who became one of the pioneers of oncology and was a legend in the New York medical community and beyond. I also mention his equally-famous daughter, Dr. Jane Wright, who took over her father's cancer research when he died and made significant contributions in the field of chemotherapy.

My second piece was written for Women's History Month, and I provide five very brief vignettes on some of my heroes of medicine who happen to be women: Rosalind Franklin; Florence Nightingale; Helen Keller; Marie Curie, and Mary Walker. I have pictures of all of them hanging in my office at the University of Missouri.

In the Clinic Stuff category, Dr. Scott and the pathology team at the University of Missouri wrote up a case of cryptococcal meningitis in an immunocompetent man to remind us that this does occur. Dr. Jeff Elliott, my colleague from my UT Southwestern days, describes a 23-year-old woman with a congenital myasthenia syndrome due to a novel mutation in the MUSK gene. Dr. Jeremy Hill and our very own associate journal facilitator Dr. Yuebing Li provide a description of a generalized myasthenia gravis patient having an exacerbation after receiving the BRAF inhibitor vemurafenib and the MEK inhibitor cobimetnib for metastatic melanoma. Our colleagues in neurology at the Medical College of Wisconsin, including Brittany Bureau and my old friend Paul Barkhaus, report a fascinating case of numb chin syndrome from cancer that is atypical and spread to involve the ipsilateral maxillary branch of the trigeminal nerve—so NCS Plus! The Wisconsin group pointed out that Charles Bell (of Bell's palsy fame) first described the NCS. I did not know that.

In the New Stuff category, I was glad to see the report by Dr. Nakul Katyal and Dr. Raghav Govindarajan from when they were in the neurology department at the University of Missouri, in which they report the lack of effectiveness of eculizimab in three cases of generalized myasthenia gravis. We are all excited about the introduction of complement inhibitors into the treatment armamentarium for MG, but it is important to be aware they do not have an effect in all cases. Our colleagues at the University of Miami, Dr. Carbunar, Dr. Gultekin, and Dr. Saporta, report two cases of distal myofibrillar myopathy with new pathogenic mutations in the DES gene that codes for desmin.

I am so happy to see the paper on quantitative sensory testing in neuropathy patients finally get published. I started this study with colleagues at UT Southwestern in the 1990s and the data has been sitting in my files for a LONG TIME. I finally retrieved it and was delighted when a group of younger neuromuscular docs agreed to analyze it and put it in order. We performed QST testing on over 500 consecutive patients that we were seeing for peripheral neuropathy to see if it had much utility to separate out patients. Dave Saperstein had presented this at a meeting and we had published an abstract, but we never did a detailed analysis and manuscript until now. I am indebted to Alexis Lizarraga, Salman Bhai and Morgan McCreary for taking the time to analyze and describe the data. A group of colleagues from New York, Boston, California and Ohio, led by Jonathan Morena, describes two new cases of facial onset sensory and motor neuronopathy (FOSMN), and did all of us great service by analyzing 98 other published cases to give us a very complete picture of what is known so far about this unusual multiple cranial neuropathy.

Finally in the New Stuff category, Dr. Kanatas and Dr. Stathpoulos from Athens, Greece and Dr. O'Connor from Yale provide an in depth discussion on the status of CD20 depletion therapy in myasthenia gravis.

In the Other Stuff section, Bud and Betsy Rowe co-authored a prose piece they call "Survival of the Fittest." Dr. Michael Abraham, our poet laureate in the neurology department at the University of Kansas, has allowed us to publish another of his wonderful poems. And finally, a brilliant medical student at the University of Kansas, Vincent Czerwinski, wrote a wonderful prose piece about a hospital experience by his protagonist "Rick"... I loved that.

The cover art is a Vermeer. I thought you can never go wrong with a Vermeer. The painting of a woman using a renaissance-era scale to weigh an object was fitting for the issue highlighting Women's History Month. This painting is in the National Gallery in Washington DC--a Smithsonian museum--and thus can be printed without permission because we, US citizens, all own it!

Rick

Access to Healthcare: More primary care and no financial barriers for anyone

Joshua Freeman, MD

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

A recent study by Matthew Toth and Lauren Palmer from the Research Triangle Institute (RTI) evaluated the impact of the Center for Medicare and Medicaid Services (CMS) Financial Alignment Initiative (FAI) on access to primary care by those people who are eligible for both Medicare and Medicaid. These people are called "dual-eligibles" and represent about 13% of Medicare recipients. The FAI aimed to increase coordination of care, and the authors discovered that it did increase primary care access, to some degree, in 6 of the 9 states in which this demonstration project was implemented. In one state where it did not, Washington, eligibility for the program required people to have multiple morbidities (chronic diseases), and so the authors speculate that it increased access in other states for "healthier" dual eligibles.

There is nothing wrong with this study, or the program it studies, insofar as they go. But it raises two major issues. The first is that the program is yet another example of how the federal government continues to tinker around the edges of a completely flawed healthcare system by experimenting with one program after another that *might possibly* help, *to some degree,* a small portion of our population. This is not to say that the people who were studied, those eligible for both Medicare (by age or disability) and Medicaid (by poverty) are not deserving of better access to care and care coordination; certainly, they are. But we all are. Because we have some people who are eligible for Medicare and some people who are eligible for Medicaid and lots of people who are eligible for neither, and many people who are uninsured, and many more are grossly underinsured, we have fragmented our population and made financial access both unwieldy, far from comprehensive, and incredibly expensive. If this study (maybe) shows that the improvement in access was more for those "dual-eligibles" without multiple morbidities, is this bad? Well, it's bad that they weren't getting coordinated care in the first place!

Here I need to take a break, before going on to the second issue, to put in a word or two for our medical insurance companies and large hospital systems. They are not doing badly. Indeed, the outrageous excess cost of our health system, two to three times (or more) per capita than other OECD countries despite leaving large numbers of people uncovered, is due almost entirely to their profit-taking. They are doing well, thank you, along with the drug manufacturers, even while rural and inner-city safety net hospitals are going broke taking care of poor and uninsured (and sick) people, and millions of Americans go without care or receive inadequate care. The words – I'll go with two – are *rapacious thieves.*

The second issue is that while financial access, being covered by adequate insurance, is very important, it is only part of the picture. The other part is having doctors (or other appropriate clinicians) who are available to see patients. This is the other area in which the US (and, in fairness, a few other countries including Canada) are failing. Have you tried to get an appointment to your primary care clinician lately? Maybe you can get in easily, but if so, you are the exception. Most people have to wait weeks or months. If they go to the ER, they wait many hours, even for urgent or emergent problems. It would be good to be able to see a doctor who knows you, and knows your history, right? Instead of someone in an Urgent Care Center. I can answer all of these for people I know (or me), and the answers are not positive, and these are folks who are well insured and live in a major metropolitan area, not in a rural one or an inner-city health care desert! In Canada, there are suggestions that the way to fix the wait is to – wait – privatize health care! Hah! Come on down and see how that works here!

Why is it that people cannot get appointments to see primary care clinicians? Shouldn't there be enough? Years ago, on *Saturday Night Live*, Don Novello portrayed a character called Father Guido Sarducci who offered a "5-minute university" where you were only taught what you would remember years later anyway. For Economics, it was "supply and demand." So, if there is so much demand for doctor visits, especially primary care visits, why is there not enough supply to meet it? This is, as you would guess, kind of complicated.

Obviously, there are not enough primary care clinicians, either as a whole or as a percent of all physicians. If there were enough, you could call your doctor and get in today if you were sick or had a worsening problem, like on TV (pick your favorite FP/GP show). So, we don't have enough. This is all about money. To some degree, it is about doctors wanting to make as much as they can. This results in far too small a proportion of graduates entering primary care, since they can make two or three times as much in some other specialties, which is enough to convince even many who liked the idea of primary care that, especially with their debt load, they liked anesthesiology more. We are at about half the percentage of primary care that we should be. For this I

blame the system that pays other specialties so much more (or primary care so much less). In addition, the distribution is poor – not enough doctors in rural areas, or certainly poor urban areas, but all concentrated in wealthier urban and suburban areas.

Ultimately this is all about the corporatization of health care, and the treatment of providers as widgets in a factory. Put this many in clinics, make sure that they are totally booked and have no room for anyone who needs to get in on short notice, put others in the hospital, put others in urgent care or ERs. Have no flexibility in the system because if you have the capacity to expand when needed, that means that at other times you have down time, and that is unacceptable for making maximum corporate profit. Of course, this is not good for your health, which is better when you can see a doctor who knows you, especially when you are sick and couldn't plan two to eight weeks ahead of time (or more!) to make an appointment.

Creating doctors and other health professionals takes many years, and cannot change on a dime, but it will never change if that change doesn't start. If we care about people's health and health care, we need to dramatically decrease the difference between primary care and other specialists' income so it doesn't discourage students from choosing primary care. We need to ban for-profit corporations (or ostensibly non-profit systems that act like for-profits) from being in our health system at all. All of health care and its components should be about ensuring better quality health for our people, not making money for businesses.

The usual pattern in the US is to have funding for public services cut by politicians who are receiving money from private corporations to the point that they do not function well at meeting public needs. Then those same politicians say "privatize!" and they do, and the cost goes way up, and the public needs are still not met, because, well, that's not what private enterprise is there for. (See this good video by Brittlestar on why privatization is not a good choice for Canadian healthcare.)

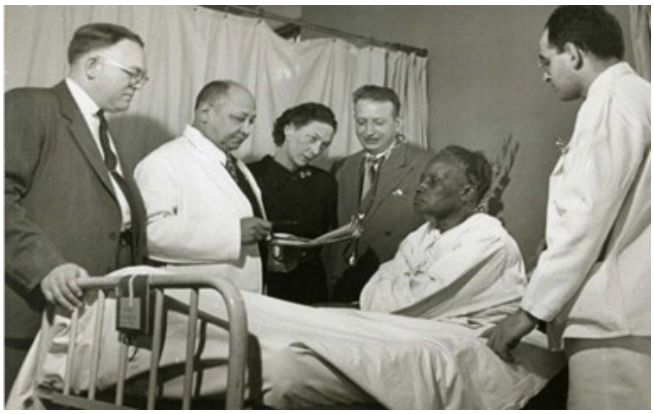
Jimi Hendrix said, "castles made of sand fall into the sea eventually," but our health care system is not built on sand. It is built on rocks of intransigent corporate profit, and it is not going to change without a fight. You and your health don't count as much as big business making money. So there. Pick up the gauntlet, and fight for yourself, your family, your community.

Dr. Louis Tompkins Wright: One of the early Black men in white coats

Richard J. Barohn, MD
Department of Neurology, University of Missouri, Columbia, MO

Two months ago, we had a viewing of the documentary called "Black Men in White Coats" at the MU School of Medicine followed by a panel discussion. The documentary pointed out that fewer and fewer Black men are entering into medicine. I would like to share about one inspiring physician who epitomizes the need for more Black men in white coats, Louis Tompkins Wright, MD.

Dr. Wright was part of a family of physicians going back to the 1800s. He attended Clark University and Harvard Medical School, where he experienced discrimination on many fronts as a Black student. He initially was told he could not deliver babies at one of the Boston hospitals, but he objected and persevered. Prior to that, Black students were only allowed to deliver Black babies. His stance abolished this practice.



Dr. Louis T. Wright, second from left, and colleagues at a patient's bedside in Harlem Hospital[1]

Despite graduating with honors, because he was Black, he could not get an internship at Massachusetts General Hospital or Peter Bent Brigham Hospital. He did his internship at Freedmen's Hospital, now Howard University Hospital, a hospital for for the African American community in Washington, D.C. He practiced briefly in Atlanta before entering the U.S. Army as a doctor in WWI. During this time, he introduced the intradermal method of vaccination for smallpox, which was adopted by the U.S. Army Medical Corps. Later, he was placed in charge of a military hospital in France, the youngest surgeon to hold such a position. He was awarded the Purple Heart, remained in the Reserves, and rose to the rank of Lieutenant Colonel.

After the war, he began a surgical practice in New York City and became the first Black physician appointed to the staff of Harlem Hospital or any New York City hospital. Four white doctors resigned in protest. Twenty-three years later, he became director of surgery and ultimately became the president of the medical board. Dr. Wright specialized in head injuries and fractures and invented several braces and surgical devices.

His accomplishments in surgery led him to become the first Black physician admitted to the American College of Surgeons. He excelled not only in surgery but became an expert in the use of antibiotics such as Aureomycin and Terramycin for infections. A man of many talents, he also became a leader in cancer therapy and founded the Harlem Hospital Cancer Research Foundation where early chemotherapeutic research trials were performed.

Dr. Louis T. Wright and his daughter Dr. Jane Wright, who followed in her father's footsteps. She became his research partner in the era of chemotherapy and eventually took over his work. If that name sounds familiar, it is because she was the subject of a previous "What's on your Mind?" piece.

Dr. Wright was an outspoken and forceful fighter for equal rights for Blacks and led efforts to stop segregated hospitals which he maintained "represent a duality of citizenship in a democratic government that is wrong." In 1952, Dr. Wright received a citation from the John A. Andrews Memorial Hospital of the Tuskegee Institute for his contributions to interracial health programs in the North and South. He was cited for his "distinguished services in the cause of humanity, for resolute leadership of allied humanitarian and civic organizations dedicated to the advancement of social, economic and related conditions basic to the health of all the people."

As we think about Black History Month, please honor and appreciate some of the giants like Dr. Louis Tompkins Wright. The world needs many more Black men in white coats such as him — and Black women in white coats like his daughter, Dr. Jane Wright.

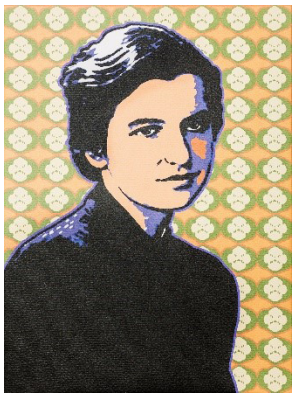
[1] Louis Tompkins Wright papers, 1879, 1898, 1909-1997. H MS c56. Harvard Medical Library, Francis A. Countway Library of Medicine, Boston, Mass.

Women's History Month vignettes

Richard J. Barohn, MD
Department of Neurology, University of Missouri, Columbia, MO

Following up Black History Month was Women's History Month. In my other "What's on your Mind?" piece in this issue, I highlight an extraordinary Black father and daughter who shaped medicine and specifically cancer medicine in the United States, Drs. Louis and Jane Wright. This is a remarkable family with multiple generations of physicians.

For Women's History Month, I would like to share about five additional women who have made an international impact on health and medicine. I have photos or artistic impressions of these amazing scientists and leaders in this piece. Please read on to find out more about them.



Rosalind Franklin (1920-1958)

While James Watson and Francis Crick received the credit — and the Nobel Prize — for discovering DNA, it was actually Dr. Rosalind Franklin who determined the structure of DNA. She was a chemist who worked in the field of X-ray crystallography. She took images of DNA that showed the double helix structure. Dr. Watson saw the pictures in her laboratory in London, then went to Cambridge and constructed the now famous model of the double helix and published it in a medical journal without giving Dr. Franklin credit. Unfortunately, she died of cancer at age 38, never receiving the credit she was due.

Florence Nightingale (1820-1910)

While serving as a manager of nurses in the Crimean War, Florence made incredible progress in reducing death rates by improving hygiene in military medical facilities. Under her leadership, the death rate in the military hospital declined from 42% to 2%. Upon returning to England, she was able to incorporate the sanitary practices in peacetime hospitals. She established a training program for nurses, later called the Nightingale School, and wrote the book "Notes on Nursing," becoming a best seller by the medical and lay public. She is also famous for using statistics as a tool to come to her conclusions about health care and is considered the founder of modern nursing.

Helen Keller (1880-1968)

Most know the life of Helen Keller from the wonderful movie, "The Miracle Worker," about how she overcame the challenges of deafness and blindness as a girl. Subsequently, she went on to be an author and advocate for disability rights. From 1924 to her death in 1968, she worked for the American Foundation for the Blind and lectured throughout the world advocating for those with visual loss. A voice against discrimination of any kind, she was a founding member of the American Civil Liberties Union (ACLU).

Marie Salomea Sklodowska-Curie (1867-1934)

Born in Poland, she attended university in Warsaw and moved to Paris to continue her scientific education. There she married the French physicist Pierre Curie and together they uncovered "radioactivity," a term she invented. Together, she and her husband won the Nobel Prize in physics for their joint discovery. She was the first woman to receive a Nobel. She continued her work and after she discovered radium and polonium, she received a second Nobel Prize in chemistry. She conducted the first studies to treat cancer using radioactive isotopes and founded the Curie Institute in Paris and Warsaw.

Mary Walker (1888-1974)

All the women I described above are probably well known to many of you. Dr. Walker, however, may not be. Born in Scotland, she attended the Edinburgh College of Medicine for Women. In World War I, she served in the Royal Army Medical Corps in Malta. She then was an Assistant Medical Officer at St. Alfeges Hospital in Greenwich, London. It was here taking care of patients with the neurologic disorder myasthenia gravis, that she recognized the similarity

between the symptoms of that disease and poisoning from the toxin curare. Both have eye droop and muscle weakness and slurred speech. The compound physostigmine, which was extracted from the West African Calabar bean, had been shown to be an effective antidote for curare poisoning. In 1934, she made the medical judgement and administered the drug physostigmine to several patients with myasthenia gravis. The effect was dramatic and resolved the symptoms within minutes. That class of drugs remains the first line treatment for myasthenia gravis nearly 100 years later.

These vignettes are why I have portraits of all these amazing scientists in my office at the University of Missouri School of Medicine. You are welcome to stop by and see them some time.

Cryptococcal Meningitis in an Immunocompetent Male: Case Report

[1]Keela R. Scott MD, [2]Caitlyn J. Smith BS, [1]Daniel R. Walker MD, [1]Belinda R. Fender MD

[1]Department of Pathology and Anatomical Sciences, University of Missouri School of Medicine, Columbia, Missouri, 65212
[2]University of Missouri School of Medicine Columbia, MO 65212

Introduction

Cryptococcal meningitis is a life-threatening condition caused by an invasive, opportunistic, encapsulated saprophytic fungus, either *Cryptococcus neoformans* or *Cryptococcus gattii*. Cryptococcal meningitis is commonly seen in immunocompromised patients, especially those with human immunodeficiency virus (HIV). Overwhelming invasive infection of immunocompetent patients is rather uncommon, and diagnosis is often challenging. We present a case of cryptococcal meningitis (CM) in an immunocompetent male following a recent motor vehicle accident.

Case Presentation

A72-year-old immunocompetent male presented to the emergency department with a 7-day history of persistent headache, intermittent fever, progressive generalized weakness, upper airway congestion, and lower back pain. Of note, this patient sustained a complete T12 burst fracture following a motor vehicle accident one month prior for which he was treated conservatively and doing well at follow-up. Additionally, the patient's medical history was significant for congestive heart failure (CHF) with permanent pacemaker placed in 2009, hypertension (HTN), and peripheral neuropathy. The severity of the patient's CHF was unable to be obtained via the medical record. He did not endorse any current or past alcohol use. Upon presentation, he was tachycardic and hypotensive with positive upper neuron motor signs on physical exam including hyperreflexia of the bilateral lower extremities, positive Babinski sign and positive Hoffman's sign.

Initial lab studies revealed a normocytic normochromic anemia with a hemoglobin of 9.6 g/dL (normal reference range: 13.5 – 17.5 g/dL), decreased platelet count of 109,000 platelets/μL (normal reference range: 150 – 450 platelets/μL), elevated total bilirubin of 1.66 mg/dL (normal reference range: 0 – 1.60 mg/dL) and alkaline phosphatase of 131 units/L (normal reference range: 40 – 129 units/L). Both the serum total white blood cell (WBC) count and absolute neutrophil count (ANC) were within normal range at 8.64 cells/μL (normal reference range: 3.50 – 10.50 cells/μL) and 4.66 cells/μL (normal reference range: 1.70 – 7.00 cells/μL), respectively. Additionally, other liver function tests included the following: normal aspartate aminotransferase (AST) of 34 units/L (normal reference range: ≤ 40 units/L), normal alanine transaminase (ALT) of 24 units/L (normal reference range: 10 – 50 units/L), and mildly decreased albumin of 3.4 g/dL (normal reference rang: 3.5 – 5.2 g/dL). The remainder of the initial lab tests were within normal limits. Of note, the patient was prescribed spironolactone (25 mg, twice daily) as a diuretic, which may have influenced the observed thrombocytopenia as well provided some baseline immunomodulatory effect.

Computed tomography (CT) of the head revealed no abnormalities. Magnetic resonance imaging (MRI) studies were unable to be obtained as the patient had a pacemaker. CT imaging of the chest, abdomen, and pelvis revealed progressive vertebral body height loss of the T12 burst fracture with intraosseous gas compatible with interval osteonecrosis of the T12 vertebral body. There was also surrounding prevertebral soft tissue thickening concerning for an organizing hematoma; however, a superimposed infection could not be excluded.

The patient was admitted and the cerebrospinal fluid (CSF) analysis revealed colorless, clear fluid with a normal opening pressure; however, the protein level was critically high (194 mg/dL) and the glucose level was critically low (3 mg/dL). There were 16 white blood cells/μL, of which 6% were neutrophils, 21% lymphocytes, 71% monocytes, and 2% eosinophils. Histopathological examination of the CSF with gram staining revealed budding yeast forms consistent with *Cryptococcus* (Figure 1). Cytopathology of the CSF redemonstrated the presence of *Cryptococcus* and no evidence of malignant cells were identified. The CSF culture was positive for *Cryptococcus neoformans/gattii* and negative for both bacteria and mycobacterium species. Repeated blood cultures were also positive for *Cryptococcus neoformans*. Additionally, the patient's CSF was positive for Cryptococcus antigen with a titer of greater than 1:2560. The remainder of the workup was negative including testing for mycobacterium species, HIV, influenza, COVID-19, other fungal species, as well as a comprehensive viral and bacterial panel.

Subsequently, empiric bacterial coverage was discontinued, and the patient was treated with a 14-day course of intravenous liposomal amphotericin B (5 mg/kg/day) and flucytosine (800 mg/day) with improvement of symptoms. He was then discharged and completed an 8-week course of fluconazole (800 mg/day) for

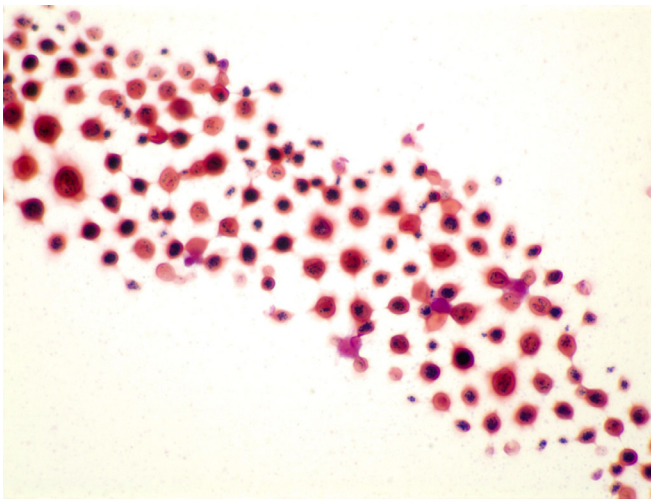


Figure 1. Gram staining of the cerebrospinal fluid reveals clusters of thin-walled, encapsulated yeast forms of various sizes with narrow-based budding consistent with Cryptococcus (Gram stain, 6000x magnification).

consolidation therapy. Today he is healthy with no residual neurological or serological evidence of disease.

Discussion

Cryptococcal infection is a life-threatening condition caused by invasive, opportunistic fungal pathogens, the most common of which include *Cryptococcus neoformans* and *Cryptococcus gattii*. Two serotypes of *C. neoformans* are currently identified, serotype A and serotype D, the former of which is more virulent. Additionally, two serotypes of *C. gattii* are currently identified, serotype B and serotype D, although no difference in virulence has been noted.[1] Both species grow as budding yeast and are often found in tree hollows and pigeon droppings.

Infection in immunocompromised patients often presents as overwhelming meningitis or meningoencephalitis with a high mortality rate; however, cryptococcal meningitis (CM) in immunocompetent patients is less common although cases have been reported.[1] Immunocompromised states that typically confer a more severe disease course include patients with hematologic malignancies, organ transplant recipients, and those receiving disease-modifying agents. Patients particularly at risk of contracting this disease are HIV positive individuals especially those with a CD4 count less than 100 cells/μL. In fact, the most common cause of adult meningitis in areas with high HIV rates is CM.[2]

The most common symptom of CM upon initial presentation is headache and may be accompanied by some degree of altered level of consciousness. Classic features of meningitis such as neck stiffness are present in less than 20% of cases.[3] To further complicate the matter, infection in immunocompetent patients can also prove to be quite difficult due to a more indolent course which may delay appropriate treatment and hasten neurological sequelae.

According to a retrospective cohort study conducted by Brizendine et al.,[4] significant risk factors of mortality from cryptococcosis include cryptococcemia, high intracranial pressure, HIV-status, and transplant status. Furthermore, a study conducted by Henao-Martinez et al.[5] demonstrated that a diagnosis of HIV infection or a positive serum cryptococcal antigen test were both significant predictors of CM. Amongst healthy patients several etiologies for possible immunosuppression are suggested including diabetes mellitus, alcoholism, and cirrhosis, which are thought to induce some level of immunosuppression.[6]

Although CM largely remains a disease of immunodeficient individuals, several case reports have been published describing CM affecting immunocompetent patients. Garcia-Villa et al.[7] described a 23-year-old Latino female with no significant medical history who presented with a one-month history of intermittent abrupt onset severe headaches. She received appropriate antifungal treatment and improved with no residual symptoms. Shokouhi et al.[2] described the case of a 55-year-old immunocompetent Iranian man with a 20-day history of gradual onset of headache that was treated and fully recovered. Newson et al.[8] reported the case of a previously healthy 22-year-old active-duty soldier that was admitted for a 2-month history of persistent headache, nausea, vomiting, weight loss, and nocturnal fevers. He was diagnosed with CM and experienced a full recovery after receiving appropriate antifungal therapy.

In this report, we present the case of a Caucasian man who was admitted with a one-week history of headache, intermittent fevers, and weakness in the setting of a recent traumatic burst fracture. It is important to consider the patient's recent history of a vertebral burst fracture as a potential etiology of an immunocompromised state which may have made him more susceptible to infection. Although the exact mechanism is not clearly delineated in the literature, it is possible that a cellular immune response to inflammation via release of interleukin-10 (IL-10) may lead to immunosuppression. Additionally, immunosenescence may be an additional risk factor in a patient over 70 years of age.

While diagnosis of CM in immunocompetent patients is less common, it is important to consider this diagnosis in patients presenting with headache and CSF specimens with high protein and low glucose levels. This case demonstrates the importance of broadening the differential in immunocompetent patients present with otherwise nonspecific symptoms, so appropriate and timely treatment can be initiated and effectively reduce the possibility of permanent neurological sequela.

Corresponding Author
Keela R. Scott
1 Hospital Drive Department of Pathology M263, MSB
Columbia, MO 65212
(573) 882-3014
krshr3@health.missouri.edu

Declaration of Conflicting Interest
The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Source of Support
The author(s) received support from the University of Missouri Department of Pathology and Anatomical Sciences in the form of laboratory equipment and supplies used for the morphologic examination of the patient's specimens. No payments were made to us.

Acknowledgement
The authors would like to thank the Department of Pathology & Anatomical Sciences for the opportunity.

References

1. Kozubowski L, Heitman J. Profiling a killer, the development of Cryptococcus neoformans. FEMS Microbiol Rev. 2012 Jan;36(1):78-94. doi: 10.1111/j.1574-6976.2011.00286.x. Epub 2011 Jul 4. PMID: 21658085; PMCID: PMC3318972.

2. Shokouhi S, Hakamifard A. Meningitis Caused by *Cryptococcus neoformans* in an Apparently Immunocompetent Patient. J Investig Med High Impact Case Rep. 2022 Jan-Dec;10:23247096221111779. doi: 10.1177/23247096221111779. PMID: 35848079; PMCID: PMC9290167.

3. Mwaba P, Mwansa J, Chintu C, et al. Clinical presentation, natural history, and cumulative death rates of 230 adults with primary cryptococcal meningitis in Zambian AIDS patients treated under local conditions. *Postgrad Med J*. 2001;77(914):769-773.

4. Brizendine KD, Baddley JW, Pappas PG. Predictors of mortality and differences in clinical features among patients with Cryptococcosis according to immune status. PLoS One. 2013;8(3):e60431. doi: 10.1371/journal.pone.0060431. Epub 2013 Mar 26. PMID: 23555970; PMCID: PMC3608592.

5. Henao-Martínez AF, Gross L, Mcnair B, McCollister B, DeSanto K, Montoya JG, Shapiro L, Beckham JD. Risk Factors for Cryptococcal Meningitis: A Single United States Center Experience. Mycopathologia. 2016 Dec;181(11-12):807-814. doi: 10.1007/s11046-016-0048-x. Epub 2016 Aug 8. PMID: 27502502; PMCID: PMC5121069.

6. Poley M, Koubek R, Walsh L, McGillen B. Cryptococcal meningitis in an apparent immunocompetent patient. *J Investig Med High Impact Case Rep*. 2019;7:2324709619834578.

7. Garcia-Villa M, Gonzalez-Lara A, Rodriguez-Leyva I. Cryptococcal meningitis due to Cryptococcus gattii in an immunocompetent patient: uncommon presentation of a thunderclap headache. BMJ Case Rep. 2022 Apr 4;15(4):e246158. doi: 10.1136/bcr-2021-246158. PMID: 35379676; PMCID: PMC8981403.

8. Jelaun Newsome, MC USA, Dana Nguyen, MC USA, Cryptococcal Meningitis Caused by Cryptococcus neoformans in an Immunocompetent Soldier, Military Medicine, Volume 179, Issue 9, September 2014, Pages e1059–e1061, https://doi.org/10.7205/MILMED-D-14-00020

A novel MUSK mutation in a patient with CMS9

Jeffrey L. Elliott, MD

Department of Neurology, UT Southwestern Medical Center, Dallas, Texas

Introduction

Congenital myasthenic syndromes (CMS) are a relatively rare cause of fatigable muscle weakness, often with significant ocular, bulbar and respiratory impairment1. Mutations in the gene encoding muscle-specific tyrosine kinase (MuSK) can lead to abnormal endplate and acetylcholine receptor functioning and cause an autosomal recessive post-synaptic CMS (CMS9). Only 23 patients with CMS9 have been characterized in the literature since the initial description in 20042. Here, we report a newly diagnosed case of CMS9 in a 23-year-old female who harbored a novel c.296G>T (Cys99Phe) mutation in the MUSK gene, thereby expanding the phenotypic/genotypic characterization of this rare disorder.

Case Report

A 23-year-old woman presented with a 13-month history of fluctuating limb weakness, fatigue, ptosis, double vision, dysphagia, and orthopnea. She had been consequently diagnosed with autoimmune myasthenia gravis, although AChR binding/modulating antibodies were negative, and treated with mestinon (60mg TID) and prednisone 30mg daily. She had also had one prior hospitalization for worsening bulbar /respiratory symptoms treated with a single IVIG course. She did not have a satisfactory response to overall therapy and was consequently referred for further neuromuscular evaluation. However, she developed worsening dysphagia and orthopnea, requiring local ER visitation, intubation, and transfer to our medical center. On exam, she had limited horizontal and vertical gaze with bilateral ptosis, bifacial weakness, and proximal (4/5) weakness in neck flexion, shoulder abduction, and hip flexion. Reflexes and sensations were normal. She was able to be extubated quickly (prior to PLEX) and then underwent six cycles of plasma exchange. She was discharged on mestinon and prednisone (50 mg daily) and scheduled for IVIG 2 grams/kg infusion with a follow-up in the NM clinic. Admission antibodies, including AChR, MuSK, LRP-4, and VGCC, were drawn and resulted in a negative.

She presented for an initial NM clinic visit about one-month post-discharge, just before the initial IVIG infusion. She had discontinued Mestinon as it provided no benefit. Her exam was notable for bilateral asymmetric ptosis, limited vertical and horizontal gaze, and bifacial weakness. Flaccid dysarthria, fatigable proximal weakness, and finger extension weakness. She was also still bothered by orthopnea with morning headaches. Additional workup included a low CK (23 U/l), normal TSH (3.17 mcIU/ml), normal lactate (2.1 mmole/l), and normal pyruvate (1mg/dl). Three hz repetitive nerve stimulation (RNS) of the trapezius showed a maximum baseline decrement of 22% with immediate post-exercise repair (Figures 1A and B). SFEMG on the frontalis showed increased jitter with an increased MCD of 87 (Table 1). These results confirmed a defect in NMJ transmission, and a diagnosis of seronegative myasthenia gravis was given. Cellcept was added to her prednisone and IVIG therapy. Pulmonary function testing showed a restrictive pattern with significant worsening in the supine position (Table 2). Nocturnal BiPAP was started, which helped with her morning headaches.

At a follow-up NM visit, the patient reported no significant improvement in symptoms, and her exam remained unchanged. Given her seronegative status and lack of response to necessary immunomodulatory therapy, we sent a genetic panel for congenital myasthenic syndromes through Invitae Genetics. Analysis showed a known pathogenic c2368G>A (p.Val790Met) mutation in MUSK as well as a variant c.296G>T (p.Cys99Phe) of unclear significance. To help determine the phase of these mutations (cis/trans), we sequenced the MUSK gene in both parents. Father harbored the c.296G>T (p.Cys99Phe) mutation while mother possessed the c2368G>A (p.Val790Met) mutation proving the MUSK mutations in the proband were in trans. Both parents were asymptomatic and had normal exams. There was no family history of anyone with similar symptoms. With a diagnosis of CMS9, immunosuppressive medications were stopped without any change in her symptoms. She had no benefit from a trial of 3.4 aminopyridine (Firdapse), discontinued at the dose of 15 mg TID due to side effects. She was then started on Albuterol with modest improvement.

Discussion

Here we present a 23-year-old female with CMS9 who harbors an established pathological c2368G>A mutation in compound heterozygosity with. a novel .c296G>T mutation in exon 3. This novel sequence change replaces cysteine with phenylalanine at codon 99 of the MuSK protein (p.Cys99Phe), which resides in the first three immunoglobulins (Ig)-like domains of the protein. The cysteine 99 residue is highly conserved across species, and a marked physicochemical difference exists between the uncharged polar cysteine and uncharged non-polar phenylalanine (Figure 2A). Such a mutation would be

expected to disrupt normal protein function based on a functional modeling platform (Sherloc) performed at Invitae[3].

MuSK is a postsynaptic muscle-specific tyrosine kinase receptor comprised of three extracellular immunoglobulin-like domains, a frizzled cysteine-rich domain, a transmembrane-spanning region, and an intracellular region including a juxta-membrane domain, a kinase domain, and a short C-terminal tail (Figure 2B). It is part of a signaling pathway critical for the clustering of acetylcholine receptors and maintenance 4,5,6. Disease-causing mutations have been reported in all MuSK domains, save the transmembrane and c-terminal tail regions, with a majority occurring in the kinase domain 2,4-14. These mutations can reduce MuSK protein stability and expression and interfere with its ability to interact with other critical postsynaptic junction proteins, including LRP-4 and Dok7. As LRP-4 binds to MuSK in the first Ig-like domain, it is reasonable to hypothesize that the novel Cys99 Phe mutation presented here may impair normal LRP4-MuSK interaction.

Although there is some variability in the clinical presentation of CMS9, a review of the published cases suggests two distinct phenotypic presentations (Table 3). The most common is neonatal onset, with an overwhelming respiratory presentation either from diaphragm weakness or vocal cord dysfunction. All patients carrying one truncation or stop codon mutation and one KD mutation, save one, had this severe phenotype. A minority of patients presented in adolescence or early adulthood with proximal limb girdle weakness and ocular symptoms. Patents harboring at least one Ig-like or JM domain mutation presented with this later-onset phenotype. Our patient is the first case reported in the literature carrying one Ig-like and 1 KD mutation. Interestingly, she appears to have a phenotype characterized by later onset presentation but with significant respiratory complaints requiring nocturnal non-invasive ventilation. She has had a partial response to albuterol with improvement in fatigue, limb strength ptosis, and double vision, similar to other published CMS9 patients.

In summary, we report a patient with a novel (C99F) mutation and an established M790V mutation in the MUSK gene, causing a rare form of CMS9. She has a later age presentation phenotype with a significant respiratory component. Her case emphasizes the importance of genetic testing in seronegative myasthenia patients so that exposure to immunosuppressive medications can be minimized with a correct genetic diagnosis.

Corresponding Author
Please address correspondence to Dr Jeffrey L. Elliott
E-mail: jeffrey.elliott@utsouthwestern.edu
Phone: 214-648-8816
Fax: 214-648-5080

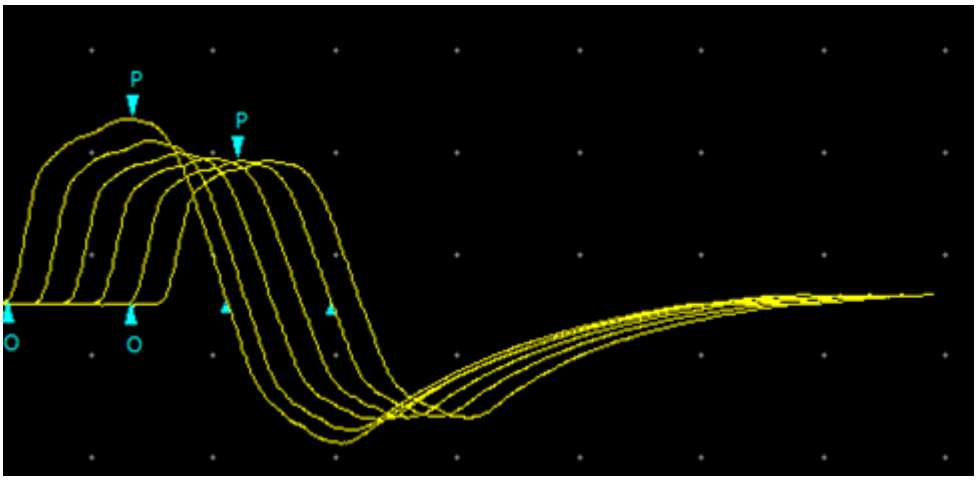


Figure 1A. 3Hz repetitive nerve stimulation of the spinal accessory nerve recording from the trapezius at baseline.

Trace #	Amp (mV)	Amp % Dif	Area (mV·ms)	Area % Dif
Right Trapezius				
Tr 1: Baseline: Trace 1	3.54	100	34.15	100
Tr 1: Baseline: Trace 2	3.16	-10.9	29.15	-14.6
Tr 1: Baseline: Trace 3	2.90	-18.1	26.33	-22.9
Tr 1: Baseline: Trace 4	2.82	-20.4	25.38	-25.7
Tr 1: Baseline: Trace 5	2.76	-22.0	24.72	-27.6
Tr 1: Baseline: Trace 6	2.78	-21.5	24.81	-27.3
Tr 2: Post Exercise: Trace 1	3.68	100	34.46	100
Tr 2: Post Exercise: Trace 2	3.45	-6.4	31.02	-10.0
Tr 2: Post Exercise: Trace 3	3.22	-12.4	28.68	-16.8
Tr 2: Post Exercise: Trace 4	3.15	-14.6	27.86	-19.2
Tr 2: Post Exercise: Trace 5	3.15	-14.4	27.66	-19.7
Tr 2: Post Exercise: Trace 6	3.17	-13.8	27.83	-19.3

Figure 1B. Data from 3 Hz RNS at baseline and after 1 minute of exercise.

Table 1. Single Fiber EMG Frontalis study

Run	Samples	Blocks	IPI	Jitter	Jitter Norm	MCD	MSCD	Freq.	Stored
Right Frontalis									
1.1	63	0	1818.4	33.4		34.9	33.4	23.5	Yes
2.1	90	0	2801.5	127.8		127.8	132.9	27.0	Yes
3.1	69	0	1467.3	133.0		133.0	138.4	17.3	Yes
4.1	94	0	1256.3	50.0		50.0	50.6	17.1	Yes
5.1	91	0	1220.6	55.5		56.6	55.5	16.3	Yes
5.2	91	0	2054.2	77.1		77.1	77.1	16.3	Yes
6.1	95	0	2948.7	45.4		45.4	46.2	23.3	Yes
6.2	96	0	1309.5	26.8		28.4	26.8	23.3	Yes
7.1	83	0	1583.6	77.3		79.7	77.3	15.3	Yes
7.2	65	0	442.1	136.6		136.6	152.0	15.8	Yes
8.1	94	0	1884.9	37.6		39.2	37.6	23.1	Yes
8.2	34	0	853.6	211.9		234.9	211.9	23.3	Yes
Mean			1636.7	84.4	<34	**87.0**	86.6	20.1	
StdDev			697.8	54.0		58.2	56.0	3.9	

Block Ratio: 0% Fiber Density: 0.00

Table 2. Pulmonary Function Testing

		Pred	Pred LL	Pre	Pre%Ref	Post	Post%Ref	%Chg
FVC	**L**	4.38	3.50	3.24	74	2.85	65	-12
FEV 1	**L**	3.74	3.01	2.73	73	2.48	66	-9

		Pred	Pred LL	Pre	Pre%Ref	Post	Post%Ref	%chg
MIP	**cmH2O**	72.9	31.1	56.4	77	50.4	69	-11
MEP	**cmH2O**	93.3	41.8	46.6	50	50.3	54	8

Pre = sitting position; Post = supine position.

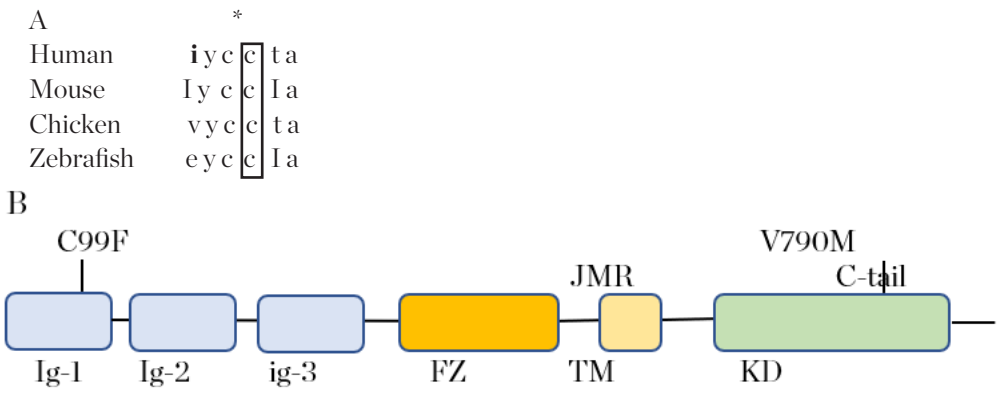


Figure 2 A) Alignment of amino acid sequences across multiple species encompassing human C99 (*). B) Schematic representation of MuSK including the various functional domains. The two mutations of this case report are shown. Ig= immunoglobulin-like; Fz=frazzled domain; TM= transmembrane; JMR = juxtamembranous region ; KD = kinase domain

Table 3 Genotypic/phenotypic correlations

Genotype	Domains	Presentation	Weakness
M605I/A727V	KD/KD	Neonatal	Respiratory
V722A/ c.79 +2T	KD/#	Neonatal	Vocal cord, Respiratory
Q688X/F775S	KD/KD	Neonatal	Respiratory
N103S/R166X	Ig/*	Neonatal	Respiratory
C317R/ A617V	FZ/KD	Neonatal	Respiratory, Hypotonia
V790M/Lys156Argfsstop20	KD/*	Neonatal or adult	Respiratory or Ocular
V790M/ c.220insC	KD/#	Neonatal	Respiratory, Ocular
K720E/c.79 +2T	KD/ #	Neonatal	Vocal cord, Respiratory
A763T/R816X	KD/ *	Neonatal	Vocal cord, Respiratory
P344R/P344R	FZ/FZ	Early childhood	Ocular, Limb-girdle
D38E/ genomic deletion encompassing exons 2–3	Ig/#	Early childhood	Limb-girdle
M835V/M835V	KD/KD	Childhood	Ocular, Limb-girdle
P650T/ I795S	KD/KD	Childhood	Limb-girdle
I581P/I581P	KD/KD	Adolescence	Limb-girdle
L545P /R166X	JM/*	Adolescence or adult	Limb-girdle
C99F/V790M	Ig/KD	Adult	Ocular, Respiratory, LG

References

1. Vanhaesebrouck AE, Beeson D. The congenital myasthenic syndromes: expanding genetic and phenotypic spectrums and refining treatment strategies. Curr Opin Neurol. 2019 Oct;32(5):696-703. doi: 10.1097/WCO.0000000000000736 PMID: 31361628.

2. Chevessier F, Faraut B, Ravel-Chapuis A, Richard P, Gaudon K, Bauché S, Prioleau C., et al., MUSK, a new target for mutations causing congenital myasthenic syndrome. Hum Mol Genet. 2004 Dec 15;13(24):3229-40. doi: 10.1093/hmg/ddh333 PMID: 15496425

3. Nykamp K, Anderson M, Powers M, Garcia J, Herrera B, Ho YY, et al., Sherloc: a comprehensive refinement of the ACMG-AMP variant classification criteria. Genet Med. 2017 Oct;19(10):1105-1117. doi: 10.1038/gim.2017.37. Epub 2017 May 11. PMID: 28492532

4. Maselli RA, Arredondo J, Cagney O , Ng JJ , Anderson JA , Williams C et al., Mutations in MUSK causing congenital myasthenic syndrome impair MuSK-Dok-7 interaction. Hum. Mol. Genet. 2010 Jun 15;19(12):2370-9. Published online 2010 Apr 6. doi: 10.1093/hmg/ddq110 PMID: 20371544

5. Ben Ammar A, Soltanzadeh P, Bauché S, Richard P, Goillot E, Herbst R, et al., A mutation causes MuSK reduced sensitivity to agrin and congenital myasthenia. PLoS One. 2013;8(1):e53826. doi:10.1371/journal.pone.0053826. Epub 2013 Jan 9. PMID: 23326516

6. Rodríguez Cruz PM, Cossins J, Cheung J, Maxwell S, Jayawant S, Herbst R e al., Congenital myasthenic syndrome due to mutations in MUSK suggests that the level of MuSK phosphorylation is crucial for governing synaptic structure. Hum. Mutat. 2020 Mar;41(3):619-631. doi: 10.1002/humu.23949. Epub 2019 Nov 25. PMID: 31765060

7. Pinto MV, Saw JL, Milone M. Congenital Vocal Cord Paralysis and Late-Onset Limb-Girdle Weakness in MuSK-Congenital Myasthenic Syndrome. Front Neurol. 2019 Dec 20;10:1300. doi: 10.3389/fneur.2019.01300. eCollection 2019. PMID: 31920924

8. Shen Y, Wang B, Zheng X, Zhang W, Wu H, Hei M. A Neonate With MuSK Congenital Myasthenic Syndrome Presenting With Refractory Respiratory Failure. Front Pediatr. 2020 Apr 16;8:166. . doi: 10.3389/fped.2020.00166. eCollection 2020. PMID: 32373561

9. Giarrana ML, Joset P, Sticht H, Robb S, Steindl K, Rauch A, et al. A severe congenital myasthenic syndrome with "dropped head" caused by novel MUSK mutation. Muscle Nerve. 2015 Oct;52(4):668-673.P doi: 10.1002/mus.24687. Epub 2015 Jun 1MID: 25900532

10. Al-Shahoumi R, Brady LI, Schwartzentruber J, Tarnopolsky MA. Neurology. Two cases of congenital myasthenic syndrome with vocal cord paralysis. 2015 Mar 24;84(12):1281-2. doi: 10.1212/WNL.0000000000001396 PMID: 25695962

11. Maggi L, Brugnoni R, Confalonieri P, Scaioli V, Winden T, Morandi L, et al., Marked phenotypic variability in two siblings affected by congenital myasthenic syndrome caused by mutations in MUSK. J Neurol. 2013

Oct 12:10. 7118-5. doi: 10.1007/s00415-013-7118-5 PMID: 24122059

12. Gallenmüller C, Müller-Felber W, Dusl M, Stucka R, Guergueltcheva V, Blaschek A., et al., Salbutamol-responsive limb-girdle congenital myasthenic syndrome due to a novel missense mutation and heteroallelic deletion in MUSK Neuromuscul Disord. 2014 Jan;24(1):31-5. doi: 10.1016/j.nmd.2013.08.002. Epub 2013 Aug 7 PMID: 24183479

13. Owen D, Töpf A, Preethish-Kumar V, Lorenzoni PJ, Vroling B, Scola RH, et al., Recessive variants of MuSK are associated with late onset CMS and predominant limb girdle weakness. Am J Med Genet A. 2018 Jul;176(7):1594-1601. doi: 10.1002/ajmg.a.38707. Epub 2018 Apr 28 PMID: 2970430.

14. Luan X, Tian W, Cao L Limb-girdle congenital myasthenic syndrome in a Chinese family with novel mutations in MUSK gene and literature review. Clin Neurol Neurosurg. 2016 Nov;150:41-45. doi: 10.1016/j.clineuro.2016.08.021. Epub 2016 Aug 22. PMID: 27588369

Myasthenia Gravis Exacerbation Following BRAF and MEK Inhibitor Therapy

Jeremy Hill MD, Yuebing Li MD PhD

Neuromuscular Center, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195

Introduction

While there is a well-known association of immune check point inhibitors and myasthenia gravis (MG), there has also been three previous cases of new onset MG being associated with B-Raf proto-oncogene serine/threonine-protein kinase (BRAF) and/or mitogen-activated protein kinase (MEK) inhibition treatment. The previously associated medications include binimetinib (MEK inhibitor) and the combination of dadrafenib (BRAF inhibitor) and trametinib (MEK inhibitor).[1–3] We report a novel case of a patient with well controlled generalized MG who developed exacerbation after treatment for metastatic melanoma with vemurafenib, a BRAF inhibitor, and cobimetinib, a MEK inhibitor.

Case Presentation

An 84-year-old male with a history of MG, chronic obstructive pulmonary disease, hypertension, and melanoma on the right chest, status post resection 4 years prior, presented with left posterior rib cage pain. CT of chest and abdomen revealed innumerable bilateral pleural nodules and scattered hypodensities in the liver, and MRI found a small enhancing cerebellar lesion, all concerning for metastasis. An excisional biopsy of an enlarged right supraclavicular lymph node was consistent with metastatic melanoma with BRAF mutation. A plan to treat with nivolumab and ipilimumab was discussed. Due to his prior MG history, a neuromuscular consultation was requested to evaluate the pros and cons of the above immune-check point inhibitor therapy.

The patient presented 6 years prior with symptoms of diplopia, ptosis, and dysphagia. Acetylcholine receptor binding and modulating antibodies were elevated at 11.5 nM and 80%, respectively. Striational antibodies were positive at a titer of 1:7680. CT chest revealed a thymoma which was subsequently removed via robotic right thoracoscopic thymectomy. Pathology revealed a non-invasive thymoma of the AB type, modified Masaoka stage 1. His myasthenia was initially treated with prednisone and maintenance plasma exchange for about 2 years. Mycophenolate mofetil therapy was initiated later and plasmapheresis was discontinued. At the time of metastatic melanoma diagnosis, the patient had a normal neurologic examination. His immunosuppression regimen included prednisone at 5 mg daily and mycophenolate mofetil 500 mg twice daily. It was thought that his MG control was optimized to allow treatment with nivolumab and ipilimumab.

Patient was given a single infusion of nivolumab which did not halter tumor growth. No further nivolumab nor iplimumab were given. Three months later, treatment was transitioned to vemurafenib and cobimetinib. After being on this combination therapy for 2 weeks, the patient presented with significant worsening of his myasthenic symptoms that included ptosis, diplopia, dysphagia, and dyspnea. He was intubated for myasthenic crisis. High dose corticosteroid therapy of prednisone 60 mg daily and plasmapheresis were initiated, without leading to clinical improvement. Due to the poor prognosis of his metastatic melanoma, the patient and family elected for conservative treatment without further escalation of care. The patient died 16 days after presentation with MG exacerbation.

Discussion

Immune check point inhibitors inducing or exacerbating myasthenia gravis (MG) have been well reported in the literature.[4–6] To our knowledge, this is the first reported case of vemurafenib and cobimetinib causing MG exacerbation. A literature review reveals that such a combined treatment could result in subacute immune-mediated motor polyneuropathy.[7] In addition, three cases of MG development or exacerbation following similar BRAF and/or MEK inhibitor therapy have been reported previously.[1–3]

The mechanism by which BRAF and MEK inhibition could cause development or exacerbation of MG is currently still unknown. Demichelis et al. proposed possible mechanisms of off-target effects on tyrosine kinases that could alter the structure, stability, or function of the neuromuscular junction and/or decreased immune surveillance that may enhance autoimmunity.[7]

As these novel immune therapies are increasingly used in metastatic melanoma, clinicians should be aware of their associated risk of exacerbating MG and causing other immune-mediated neuromuscular disorders.

Disclosures

Financial Disclosures: Yuebing Li has served as a consultant for Argenx, Catalyst, Immunovant and UCB Pharma, and has received grant support from Argenx.

Conflict of Interest: None

The described work has been presented at the 2022 Annual Meeting of American Association of Neuromuscular and Electrodiagnostic Medicine.

Corresponding Author

Yuebing Li, MD, PhD, Department of Neurology, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195, email: liy@ccf.org

References

1. Alabdali M, Bril V, Morgan E, Pereira A, Maurice C. An Unprecedented Case of Myasthenia Gravis Induced by Binimetinib. J Clin Case Rep 2019; 9:1291.

2. Zaloum A, Falet JPR, Elkrief A, & Chalk C. Myasthenia gravis following dabrafenib and trametinib for metastatic melanoma. *Neurology*, 2020; *94*(7), 322-323.

3. Ziogas DC, Mandellos D, Theocharopoulos C, Lialios PP, Bouros S, Ascierto PA, & Gogas H. Neuromuscular Complications of Targeted Anticancer Agents: Can Tyrosine Kinase Inhibitors Induce Myasthenia Gravis? Getting Answers From a Case Report up to a Systematic Review. *Frontiers in Oncology*, 2021; *11*, 727010.

4. Dalakas MC. Neurological complications of immune checkpoint inhibitors: what happens when you 'take the brakes off' the immune system. *Therapeutic advances in neurological disorders*, 2018; *11*, 1756286418799864.

5. Hottinger AF. Neurologic complications of immune checkpoint inhibitors. Curr Opin Neurol. 2016;29(6):806-812. doi: 10.1097/WCO.0000000000000391. PMID: 27653290.

6. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med. 2018;378(2):158-168. doi: 10.1056/NEJMra1703481. PMID: 29320654.

7. Demichelis C, Balestra A, Lapucci C, Zuppa A, Grisanti SG, Prada V, Pesce G, Grasso I, Queirolo P, Schenone A, Benedetti L, Grandis M. Neuromuscular Complications Following Targeted Therapy in Cancer Patients: Beyond the Immune Checkpoint Inhibitors. Case Reports and Review of the Literature. *Neurol Sci* 2021; 42(4):1405–9. doi: 10.1007/s10072-020-04604-1

Numb Chin Syndrome: Atypical presentation of metastatic breast cancer

Britta L. Bureau MD[1], Jennifer M. Connelly MD[1], Paul E. Barkhaus MD[1], Ryan Brennan DO[1]

[1]Department of Neurology, Medical College of Wisconsin, Milwaukee, WI

Introduction

In 1830, Charles Bell described two cases of "Numb Chin Syndrome" (NCS) as a mental neuropathy manifested by numbness of the chin and lip.[1] One case had breast cancer and presented with normal lip movement but no sensation on the left half of her lip. Ultimately, it was discovered she had a glandular tumor at the jaw angle where the alveolar branch of the trigeminal nerve courses.[1]

We report a variant of the NCS. Traditionally, NCS is defined by ipsilateral loss of chin sensation. This case is unique in that she had the expected unilateral loss of chin sensation, but her "numb chin" rapidly expanded to include the lower distribution of the ipsilateral maxillary branch of the trigeminal nerve. In addition, she also presented with isolated weakness of the depressor labii inferioris which is innervated by the buccal branch of the facial nerve.

Clinical presentation

A 53-year-old female with past medical history of estrogen receptor positive invasive ductal carcinoma of the right breast underwent partial mastectomy, chemotherapy, and radiation. She was in remission for 6 years when she was diagnosed with new lung and liver metastatic lesions and subsequently resumed chemotherapy. She then developed left chin numbness followed by progressive difficulty retaining food and drink in her mouth. Her left lower lip then became weak. MRI with contrast of the brain/face and dental x-rays were negative eight weeks prior to symptom onset.

Neurological exam revealed left lower lip weakness that appeared to "droop" when attempting to smile (Figure 1). The area of decreased sensation to sharp and light touch over her left lower face had enlarged to between the naso-labial fold and the inferior mandibular border. There was slight extension of reduced sharp touch in the right medial chin that was due to midline overlap of sensory fibers. The remainder of her neurological examination was unremarkable, particularly for any sensory or motor deficits.

The contrast-enhanced MRI was repeated which revealed a 1.9 cm enhancing left parotid mass (Figure 2), not previously seen in the MRI Brain and face completed eight weeks prior at symptom onset. The patient was subsequently referred for palliative radiation therapy, therefore electrodiagnostic studies were deferred. The patient deceased 5 weeks post-onset of her cranial neuropathies.

Discussion

This case is unique because her "numb chin" rapidly expanded to include the lower distribution of the ipsilateral maxillary branch of the trigeminal nerve. In addition, she also presented with isolated weakness of the depressor labii inferioris which is innervated by the buccal branch of the facial nerve. Our primary differential diagnoses included atypical NCS due to metastasis, infection, or trauma.

What began as an uncomplicated NCS that rapidly expanded to involve a greater portion of the trigeminal nerve distribution in addition to a motor branch of an additional cranial (facial) nerve. Both can be accounted for by the parotid metastasis based on their anatomy. Noteworthy is the pseudo-localization because the apparent focal deficits in both cranial nerves did not signify a distal lesion in each, but rather partial lesions of their proximal segments. Thus, her focal neurologic deficits corresponded with the findings on imaging.

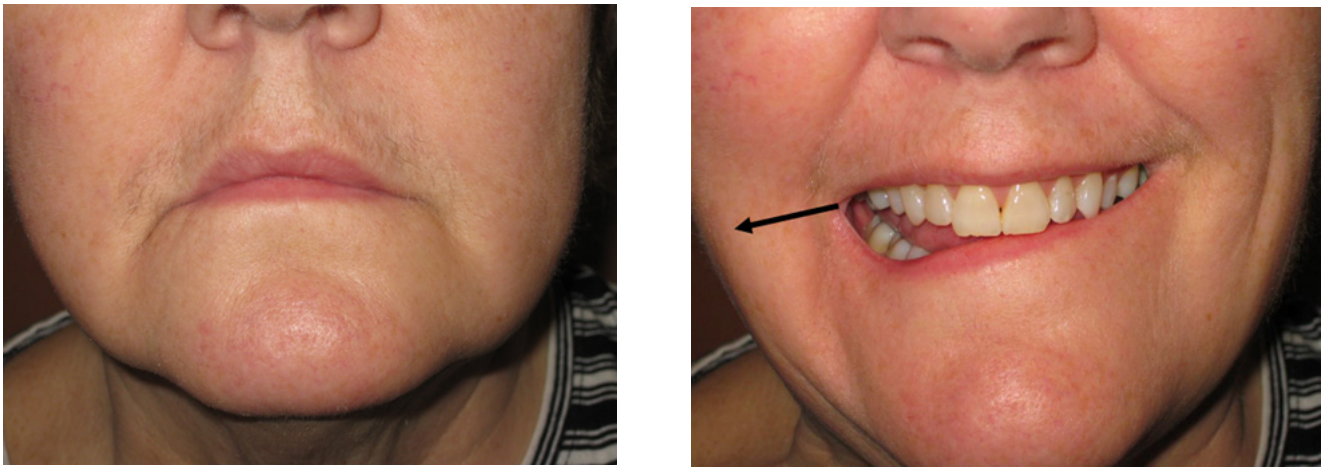


Figure 1: Left lower facial weakness, most likely explained by lack of Buccal nerve innervation to the Depressor Labii Inferioris (© R. Brennan, DO, with permission)

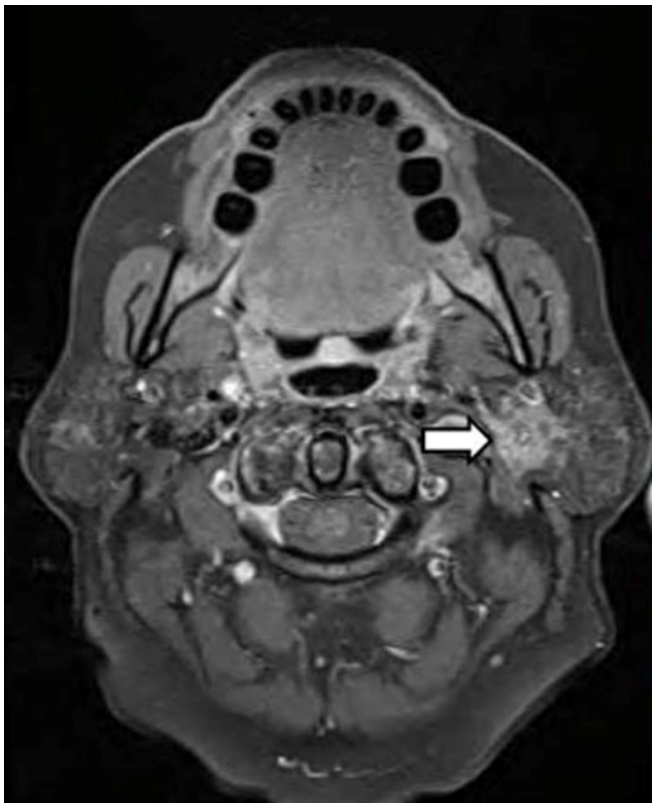


Figure 2: T1-weighted MRI with gadolinium illustrates 1.9 cm enhancing left parotid gland mass in the expected location of the facial nerve (© R. Brennan, DO, with permission)

In typical NCS, the most likely etiology is cancer if there is no history of trauma or dental injury to the inferior alveolar nerve, then the most likely etiology is cancer. NCS may precede diagnosis of malignancy in 47% of patients.[2] Kuroda et al. describe a case of NCS as the initial presentation of Burkitt's cell acute lymphoblastic leukemia.[3] As standard MRI sequences do not usually include the oromandibular region, a mandibular or facial MRI should be performed in NCS.[2] Lossos et al. report in their study that 67% of NCS was a late manifestation of cancer associated with disease progression and 31% NCS signified relapse.[4] The majority of NCS cases described are isolated sensory deficits. Combined cranial neuropathies with additional neurologic symptoms have been reported.[4] Approximately 10% of NCS present with bilateral symptoms.[5] Brazis et al. describe a case of recurrent squamous cell carcinoma where the mental foramen and the infraorbital foramen were involved which resulted in simultaneous, progressive numb chin and cheek syndromes respectively.[6] Their patient had unilateral lip paresis similar to our patient.[6]

Mechanisms of NCS include compression of the mental or inferior alveolar nerves by mandibular metastases [50%], intracranial involvement of the mandibular nerve by skull base lesions such as Meckel's cave tumor [14%], leptomeningeal metastasis [22%], or malignant infiltration of the mental nerve.[3,4,7] In females, the most common malignancy is breast due to metastatic lesions along the sheath of the mentalis branch of the inferior alveolar nerve, often at the mental foramen, or metastatic involvement of the jaw. NCS syndrome is also a common presentation in lymphoma and less often in leukemia, prostate, and lung cancer.[2,3,4] Nonmetastatic causes of NCS are rare including Sjogren's, multiple sclerosis, diabetes mellitus, temporal arteritis, systemic amyloidosis, HIV, drug toxicity, local infection, and natural aging.[2,4,8]

NCS is clinically significant as it is an ominous sign for underlying malignancy and often associated with a poor prognosis as it can be a late manifestation of a systemic malignancy.[3,4,9] Brady et al. found that mean survival of NCS was 6.9 months, having only 15% of patients who present with NCS survive more than nine months.[2]

Conclusion

We present a unique case of NCS which resulted from metastatic breast cancer. This case is unique because it evolved quickly from a "simple" clinical left NCS to proximal left partial fifth and partial cranial neuropathies. Our case reinforces the point that a seemingly harmless NCS should be considered an ominous sign until malignancy is excluded. Awareness and early localization of NCS are critical to efficiently develop a targeted treatment plan to prevent tumor spread and potentially improve clinical outcomes and survival.

Corresponding Author

Britta L. Bureau, MD
Medical College of Wisconsin
8701 W Watertown Plank Road
Wauwatosa, WI, USA 53226
bbureau@mcw.edu

Disclosures

Ryan Brennan DO has received speaking and consulting fees from Abbvie. Also has received consulting fees from Medtronic.

Britta L. Bureau BS has nothing to disclose.

Jennifer M. Connelly MD has nothing to disclose.

Paul E. Barkhaus MD has nothing to disclose.

Poster Presentations

1. Society for Neuro-Oncology Annual Scientific Meeting in November 2022 in Tampa, FL
2. American Association of Neuromuscular & Electrodiagnostic Medicine Annual Meeting in September 2022 in Nashville, TN.

Oral Presentation

Wisconsin Neurological Society Annual Meeting. October 2022 in Wisconsin Dells, WI.

References

1. Furukawa T. Charles Bell's description of Numb Chin Syndrome. *Neurology*. 1988;38(2):331-331. doi:10.1212/wnl.38.2.331

2. Brady B, Coughlan AM, O'Brien T. Numb Chin Syndrome: A Case Report. J Pain Symptom Manage. 2016 Jan;51(1):e3-4. doi: 10.1016/j.jpainsymman.2015.10.007. Epub 2015 Oct 24. PMID: 26598041.

3. Kuroda Y, Fujiyama F, Ohyama T, Watanabe T, Endo C, Neshige R, Kakigi R. Numb chin syndrome secondary to Burkitt's cell acute leukemia. Neurology. 1991 Mar;41(3):453-4. doi: 10.1212/wnl.41.3.453. PMID: 2006020.

4. Lossos A, Siegal T. Numb chin syndrome in cancer patients: etiology, response to treatment, and prognostic significance. Neurology. 1992 Jun;42(6):1181-4. doi: 10.1212/wnl.42.6.1181. PMID: 1603345.

5. Baskaran RK, Krishnamoorthy, Smith M. Numb chin syndrome--a reflection of systemic malignancy. *World J Surg Oncol*. 2006;4:52. Published 2006 Aug 9. doi:10.1186/1477-7819-4-52

6. Brazis PW, Vogler JB, Shaw KE. The "numb cheek-limp lower lid" syndrome. Neurology. 1991 Feb;41(2 (Pt 1)):327-8. doi: 10.1212/wnl.41.2_part_1.327. PMID: 1992387.

7. Beck DW, Menezes AH. Lesions in Meckel's cave: variable presentation and pathology. *Journal of Neurosurgery*. 1987;67(5):684-689. doi:10.3171/jns.1987.67.5.0684

8. Furukawa T. Numb chin syndrome in the elderly. J Neurol Neurosurg Psychiatry. 1990 Feb;53(2):173. doi: 10.1136/jnnp.53.2.173. PMID: 2313307; PMCID: PMC487962.

9. Aerden T, Grisar K, Neven P, Hauben E, Politis C. Numb chin syndrome as a sign of mandibular metastasis: A case report. Int J Surg Case Rep. 2017;31:68-71. doi: 10.1016/j.ijscr.2017.01.001. Epub 2017 Jan 4. PMID: 28110186; PMCID: PMC5256673.

Poor response to Eculizumab in Caucasian Patients with Treatment Refractory Generalized Myasthenia Gravis: A case series

Nakul Katyal and Raghav Govindarajan

Department of Neurology, University of Missouri-Columbia, USA

ABSTRACT

Background

Eculizumab, a C5 complement inhibitor, has been approved to manage patients with treatment-refractory acetylcholine receptor positive (AChR+) Generalized Myasthenia Gravis (gMG). Though most patients receiving eculizumab experience clinical improvement, a small number of patients may respond poorly.

Objective

To report three cases of poor response to eculizumab in young caucasian patients with treatment refractory gMG.

Methods

Case Series

Results

All three patients were young, caucasian, thymectomized, females with MGFA class III, treatment-refractory MG on multiple immunosuppressant medications. All three patients had an initial worsening of MG- ADL score, one-month post eculizumab, followed by an unchanged MG ADL and MGC score three months after eculizumab therapy. No changes were noted in the number of acute exacerbations of MG, pre and post-eculizumab treatment. All patients were eventually started on maintenance Plasma-exchange (PLEX) therapy, post eculizumab failure, and had clinical improvement in MG-ADL and MGC scores and a reduction in the number of acute exacerbations of the disease.

Conclusion

The exact mechanism contributing to poor clinical response to eculizumab in gMG patients remains unclear. Further studies are warranted to undermine the underlying pathogenesis.

Introduction

Myasthenia gravis (MG) is an autoimmune, neuromuscular-junction disorder characterized by skeletal muscle weakness (1). Although established immunosuppressant therapies are effective in most patients with MG, 10–20% of patients are refractory to treatment (2). In Phase 3, a randomized, double-blind, placebo-controlled study (REGAIN) and its open-label extension, eculizumab, a recombinant humanized monoclonal antibody, was shown to be effective in patients with treatment-refractory AChR antibody-positive (AChR+) gMG (3, 4, 5). Eculizumab has been approved by Food and Drug Administration (FDA) for the management of patients with paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (HUS), and AChR+ gMG (6-8). Though most patients receiving eculizumab experience clinical improvement, many patients may respond poorly to eculizumab therapy.

In this case series, we have described three patients with treatment-refractory MG who had poor responses to eculizumab therapy. In addition, we reviewed the current literature highlighting possible mechanisms for poor response to complement inhibitor therapy.

Case Presentation

Patient 1

A 32-year-old thymectomized caucasian female with MGFA Class III, treatment-refractory MG on Prednisone 50 mg daily, pyridostigmine 60mg TID and IVIG 1g/kg/q4weeks with MG-ADL score of 9, MGC score of 30 was started on Eculizumab after vaccination against Neisseria meningitides, at an induction dose of 900 mg per week for four weeks (at Weeks 0, 1, 2, and 3), then at 1200 mg at Week 4, followed by 1200 mg every two weeks after that (7). 1-month post eculizumab initiation, her MG-ADL score worsened to 10, and no changes were noted in the MGC score. Her MG- ADL and MGC scores did not improve after three months of eculizumab use (Figure 1, 2). No changes were noted in the number of acute exacerbations of MG, pre and post-eculizumab therapy (figure 3). Given no clinical improvement, Eculizumab was eventually discontinued after three months. The patient experienced nausea with eculizumab use which was managed conservatively. The patient was then started on PLEX therapy with three exchange sessions every 4-6 weeks. Clinically meaningful improvement was noted in MG-ADL score (>2) six months post PLEX therapy which was maintained for up to 9 months. Clinically significant improvement was noted in MGC score (>3) three months post PLEX therapy and was maintained for up to 9 months (Figure 1, 2). Post

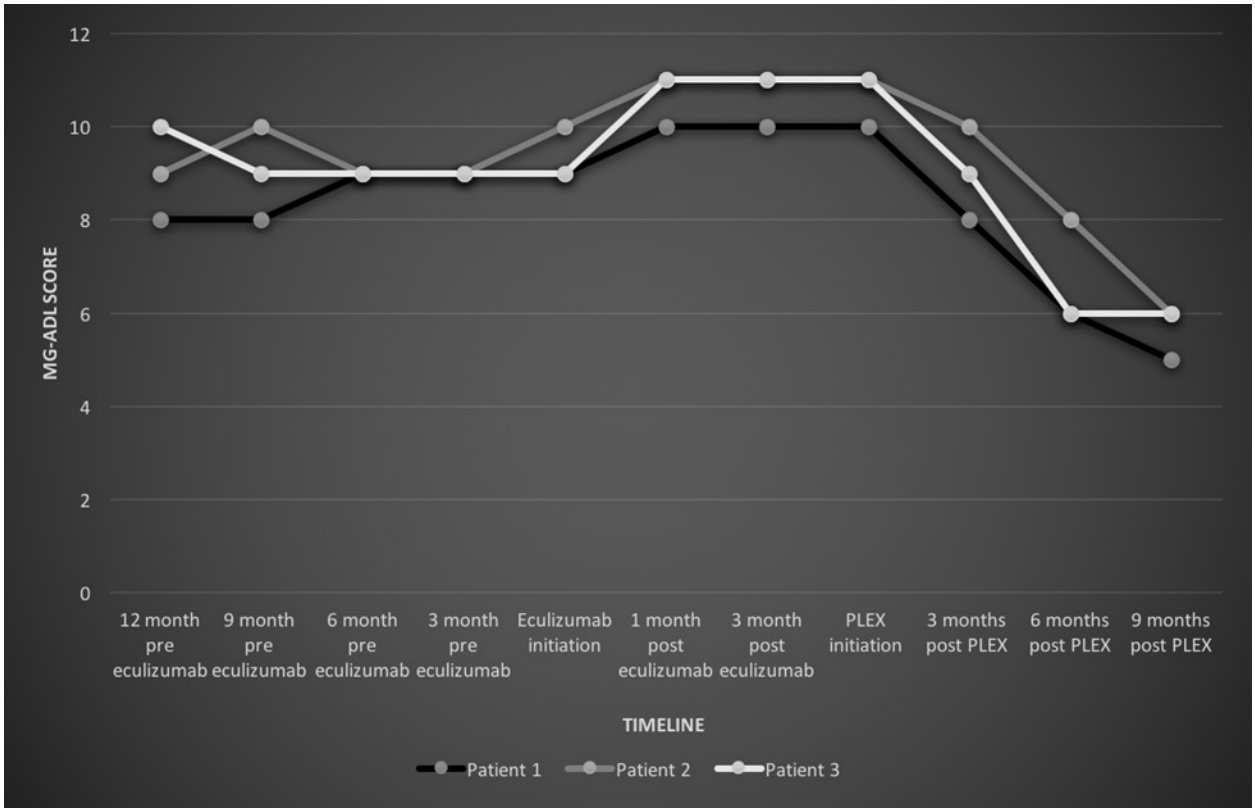


Figure 1: MG-ADL scores, before and after eculizumab initiation. MG-ADL: Myasthenia gravis activity of daily living score; PLEX: Plasma exchange.

PLEX initiation, the patient had two episodes of acute exacerbations at three-month intervals and none at the six-month interval (figure 3).

Patient 2

A 25-year-old thymectomized caucasian female with MGFA Class III, treatment-refractory MG on Prednisone 40 mg daily, pyridostigmine 60mg TID, and Cellcept 1000 mg BID with MG-ADL score of 10, MGC score of 33 was started on Eculizumab after vaccination against Neisseria meningitides, at an induction dose of 900 mg per week for four weeks (at Weeks 0, 1, 2, and 3), then at 1200 mg at Week 4, followed by 1200 mg every two weeks after that (7) (figure 1, 2). The MG-ADL score worsened to 11, 1-month post eculizumab initiation, and both MG- the ADL score and MGC score did not improve after three months of eculizumab use (Figure 1, 2). The patient experienced no side effects with Eculizumab. In the absence of clinical improvement, Eculizumab was discontinued after three months, and the patient was then started on PLEX therapy with three exchange sessions every 4-6 weeks.

After initiation of PLEX, clinically meaningful improvement was noted in MG-ADL (>2) and MGC score (>3) three months post-PLEX therapy, which was maintained for up to 9 months (Figure 1, 2). The patient had two episodes of acute exacerbations at the three-month interval and none at the six-month interval (Figure 3).

Patient 3

A 36-year-old thymectomized caucasian female with MGFA Class III, treatment-refractory MG on Prednisone 30 mg daily, pyridostigmine 60mg TID, Azathioprine 200 mg BID and IVIG 1g/kg/q4weeks with MG-ADL score of 9 and MGC score of 32. Her prednisone dose couldn't be increased due to side effects of weight gain and mood changes. Azathioprine was stopped after one month due to nausea. IVIG was stopped after three sessions due to headaches, refractory to medications. The patient was started on Eculizumab after vaccination against Neisseria meningitides at an induction dose of 900 mg per week for four weeks (at Weeks 0, 1, 2, and 3), then at 1200 mg at Week 4, followed by 1200 mg every two weeks after that (7).

Her MG-ADL score worsened 11 1-month post eculizumab initiation, and no improvements were noted in both MG- ADL score and MGC score three months post eculizumab use (Figure 1, 2). The patient experienced nausea with eculizumab use which was managed conservatively. Eculizumab was eventually discontinued, and the patient was started on PLEX therapy with three exchange sessions every 4-6 weeks.

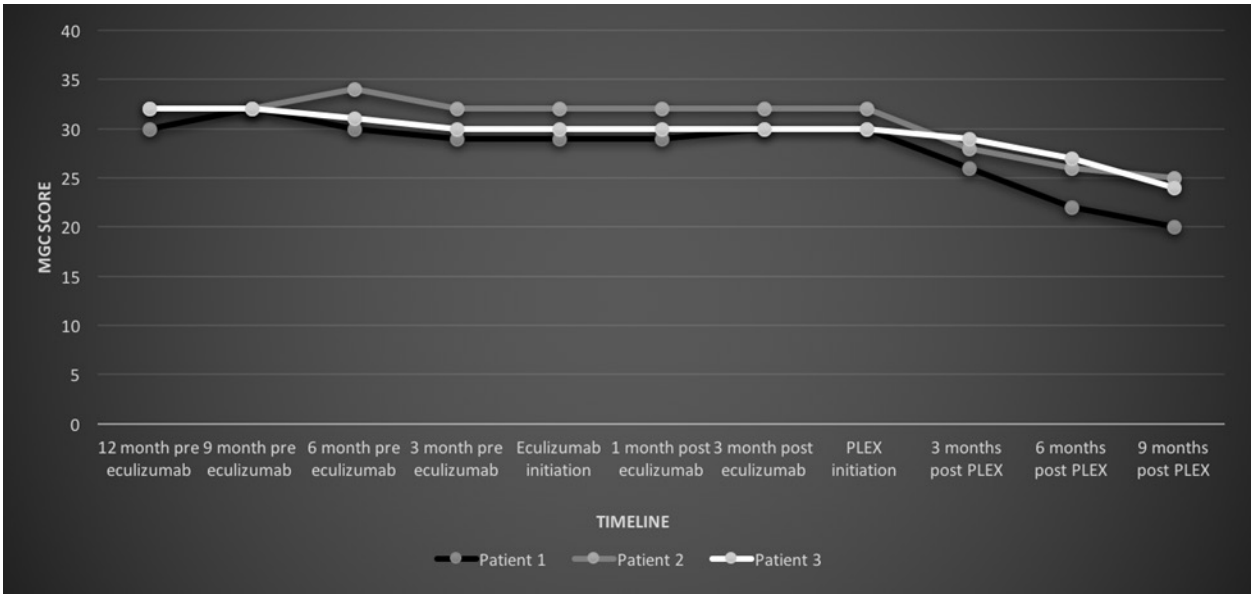


Figure 2: MGC scores, before and after eculizumab initiation. MGC: Myasthenia gravis composite score; PLEX: Plasma exchange.

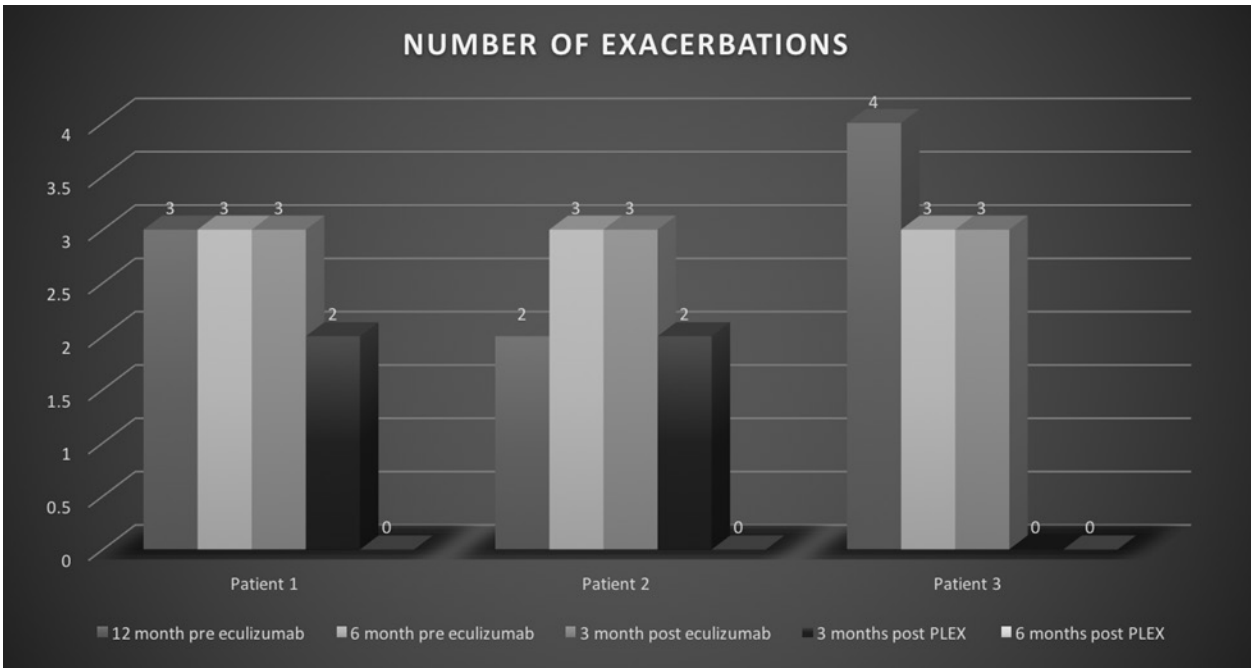


Figure 3: Number of exacerbations, pre and post eculizumab.

The patient had clinically meaningful improvement in MG-ADL score (>2) and MGC score (>3) three months post-PLEX therapy which was maintained for up to 9 months (Figure 1, 2). Post PLEX initiation, the patient had no acute exacerbations of MG at six months intervals (Figure 3).

Table 1 describes baseline demographics of patients included in the analysis.

Discussion

This case series highlighted poor response to eculizumab therapy in 3 patients with treatment-refractory MG. All patients had similar demographic and disease profiles. All three were young, caucasian, thymectomized, female patients with MGFA class III, treatment-refractory MG on multiple immunosuppressant medications. All three patients had an initial worsening of MG- ADL score, one-month post eculizumab, followed by an unchanged MG ADL

Table 1: Baseline demographics of patients included in the analysis

Patient	Age (years)	Gender	Ethnicity	MGFA class	Thymectomy	Therapy at eculizumab initiation	Duration of Eculizumab Therapy	Therapy post eculizumab
1	32	F	Caucasian	IIIa	Yes	Prednisone 50mg daily + Pyridostigmine 60mg TID + IVIG 1g/kg/q4weeks	3 months	PLEX every 4-6 weeks, 3 exchanges
2	25	F	Caucasian	IIIa	Yes	Prednisone 40mg daily + Cellcept 1000mg BID + Pyridostigmine 60mg TID	3 months	PLEX every 4-6 weeks, 3 exchanges
3	36	F	Caucasian	IIIa	Yes	Prednisone 30mg daily + Pyridostigmine 60mg TID, Azathioprine 200 mg + IVIG 1 gm/kg/q4 weeks	3 months	PLEX every 4-6 weeks, 3 exchanges

BID, twice daily; F, female; IVIg, intravenous immunoglobulin; M, male; MGFA, Myasthenia Gravis Foundation of America; qnw, every n weeks; TID, three times daily.

and MGC score three months after eculizumab therapy. No changes were noted in the number of acute exacerbations of MG, pre and post-eculizumab treatment. All patients were eventually started on maintenance PLEX therapy, post eculizumab failure, and had clinical improvement in MG-ADL and MGC scores and a reduction in the number of acute exacerbations of the disease.

In the REGAIN trial, six patients (10%) in the eculizumab group experienced acute exacerbation requiring rescue therapy (3). One of the patients had a worsening MG-ADL score from 13 at baseline to 18 and had to discontinue the study due to the MG crisis (3). The patient, unfortunately, died from crisis-related complications 90 days after the last eculizumab dose (3).

Genetic variations in the C5 complement can lead to poor response to eculizumab (9). Nishimura et al. assessed the sequences of the gene encoding C5 in Japanese patients with PNH with poor response to eculizumab. They noted all patients with inadequate response had a single missense C5 heterozygous mutation, c.2654 G->A, which predicts the polymorphism p.Arg885His (9). Another patient of Asian ancestry with a poor response to eculizumab had a similar mutation

c.2653C→T, which indicates p.Arg885Cys (9). Similar C5 polymorphism was reported in a Dutch patient with PNH with poor response to eculizumab who was noted as having a single C5 heterozygous missense mutation, c.2653C>A, which predicts p.Arg885Ser (10). The mutation at Arg885 results in the failure of binding and blockade of eculizumab at the C5 domain, accounting for the poor response (9). No similar studies have been conducted in MG patients with inadequate response to eculizumab.

Another potential mechanism for poor response could be the development of antidrug antibodies. However, studies looking into this possible mechanism have thus far been negative. The administration of any large-molecule therapeutics potentially induces an unwanted immune response by developing antidrug antibodies (11-14). Hillmen et al. evaluated the immunogenicity of eculizumab in PNH patients after long-term treatment and found no anti-eculizumab human anti-human antibodies (HAHs) in the enrolled patient population (11). Neutralizing antibodies to the C5 monoclonal antibody have not been found to the degree that inhibits the therapeutic effects of the drug (15).

The three pathogenic mechanisms for AChR antibodies include blockade of AChR channel function, antigenic modulation, and complement activation (15). In patients with poor response to eculizumab, the primary mechanism contributing to the clinical worsening of MG may not be complement activation.

This study has several limitations, including a need for proof of theory utilizing genetic testing. This was a case series of medical records at a single institution, with a small sample size and the need for a control group, limiting the findings' generalizability. More extensive controlled studies with a more robust design are warranted to explore the mechanism for poor response to eculizumab in treatment-refractory AChR+ gMG.

Conclusion

The exact mechanism contributing to poor clinical response to eculizumab in generalized MG patients remains unclear. Further studies are warranted to undermine the underlying pathogenesis.

Corresponding Author

Nakul Katyal[1]
CE 540, One Hospital Drive
Department of Neurology- University of Missouri
Columbia, USA, 65212

Declaration

All authors contributed to the work, agree with the presented findings, and that the work has not been published before nor is being considered for publication in another journal. The University of Missouri IRB approved the project, Approval #2058362. No animal subjects were involved. No financial support was obtained for this study. Both authors have no conflict of interest to report.

References

1. Juel VC, Massey JM. Myasthenia gravis. Orphanet J Rare Dis. 2007;2:44. doi: 10.1186/1750-1172-2-44.

2. Schneider-Gold C, Hagenacker T, Melzer N, Ruck T. Understanding the burden of refractory myasthenia gravis. Ther Adv Neurol Disord. 2019;12:1756286419832242. Doi: 10.1177/1756286419832242.

3. Howard JF, Jr., Utsugisawa K, Benatar M, Murai H, Barohn RJ, Illa I, et al. Safety and efficacy of eculizumab in anti- acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. Lancet Neurol. 2017;16(12):976-86. Doi: 10.1016/S1474-4422(17) 30369-1

4. Muppidi S, Utsugisawa K, Benatar M, Murai H, Barohn RJ, Illa I, et al. Long-term safety and efficacy of eculizumab in generalized myasthenia gravis. Muscle Nerve. 2019; 60(1):14-24. doi: 10.1002/mus.26447

5 Howard JF, Jr., Barohn RJ, Cutter GR, Freimer M, Juel VC, Mozaffar T, et al. A randomized, double-blind, placebo-controlled phase II study of eculizumab in patients with refractory generalized myasthenia gravis. Muscle Nerve. 2013;48(1):76-84. doi: 10.1002/mus.23839

6. US Food and Drug Administration, "Drugs@FDA: soliris (BLA 125166)," 2018, https://www.accessdata.fda.gov/scripts/ cder/daf/index.cfm?event=BasicSearch.process.

7. Alexion Pharmaceuticals," Soliris (Eculizumab), Alexion Pharmaceuticals, Cheshire, CT, USA, 2018, https://www. accessdata.fda.gov/drugsatfda_docs/label/2018/125166s426lbl.pdf.

8. Katyal N, Narula N, Govindarajan R. Clinical Experience with Eculizumab in Treatment-Refractory Acetylcholine Receptor Antibody-Positive Generalized Myasthenia Gravis. J Neuromuscul Dis. 2021;8(2):287-294. doi: 10.3233/JND-200584. PMID: 33325394; PMCID: PMC8075396.

9.Nishimura J. [Genetic variants in C5 and poor response to eculizumab]. Rinsho Ketsueki. 2015 Jul;56(7):855-60. Japanese. doi: 10.11406/rinketsu.56.855. PMID: 26251149.

10.Saskia Langemeijer, Jun-Ichi Nishimura, Wynne Weston-Davies, Miles A Nunn, Yuzuru Kanakura, Ian J Mackie, Petra Muus; C5 Polymorphism in a Dutch Patient with Paroxysmal Nocturnal Hemoglobinuria (PNH) and No Asian Ancestry, Resistant to Eculizumab, but in Vitro Sensitive to Coversin. *Blood* 2015; 126 (23): 1209. Doi: https://doi.org/10.1182/blood.V126.23.1209.1209.

11.Hillmen P, Muus P, Szer J, Hill A, Höchsmann B, Kulasekararaj A, Risitano AM, Van Den Neste E, Liljeholm M, Ebrahim KS, Bedrosian CL, Gao X, Ames D, Socié G. Assessment of human antihuman antibodies to eculizumab after long-term treatment in patients with paroxysmal nocturnal hemoglobinuria. Am J Hematol. 2016 Mar;91(3):E16-7. doi: 10.1002/ajh.24280. PMID: 26690023.

12. Koren E, Zuckerman LA, Mire-Sluis AR. Immune responses to therapeutic proteins in humans–clinical significance, assessment and prediction. *Curr Pharm Biotechnol* 2002; 3: 349– 360.

13. Hwang WY, Foote J. Immunogenicity of engineered antibodies. *Methods* 2005; 36: 3– 10.

14. Nechansky A. HAHA—nothing to laugh about. Measuring the immunogenicity (human anti-human antibody response) induced by humanized monoclonal antibodies applying ELISA and SPR technology. *J Pharm Biomed Anal* 2010; 51: 252– 254.

15. Albazli K, Kaminski HJ, Howard JF Jr. Complement Inhibitor Therapy for Myasthenia Gravis. *Front Immunol*. 2020;11:917. Published 2020 Jun 3. doi:10.3389/fimmu.2020.00917

Two new rare pathogenic variants in DES gene causing distal myofibrillar myopathy

Olimpia Carbunar, MD[1],
Sakir Humayun Gultekin, MD, FCAP[2],
Mario A. Saporta MD, PhD, MBA, FAAN[1]

[1] Department of Neurology
[2] Department of Pathology, University of Miami
Miller School of Medicine, Miami, FL

Introduction

Myofibrillar myopathy (MFM) is a clinically and genetically heterogeneous disorder characterized by the abnormal finding of myofibrillar disruption on EM and excessive desmin deposition in muscle fibers[1, 2]. Desmin deposits are not specific to MFM and can be found in other neuromuscular conditions such as x-linked myotubular myopathy, congenital myotonic dystrophy, SMA, nemaline rod myopathy, and inclusion body myositis [3]. On the other hand, MFM has been linked to mutations in desmin, alphaB-crystallin, myotilin, filamin C, and ZASP. MFM is associated with a broad spectrum of clinical phenotypes, affecting individuals between the ages of 25-45 with proximal, distal, or generalized weakness[1]. MFM can be transmitted in an autosomal dominant, autosomal recessive, or x-linked pattern[4]. There are also a few sporadic cases. In addition to the skeletal muscle being involved, the heart can be affected, and congestive heart failure and arrhythmias can be the predominant feature of the disease. There is no proven medical therapy to improve skeletal muscle weakness. Cardiac transplantation can be lifesaving in patients with severe cardiomyopathy. Here, we present two new variants in DES causing desmin-myofibrillary myopathies demonstrated by muscle biopsies.

Case 1

This is the case of a young adult diagnosed with Epstein's anomaly of the tricuspid valve at birth. His cardiologic symptoms started at age 11 with chest pain and shortness of breath. His heart transplant was performed at the age of 13. He had a challenging course but eventually recovered and had a very active life, working in construction and playing soccer and the drums. At 26, he started noticing tiredness and difficulty climbing stairs. One year later, he developed atrial fibrillation, and he was cardioverted. At that point, he decided to stop working in construction and reduced his physical activities. This was followed by worsening his weakness, with progressive difficulty in walking and frequent trips and falls. His symptoms also progressed to involve his arms and hands. For the last eight months, he has also noticed neck extension weakness. He had no visual or hearing problems and no chewing or swallowing issues. He had no family history of neuromuscular diseases. His neurological examination was pertinent for distal more than proximal weakness in the lower and upper extremities, left worse than right, with significant bilateral foot drop. His reflexes were 1+ throughout. He had a steppage gait with a Trendelenburg component. His CPK was 800. HMGCR was negative. EMG showed diffuse, irritable myopathy. Muscle biopsy showed a progressive non-inflammatory chronic myopathy with rimmed vacuoles, favoring a myofibrillar myopathy (MFM). Immunostaining for Desmin in the muscle biopsy sample demonstrated immunoreactivity in myofibers with focal accumulations of Desmin-positive material in myofibers (figure 1 B).

Comprehensive Neuromuscular Disorders Panel was performed (Table 1), and a variant of uncertain significance in the DES gene c.1255C>A (p.Pro419Thr) in heterozygosis was found (Table 2).

A few months later, he developed shortness of breath at rest and chest pain. He was found to have severe coronary

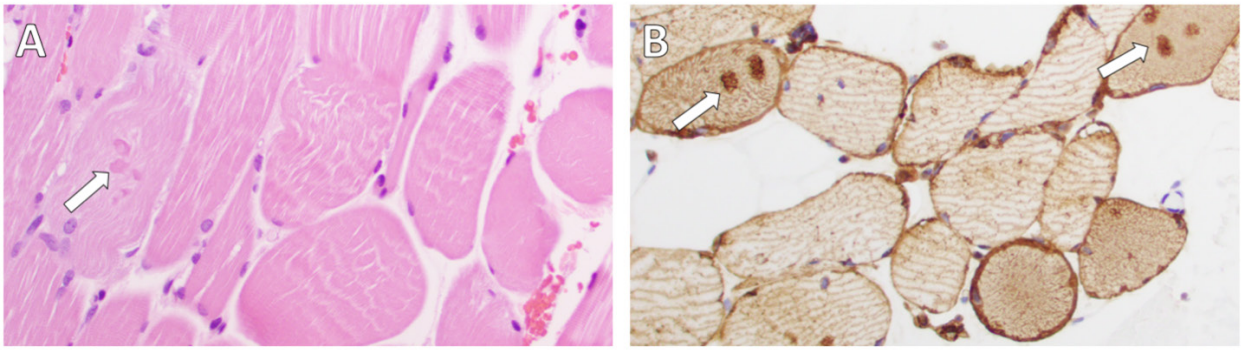


Figure 1: Muscle biopsy of Case 1. (A) H&E staining reveals cytoplasmic deposits in one fiber (arrow); (B) Desmin immunohistochemistry demonstrates the deposits to be Desmin-reactive (arrow).

Table 1: Features of the two new *DES* variants

	c.1243 C>T, p. Arg415Trp	c.1255C>A, p.Pro419Thr
Population frequency	Rare (Allele frequency on gnomAD: 0.00002172).	Private (no cases reported on gnomAD)
In silico prediction	Polyphen: probably damaging (Score: 1.0); SIFT: deleterious Mutation t@sting: prediction disease causing	Polyphen: probably damaging (Score: 0.988); SIFT: deleterious Mutation t@sting: prediction disease causing
Conservation	PhyloP: 5.344 PhastCons: 1	PhyloP: 5.11 PhastCons: 0.99
Further information	Missense variants in the same (R415Q) and nearby residues (E413K, P419S) have been reported in the Human Gene Mutation Database in association with DES-related disorders.	A different missense substitution at this codon (p.Pro419Ser) has been determined to be pathogenic[5-8].

gnomAD: genome aggregation database

Table 2: Other variants identified in the two patients

	Variants identified	**Genes tested**
Case 1	*ANO5*, c.692G>T (p.Gly231Val) *DES*, c.1255C>A (p.Pro419Thr) *CHKB*, c.577G>A (p.Glu193Lys) *MYPN*, c.1952C>A (p.Pro651Gln) *NEB*, c.23753C>T (p.Ser7918Leu)	*ACTA1, AGRN, ALG2, ANO5, ATP2A1, B3GALNT2, B4GAT1, BAG3, BIN1, CACNA1S, CAPN3, CAV3, CCDC78, CFL2, CHAT, CHKB, CHRNA1, CHRNB1, CHRND, CHRNE, CLCN1, CNTN1, COL6A1, COL6A2, COL6A3, COLQ, CPT2, CRYAB, DAG1, DES, DMD, DNAJB6, DNM2, DOK7, DPAGT1, DPM1, DPM2, DPM3, DYSF, EMD, FHL1, FKBP14, FKRP, FKTN, FLNC, GAA, GFPT1, GMPPB, GNE, ISPD, ITGA7, KBTBD13, KCNJ2, KLHL40, KLHL41, LAMA2, LAMP2, LARGE1, LDB3, LMNA, LMOD3, MATR3, MEGF10, MTM1, MUSK, MYH2, MYH7, MYL2, MYOT, MYPN, NEB, PLEC, PNPLA2, POMGNT1, POMGNT2, POMK, POMT1, POMT2, RAPSN, RYR1, SCN4A, SELENON, SGCA, SGCB, SGCD, SGCG, SMN1, SMN2, SQSTM1, STAC3, STIM1, TAZ, TCAP, TIA1, TMEM5, TNNT1, TNPO3, TPM2, TPM3, TRAPPC11, TRIM32, TTN, VCP, VMA21*
Case 2	*BAG3*, c.1634C>G (p.Pro545Arg) *DES*, c.1243C>T (p.Arg415Trp) *SGCB*, c.419A>G (p.Asn140Ser)	*ACTA1, ANO5, ASAH1, ATP2A1, B3GALNT2, B4GAT1, BAG3, BICD2, BIN1, BVES, CACNA1S, CAPN3, CAV3, CCDC78, CFL2, CHKB, CLCN1, CNTN1, COL12A1, COL6A1, COL6A2, COL6A3, CRYAB, DAG1, DES, DMD, DNAJB2, DNAJB6, DNM2, DOK7, DPM1, DPM2, DPM3, DYNC1H1, DYSF, EGR2, EMD, FHL1, FKRP, FKTN, FLNC, GAA, GBE1, GMPPB, GNE, IGHMBP2, ISPD, ITGA7, KBTBD13, KLHL40, KLHL41, LAMA2, LAMP2, LARGE, LDB3, LMNA, LMOD3, MEGF10, MICU1, MTM1, MYH2, MYH7, MYOT, NEB, PHKA1, PLEC, PLEKHG5, POMGNT1, POMK, POMT1, POMT2, PYGM, RYR1, SCN4A, SEPN1, SGCA, SGCB, SGCD, SGCG, SIL1, SLC52A2, SLC52A3, SYNE1, TCAP, TMEM5, TNNI2, TNNT1, TNPO3, TOR1AIP1, TPM2, TPM3, TRAPPC11, TRIM32, TRIP4, TRPV4, TTN, UBA1, VCP, VRK1*

artery disease, presumed due to non-compliance with his medication over time. The patient passed away at 30 due to cardiac arrest, likely secondary to myocardial infarction.

Case 2

A 59-year-old man with no significant past medical history presents with slowly progressive distal lower extremity weakness. He refers that he used to be very active and was a runner but that his symptoms started around six years prior when he started noticing that he was walking differently. He noticed difficulty clearing his left foot during ambulation, and this caused his running to be difficult as well. Weakness gradually progressed to involve his right ankle. He also describes some muscle soreness and stiffness that appear as the day progresses. His physical exam is remarkable for bilateral calf hypertrophy, weakness limited to around his ankles bilaterally, but no significant sensory deficits. His father had similar calves and had died from congestive heart failure complications. He has had extensive testing done, including genetic testing (Table 2) that reported a variant of uncertain significance in the DES gene (c.1243 C>T, p. Arg415Trp) (Table 1), but likely pathogenic based on the predicted protein alteration, and also had a muscle biopsy which reported that desmin immunostaining revealed uneven immunoreactivity in myofibers with apparent focal accumulations of desmin positive material in some myofibers.

Discussion

These are 2 cases of adults presenting with a rare form of muscular dystrophy, myofibrillary myopathy. The comprehensive neuromuscular gene panel revealed in each case a variant of uncertain significance on the DES gene, c.1255C>A (p.Pro419Thr) and c.1243 C>T (p. Arg415Trp), respectively. These variants are not present in population databases, and it has not been reported in the literature in individuals with DES-related disease. However, given the clinical phenotypes and the muscle biopsy with findings of MFM and staining positive for desmin, the previously unreported DES gene mutations Pro419Thr and Arg415Trp are most likely pathogenic.

MFM is rare but should remain a diagnostic consideration in young adults presenting with slowly progressive proximal and distal weakness, and cardiomyopathy discovery of new pathogenic variants such as the ones discussed in these cases will help further understand this disease and facilitate the diagnosis in future patients.

Disclosure

Dr Olimpia Carbunar reports no disclosures relevant to the manuscript.

Dr Sakir "Hume" Gultekin reports no disclosures relevant to the manuscript.

Dr Mario Saporta reports no disclosures relevant to the manuscript.

Corresponding Author
Olimpia Carbunar, MD, MS
Assistant Professor of Neurology
Univerisity of Miami
1150 NW 14th Street, Suite 609
Miami, FL 33136
Tel. 305-243-6732
Fax.305-243-4678
Email:oxc163@med.miami.edu

Author Contribution

- Olimpia Carbunar: Study concept and design, acquisition of data, lead role in writing manuscript, analysis and interpretation
- Sakir "Hume" Gultekin: Acquisition of data, intellectual contribution
- Mario A. Saporta: Study concept and design, acquisition of data, analysis and interpretation, critical revision of manuscript for intellectual content, intellectual contribution, study supervision

References:

1. Amato AA, Kagan-Hallet K, et al. The wide spectrum of myofibrillar myopathy suggests a multifactorial etiology and pathogenesis. Neurology 1998; 51(6):1646-55.
2. Amato AA, Russel J. Neuromuscular disorders 2008. Chapter 24: Muscular dystrophies, 563-5.
3. Goebel HH. Desmin-related neuromuscular disorders, Muscle Nerve 1995;18 (11):1306-20.
4. Selcen D, Ohno K, et al. Myofibrillar myopathy: Clinical, morphological and genetic studies in 63 patients. Brain 2004;127 (Pt 2): 439-51.
5. Maerkens A, Kley RA, et al. Differential proteomic analysis of abnormal intramyoplasmic aggregates in desminopathy. J Proteomics 2013; 90:14-27.
6. Olivé M, Armstrong J, et al. Phenotypic patterns of desminopathy associated with three novel mutations in the desmin gene. Neuromuscul Disord 2007; 17(6):443-50.
7. Hedberg C, Melberg A, et al. Autosomal dominant myofibrillar myopathy with arrhythmogenic right ventricular cardiomyopathy 7 is caused by a DES mutation. Eur J Hum Genet 2012; 20(9): 984-5.
8. Olivé M, Odgerel Z, et al. Clinical and myopathological evaluation of early- and late-onset subtypes of myofibrillar myopathy. Neuromuscul Disord. 2011; 21(8):533-42.

Quantitative sensory testing in a large cohort of neuropathy patients: QST in Neuropathy

Alexis A. Lizarraga MD, MS[1*], Salman Bhai MD[2*], Gil Wolfe MD[3], Laura Herbelin[4], Sharon Nations MD[2], Morgan McCreary PhD[2], David Saperstein MD, Richard J. Barohn MD[5]

[1] University of Rochester
[2]University of Texas Southwestern Medical Center
[3] State University of New York at Buffalo
[4] University of Kansas Medical Center
[5]University of Missouri
* Co-first authors

Introduction

Quantitative sensory testing (QST) is a set of largely painless, noninvasive techniques developed more than 30 years ago to determine specific patient threshold to accurately calibrated sensory stimuli.[1,2,3,4] QST can measure small- and large-fiber function in the peripheral and central somatosensory pathways, including warming, cooling, heat-pain sensation and vibratory perception, but cannot distinguish between central and peripheral impairment. The most commonly tested modalities are vibratory perception and thermal pain. Although QST is a psychosocial measure derived from subjective responses, there is good reliability and reproducibility of QST results on both an individual and population level.[5,6]

QST may have some use as a diagnostic, staging and outcome measure in peripheral neuropathy (PN) research, but its usefulness in the routine clinical setting is unclear.[4] PN is typically diagnosed based on a combination of clinical and electrophysiological data, with slowly progressive, distally predominant sensory loss being the most common clinical pattern.[7,8] QST may provide evidence of peripheral nerve pathology in the setting of normal nerve conduction studies (NCS) and electromyography (EMG) and may be particularly helpful in small-fiber pathology as routine electrophysiologic studies do not detect small-fiber sensory dysfunction.[9] The utility of QST, however, to distinguish between types of peripheral neuropathy is not established.

Although up to 30% of PNs referred to specialty clinics do not have a clear etiology identified and are ultimately categorized as cryptogenic sensory PN (CSPN), most PNs are categorized to a variety of etiologies.[4,10] The most common cause in the United Status of acquired PN is diabetes mellitus. Other causes of PN include infection (e.g., leprosy, HIV), toxic (e.g., alcohol-induced), nutritional (e.g., B12 deficiency) in addition to autoimmune etiologies (e.g., chronic inflammatory demyelinating polyneuropathy [CIDP]) and hereditary neuropathies (e.g., Charcot Marie Tooth [CMT] disease).[11] While different forms of PN at times present with unique clinical patterns and electrodiagnostic signatures on NCS/EMG, the neurological examination and electrophysiological studies may not distinguish different etiologies of PN, especially when of predominantly axonal pathophysiology. A non-invasive method to distinguish between types of PN would be helpful in differential classification and management.

The objective of this study was to retrospectively evaluate patterns of QST findings among different categories of neuropathy in a large cohort of PN patients evaluated at the University of Texas Southwestern Medical Center from 1995-2000.

Methods

This retrospective study consists of patients who presented to the University of Texas Southwestern Medical Center PN tertiary clinic between 1995 and 2000. Patients who were diagnosed with any form of neuropathy underwent routine QST using the Computer-Assisted Sensory Examination system (CASE IV, WR Medical Electronics, Stillwater, MN) using a 4, 2, and 1 stepping protocol.[12] This test typically lasts approximately one hour. The CASE IV system used during the enrollment period had age-matched control values for vibration and cooling sensory thresholds. Thresholds for heat-pain had not been fully validated. Abnormal results were established at the greater than 95th percentile for age. Patients were categorized by a single etiology of neuropathy as diagnosed by neuromuscular medicine specialists.

All analyses were performed in R (version 4.0.5). Chi-squared tests were used to compare the prevalence of abnormal responses between tests. Due to the limited number of observations and normal results for some diseases, Fisher's Exact test was used to perform pairwise comparisons of the prevalence of abnormal tests between diseases for each test. To account for multiple comparison, false detection rate (FDR) adjusted p-values are reported. The FDR-adjusted p-values were computed independently for each set of pairwise comparisons. For instance, FDR-adjusted p-values were computed for the pairwise comparisons of the abnormal cold test amongst diagnoses and the abnormal vibration test.

To determine the impact of disease and test on the prevalence of abnormal responses, meta regression was implemented with a logit link function. Meta regression was performed independently for the cold and vibration tests and the pure thermal and pure vibration tests due to the

greater proportion of abnormal cold and vibration results relative to pure thermal and pure vibration results.

Results

A total of 559 QST studies were performed in this study. The average age of patients (n=557) was 60 years with a male-to-female ratio of 1:1. The most common diagnosis was CSPN (n=294), followed by CMT disease (n=84) (Table 1).

Meta-regression of cold and vibration indicate that the expected proportion of abnormal responses is less for the vibration test (p = 0.0002), relative to the cold test (Figure 1). However, no differences were observed between diagnoses, as previously found in Table 5. Meta-regression indicate that the expected proportion of pure vibration is less than the pure thermal (p < 0.0001); however, no differences were observed between diagnoses, as previously found in Table 5 (Figure 2).

Vibration and cold detection thresholds were measured in all patients, whereas heat-pain was measured in 284 patients (Table 2). In this cohort, patients were more often abnormal for cold sensation testing relative to vibration (p < 0.0001) and heat (p < 0.0001). Additionally, the data suggest that more subjects were abnormal for vibration relative to heat (p<0.0001) (Table 3).

Table 1: Patient characteristics and diagnoses

Total patients	557
Men	277
Women	280
Mean Age (range) [years]	60 (14-93)
Diagnoses	
CSPN	294 (53%)
CMT	84 (15%)
CIDP	39 (7%)
Diabetic	39 (7%)
B12 deficiency	18 (3%)
Leprosy	11 (2%)
Alcoholic	7 (1%)
Other	65 (12%)

Other includes several diagnoses with a small number of cases. These diagnoses include: amyotrophic lateral sclerosis, primary lateral sclerosis, distal acquired demyelinating symmetric neuropathy, monoclonal gammopathy of undetermined significance associated neuropathy, various rheumatologic etiologies (Sjögren's syndrome, vasculitis, other connective tissue diseases), paraneoplastic neuropathy, Guillain-Barré syndrome, multifocal motor neuropathy.

Table 2. Distribution of abnormal responses by test for entire sample

	Abnormal	Total
Cold	534 (95.53%)	559
Vibration	404 (72.27%)	559
Heat	99 (34.86%)	284

Table 3. Results of pairwise comparison of abnormal results by test with FDR-adjusted p-values

Groups Compared	Adjusted p-value
Cold vs. Vibration	< 0.0001
Cold vs. Heat	< 0.0001
Vibration vs. Heat	< 0.0001

Figure 1. Forest plot of the meta-regression results for the cold and vibration tests by PN diagnosis

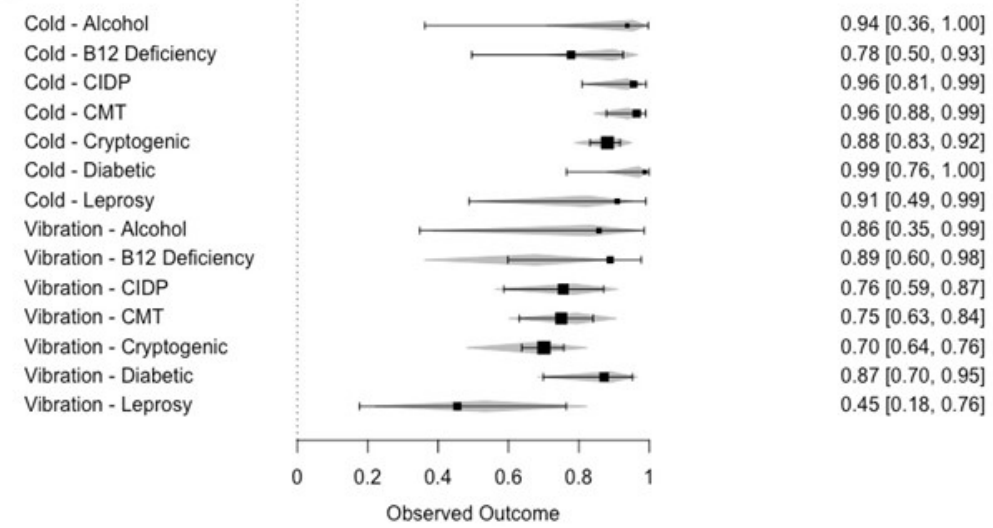


Figure 2. Forest plot of the meta-regression results for the pure thermal and pure vibration tests by PN diagnosis

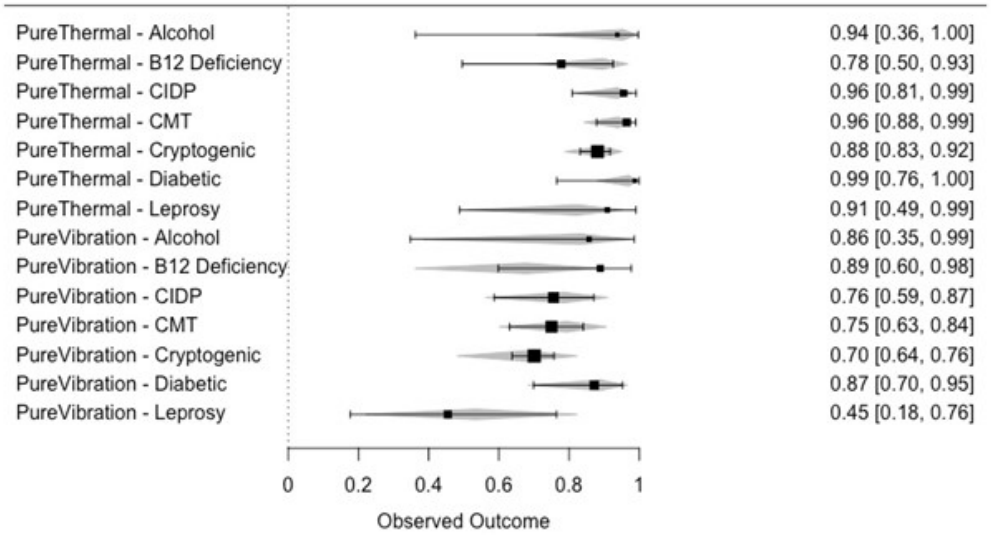


Table 4. Prevalence of abnormal results by PN diagnosis and test.

	Cold	Vibration	Abnormal	Pure Thermal	Pure Vibration	Total
Alcohol	7	6	7	1	0	7
B12 Deficiency	14	16	17	3	3	18
CIDP	43	34	44	12	3	45
CMT	81	63	84	20	3	84
CSPN	259	206	275	68	21	294
Diabetic	39	34	39	5	0	39
Leprosy	10	5	10	5	0	11

Table 5. Pairwise comparison of the proportion of abnormal results for each test by PN classification with FDR-adjusted p-values

Groups Compared	Adjusted p-value				
	Cold	Vibration	Pure Thermal	Pure Vibration	Abnormal
Alcohol vs. B12 Def.	0.687	> 0.99	> 0.99	> 0.99	> 0.99
Alcohol vs. CIDP	> 0.99	> 0.99	> 0.99	> 0.99	> 0.99
Alcohol vs. CMT	> 0.99	> 0.99	> 0.99	> 0.99	> 0.99
Alcohol vs. CSPN	> 0.99	0.949	> 0.99	> 0.99	> 0.99
Alcohol vs. Diabetic	> 0.99	> 0.99	> 0.99	> 0.99	> 0.99
Alcohol vs. Leprosy	> 0.99	0.367	0.736	> 0.99	> 0.99
B12 Def. vs. CIDP	0.212	0.603	> 0.99	0.895	> 0.99
B12 Def. vs. CMT	0.123	0.613	> 0.99	0.695	0.924
B12 Def. vs. CSPN	0.678	0.329	> 0.99	0.795	> 0.99
B12 Def. vs. Diabetic	0.123	> 0.99	> 0.99	0.586	0.938
B12 Def. vs. Leprosy	0.933	0.197	0.686	0.895	> 0.99
CIDP vs. CMT	> 0.99	> 0.99	> 0.99	0.980	0.938
CIDP vs. CSPN	0.660	0.732	> 0.99	> 0.99	> 0.99
CIDP vs. Diabetic	0.869	0.557	0.686	0.895	> 0.99
CIDP vs. Leprosy	0..869	0.300	0.734	> 0.99	0.938
CMT vs. CSPN	0.123	0.670	> 0.99	0.895	0.215
CMT vs. Diabetic	0.900	0.367	0.686	> 0.99	> 0.99
CMT vs. Leprosy	0.827	0.300	0.686	> 0.99	0.924
CSPN vs. Diabetic	0.123	0.197	0.686	0.795	0.924
CSPN vs. Leprosy	> 0.99	0.329	0.686	> 0.99	> 0.99
Diabetic vs. Leprosy	0.660	0.166	0.628	> 0.99	0.924

Among the various etiologies of neuropathy and the abnormalities detected, no statistically significant differences were observed between any pair of diagnoses for any of the QST modalities (Tables 4 and 5).

Of the 294 CSPN patients, 47 patients underwent QST and NCS with 7 (15%) patients having normal NCS. QST was abnormal in 3 (43%) of these 7 patients. All the 7 patients had abnormal pinprick documented on exam. A total of 97 CSPN patients had documented sensory exams. Ten (10%) patients had only pinprick (and not vibration) deficits on exam. QST vibration and cold thresholds were abnormal in 1 (10%) and 3 (30%) of these 10 patients, respectively. In this group of 10 patients, NCS was abnormal in 5 (50%) patients.

Discussion

In our 5-year study, no pattern of QST abnormalities was useful in distinguishing between the different classes of neuropathy. The largest proportion of patients tested had CSPN, followed by CMT disease and CIDP. Due to low numbers, the generalizability of the QST findings in other common etiologies of PN, including diabetes; alcohol overuse; and B12 deficiency, is limited. The inability to separate these types of neuropathies from each other in a routine clinical setting may limit the utility of QST to research investigations.

We found that QST was abnormal in >95% of established PN patients. This high rate of abnormal QST findings is expected in patients diagnosed with PN diagnosis in a referral clinic, and reflects the high frequency of QST abnormalities in other studies.[2,13,14] Since QST is a psychosocial measure reliant on patient cooperation, it should be emphasized that abnormal QST alone should not be used to diagnose PN. Abnormal QST results should be interpreted in the context of the neurologic examination and appropriate laboratory testing such as NCS/EMG, skin biopsy and nerve biopsy, highlighted by a subset of our cohort having variable patterns of exam, NCS, and QST results.[2,13]

Since NCS only effectively measures large-fiber peripheral nerve function, there has been interest in the use of QST to determine thermal threshold changes in patients with predominantly small-fiber involvement. Vibration thresholds reflect large myelinated A-β fibers that conduct via the dorsal columns, whereas cold thresholds measure both A-δ (thin myelinated) and C fiber (unmyelinated) function that travel centrally via the spinothalamic tracts.[4,15] Heat-pain is also mediated through A-δ and C fibers, whereas warm stimuli are mediated through C fibers exclusively.

In the current study, cold detection thresholds were most frequently abnormal, followed by vibration thresholds. Heat-pain thresholds demonstrated the lowest rate of abnormality, although control values for this modality were not fully validated at the time of the study. In addition, threshold abnormalities for cold stimuli are more commonly observed than those for heat in a variety of neuropathies including those related to diabetes and alcohol abuse.[16,17] Overall, thermal threshold abnormalities were more common than those for vibration, likely reflecting the predominance of small-fiber abnormalities characteristic of the types of PN enrolled in the study. A large proportion of the cohort had a diagnosis of CSPN, in which small-fiber deficits and neuropathic pain often predominate.

A limitation of the study includes its retrospective design, with data obtained via chart review. This resulted in a minor discrepancy in the number of QST studies recorded (n=559) compared to the total number of patient diagnoses recorded (n=557). This minor difference should not have skewed the data given the large number of QST studies performed. Additionally, there was limited data comparing the QST findings to the clinical exam. Another limitation is the lack of duration the neuropathy had been present; however, the goal of the study was to distinguish forms of neuropathy with QST regardless of the duration the neuropathy was present. We realize that the tertiary nature of the PN clinic at UTSW led to skewed percentages of etiologies on PN. The low numbers of diabetes and alcohol-related PN and large population of CMT, leprosy, CSPN, and CIDP patients do not reflect a more general PN population. In particular, the larger percentage of CSPN patients compared to other studies may be due to greater recognition of etiologies, accessibility of genetic testing, and improved diagnostics for immune-mediated neuropathies. Additionally, patients were diagnosed by several neurologists without defined protocols in place to classify PN etiologies. This may have resulted in variability in the selection of laboratory testing (e.g., serologic and genetic testing) to establish an etiology for the neuropathy. However, all patients were seen by neuromuscular specialists, and QST was widely utilized during the time period of the study.

In conclusion, QST was abnormal in the vast majority of a large cohort of patients with PN encountered over a 5-year period. The utility of QST in routine practice appears limited due to its inability to distinguish between types of neuropathy, and does not meaningfully supplement information gleaned from the neurological examination and routine and more widely-available laboratory studies.

References

1. Fruhstorfer H, Lindblom U, Schmidt WG: Method for quantitative estimation of thermal thresholds in patients. J Neurol Neurosurg Psychiatry 1976;39:1071-1075. doi: 10.1136/jnnp.39.11.1071. PMID: 188989

2. Shy ME, Frohman EM, So YT, Arezzo JC, Cornblath DR, Giuliani MJ, Kincaid JC, Ochoa JL, Parry GJ, Weimer LH; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Quantitative sensory testing: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2003 Mar 25;60(6):898-904. doi: 10.1212/01.wnl.0000058546.16985.11. PMID: 12654951.

3. Wolfe G.I. Quantitative sensory testing: basic principles and clinical applications. In: Dumitru D., Amato A.A. and Zwarts M.J., eds. Electrodiagnostic Medicine. Philadelphia: Hanley & Belfus, 2nd ed., 2001; pp 429-437.

4. Wolfe GI, Baker NS, Amato AA, et al. Chronic Cryptogenic Sensory Polyneuropathy: Clinical and Laboratory Characteristics. *Arch Neurol.* 1999;56(5):540–547. doi:10.1001/archneur.56.5.540. PMID: 10328248.

5. Wittenberg B, Svendsen TK, Gaist LM, Itani M, Gylfadottir SS, Jensen TS, Gaist D, Sindrup SH, Krøigård T. Test-retest and time dependent variation and diagnostic values of vibratory sensation determined by biothesiometer and the Rydel-Seiffer tuning fork. Brain Behav. 2021 Aug;11(8):e2230. doi: 10.1002/brb3.2230. Epub 2021 Jun 4. PMID: 34087955; PMCID: PMC8413738.

6. Backonja MM, Attal N, Barohn R, et al. Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. Pain. 2013;154:1807–1819. doi: 10.1016/j.pain.2013.05.047. PMID: 23742795.

7. Lehmann, H.C., Wunderlich, G., Fink, G.R. et al. Diagnosis of peripheral neuropathy. Neurol. Res. Pract. 2, 20 (2020). https://doi.org/10.1186/s42466-020-00064-2. PMID: 33324924; PMCID: PMC7650053.

8. Watson JC, Dyck PJ. Peripheral Neuropathy: A Practical Approach to Diagnosis and Symptom Management. Mayo Clin Proc. 2015 Jul;90(7):940-51. doi: 10.1016/j.mayocp.2015.05.004. PMID: 26141332.

9. Egenolf N, Zu Altenschildesche CM, Kreß L, Eggermann K, Namer B, Gross F, Klitsch A, Malzacher T, Kampik D, Malik RA, Kurth I, Sommer C, Üçeyler N. Diagnosing small fiber neuropathy in clinical practice: a deep phenotyping study. Ther Adv Neurol Disord. 2021 Mar 23;14:17562864211004318. doi: 10.1177/17562864211004318. PMID: 34335876; PMCID: PMC8283814.

10. Pasnoor M, Dimachkie MM, Barohn RJ. Cryptogenic sensory polyneuropathy. Neurol Clin. 2013;31(2):463-476. doi:10.1016/j.ncl.2013.01.008. PMID: 23642719; PMCID: PMC4090929.

11. Hanewinckel R, van Oijen M, Ikram MA, van Doorn PA. The epidemiology and risk factors of chronic polyneuropathy. Eur J Epidemiol. 2016 Jan;31(1):5-20. doi: 10.1007/s10654-015-0094-6. Epub 2015 Dec 23. PMID: 26700499; PMCID: PMC4756033.

12. Dyck PJ, O'Brien PC, Kosanke JL, Gillen DA, Karnes JL. A 4, 2, and 1 stepping algorithm for quick and accurate estimation of cutaneous sensation threshold. Neurology. 1993 Aug;43(8):1508-12. doi: 10.1212/wnl.43.8.1508. PMID: 8351003.

13. Devigili G, Cazzato D, Lauria G. Clinical diagnosis and management of small fiber neuropathy: an update on best practice. Expert Rev Neurother. 2020 Sep;20(9):967-980. doi: 10.1080/14737175.2020.1794825. Epub 2020 Jul 23. PMID: 32654574.

14. Navarro X, Kennedy WR: Evaluation of thermal and pain sensitivity in type-1 diabetic patients. J Neurol Neurosurg Psychiatry 1991;54:60-64. doi: 10.1136/jnnp.54.1.60. PMID: 1849171; PMCID: PMC1014301.

15. Yarnitsky D. Quantitative sensory testing. Muscle Nerve. 1997 Feb;20(2):198-204. doi: 10.1002/(sici)1097-4598(199702)20:2<198::aid-mus10>3.0.co;2-#. PMID: 9040659.

16. Ziegler D, Mayer P, Wiefels K, et al.: Assessment of small and large fiber function in long-term type 1 (insulin-dependent) diabetic patients with and without painful neuropathy. Pain 1988;34:1-10. doi: 10.1016/0304-3959(88)90175-3. PMID: 3405615.

17. Hilz MJ, Claus D, Neundörfer B, et al.: Is heat hypoalgesia a useful parameter in quantitative thermal testing of alcoholic polyneuropathy? Muscle Nerve 1994;17:1456-1460. doi: 10.1002/mus.880171215. PMID: 7969246.

Facial Onset Sensory and Motor Neuronopathy: A Case Series and Literature Review

Jonathan Morena DO[1,2*], Hera A. Kamdar MD[3], Rabia Yasin MD[4], J. Chad Hoyle MD[5], Adam Quick MD[5], Stephen J. Kolb PhD[5,6]

[1] Department of Neurology, Hospital for Special Surgery, New York, NY
[2] Department of Neurology, NewYork-Presbyterian/ Weill Cornell Medical Center, New York, NY
[3] Department of Neurology, Massachusetts General Hospital, Brigham & Women's Hospital, Harvard Medical School
[4] Department of Neurology, Temecula Valley Hospital, Temecula, CA
[5] Department of Neurology, The Ohio State University Wexner Medical Center, Columbus, OH
[6] Department of Biological Chemistry & Pharmacology, The Ohio State University, Columbus, OH

ABSTRACT

Introduction: Facial Onset Sensory and Motor Neuronopathy (FOSMN) typically presents with paresthesias in the trigeminal nerve distribution and weakness that progresses rostro-caudally.

Objective: To present two new cases of FOSMN, summarize the current literature, and address areas for future study.

Methods: Observational data was collected from two patients with FOSMN from our institution. A literature review of FOSMN was completed using PubMed.

Results: We reviewed 100 cases of FOSMN, including our two new cases. 93% presented with facial paresthesias. 97% had bulbar symptoms. Five had family history of ALS. Abnormal Blink reflex was most common on EMG/ NCS. CSF was typically normal, but a rare severe case showed elevated protein. Mutations included: TARDBP, OPMD, D90A-SOD1, CHCHD10, VCP, and SQSTM1. Neuropathological studies showed neurodegenerative changes without inflammation. Some cases have reported transient stabilization or improvement to immunomodulatory therapy.

Case Reports: A 72-year-old man presented with right-sided trigeminal paresthesias that progressed in a rostro-caudal fashion, dysphagia, and hand weakness. He died 4-5 years after symptom onset. A 69-year-old man presented with left-sided jaw paresthesias, dysphagia and dysarthria. He was trialed on IVIG for 1.5 years without improvement and died 2.6 years after symptom onset.

Conclusion: FOSMN is a rare disorder with a unique clinical and electrophysiological phenotype. The pathophysiology has been associated with neurodegeneration and multiple gene mutations have correlated to FOSMN. Some reports suggest transient response to immunomodulatory therapy, though prospective studies are lacking. CSF protein elevation may be seen in severe disease. Future studies will help further elucidate the approach to diagnosis, treatment, and prognostic counseling (biomarkers).

Keywords: FOSMN, Facial Onset Sensory and Motor Neuronopathy, Neurodegenerative disorders

Introduction

In 2006, Vucic et al. were the first to report a "syringomyelia-like syndrome" that involved facial sensory loss and progressive motor deficits seen in four adult male patients.[1] Later this disease was coined Facial Onset Sensory and Motor Neuronopathy (FOSMN), which manifests as a mild asymmetric facial sensory deficit commonly in the trigeminal nerve distribution that advances caudally to include the scalp, neck, upper trunk, and upper extremities. Progressive motor symptoms such as weakness in the bulbar, neck, upper limbs, and later the lower limbs can develop months to years following the initial onset of sensory symptoms and can lead to functional impairments such as dysphagia and dysarthria.

There have subsequently been at least 98 cases of FOSMN described in the literature. It is a rare syndrome with unknown incidence. FOSMN affects both males and females, with a male predominance.[2] Onset of disease is typically between the fourth to seventh decade with one case onset reported at seven years old.[3] FOSMN duration can span from months to decades.[4] The diagnosis is mostly made based on clinical features but absent or latent corneal blink reflex is a hallmark of electrodiagnostic testing in many cases.[5]

The pathogenesis of this heterogeneous disease remains a topic of debate. An immunologic process has been suggested due to transient clinical response to intravenous immunoglobulin (IVIg) and the presence of autoantibodies at low concentrations observed in some patients.[6] However, it is this same transient or absent response to immunomodulatory therapy along with a stereotyped clinical picture of a chronically progressive disease that suggests a primary neurodegenerative mechanism. In many cases, it is a diagnosis of exclusion. Many of the diseases to be

excluded have a neurodegenerative pathology, one of which is amyotrophic lateral sclerosis (ALS). Recent literature has suggested a link between ALS and FOSMN, which would further confirm a neurodegenerative pathway. For example, corneal confocal microscopy has revealed a reduction of corneal small fiber sensory nerves in ALS patients, which may suggest a link with FOSMN as patients with FOSMN typically have early trigeminal nerve distribution sensory symptoms.[7] Cervical cord atrophy can be seen in both ALS and FOSMN.[6,8,9] Similar genetic variants have also been found in FOSMN including SOD1.[10]

Our objective is to characterize the key clinical findings, diagnosis, treatment, and outcomes of patients with FOSMN while adding two additional cases to the literature. Our study will not only review the current literature, but also address gaps that future studies must consider to advance our understanding of FOSMN in order to optimize management of those with the condition.

Methods

This is a case series presenting observational data collected from two patients at The Ohio State University, Wexner Medical Center with a diagnosis of FOSMN. Verbal consent was obtained from the patients prior to publication. Furthermore, a comprehensive literature review was performed through PubMed. The following MeSH terms were used: "FOSMN" and "Facial Onset Sensory Motor Neuronopathy." Articles included all previously reported cases with the diagnosis of FOSMN.

We evaluated patient characteristics, clinical features, physical examination findings, comorbidities, laboratory, electromyogram/nerve conduction study (EMG/NCS) and magnetic resonance imaging (MRI) findings, genetic testing, disease course, autopsy, requirements for tracheostomy or percutaneous endoscopic gastrostomy (PEG) tube, and treatments.

Case Summary

Case Presentation 1

A 72-year-old male with past medical history of monoclonal gammopathy of undetermined significance (MGUS) complicated by distal small fiber neuropathy, gastro-esophageal reflux disease (GERD), and esophageal stricture post balloon dilatation, presented to our hospital with an acute choking episode in the setting of a progressive three-year history of recurrent choking episodes, sensory loss in the face, mouth, and limbs, and reduced hand dexterity.

His symptoms initially started with paresthesias in the trigeminal (V2) distribution on the right side of his face that slowly spread to involve all trigeminal nerve sensory areas and then later progressed in a rostro-caudal fashion to involve his scalp, neck, trunk and arms. Within three months, he developed dysphagia (to both solids and liquids), throat numbness, and loss of taste. Two years after symptom onset, he noticed trouble with hand dexterity and sensory loss in the lower extremities. He reported no changes in cognition, fluctuation of his symptoms or visual complaints. There was no family history of motor neuron disease.

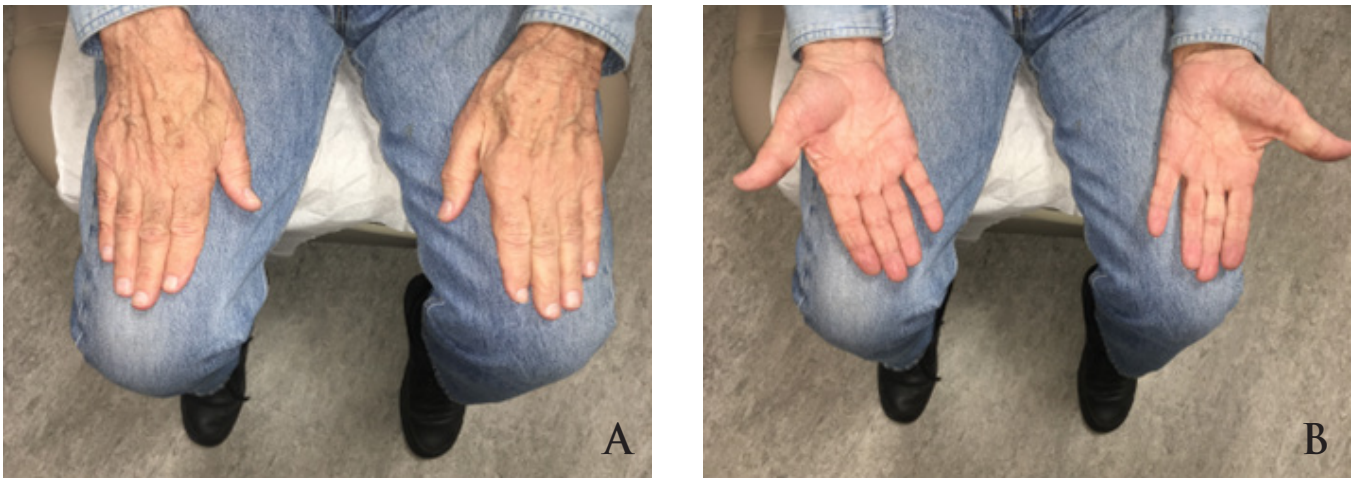
On exam, he had loss of sensation to sharp involving the face, head, neck, arms and trunk above a suspended T4 level. There was atrophy of the tongue and thenar muscles in the hand, similar to the split hand sign seen in ALS (Figure 1), along with moderate intrinsic hand muscle weakness. Tongue fasciculations were prominent. Lower extremities had absent reflexes and loss of vibratory sensation (attributed to MGUS).

Work up included unremarkable laboratory studies, including basic metabolic, autoimmune testing and vitamin levels. CK was 120 U/L. MRI of the brain without contrast showed no atrophy or focal abnormalities. MRI of the cervical spine without contrast showed an atrophic spinal cord, measuring 0.43 cm in antero-posterior diameter (Figure 2). NCS was suggestive of a non-length-dependent sensorimotor polyneuropathy or neuronopathy with decreased sensory conduction amplitudes in the upper extremity and normal amplitudes in the lower extremity. Blink reflexes were absent. EMG showed active and chronic denervation in cranio-bulbar, cervical, and lumbosacral regions. Given the clinical symptoms, exam findings, cervical cord atrophy, and EMG/NCS findings, FOSMN syndrome was considered the most likely diagnosis. During his hospital stay, he was treated for aspiration pneumonitis, had his diet modified, and he was discharged. He was not trialed on any immunotherapies for FOSMN.

He was followed in neuromuscular clinic and underwent speech therapy with clinical stability for approximately one year at follow up, or four years after symptom onset. Subsequently he required admissions for aspiration pneumonia and eventually died after a hospitalization for a hernia causing small bowel obstruction which was complicated by a cardiac arrest event secondary to respiratory failure.

Case Presentation 2

A 69-year-old male with no past medical history presented to our neurology clinic with left sided jaw paresthesias, difficulty chewing, and dysarthria. His symptoms started seven months prior to presentation with initial symptoms of left jaw and tongue numbness. A few months later, his facial paresthesias progressed to involve his



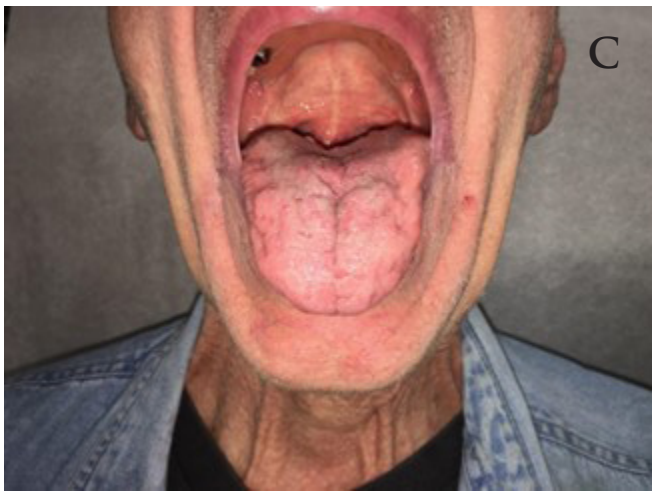


Figure 1: Case 1 with A) left greater than right first dorsal interossei (FDI) atrophy, B) left greater than right thenar atrophy, and C) prominent tongue atrophy

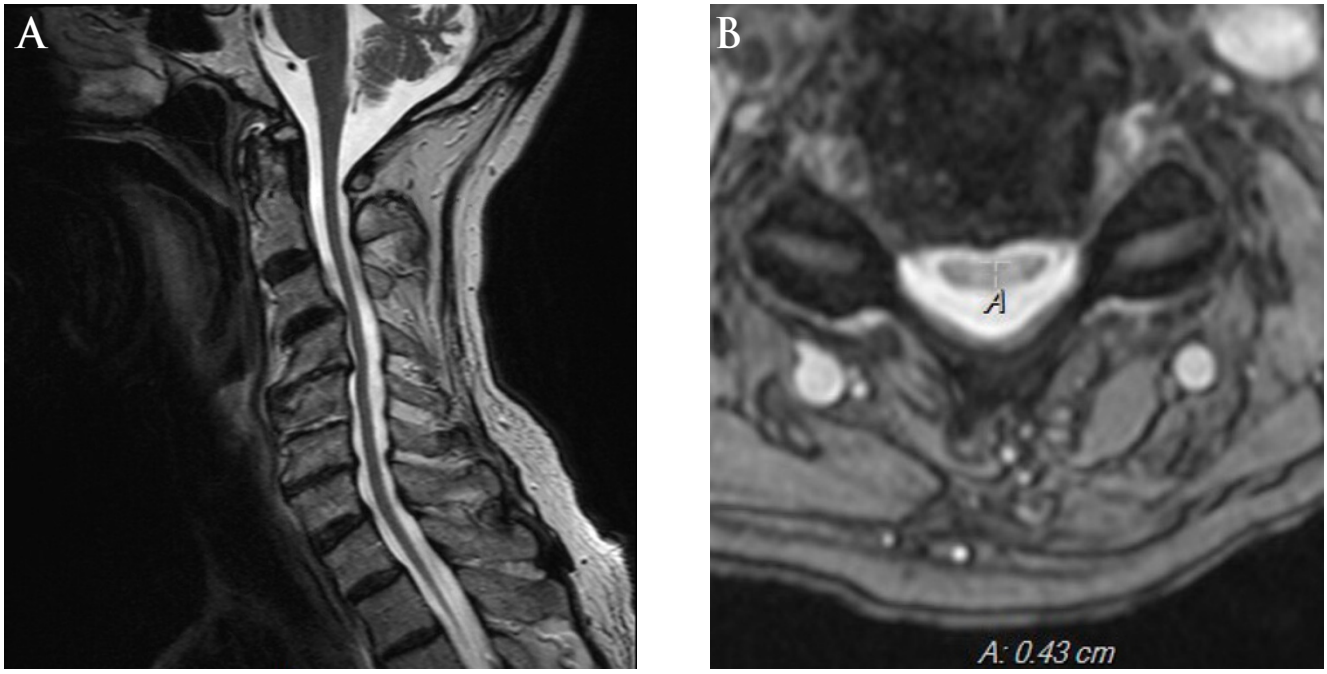


Figure 2: Case 1's MRI of the cervical spine
A: Sagittal T2-weighted image showing cervical cord atrophy
B: Axial T2-weighted image showing cervical cord anterior-posterior diameter of 0.43 cm

entire face and he developed dysarthria, difficulty chewing foods, and neck muscle weakness. He ultimately also had an unintentional 40lb weight loss over the proceeding months. He denied any cognitive or visual changes. There was no family history of motor neuron disease.

On exam, he had sensory loss to light touch and pin prick in the left V1-V3 trigeminal nerve region, bilateral orbicularis oris and tongue weakness, bitemporal wasting, and tongue fasciculations. He had generalized decreased muscle bulk. On initial strength testing, he had slight infraspinatus weakness on the left, but all other muscles of the upper and lower extremities were 5/5 on the Medical Research Council Manual Muscle Testing scale.

Lab and imaging tests were negative for autoimmune disorders, myasthenia gravis, leptomeningeal disease and Kennedy's disease. Anti-NR1 antibody was initially positive in serum paraneoplastic panel testing but later became negative twice on repeat testing. CT chest, abdomen and pelvis were negative for malignancy. CK was 140 U/L. CSF protein was mildly elevated at 48 mg/dL and all other basic CSF labs were unremarkable. MRI brain showed an incidental meningioma over the right cavernous sinus. Nerve conduction studies, including upper and lower limb sensory and motor studies, were normal. EMG revealed active and chronic denervation in his cranio-bulbar, cervical, and lumbar regions. Blink reflex testing showed absent ipsilateral and contralateral R1 and R2 potentials when stimulating the left side. When stimulating the right side, the ipsilateral R1 and R2 and contralateral R2 potentials were mildly prolonged. 3-hz repetitive nerve stimulation (RNS) of both the left orbicularis oris and right trapezius showed a CMAP decrement of >10% at rest with evidence of partial improvement in decrement immediately post-exercise. This may have been secondary to denervation and reinnervation changes.

He had a significant choking event nine months from symptom onset. Around this same time, his weakness progressed to involve his upper and lower extremities, left worse than right. He regressed from being able to tolerate a thick pureed diet to only broth and had to wear a jaw brace to combat his jaw drop. Given the degree of involvement of his bulbar musculature, he was trialed on IVIg monthly for three months. He reported improvement in his swallowing and had improvement in his Dysphagia Scoring Scale as well. His IVIg frequency was increased to weekly, and he was started on prednisone 30 mg daily. He was on this regimen for about a year and a half. However, his swallowing and weakness progressed, and he eventually required a PEG tube 22 months after symptom onset. He ultimately died due to respiratory failure 31 months after symptom onset.

Results

We reviewed 100 total cases, including our two new cases. Table 1 outlines a summary of the characteristics of patients with FOSMN. The mean age of onset is 54.5 years old. The male to female ratio is about 2:1. Initial symptoms typically include sensory loss in the trigeminal nerve distribution. When previous literature mentioned initial symptoms, 93% had facial sensory loss at onset. This typically advances rostro-caudally into the scalp, neck, upper back and arms. Lower motor neuron findings, including fasciculations, muscle atrophy and weakness, are present in almost all cases and progress in a rostro-caudal manner. Upper motor neuron findings have been mentioned in at least 23 patients. 97% of patients have bulbar symptoms. 27% of patients required percutaneous endoscopic gastrostomy (PEG) placement. The average time from symptom onset to PEG placement was 2.3 years. Taste disturbance has been reported as an initial symptom in two case reports[11,12] and loss of taste was seen in three out of four of the originally described FOSMN patients.[1] Five patients had a family history of ALS.[13,14] Five patients were also diagnosed with behavioral variant frontotemporal dementia (bvFTD) and met Rascovsky criteria.[5,15] There are no known social risk factors for FOSMN.

Common clinical examination findings include absent to decreased corneal reflex, decreased sensation in the trigeminal nerve distribution, dysarthria, weak cough and gag reflex, decreased upper extremity reflexes, fasciculations and atrophy. There can be facial, tongue and upper extremity weakness.

Cervical cord atrophy has been found in seven patients[6,9,14,16] and one of our patients had cervical cord atrophy as well (Figure 2). Frontotemporal atrophy has been seen in at least one patient with FOSMN.[17] The "bright tongue sign" has been reported in three cases, which can also be seen in ALS.[14] This sign is found on brain MRI and consists of hyperintense signaling in tongue muscles.

Blink reflex abnormalities on EMG/NCS are seen in almost all patients with FOSMN.[15] The most common abnormality is seen in the R2 response. All but one patient had either a unilateral or bilateral R2 abnormality. 82% had bilateral R2 abnormalities. If an article mentioned an R1 response, it was abnormal 77% of the time. Other common findings on EMG include decreased SNAPs and neurogenic findings in bulbar or cervical muscles.[14,18] One of our patients had a >10% CMAP decrement on RNS with immediate post-exercise repair.

Cerebrospinal fluid (CSF) is typically normal in most patients. There have been rare, reported cases of elevated protein and IgG. The patient with elevated CSF protein

had a more rapid disease course and died within 18 months of symptom onset.[5] CK can be mildly elevated, with the highest reported CK being 894.[5] Antibodies have been found in some cases and include anti-sulfatide antibodies (five patients; two titers reported at 10,350 IU/L and 4,521 IU/L), anti-GD1b antibodies (three patients), anti-myelin-associated glycoprotein (anti-MAG) IgG (one patient), anti-sulfo-glucuronyl paragloboside (SGPG) IgG (one patient), antinuclear antibodies (two patients; one titer reported at 1:100), and anti-Ro antibodies (one patient).[1,6,9,19,20]

Four patients have been found to have TAR-DNA binding protein (TDP-43) inclusions on autopsy.[4,12,20,21] There are two cases with autopsy showing no inclusions.[1,9] TDP-43 inclusions have been found at various locations, but all have included the cervical spinal cord motor neurons. Genetic variants that have been found in FOSMN patients include: TARDBP (three patients), OPMD (one patient), D90A-SOD1 (one patient), CHCHD10 (one patient), VCP (one patient), and SQSTM1 (one patient).[9,10,17,22,23]

Sural nerve biopsy has revealed loss of myelinated fibers and Wallerian degeneration without inflammatory cell infiltrates, evidence of vasculitis, or amyloid deposition.[1,10,24] Skin biopsy has shown decreased intraepidermal nerve fiber density with severe myelinated fiber involvement but sparing of unmyelinated fibers.[10,13,25]

For treatment of patients with FOSMN, there are no FDA-approved therapies. However, clinicians have trialed IVIg and other immunomodulatory therapies. Knopp et al. presented a case of a patient with FOSMN and positive low titer ANA (1:100) and anti-Ro antibodies who had improvement in swallowing, speech, and lower extremity strength with IVIG.[6] Fluchere et al. described a case of FOSMN who had transient improvement in bulbar symptoms. However, her symptoms eventually deteriorated, and she died of aspiration pneumonia before being able to have a PEG placed.[18] Hokonohara et al. described a patient with FOSMN who received IVIg and had resultant improvement in paresthesias of his face and fingers, masticatory and tongue strength, swallowing, and increased SNAP amplitudes of the median and ulnar nerves. He had improvement for two weeks after treatment but worsened after this.[16] Sonoda et al. described a FOSMN case with anti-sulfoglucuronyl paragloboside (SGPG) IgG and anti-myelin-associated glycoprotein (MAG) IgG antibodies who received IVIg and had transient improvement in facial strength and paresthesias.[20] Cruccu et al. trialed IVIg on four patients with FOSMN and two had subjective improvement but no improvement in clinical or neurophysiological status.[24] Watanabe et al. reported three additional cases with partial improvement from IVIg, with all three cases having improvement in their sensory symptoms.[26]

Discussion

Clinical Presentation

FOSMN is a rare disorder that presents with initial sensory loss in the trigeminal nerve distribution that progresses rostro-caudally, along with weakness that progresses in a similar manner and involves the bulbar, neck and upper extremities. There is typically an absent corneal reflex and lower motor neuron findings on exam, however, upper motor neuron findings can be present as well. Taste can be affected and neuronal loss and reactive astrocytes with TDP-43 inclusions have been revealed in the solitary nucleus, potentially explaining this.[1] FOSMN can lead to severe dysphagia requiring PEG tube placement, and potentially lead to severe weight loss, aspiration pneumonia, and/or death.

Pathogenesis

The pathogenesis of FOSMN is an area of debate with neurodegeneration and autoimmunity at the forefront of potential hypotheses. However, over the years, evidence continues to build towards a primary neurodegenerative process. Previous neuropathological studies by Vuvic et al. have shown neurodegenerative changes without inflammation.[1,9] There have been few cases with response to immunomodulatory therapy, and these have not generally been sustained responses. The progressive disease course is also more typical of a neurodegenerative disorder. Furthermore, similarities between FOSMN and ALS patients have been described. Both conditions have a male predominance. Although FOSMN starts with sensory symptoms, motor symptoms become most prominent. Corneal confocal microscopy has interestingly revealed a corneal small fiber sensory neuropathy in ALS patients as well, and anatomical damage was related to bulbar function disability scores.[7] The progression of worsening dysphagia leading to PEG tube placement and death from aspiration pneumonia or respiratory failure can be a very similar progression between the disorders. Although upper motor neuron signs are rare, they can occur in FOSMN. Our patient had thenar atrophy, similar to the split hand sign seen in ALS. Cervical cord atrophy, frontotemporal atrophy, and the "bright tongue sign" are radiographic findings that can be seen in both FOSMN and ALS. CK can be normal to moderately elevated. Furthermore, at least five patients with FOSMN have been diagnosed with behavioral variant frontotemporal dementia and met Rascovsky criteria, suggesting that there may be a continuum with FTD.[5,15] TARDBP and SQSTM1 variants, which have been previously reported as causal in ALS and FTD and encode

Table 1: Characteristics of patients with FOSMN

	n (%)	n tested out of
Patients	**100**	
Male	**75 (75%)**	**100**
Mean age of onset (years)	**54.5**	
Onset with facial sensory symptoms	**83 (93%)**	**89**
Onset with loss of taste	**5**	
Bulbar symptoms	**97 (97%)**	**100**
Family history of ALS	**5**	
Patients diagnosed with bvFTD	**5**	
Upper motor neuron findings	**23**	
PEG placement	**17 (27%)**	**62**
Average time of symptom onset to PEG (years)	**2.3**	
Tracheostomy placement	**1**	
Time of symptom onset to tracheostomy (years)	**3**	
Patients with positive antibodies	**13**	
Patients with negative genetic testing for Kennedy's disease	**23**	
Neuroimaging findings Cervical cord atrophy Frontotemporal atrophy Bright tongue sign	 **8** **1** **3**	
EMG/NCS R1 abnormality R2 abnormality Bilateral R2 abnormality SNAPs reduced Neurogenic changes in bulbar or cervical muscles	 **43 (77%)** **56** **47 (82%)** **26** **23**	 **56** **57** **57**
Patients trialed on IVIg	**42**	
Patients with partial or transient improvement from IVIg	**11 (26%)**	**42**
Causes of death Respiratory failure Bulbar weakness/ aspiration pneumonia Pulmonary embolus Lung cancer Sepsis Traumatic head injury	 **11** **7** **1** **1** **1** **1**	
Average symptom onset to death (years)	**7**	

The last column represents the total amount of cases where reports mentioned either a positive or negative finding (not all reports mentioned what we were evaluating). If there is not a value in the last column, this means the number in the middle column is the total number that was mentioned, and other reports did not mention a positive or negative finding.

for TDP-43 proteins, have been reported in one patient with FOSMN.[17] A D90A-SOD1 variant has been reported in FOSMN as well.[10] Four FOSMN patients have been found to have TDP-43 inclusions on autopsy and all involved the cervical spinal motor neurons.[21]

Despite evidence to suggest that FOSMN is a neurodegenerative disorder similar to ALS, there is further hesitancy to classify this disease within the ALS-FTD spectrum. TMS studies have not shown cortical hyperexcitability in FOSMN, as they have in ALS.[9] There are no Bunina bodies on neuropathological examination in patients with FOSMN, which are classically seen in ALS.[1,9] The blink reflex is almost always abnormal in FOSMN, whereas it is not typically abnormal in ALS.

EMG/NCS

Almost all patients have an abnormal blink reflex. In previous studies that have mentioned the R2 value, almost all patients had a delayed or absent R2 response and a large proportion had bilateral R2 abnormalities. R1 abnormalities were found less frequently than R2 abnormalities, but still at a very high rate. This indicates that there may be an abnormality within the spinal trigeminal tract or nucleus in the medulla. Previous pathological studies have correlated with this as well and have found neuronal loss with reactive gliosis in the spinal trigeminal nucleus and tract.[1,9] Of note, this is near the solitary nucleus of the medulla, which as previously mentioned, may be involved in patients' loss of taste. This is also in line with nearby cervical cord atrophy findings that can be seen on MRI. Other common findings on EMG include decreased SNAPs and neurogenic changes in bulbar or cervical muscles. One of our patients had abnormal decrement on RNS, and this has been reported before.[27] This may be due to denervation and reinnervation changes, but further studies could be done to further elucidate these findings.

Treatment

IVIg has been trialed as a treatment approach due to a potential inflammatory component to the disease. There are 11 reported cases with transient or partial response to IVIg. In these cases, at least five patients had some improvement in facial sensory symptoms. IVIg has generally not been shown to prevent progression of weakness or bulbar symptoms. Of note, autoimmune disorders, such as Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis and mixed connective tissue disease can be associated with bilateral trigeminal neuropathy and other cranial neuropathies.[28,29] As there are alternative, treatable conditions, it is crucial to rule these disorders out. Other differential diagnoses include Kennedy's disease, Tangier disease, neurosarcoidosis, amyloidosis, syringomyelia, and Fabry's disease.

There are currently no FDA-approved treatments for FOSMN. Based on the current literature, it may be reasonable to have a discussion with the patient about trialing IVIg if the sensory symptoms are burdensome, but with the knowledge that it will not likely stop disease progression or alleviate bulbar, neck or upper extremity weakness. Since FOSMN appears to have some clinical and pathological similarities to ALS, use of medications known to slow ALS progression could also be trialed in FOSMN patients. As FOSMN patients share similar variants with ALS patients, similar treatments such as antisense oligonucleotide therapies could be targeted at these.

Conclusion

FOSMN is a diagnosis that was first described in 2006 and at least 100 cases have since been reported. We have been able to identify patients with this disease clinically and through exam, but there are currently no standardized criteria for diagnosis. Further clarifying the pathogenesis, social risk factors, behavioral and cognitive changes, abnormalities in diagnostic tests, and associated genetic variations can help lead to better treatment targets and our ability to identify potential biomarkers to predict prognosis.

Acknowledgements

The authors would like to express their gratitude to the patients who contributed to this study. There was no funding for this project.

Corresponding Author

Jonathan Morena, DO
535 E 70th St.
New York, NY 10021
330-546-6168
Jonmorena21@gmail.com

Disclosures

Jonathan Morena, Hera Kamdar, Rabia Yasin, J. Chad Hoyle, Adam Quick, and Stephen Kolb report no conflicts of interest. There was no funding received for this work.

This work has been formally presented at the AANEM conference on September 22, 2022, in Nashville, TN.

References

1. Vucic S, Tian D, Chong PS, Cudkowicz ME, Hedley-Whyte ET, Cros D. Facial onset sensory and motor neuronopathy (FOSMN syndrome): a novel syndrome

in neurology. *Brain*. Dec 2006;129(Pt 12):3384-90. doi:10.1093/brain/awl258

2. Zheng Q, Chu L, Tan L, Zhang H. Facial onset sensory and motor neuronopathy. *Neurol Sci*. Dec 2016;37(12):1905-1909. doi:10.1007/s10072-016-2686-7

3. Karakis I, Vucic S, Srinivasan J. Facial onset sensory and motor neuronopathy (FOSMN) of childhood onset. *Muscle Nerve*. Oct 2014;50(4):614-5. doi:10.1002/mus.24299

4. Rossor AM, Jaunmuktane Z, Rossor MN, Hoti G, Reilly MM. TDP43 pathology in the brain, spinal cord, and dorsal root ganglia of a patient with FOSMN. *Neurology*. 02 26 2019;92(9):e951-e956. doi:10.1212/WNL.0000000000007008

5. Broad R, Leigh PN. Recognising facial onset sensory motor neuronopathy syndrome: insight from six new cases. *Pract Neurol*. Aug 2015;15(4):293-7. doi:10.1136/practneurol-2014-000984

6. Knopp M, Vaghela NN, Shanmugam SV, Rajabally YA. Facial onset sensory motor neuronopathy: an immunoglobulin-responsive case. *J Clin Neuromuscul Dis*. Jun2013;14(4):176-9.doi:10.1097/CND.0b013e31828ee8fe

7. Ferrari G, Grisan E, Scarpa F, et al. Corneal confocal microscopy reveals trigeminal small sensory fiber neuropathy in amyotrophic lateral sclerosis. *Front Aging Neurosci*. 2014;6:278. doi:10.3389/fnagi.2014.00278

8. Wimmer T, Schreiber F, Hensiek N, et al. The upper cervical spinal cord in ALS assessed by cross-sectional and longitudinal 3T MRI. *Sci Rep*. 02 04 2020;10(1):1783. doi:10.1038/s41598-020-58687-z

9. Vucic S, Stein TD, Hedley-Whyte ET, et al. FOSMN syndrome: novel insight into disease pathophysiology. *Neurology*. Jul 03 2012;79(1):73-9. doi:10.1212/WNL.0b013e31825dce13

10. Dalla Bella E, Rigamonti A, Mantero V, et al. Heterozygous D90A-SOD1 mutation in a patient with facial onset sensory motor neuronopathy (FOSMN) syndrome: a bridge to amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*. Sep 2014;85(9):1009-11. doi:10.1136/jnnp-2013-307416

11. Ohashi N, Nonami J, Kodaira M, Yoshida K, Sekijima Y. Taste disorder in facial onset sensory and motor neuronopathy: a case report. *BMC Neurol*. Feb 29 2020;20(1):71. doi:10.1186/s12883-020-01639-x

12. Ziso B, Williams TL, Walters RJ, et al. Facial Onset Sensory and Motor Neuronopathy: Further Evidence for a TDP-43 Proteinopathy. *Case Rep Neurol*. 2015 Jan-Apr 2015;7(1):95-100. doi:10.1159/000381944

13. Dalla Bella E, Lombardi R, Porretta-Serapiglia C, et al. Amyotrophic lateral sclerosis causes small fiber pathology. *Eur J Neurol*. Feb 2016;23(2):416-20. doi:10.1111/ene.12936

14. Pinto WBVR, Naylor FGM, Chieia MAT, de Souza PVS, Oliveira ASB. New findings in facial-onset sensory and motor neuronopathy (FOSMN) syndrome. *Rev Neurol (Paris)*. Apr 2019;175(4):238-246. doi:10.1016/j.neurol.2018.04.010

15. de Boer EMJ, Barritt AW, Elamin M, et al. Facial Onset Sensory and Motor Neuronopathy: New Cases, Cognitive Changes, and Pathophysiology. *Neurol Clin Pract*. Apr 2021;11(2):147-157. doi:10.1212/CPJ.0000000000000834

16. Hokonohara T, Shigeto H, Kawano Y, Ohyagi Y, Uehara M, Kira J. Facial onset sensory and motor neuronopathy (FOSMN) syndrome responding to immunotherapies. *J Neurol Sci*. Dec 15 2008;275(1-2):157-8. doi:10.1016/j.jns.2008.07.021

17. Vázquez-Costa JF, Pedrola Vidal L, Moreau-Le Lan S, et al. Facial onset sensory and motor neuronopathy: a motor neuron disease with an oligogenic origin? *Amyotroph Lateral Scler Frontotemporal Degener*. 05 2019;20(3-4):172-175. doi:10.1080/21678421.2019.1582671

18. Fluchere F, Verschueren A, Cintas P, et al. Clinical features and follow-up of four new cases of facial-onset sensory and motor neuronopathy. *Muscle Nerve*. Jan 2011;43(1):136-40. doi:10.1002/mus.21884

19. Dobrev D, Barohn RJ, Anderson NE, et al. Facial onset sensorimotor neuronopathy syndrome: a case series. *J Clin Neuromuscul Dis*. 09 2012;14(1):7-10. doi:10.1097/CND.0b013e31825f82b3

20. Sonoda K, Sasaki K, Tateishi T, et al. TAR DNA-binding protein 43 pathology in a case clinically diagnosed with facial-onset sensory and motor neuronopathy syndrome: an autopsied case report and a review of the literature. *J Neurol Sci*. Sep 15 2013;332(1-2):148-53. doi:10.1016/j.jns.2013.06.027

21. Agirre-Beitia G, Moreno-Estébanez A, González-Pinto González T, et al. FOSMN: A possible TDP-43 proteinopathy to consider in a patient with facial sensory symptoms. *Neurol Clin Pract*. Oct 2020;10(5):e47-e50. doi:10.1212/CPJ.0000000000000753

22. Pinto WBVR, Debona R, Nunes PP, et al. Atypical Motor Neuron Disease variants: Still a diagnostic challenge in Neurology. *Rev Neurol (Paris)*. Apr 2019;175(4):221-232. doi:10.1016/j.neurol.2018.04.016

23. Zhang Q, Cao B, Chen Y, et al. Facial Onset Motor and Sensory Neuronopathy Syndrome With a Novel TARDBP Mutation. *Neurologist*. Jan 2019;24(1):22-25. doi:10.1097/NRL.0000000000000201

24. Cruccu G, Pennisi EM, Antonini G, et al. Trigeminal isolated sensory neuropathy (TISN) and FOSMN

syndrome: despite a dissimilar disease course do they share common pathophysiological mechanisms? *BMC Neurol*. Dec 19 2014;14:248. doi:10.1186/s12883-014-0248-2

25. Truini A, Provitera V, Biasiotta A, et al. Differential trigeminal myelinated and unmyelinated nerve fiber involvement in FOSMN syndrome. *Neurology*. Feb 03 2015;84(5):540-2. doi:10.1212/WNL.0000000000001216

26. Watanabe M, Shiraishi W, Yamasaki R, et al. Oral phase dysphagia in facial onset sensory and motor neuronopathy. *Brain Behav*. 06 2018;8(6):e00999. doi:10.1002/brb3.999

27. Yamamoto D, Yamada M, Cao B, Suzuki S, Hisahara S, Shimohama S. [A case of facial-onset sensory and motor neuronopathy (FOSMN) with cerebellar ataxia and abnormal decrement in repetitive nerve stimulation test]. *Rinsho Shinkeigaku*. Feb 23 2021;61(2):115-119. doi:10.5692/clinicalneurol.cn-001508

28. Lecky BR, Hughes RA, Murray NM. Trigeminal sensory neuropathy. A study of 22 cases. *Brain*. Dec 1987;110 (Pt 6):1463-85. doi:10.1093/brain/110.6.1463

29. Mori K, Iijima M, Koike H, et al. The wide spectrum of clinical manifestations in Sjögren's syndrome-associated neuropathy. *Brain*. Nov 2005;128(Pt 11):2518-34. doi:10.1093/brain/awh605

CD20-mediated B cell depletion in acetylcholine receptor autoantibody-positive myasthenia gravis

Panagiotis Kanatas, MD[1], Kevin C O'Connor, PhD[2], Panos Stathopoulos, MD PhD[1*]

[1]First Department of Neurology, School of Medicine, National Kapodistrian University of Athens, Greece
[2]Departments of Neurology and Immunobiology, School of Medicine, Yale University.
[*]Corresponding author,
e-mail: panosst@eginitio.uoa.gr;
pmstathopoulos@gmail.com.

ABSTRACT

Myasthenia gravis (MG) is an autoimmune disorder characterized by muscle weakness and fatigue, mediated in the majority of cases by IgG1 autoantibodies targeting the acetylcholine receptor (AChR). As AChR autoantibodies have been shown to be pathogenic, therapies targeting B cells have been applied in patients with AChR MG for more than a decade. Recently, a phase 2 trial of the CD20-targeting agent, rituximab, in AChR MG unfortunately failed to meet its primary endpoint. Converging data however from non-randomized clinical series, some of which with more participants than the phase 2 trial, as well as a randomized trial in new onset disease support efficacy of rituximab in AChR MG, especially early onset disease. In this opinion article, we summarize both clinical data and mechanistic principles on the use of CD20 depletion therapy in AChR MG, which we believe lend support to the argument that CD20 depletion can still be a useful therapeutic strategy for patients with AChR MG.

Key words: acetylcholine receptor (AChR), myasthenia gravis, autoantibody, rituximab, muscle specific kinase (MuSK).

Introduction

Myasthenia gravis (MG) is an autoimmune disorder characterized by muscle weakness and fatigability, most commonly mediated by autoantibodies targeting extracellular components of the neuromuscular junction (NMJ), the acetylcholine receptor (AChR), muscle-specific kinase (MuSK), and low-density lipoprotein receptor–related protein 4 (LRP4) [1]. Serum AChR antibodies are found in up to 85% of MG cases and AChR MG can initiate as ocular with involvement limited to ophthalmic muscles [2,3]; early onset AChR MG is associated with thymic hyperplasia. MuSK MG is associated with bulbar symptoms (e.g. dysarthria, dysphagia), lack of thymic involvement, resistance to symptomatic treatment with pyridostigmine and an excellent response to CD20 B cell depletion, thus underlining mechanistic differences between AChR and MuSK MG [3–8]. In general, therapies of MG include symptomatic treatment with cholinesterase inhibitors in the case of AChR MG [9], and immunotherapy. In life-threatening myasthenic crises, where respiratory muscles can be affected, acute therapy includes intravenous immunoglobulin and plasma exchange [10]. Chronic immunotherapy can be divided into broadly-acting immunosuppressants such as corticosteroids [11], and non-steroid immunosuppressants (azathioprine, mycophenolate, methotrexate, cyclosporine or tacrolimus) [12–16]; and targeted immunosuppression with CD20-mediated B cell depletion, inhibition of the complement pathway, and antagonists of the neonatal Fc receptor [17,18]. Finally, thymectomy has been shown to be moderately effective in a phase 3 trial and can be considered in young patients with non-thymomatous AChR MG [19].

Pathophysiology

MG is a prototypic antibody-mediated autoimmune disease. Different mechanisms underlie the presence of AChR and MuSK autoantibodies, and these autoantibodies do not typically co-occur [20]. The more prevalent AChR autoantibodies are predominantly of the IgG1 subclass and can: 1. block the acetylcholine binding site on the receptor, 2. cross-link the receptor leading to its internalization, and 3. activate complement-dependent cytotoxicity (CDC) as well as antibody-dependent cytotoxicity (ADCC) [21]. Activation of complement leads to formation of the membrane attack complex that both damages and reduces the surface area of the post-synaptic membrane, thereby decreasing the density of AChR molecules and voltage-gated sodium channels, and hence, the amplitude of endplate potentials and the efficiency of the neuromuscular transmission.

The majority of AChR autoantibody-seronegative MG patients produce antibodies against MuSK, which is found in the post-synaptic membrane of the NMJ, along with AChR. MuSK is part of the agrin-induced pathway leading to clustering of AChRs and associated synaptic differentiation, consequently its targeting by autoantibodies results in impaired AChR clustering and affects NMJ function causing MG symptoms [22]. MuSK autoantibodies are mainly of the IgG4 subclass. Characteristics of IgG4 antibodies include Fab-arm exchange, functional monovalency resulting in

a lack of ability to cross-link the antigen, and a limited ability to initiate complement and ADCC [23,24]. These characteristics notwithstanding, MuSK autoantibodies are pathogenic (just like AChR autoantibodies), as shown by passive transfer and active immunization studies in laboratory animals [25].

One particular feature of the immunopathology of autoantibody-mediated disorders (including MG) is varying longevity of the cells producing the pathogenic autoantibodies [26,27]. In AChR MG, cultured bone marrow cells produced higher concentrations of AChR autoantibodies compared to lymphocytes in the peripheral blood, thymus, and lymph node, thus providing direct evidence for long-lived plasma cell (LLPC) involvement in autoantibody production, as these typically reside in the bone marrow. Moreover, the presence of germinal centers in the thymus of early onset AChR MG patients underscores their ability to produce AChR-specific LLPCs, as these are commonly the products of germinal center reactions. In MuSK MG however, autoantibody-secreting B cells appear to be much shorter-lived: depletion of their immediate progenitors, CD20+ memory cells, is succeeded by a rapid decline of mostly CD20- short-lived autoantibody-producing cells (termed plasmablasts) and, consequently, a rapid decline in MuSK autoantibody titers, as observed in MuSK-MG patients treated with rituximab [28–31].

CD20-specific monoclonal antibodies as a therapeutic strategy in MG

Given the central role of B cells in the pathophysiology of the disease, depleting B cells or suppressing B cell function can target immunopathology and result in clinical improvement. CD20 is a 33-37 kDa transmembrane protein that regulates calcium influx and thereby signaling pathways involved in B cell differentiation into antibody-secreting cells [32]. It is expressed during several stages of B-cell maturation (**Figure 1**), i.e. in pre-B cells and mature B cells, not including stem cells and plasma cells, and is therefore an attractive target for monoclonal antibody-based therapy [33]. B cells targeted by CD20-specific monoclonal antibodies are eliminated via three main mechanisms: programmed cell death/apoptosis, complement-dependent cytotoxicity (CDC), or antibody-dependent cellular cytotoxicity (ADCC) [34]. Rituximab is a 1st generation chimeric monoclonal antibody (IgG1κ), engineered by fusing a murine Fab with a human Fc domain [35]. Its elimination half-time is estimated to be 20 days, which may vary according to sex, body weight and renal function.

CD20-mediated B cell depletion in AChR MG

Several early, uncontrolled mostly retrospective studies support the safety and efficacy of rituximab in AChR autoantibody-seropositive MG [36–41,28,42–60] (**Table 1**). Patients were typically followed for 6, 12 or even 24 months, and were evaluated both clinically, with the use of scales such as the Myasthenia Gravis Foundation of America–post-intervention status (MGFA-PIS), the quantitative MG (QMG) score, the manual muscle testing (MMT) score, as well as serologically. These collective studies demonstrated clinical improvement and either stability or mild decline in AChR autoantibody titers, and all studies confirmed that rituximab is a safe and well-tolerated therapeutic strategy. Several of these uncontrolled studies included more than 15 patients without producing different results than the smaller studies [43,44,49,53,55,56].

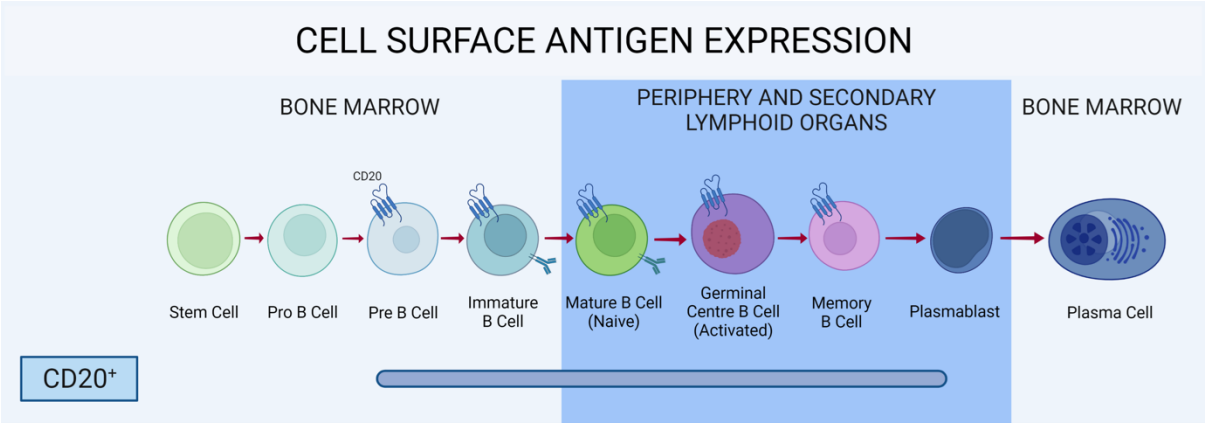


Figure 1. Expression of cell surface antigens through B cell maturation. CD20 is not present on plasma cells, pro B-cells and stem cells (plasmablasts being CD20+/-). Figure created with Biorender.com.

Table 1. Studies of CD20-mediated B cell depletion in AChR MG.

AUTHOR	YEAR	N	TYPE OF STUDY	MAIN OUTCOMES
Piehl et al. [65]	2022	45	RCT (vs. placebo), double-blind, phase 2	QMG score <4 in 71% of treated patients (p=0.007)
Heckmann [60]	2022	10	Retrospective, uncontrolled	70% of patients reduced prednisone
Castiglione et al. [59]	2022	8	Retrospective, uncontrolled	No relapses during at least 24 months of follow-up
Nelke et al. [62]	2022	57	Retrospective controlled (vs. eculizumab)	Unchanged QMG in patients receiving RTX at 24 months. Both treatments reduced daily prednisone similarly after 24 months (P=0.89)
Du et al. [58]	2022	13	Retrospective, uncontrolled	All patients achieved a MGFA-PIS of minimal manifestations
Ramdas et al. [57]	2022	8	Retrospective, uncontrolled	60% of patients achieved stable remission.
Nowak et al. [66]	2021	52	RCT (vs. placebo), double-blind, phase 2	60% of patients on RTX achieved a steroid-sparing effect, as compared to 56% in the placebo arm (p=ns)
Doughty et al. [56]	2021	28	Retrospective, uncontrolled	68% of patients (that were all >65) achieved a MGFA-PIS of minimal manifestations
Brauner et al. [61]	2020	60	Retrospective, controlled (several subgroups, early vs. late RTX)	76% of patients receiving RTX achieved a QMG score of 2 or lower. Shorter time to remission for RTX in early onset vs. refractory MG (p=0.009).
Dos Santos et al. [55]	2020	20	Prospective, uncontrolled	90% of patients achieved a MGFA PIS of I or better.
Sahai et al. [54]	2020	7	Retrospective, uncontrolled	All 7 late-onset MG patients significantly reduced or discontinued maintenance medications.
Litchman et al. [53]	2020	17	Retrospective, uncontrolled	70.6% of patients achieved clinical remission-
Lu et al. [52]	2020	12	Prospective, uncontrolled	Median decrease in QMG score from 18.3 (baseline) to 8.4 (P <0.001)
Roda et al. [51]	2019	10	Retrospective, uncontrolled	80% of refractory patients reduced their steroid dosage by 9.6mg on average
Choi et al. [50]	2019	9	Retrospective, uncontrolled	65% of patients achieved a MGFA-PIS of minimal manifestations or better
Topakian et al. [49]	2019	39	Retrospective, uncontrolled	35.9% of patients achieved clinical remission
Jing et al. [48]	2019	14	Retrospective, uncontrolled	Mean decrease in QMG score by 6.6
Singh et al. [47]	2019	6	Retrospective, uncontrolled	All patients achieved a MGFA-PIS of at least minimal manifestations-2.
Beecher et al. [46]	2018	10	Prospective, uncontrolled	Mean MMT score reduction from 10.3 to 5.5 (P = 0.018)
Landon-Cardinal et al. [45]	2018	12	Retrospective, uncontrolled	2 patients presented an improvement of >18 points on MMS at 12-months. 55% of patients improved their MGFA-PIS
Robeson et al. [44]	2017	16	Retrospective, uncontrolled	63% of patients achieved complete stable remission
Afanasiev et al. [43]	2017	21	Retrospective, uncontrolled	Mean improvement of MMS by 74.5 (p <0.001) vs. baseline
Peres et al. [42]	2017	4	Retrospective, uncontrolled	Mean decrease in MGCS by 53% (p<0.05) vs. baseline
Diaz-Manera et al. [28]	2012	11	Retrospective, uncontrolled	91% of patients achieved an improved MGFA-PIS. Decrease in the average dose of prednisone by 13.3 mg/day
Collongues et al. [41]	2012	8	Retrospective, uncontrolled	Decrease of annualized relapse rate from 2.1 to 0.3 (P < 0.001) vs. baseline.
Nowak et al. [40]	2011	6	Retrospective, uncontrolled	Reduction of mean daily prednisone by 65.1%, 85.7%, and 93.8% after cycle 1, 2, and 3, respectively and of PLEX sessions (all p values<0.05)
Blum et al. [39]	2011	11	Retrospective, uncontrolled	79% of patients achieved an improved MGFA-PIS
Maddison et al. [38]	2011	7	Retrospective, uncontrolled	42.9% of patients achieved an improved MGFA-PIS
Lindberg et al. [37]	2010	5	Retrospective, uncontrolled	Median decrease of 13 in QMG score
Illa et al. [36]	2008	3	Retrospective, uncontrolled	All patients achieved an improved MGFA-PIS

AChR, acetylcholine receptor; MG, myasthenia gravis; MGFA-PIS, Myasthenia Gravis Foundation of America – post-intervention status; MM, minimal manifestation; QMG, quantitative MG; MMT, manual muscle testing; MMS, myasthenic muscle score; MGCS, Myasthenia Gravis Composite Score; MG-ADL, Myasthenia Gravis Activity of Daily Life; MG-QoL, Myasthenia Gravis Quality of Life; RTX, rituximab; ns, non-significant.

Uncontrolled studies were followed by two nonrandomized retrospective controlled ones. Of those, the first examined timing of rituximab therapy MG (early administration i.e. within one year of disease onset versus later administration). Several subgroups were examined (early administration, late administration in immunotherapy naïve patients, late administration in refractory patients, and conventional immunotherapy). Differences were more pronounced when comparing early administration of rituximab with later administration in patients that were refractory to conventional immunosuppression. In this setting, median time to remission was significantly shorter when rituximab was applied early (7 versus 16 months). Apart from that however, when rituximab-treated patients were examined as one group, they fared better than patients not treated with rituximab [61]. The second retrospective controlled study compared rituximab with eculizumab, the complement C5 inhibitor approved for the treatment of AChR MG [62–64]. Although eculizumab was more effective in improving the clinical status (achieving, in contrast to rituximab, a reduction in QMG after 24 months; and a greater proportion of patients with minimal manifestations-36.9% versus 12.7% with rituximab), both groups were able to reduce thee mean prednisone daily dosage similarly. Of interest, both drugs were safe and well-tolerated with equal risk of severe infections [62].

As far as rituximab dosing is concerned, the more common induction protocols that have been used include the lymphoma induction protocol (a dose of 375 mg/m^2 repeated four times at weekly intervals, considered as one cycle of treatment) [72] and the rheumatoid arthritis induction protocol (two infusions of 1000 mg each, 15 days apart) [73], however different centers have applied slightly different versions ranging from more intense regimens (e.g. two cycles of 4 x 375/m^2 6 months apart) to lower dosing and frequency regimens (e.g. 600 mg at months 0, 6, 12) [74]. Interestingly, a meta-analysis found lower intensity regimens to be equally effective coupled with less side effects, however formal side-to-side control of high versus low rituximab dosages in a prospective randomized study is missing [74]. After the initial induction that can span 6 to 12 months, rituximab therapy in MG can be repeated if clinically necessary or at regular intervals (6 months or yearly). Of note, in multiple sclerosis and aquaporin 4 autoantibody-positive neuromyelitis optica spectrum disorders, CD20 depletion therapy is usually administered every six months and a prolonged CD20 B cell depletion status is maintained indefinitely, often at the cost of late hypogammaglobulinemia and infection [75]. In MG, rituximab side effects were reported in less than 20% of the patients and mainly concerned infusion-related reactions and treatable infections, such as pneumonia and herpes reactivation, while hematological reactions such as cytopenia were rare [67,69,70]. Progressive multifocal leukoencephalopathy was reported in only one patient [43].

The positive effect described in the many case series and prospective open-label studies was challenged by the result of a recent phase 2 randomized controlled trial (BeatMG – NCT02110706) that consisted of 52 mild to moderately symptomatic AChR MG patients. The patients were on prednisone with or without additional immunosuppressants prior to study entry and received two cycles of rituximab (lymphoma protocol), six months apart. The study failed to meet its primary endpoints (at the end of the one-year follow up), which were a significant reduction in daily prednisone dose as well as clinical stabilization or improvement of the neurological status as assessed by the standardized scale MG composite [66]. It is however noteworthy that a post-hoc analysis showed that the patients in the rituximab arm suffered fewer relapses than patients in the placebo arm.

A thorough examination of BeatMG trial data may shed light on the factors that contributed to the negative primary outcome [76,77]: First, recruited patients had relatively mild disease, which may have precluded significant rituximab treatment-related therapeutic effects. Second, recruited patients were possibly overtreated, as prednisone had to be titrated to a stable dose prior to study initiation. The large placebo effect that was seen, i.e. improvement in patients not treated with rituximab, supports this hypothesis. Moreover, steroids lower lymphocyte count, including B cells, and may mask rituximab-associated therapeutic effect. Third, the study may have been too short (one year) to observe measurable differences [78,79]. Fourth, the primary study endpoint may have not captured the rituximab effect well (compared e.g. to a minimal manifestations post-intervention status).

In contrast to BeatMG, RINOMAX, another phase 2, randomized controlled trial (NCT02950155) that tested the efficacy of a single 500 mg rituximab infusion as an add-on induction treatment to the standard of care in 25 adult patients with early onset AChR MG (verssus 22 patients receiving placebo), succeeded in achieving a significant difference in its primary endpoint, minimal disease manifestations at week 16, as defined by QMG of <4 with daily prednisone of 10mg or less [65]. Indeed, 17 of 24 rituximab-treated patients achieved a QMG score of 4 with no need of rescue treatment, as compared to 6 of 21 in the placebo arm (p=0.007) [65]. Finally and in addition to all of the above described trials and case series, the beneficial effect of rituximab in AChR MG has been confirmed by several systematic reviews and meta-analyses of these studies, with the magnitude of the response rate however ranging widely from 30% to 80% (**Table 2**) [67–71].

Table 2. Systematic reviews and meta-analyses of CD20-mediated B cell depletion in AChR MG.

AUTHOR	YEAR	STUDIES	PATIENTS	RESPONSE RATE
Zhao et al. [67]	2021	45	91	64%
Bastakoti et al. [68]	2021	29	N/A	N/D
Di Stefano et al. [69]	2020	13	165	68%
Tandan et al. [70]	2017	47	99	30%
Iorio et al. [71]	2015	24	91	80.4%

N/A, not applicable; N/D, not done.

Mechanistically, rituximab does not directly target the long-lived plasma cells (LLPC) that contribute to production of AChR autoantibodies, but it can kill memory B cells and may therefore prevent the formation of new AChR-specific plasma cells that arise from continued autoantigenic stimulation and ongoing germinal center reactions [26,80,81]. Therefore, it is possible that two rituximab treatment cycles in established disease are insufficient (as in the BeatMG study), and follow-up period of one year does not capture the clinical benefits of the therapy [82]. Possibly in the same context, the recent retrospective controlled study that compared early and late administration of rituximab demonstrated that clinical improvement manifested faster with early administration, perhaps because less LLPCs have formed in early disease [61]. The positive RINOMAX trial results, where recent onset patients were randomized to one-off rituximab add-on administration, also support this conclusion of less LLPC presence in early disease. In refractory MG with long disease duration, it might be the case that more rituximab cycles are required over a longer period of time due to the presence of more LLPCs in the bone marrow. If this is true one would have to preserve a CD20-depleted state and prevent generation of new autoantibody-producing cells while waiting for the persistent clones to be eliminated. Accordingly, this result might be achieved faster with CD19 depletion, found to be effective in the immunologically similar neuromyelitis optica spectrum disorders [83], however its long-term safety is yet untested. CD19-mediated B cell depletion therapy (with CD19-specific monoclonal antibodies and CD19-specific chimeric antigen receptor T cells) could both target a larger fraction of antibody-secreting cells (compared to CD20), and additionally target pathogenic CD20-negative memory B cells resistant to CD20-mediated depletion [81]. Another explanation however for the diminished effect of rituximab in MG with long disease duration could be a degree of irreversible deficit of the NMJ in long-duration or refractory MG.

Although there is no definite rule as to which patients and under which conditions will benefit from CD20 depletion with rituximab or other agents, several lines of evidence support its early application in AChR MG. This however should not be interpreted as complete lack of efficacy in late, refractory MG. With specific regard to age, a systematic review showed that younger age (<45 years) was a prognostic factor for better response to CD20 B cell depletion [70], and several further studies have confirmed its efficiency in young [84] and pediatric patients [57,85,86]. On the other hand, two studies have specifically examined the use of rituximab in elderly patients and have shown significant efficacy in this population, thus underscoring that rituximab should not be excluded as an option due to advanced age [54,56]. Dosing of rituximab is also not subject to specific rules, however a reasonable approach could be to use smaller doses when administrating the treatment early in the disease course (based on the RINOMAX trial and the preceding data from Brauner *et al*) [61], and larger and repeated doses in established disease with persistent autoantibody titers, while taking at the same time caution to not depress total IgG levels and therefore increasing susceptibility to infection (based on data on autoantibody titers decreasing more after each cycle of rituximab as shown by Nowak *et al* [40]).

Rituximab in MuSK MG and seronegative MG

Contrary to AChR MG, there is little controversy in regard to application of rituximab in patients with MuSK MG, as they respond impressively to induction therapy, with dramatic improvement, a shorter time to improvement or complete remission, and a long-lasting treatment effect without the need for repetitive dosing [87]. A multicenter, blinded, prospective review, comparing anti-MuSK-positive patients with MG treated with rituximab to those not treated with rituximab showed significantly favorable results in the rituximab arm, hence providing class IV evidence in favor of rituximab use in MuSK MG patients [88]. The clinical difference between MuSK and AChR MG response to B cell depletion is further reflected in autoantibody titers post-rituximab. In contrast to AChR MG titers, almost all patients with MuSK MG receiving rituximab show a rapid (within weeks) and marked decline in MuSK autoantibody titer. Interestingly, the intensity of rituximab induction seems to

be proportionate to the durability of the response of MuSK MG patients [89], however historic clones (not efficiently depleted by CD20-mediated therapy) can reemerge in many cases, even with intense induction, and cause relapse [31,90]. Finally, in seronegative MG, successful application of rituximab in selected cases points to B cell involvement in pathogenesis and to the fact that seronegative MG may be 'false seronegative' due to the sensitivity threshold of autoantibody detection assays [91,92].

Conclusion

Although the response of MuSK MG patients to rituximab is impressive, the treatment should not be dismissed in AChR MG based on the randomized controlled BeatMG trial (NCT02110706) [66]. The combination of trial limitations and abundance of data from uncontrolled case series and retrospective controlled studies including patients with AChR MG successfully treated with rituximab (some of those studies with more patients than the BeatMG trial), and most importantly the recent positive RINOMAX study of early rituximab administration all lend support to the continuation of CD20 depletion application in AChR MG [65]. It seems clear that rituximab can still offer significant help to AChR MG patients given its efficacy, reasonable safety profile, targeted immunosuppression that is relevant to disease mechanisms, and reasonable pricing compared to the newer agents eculizumab and efgartigimod. However, in the aftermath of COVID-19 and given that CD20-mediated B cell depletion increases the risk for severe SARS-CoV-2 infection, caution needs to be applied and vaccination prior to application with all available vaccines is imperative [93].

Funding

KCO is supported by the National Institute of Allergy and Infectious Diseases of the NIH under award numbers R01-AI114780 and R21-AI142198, and through an award provided through the Rare Diseases Clinical Research Consortia of the NIH and MGNet (award number U54-NS115054). PS is supported by research funding from the Onassis Foundation.

Disclosures and competing interests

KCO has received research support from Alexion, now part of AstraZeneca, Viela Bio, now part of Horizon Therapeutics, Cabaletta Bio and Argenx. KCO is an equity shareholder of Cabaletta Bio. During the last two years, KCO has served as consultant/advisor for Alexion Pharmaceuticals, now part of AstraZeneca, and for Roche, and he has received speaking fees from Alexion, Roche, Genentech, Viela Bio, now part of Horizon Therapeutics, and UCB. PS has received travel grants from Sanofi, Roche, Bristol-Mayers-Squibb, and consulting fees from Imcyse and Medicxi. These entities had no role in the development, preparation, review, or approval of the manuscript or the decision to submit the manuscript for publication.

Acknowledgments

The figure was created with Biorender.com. We thank Dr. Richard Nowak for valuable discussions.

References

[1] N.E. Gilhus, Myasthenia Gravis, N. Engl. J. Med. 375 (2016) 2570–2581. https://doi.org/10.1056/NEJMra1602678.

[2] E. Kerty, A. Elsais, Z. Argov, A. Evoli, N.E. Gilhus, EFNS/ENS Guidelines for the treatment of ocular myasthenia., Eur. J. Neurol. 21 (2014) 687–693. https://doi.org/10.1111/ene.12359.

[3] D. Grob, N. Brunner, T. Namba, M. Pagala, Lifetime course of myasthenia gravis: Course of Myasthenia Gravis, Muscle Nerve. 37 (2008) 141–149. https://doi.org/10.1002/mus.20950.

[4] D. Grob, E.L. Arsura, N.G. Brunner, T. Namba, The Course of Myasthenia Gravis and Therapies Affecting Outcome, Ann. N. Y. Acad. Sci. 505 (1987) 472–499. https://doi.org/10.1111/j.1749-6632.1987.tb51317.x.

[5] M.K. Hehir, N.J. Silvestri, Generalized Myasthenia Gravis, Neurol. Clin. 36 (2018) 253–260. https://doi.org/10.1016/j.ncl.2018.01.002.

[6] J.S. Yi, J.T. Guptill, P. Stathopoulos, R.J. Nowak, K.C. O'Connor, B cells in the pathophysiology of myasthenia gravis, Muscle Nerve. 57 (2018) 172–184. https://doi.org/10.1002/mus.25973.

[7] M.J. Thieben, D.J. Blacker, P.Y. Liu, C.M. Harper, E.F.M. Wijdicks, Pulmonary function tests and blood gases in worsening myasthenia gravis, Muscle Nerve. 32 (2005) 664–667. https://doi.org/10.1002/mus.20403.

[8] M. Pasnoor, G.I. Wolfe, S. Nations, J. Trivedi, R.J. Barohn, L. Herbelin, A. McVey, M. Dimachkie, J. Kissel, R. Walsh, A. Amato, T. Mozaffar, M. Hungs, L. Chui, J. Goldstein, S. Novella, T. Burns, L. Phillips, G. Claussen, A. Young, T. Bertorini, S. Oh, Clinical findings in MuSK-antibody positive myasthenia gravis: A U.S. experience, Muscle Nerve. 41 (2010) 370–374. https://doi.org/10.1002/mus.21533.

[9] L. Maggi, R. Mantegazza, Treatment of Myasthenia Gravis: Focus on Pyridostigmine, Clin. Drug Investig. 31 (2011) 691–701. https://doi.org/10.2165/11593300-000000000-00000.

[10] P. Gajdos, S. Chevret, K.V. Toyka, Plasma exchange for generalised myasthenia gravis, Cochrane Database

Syst. Rev. 2011 (2002). https://doi.org/10.1002/14651858.CD002275.

[11] C. Schneider-Gold, P. Gajdos, K.V. Toyka, R.R. Hohlfeld, Corticosteroids for myasthenia gravis, Cochrane Database Syst. Rev. 2011 (2005). https://doi.org/10.1002/14651858.CD002828.pub2.

[12] C. Rodolico, C. Bonanno, T. Brizzi, G. Nicocia, G. Trimarchi, A. Lupica, A. Pugliese, O. Musumeci, A. Toscano, Methotrexate as a Steroid-Sparing Agent in Myasthenia Gravis: A Preliminary Retrospective Study, J. Clin. Neuromuscul. Dis. 23 (2021) 61–65. https://doi.org/10.1097/CND.0000000000000342.

[13] H. Yoshikawa, T. Kiuchi, T. Saida, M. Takamori, Randomised, double-blind, placebo-controlled study of tacrolimus in myasthenia gravis., J. Neurol. Neurosurg. Psychiatry. 82 (2011) 970–977. https://doi.org/10.1136/jnnp-2011-300148.

[14] D.B. Sanders, I.K. Hart, R. Mantegazza, S.S. Shukla, Z.A. Siddiqi, M.H.V. De Baets, A. Melms, M.W. Nicolle, N. Solomons, D.P. Richman, An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis., Neurology. 71 (2008) 400–406. https://doi.org/10.1212/01.wnl.0000312374.95186.cc.

[15] R.S. Tindall, J.T. Phillips, J.A. Rollins, L. Wells, K. Hall, A clinical therapeutic trial of cyclosporine in myasthenia gravis., Ann. N. Y. Acad. Sci. 681 (1993) 539–551. https://doi.org/10.1111/j.1749-6632.1993.tb22937.x.

[16] J. Palace, J. Newsom-Davis, B. Lecky, A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group., Neurology. 50 (1998) 1778–1783. https://doi.org/10.1212/wnl.50.6.1778.

[17] M.C. Dalakas, Progress in the therapy of myasthenia gravis: getting closer to effective targeted immunotherapies., Curr. Opin. Neurol. 33 (2020) 545–552. https://doi.org/10.1097/WCO.0000000000000858.

[18] P. Stathopoulos, M.C. Dalakas, Evolution of Anti-B Cell Therapeutics in Autoimmune Neurological Diseases., Neurother. J. Am. Soc. Exp. Neurother. (2022). https://doi.org/10.1007/s13311-022-01196-w.

[19] G.I. Wolfe, H.J. Kaminski, I.B. Aban, G. Minisman, H.-C. Kuo, A. Marx, P. Ströbel, C. Mazia, J. Oger, J.G. Cea, J.M. Heckmann, A. Evoli, W. Nix, E. Ciafaloni, G. Antonini, R. Witoonpanich, J.O. King, S.R. Beydoun, C.H. Chalk, A.C. Barboi, A.A. Amato, A.I. Shaibani, B. Katirji, B.R.F. Lecky, C. Buckley, A. Vincent, E. Dias-Tosta, H. Yoshikawa, M. Waddington-Cruz, M.T. Pulley, M.H. Rivner, A. Kostera-Pruszczyk, R.M. Pascuzzi, C.E. Jackson, G.S. Garcia Ramos, J.J.G.M. Verschuuren, J.M. Massey, J.T. Kissel, L.C. Werneck, M. Benatar, R.J. Barohn, R. Tandan, T. Mozaffar, R. Conwit, J. Odenkirchen, J.R. Sonett, A. Jaretzki, J. Newsom-Davis, G.R. Cutter, Randomized Trial of Thymectomy in Myasthenia Gravis, N. Engl. J. Med. 375 (2016) 511–522. https://doi.org/10.1056/NEJMoa1602489.

[20] W. Hoch, J. McConville, S. Helms, J. Newsom-Davis, A. Melms, A. Vincent, Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies, Nat. Med. 7 (2001) 365–368. https://doi.org/10.1038/85520.

[21] M.L. Fichtner, R. Jiang, A. Bourke, R.J. Nowak, K.C. O'Connor, Autoimmune Pathology in Myasthenia Gravis Disease Subtypes Is Governed by Divergent Mechanisms of Immunopathology., Front. Immunol. 11 (2020) 776. https://doi.org/10.3389/fimmu.2020.00776.

[22]K. Takata, P. Stathopoulos, M. Cao, M. Mané-Damas, M.L. Fichtner, E.S. Benotti, L. Jacobson, P. Waters, S.R. Irani, P. Martinez-Martinez, D. Beeson, M. Losen, A. Vincent, R.J. Nowak, K.C. O'Connor, Characterization of pathogenic monoclonal autoantibodies derived from muscle-specific kinase myasthenia gravis patients, JCI Insight. 4 (2019) e127167. https://doi.org/10.1172/jci.insight.127167.

[23] M. van der Neut Kolfschoten, J. Schuurman, M. Losen, W.K. Bleeker, P. Martínez-Martínez, E. Vermeulen, T.H. den Bleker, L. Wiegman, T. Vink, L.A. Aarden, M.H. De Baets, J.G.J. van de Winkel, R.C. Aalberse, P.W.H.I. Parren, Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange, Science. 317 (2007) 1554–1557. https://doi.org/10.1126/science.1144603.

[24] M.G. Huijbers, J.J. Plomp, S.M. van der Maarel, J.J. Verschuuren, IgG4-mediated autoimmune diseases: a niche of antibody-mediated disorders: IgG4-mediated autoimmune diseases, Ann. N. Y. Acad. Sci. 1413 (2018) 92–103. https://doi.org/10.1111/nyas.13561.

[25] S. Viegas, L. Jacobson, P. Waters, J. Cossins, S. Jacob, M.I. Leite, R. Webster, A. Vincent, Passive and active immunization models of MuSK-Ab positive myasthenia: Electrophysiological evidence for pre and postsynaptic defects, Exp. Neurol. 234 (2012) 506–512. https://doi.org/10.1016/j.expneurol.2012.01.025.

[26] C. Zografou, A.G. Vakrakou, P. Stathopoulos, Short- and Long-Lived Autoantibody-Secreting Cells in Autoimmune Neurological Disorders, Front. Immunol. 12 (2021) 686466. https://doi.org/10.3389/fimmu.2021.686466.

[27]J.S. Yi, J.T. Guptill, P. Stathopoulos, R.J. Nowak, K.C. O'Connor, B cells in the pathophysiology of myasthenia gravis, Muscle Nerve. 57 (2018) 172–184. https://doi.org/10.1002/mus.25973.

[28] J. Diaz-Manera, E. Martinez-Hernandez, L. Querol, R. Klooster, R. Rojas-Garcia, X. Suarez-Calvet, J.L. Munoz-Blanco, C. Mazia, K.R. Straasheijm, E. Gallardo, C. Juarez, J.J. Verschuuren, I. Illa, Long-lasting treatment effect of rituximab in MuSK myasthenia,

Neurology. 78 (2012) 189–193. https://doi.org/10.1212/WNL.0b013e3182407982.

[29] P. Stathopoulos, A. Kumar, R.J. Nowak, K.C. O'Connor, Autoantibody-producing plasmablasts after B cell depletion identified in muscle-specific kinase myasthenia gravis, JCI Insight. 2 (2017) e94263. https://doi.org/10.1172/jci.insight.94263.

[30] P. Stathopoulos, A. Kumar, J.A.V. Heiden, E. Pascual-Goñi, R.J. Nowak, K.C. O'Connor, Mechanisms underlying B cell immune dysregulation and autoantibody production in MuSK myasthenia gravis: B cell abnormalities in MuSK myasthenia gravis, Ann. N. Y. Acad. Sci. 1412 (2018) 154–165. https://doi.org/10.1111/nyas.13535.

[31] M.L. Fichtner, K.B. Hoehn, E.E. Ford, M. Mane-Damas, S. Oh, P. Waters, A.S. Payne, M.L. Smith, C.T. Watson, M. Losen, P. Martinez-Martinez, R.J. Nowak, S.H. Kleinstein, K.C. O'Connor, Reemergence of pathogenic, autoantibody-producing B cell clones in myasthenia gravis following B cell depletion therapy, Acta neuropathol commun **10**, 154 (2022). https://doi.org/10.1186/s40478-022-01454-0.

[32] T.F. Tedder, A. Forsgren, A.W. Boyd, L.M. Nadler, S.F. Schlossman, Antibodies reactive with the B1 molecule inhibit cell cycle progression but not activation of human B lymphocytes, Eur. J. Immunol. 16 (1986) 881–887. https://doi.org/10.1002/eji.1830160802.

[33] M. Bofill, G. Janossy, M. Janossa, G.D. Burford, G.J. Seymour, P. Wernet, E. Kelemen, Human B cell development. II. Subpopulations in the human fetus, J. Immunol. Baltim. Md 1950. 134 (1985) 1531–1538.

[34] P. Kanatas, I. Stouras, L. Stefanis, P. Stathopoulos, B-Cell-Directed Therapies: A New Era in Multiple Sclerosis Treatment, Can. J. Neurol. Sci. J. Can. Sci. Neurol. (2022) 1–10. https://doi.org/10.1017/cjn.2022.60.

[35] D.H. Whittam, E.C. Tallantyre, S. Jolles, S. Huda, R.J. Moots, H.J. Kim, N.P. Robertson, B.A.C. Cree, A. Jacob, Rituximab in neurological disease: principles, evidence and practice., Pract. Neurol. 19 (2019) 5–20. https://doi.org/10.1136/practneurol-2018-001899.

[36] I. Illa, J. Diaz-Manera, R. Rojas-Garcia, J. Pradas, A. Rey, R. Blesa, C. Juarez, E. Gallardo, Sustained response to Rituximab in anti-AChR and anti-MuSK positive Myasthenia Gravis patients., J. Neuroimmunol. 201–202 (2008) 90–94. https://doi.org/10.1016/j.jneuroim.2008.04.039.

[37] C. Lindberg, M. Bokarewa, Rituximab for severe myasthenia gravis--experience from five patients., Acta Neurol. Scand. 122 (2010) 225–228. https://doi.org/10.1111/j.1600-0404.2010.01345.x.

[38] P. Maddison, J. McConville, M.E. Farrugia, N. Davies, M. Rose, F. Norwood, H. Jungbluth, S. Robb, D. Hilton-Jones, The use of rituximab in myasthenia gravis and Lambert-Eaton myasthenic syndrome., J. Neurol. Neurosurg. Psychiatry. 82 (2011) 671–673. https://doi.org/10.1136/jnnp.2009.197632.

[39] S. Blum, D. Gillis, H. Brown, R. Boyle, R. Henderson, D. Heyworth-Smith, P. Hogan, P. Kubler, C. Lander, N. Limberg, P. Pillans, K. Prain, C. Staples, M. Walsh, P. McCombe, R. Wong, Use and monitoring of low dose rituximab in myasthenia gravis., J. Neurol. Neurosurg. Psychiatry. 82 (2011) 659–663. https://doi.org/10.1136/jnnp.2010.220475.

[40] R.J. Nowak, D.B. Dicapua, N. Zebardast, J.M. Goldstein, Response of patients with refractory myasthenia gravis to rituximab: a retrospective study, Ther. Adv. Neurol. Disord. 4 (2011) 259–266. https://doi.org/10.1177/1756285611411503.

[41] N. Collongues, O. Casez, A. Lacour, C. Tranchant, P. Vermersch, J. de Seze, C. Lebrun, Rituximab in refractory and non-refractory myasthenia: a retrospective multicenter study., Muscle Nerve. 46 (2012) 687–691. https://doi.org/10.1002/mus.23412.

[42] J. Peres, R. Martins, J.D. Alves, A. Valverde, Rituximab in generalized myasthenia gravis: Clinical, quality of life and cost-utility analysis, Porto Biomed. J. 2 (2017) 81–85. https://doi.org/10.1016/j.pbj.2017.02.002.

[43] V. Afanasiev, S. Demeret, F. Bolgert, B. Eymard, P. Laforêt, O. Benveniste, Resistant myasthenia gravis and rituximab: A monocentric retrospective study of 28 patients, Neuromuscul. Disord. 27 (2017) 251–258. https://doi.org/10.1016/j.nmd.2016.12.004.

[44] K.R. Robeson, A. Kumar, B. Keung, D.B. DiCapua, E. Grodinsky, H.S. Patwa, P.A. Stathopoulos, J.M. Goldstein, K.C. O'Connor, R.J. Nowak, Durability of the Rituximab Response in Acetylcholine Receptor Autoantibody–Positive Myasthenia Gravis, JAMA Neurol. 74 (2017) 60–66. https://doi.org/10.1001/jamaneurol.2016.4190.

[45] O. Landon-Cardinal, D. Friedman, M. Guiguet, P. Laforêt, N. Heming, E. Salort-Campana, F. Jouen, Y. Allenbach, O. Boyer, L. Chatenoud, B. Eymard, T. Sharshar, O. Benveniste, Efficacy of Rituximab in Refractory Generalized anti-AChR Myasthenia Gravis., J. Neuromuscul. Dis. 5 (2018) 241–249. https://doi.org/10.3233/JND-180300.

[46] G. Beecher, D. Anderson, Z.A. Siddiqi, Rituximab in refractory myasthenia gravis: Extended prospective study results, Muscle Nerve. 58 (2018) 452–455. https://doi.org/10.1002/mus.26156.

[47] N. Singh, V. Goyal, Rituximab as induction therapy in refractory myasthenia gravis: 18 month follow-up study., J. Neurol. 266 (2019) 1596–1600. https://doi.org/10.1007/s00415-019-09296-y.

[48] S. Jing, J. Lu, J. Song, S. Luo, L. Zhou, C. Quan, J. Xi, C. Zhao, Effect of low-dose rituximab treatment on T-

and B-cell lymphocyte imbalance in refractory myasthenia gravis., J. Neuroimmunol. 332 (2019) 216–223. https://doi.org/10.1016/j.jneuroim.2019.05.004.

[49] R. Topakian, F. Zimprich, S. Iglseder, N. Embacher, M. Guger, K. Stieglbauer, D. Langenscheidt, J. Rath, S. Quasthoff, P. Simschitz, J. Wanschitz, D. Windisch, P. Müller, D. Oel, G. Schustereder, S. Einsiedler, C. Eggers, W. Löscher, High efficacy of rituximab for myasthenia gravis: a comprehensive nationwide study in Austria., J. Neurol. 266 (2019) 699–706. https://doi.org/10.1007/s00415-019-09191-6.

[50] K. Choi, Y.-H. Hong, S.-H. Ahn, S.-H. Baek, J.-S. Kim, J.-Y. Shin, J.-J. Sung, Repeated low-dose rituximab treatment based on the assessment of circulating B cells in patients with refractory myasthenia gravis, Ther. Adv. Neurol. Disord. 12 (2019) 1756286419871187–1756286419871187. https://doi.org/10.1177/1756286419871187.

[51] R.H. Roda, L. Doherty, A.M. Corse, Stopping oral steroid-sparing agents at initiation of rituximab in myasthenia gravis., Neuromuscul. Disord. NMD. 29 (2019) 554–561. https://doi.org/10.1016/j.nmd.2019.06.002.

[52] J. Lu, H. Zhong, S. Jing, L. Wang, J. Xi, J. Lu, L. Zhou, C. Zhao, Low-dose rituximab every 6 months for the treatment of acetylcholine receptor-positive refractory generalized myasthenia gravis., Muscle Nerve. 61 (2020) 311–315. https://doi.org/10.1002/mus.26790.

[53] T. Litchman, B. Roy, A. Kumar, A. Sharma, V. Njike, R.J. Nowak, Differential response to rituximab in anti-AChR and anti-MuSK positive myasthenia gravis patients: a single-center retrospective study., J. Neurol. Sci. 411 (2020) 116690. https://doi.org/10.1016/j.jns.2020.116690.

[54] S.K. Sahai, A.H. Maghzi, R.A. Lewis, Rituximab in late-onset myasthenia gravis is safe and effective., Muscle Nerve. 62 (2020) 377–380. https://doi.org/10.1002/mus.26876.

[55] A. Dos Santos, J.-B. Noury, S. Genestet, A. Nadaj-Pakleza, J. Cassereau, C. Baron, D. Videt, L. Michel, Y. Pereon, S. Wiertlewski, A. Magot, Efficacy and safety of rituximab in myasthenia gravis: a French multicentre real-life study., Eur. J. Neurol. 27 (2020) 2277–2285. https://doi.org/10.1111/ene.14391.

[56] C.T. Doughty, J. Suh, W.S. David, A.A. Amato, A.C. Guidon, Retrospective analysis of safety and outcomes of rituximab for myasthenia gravis in patients ≥65 years old, Muscle Nerve. 64 (2021) 651–656. https://doi.org/10.1002/mus.27393.

[57] S. Ramdas, A.D. Marina, M.M. Ryan, K. McWilliam, A. Klein, D. Jacquier, S. Alabaf, A.-M. Childs, D. Parasuraman, D. Beeson, J. Palace, H. Jungbluth, Rituximab in juvenile myasthenia gravis-an international cohort study and literature review, Eur. J. Paediatr. Neurol. 40 (2022) 5–10. https://doi.org/10.1016/j.ejpn.2022.06.009.

[58] Y. Du, C. Li, Y.-F. Hao, C. Zhao, Q. Yan, D. Yao, L. Li, W. Zhang, Individualized regimen of low-dose rituximab monotherapy for new-onset AChR-positive generalized myasthenia gravis., J. Neurol. (2022). https://doi.org/10.1007/s00415-022-11048-4.

[59] J.I. Castiglione, A.D. Rivero, F. Barroso, P. Brand, A. Lautre, A.A. Kohler, Long-Term Remission With Low-Dose Rituximab in Myasthenia Gravis: A Retrospective Study, J. Clin. Neuromuscul. Dis. 24 (2022). https://journals.lww.com/jcnmd/Fulltext/2022/09000/Long_Term_Remission_With_Low_Dose_Rituximab_in.3.aspx.

[60] J.M. Heckmann, A single low-dose rituximab infusion in severe chronic refractory myasthenia gravis in resource-limited settings., J. Neurol. Sci. 442 (2022) 120394. https://doi.org/10.1016/j.jns.2022.120394.

[61] S. Brauner, A. Eriksson-Dufva, M.A. Hietala, T. Frisell, R. Press, F. Piehl, Comparison Between Rituximab Treatment for New-Onset Generalized Myasthenia Gravis and Refractory Generalized Myasthenia Gravis, JAMA Neurol. 77 (2020) 974–981. https://doi.org/10.1001/jamaneurol.2020.0851.

[62] C. Nelke, C.B. Schroeter, F. Stascheit, M. Pawlitzki, L. Regner-Nelke, N. Huntemann, E. Arat, M. Öztürk, N. Melzer, P. Mergenthaler, A. Gassa, H. Stetefeld, M. Schroeter, B. Berger, A. Totzeck, T. Hagenacker, S. Schreiber, S. Vielhaber, H.-P. Hartung, A. Meisel, H. Wiendl, S.G. Meuth, T. Ruck, Eculizumab versus rituximab in generalised myasthenia gravis., J. Neurol. Neurosurg. Psychiatry. 93 (2022) 548–554. https://doi.org/10.1136/jnnp-2021-328665.

[63] J.F.J. Howard, K. Utsugisawa, M. Benatar, H. Murai, R.J. Barohn, I. Illa, S. Jacob, J. Vissing, T.M. Burns, J.T. Kissel, S. Muppidi, R.J. Nowak, F. O'Brien, J.-J. Wang, R. Mantegazza, Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study., Lancet Neurol. 16 (2017) 976–986. https://doi.org/10.1016/S1474-4422(17)30369-1.

[64] S. Muppidi, K. Utsugisawa, M. Benatar, H. Murai, R.J. Barohn, I. Illa, S. Jacob, J. Vissing, T.M. Burns, J.T. Kissel, R.J. Nowak, H. Andersen, C. Casasnovas, J.L. de Bleecker, T.H. Vu, R. Mantegazza, F.L. O'Brien, J.J. Wang, K.P. Fujita, J.F.J. Howard, Long-term safety and efficacy of eculizumab in generalized myasthenia gravis., Muscle Nerve. 60 (2019) 14–24. https://doi.org/10.1002/mus.26447.

[65] F. Piehl, A. Eriksson-Dufva, A. Budzianowska, A. Feresiadou, W. Hansson, M.A. Hietala, I. Håkansson,

R. Johansson, D. Jons, I. Kmezic, C. Lindberg, J. Lindh, F. Lundin, I. Nygren, A.R. Punga, R. Press, K. Samuelsson, P. Sundström, O. Wickberg, S. Brauner, T. Frisell, Efficacy and Safety of Rituximab for New-Onset Generalized Myasthenia Gravis: The RINOMAX Randomized Clinical Trial, JAMA Neurol. (2022). https://doi.org/10.1001/jamaneurol.2022.2887.

[66] R.J. Nowak, C.S. Coffey, J.M. Goldstein, M.M. Dimachkie, M. Benatar, J.T. Kissel, G.I. Wolfe, T.M. Burns, M.L. Freimer, S. Nations, V. Granit, A.G. Smith, D.P. Richman, E. Ciafaloni, M.T. Al-Lozi, L.A. Sams, D. Quan, E. Ubogu, B. Pearson, A. Sharma, J.W. Yankey, L. Uribe, M. Shy, A.A. Amato, R. Conwit, K.C. O'Connor, D.A. Hafler, M.E. Cudkowicz, R.J. Barohn, on behalf of the NeuroNEXT NN103 BeatMG Study Team, Phase 2 Trial of Rituximab in Acetylcholine Receptor Antibody-Positive Generalized Myasthenia Gravis: The BeatMG Study, Neurology. 98 (2022) e376–e389. https://doi.org/10.1212/WNL.0000000000013121.

[67] C. Zhao, M. Pu, D. Chen, J. Shi, Z. Li, J. Guo, G. Zhang, Effectiveness and Safety of Rituximab for Refractory Myasthenia Gravis: A Systematic Review and Single-Arm Meta-Analysis., Front. Neurol. 12 (2021) 736190. https://doi.org/10.3389/fneur.2021.736190.

[68] S. Bastakoti, S. Kunwar, S. Poudel, J. Quinonez, S. Bista, N. Singh, V. Jha, S. Ruxmohan, S. Paesani, W. Cueva, J. Michel, Rituximab in the Management of Refractory Myasthenia Gravis and Variability of Its Efficacy in Anti-MuSK Positive and Anti-AChR Positive Myasthenia Gravis., Cureus. 13 (2021) e19416. https://doi.org/10.7759/cureus.19416.

[69] V. Di Stefano, A. Lupica, M.G. Rispoli, A. Di Muzio, F. Brighina, C. Rodolico, Rituximab in AChR subtype of myasthenia gravis: systematic review, J. Neurol. Neurosurg. Psychiatry. 91 (2020) 392–395. https://doi.org/10.1136/jnnp-2019-322606.

[70] R. Tandan, M.K. 2nd Hehir, W. Waheed, D.B. Howard, Rituximab treatment of myasthenia gravis: A systematic review., Muscle Nerve. 56 (2017) 185–196. https://doi.org/10.1002/mus.25597.

[71] R. Iorio, V. Damato, P.E. Alboini, A. Evoli, Efficacy and safety of rituximab for myasthenia gravis: a systematic review and meta-analysis., J. Neurol. 262 (2015) 1115–1119. https://doi.org/10.1007/s00415-014-7532-3.

[72] D. Maloney, T. Liles, D. Czerwinski, C. Waldichuk, J. Rosenberg, A. Grillo-Lopez, R. Levy, Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma, Blood. 84 (1994) 2457–2466. https://doi.org/10.1182/blood.V84.8.2457.2457.

[73] A.A. den Broeder, L.M. Verhoef, J. Fransen, R. Thurlings, B.J.F. van den Bemt, S. Teerenstra, N. Boers, N. den Broeder, F.H.J. van den Hoogen, Ultra-low dose of rituximab in rheumatoid arthritis: study protocol for a randomised controlled trial, Trials. 18 (2017) 403. https://doi.org/10.1186/s13063-017-2134-x.

[74] T. Li, G.-Q. Zhang, Y. Li, S.-A. Dong, N. Wang, M. Yi, Y. Qi, H. Zhai, L. Yang, F.-D. Shi, C.-S. Yang, Efficacy and safety of different dosages of rituximab for refractory generalized AChR myasthenia gravis: A meta-analysis, J. Clin. Neurosci. 85 (2021) 6–12. https://doi.org/10.1016/j.jocn.2020.11.043.

[75] S.-H. Kim, N.Y. Park, K.H. Kim, J.-W. Hyun, H.J. Kim, Rituximab-Induced Hypogammaglobulinemia and Risk of Infection in Neuromyelitis Optica Spectrum Disorders: A 14-Year Real-Life Experience, Neurol. - Neuroimmunol. Neuroinflammation. 9 (2022) e1179. https://doi.org/10.1212/NXI.0000000000001179.

[76] M.L. Vo, Rituximab Treatment for AChR Myasthenia Gravis: Results of the BeatMG Study, Neurol. Alert. (2022). https://www.reliasmedia.com/articles/149162-rituximab-treatment-for-achr-myasthenia-gravis-results-of-the-beatmg-study.

[77] D. Menon, C. Barnett, V. Bril, Novel Treatments in Myasthenia Gravis, Front. Neurol. 11 (2020) 538. https://doi.org/10.3389/fneur.2020.00538.

[78] D.B. Drachman, Another Failed Trial of Treatment for Myasthenia Gravis, NEJM J. Watch. (2021). https://www.jwatch.org/na54416/2021/12/21/another-failed-trial-treatment-myasthenia-gravis.

[79] A. Behin, R. Le Panse, New Pathways and Therapeutic Targets in Autoimmune Myasthenia Gravis, J. Neuromuscul. Dis. 5 (2018) 265–277. https://doi.org/10.3233/JND-170294.

[80] V. Damato, J. Theorell, A. Al-Diwani, A.-K. Kienzler, M. Makuch, B. Sun, A. Handel, D. Akdeniz, A. Berretta, S. Ramanathan, A. Fower, D. Whittam, E. Gibbons, N. McGlashan, E. Green, S. Huda, M. Woodhall, J. Palace, F. Sheerin, P. Waters, M.I. Leite, A. Jacob, S.R. Irani, Rituximab abrogates aquaporin-4–specific germinal center activity in patients with neuromyelitis optica spectrum disorders, Proc. Natl. Acad. Sci. 119 (2022) e2121804119. https://doi.org/10.1073/pnas.2121804119.

[81] E. Crickx, P. Chappert, A. Sokal, S. Weller, I. Azzaoui, A. Vandenberghe, G. Bonnard, G. Rossi, T. Fadeev, S. Storck, J. Fadlallah, V. Meignin, E. Rivière, S. Audia, B. Godeau, M. Michel, J.-C. Weill, C.-A. Reynaud, M. Mahévas, Rituximab-resistant splenic memory B cells and newly engaged naive B cells fuel relapses in patients with immune thrombocytopenia, Sci. Transl. Med. 13 (2021) eabc3961. https://doi.org/10.1126/scitranslmed.abc3961.

[82] R. Huda, New Approaches to Targeting B Cells for Myasthenia Gravis Therapy, Front. Immunol. 11 (2020)

240. https://doi.org/10.3389/fimmu.2020.00240.

[83] B.A.C. Cree, J.L. Bennett, H.J. Kim, B.G. Weinshenker, S.J. Pittock, D.M. Wingerchuk, K. Fujihara, F. Paul, G.R. Cutter, R. Marignier, A.J. Green, O. Aktas, H.-P. Hartung, F.D. Lublin, J. Drappa, G. Barron, S. Madani, J.N. Ratchford, D. She, D. Cimbora, E. Katz, Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial, The Lancet. 394 (2019) 1352–1363. https://doi.org/10.1016/S0140-6736(19)31817-3.

[84] J.C.S. López-Hernández, J.A. Galnares-Olalde, E. Gómez-Figueroa, A. Jorge de Sarachaga, E.S. Vargas-Cañas, Rituximab in Refractory Myasthenia Gravis: Experience in a Single Healthcare Center in Mexico., Cureus. 13 (2021) e13226. https://doi.org/10.7759/cureus.13226.

[85] M.E. Wylam, P.M. Anderson, N.L. Kuntz, V. Rodriguez, Successful treatment of refractory myasthenia gravis using rituximab: a pediatric case report., J. Pediatr. 143 (2003) 674–677. https://doi.org/10.1067/S0022-3476(03)00300-7.

[86] Agathe Molimard, Cyril Gitiaux, Christine Barnerias, Frédérique Audic, Arnaud Isapof, Ulrike Walther-Louvier, Claude Cances, Caroline Espil-Taris, Jean-Baptiste Davion, Susana Quijano-Roy, Coraline Grisel, Brigitte Chabrol, Isabelle Desguerre, Rituximab Therapy in the Treatment of Juvenile Myasthenia Gravis, Neurology. 98 (2022) e2368. https://doi.org/10.1212/WNL.0000000000200288.

[87]B. Keung, K.R. Robeson, D.B. DiCapua, J.B. Rosen, K.C. O'Connor, J.M. Goldstein, R.J. Nowak, Long-term benefit of rituximab in MuSK autoantibody myasthenia gravis patients., J. Neurol. Neurosurg. Psychiatry. 84 (2013) 1407–1409. https://doi.org/10.1136/jnnp-2012-303664.

[88] M.K. Hehir, L.D. Hobson-Webb, M. Benatar, C. Barnett, N.J. Silvestri, J.F.J. Howard, D. Howard, A. Visser, B.A. Crum, R. Nowak, R. Beekman, A. Kumar, K. Ruzhansky, I.-H.A. Chen, M.T. Pulley, S.M. LaBoy, M.A. Fellman, S.M. Greene, M. Pasnoor, T.M. Burns, Rituximab as treatment for anti-MuSK myasthenia gravis: Multicenter blinded prospective review., Neurology. 89 (2017) 1069–1077. https://doi.org/10.1212/WNL.0000000000004341.

[89] E. Cortés-Vicente, R. Rojas-Garcia, J. Díaz-Manera, L. Querol, C. Casasnovas, A. Guerrero-Sola, J.L. Muñoz-Blanco, J.E. Bárcena-Llona, C. Márquez-Infante, J. Pardo, E.M. Martínez-Fernández, M. Usón, P. Oliva-Nacarino, T. Sevilla, I. Illa, The impact of rituximab infusion protocol on the long-term outcome in anti-MuSK myasthenia gravis, Ann. Clin. Transl. Neurol. 5 (2018) 710–716. https://doi.org/10.1002/acn3.564.

[90] R. Jiang, M.L. Fichtner, K.B. Hoehn, P. Stathopoulos, R.J. Nowak, S.H. Kleinstein, K.C. O'Connor, Single-cell repertoire tracing identifies rituximab refractory B cells during myasthenia gravis relapses, Immunology, 2019. https://doi.org/10.1101/840389.

[91] R. Koul, A. Al Futaisi, R. Abdwani, Rituximab in Severe Seronegative Juvenile Myasthenia Gravis: Review of the Literature, Pediatr. Neurol. 47 (2012) 209–212. https://doi.org/10.1016/j.pediatrneurol.2012.05.017.

[92] G. Masi, Y. Li, T. Karatz, M.C. Pham, S.R. Oxendine, R.J. Nowak, J.T. Guptill, K.C. O'Connor, The clinical need for clustered AChR cell-based assay testing of seronegative MG, J. Neuroimmunol. 367 (2022) 577850. https://doi.org/10.1016/j.jneuroim.2022.577850.

[93] I. Schiavetti, M. Ponzano, A. Signori, F. Bovis, L. Carmisciano, M.P. Sormani, Severe outcomes of COVID-19 among patients with multiple sclerosis under anti-CD-20 therapies: A systematic review and meta-analysis., Mult. Scler. Relat. Disord. 57 (2022) 103358. https://doi.org/10.1016/j.msard.2021.103358.

Survival of the Fittest

Elizabeth S. Rowe PhD MBA, Vernon Rowe MD

> A tinny voice over the VHF marine radio commanded, "State your position."
> Bud said, "Uh--unsure of position. In the Gulf Stream. Somewhere between Marathon and Miami."
> Silence. Then the tinny voice commanded, "State your vessel size."
> Bud said, "Thirty-two-foot sailboat. Engine malfunctioning. Four sick passengers." After an endless pause, the voice asked, "Will you accept a commercial tow?"
> Bud hesitated. He knew a commercial tow would be expensive.
> "Yes!" we all screamed into the microphone.
> With this, the rescue began.

Bud and I were sailing our second bareboat charter while still in school. We furnished our own captains (Dan and Bud), supplied our own food, cooked our own meals, and took responsibility for the boat, and ourselves. We planned to pick up the charter boat in Miami, sail the Intracoastal Waterway part way down the Florida Keys to Buttonwood Sound, then sail back up to Miami in the open ocean.

To get to the Atlantic Ocean, we had to cross the reef of the Florida Straits through a narrow channel, at Alligator Reef Light. This was our first attempt at offshore sailing but expected it to be the first of many. We planned someday to circumnavigate the globe.

The previous year we took a four-day bareboat charter in the Keys and loved it. After that, we studied offshore sailing in periodicals like *Sail Magazine* and *Yachting* and read all the books we could find. We dreamed of following in the footsteps of Joshua Slocum, Sir Francis Chichester, and the intrepid sailors who told their stories in the sail-cruising magazines.

The crew was Bud, Dan, me, Jim from our previous trip, and Al and his new wife Carolyn. Dan had been a sailor all of his life and was from a nautical family. Al and Carolyn had never been on a sailboat before, and this trip was to be their honeymoon.

We spent hours planning meals and charting courses. Each member of the crew planned to cook one meal onboard and to bring the necessary ingredients. The experienced sailors chose hot dogs and spaghetti. Carolyn planned *coq au vin*, a gourmet meal requiring extensive preparation and lengthy simmering.

Bud and Dan meticulously plotted the course we would take through a narrow channel between the keys and the barrier reef which leads to the open ocean. Past the infamous Alligator Reef light. Then they planned to sail north to Miami, a distance of only seventy miles. The boat would be in the axis of the Gulf Stream and gain three and a half knots as we sailed north. This meant seven hours of offshore sailing.

When we arrived in Miami to meet the owner and check out the Gulf 32 sailboat, we were told that the only forward sail available was the large Genoa jib. The storm jib and the working jib had been stolen the week before. Uh-oh.

Also, there was a whiff of diesel fuel from the auxiliary engine. No big deal. Diesel fuel was not explosive. We were cocky and eager, so we took the boat, loaded up our supplies, and sailed out of the harbor and into the afternoon breeze.

We traveled southwest for several idyllic days, via the Intracoastal Waterway through the Keys, in smooth waters, with perfect winds, and beautiful sunsets. We had fabulous *coq au vin*, simmered for hours on the gimballed alcohol stove during gentle broad reaches. We had brought a guitar, so we relaxed in the evenings over beer and sea shanties, as we rocked gently to sleep on the anchor. The newlywed couple was hooked on sailboat cruising, and already dreaming about their next one.

On the day before our planned exit from usually calm waters to the ocean, we crossed Buttonwood Sound. The charts indicated the water there to be deep enough for our five-and-a- half-foot draft. But on the day we sailed across it, the water was much shallower than predicted, because a brisk wind out of the northeast, after a frontal passage, had blown a lot of water out of the sound. Uh-oh.

As we sailed across Buttonwood Sound, we felt the irregular "thump" of boulders against the hull. Bud kept the sails trimmed, and the crew sat on one side, to heel the boat over as much as possible. We sailed across the sound without running aground.

Then we anchored for the night in choppy waters in the deeper part of the sound, near the narrow channel we planned to take the next day. Just one more day, the Gulf Stream, then home. The weather forecast was good, and we were looking forward to some great blue-water sailing.

The weather check still sounded good the next morning, though the forecast winds and seas had picked up. After breakfast, we motored through the narrow channel between the islands and through the barrier reef, into the open ocean. We hoisted our sails as we passed Alligator Reef light.

The first sign of trouble came when we passed the light and took up our planned heading. The ocean swells were a lot larger than forecast. The wind direction was out of the northeast, and scudding clouds were beginning to form in the sky. When we entered the Gulf Stream, the updated forecast was for a higher wind, bigger swells, and small craft warnings. But we were committed; there was no way to find our way back to the channel through the reef, even if we had wanted to.

To make matters worse, the wind was in the opposite direction to the axis of the Gulf Stream, so the current at the surface became zero. Further, the wind created choppy seas

and a huge swell.

If we'd had it, we would have used a storm jib, so we could head up higher into the wind. But we didn't have one. It had been stolen...So the genoa jib forced us to sail at greater angles to the wind and reach further into the ocean with each port tack. Our progress toward Miami slowed to a crawl.

We had planned to navigate following our nautical chart using specific landmarks along the shore. But as we sailed further and further from land, and as the swells got bigger and bigger, land disappeared. All we had was dead reckoning and the seat of our pants to find our way to Miami.

At eleven in the morning, Carolyn was the first to succumb to seasickness. The rolling of the boat, fear stoked by the strong wind and swell, and our resulting heel, all played their part. She was not prepared for the lee rail to be under, and for big waves to break over the bow, spilling into the cockpit.

I have never been seasick in my life, but after Al, her husband, and Jim joined her, I became seasick too. We all retreated to the cabin with buckets. Al and Jim crouched on the benches, while Carolyn and I crawled into the bow berth, sharing a bucket between us. After a couple hours of watching waves crash over the clear hatch cover, Carolyn whispered to me in tremulous voice, "Is there any chance at all that we will survive?"

Surprised, I said "Wow! I didn't know you were so worried! We are going to be fine! We are just going to be miserable for a while." I didn't say aloud the thought that crossed my mind, that it would be ironic if we were lost at sea the same day Dwight Eisenhower died. When I recovered enough to go topside, I looked at Bud and he seemed cheerful and confident. But he didn't quite meet my eyes. He asked, "How is everybody doing down there? This is great sailing!" ,

I said, "They will live. How is it going? How far are we from Miami?" "Unhhh....well, we are not sure exactly where we are—we can't see the markers on the shore. If we head closer to the reef, though, we could rip a hole in the hull with a coral head." "But," he said confidently, "No problem. We know we are heading in the right direction, and we will find a good landmark soon." Then he said as he looked away, "Anyway, we know that Miami is up ahead somewhere, and we can't miss it."

I felt better getting out of the cabin and into the cockpit, so I stayed there and tried to help. The wind was strong against the sails and was increasing and whistling through the rigging.

Clouds raced along the horizon. It was good sailing, all right. Maybe too good. For the passengers huddled in the cabin below, however, as they heaved into a bucket, their only thoughts were surviving the misery.

Bud and Dan did all the work, with a little help from me. I partially recovered, but our passengers stayed sick. I moved between the pitching cockpit and cabin, carrying an occasional sandwich for captain and crew topside. We had only an occasional glimpse of land, surrounded as we were by the seething ocean.

Al and Carolyn held hands as they gazed heavenward through the clear hatch cover.

Bud eventually started the diesel auxiliary to help keep the boat pointed closer to the wind, and to keep some charge on the battery. But diesel fuel began to leak into the bilge and was thrown onto the floor of the cabin by the engine flywheel. The cabin floor became slick as grease.

For what seemed like an eternity, we slogged on, with the smell of diesel fuel permeating the pitching cabin. The beauty of the ocean and sky was gone. Its enraged terror was unleashed. It was a matter of survival for all of us.

It was late afternoon when Bud and Dan declared our emergency, broadcasting on the hailing channel.

The tinny voice on the radio said "Acknowledged. Stand by". And stand by we did, for hours.

The suffering crew were overjoyed that help was coming, and our ordeal would be over. Bud and Dan stopped trying to sail upwind and stowed the oversized jib. We still bobbed like a cork on the seething ocean.

As we awaited our rescue, the engine continued to cough away. But we all felt a huge sense of relief. The Coast Guard said they were sending a plane, homing on our radio signal.

After several hours of staring into the sky, just before sunset, we saw a small plane circling high above us. Over the radio the pilot said he saw us, and everyone came to the cockpit to cheer. He said he would continue to circle above us and guide a cutter to our location. We expected that to be any minute. But as it turned out, it took a lot longer.

Bud asked the pilot to say our location, so we could place ourselves on the nautical chart. After a pause, he gave us our coordinates. They were so far from our intended course that Bud and Dan thought they must be wrong.

Battery power was getting low, so the pilot told us to turn off the radio. We'd need to talk with the cutter captain when he arrived.

And so, we waited in the dark for our rescue. Bud and Dan were clipped to the lifeline topside, while the rest of us huddled below in the cabin. The wind velocity decreased, but the boat still lurched on the huge swell.

Finally, about midnight, a floodlight appeared out of the darkness. It was the Coast Guard cutter, Cape Knox. Her stern looked huge, towering above us.

We were happy to be rescued at last. We hoped we would be taken aboard the cutter and whisked back to civilization. But ahead lay one of the toughest nights of our lives. With both boats pitching and rolling as they were, the captain said it was unsafe for a Coast Guard midshipman to board us. He planned to tow us to Miami, and we would have to handle our end of the tow rope.

After several attempts, Dan caught the two-inch hawser pitched over to us, and attached it to the foot of our mast.

Bud struggled at the helm to keep the boat in position.

We had to keep the boat directly behind the cutter, with the hawser taught and always on the port side of the forestay. The cutter would tow us "above hull speed," to help us maintain our position, and keep the hawser taught. If we relaxed for a second, the hawser could swing around and snap off the mast.

Bud and Dan took turns at the helm every hour. They were exhausted and wet from the effort and spray. In the dark night, lit only by the spotlight of the Cape Knox, they kept the hawser taut and our boat in its necessary position.

The rest of us collapsed below in the dark, lurching cabin, with its diesel stench, as the boat slammed from one huge swell to the next. "BLAM!" "BANG!" came the sounds from the cans in the cabinets, as they were tossed with every wave.

We braced ourselves, as best we could, drenched, groggy, and sick, as we were dragged across the sea. The ordeal lasted the rest of the night, as we struggled in the violently pitching sailboat.

As dawn was breaking, the lights of Miami appeared on the horizon. We all began to cheer and shout. Our fatigue vanished, as we hugged each other.

When we arrived at the pier, we staggered up on to the dock. A young man in khaki pants and a blue shirt approached us and asked who the skipper was. Bud came up and introduced himself. The young man said he was the pilot who had found us and circled above, guiding the cutter to our location. He said he was glad to see us safe.

After thanking him profusely, Bud asked him about the coordinates he gave us, since they were so far from where we thought we were. The young pilot said, "Yes, well we have a hard time knowing where we are up there," and smiled as he walked away. He probably didn't have the heart to tell us just how lost we really were. It was years later we realized that those coordinates were probably correct.

The Cape Knox circled around as soon as she dropped us off at the dock. Before we left the little sailboat for good, Bud broadcast on the hailing channel: "To the Captain and crew of the Cape Knox: We are alive because of you. Thank you." Those are joyous words, even today.

As the years went by, we continued to sail on many cruises and bareboat charters. We even owned our own sailboat on the Chesapeake. We have had many other boating adventures, the subjects of many another story.

But since that trip, our sailing has always been on inland waters like the Chesapeake Bay, Puget Sound, and the British Virgins. These are protected waters. We never dreamed of sailing offshore again, or of circumnavigation. The ocean is a very unforgiving place, especially for the ignorant and unaware.

Our *Sail Magazine* subscription lapsed, and we moved to Kansas, where we live today. Though as soon as our sons reached sailboat age, we took them on their first bareboat charter. In protected waters, and always in sight of land.

A Wikipedia entry shows the Cape Knox is a 95-foot Coast Guard cutter. Under her current name, Yoshka, she sails the waters of the Galapagos Islands, patrolling against poachers of sharks and whales. Protecting and ensuring the survival of the fittest. As well as the lucky.

Under the Watchful Eye of the Knife

Michael Abraham

University of Kansas Medical Center

Kansas City, Kansas

I walked in, I came in, the same as I ever did.
I spoke, I explained, we discussed, you and me.
Like all before, I did the same.
Focused but was I out of focus?
No ill will.
The writing all over the wall.
I see my flesh. Running around. Have I let them down?
The solace they bring, the everlasting comfort from their eyes and voices.
How much longer can I play these songs?
The weight of the chords coming crashing down.
Dizzy but at no height.
Pulse flickering up and down.
Head swimming.
Who do I cry to? The reflection staring back at me.
Can someone make it go away?
Though no ill will the ill feeling lingers and weighs.
In the doors or outside, the clock is always on, always ticking.
Sometimes I want to escape this never-ending spherical chamber but alas this is my home.
I am a father.
Amen.

Internal Medicine: A short story written during medical school

Vincent Czerwinski

Student, University of Kansas Medical Center

After a long shift, Rick was desperate to have some time to himself. He walked slowly across the beach- the spot he always found himself drawn to in the brief interlude between shifts. He spent a precious moment of time off absorbing the sights and sounds of the coast. Not that there was much to see, covered under the blanket of night. I could be anywhere in the world, Rick thought to himself. Do I really want to spend my moments off at [the beach]? Rick looked down and saw a hermit crab scuttling across the sand. Picking it up, he turned the animal over to inspect its legs. Instead of the flailing appendages he expected, Rick found himself looking at the exposed, undulating foot of a conch. Despite the intrusion, the creature made no attempt to cower in its home. The slimy foot bulged impossibly outwards, at once totally extruded yet still stably adhered to the carapace. Rick quickly tossed the shell on the ground and began walking away. It wasn't a luSignal according to the book, but Rick knew his time was limited.

Suddenly, Rick found himself back in the Emergency Department of New Langone Medical Center. Even if inexorably chained to the institution, he couldn't help but appreciate the modern, minimalist design of the academic center. Staff milled around him tending to patients, passing by him as if he didn't exist. That qualified as a luSignal- inarguably. He looked up at the clock and noted that the seconds hand failed to move forward. Another luSig.

Sighing, Rick pinched the skin on his forearm, lifting it two inches. When he let go, it remained elevated, as if suspended by an invisible clamp, instead of returning to a relaxed position. No avoiding the inevitable. How long had his break been? Not more than an hour. Rick navigated his way into an unoccupied room in the department and shut the door behind him. The sparsely decorated space featured a neatly folded bed, vitals monitoring equipment, and a bedside table.

"Dr. Rick Martin, clocking-in," he said to no-one in particular.

"Dr. Martin," came a voice from nowhere in particular. "You know the protocol, two luSignals and it's time to acknowledge."

"Was I over?" Rick asked innocently.

"The hermit crab," the voice responded matter-of-factly, "that turned into a conch."

"I must have missed that."

"We both know you didn't, Dr. Martin." The voice continued, "Just because it's not formally documented doesn't mean it's not a luSignal. The disciplinary committee will almost certainly understand it to qualify under the category 'transforming object.' If you continue to be tardy for your lucid shift then your transgressions will be formally documented and filed," the voice paused. "Again."

"I understand. I'm lucid now, let's begin. As I recall, there were five patients needing management before I went to sleep. We'll start with Mrs. Barnette."

"Julia Barnette, age 64," began the voice. "Presented to the Emergency department with a chief complaint of pain upon urination." As the voice spoke, Rick visualized the patient in the previously empty bed before him. There was a pause as the computer with whom Rick was speaking to accessed the patient's records. "Her vital signs are significant for blood pressure 91-over-65 and fever of 101.3 degrees Fahrenheit." The array of monitors at the patient's bedside came to life reading out the vitals as the computer relayed them. "Physical exam revealed a costovertebral angle tenderness." The patient clutched her flank. "Patient reports no hem-"

"I remember her now," Rick interrupted. "Kidney stones. Likely infected. Urology didn't want her?" As he spoke, the rest of the patient's details manifested themselves in his imagined room. She had frail skin, silvery white hair, and forlorn resignation that accompanied those who knew that hospital visits were a new fixture in their lives.

Another pause from the computer as it analyzed the Urology note. "They were of the opinion that the stones would not require specialty care, as hospital guidelines state that stones under 5mm are to be passed without surgical assistance."

"Any update on urine or blood cultures?"

Another pause. "Microbiology has yet to update."

"Ok, let's continue to treat possible infection empirically, maintain fluids, and administer fentanyl for pain control." Rick continued, "Petition Urology once more as this patient's complications warrant specialty care. If I have to, I'll cart her over there myself when I'm awake."

"I'll update the orders." Another pause. "Nursing has received."

And so, they continued their work. Rick's fifth and final patient was Mr. Kyle Palmer, an 11 y/o boy having an allergic asthma attack. Upon sending orders for epinephrine and concluding his treatment, Rick turned to leave.

"Ok, that's it for me," Rick announced.

"Thank you, Dr. Martin," replied the voice. "Have a good rest of your night."

Rick stepped out of the room and back onto the beach. Back when Rick had first been taught to lucid dream, he would have treasured these few moments- when the lucid shift was concluded, and the rest of the dream was available to explore. Now, modifying the content of his dream only reminded Rick of work, and so he accepted whatever his subconscious served to him. Enveloped in night, he walked towards the waves and sat down as he always did: at the

point where the breaking waves just reached his feet. Rick sat motionless on the beach. The tide progressively rose until he was up to his neck. Rick sat motionless. The tide splashed against his face and eventually covered his head.

—

Eventually, Rick woke up. He was in his office, in New Langone Medical Center. The clock read 5:27AM, and the seconds hand was moving predictably forward. Rick pinched the skin on his forearm, and when released it relaxed. He sat up and began removing the meshwork of electrodes covering his scalp. Once off, he looked at the device in his hands. This was DreamCAP, the advancement which enabled him and other professionals around the country to work their lucid shifts. The machine transmitted information to the user through direct stimulation of the auditory nerve, enabling communication to people as they slept. DreamCAP also traced the pattern of cortical behavior and processed these signals into responses. All Rick had to do was recognize he was dreaming, and he could begin lucidly communicating along a two-way channel. The wires connecting the electrodes converged to a thick cord which fed into a processing station on his desk. This processing station connected to the hospital database, providing a feed of patient information. Finally, the problem of doctors not getting enough sleep had been solved. A display on the processing station displayed the message 'Remember to enjoy your shift.'

Rick grabbed his hygiene bag and headed down the hall to the bathroom. In the bathroom, Rick began brushing his teeth. He looked at the mirror. Dark circles hung beneath his eyes. The harsh angularity of the lines on his face contrasted with the soft glow and rounded edges of the chic bathroom. There are worse prisons, Rick thought to himself, in an attempt to psyche himself up for the next shift. Working through your dreams decreased the quality of sleep, that much was clear, but it also enabled the hospital administrators to skirt the 80-hour work week maximum that had been imposed following the nationwide adoption of the Libby Zion Law. In the increasingly bureaucratized healthcare system, time spent working while awake was categorized, billed, and counted separately than work done while dreaming. The toll extracted from physicians was one of the few similarities between the two types of work.

Rick finished washing himself and packed away his hygiene bag. He returned from the bathroom to his office where he made a cup of coffee and finally headed back to the Emergency Department. As he walked through the halls, he acknowledged his coworkers with a curt nod and was pleased to see that they responded in turn. Upon arriving in the ED, Rick approached James, the colleague who had been covering the conscious shift.

"Dr. Hartman," said Rick.

"Dr. Martin," replied James.

"Did I say anything weird in my sleep?" joked Rick.

"Ha-ha" responded James. "Thanks for petitioning kidney-stones to be transferred to Urology, I don't know why they didn't take her the first time."

"Must've been half-asleep when they were looking at her." Another well-worn joke between the two of them.

"The only other matter is the fifth patient on your docket, Kyle Palmer." Seeing Rick's confused expression James continued, "I looked at the neurolog from your lucid shift, it seems like you disconnected after your fourth patient."

Rick was confused. He clearly remembered treating the young man. "Allergic asthma, right?" Rick asked. "I sent in orders for epi."

"That is Kyle Palmer," replied James, "but nursing never got the orders. Don't worry too much about it, Rick. I went in and managed it myself." There was a moment of silence between them, as both physicians processed the implications of this finding. "Maybe recalibrate your DreamCAP. I've had some trouble with mine as well. Still," James thought out loud "I wonder why you remember seeing them."

"Who knows?" Rick said brusquely, ready to move on. "I'll worry about it later. Thanks for covering Palmer."

"No problem," responded James as he rose from his desk and began to leave. "Remember to enjoy your shift."

—

Rick worked methodically through his patients during the day. After this conscious shift was done, he only had one more cycle of sleep-conscious shifts and then he would have the rest of the week off. He might actually head to the beach.

With another five minutes remaining in his shift, Rick still had four patients to attend to. He'd managed time well today, despite the quickly compounding exhaustion. He could see another patient during his conscious shift and then manage the three remaining ones lucidly. With so few patients he might actually get a good night's sleep. Rick's next patient was in room 26C- Micheal Rodruigez, age 34. Vitals were unremarkable, save for an elevated heart rate. The intake nurse had noted that Rodruigez dislocated his right shoulder, apparently 'while putting his shirt on.' With a sense that this case would be fairly cut-and-dry, Rick headed into the room. An X-ray had been ordered and the technician was on the way over.

"Mr. Rodruigez," said Rick, invigorated by the recognition of a familiar patient "good to see you again."

"Hello doctor," said Micheal. "I'm sorry to bother you again like this."

"It's not a problem, we'll be able to get you sorted out."

"It feels like it's happening more and more." Micheal's normally upbeat voice betrayed his concern. "So make sure you really get it right this time." He joked.

"The more it happens the worse it'll be," explained Rick. "The socket will wear down and it'll fall out more and more easily. How did it happen this time?"

"I was playing soccer and all of a sudden I just felt it happen. Then I called my friend who drove me over."

Rick mentally noted the inconsistency in the story- it was out of character for Micheal to lie. "Well, you know the drill," he said to Micheal "we'll get an X-ray, give you some pain meds and pop it back into place." As if on cue, the X-ray technician arrived and began gingerly positioning Micheal for his X-ray. "They're going to take some pictures, ok?" Rick said, exiting the room.

Once outside, Rick pinched the skin on his forearm. When released, it sloughed back down. So Micheal was being deceitful. Rick flagged down a nurse.

"Prepare propofol for the patient in 26C," Rick instructed the nurse "and let's also grab some ketamine, just in case."

"You got it, doc," the nurse replied, moving to grab the anesthesia.

Rick went back to 26C and inspected the X-ray tech's film. Textbook right anterior dislocation. "Shouldn't be too hard to get you fixed up," Rick said walking over to Micheal. "Just try to be careful with it, like I said- it'll only happen more frequently." The nurse, having prepared the medications, entered the room. "Let's start him off with [high dose] of propofol."

The nurse attached the syringe full of the milky white anesthetic to Micheal's IV. As the drug entered his system, Micheal's eyes fluttered, and he relaxed. With Micheal on his back, Rick gently placed Micheal's right arm against his side, and held Micheal's elbow bent 90 degrees extended forward. Rick glanced at Micheal to make sure he wasn't in excess pain, and not seeing any obvious distress, began slowly rotating the forearm away from the midline.

"I feel it! I feel it!" exclaimed Micheal, suddenly tensing up.

"Ok, Micheal, just relax," said Rick. "Breathe with me: in-and-out, in-and-out." Turning to the nurse, Rick said "Another [moderate dose]."

The nurse pushed in Propofol. Micheal seemed to relax, but when Rick started rotating his arm again, he cried out, "I still feel it! I feel everything!"

"Another [moderate dose]," said Rick, still holding Micheal's arm. The nurse complied. Rick waited for Micheal to relax, but fear had settled upon Micheal, and Rick could feel the tension in his patient. The clock was ticking, and every second that went by, Rick was one step closer to the propofol being metabolized and no longer controlling Micheal's pain. Rick briefly wondered if Micheal was lying about the pain, hoping that a shot of fentanyl was in his future. "Let's try one more, same size." After a moment of hesitation, the nurse complied, and pushed almost all of the remaining drug into Micheal's arm. Rick paused for a precious second and then gradually began to move Micheal's arm once again.

"Doctor, I still feel it! I feel everything! It hurts, doctor," Micheal wailed, resisting with all his might against Rick's attempt to rotate. "Please doctor, the pain- help me!" Tears ran down the Micheal's face. Probably not faking.

"Give him the ketamine, [high dose]," Rick told the nurse.

The nearly-depleted syringe of Propofol was exchanged for a new one, containing a clear liquid. The substance entered Micheal's arm, and Rick felt him relax. Expression vanished from Micheal's face as the dissociative took hold. Rick began moving Micheal's arm once again.

"I feel it, I feel it, I feel it," Micheal whispered. Despite the protest, Micheal's arm remained relaxed. Rick continued to rotate, feeling for the socket. "I feel it, I feel it." Rick persisted, and eventually the tension gave way. The shoulder snapped back into position with a satisfying "thunk." Relief washed over Rick. He waved in the X-ray tech, who had been waiting in the hall.

"I'm almost positive it's back in place, but let's take a picture just to cover our bases," Rick said to the tech. "You're good to take off, thanks for your help," he said to the nurse as he stepped outside the room.

The X-ray tech re-imaged Micheal's shoulder. "Man, this guy is really out of it," he said to Rick.

"What's he saying?" asked Rick.

"He just keeps repeating: 'I see myself, I see myself,'" responded the tech.

"Ketamine is a helluva drug," conceded Rick. "Propofol wasn't doing the trick." The tech finished his shot and walked out of the room joining Rick outside.

"Looks pretty good," the tech stated.

Rick examined the new X-ray. "It's back in. You want to take a look at him again?"

"Sure, no one else needs an X-ray shot right now," agreed the tech.

The two walked back into the room. Micheal, still deep in his dissociation, turned to the tech, "I see us. I see myself, with my arm back in place. I see you, with the X-ray machine." Micheal turned and looked directly into Rick's eyes "I don't see you, doctor. You're not here, doctor."

If Rick was unsettled, he didn't show it. "Ketamine is a helluva drug," said the tech.

"Helluva," agreed Rick. "Well, that's the end of my shift. Thanks for your help." The two turned and began to leave Micheal's room.

"Doc," declared Micheal from his bed, "you're not here. You're at the beach."

—

Rick closed the door of 26C. The tech walked away from Rick, without saying a word. Rick's coworkers slipped by him, as he stood mutely. A luSig? Rick thought to himself. He looked down and pinched his arm. He let go and the skin relaxed. All at once, Rick became acutely aware of how exhausted he was. Rick grabbed his lucid shift patient list and scanned the contents as he walked back to his office. Upon reaching his office, Rick pushed against the bar of the door. It wouldn't budge. Rick was surprised, he never locked his office door. The most expensive object in the small space was his DreamCAP, and Rick would be thankful to find the

object stolen. Rick pushed the bar once again. Still, the door didn't move. Rick looked down at the mechanism and saw his error- the door had a handle. Rick turned the knob and the door yielded. Rick tested his forearm again. Once again, it relaxed back down. Rick entered his room, collapsed into his chair. As his eyes closed and the world faded around him, he saw the glowing monitor on his desk display 'Remember to enjoy your shift.'

Rick was back at the beach. He knew a few minutes to enjoy before the computer called him into work. As long as he stayed on the beach, he'd be able to feign ignorance- pretend not to see the signs indicating he was dreaming. Rick sat at the water's edge and allowed the waves to gradually rise. A wave hit his open eyes, and when his vision cleared, he was in New Langone Medical Center. Damn the luSigs, Rick thought, pinching his arm. The skin remained predictably elevated. "Ok, computer," Rick called out. "Let's get this over with."

"Welcome back Dr. Martin," said the computer.

Rick strode into the department room where he would visualize his patients. "Three on the docket, let's deal with Karen Fisher."

"Karen Fisher, age 34," began the voice. "Presented to the Emergency department with a chief complaint of a new rash covering her hands and upper legs." As the voice described the patient, Rick walked to the bed and yanked away the covers. He saw an array of angry red boils covering the patient's arms and legs.

"Sexual history?" Rick asked bluntly.

A pause. "Since breaking up with my boyfriend last year I've had nine new partners," said Karen.

Rick consulted a lab-print out that had materialized at Karen's bedside. Platelets: 151, D-dimer: 47, PT: 2 seconds. Normal clotting, Rick thought to himself. White blood cells: 15, ESR: twice normal level. Likely infectious. STD? "I suspect this is syphilis," Rick announced. "We'll order a confirmatory test and circle back for treatment. In the meantime, we'll begin IV penicillin prophylactically. Any questions?"

The computer said nothing.

"I'll go ahead and order the medication then, and I'll check in on the lab results later," said Rick clearing the encounter from his mind.

Rick prepared himself for the next encounter.

"Next patient Robert Perry, age 46," announced the computer. "He is currently sleeping. Presented with diabetic metabolic acidosis. Patient received IV fluids and insulin."

Rick approached the bedside and once again regarded the materializing lab sheet. Na+: 141, Cl-: 106, HCO3-: 23. 141 - 106 - 23 = 12, Rick though. 12 is less than 15. Non-anion gap. Seems like the treatment is working. "Well, as long as the patient is not in anion-gap, there doesn't appear to be the need to modify treatment," said Rick. Easy enough. "Maintain insulin and hydration, if the patient's condition worsens redraw labs-".

"Rick, get the fuck up," said the voice of Dr. James Hartman. "Wake up Rick."

Rick was confused. It wasn't like Dr. Hartman to send direct transmission via DreamCAP, and even rarer for him to swear while doing so. The room where Rick was working began shaking, and suddenly he was torn from his dream and looking his colleague in the face. "Wha-?"

"Rick, your neurolog was empty," said Dr. Hartman. "What's going on?" Dr. Hartman looked at Rick's desk. "You didn't even put your damn DreamCAP on before you went to sleep!"

"I- I don't- I was in the rooms with the patients!" said Rick. "Karen Fisher, Robert Perry. I saw both of them!"

"Christ," said James. "You dreamt it, Rick. You never even put your cap on. Listen, I'll call in Rebecca, but help with patients until she gets here." James paused. "And figure out what the hell is going on with your DreamCAP. We can't afford to have you dropping shifts like this."

Rick nodded. "I'll head there right now." The two physicians walked together in silence back to the emergency department. Once they arrived, James handed Rick a sheet of patients. Rick headed towards the room where Karen Fisher was. Rick walked into the room.

"Name and age?" he asked.

"Karen Fisher, age 34," began the patient.

"You presented to the Emergency department with a chief complaint of a new rash covering your hands and legs," said Rick, walking to the bed. He yanked away the covers and saw an array of small purple bruises covering the patient's legs.

"Sexual history?" Rick asked bluntly.

A pause. "Since breaking up with my boyfriend last year I've had no new partners," said Karen.

Rick consulted a lab-print out that had been placed at Karen's bedside. Platelets: 49, D-dimer: 741, PT: 6 seconds. Normal clotting, Rick thought to himself. White blood cells: 7, ESR: normal level. Likely infectious. STD? "I suspect this is syphilis," Rick announced. "We'll order a confirmatory test and circle back for treatment. In the meantime, we'll begin IV penicillin. Any questions?"

Rick heard nothing.

"I'll go ahead and order the medication then, and someone will check in on the lab results later," said Rick walking out of the room.

Rick walked into the next encounter.

Next patient Robert Perry, age 46, thought Rick as he inspected the sleeping man. Patient presented with diabetic metabolic acidosis. They received IV fluids and insulin.

Rick approached the bedside and once again regarded the lab sheet on the bedside table. Na+: 142, Cl-: 105, HCO3-: 18. 142 - 105 - 18 = 12, Rick thought 12 is less than 15. Non-anion gap. Seems like the treatment is working. Well, as long as the patient is not in anion-gap, there doesn't appear to be the need to modify treatment. Easy enough. Rick left the room and approached the nurse, "Maintain insulin and

hydration, if the patient's condition worsens redraw labs."

Rick worked through another two patients. As he was headed towards his third, Dr. Hartman intercepted him. "Rick," he said, "syphilis? For Karen Fisher? She has DIC Rick- an internal bleeding crisis. How did you not catch that? Did you not look at the bruises all along her legs, or her labs? I had to admit her to the ICU. She's not going to make it. And Robert Perry," he continued, "he's clearly in anion gap. I had to call anesthesiology to intubate him."

"What?" protested Rick. "I calculated it. He wasn't in anion gap. And Karen- she didn't have bruises, she had syphilis lesions."

"Look Rick, Rebecca just arrived," said Dr. Hartman. "I don't know what to tell you. Maybe after you get some sleep, you should look back at those patients' charts again. You're cut Rick. Christ," exasperation crept into James' voice. "You've done enough damage for one night."

Rick left the Emergency Department and went to his car. He pinched his forearm. When released, the skin sloughed back down. This nightmare was real.

—

Back at home, Rick dug around his nightstand. He found the syringe: Dremantidone. Developed shortly after the widespread adoption of DreamCAP, the drug was a combination of Zolpidem, commonly sold as Ambien, and a THC-analog. While not psychoactive, the THC derivative capitalized on a side-effect of the drug: inhibition of dreams. Rick inserted the needle into his arm and pushed the elixir into his bloodstream. As he tipped back and the world faded to black around him, Rick felt relief. Finally, he could escape the hell of these last few days in the blanket of a dreamless night.

Yet somehow, despite the drug, Rick was back on the beach. Exasperated, he pinched the skin on his arm. Upon seeing the result, he resignedly turned back to the beach. The ocean lapped gently against the shore. Rick felt himself pulled inexorably towards the swelling sea. Enveloped in night, he walked towards the waves and sat down as he always did: at the point where the breaking waves just reached his feet. Rick sat motionless on the beach. The tide progressively rose until he was up to his neck. Rick sat motionless. The tide splashed against his face and eventually covered his head.

—

When morning broke, Rick was still on the beach. The tide had receded so that Rick's body was visible once again. The waves had drawn Rick deeper into the sand, so that only his head, arms, and torso were exposed. Seaweed matted Rick's hair, and crabs scuttled about Rick's corpse, picking away at their newest bounty. Rick's lifeless face was placid. The skin on his forearm was suspended- as if pinched by invisible fingers.

Book your trip!

It’s time to register for the 24th Annual NMSG Scientific Meeting

24th Annual NMSG Meeting

will be held in

Orlando, Florida

September 22-24, 2023

Amedco LLC designates this live activity for up to **12.00 CME credits**

AMA PRA Category 1 Credits

Draft Meeting Agenda

ALL NEW

YOUNG INVESTIGATORS SESSION

This year's Planning Committee has been working very hard on our Young Investigator session (held at the Annual Meeting) and topics may include:

- How to give an effective elevator pitch
- Tips for successful Grant Writing
- Failing well, overcoming rejections, criticisms and changing direction

Committed sponsors of the 2023 meeting to date are: UCB, Argenx, Sarepta Therapeutics, Fulcrum Therapeutics, PepGen Inc, NMD Pharma, PTC Therapeutics, Dyne Therapeutics, Amylyx Pharmaceuticals, Amicus Therapeutics, Janssen Biotech Inc.

****Abstract Portal is OPEN. All accepted submitted will be published in this Journal. Deadline for Abstract submission is June 1st, 2023****