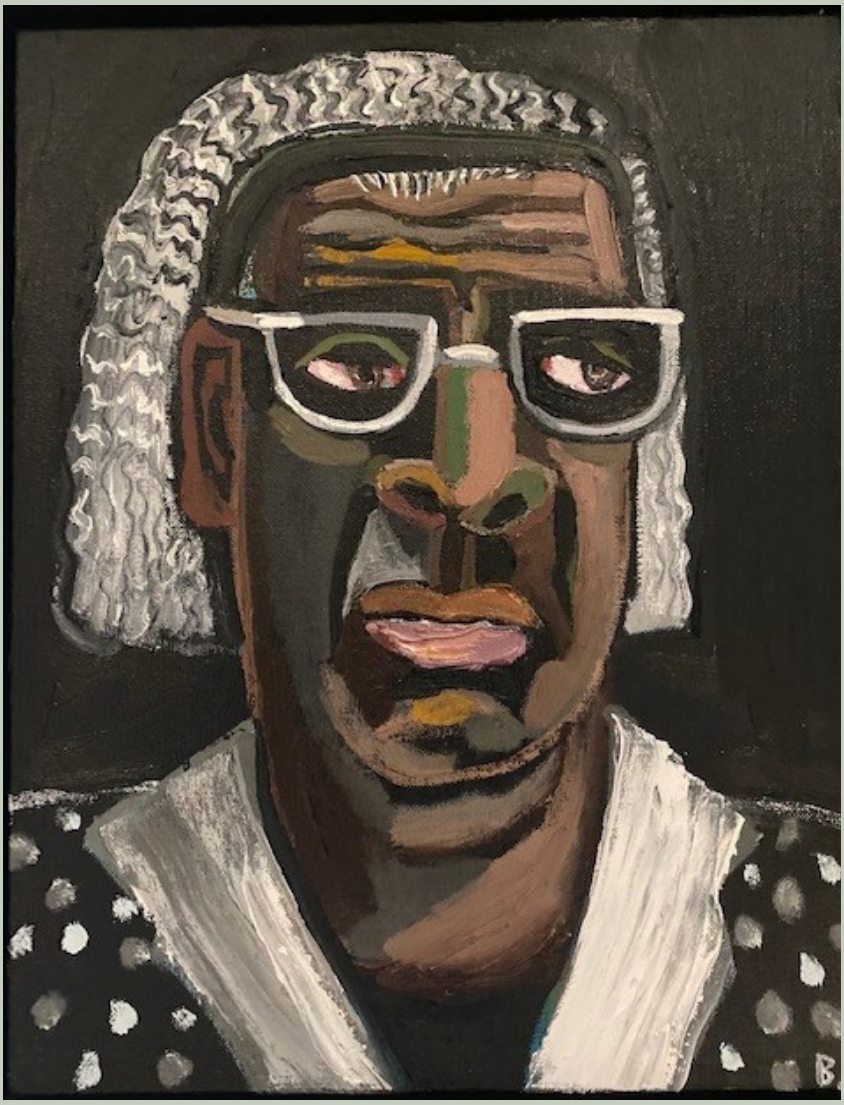
RRNMF Neuromuscular Journal

vol. 2:2 May 2021



FACILITATORS

Cover Image: "Woman with Silver Glasses" (2007) by David Bates.
From the Katrina paintings series.

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Letter from the Founding Facilitator

Richard J. Barohn, MD

RRNMF Neuromuscular Journal is 1 year old!

Publication of the written word is a critical communication vehicle. To have access to venues where this can be done easily is important. Once published, the message can be accessed online, shared, and cited. It is necessary to have a publication vehicle that provides a digital journal structure format, that can be registered with the Library of Congress, and that is searchable through web search tools and scholarly databases. Here are the essential steps to this process:

1. Have an idea for a journal
2. Have access to an online journal software system
3. Have assistance in developing and launching the project
4. Have interested colleagues who share the vision of such a venue and have articles to submit
5. Have students interested in being part of the production process
6. Have colleagues interested in helping to be facilitators (reviewers)

As we honor our one-year anniversary, the *RRNMF Neuromuscular Journal* is now truly a real academic publication. It is not PubMed indexed yet, but we are getting closer. We have published 5 issues in volume 1 in 2020 and this is the second issue in volume 2 for the year 2021. There are several steps to get started with publishing a new journal. One of the first steps is to get an International Standard Serial Number (ISSN) for the journal from the Library of Congress's ISSN site. The ISSN is a unique number that belongs to each journal. RRNMF journal's ISSN is **2692-3092** and is the key to getting other services that help make the article visible to web search engines. It is easy to apply for an ISSN and free, but you need to publish the first issue before you request it. Once we had the ISSN, the University of Kansas Libraries' Digital Publishing Services group worked with a company called Crossref to get us a Digital Object Identifier (DOI) link (all starting with https://doi.org/17161/rrnmf) that we could add to each article page. The KU Libraries pay a small fee for registering DOIs with Crossref. DOIs are great because they give each article a permanent link that will never change. Finally, the *RRNMF Neuromuscular Journal* is searchable on Google Scholar and our publications go into the calculation of your Google Scholar H - Index if it is cited.

How is this done at no cost to us? The University of Kansas Libraries in their wisdom established a publishing program to support open access publications edited by faculty from the University of Kansas. They installed the software for an online digital publishing platform called Open Journal Systems (OJS), which was originally developed through a Mellon grant. There are several of these available commercially, with OJS being one of the frequently used models because it is free, open source, and has an active user/developer community that is passionate about making research openly available to the world. The Libraries' digital publishing office now has over 42 journals published by KU faculty – only 2 are medical: the *RRNMF Neuromuscular Journal* and the *Kansas Journal of Medicine*. There is a staff that is essential to help faculty learn about the process and access the software program. I, like all faculty, was willing to do this on my own time; I found neurology colleagues who were willing to help; and I found two amazing medical students who were willing to help me as well. When I launched the journal prior to having the help of the medical students, I struggled. Their energy and youthful computer capabilities got us over the hump to sustainability. I currently put about several hours a week into this project, after typical work hours.

The other obvious factor to get such a project to happen is that I and my other neurology colleagues have actual real jobs that we get paid for and that we do not need income from publishing. This type of self-publishing is a non-paid labor of love done in our spare time. I wish we could pay our authors and reviewers for their time and creative work. In an ideal situation, we would have funds to do so, perhaps industry support. As for now this does not exist. In my opinion it is problematic that authors and editorial board members and reviewers do not get compensated for their time. And in our modern open access format authors often must PAY the journal to be published, often at exorbitant costs. Clearly there is a lot of profit to be made in the publishing houses. These publishers historically charged not only individuals for their subscription fees, but charged academic libraries enormous fees for publishing their catalogue of journals. As these costs rose and libraries had limited budgets, the next step was to pass this cost on to the authors. And the authors are paying these high fees because they need publications for promotion and academic advancement. This coincided historically with the push for "open access" so that research results are quickly and widely disseminated to the academic readership and public especially when the author used federal research funds to finance the research described in the publications.

So, we have circumvented this cycle through establishing our own academic publishing project. This is free of predatory financial motivated publishers, and it is free of elitist establishment editorial boards and "gotcha" reviewers. We are indeed Free at Last!

Another component of this freedom is for the author(s) to own their copyrights in the research that they publish and not the publisher. For this to happen, the journal has an agreement with each author that specifies that copyright is held by the author(s). This information is put in the copyright notice section of the journal. Our statement says:

If you want to publish a case or series or your research results, or video/photographs, or a prior grant proposal, or simply an idea, then this is the journal for you.

We have put a number of unique features in this journal and we have changed journal terminology. The editorial board members and reviewers are now called facilitators as the goal is to help the author(s) get their paper published. We are not hampered by the length of an issue since we are digital, only by the time commitments of our technical partners in the digital publishing office and our facilitators. In general, our goal is to provide peer review for cases and research articles and reviews and give positive feedback so authors can improve their article. We would like to publish most submitted articles if they are sound and well written and make a good point. We do not have a goal to have a set rejection rate. We do not reject submissions if they are reasonable but we do ask authors to address the reviewer's suggestions and modify their manuscripts based on the comments.

This allows our authors additional freedoms. If their article has been rejected by a traditional journal they can come to this friendly journal. If they have a junior faculty or student or resident or fellow who is just getting started publishing, they can come to this journal. If they do not have funds to publish in an open access journal that charges authors, they can come to this journal.

Other new terminology includes "what's on your mind" instead of editorials or letters to the editor; "clinic stuff" instead of case reports; "new stuff "instead of case series and other new research; "looking back/looking forward stuff" for reviews; "visual stuff" for photographs and videos; "meeting stuff" for abstracts and summaries of meetings; and finally, the most unique feature is "proposed stuff" where you can publish a prior grant submission that was either accepted or rejected along with the peer reviewers' comments.... the ultimate in peer review. We spend countless hours preparing and submitting grants; most are rejected. Traditionally it ends there with no academic output. But now you can publish your prior grants, with a paragraph introducing why you and your team wrote it; where it was submitted to; and if it was funded or not, and what the outcome was. I hope more of our readers and writers take advantage of this important and unique feature.

Moving forward we would like to increase our readership and also our reviewers. Anyone who registers to receive the journal can indicate if they want to be contacted as a reviewer and what their area of expertise is. We would like to find more female reviewers and reviewers that are from minority groups to get them more engaged in this process. I recently put a call out to get more reviewers in these categories involved and it has been successful. And of course, we want more articles submitted!

Also, moving forward we probably will apply to get PubMed indexing. The typical process requires the journal to be publishing for at least two years and to have at least 25 peer reviewed publications. We have the publication numbers but we still have another year to go before we can submit a formal application. However, I do want all of you to keep an open mind about the necessity for PubMed. How important is it really? I realize some want their articles to be in a journal indexed in PubMed for promotion and tenure purposes. From my senior perspective, I am not sure of the value of PubMed however. What if when we apply and it was determined we are not worthy because we did not reject enough submissions? I would take that as a badge of honor. That is our goal, to facilitate authors to publish their work. And as I mentioned above, all our articles are indexed and are searchable in Google Scholar.

Clearly you do not need a formal journal to get your ideas into the internet universe. There are social media outlets; you can set up a blog site and write pieces and send them to folks who want to receive your blog. This is an excellent way to communicate and my close friend, Dr. Josh Freeman, has done this for years in his two excellent blog sites. But when I offered Josh the opportunity to publish some of his excellent blogs in this journal, he agreed. It gives him another avenue to communicate. Another option is to set up a website that does not have a journal type of academic format, such as the excellent BrainPickings.org website. Check this amazing site out. It has a wide readership and is a place where arts and science ideas can intersect.

I have one more big idea for this type of venue and that is to create a general arts and science journal that would be a place for any artist or scientist to publish their work. I particularly would like authors to submit work that describes an intersection of art and science. I am tentatively am calling this the **Midwest Journal of Arts and Science.** If anyone is interested in participating or if you have Arts and Science colleagues who might want to be involved, please have them contact me. And in the meantime, before we launch another journal, I am soliciting various non-medical manuscripts for publication in the *RRNMF Neuromuscular*

Journal. You will be seeing poems, short stories, and even a movie screenplay in the upcoming issues! The first poem for the journal is in this anniversary issue.

Thanks for reading this long anniversary note and for supporting the journal. And THANK YOU to our digital publishing gurus at KU, Marianne Reed and Eric Bader, who are wonderful partners and team players. Recently Pam LeRow worked in that office and she and Marianne helped us get this journal off the ground. Thanks to our amazing medical students Jiji Oufattole and Breanna Tuhlei who serve as editors. Thanks to Lauren Peck, a freshman undergraduate at MIZZOU who has helped me a great deal in getting manuscripts loaded onto the journal platform. Thanks to our associate facilitators, Drs. Yeubing Li and Michael Pulley who give us more of their time than we deserve. Thanks to our founding Board of Facilitators, and thanks to our many facilitators who I have asked to review papers who are not on the board. I will be inviting more of you to help as facilitators, and if you enjoy being part of the project, we can put you on the Board of Facilitators Thanks to all of you readers. And most importantly thank you to all authors who have taken a gamble to send their creative material to a new type of publication.

Rick

Reflections on One Year of RRNMF — Medical Student Perspective

Breanna Tuhlei, University of Missouri-Columbia Medical Student

I am a fourth-year MD-PhD student at the University of Missouri-Columbia, nearly done with MS3 year and about halfway through my PhD in neuroimmunology. I have had the privilege of collaborating with Dr. Barohn on this journal for almost one year. I happened to be introduced to Dr. Barohn by a faculty member I was doing research with and initially met with Dr. Barohn to discuss my endeavors as an MD-PhD student interested in neurology. He mentioned some of his struggles with launching a new project, the RRNMF journal, and I quickly seized this unique opportunity by volunteering myself and a fellow medical student to help. I was not actually sure what I would be doing but I was excited to be on the forefront of something new. I had been a copyeditor for the American Journal of Hospital Medicine at MU, and I was eager to continue building my experience with the editorial process and take on new responsibility. As an MD-PhD student, I have always been fascinated with the peer-review pipeline that manuscripts must go through to be published. Most of us do not get exposure to the intricacies of this process; we submit a manuscript through a website or email and then eagerly await further instructions, reviews, and hopefully acceptance.

During my experience as a managing editor for RRNMF, I have come to appreciate how much effort it really takes to publish a manuscript. Manuscripts must first be screened and assigned to the appropriate team members. Reviewers must be assigned, notified, and followed up with. This feedback is communicated with authors, and then manuscripts are carefully combed for grammatical and typographical errors as well as ensuring the formatting is consistent across papers. These word documents are then transformed to their final layout and sent to authors for final approval. As one of the managing editors, I am responsible for guiding the manuscript through its journey in this pipeline and communicating each step with the authors, starting from submission by the authors and ending with all of us approving of the final product.

Perhaps the most enlightening step for me as a future physician-scientist has been to read the feedback from reviewers on the various manuscripts and observing how authors make changes accordingly. It is impressive to see collaboration on such a large scale – attending physicians and academics from literally all over the world coming together to critique each other's work and share ideas on these manuscripts. On a more practical level, I am more aware of some of the common pitfalls to avoid as I craft a manuscript and the scientific expectations I might hear from reviewers. Getting involved with a journal at any level is an experience I would strongly recommend for MD or PhD students interested in research. It can be difficult to find these opportunities but networking with as many colleagues as possible will often take one a long way. You never know who might be trying to launch a journal in your department!

Reflections on One Year of RRNMF — Managing Editor Perspective

Jihane (Jiji) Oufattole, MD Student
University of Missouri-Columbia

I have thoroughly enjoyed my role as a Managing Editor of the *RRNMF Neuromuscular Journal*. I was introduced to Dr. Barohn and the journal through Breanna Tuhlei at the start of my second year at the University of Missouri-Columbia School of Medicine. I am currently finishing the last week of M2 year, preparing to take the USMLE Step 1 exam in a month, and then will be taking a leave of absence to embark on a 1-year Pre-Doctoral Fellowship in Pathology at the Brigham and Women's Hospital in Boston, MA. As a neuroscience major equipped with a revamped interest in the neuromuscular discipline, I hope to devote part of this upcoming year to neuropathology specialty work and research.

The managing editorial position at *RRNMF Neuromuscular Journal* has been like no other role I have ever held. Having founded an undergraduate organization, carried out multiple quality improvement projects, and directed a Women's Health Community Clinic, I approached the role with eagerness for the engagement and commitment this opportunity would demand. I looked forward to the illuminating experience of managing workflow, copyediting, and interacting with authors and reviewers. What I didn't expect, however, was how phenomenal the *RRNMF* staff members would be. It is inspiring to watch Dr. Barohn speak passionately of new submissions, articles he is selecting for upcoming issues, and the cherished art pieces he intends to put on the future issue covers. I also revere his vehement stance towards public access of novel medical research and encouragement of uncomplicated publication and dialogue of contemporary neuromuscular revelations. Another phenomenal team member I have had the privilege of working with is Marianne Reed – the QUEEN of publishing editors. She has been incredibly resourceful and patient with all of us as we have learned the ropes of our roles, all carried out with her trademarked humor and verve. Eric, our layout editor, is an outright beast when it comes to prompt galley production and revisions; Breanna and I are two Managing Editors-in-a-pod when cranking out our shares of the workload. Lastly, I have discovered the immense value of peer reviewers' time, expertise, and constructive recommendations. Their generosity noticeably makes a difference in our publications, and it is inspiring to see how this process far often strengthens the scientific argument and leads to high quality output. I am privileged to be a part of this team and proud of the influence the journal has had.

I have also been impressed with the incredible efficiency and rapid troubleshooting that our staff has carried out in a short amount of time. Through multiple workflow meetings and discussions, swift trial-and-error turnaround, and the assignment of clearly defined roles, we have put protocols and measures in place that have spawned a culture of efficiency, transparency, and accountability. It has been incredibly rewarding to witness improvements with each issue publication as we gain more and more experience. The Open Journal System (OJS) website has been an additional massive convenience – allowing the seamless transition of text through the various workflow stages: submission, peer-review, revisions, copyediting, layout, page proofing, and publication. A complete history of every submission is conveniently in one place for easy access and reference, which allows us all to stay on top of the workflow from wherever we are.

Finally, and perhaps the most rewarding aspect of this role, observing such important and novel research submitted to this journal has been such an intellectually fulfilling experience. I have had the privilege of observing how the neuromuscular discipline is evolving through an unparalleled lens. Whenever I log into OJS, I first eagerly peruse through the new submission titles, catching a glimpse of the topics I will soon have the chance to systematically explore. Where the real fun begins is the copyediting stage. This process requires me to meticulously comb through each article looking for spelling and grammar errors; inadvertently, this offers me an uninterrupted opportunity to comprehend the material at a profound and dynamic level. As I read through manuscripts, it's exhilarating to anticipate how these novel findings may become cited primary sources in the textbooks and guidelines that I use as a medical student and will continue to refer to as a physician. It reminds me that our knowledge of medicine is constantly evolving and that by committing to a role in medicine you also commit to becoming a life-long learner and, hopefully, a contributor to new discoveries and knowledge to pass on to the next generation of students and physicians.

Reflections on One Year of RRNMF — Note from the Publishing Facilitator

Marianne Reed, Digital Initiatives Manager
Eric Bader, Publishing Specialist
University of Kansas Libraries

Congratulations to *RRNMF Neuromuscular Journal* on a very successful first year! Dr. Barohn has assembled a dedicated team of "facilitators": editors, managing editors, and reviewers, resulting in the publication of six issues in 12 months. It is extremely rare for a new journal to publish more than a single issue during its first year of operation, so this is quite an accomplishment. Dr. Barohn's dedication to and enthusiasm for this journal is infectious and he brings us all along with him on his quest to publish neuromuscular research that can be seen by a worldwide audience.

The publication of this journal is made possible by Dr. Barohn's partnership with the KU Libraries' Digital Publishing Services unit. Library publishing programs are uniquely qualified to support the publication of journals edited by their institution's faculty[1]. Libraries bring to the table a commitment to enhancing the impact of high-quality scholarly research through open access publishing and a dedication to technical standards that ensure that scholarly work can be easily discovered. Also, since Library publishers are not driven by the need to make a profit, they can provide a home for new kinds of scholarly research that may not be viable from a commercial perspective.

We are delighted to have played a part in bringing the *RRNMF Neuromuscular Journal* to its audience of thousands of readers from around the globe. We hope that it will continue to thrive long into the future.

Reference

1. Reed, M. A. (2019). Journal Programs and Cross-Disciplinary Research. Merrill Series on The Research Mission of Public Universities, 16–22. https://doi.org/10.17161/merrill.2019.13290

What's In This Issue?

Letter from the founding facilitator for Volume 2, issue 2

Richard J. Barohn, MD

We have packed a lot into this anniversary issue. I open the journal with my thoughts about the journal one year into this project. Then, I am very pleased that the two University of Missouri medical students, Breanna Tuhlei and Jihane (Jiji) Oufattole, who serve as managing editors, have both written wonderful pieces about their experience with the journal. What a treat to have these two bright young medical students as part of the RRNMF Neuromuscular Journal team! It is an additional pleasure to have Marianne Reed, our digital publishing facilitator, also share some thoughts for our anniversary issue. We would never have gotten this journal launched without her steady assistance.

I wrote a piece for black history month on a scientist some of you may not know about, Dr. Percy Julian, who was instrumental in developing synthetic acetylcholinesterase inhibitors and various cortisol compounds. Dr. Freeman provides thoughts about issues regarding the unequal distribution of COVID-19 vaccinations for underserved populations. Dr. Govindarajan has written a piece for "What's on Your Mind" called "Lost Muse." In the New Stuff category, the University of Kansas Medical Center team, led by Dr. John Stanford, describes encouraging results using ketamine in the SOD mouse model of ALS. Dr. Farheen and his team discuss how residency training programs had to adapt to the COVID-19 pandemic. Dr. Lestayo and her colleagues from Cuba describe a large series of GBS cases with excellent clinical-epidemiological data. There are four very interesting cases described in the Clinic Stuff section: a case with a novel CMTX mutation and a novel RYR1 mutation from the University of Missouri, and two COVID-19 cases; one case describes a patient who had two confirmed COVID-19 infections and another describes an exacerbation of MG after a second dose of the COVID-19 vaccine. In the Visual Stuff section, there is a great recording of eyelid myotonia and facial stiffness in a patient with a sodium channel mutation from the Kansas clinic. There are two articles in the Looking Backwards/Looking Forward section. Dr. Murala and team have written an excellent review of infectious myositis. The international team of scientists from academia and industry tells the story of how the arimoclomol study for Inclusion Body Myositis got started that led to the ongoing phase 3 efficacy trial. We are also publishing our first poem in the journal, by Michael Abraham, MD, a neurologist at the University of Kansas Medical Center! In future issues, we hope to publish more art pieces: poetry, short stories, and other art forms. Finally, for the second consecutive issue, our cover art is a painting by the artist David Bates. This is another painting from his Katrina series in my art collection. What a good way to finish year one and start year two of the RRNMF Neuromuscular Journal.

Rick

P.S. After we were nearly done with this issue I wrote another 'What's on your Mind' called IMAJN.

Percy Lavon Julian PhD — The Man Who Wouldn't Give Up

Richard J. Barohn

In the Volume 2, Issue 1 of this journal, I told the story of Vivien Thomas, an incredibly bright and technically adept laboratory technician who had to take a role behind the physician Alfred Blalock, literally in the operating room where he would tell Dr. Blalock how to proceed in the new open heart surgeries Vivien developed, and throughout his whole life as he struggled as a black man in the scientific world. He is indeed a scientific hero worthy of honor for Black History Month.

Let me tell you the story of another black pioneer in health care science that has touched millions of lives but who you may never have heard of, and while February was officially Black History month, we should consider any month or day a good time to honor great scientists of all backgrounds. The scientists I will tell you about now will be of particular interest to neuromuscular health care researchers and providers.

Percy Lavon Julian, PhD was born in Montgomery, Alabama in 1899, the son of a railway mail clerk and the grandson of slaves. He was one of six children. His father and mother also worked as schoolteachers and filled their house with books for their children. His grandfather had lost two fingers as punishment for daring to read and write. His grandmother was known to pick more than 350 pounds of cotton a day. Julian attended the State Normal School for Negroes where he excelled, graduating at the top of his class. This was a school with the goal of training teachers and provided the equivalent of a tenth grade education. He told a story that a white policeman chased Percy from a fence as he watched young white boys conducting chemistry experiments in a school he could not attend because he was black. He also experienced coming across a black man in the woods near his house that had been lynched a few hours before. He then was admitted to DePauw University in Greencastle, Indiana as a sub freshman. DePauw admitted a handful of black students but required they simultaneously take additional high school classes to catch up with the white students. He had to take additional high school courses the first two years to fill in the gaps of his Alabama education, along with the full load of freshman classes. He also worked as a waiter in a white fraternity house and lived in the attic.

The Dean tried to discourage him from going into science, but he persisted, and he graduated first in his class,

Figure 1. Percy Julian is seen here in this 1920 photo at DePauw University.

and was that year's valedictorian, majoring in chemistry.

He applied to graduate school at DePauw and at many other institutions around the country, but he was denied admission. In 1960 he told this story as follows:

> I shall never forget the week of anxious waiting in 1920 to see if I could get to graduate school. I had worked hard for four years. I stood by as day by day my fellow students in Chemistry came by saying, "I am going to Illinois"; "I am going to Ohio State"; "I am going to Michigan"; "I am going to Yale.". "Where are you going?" they asked, and they answered for me, "You must be getting the Harvard plum." I could stand the suspense no longer. I went to Professor Blanchard, as staunch a friend as he knew how to be, and certainly later my most unforgettable friend, and asked timidly, "Professor, did you get me a fellowship?" And then this dear fellow with resignation told me "Now, now, Julian I knew you would be asking me that. Come into my office." There he showed me numerous letters from men who had really meant God to me- great American chemists of their day. And they had written to him, "I'll take your Mr..., but I'd advise you to discourage your bright colored lad. We couldn't get him a job when he's done, and it'll only mean frustration. In industry, research demands co-work, and white boys would so sabotage his work that an industrial research leader would go crazy! And of course, we couldn't find him a job as a teacher in a white university. Why don't you find him a teaching job in a Negro college in the South?

He doesn't need a P.D for that!" There went my dreams and hopes for four years, and as I pressed my lips to hold back the tears. I remembered my breeding, braced myself and thanked him for thinking of me.

So he took a position teaching chemistry for two years at Fisk University, a historic black university. He won an Austin Fellowship to attend Harvard where he obtained a master's degree in organic chemistry, again graduating at the top of his class. But while others were offered jobs as teaching assistants, Julian was not and he was told by Harvard officials that southern white students would be offended by being taught by an African American. By not being able to be a teaching assistant he could not go onto obtaining his PhD as he had no way to financially support himself. So Julian went to the West Virginia College for Negroes to teach chemistry. After only a year he moved to yet another historic black institution, Howard University as an associate professor of chemistry. His research involved the potential of using the ingredients of soybeans as a potential medical compound. In 1929 he was awarded a Rockefeller Foundation fellowship grant to study in Vienna, Austria, and there he completed his PhD in organic chemistry. He studied natural products chemistry. In 1931 he returned to Howard University as the head of the chemistry department. Dr. Josef Pikl, a Viennese colleague who he began working with as a doctoral student, also moved to Howard so they could continue working together.

Then DePauw University, which had previously rejected his graduate school application, asked him to return as a research fellow along with Dr. Pikl. From 1932 to 1935, they focused on coming up with a way to synthesize the compound physostigmine. This compound was first isolated from the Calabar bean in the 1800s. Extracts from the Calabar bean were shown to reduce intraocular pressure in the eye caused by glaucoma by causing the pupil to constrict and by doing so improves drainage of intraocular fluid. As early as 1864 the active ingredient was shown to be physostigmine. But no one had figured out how to synthetically make the compound and this was necessary to be able to provide a less expensive and larger supply of the drug. Julian and Pikl published a series of amazing papers in scientific journals culminating in the pivotal 1935 publication: "Studies in the Indole Series V. The complete Synthesis of Physostigmine (Eserine)". They utilized a team science approach that incorporated several undergraduate DePauw students. They were also in a race with a chemistry team of superstars in Oxford, England. The prestigious Oxford group published a paper around the same time saying they had manufactured the compound. But Percy believed the Oxford method was faulty and he challenged their process, and his teams results prevailed. This was the first complete synthesis of what is known in chemistry as an indole alkaloid. Since then, physostigmine and its many derivative compounds have been used to treat glaucoma and help literally millions of patients with this disorder, which can cause loss of vision.

It turns out physostigmine is very helpful for another much rarer condition called myasthenia gravis. This is a rare disorder of skeletal muscle and it is one of the diseases that I specialize in. With myasthenia, patients become weak because they make autoantibodies that block the acetylcholine receptor in muscle so the signal from the nerve carried by the compound acetylcholine to activate the muscle is blocked. One way to overcome the block is to prevent the acetylcholine from being degraded. It turns out physostigmine does exactly that and if you give a myasthenia gravis patient physostigmine their muscles become stronger. This was first discovered in 1934 using naturally occurring physostigmine by a young British physician named Mary Walker and it was a major breakthrough in the treatment of myasthenia gravis. But obtaining naturally occurring physostigmine was just as difficult to obtain for myasthenia gravis patients as it was for glaucoma patients. Once this compound could be made synthetically using the discovery of Julian and colleagues, physostigmine and its derivatives became the standard treat for myasthenia gravis. I still use a related drug called pyridostigmine in almost all of my myasthenia gravis patients. This all is due to Dr. Julian and his team. Other drugs that are derivatives of physostigmine are used for many other conditions. The class of drugs currently used to treat Alzheimer's disease (Aracept, Exelon and Razadyne) are derivatives of physostigmine.

The discovery of how to manufacture physostigmine is definitely the most important scientific discovery to ever come from the DePauw University laboratories. The research fellowship funding had come to an end in 1935 and Dr. Julian was proposed to be the chair of the chemistry department. But he was not offered the position as some of DePauw's staff objected to working for an African American.

He was offered a position as a researcher at the Institute of Paper Chemistry in Appleton, Wisconsin. The head of the institute visited Dr. Julian at DePauw and they made plans for the research projects he would work on. But just before

he was to move it was discovered that an old city statue of Appleton prohibited the "housing of a Negro overnight". He could not live in Appleton!

So he left for the world of industry and he took a position with the Glidden Company, becoming their chief chemist and Director of Research. He moved to Chicago. There, he became an expert in soybean products and developed pathways to synthesize numerous substances starting from soy-based ingredients. His laboratory was the first to extract the proteins from soybeans which he called the "Alpha" Proteins, and this became the basis for dozens of home and food products. But he and his family continued to be confronted by racism in the north. One Thanksgiving Day arsonists tried to burn down Dr. Julian's new home in Oak Park, an exclusive white suburb (the hometown of Ernest Hemingway). On another occasion someone hurled a dynamite bomb into the house, but no one was injured. He and his son often felt it necessary to stand sentry duty around their home with shotguns.

His career in the Glidden company was spectacular. He discovered a protein in soybeans that could be used to coat paper and make it less flammable. This was then made into a fire-retardant foam that could be packaged in canisters and sprayed on fires. It was used extensively on ships in World War II and it is estimated that it saved the lives of thousands of sailors. It was called Julian's "Bean Soup".

While still at DePauw, Dr. Julian had discovered the steroid stigmasterol was created as a byproduct of physostigmine isolation from the Calabar bean. This was a serendipitous discovery, a byproduct of his search for a way to synthesize physostigmine. Stigmasterol is a steroid and has a similar structure of many biologically significant compounds such as cholesterol and the sex hormones progesterone, estradiol, and testosterone. The science of steroids such as progesterone and other sex hormones was being developed in a number of laboratories and clinics around the world in the 1930s and subsequent decades. Progesterone was found to be useful in helping pregnant women avoid miscarriages. While at DePauw he had actually written the Glidden company to ask for extracts of their soybean oil so he could pursue work on trying to isolate these compounds from soybean. Instead Glidden hired him!

At Glidden, as the director of research in the Soya Products Division, one day he was asked to go to the large soybean oil storage tanks because water had seeped into the oil and resulted in the formation of a white solid material at the bottom of the tank. Dr. Julian figured out that this material was stigmasteroid and he realized he had stumbled on a method for producing large amounts of the steroid from soybeans. He then figured out how to synthesize progesterone from stigmasterol on a massive scale. Soon Glidden was producing 5 to 6 pounds of progesterone a day and soon after other sex hormones were in production. The Readers Digest Magazine did an article about Dr. Julian in 1946 titled "The Man who Wouldn't Give Up."

But Julian was not done finding amazing new uses for soybeans. In 1949 at the Mayo Clinic, cortisone was first used to treat patients with rheumatoid arthritis. It worked like a miracle. Bedridden patients could walk again. The Mayo doctors, Hench and Kendall, received the Nobel prize for their discovery in 1950. They extracted cortisone from the adrenal glands. The chemical extraction was laborious and expensive. An ounce of cortisone cost $4,000 in 1949 dollars. As the word spread around the world of this discovery, Dr. Julian had a flash

of inspiration: to synthesize a substance very close to cortisone, called cortexolone, from soybean derivatives. This was called "substance S" and it could be easily converted to cortisol, also known as hydrocortisone and then to cortisone. This was a huge breakthrough. This led the way to a low-cost production of these compounds. Dr. Julian was honored as Chicagoan of the Year in 1950 for this discovery.

I use prednisone as a mainstay for treating autoimmune neuromuscular disorders such as myasthenia gravis, polymyositis, and inflammatory neuropathy. While we all know of the side effects that can come from cortisone derived drugs, they are life saving for millions of patients.

Intravenous solumedrol is used in caring for COVID-19 patients in the intensive care unit. Asthma patients depend on steroid inhalation therapies as well as oral steroids. If you buy over- the-counter 1% hydrocortisone cream at your local drug store or grocery for a rash, you are benefiting from Dr. Julian's discoveries.

Others then discovered that Mexican yams (yes, the potato!) were a plentiful source of steroid precursors that could lead to progesterone and other steroids. Julian tried to convince the leaders at Glidden to stop manufacturing steroids from soybeans and switch to Mexican yams. This was a step too much for the paint company! So Julian left Glidden in 1954 and set up Julian Laboratories, initially located in Chicago and then he opened Laboratoires de Julian de Mexico near Mexico City. He was ready to enter the field of competitive steroid production in a big way.

But... there was politics to deal with and the Mexican government would not allow Julian to harvest the yams he

needed. Julian did not give up and a man named Abraham Zlotnik came to his aid. Julian met Mr. Zlotnik in Austria and helped him escape from Nazi Germany. Now Zlotnik wanted to return the favor. He told Julian the same yams were readily available in Guatemala and he arranged for a steady supply of tubers to be send from Guatemala to Mexico. In subsequent years Julian's further breakthroughs were made so that they could quadruple the production of steroids from yams. Rather than increasing their profit margin, Julian insisted the company reduce the price of synthesized drugs like progesterone from $4,400 a kilo to $400 a kilo and the drugs became even more available.

In 1961 Julian sold his laboratory to Smith, Klein and French for $2.5 million dollars and he was one of the richest black men in America. He retired from business, spending time as a public speaker and he remained socially active seeking to advance the conditions for blacks, helping to fund the Legal Defense and Educational Fund of Chicago. He raised money for the NAACP Legal Defense and Educational Fund throughout the country. He financially supported Dr. Martin Luther King Jr. and the Southern Christian Leadership Conference. He said, "All Negros identify with the civil rights movement because none, no matter what his income level, can escape racial discrimination." He served on the board for Howard University, Fisk University, Roosevelt University and Southern Union College, the Chicago Theological Seminary, the State of Illinois Colleges and Universities, the NAACP Legal Defense and Educational Fund and the Center for the Studies of Democratic Institutions. In 1967 Dr. Julian was appointed to the DePauw University Board of Trustees! He was a Fellow of the American Institute of Christ, of the Chemical Society of London and of the New York Academy of Science. He was voted into the National Academy of Sciences in 1973.

Figure 2. In 1993 the US Postal Service issued a stamp honoring Percy Julian for Black Heritage USA.

In 1972 a new Science and Mathematics center was opened at DePauw and Percy Julian gave the dedication address "Science and the Good Life of Man." Dr. Percy Lavon Julian, the man who would not give up, died in 1975 of liver cancer, possibly caused by the many dangerous solvents and chemicals to which he had been exposed. Following his death, DePauw University named the Percy L. Julian Science and Mathematics Center in his honor.

I would like to quote remarks by Dr. Julian regarding racial issues facing black scientists:

"The ghetto gloom of apartheid is slowly but surely fading on the horizon. And a completely new day is dawning for the hitherto schizophrenic Negro scientist. As he is finding his way into university faculties, where his creative talents may find uninhibited outlet, his total intellectual integrity is taking mastery over the frustrating necessity to bolster his own waning spirits. He is slowing arriving; he has faith in himself; and he is becoming a calm, determined scholar – eager, anxious, and definitely destined to write new chapters in the history of discipline. Indeed he is doing so already!...The Negro scientist now need neither starve nor be condemned to a frustrating intellectual ghetto if he chooses pure science as a career." "It will be exciting to see the success of this new Negro intellectual in passing his experience and rebirth on to the less fortunate among his fellow men."

He was such a remarkable man, but I did not know about Dr. Julian until very recently. I wrote an article that included a history of the use of physostigmine and similar drugs for myasthenia gravis and my research did not turn up his name. But then I began researching the early use of steroid drugs for myasthenia gravis and I began reading on the discovery of cortisone and the first miraculous treatment of rheumatoid arthritis patients at the Mayo Clinic. In the book *The Quest for Cortisone* I learned the role of Dr. Julian and it also told of his earlier role in the synthesis of physostigmine. Who knew? Not me. But it turns out PBS knew! After I wrote this EVC message, my Sr. Executive Assistant, Amanda Sebok, discovered that a bio-documentary about Dr. Julian was made by PBS in 2007! I just watched it this week and learned much about Percy Lavon Julian. Check out this amazing video and learn about the dozens of other soy products his Glidden team invented. From soy-based paint, cosmetics, salad oils, margarine, plastics, linoleum, dog food, and soy cheese.

Dr. Julian is an inspirational and accomplished scientist worthy of even more renown. Here is to Percy Lavon Julian, PhD in Black History Month and beyond... son of the south and benefactor to the world through his many discoveries. And, like me until very recently, I bet many of you did not

know this story so I am so glad to be able to tell you about Dr. Julian.

Rick

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COVID Vaccine and Privilege: When Is It Not About You?

Joshua Freeman, MD

Originally published in the *Medicine and Social Justice* blog, https://medicinesocialjustice.blogspot.com/2021/02/covid-vaccine-and-privilege-when-is-it.html

Recently, an article from CNN, "A vaccination site meant to serve a hard-hit Latino neighborhood in New York instead serviced more Whites from other areas", was posted on a medical social justice page of which I am a member. Among a number of others, I expressed my displeasure at this, but I also posted a comment in which I unfortunately said "People are scum". It did not specifically refer to the white people who had obtained these vaccines, perhaps inappropriately, but certainly could be seen as that. I was called out for that comment, and that was appropriate. People are not scum, for better and worse. Scum is a substance that exists without intentionality. People, however, do have intentionality, and that can make them do things that are very good and very bad and everything in between. Certainly, doing something bad, or wrong, does not make a person bad; many religions have doctrines that are more or less comparable to "hate the sin, love the sinner".

More to the point is whether the people referred to in the article did anything wrong or objectionable at all. While those quoted in the article were very critical of this behavior, some of those posting comments on the page felt that these people (presumably people who otherwise met the current criteria in NY for the vaccine, by age or health status) were just trying to do what they could, and not trying to use their privilege to obtain vaccine intended for the minority community. They agreed that the system, and the structure for distributing the vaccine was severely flawed and probably inequitable, but that the individuals pursuing the vaccine should not be condemned. They acknowledged that some people, by virtue of education, wealth, computer-savvy, connections to other family members who may be more computer-savvy, and other characteristics, are more able to avail themselves of benefits. Even when this results in preferentially vaccinating white people rather than the minorities for whom it was intended (by placing vaccination sites in minority communities), it does not mean those individuals (many of whom are sick and elderly) are doing a bad thing, still less are bad people, or certainly scum. Nonetheless, the result is the result; the *New York Times* on January 31, 2021 reports that "Data showed that while 24% of city residents are Black, only 11% of vaccine recipients were. White New Yorkers received a disproportionate share of the shots.

The CNN report was not the only one critical of people "jumping the queue". In a *NY Times* Op-Ed on January 28, 2021, Elisabeth Rosenthal MD, editor of Kaiser Health News, writes "Yes, It Matters That People Are Jumping the Vaccine Line":

For weeks Americans have watched those who are well connected, wealthy or crafty "jump the line" to get a vaccine, while others are stuck, endlessly waiting on hold to get an appointment, watching sign-up websites crash or loitering outside clinics in the often-futile hope of getting a shot.

She adds, agreeing with some of the points made by the commenters on the site, "I don't blame the lucky recipients; after all, hospitals would just offer the unused vaccine to the next person on the list," but also notes that "The problem is that often, people are not really being "offered" the vaccine; in some cases, they are grabbing it through position, influence or deceit." How often? I don't know, and probably Rosenthal does not either. Or, for that matter, those who posted comments on the page, although they seem to be from NY and likely to know a lot more about the situation there than I do.

Most likely, the predominantly white recipients of the vaccine being offered in minority neighborhood represent a spectrum of people. They would include those who consciously believe that they are special and privileged and deserve to be at the head of the line, those who believe in equity but let that concern be overcome by their self-interest, and those who are appropriately candidates for the vaccine in the current phase but are desperate, confused, and, with no negative or ignoble intent, found their way to that place and time. Defending the latter, however, does not excuse the former, and there are certainly many of them. *Freeman's Law* (which I should probably rename "Freeman's First Law" so as not to confuse it with *Freeman's Second Law*, to which I referred in my blog post of January 28, 2021, "Vitamin D, false nostrums, and conspiracy theories: The world has enough real problems,") states that in any program designed to help a group of people, no matter how narrowly defined, those with the relatively least need are most likely to benefit. Thus in a program designed, say, to help homeless pregnant teenagers with HIV living under bridges, those who have some greater resources (a bit more education, a slightly less traumatic childhood, etc.) will be the ones who are able to access it first. The larger

the universe of people who are targeted, the more people who would qualify for services, the greater the disparity is likely to be. This is of course especially true in the case of COVID vaccine, where the target population is, ultimately, everyone.

Another aspect of the comments posted that was interesting to me was that they referred to those seeking to get the vaccine as "patients". Perhaps this is understandable on a medical site, and it is quite possible that some of those involved were patients of those doctors who made the comments. I have sometimes been critical of the use of the term "patients", noting that it was the "medical" word for what in English are called "people", and that it could tend to diminish their humanity. I am quite sure this was not the intent of those using it, but in this context it has quite another flaw. Calling folks "patients", especially when they are not your patients, carries a connotation of dependency, needing help from their doctor. Calling them "people" implies more that they have agency, the ability to make decisions, prioritize needs and values, and act on them. While it is often true that many people, particularly the sickest and oldest and least educated and least empowered do need help, it is also true that when the affected universe is the entire population, it includes all of us, all people, adults and children, young and old, Black and White, rich and poor, doctors and "patients". It includes those who are the wealthiest, most educated, most connected, and most empowered, who are often find ways to get to the head of the line. Thus, prioritizing who should get the vaccine first and enforcing that is critical. Social justice is about promoting equity, which means giving more help to those who have the least and need it the most, and reducing the temptation to give in to those whose privilege or loud voice is most demanding.

Rosenthal writes:

The United States has allowed its public health system to become a hollowed-out underfunded mess, and many vaccination clinics are being run and staffed by contracted private companies. And the private sector has so far proved too vulnerable to private favoritism.

Until the supply is sufficient, the government needs to give the shots to the people and places that need it most, and find ways to ensure that the plan is followed; the system could prioritize ZIP codes that have high Covid-19 infection rates or target low-income populations who might otherwise have a difficult time securing an appointment.

She is absolutely correct, but clearly targeting certain ZIP codes is not sufficient, as the Times describes on February 2, 2021 in 'Even in Poorer Neighborhoods, the Wealthy Are Lining Up for Vaccines' (Feb 3 print title: 'Where poor suffer most, wealthy find vaccines'). And a 52-year old celebrity on-line fitness trainer got the vaccine as an 'educator'. Meanwhile the COVID surge most hurts those in the poorest neighborhoods, as in LA. And people behaving as though the doors were opening at a department store the day after Thanksgiving is not just a NY problem. a friend in another city, on seeing the pushing and shoving, both literal and figurative, that went on when they went to get their vaccine, said "I wouldn't want to be in a concentration camp with those people."

The problem, if you think it is a problem, of empowered people going to poor neighborhood to get their vaccines is real and ongoing. I think that folks who do so are doing a selfish thing, a bad thing. This in itself does not make them bad people, or certainly scum. However, for the record, I personally believe that there are indeed bad people, and that doing enough bad things often enough, predictably enough, and bad enough does make someone a bad person (see, e.g.,"Nazis").

We should have compassion for those with need, and the most compassion for the greatest need. And recognize that "me" is not the hallmark of social justice.

The Lost Muse

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Paul was a 40-something vivacious guy who loved his paint brush and was ever eager to revive the modern art scene in the city. He spent hours in his basement working on the canvas which he called his 'Muse'. He had noted to his friends that this particular painting would bring the city alive. One day when his friends came to visit him they noticed that he was holding the paintbrush awkwardly. He still had the finesse but he was just struggling with his brush. They urged him to meet his primary care physician who in turn referred him to us.

On our first meeting we spent a great deal of time talking about the 'MOMA' in New York and he seemed cheerful and even optimistic that I could fix him and he could go back to his Muse. As I continued to examine him I noticed that he had twitching all over his body. He could not tightly squeeze my fingers and his hand movements just seemed clumsy. We put him through the grind of medical testing including multiple blood work, MRI scans and the dreaded EMG. When I met him back in the clinic the tension and anxiety was palpable in the room. This time around his hair was unkempt, clothes loosely hanging and he seemed queasy.

I slowly went over all the testing that I had done so far. Then holding his hand I gave him the inevitable diagnosis of Lou Gehrig's disease. There was a hush of silence in the room and after a while Paul asked me how long would he live. He told me that he didn't fear dying but he just wanted to get back to his Muse and complete the painting.

As the months passed by he progressively became weaker and had even greater difficulty painting. He read about stem cell therapy in Mexico and traveled all the way there to try it. It didn't help him and in turn only made his symptoms worse. He read about an antibiotic infusion that helped a few patients with Lou Gehrig's and traveled to a 'special clinic' to get these. Even this didn't help. Then he read about lithium (the medication that is used in mood disorders) that seemed to have helped a few patients with Lou Gehrig's. He tried it. He had also heard about an herbal medication that helped a few patients and spent his life savings on buying that.

None of these so-called therapies helped him. He told his friends that he tried all these medications not because he wanted to live longer or enjoy his life. He hoped that at least one of these treatments would give him enough strength to go back to his Muse and complete his work.

By the time I saw him 8 months later, he had become wheelchair bound. He could no longer hold his head up and was drooling saliva. I talked to him about getting a feeding tube as well as getting an assist device for his breathing. He seemed more at ease this time but he still spoke to me about his unfinished Muse. That was a last I ever saw of Paul. A year later I got a letter from his friend noting that Paul had passed away in his sleep. His Muse though still remained incomplete.

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Chewing Ice

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Sitting in this room alone
Eating ice while the wind blows,
Watching tv with the actor in my room,
Blowing smoke into my face.

Blowing out the sunny sun.
Riding waves that have washed away.
Climbing trees that I cut down.
Selling candy to a clown.
Telling jokes at a funeral.
Crying when the laughter rains.
Chewing ice with the wind on.
Flaming up a burned down house.

Catching stars by shooting them down.
Flying up to the moon tonight
Without a ticket back home.
Selling gold to an alien.
Shooting him when making truce.
Falling back all the way down
To this hell I have borne today.

Putting holes in my umbrella
The night the storm it catches me
In a state of sleepy slumber.
Waiting for the stars to shine.
Waiting for the sun to rise.
As I shoot them from the sky.
Watching the fireworks fire away.
Watching my dreams explode and run.

Ice, ice is melting away
As I chew it under the snow.
Falling slowly into my mind.
Freezing all the thoughts of love.

Coming together.

IMAJN and the RRNMF Neuromuscular Journal

Richard J. Barohn, MD

Imagine there's no countries
It isn't hard to do
Nothing to kill or die for
And no religion, too

Imagine all the people
Livin' life in peace

You may say I'm a dreamer
But I'm not the only one
I hope someday you'll join us
And the world will be as one

From John Lennon's "Imagine"

The news from the Middle East this past week is as bad as it can be. There does not seem to be any solution to stem the violence and hatred between Israelis and Palestinians. Nevertheless, something needs to be done to improve the grave situation on the ground and literally in the air. I am a physician and neuroscientist and I know very little about the problems in the Middle East. Being raised in a secular Jewish American family in a middle-class St. Louis suburb shielded me from the growing problems in the Middle East while I grew up in the 50s, 60s, and 70s. It was not until I left active duty in the U.S. Air Force in 1989 and began rising through the academic ranks in the University of Texas Health Systems in San Antonio and then Dallas that I began to work closely with Arab and Muslim physicians. Over the years, as the situation in the Middle East kept getting worse and worse, I met more and more colleagues from the region who came to the U.S. for a variety of reasons to further their medical career and who would become close friends. But at its root, the reasons to come to the U.S. were similar to how my great grandparents left Eastern Europe to move to the U.S. at the turn of the 19th century: both groups of immigrants wanted a better life. The USA for so many immigrants has become a melting pot of numerous cultures and the lines of division between various religions that occur in their homelands of origin are largely diffused in the U.S. Here, in whatever field you choose to enter, what should count is what you do in your work and career, not what tribe you came from. So I am blessed with many Arab and non-Arab Mediterranean friends, some Muslim and some Christian, from many countries, who I work with, see patients with, write papers and grants with, put on courses with, and socialize with. And while I know the issues in Israel and Palestine are deep-rooted and do not lend themselves to easy solutions, I take solace in the close network of neuromuscular neurologists from all religions and regions we have created that really do work as a team and network to advance our field and to help patients.

About ten years ago, after a similar major upheaval in the Middle East when I was again pondering "What can be done?", I had an idea called IMAJN: Initiative for Muslim and Arab and Jewish Neurologists. The idea was to create a scientific forum for us to work together that could be in the form of meetings or work groups or training programs. The idea was to show how Muslims, Arabs and Jews could work productively together at least in our narrow field of neurology, and in particular, neuromuscular diseases. I ran it by one of my very close Arab/Muslim friends, Dr. Aziz Shabani, who many of you know. He nicely and kindly told me, "Rick, it's a nice thought but I don't think this is a good plan." And I think he was worried that if we announced such a program then the next step is: ok, now what do we do? I am sure he felt I was setting myself up for a big disappointment. And Aziz has emphasized to me over the years that the problem is not religion. People of various religious backgrounds have been able to coexist under the same country and city throughout civilization. Aziz recently wrote to me: "Mandela did not resist the apartheid because of religion; the Indians did not resist the British because of religion; the Iraqis resisted the Iranian and Turkish occupation despite the occupiers were Muslims. Arabs in Andalusia cherished Jewish contributions for hundreds of years (Maimonides, etc.) with no regard to religion." And, of course, Dr. Shabani is right. The problem is not religion. The problem occurs when one group does not consider another group fully human, or treat them and respect them as fully human beings. It is an ethical issue. As Dr. Shabani further stated in a note to me: "Condemnation of the settler-colonial project, instead of equating the victimizer with the victim, is the only way for justice." So, I kept my idea quiet between the two of us and we went about our business working closely together as we always have, advancing our field, and becoming closer and closer friends.

After reading, seeing, hearing the news over the last week from Palestine and Israel, I again thought of IMAJN. But now it is ten years later and I realized that through our continued work in the RRNMF website, the RRNMF Neuromuscular Journal, and the Neuromuscular course that we do in many cities around the country (virtually for the last year), I think we have our IMAJN. We have many forums where Muslims, Christians, Jews, Hindus, Buddhists, and atheists or nonbelievers all vigorously participate. And while there are large groups such as the AAN and AANMEM that many of us are members of, these smaller projects that we have developed via the website, journal, and the course really allow us to know each other so much better and work together more intimately.

So I think we really have our IMAJN in our small neuromuscular neurology world. I just wish it was that easy for the Middle East. Once again, as Aziz said to me: "The good friendships that you mentioned confirm that the issue is not religion."

Rick

Effect of the COVID-19 Pandemic on Neurology Trainees' Education and Practice

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Keywords: *PPE, COVID-19, resident, trainee, education*

ABSTRACT

Glossary: PPE = Personal Protective Equipment; COVID-19 = Coronavirus Disease 2019.

Introduction

Since December 2019, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), that spreads by close proximity between humans[1], has produced a global pandemic known as COronaVIrus Disease-19 (COVID-19)[2]. The World Health Organization declared COVID-19 a global pandemic on March 11, 2020[3]. In the United States, cases of COVID-19 have surpassed 6 million with more than 200,000 deaths[4]. The virus has had a significant impact not only on health care systems but nearly all aspects of life[5]. Residents and fellows are at the frontline of patient care at most academic and teaching hospitals with an increased risk of exposure to communicable diseases[6]. They face challenges with personal safety and well-being, disruptions in training and practice, and relationship strain[7].

Neurology resident education and service continued to be affected by the COVID-19 pandemic[8]. Trainees on inpatient rotations have been at the forefront of caring for afflicted patients, whereas the challenge in outpatient rotations has been the rapid adoption of telemedicine practices and transitioning to virtual visits[9]. The required social distancing has been affecting education, including daily resident lectures, grand rounds and conferences. Physical and emotional strain on trainees in New York City, an epicenter of the pandemic in the US early on, was palpable[6].

As the pandemic unfolded, neurology trainees anecdotally reported modifications to their schedules, educational and academic activities, and administration of inpatient and outpatient services. This survey aimed at gathering data on the varied experiences by neurology trainees across the country.

Methods

The authors developed a self-administered, English-language survey of 36 questions using Google forms. The questions were developed based on consensus amidst the authors and focused on issues raised during the COVID-19 pandemic that warranted further exploration. The survey was sent to US-based trainees in neurology (residents and fellows) through a number of mechanisms including social media platforms (Facebook©, Twitter©), email list services (program director mailing lists, residency lists, and local state neurology societies), and the American Academy of Neurology (AAN) Synapse platform. Participation in the survey was voluntary and anonymous, and consent was obtained by agreeing to participation. The target audience was any active resident or fellow in neurology or a neurology subspecialty. The survey was open online from June 27, 2020 to August 18, 2020.

Questions included basic demographics (age, sex, state, graduate year training), practice and education before the pandemic, and practice changes due to the pandemic (telemedicine, use of personal protective equipment (PPE), institutional guidelines, impact of the pandemic on the well-being of trainees).

Potential confounders included the possibility that the survey could be taken twice by the same individual—given desire to preserve anonymity, we chose not to track respondents or require sign-in but encouraged respondents to only take the survey once. Missing data points were handled by reducing the total number of respondents as applicable. However, there were very few relevant missing data points. One respondent did not check "yes" in the consent-landing page and that response was not included in the final dataset.

Data Availability

The complete survey and the raw anonymized data will be shared by request from any qualified investigator.

Standard Protocol Approvals

The study protocol was reviewed by the Emory Institutional Review Board and was deemed to meet criteria for exemption under 45 CFR 46.104(d)(2). The study was approved for indefinite exemption, barring significant changes in the protocol.

Table 1. Demographics (N=285)

Sex[a]	Male				Female
	91 (32%)				192 (67%)
Training Status	PGY2	PGY3	PGY4	Fellow	Child Neurology
	57 (20%)	75 (26.3%)	76 (26.6%)	50 (17.5%)	27 (9.5%)
Setting	Academic				Community
	266 (93.3%)				19 (6.7%)

[a] One respondent preferred not to answer, one non-binary

Results

286 US trainees participated in the survey. One participant did not consent and was excluded. Of the 285 trainees whose responses were analyzed, two-thirds (67%) identified as female, and almost all (93%) practiced in a university setting. Thirty-four states and the District of Columbia were represented with the most respondents from California (35/285, 12%), Pennsylvania (31/285, 11%), Georgia (29/285, 10%), and New York (23/285, 8%). There was an even breakdown of responses by post-graduate year as shown Table 1.

Telemedicine

More than half of trainees (60%) reported telemedicine being available prior to the pandemic at their institutions, used mainly in the inpatient setting for stroke care (45%). Among trainees, only 13% reported using these available telemedicine platforms prior to the pandemic. Up to 84% did not have training in telemedicine prior to the pandemic.

After the onset of the pandemic, the vast majority (91%) of respondents reported using telemedicine as a medium for patient care. Telemedicine was used in the outpatient setting (48.1%) and combined outpatient and inpatient (43.2%) settings. In the outpatient setting, 70% of respondents reported using telemedicine for general neurology visits and 54% reported using it for subspecialty neurology clinics.

The majority of trainees (78%) reported using telemedicine for both new patients and follow up visits. Notably, only 42% received education in telemedicine including how to perform a neurological examination. Despite this, 50% (143) trainees reported performing tele-neurological examinations including validated scales such as the NIHSS, UPDRS, MoCA as shown in figure 1. Supervision by an attending was synchronous during the tele-visit in most instances (57.6%), however 41.5% reported asynchronous supervision, and less than 1% reported no supervision at all.

Impact on Practice

Respondents were surveyed regarding alterations to inpatient and outpatient schedules. Almost a third of trainees (33.6%) reported a decrease in inpatient schedules, while more than half reported no change (29%) or increase (28%) in inpatient schedules. More than half (56%) reported a reduced clinic schedule in the outpatient settings, about 11% reported increase in clinic schedule while about one third (32%) had no change in outpatient schedules.

These changes caused 32% of respondents to feel worried about losing their neurological examination skills, and 73% of respondents to feel that their patients' access to care was reduced by the pandemic.

Figure 1. Validated scales used during telemedicine visits.

Breakdown of the validation scales used by 50% (143) trainees during televisits.
NIHSS = National Institutes of Health Stroke Scale, MoCA = Montreal Cognitive Assessment (MoCA), UPDRS = Unified Parkinson's Disease Rating Scale, SARA = Scale for Assessment and Rating of Ataxia, Other measures (<1%) = MMSE, ABCD2, SLUMS, etc.

Impact on Education and Research

A majority (77%) of respondents believed that the pandemic affected their education. Almost half (48%) noted fewer lectures, and virtually all respondents (98%) reported transition of lectures to telephone or video-conferencing platforms.

Forty percent reported a reduction in grand rounds, and 17% reported that there were no grand rounds at all during the pandemic. Almost half (48%) stated that morning rounds continued at a similar frequency but in a virtual setting, while 33% indicated less frequent morning rounds. 77% of trainees accessed lectures outside their institutions, and 84% believed that tele-lecturing was an effective educational tool.

Among trainees involved in research, 48% stated that their research continued during the pandemic uninterrupted, while 32% reported that their research activities were reduced.

Impact on Trainees' Mental Health

A majority (75%) of respondents indicated that they experienced moderate to very high levels of additional stress during the pandemic. A positive trend was found between respondents reporting very high stress and increased inpatient workload (Pearson Chi Square 21; df=4; $p<0.001$) (Figure 2).

When asked about PPE availability and institutional guidance about the pandemic, a third (33%) reported that they had insufficient PPE (Table 2). Several respondents provided additional comments noting that during the onset of the outbreak, PPE was insufficient causing re-use of masks for weeks at a time, but as the pandemic went on, they were able to secure sufficient PPE.

A majority (64%) of trainees felt somewhat to very unsafe, and almost all (95%) of them reported feeling somewhat to greatly worried about exposing themselves and their families to COVID-19.

On a personal level, 38% of trainee's stated needing childcare, and of these 33% described difficulty obtaining childcare during the pandemic.

Discussion

This is the first study to our knowledge looking at the impact of COVID-19 on neurology trainees across the United States. The responses of the trainees closely reflect much of the global experience with COVID-19, with rapid modifications to include quick implementation of telemedicine, remote online lectures, and personal feelings of uncertainty.

While in previous natural disasters training programs impacted by calamity were able to rely on the support of other institutions, a global pandemic with no unaffected region to support or relieve the pressures, has caused significant strain on the training system. Prior natural disasters like the Hurricane Katrina in 2005 in New Orleans disrupted medical training causing a drop in USMLE step 2CK scores[10]. In Texas, hurricane Harvey put trainees and their patients through significant stress with increased signs of burnout[11].

As with previous disasters, resident practice patterns have been affected[10,11]. A majority of trainees have noted an overall decrease in clinical time. This reduction in clinical exposure is likely due to reduced overall clinical operations. This was partially mitigated by the implementation of telemedicine with a striking seven-fold increase in use of telemedicine among trainees. The rapidity of the pandemic engulfing the country however did not allow for enough time for proper training in telemedicine, with the majority of trainees (63%) having to use this new technology without training, and in half the visits without proper synchronous

Table 2. Responses regarding stress and PPE availability

Stress at Work	Minimal	Modest	Very High
	26%	47%	27%
PPE availability	Yes	No	Other
	58%	32%	Variable at different points in pandemic with difficulty in the initial phase
Feeling safe at work	To a great extent	Somewhat	Not at all
	36%	58%	6%
Worry about exposing family	To a great extent	Somewhat	Not at all
	37%	58%	5%

PPE = Personal Protective Equipment

supervision by an attending. The AAN Telemedicine Work Group recommends comprehensive training in clinical bedside neurology for the safe practice of teleneurology[12].

Neurology has had a longstanding history of using telemedicine, with the first telestroke pilot programs developed about twenty years ago[13,14], then expansion throughout multiple neurologic subspecialties[15,16,17]. Moreover the remote utilization of functional and outcome metrics has been validated, including the NIHSS[18], stroke dysphagia screen[19], modified UPDRS[20], and MoCA[21]. Despite lack of training, most trainees were able to incorporate telemedicine into their patient care and remotely manage patients, ensuring continuity of care as much as possible. Development of more structured and focused training on telemedicine education is likely needed to better serve residents in the future.

In addition to the impact on bedside teaching, curricula and their method of delivery have been drastically affected as well. COVID-19 and associated social distancing practices have limited group lectures, cancelled or delayed major and minor conferences, and pushed many into the world of online learning. Our survey confirms that trainees report fewer lectures in addition to a reduced number of grand rounds and morning rounds lectures. Many trainees engaged in outside lectures, this could be related to increased availability of virtual grand rounds and other online accessible resources. While 84% found tele-lecturing an effective medium, this still represents a marked change in education style. Combining the reduced didactic education with reduced clinical exposure, the practical impact on training could be substantial.

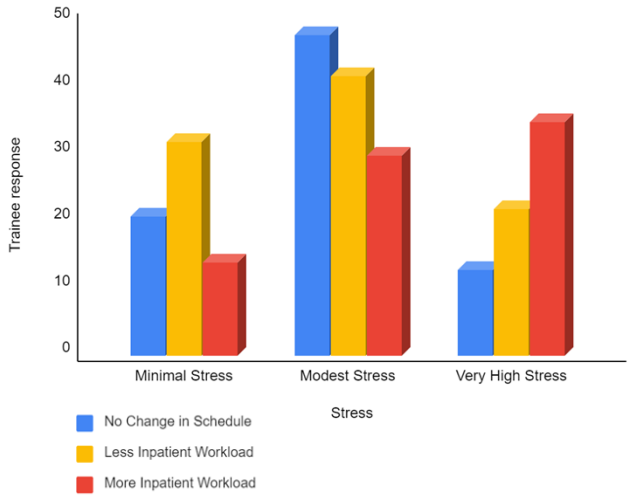

Figure 2. Correlation of stress levels among trainees with inpatient service.

As seen in previous natural disasters, we also note that residents suffered emotional distress. While there is no tangible environmental destruction as seen in previous disasters directly affecting housing, childcare, and physical structures, COVID-19 has caused significant economic and social disruption, as well as the constant looming threat of exposure to infection. The majority (75%) of residents reported at least a moderate increase in stress. Increase in inpatient service load was a significant factor in increasing stress as seen in figure 2. Inadequate PPE was also felt to be a factor in increased stress and feeling unsafe. On a personal level, trainees noted challenges with childcare, concern of spreading COVID-19 to family at home, and simply increased overall stress.

Limitations

Our survey questions were developed with consensus amidst authors, which could be a limitation. Although we had a good representation of trainees, the number of survey participants was small, around 8% of neurology trainees[22] (3643 US based combined residents, child neurology residents and subspecialty fellows per AAMC reports 2018-2019). Low response rate is possibly due to time requirement on behalf of trainees and survey availability on limited platforms. Female neurology trainees were overrepresented in our sample as the survey was posted on the Women's Neurologist Group on social media. We had representation from 34 states, even though California and New York had good response rates, together they represented 20% of the study sample. Another aspect is the timing of the survey as the stress level, use of technology was different in the initial phase of pandemic. As neurology training programs adjust policies and embrace technology and tele-neurology education, responses may change. We plan to send a repeat survey at a later time point to gather data on the changing practices and experiences of the neurology trainees.

Conclusion

This study demonstrates that neurology trainee clinical practice and education was significantly affected by the COVID-19 pandemic. Most trainees had no training in tele-neurology prior to the pandemic, yet the majority of them were thrust into the world of telemedicine, often without much training. An overall negative impact was noted on trainee education and wellbeing, with reduced educational activities and increased stress. As the long-term effects of the pandemic on society, patient care, and medical training

remain unknown, neurology training programs must remain adaptable and innovative to meet these changing needs.

Experience gained in this pandemic should lead to formulation of residency and fellowship curricula with optimal preparedness and safe practice measures for trainees. Programs should incorporate training on teleneurology examination techniques, including the use of validated scales such as the MoCA and modified UPDRS remotely. It is critical to ensure safety of trainees, provide adequate PPE, and ensure adequate mental health assessment and support for their wellness as mandated by ACGME. Incorporation of innovative and dynamic modes of education using technology, simulation labs, and video conferencing will promote safe education and preparedness in the event of future global catastrophes.

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Appendix: Authors

Name	Location	Contribution
Amtul Farheen, M.D.	Penn State Hershey Medical Center, Hershey, PA	Design and conceptualized study; survey development; contributed to data analysis; contributed to manuscript writing, revision and created final draft
James Grogan, M.D.	Penn State Hershey Medical Center, Hershey, PA	Survey development; contributed to manuscript writing, analysis and revision
William K. Jens, D.O.	Penn State Hershey Medical Center, Hershey, PA	Survey development; contributed to manuscript writing, analysis and revision
Christina Maxwell, PhD	Global Neurosciences Institute, Pennington, NJ	Survey development; performed majority of data analysis and interpretation and contributed to manuscript
Karima Benameur, M.D.	Emory University, Atlanta, GA	IRB process; survey design and development; contributed to manuscript writing, data analysis and manuscript revision

Clinical-Epidemiological Characterization of Guillain Barré Syndrome in a Cuban Case Series

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Keywords: *Guillain Barré syndrome, case series, prognosis*

ABSTRACT

The broad spectrum of Guillain Barré Syndrome (GBS) includes different pathological phenotypes, with a heterogeneous distribution. The reports, by country and region, have shown its great variability and clarified its behavior.

Objective: Characterize GBS and define the most frequent phenotypes.

Methods: A time series was constructed to analyze the epidemiological behavior of GBS. The demographic, epidemiological, clinical, and complementary aspects of 167 patients were retrospectively described. The severity was analyzed and the patients were classified.

Results: The mean age was 33 years, 22.8% were children. The incidence decreased with age and a seasonal preference was seen for the month of August, that usually coincides with higher rates of respiratory and digestive infections. Dengue preceded some GBS outbreaks. The Acute Inflammatory Demyelinating Polyradiculopathy (AIDP) variant predominated and was most severe. Regional variants, a recurrent GBS and a family one were detected. Age, personal history of autoimmune disease, preceding infectious phenomenon, latency between the preceding phenomenon and the onset of the clinical picture, the extent of the motor disorder, facial involvement, gait impairment, ventilatory compromise, and degradation of the osteotendinous reflexes, significantly correlated with the severity.

Conclusions: The predominance of AIDP coincides with some countries in the area, with varying geographical location and climatic conditions. The incidence decreases with age. The relationship between the severity and the personal history of autoimmune disease, the preceding infectious phenomenon, and the latency between the preceding phenomenon and the onset of the clinical picture, could be reflecting an underlying autoimmune mechanism in each case.

Introduction

GBS is the most common, rapidly evolving, and potentially fatal acute neuropathy. It is an autoimmune, self-limited, monophasic disease, generally triggered by an infectious process, in which the spinal and cranial peripheral nervous systems are widely affected, and courses with somatic (motor and sensory) and dysautonomic manifestations.[1]

In the first few days, the diagnosis is clinical, which can later be reinforced by the presence of albumin-cytologic disassociation in the cerebrospinal fluid (CSF) and the neurophysiological alterations.

This kind of paralysis, over the last century has motivated continuous reports of cases in the literature. Over time, it was associated with anatomical damage to the peripheral nervous system and the typical alteration in the cerebrospinal fluid (CSF) was demonstrated. Clinical descriptions have been numerous, from Landry (1859) and Osler (1982) to 1916, "year 0" of the GBS history.[2]

This year, Guillain, Barré and Strohl reported the "radiculoneuritis with acellular hyperalbuminemia of the cerebrospinal fluid". But, in the middle of the 20th century, the controversy over whether it was or not Guillain-Barre syndrome continued and it was argued that Guillain-Barre syndrome was easy to diagnose but impossible to define.[3] The pathological findings of the disease were reported (Haymaker and Kernohan) and its autoimmune pathogenesis were considered (Waksman and Adams), which was later confirmed by Asbury.[4] Since then, various classification systems have been proposed and numerous reports show the other sides of GBS (non-classical forms). In this way, the spectrum of GBS has been markedly broadened and includes different pathological phenotypes.

GBS is known to be a worldwide-recognized disease with the geographic distribution of the different GBS variants highly variable. Most authors report that in North

America and Europe the classical demyelinating form or AIDP represents up to 90%[5] and only about 5% of patients have the axonal subtypes. Whereas in China, Japan, and some countries within Central and South America, the axonal subtype predominates.[6] In the Latin American region, information is scarce and variable. In general, a predominance of demyelinating forms is reported, such as Chile,[7] Colombia[8] and many others; while some countries report a predominance of axonal forms, such as Mexico, [9 10] Peru[11] and a few others. In this article, we will describe the clinical-epidemiological behavior of GBS in a series of Cuban patients.

Objectives

Describe the demographic-epidemiological, clinical and complementary exam variables of GBS.

Methodology

The files from the Institute of Neurology and Neurosurgery (INN) were reviewed over a period of 30 years, from 1967 to 1997, a period in which the INN was the national reference center for GBS. A total of 409 patients were admitted. With the admission dates of patients, a time series was developed to analyze the epidemiological behavior of GBS. A total of 167 of the most complete medical records were selected for a detailed description of the demographic, epidemiological, clinical and complementary exam features of the disease. Multivariate analysis was carried out exploring the existence of correlation between the different variables that could explain the etiopathogenical aspects of the disease. The correlation, according to Spearman, of severity and demographic, epidemiological, clinical and complementary exam variables were analyzed. The cases were classified according to their clinical and neurophysiological characteristics.

Results and Discussion

Demographic Variables

The mean age in the case series was 33 years, with a minimum age of 2, a maximum age of 84, and a standard deviation of 20,407. Most of the authors similarly report a wide range of age of occurrence, but with a mean age around 50 years.[12] However, some authors report lower, younger mean ages[13]. Figure 1 shows the age distribution, with classes of 10 years. It appears to be a bimodal distribution, with two peaks: one before 40 years of age and another after 50 (the lower of the two), with an intermediate class between 40 and 50 years that shows the lowest number of patients. Figure 2 shows the age distribution, with classes of 20 years. In this, a frank decrease of incidence with age was observed, with a striking decrease after the 70s.

The disease occurred in 38 children, between 2 and 15 years old, for 22.8%, with a mean of 8.37 years and a standard deviation of 4.149. The group between six and 10 years was the one with the highest frequency (16 cases for 42.1%), similarly to that reported by Maneesh Kumar et al.[14] Classes younger than six years old and older than 10 years old were presented with the same frequency in our study (11 patients for 28.9%). Four patients were 2 years old. Hung refers that the incidence in children increases with age and is rare before two years of age.[15] However, Sinan found five patients (13.8%) under two years of age.[16]

There was a predominance of whites, 134 patients (80.2%) over blacks, 28 patients (16.8%) and mixed race, 5 patients (3%). The disease was more common in men (88 patients/52.7%) than women (79 patients/47.3%).

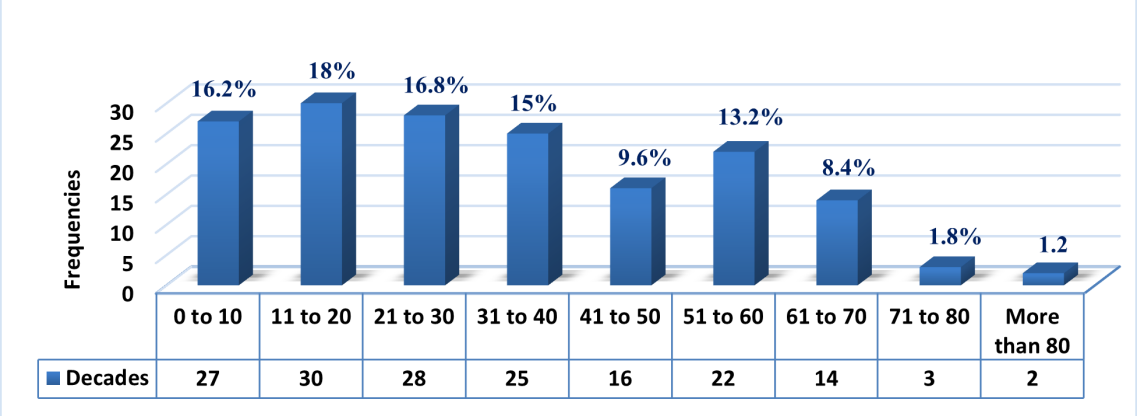


Figure 1. Frequency distribution of age (every 10 years).

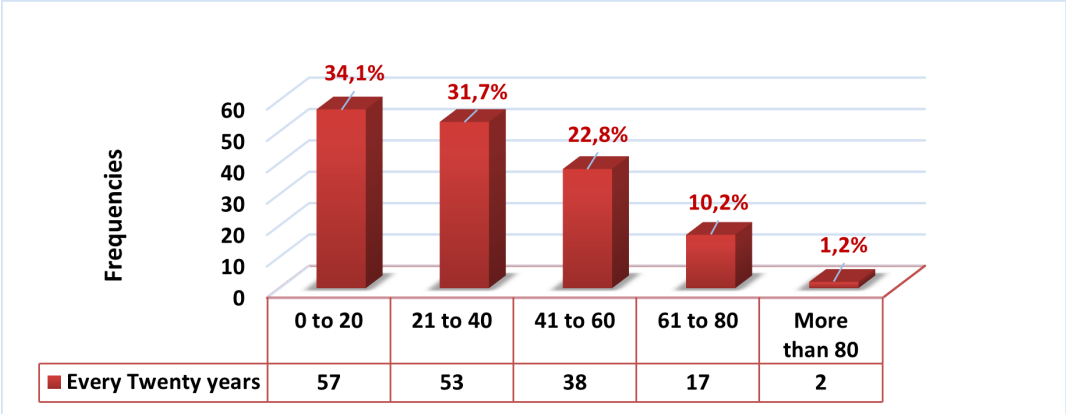


Figure 2. Frequency distribution of age (every 20 years).

Preceding Phenomenon

In 106 of the patients (63.5%) a preceding event was evidenced, which preceded the onset of the clinical picture in a mean time of 13.83 days. In 97 patients it was infectious, with respiratory infections (31.7%) more frequent than digestive ones (10.8%). One aspect of interest was Dengue as a preceding phenomenon. This was presented in 7 patients for 4.2%. In 9 patients (8.5%), the preceding event was non-infectious. In 3 patients there was a history of vaccination and in another 3 physical exercise was referred. Surgical intervention, head trauma and immediate postpartum were present in 1 patient each.

Time Series Analysis

In the annual time series, we observe the epidemic behavior of GBS in our country for 30 years (Figure 3). During this period, 409 patients were treated at the Institute, a minimum of 4 cases per year and a maximum of 31, with a mean of 13.06 and a deviation of 2.12.

Several peaks of more than 15 cases per month are observed (above the mean of 13.06 cases). The first peak, of 31 patients, in 1969, was in relation to a serious influenza epidemic. The second peak comprises years 77 and 78, with a total of 38 patients, (18 and 20 patients, respectively). This is the first report in the national and international literature of post-Dengue GBS, it was related to a serious epidemic of Dengue hemorrhagic fever, serotype 1.[17] Then another increase is observed in years 81 and 82 (23 patients in each year). This increase was reported in the national literature,[18] also after Dengue outbreak. The series highlights another increase in 1984 (20 patients), another Dengue outbreak in Cuba, followed by other increases in the number of cases, of lesser quantity, where we do not have a clear relationship with frank dengue epidemics or other preceding. In 1994, there was an increase in GBS cases in the Arroyo Naranjo municipality (200 patients). It was preceded by an epidemic of gastroenteritis, caused by an enterobacteria, due to the ingestion of contaminated water. A similar situation occurred in Florida in 1986.[19]

GBS Seasonality

It is reported in the literature that GBS seasonality is related to the epidemiological situation of the country. Cuba has a tropical climate, with a dry season, with cooler temperatures (from late November to mid-April) and a rainy, hot and humid season (mid-April to early November, mainly from May to October). In our series of cases, two annual peaks of GBS were evidenced. One small in the

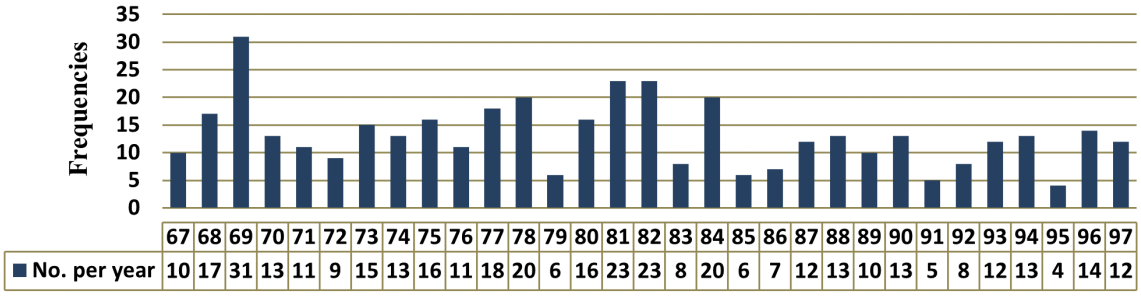


Figure 3. Number of cases per year. Serie of 30 years and 409 patients.

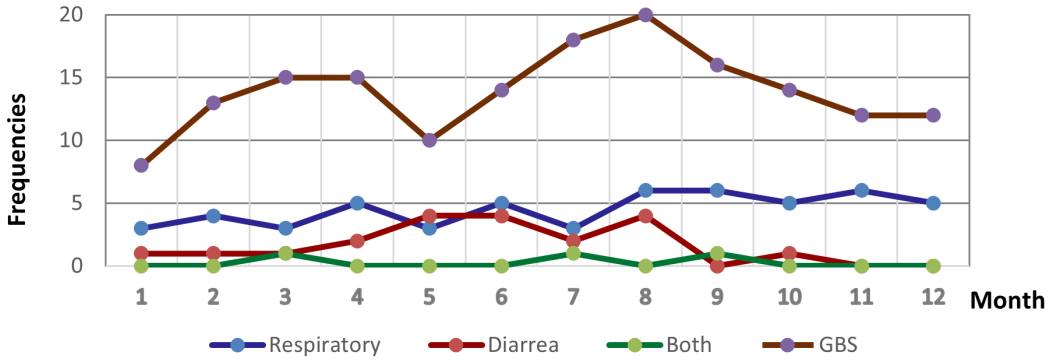


Figure 4. GBS seasonality and preceding infections.

months of March-April (at the end of the dry season) and another, larger, in the month of August (rainy season) (see Figure 4). The highest incidence of the syndrome occurred in the month of August, such that it can be clearly said that GBS in Cuba has a seasonal preference for that month. During this month there is a coincidence in the increased incidence of respiratory and digestive processes. The month of August is a rainy month, such that it also favors the growth stages of arboviruses, frequent in our country as a precedent.

Family and Personal History of Interest

Regarding the family history, we found the occurrence of GBS in two siblings, two months apart. The familial occurrence of GBS reinforces the genetic hypothesis.[20 21] One patient presented GBS on two occasions. Although exceptional, there are isolated reports in the literature of recurrent GBS.[22 23]

Time Elapsed Between the First Symptom and Admission

The average time it takes patients to see the doctor, after starting with the first symptoms of the disease is 11.82 days, with a standard deviation of 10.989 and a range that ranges from less than 24 hours to 61 days. Almost half of the patients (47.3%) attend before the first week and 88.6%, before the month.

First Symptoms

Muscle weakness was the first symptom and the most relevant reason for consultation in our study (59 patients for 35.3%), followed by sensory disorders (53 patients for 31.7%), while in 31 patients (18, 6%) pain was the first symptom and anticipated motor and sensory symptoms. In 23 (13.8%) the disease began due to combinations of two or more symptoms (motor and / or sensory and / or pain and / or dysautonomia). Only one patient (0.6%) presented from the beginning, and as cardinal manifestations, ataxia and diplopia, being a Miller Fisher syndrome (MFS).

Clinical Picture

As can be seen in Table 1, at the nadir of the disease, muscle weakness (100%), hypo / areflexic (99.4%), with significant compromise of gait (98.2%) predominated. It was followed in frequency by ventilatory disorders (32.9%), radicular signs (29.9%) and sensory disorders (26.9%). Autonomic signs were present in only 13 patients (7.8%), eight patients had ataxia for 4.8% (6 proprioceptive and 2 cerebellar) and fasciculations were found in 2 patients (1.2%).

In 164 patients the spinal musculature was affected (98.2%), in isolation in 70 patients for 41.9% and associated with cranial muscle involvement in 94 patients for 56.3%. Cranial involvement occurred in 97 patients, in 3 of them in an isolated manner (1.8%).

Of the patients with spinal implication, 22 presented a motor clinical picture limited to the lower limbs (13.2%) and in 142 both limbs were affected (85%). The cranial muscles most involved were the facial (67 patients for 40.1%), pharyngeal (55 patients for 32.9%) and extraocular (14 patients for 8.4%). Of the cases with isolated cranial compromise, one presented with a multiple cranial mononeuropathy, with bilateral facial and pharyngeal involvement, ophthalmoparesis and areflexia. The second patient presented unilateral facial weaknees, with paresthesia. We find a similar report in the literature.[24] The third case was a complete MFS (ophthalmoparesis, ataxia, and areflexia).

Table 1. Clinical manifestations of GBS, at nadir

SIGNS				TOTAL	
	Details	**No**	**%**	**No**	**%**
Weakness	Spinal	70	41,9	**167**	**100,0**
	Spinal and Cranial	94	56,3		
	Cranial	3	1,8		
Hypo/areflexia	Areflexia	114	68,3	**166**	**99,4**
	Hyporeflexia	52	31,1		
Gait impairment	Impossible	89	53,3	**164**	**98,2**
	With support	61	36,5		
	Independent	14	8,4		
Impaired ventilation	Assisted	34	20,4	**55**	**32,9**
	Controlled	21	12,6		
Radicular signs				**50**	**29,9**
Sensitive signs	Hypopalestesia	17	10,2	**45**	**26,9**
	Global Hypoesthesia	17	10,2		
	Superficial Hypoesthesia	11	6,6		
Autonomic signs				**13**	**7,8**
Ataxia	Proprioceptive	6	3,6	**8**	**4,8**
	Cerebellar	2	1,2		
Fasciculation				**2**	**1,2**

The facial involvement was bilateral in 52 patients (31.1%), symmetric rather than asymmetric (17.4% vs 13.8%). Only 15 patients presented unilateral facial involvement. According to reports, cranial nerve involvement occurs in 25% of cases, with bilateral implication being the most characteristic.[25]

A single patient had a typical clinical picture of GBS but with preservation of the deep tendon reflexes (DTRs), as reported in the literature.[26]

The percentage of patients who needed ventilatory support (32.9%/55 patients), coincides with that reported in the literature where it is stated that up to 30% of patients in the progression phase develop respiratory failure.[27] Lawn ND et al report progression to mechanical ventilation was highly likely to occur in those patients with rapid disease progression, bulbar dysfunction, bilateral facial weakness or dysautonomia. In our cases ventilatory compromise was significantly correlated (α of 0.01) only with older ages and cranial extension of the weakness.

Complementary Diagnostics

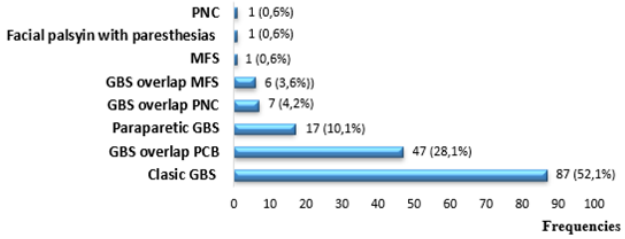
CSF data was obtained in 163 patients, conforming increased protein in 110, for 67.5%. In 85 patients (52.1%), rupture of the Blood-brain Barrier was found and in 27 (16.6%), intrathecal synthesis of IgG. Hypercellularity (less than 10 cells, lymphocytic type) was observed in 22 patients for 13.5%. These results coincide with the literature.[28] According to authorities on the subject,[29] albumin-cytological dissociation is detected in the CSF, initially in 50% of patients and is found in more than 90% of patients, if they are at the clinical nadir. In a previous study, carried out at the INN, it was found that all patients whose CSF was studied after the ninth day of evolution of GBS, presented a breakdown of the blood-CSF barrier.[30]

The result of the Nerve Conduction Studies (NCS) of 66 patients was obtained. Compromise of the peripheral nerves was evident in 50 patients (75.8%) and in 16, was normal (24.2%). Myelin involvement frankly predominated (35 patients/53%) over the axonal (2 patients/3%). In 13 patients (19.7%) the NCS showed mixed damage.

Electromyography showed signs of denervation in 50 studies of the 71 performed (70.4%). In 21 patients, the affectation was mild (29.6%), moderate in 16 (22.5%) and severe in 13 patients for 18.3.

Periods of the Disease

The average time of disease progression was from 11.46 days, with a minimum of half a day and a maximum of 60 days. The 70.7%, 118 patients, reached nadir in less than 15 days. The recovery stage lasted from a few hours to a maximum of 158 days, for an average of 22.4 days. 80.8% (135 patients) recovered within 28 days.



GBS: Guillain Barré syndrome. PCB: Pharyngeal-Cervical-Brachial. MFS: Miller Fisher syndrome. PNC: Polyneuritis cranialis. In parenthesis the relative frequency for each absolute frequency value.

Figure 5. Clinical classification of patients.

Clinical Classification of Patients

Figure 5 shows the clinical classification. Classic GBS expressed by neuropathic involvement of the upper and lower limbs, with or without facial involvement, without cranial involvement, occurred in 87 patients (52.1%). Myelin damage was confirmed in 20 patients (AIDP), 9 had normal nerve conduction and 1 (0.6%), axonal damage. This patient expressed as Axonal Motor Sensory Neuropathy (AMSAN). In the rest of these patients the data was not available.

In 47 patients (28.1%), GBS overlapped with the Pharyngeal-Cervical-Brachial variant (PCB). These patients had neuropathic compromise of the lower or upper limbs or both, with or without facial weakness and pharyngeal involvement. In patients with this overlap, who had the nerve conduction study result, 11 showed myelin damage, 3 had mixed damage and in the remaining 4, the studies were normal. The paraparetic form manifested itself in 17 patients (10.1%), in isolation in 7, with facial weakness in 4 and associated with neuropathic sensory disorders in 6 cases. Four patients had myelin damage and one, mixed damage.

GBS superimposed with PNC (Polyneuritis cranialis) was present in seven patients (4.2%). All had limb weakness, oropharynx participation and ophthalmoplegia. We found no involvement of other cranial nerves. Only one case had NCS, which was normal. GBS superimposed with Miller Fisher Syndrome was present in six patients (3.6%). In five patients, the associated MFS was incomplete (ophthalmoplegic GBS) and in 1 patient, complete. We only had a nerve conduction study in two of these patients, one showed axonal damage and the other mixed. Only one patient presented the classic symptoms of complete MFS (0.6%). Another presented acute unilateral facial weakness, accompanied by distal paresthesia in the extremities, hyporeflexia and electromyogram showing moderate denervation. This case is similar to the one reported by Verma et al.[24] Isolated cranial weakness, expression of the regional form of Polyneuritis cranialis of GBS, was present in only 1 patient who presented facial, pharyngeal and ophthalmoplegia weakness, without skeletal muscle involvement, with areflexia and alterations in the CSF. The hyperacute variant was presented in one case, which reached its nadir in one day. Two cases presented with very mild clinical forms: an MFS superimposed with a PCB and a classic demyelinating GBS, type AIDP. There was a recurrent GBS and a family case.

Functional Assessment or Severity of GBS

According to the Hughes score, GBS took severe forms in 153 patients for 91.6%. Patients with grades 4 and 5 predominated (Table 2).

Table 2. Functional evaluation of the GBS according to the Hughes Scale

GRADE	HUGHES SCALE				
	No	%		No	%
Grade 1	3	1,8	**Mild**	14	8,4
Grade 2	11	6,6			
Grade 3	35	21,0	**Severe**	153	91,6
Grade 4	63	37,7			
Grade 5	55	32,9			
TOTAL	**167**	**100,0**	**TOTAL**	**167**	**100,0**

Spearman's correlation was calculated between severity and demographic, clinical and complementary variables. It was evidenced that the severity increased with age. Neither sex nor skin color were shown to be related to severity. Within the epidemiological variables, a correlation was sought between the history of having suffered an autoimmune disease prior to GBS and the severity, and this was not significant. However, it was found that patients who had presented with a prior infectious phenomenon had a more severe neuropathic presentation. It was of interest that in patients who had antecedents preceding GBS, the longer the time between this event and the onset of GBS, coincided with greater severity.

The clinical variables that positively correlated with severity were gait disorder, compromised ventilation, and extension of weakness to the upper limbs and cranial muscles. These correlations have obvious clinical significance. However, the relationship between facial involvement and severity was interesting. Patients with bilateral and symmetric facial weakness developed

more severe GBS than those with unilateral or bilateral asymmetric facial weakness. In the same way, a positive correlation, although weaker, was evidenced between the greater compromise of the osteotendinous reflexes and the severity (Table 3).

Discussion

In our series, the behavior of the incidence according to age differs from many of the reports. The authors frequently report that the incidence increases with age[31] and consider that this behavior is related to a failure in the immunosuppressive mechanism,[32] which increases, in turn, the susceptibility to autoimmune disorders. Another relevant aspect is the bimodal aspect of the age distribution. The bimodality and age peaks found in our series have been detected in other series.[33]

The mean age of presentation and the groups with the highest incidence, found in our children, coincides with those reported in the literature.[14 34] The disease predominated in males and whites, as traditionally reported in the literature.[35] GBS is considered one of the few autoimmune disorders where the incidence is higher in men;[36] similarly, it occurs in CIDP and in multifocal motor neuropathy with conduction blocks.

The preceding infectious, respiratory rather than digestive phenomenon, predominated. One aspect of interest was Dengue as a preceding phenomenon. Dengue epidemics preceded several GBS outbreaks in our time series. Cuba was the first country in the region to report post-Dengue GBS, at a time when Dengue was an endemic disease in the region and there were few worldwide reports of GBS as a neurological complication of the disease. Already in the last decade the reports of GBS secondary to arboviruses have been highlighted; first, Dengue then Chikungunya and finally Zika and even combinations thereof.[37]

The average time between the preceding phenomenon and the onset of symptoms in our series (13.83 days) coincides with that reported by some authors (between 11 and 13 days).[32]

Table 3. Variables that showed significant correlations with severity

SPEARMAN RHO		HUGHES SCALE
Age	Corr. Coeff	,229**
	Sig.	,003
	N	167
Personal history of autoimmune disease	Corr. Coeff	-,132
	Sig.	,090
	N	167
Preceding infectious phenomenon	Corr. Coeff	,205**
	Sig.	,008
	N	167
Latency between preceding phenomenon and the onset of the clinical picture	Corr. Coeff	,235**
	Sig.	,002
	N	167
Gait impairment	Corr. Coeff	,841**
	Sig.	,000
	N	167
Ventilatory compromise	Corr. Coeff	,842**
	Sig.	,000
	N	167
Muscle weakness (espinal, craneal or both)	Corr. Coeff	,348**
	Sig.	,000
	N	167
Facial weakness	Corr. Coeff	,158*
	Sig.	,042
	N	167
Degradation of the deep tendon reflexes	Corr. Coeff	,191*

* Correlation is significant at the 0.05 level (2-tailed)
** Correlation is significant at the 0.01 level (2-tailed)

The GBS seasonal preference in our series (August) coincides with the highest incidence of respiratory and digestive infections in this month. From the meta-analysis carried out by Webb et al., we can summarize that the seasonal variation of GBS may depend on: the seasonal preference of the prodromal disease, the preferential existence of some infections in rural communities, local economic factors (health) and the differences in ethnic groups with genetic susceptibility to develop GBS or immunological tolerance due to a previous viral infection.[38]

The predominance of demyelinating forms in our series is similar to that reported by most authors, especially from North America, Europe and some South American countries, such as Chile[7] and Colombia.[8] However, other countries in South America, such as Peru,[11] and Central America such as Mexico,[9 10] the axonal subtypes predominate.[6] It cannot be said that there are geographical conditions (latitude, climatic conditions, etc.) that justify this preference. Between the classical forms, AIDP was the most frequent, followed by other variants, superimposed and regional. Only two patients (3%) had axonal damage, one case with AMSAN and the other with GBS superimposed on MFS. Verboon et al. reported differences in the spectrum of MFS overlapped with SGB.[39] On the other hand, overlapping presentations, such as those found in this series, are frequent reports today.[40 41]

According to the Hughes score, the disease was predominantly severe. Age, coinciding with what other authors report,[42 43]significantly correlated with severity, but not sex or skin color. This is possibly the reason why age is one of the variables contained in the Erasmus prognostic scale (EGOS). We only found one report where the severity was greater in women.[44]

Other variables that correlated with age and that could be better studied as prognostic determinants in GBS are: the antecedent of previous autoimmune disease, prior infections, the latency between the preceding phenomenon and the onset of neuropathic manifestations, the extension of the motor disorder, the presence and severity of facial compromise, gait impairment, the severity of ventilatory compromise, and the degradation of deep tendon reflexes.

Factors that determine a worse prognosis for GBS have been established. It can be mentioned the advanced age (57 years or older),[42 43] marked weakness on presentation and fundamentally if the upper limbs are weak (with MRC sum score below 40), hyperacute cases, infectious precedent, especially diarrhea, detection of antibodies against *Campylobacter jejuni*[42] or cytomegalovirus, the axonal variety, presence of anti-ganglioside GM1 antibodies, need for ventilatory support[43] and severe axonal neurophysiological damage.

On the other hand, biomarkers of worsening prognosis, prolonged disease or slow recovery from GBS have been studied,[45 46] such as levels of high weight neurofilaments (above 0.73 ng / ml);[47] increased levels of neuronal-specific enolase and S-100 protein,[48] as well as long-lasting increments in IgM-type antibodies against GM1 gangliosides[49] Van der Pol et al. state that future research is needed to determine whether mortality in GBS can be reduced if monitoring is intensified in patients with a high-risk profile.[50]

Conclusions

The incidence of GBS in our series decreases with age. The respiratory rather than digestive infections as preceding phenomena, predominated, and in a peculiar way, the Dengue. GBS in Cuba has a seasonal preference for the month of August. The most frequent clinical form was classic GBS and prevail the myelin damage (AIDP). Regional variants were detected: overlapping, complete and incomplete, as well as one recurrent case and another with familial GBS. The variables that showed to be linked to the greater severity were: the increase in age, the personal antecedent of previous autoimmune disease, having suffered a previous infectious disease, the increase in the average time between suffering the preceding phenomenon and the onset of the clinical manifestation, the greater corporal extension of the motor disorder, the presence and severity of the facial compromise, the deterioration of the gait, the severity of the ventilatory compromise and the degradation of the deep tendon reflexes.

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Ketamine Prolongs Survival in Symptomatic SOD1-G93A Mice

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ABSTRACT

Objective. Although riluzole and edaravone are FDA-approved for Amyotrophic Lateral Sclerosis (ALS), these drugs have negligible effect on disease progression and survival. Recent studies reporting neuroprotection from sub-anesthetic doses of ketamine support testing this drug in this rapidly progressing and fatal disease.

Methods. We administered ketamine at 0, 10, and 30 mg/kg to SOD1-G93A mice 5 days/week beginning at 90 days of age. We measured body weight, grip strength, and survival in this model of ALS.

Results. Although ketamine did not influence disease-related loss of body weight, it did delay grip strength declines in the 30 mg/kg group. Ketamine also prolonged survival in the 30 mg/kg group and dose-dependently increased the latency between 20% loss of body weight and death.

Conclusions. These results support further testing of ketamine in preclinical models of ALS to determine optimal dosing. They also support testing in the clinic given the limited efficacy of current ALS treatments and given FDA approval of ketamine for other indications like treatment-resistant depression.

Keywords: *ketamine, survival, SOD1-G93A, neuroprotection*

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a devastating neurodegenerative disease characterized by muscle weakness that rapidly progresses to paralysis due to motor neuron loss in the brain and spinal cord. There is no cure for ALS, and death typically occurs within 5 years of diagnosis (1). There are currently two FDA-approved drug treatments for ALS: riluzole and edaravone. Riluzole is thought to attenuate glutamate-related excitotoxic disease mechanisms. In addition to blocking sodium channels (2), kainate and NMDA receptors (3), riluzole also facilitates glutamate uptake (4). Edaravone is thought to provide neuroprotection through its antioxidant and free radical scavenging properties (5). Although these drugs are effective against disease mechanisms in ALS, their clinical effects on disease progression and survival are limited (6).

The demonstrated neuroprotective effects of ketamine in other brain disorders (7) makes ketamine an intriguing target of study in neurodegenerative disorders including ALS. These neuroprotective properties of ketamine have been demonstrated in animal models of stroke, traumatic brain injury, and epilepsy (reviewed in (7)). Additional examples of the neuroprotective effects of ketamine have been demonstrated in mouse models of depression, where ketamine treatment resulted in restoration of lost prefrontal cortical spine formations (8). In addition, ketamine prevented neurodegeneration induced by isoflurane anesthesia via anti-apoptotic and antioxidant effects in rats (9). Studies of ketamine for psychiatric disorders in humans date back to the year 2000. The s-enantiomer of ketamine was approved by the FDA for treatment-resistant major depression in 2019 and for suicidality associated with depression in 2020.

The mechanism behind ketamine's effects on the brain including its potential neuroprotective effects are complex (10). Unlike riluzole, ketamine likely attenuates NMDA receptor-related glutamate excitotoxicity indirectly. In vitro studies using PC-12 cells reveal that ketamine lowers intracellular D-serine concentrations (11). D-serine is a co-agonist at the NMDA receptor and contributes to NMDA excitotoxicity. Other literature suggests that ketamine treatment has downstream effects on the opioid, aminergic, and cholinergic systems in the brain (12,13).

Given the positive effects of low dose intravenous ketamine on neuropsychiatric disorders and the link between ketamine's mechanism of action and neuroprotection, we performed the first study of sub-anesthetic doses of ketamine in the SOD1-G93A mouse model of ALS.

Materials and Methods

Animals and Dosing. Thirty-six male SOD1-G93A mice were acquired from Jackson Laboratories. Mice were divided into three groups: a ketamine 10 mg/kg group, a ketamine 30 mg/kg group, and a saline vehicle group. After collecting baseline body weight and grip strength data (see below), we administered ketamine or saline vehicle (0.1 ml/kg, ip) 5 days/week beginning at 90 days of age. Drugs were administered following grip strength tests. Procedures were approved by the University of Kansas Medical Center Institutional Animal Care and Use Committee and adhered

to the Guide for the Care and Use of Laboratory Animals.

Grip Strength Testing. Mice were tested for grip strength using an inverted wire screen. Specifically, mice were placed on the screen and then the screen was inverted and held 2 feet above a cushioned surface. The duration that the mice were able to remain on the screen before releasing was recorded across two trials. The mean duration of the two trials was used as the measure of grip strength for each mouse on each day. Mice were tested until they exhibited loss of righting reflex for 30 seconds. At this point they were euthanized. Some mice were found dead in their cage. The day in age for either of these events was recorded as day of death and used for survival analysis (see below).

Data Analysis. Data for body weight and for grip strength were expressed as percentage of pre-drug baseline and analyzed using a 2-way Analysis of Variance (ANOVA) with group assignment (vehicle vs 10 mg/kg vs 30 mg/kg) as the between-subjects variable and testing day (every 7 days) as the within-subjects, repeating variable (Systat 13). Survival analyses were performed using each mouse's day of death (GraphPad Prism). We also compared latencies between the day each mouse lost at least 20% body weight and the day the mouse was euthanized or found dead in its cage using a one-way ANOVA.

Results

Body Weight. Mice in all groups exhibited significant, disease-related weight loss across time ($F=113.765$, $p<0.001$), reaching a nadir of 87% of Day 90 body weight by Day 153 (see Figure 1A).

Body weight loss did not differ between the three groups.

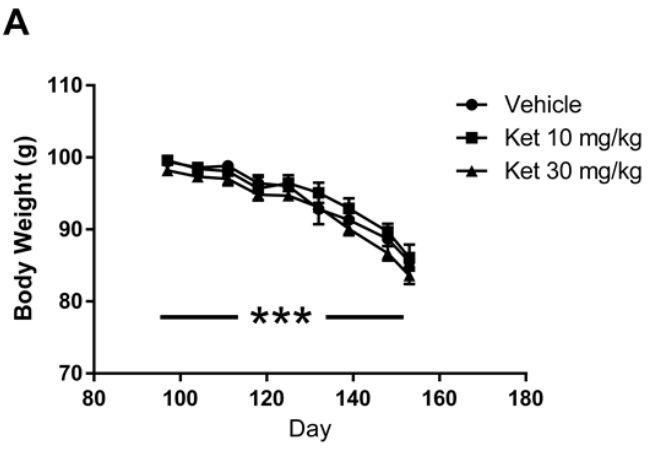

Figure 1A. Body weight as a function ketamine dose and day. Mice in each group exhibited significant loss of body weight (***$p<0.001$). This effect did not differ between dosing groups.

Grip Strength. Mice in all groups exhibited significant declines in grip strength across time ($F=219.763$, $p<0.001$), reaching ~1% of their Day 90 values by Day 153 (see Figure 1B).

The decline in grip strength was less in the 30 mg/kg ketamine group however, leading to a significant main effect for dose ($F=3.697$, $p<0.05$) and a significant dose X time interaction ($F=2.201$, $p<0.01$).

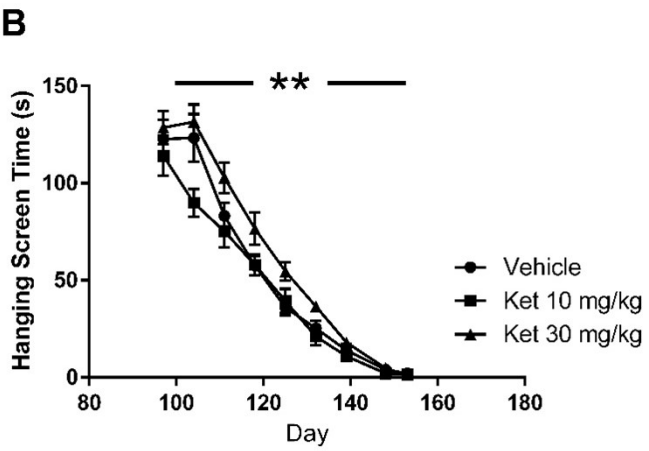

Figure 1B. Grip strength as a function of ketamine dose and day. Although mice in all groups exhibited significant declines in grip strength, the decline was less in the 30 mg/kg ketamine group leading to a significant dose X time interaction (**$p<0.01$).

Survival. Survival analysis revealed no significant between-groups differences when all groups were included ($X^2 = 3.578$, $p=0.17$; Figure 2).

A separate analysis that included only the vehicle and 30 mg/kg group, however, revealed significantly longer survival in the ketamine group than the vehicle-treated group ($X^2 = 4.442$, $p<0.05$; data not shown separately, but the curves for vehicle and 30 mg/kg are the same as in

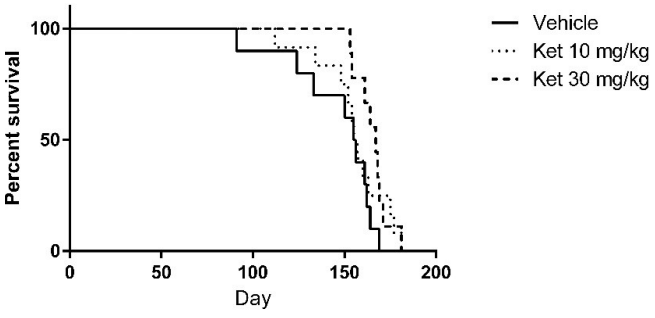

Figure 2. Survival analysis for the three treatment groups. Although survival was greater in the 30 mg/kg ketamine group, the effect did not reach statistical significance when the 10 mg/kg group was included.

Fig. 2). After conducting survival analyses, we measured the latency in days between the day in which each mouse reached 80% of its body weight and the day of death as defined above. Ketamine produced a statistically significant dose-dependent increase in the latency between body weight loss and death ($F=4.642$, $p<0.05$; Fig. 3).

Discussion

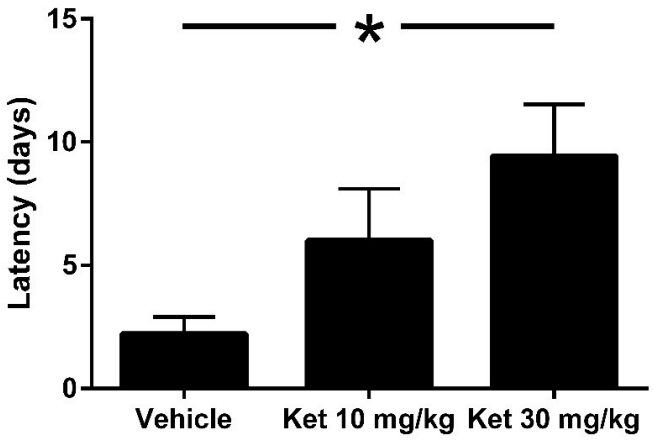

Figure 3. The latency in days between the day each mouse exhibited a ≥ 20% loss of body weight and its day of death. Ketamine produced a significant dose-dependent increase in this measure ($p<0.05$).

We report here that ketamine at sub-anesthetic doses has potential neuroprotective effects in an animal model of ALS. Compared to vehicle-treated controls, mice that were treated 5 days/week with 30 mg/kg ketamine exhibited slower declines in grip strength and prolonged survival. Although ketamine did not attenuate loss of body weight, it significantly increased the latency between 20% loss of body weight and death in a dose-dependent fashion. These data support further testing to determine whether ketamine may help to slow functional decline and improve survival in ALS. Given that ketamine's mechanism of action is similar to riluzole, which is FDA approved to treat ALS, further study of ketamine in animal models of ALS or in human trials may be warranted based on the data presented in this paper.

We tested sub-anesthetic doses of ketamine based on literature supporting the same in treating depression and in promoting neuroprotection, which suggests target modulation of the NMDA receptor at these same doses (14). We chose to dose mice 5 days/week in this study. The fact that neurotoxicity has been reported with repeated ketamine dosing in developing rats and monkeys (15,16) suggests that a more intermittent dosing regimen may result in greater neuroprotection.

It is unclear why mice in the lower dose group exhibited an earlier decline in grip strength than those in the vehicle and higher dose group. The differential effects may be related to recent reports that ketamine can increase field excitatory postsynaptic potentials (fEPSPs) at doses ≤10 mg/kg (17) while decreasing fEPSPs at doses ≥30 mg/kg (18). Although speculative, increased excitability may have been detrimental given cortical hyperexcitability at early disease stages in this model of ALS (19,20). This hyperexcitability has been postulated to drive neurodegeneration in motor neurons. The fact that grip strength declines soon followed in the vehicle group but were more delayed in our 30 mg/kg group supports this hypothesis.

The greater survival in the 30 mg/kg group and the dose-dependent increase in latency between loss of body weight and death suggest that, despite muscle wasting, ketamine delayed neuromuscular junction denervation or prolonged neuromuscular function in this model. One shortcoming of the current study was that we did not quantify neuromuscular junction (NMJ) innervation. Future studies in which muscle tissue is harvested from ketamine-treated SOD1-G93A mice at specific disease stages are necessary to determine preservation of NMJ integrity. Our findings suggest that administering a higher dose of ketamine less frequently might provide greater neuroprotective effects in this model. Optimizing the dosing and frequency of administration is a question for further research in this area. In addition, examining target modulation and collecting data on structural and functional changes in the brain before and after treatment would be desirable. Despite these considerations, concurrent human trials should be considered for several reasons: 1) ALS typically causes death within 5 years of diagnosis, 2) the current FDA approved treatments result in no slowing of the disease, and 3) ketamine, a drug which has been available for decades, is now FDA approved in non-anesthetic doses via intra-nasal application for depression (21).

Acknowledgements

This work was supported by the Kansas Intellectual & Developmental Disabilities Research Center (NIH U54 HD 090216).

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Novel I202N Mutation in CMT1X Gene

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ABSTRACT

This case report describes a novel I202N mutation in the gap junction protein beta 1 (GJβ1) gene consistent with diagnosis of Charcot-Marie Tooth disease (CMT) in a 63-year-old female who presented with slowly progressive bilateral foot weakness and foot drop over four decades. The discussion emphasizes the novel mutation and the gender difference in severity.

Introduction

Charcot Marie Tooth disease (CMT) is a heterogeneous group of hereditary motor sensory neuropathies and is the most common inherited neurological condition.[1] It consists of a spectrum of disorders caused by mutations in various genes whose protein products are expressed in myelin and/or axonal structures within peripheral nerves.[1] More than 40 causal genes have been identified. Inheritance is variable and includes autosomal recessive and dominant, X-linked, and mitochondrial inheritance patterns.[1,2] X-linked Charcot-Marie-Tooth disease (CMTX) is the second common genetic variant of CMT. CMTX type 1 causes 90% of CMTX.[3] Though the exact mechanisms by which GJB1 mutations lead to the CMT1X phenotype are not fully defined, hundereds of pathological mutations have been identified.[3] The following case discusses one such novel mutation.

Case Report

A 63-year-old female was referred to the neurology clinic for evaluation of slowly progressive weakness and foot drop. She developed bilateral foot weakness in her teenage years in conjunction with pes cavus and hammer toe deformities. She was able to walk without significant impairment at that time. Over approximately four decades leading up to the time of referral, she experienced worsening foot drop and gait difficulties functionally manifesting as stumbling and tripping. During this time, she also developed gradual weakness in her hands that interfered with writing.

Relevant past medical history at the time of presentation included nine years prior breast cancer treated with lumpectomy, chemotherapy (5-fluorouracil, cyclophosphamide, methotrexate) and radiation therapy, essential tremor, hypertension, hyperlipidemia, cataracts, prediabetes, depression, and corrective surgery for hammer toe deformities. There was no history of alcohol or illicit drug abuse.

The patient has three sons, one of whom was affected similarly although beginning at an earlier age with increased severity and speed of progression. Her two other children did not have medical problems. The patient has three siblings - one brother with a history of tremor, otherwise no relatives with neurologic disease.

Neurological exam was remarkable for significant atrophy of the small hand muscles with more prominent wasting of thenar than hypothenar groups, consistent with 'split hand sign.' Atrophy of bilateral intrinsic foot muscles and pes cavus was present. Muscle strength was significantly diminished as 0/5 bilateral toe extension, 2/5 bilateral foot dorsiflexion and 3/5 intrinsic hand muscles. Light touch and pinprick sensation were also impaired in the hands and feet bilaterally. Vibration was impaired at the fingers and absent at the ankle and toes. Proprioception was decreased in the toes. Deep tendon reflexes were absent at the ankle and biceps, diminished to a lesser degree in the triceps, and normal in the knees. Circumduction of gait was noted bilaterally secondary to foot drop, and the patient was unable to walk on her heels. There were postural and action tremors of the hands. Cranial nerves II-XII were intact. Coordination testing was unremarkable.

Needle EMG and nerve conduction studies (NCS) showed a reduction in amplitude of median and tibial nerves with marked velocity reduction in distal extremities. There were also prolonged latencies in median and tibial motor NCSs. Sensory NCS demonstrated a marked decrease in amplitude and decreased to borderline velocities. EMG of tibialis anterior and gastrocnemius muscles showed mild active denervation and prominent chronic reinnervation of the right extensor digitorum brevis, tibialis anterior, and gastrocnemius (medial head). These findings supported a demyelinating neuropathy with secondary axonal change and axonal sensorimotor polyneuropathy.

This patient presented with progressive, distal weakness with a positive family history of similar symptoms in her son raising the suspicion for hereditary neuropathy. In the setting of possible diagnosis of CMT, focused genetic testing for disease-producing mutations was performed in both the patient and her son, consistent with American Academy of Neurology evidence-based practice parameters for the evaluation of distal symmetric polyneuropathy [5]. Genetic testing performed through GeneDx revealed a novel heterozygous T to A transversion (c.605 T>A) in exon two of the GJB1 gene encoding connexon 32 resulting in p.Ile202Asn amino acid substitution predicted to be pathogenic. The patient's son was hemizygous for the same mutation.

Discussion

Charcot-Marie-Tooth neuropathy (CMT) is an inherited degenerative disorder of the peripheral nervous system that results in slowly progressive distal muscle weakness, atrophy and loss of proprioception in the affected areas.[1] CMTX neuropathy is usually associated with mutations in exon 2 of the gap junction protein β1 (GJB1) gene.[1-3] CMT1X is caused by mutations in the GJβ1gene, located on chromosome Xq13.1, that encodes the Connexin 32 (Cx32) protein. Cx32 is found in Schwann cells, oligodendrocytes, and other cell types and forms channels and hemichannels that play a role in chemical and electrical communication between cells, through transport of signaling molecules, small metabolites, and ions, and may also play a role in cell growth and resistance to cell death.[1-3]

The onset of symptoms in males with CMTX is usually around the second decade in life. CMTX has a more severe course in males than females.[1-3] It is hypothesized that X-linked inactivation may play a role in the range of phenotype severity in females.[3] Males are uniquely vulnerable to mutations in their single copy of X-linked genes, whereas females are often mosaic, having a mixture of cells expressing different sets of X-linked genes.[4] This cellular mosaicism created by X inactivation in females is most often advantageous, protecting carriers of X-linked mutations from the severe clinical manifestations seen in males.[4]

In the above case the patient's son developed symptoms at an earlier age and severity progressed rapidly as expected in males with an X linked disorder. But the patient herself also ended up having severe symptoms though gradually unlike what is expected out of females with X linked inheritance as discussed above. This brings to the question whether the novel mutation found in the above case caused gain of function although classically CMTX is thought to be caused by a loss of function mechanism.[4,5] Therefore, it is important to look for and document novel mutations to better understand the phenotypic variations and severity.[6]

Conclusion

CMTX has a more severe course in males compared to females due to mosaic partial inactivation of the X chromosome.[3] But as mentioned in the above case females do develop severe disability eventually probably secondary to gain of function mutations.[3-5] It is important to analyze and document these novel mutations to better understand the disease inheritance and variations in phenotype and severity.[6]

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Novel RYR1 genetic mutation with variable expressivity within a family

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ABSTRACT

The ryanodine receptor (RYR1) gene encodes ryanodine receptor, a calcium channel in the sarcoplasmic reticulum. In active state it releases Ca2+ from the sarcoplasmic reticulum leading to muscle contraction. Variants in RYR1 mutation are associated with the majority of cases of malignant hyperthermia (MH) and exertion heat illness. These mutations are also considered one of the causes of inherited myopathies. There is a wide spectrum of genotypic, phenotypic and histopathological presentation of various mutations of this gene. Also, families with the same mutation showcase variable phenotype and severity of phenotype as seen in this case of a 45-year-old male and his children with novel heterogeneous missense mutation- K1393R, pLys1393Arg (AAG>AGG): c4178A>G in exon 29 of RYR1. The phenotypic variability captured in this family is exertion heat intolerance, exertional urticaria, weakness of muscles of limbs and swallowing and delayed motor milestones in the younger generation. This sheds light on the occurrence of wide phenotypic variability including varying severity of phenotypes with the same gene mutation within the family and across families.

Introduction

Mutations in the skeletal muscle ryanodine receptor (RYR1) gene have emerged as a cause of inherited neuromuscular disease, ranging from various congenital myopathies and malignant hyperthermia (MH) susceptibility trait with or without associated weakness to exertional myalgia/heat illness with or without rhabdomyolysis. Approximately 200 missense variants in RYR1 have been described[1,2,3]. RYR1-related myopathies are genetically, histopathologically, and clinically more diverse than previously considered. RYR1-related myopathies may manifest throughout life, with a wide range from early-onset myopathies to rhabdomyolysis triggered by various stimuli in otherwise healthy individuals.

Recent studies have also shown the presence of wide spectrum RYR1 mutation and their novel clinical presentations. Exertion myalgia, exertion heat illness, heat stroke, and asymptomatic elevated creatinine kinase levels are some alternative presentations[1].

The objective of this case is to report one such novel mutation in RYR1 gene [heterogeneous missense mutation- K1393R, pLys1393Arg (AAG>AGG): c4178A>G in exon 29 of RYR1] in a family who shows variable expressivity among generations within the family and presents with variable phenotypes like exertional heat intolerance and exertional urticaria along with the well-known phenotype of muscle weakness.

Case Report

A 45-year-old male presented with progressive lower limb weakness and generalized fatigue for the last 5 years. He had initially noticed such weakness when getting up from the floor while playing with his children. He also had shortness of breath on climbing three flights of stairs. He has a history of recurrent episodes of heat intolerance and generalized hives with mild physical exertion since the age of 20, diagnosed as cholinergic urticaria (Figure 1 – patient's back showing itchy red hives precipitated during exertion). Except for tonsillectomy at age 10, his surgical history is unremarkable. None of his siblings or either parents had similar symptoms. On examination there was symmetric 4/5 weakness with hip flexion and knee extension and the rest of the neurological examination was normal. Laboratory work demonstrated a creatinine kinase level of 400U/L (normal range: 52-336U/L, Mayo Clinic). Nerve conduction studies and needle electromyography were normal. (Figure 2 and Figure 3 show the muscle biopsy obtained from patient's vastus lateralis reflecting fiber type variation on H & E stain and central cores with predominance of type1 fibers, respectively). Next generation sequencing of RYR1 gene showed a heterogeneous missense mutation- K1393R, pLys1393Arg (AAG>AGG): c4178A>G in exon 29 of RYR1.

He and his wife have four children: two daughters (aged 13, 9 years) and two sons (fraternal twins, aged 6 years). The daughters had no significant birth history, neonatal history, or developmental delay, but eventually developed exertional heat intolerance with dancing. However, the pregnancy of the twins was complicated by polyhydramnios. The twins were hypotonic and had poor sucking at birth. They also had delay in motor milestones. Next generation sequencing of RYR1 gene of all children revealed the identical heterogeneous missense mutation- K1393R, pLys1393Arg (AAG>AGG): c4178A>G in exon 29 of RYR1 gene.

Discussion

The RYR1 gene encodes the principal sarcoplasmic reticulum calcium release channel (RYR1 protein), with

a crucial role in skeletal muscle excitation contraction coupling by connecting sarcoplasmic reticulum to transverse tubules. The fundamental role of RYR1 in normal muscle homeostasis and functioning is reflected in the wide range of both dominant and recessive disorders associated with RYR1 mutations[1,2,3].

The clinical and pathological features of RYR1-related disorders with mainly autosomal dominant (AD) inheritance – central core disease (CCD) and the malignant hypothermia syndrome (MHS) trait based on a positive *in vitro* contracture test (IVCT) – have been recognized for a long time. The full clinico-pathological spectrum of autosomal recessive (AR) RYR1-related myopathies has only emerged in recent years and continues to expand. More recently recognized recessive RYR1-related myopathies include forms of multi-minicore disease (MmD) with external opthalmoplegia, centronuclear myopathy (CNM) and congenital fiber type disproportion[2]. In addition, King-Denborough syndrome (KDS), exertional rhabdomyolysis and late-onset axial myopathy appear to be specific myopathic manifestations of malignant hyperthermia (MH)-related RYR1 mutations[3,4]. (Figure 4 shows various phenotypic presentations with RYR1 gene mutation according to previous studies).

Recent studies have also shown additional phenotypes associated with RYR1 mutation including exertional myalgia, heat intolerance/illness, rhabdomyolysis, and cold-induced muscle stiffness. Muscle biopsies in these cases show only subtle changes and there is no evidence of MH in any of these cases[3].

Fiszer et al. reported three novel RYR1 variants associated only with exertional heat illness with unrevealing muscle biopsy and no evidence of MH either in the probands or other members of the family. Interestingly they also noted two other variants which were previously reported as centronuclear myopathy but were associated only with exertional heat illness and MH in their cohort[4].

Complete sequencing of RYR1 gene has revealed variants throughout the gene. But there are particular regions and residues within the gene that are conserved (remained essentially unchanged throughout evolution), indicating unique and indispensable functional importance of their protein products. The RYR1 protein has many direct, diverse protein and subunit interactions; hence it is not surprising that there is expanding range of variants both in genotypes and phenotypes[3].

Taken together the above-mentioned studies and this case have shed light on the wide genotypic as well as phenotypic variability seen with RYR1 mutations including varying severity of phenotypes.

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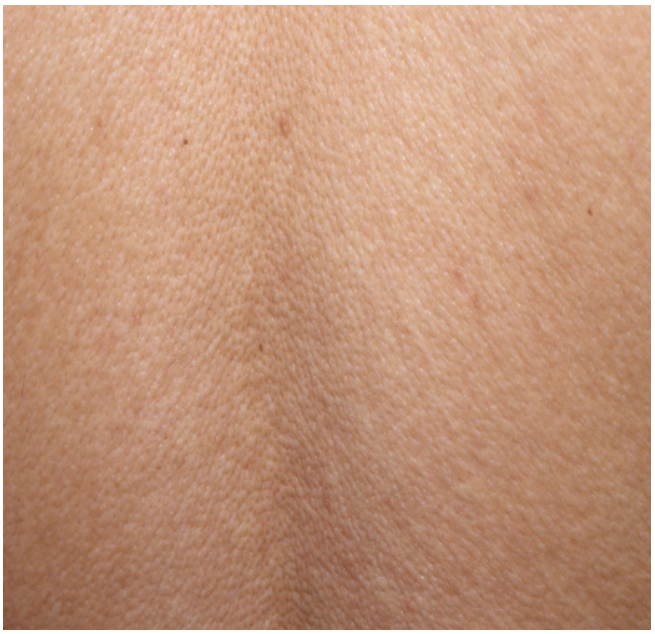

Figure 1. Back showing urticaria.

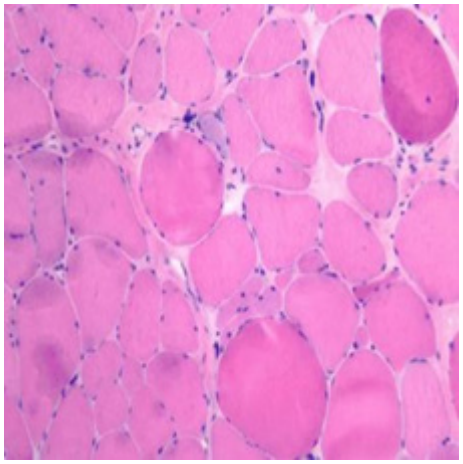

Figure 2. Vastus Lateralis biopsy with H & E stain showed mild fiber type variation with internal nuclei and mild endomysial fibrosis.

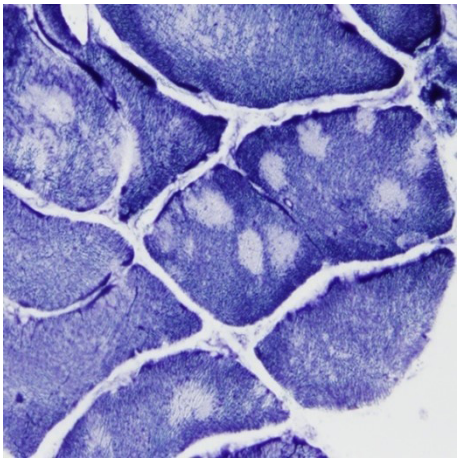

Figure 3. Vastus Lateralis biopsy with NADH stain showed multi (mini) core pattern with predominance of type 1 fibers.

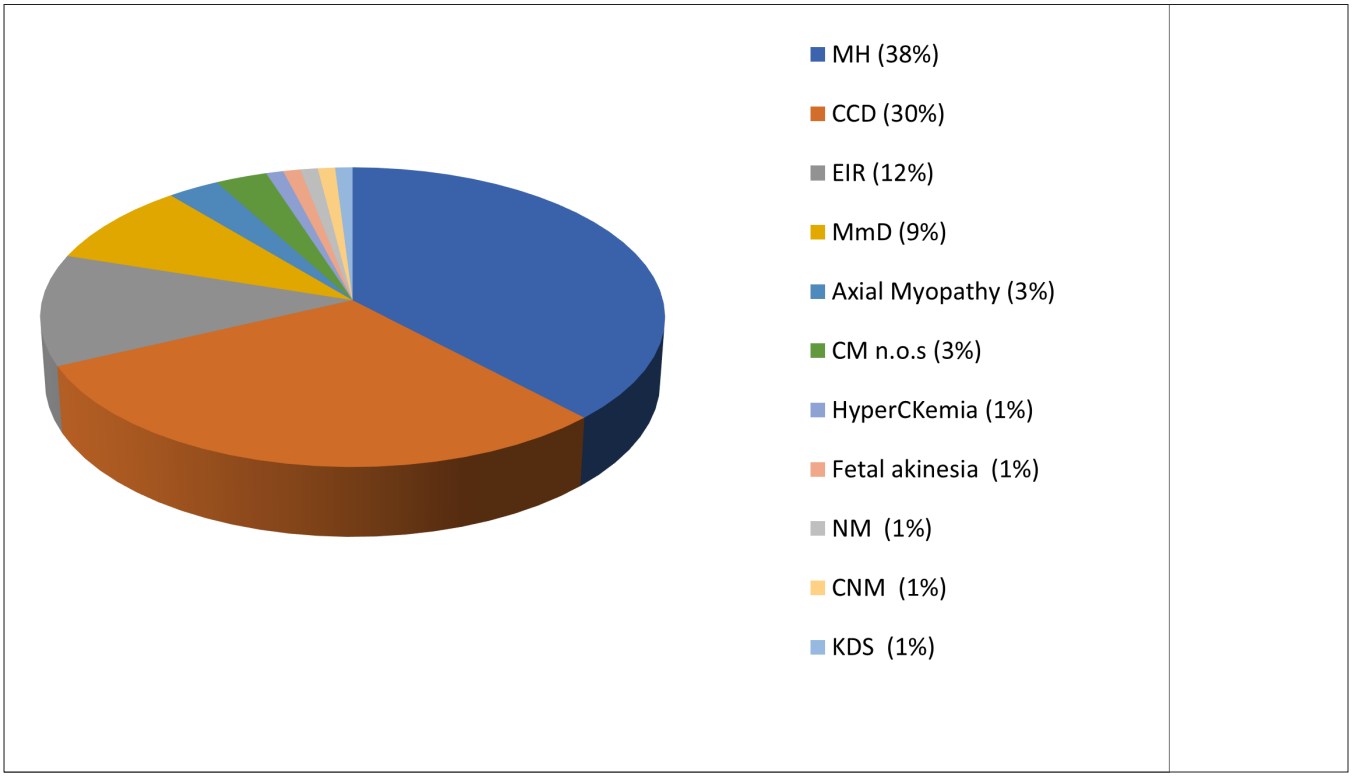

Figure 4. Various phenotypic presentations with RYR1 gene mutation according to previous studies[1]. Abbreviations: MH, malignant hyperthermia; CCD, central core disease; EIR, exercise induced rhabdomyolysis; MmD, multiminicore disease; CM n.o.s., congenital myopathy not otherwise specified; NM, nemaline myopathy; CNM, centronuclear myopathy; KDS, King-Denborough syndrome; CK, creatinine kinase.

Covid-19 Re-infection vs Prolonged Viral Shedding

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ABSTRACT

Since December 2019, the COVID-19 pandemic has devastated communities across the world. As the number of patients recovered from COVID-19 continues to rise, the question of acquired immunity versus chances of re-infection becomes critical to understand the future spread of infection. Here, we present a case of a patient previously recovered from COVID-19, develops new symptoms concerning for possible re-infection with positive reverse transcriptase-polymerase chain reaction (RT-PCR) after few months of initial infection.

Introduction

First discovered in Wuhan, China in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-COV2) and its associated disease COVID-19 spread across the world at a rapid pace. It was declared a pandemic by WHO by March 2020[2,3]. The Center of Disease Control (CDC) suggests that patients with mild to moderate illness who are not severely immune compromised, precautions can be discontinued after 10 days of symptom onset and 24 hour of symptom resolution for patients with mild to moderate symptoms. Only for limited number of patients with severe disease, isolation and precautions can be extended up to 20 days after symptom onset[4]. However, recent reports of patient re-testing positive again after well beyond 10-20 days of isolation and precautions period raise the question of re-infection[5, 6].

Case Report

A 42-year-old female presented with symptoms of generalized achiness and nausea on September 14th, 2020. She progressed to have a low-grade fever, diarrhea, and fatigue. After three days, on September 17th, 2020, she was seen at a local urgent care for persistence of symptoms. A SARS-CoV-2 RNA RT-PCR test was ordered and sample was obtained during the visit. After 4 days of symptom onset, on September 18th, the patient lost sense of taste and smell, experienced coughing and developed sore throat. On September 19th, 5 days after symptom onset, she received results of a positive PCR test. Sore throat, cough, loss of sense of taste and smell, and fatigue continued throughout the duration of the 10-day quarantine. She regained taste and smell by 14 days of first symptom onset.

After 13 days of first symptom onset, on September 27th,2020, patient had another nasal SARS-CoV-2 RNA, RT-PCR test that was reported negative. On October 23rd, 2020, patient had a procedure at local hospital after 39 days of first COVID-19 symptoms onset, patient underwent another Aptima Sars-CoV-2 assay (PCR) pre-procedure that was also reported negative.

After 61 days of first symptom onset, on November 14th, 2020, the patient presented with symptoms of achiness and fatigue like her first experience, but milder than before. On November 16th, she experienced a sore throat which progressed to swollen cervical lymph nodes. On November 18th, she was tested using the TaqPath RT-PCR COVID-19 Combo Kit at the local urgent care. The PCR test results were reported as positive on November 19th. Symptoms continued with fatigue, a sore throat and swollen lymph nodes which were painful during swallowing for 7 days. She did not develop loss of taste and smell at this time. By day 9, she was asymptomatic. No additional symptoms were experienced. She remained quarantined until November 25th, 10 days after the onset of latest symptoms.

Discussion

We present a case of possible COVID-19 re-infection after complete symptomatic resolution and laboratory evidence of RT-PCR COVID-19 negative, although alternative possibilities do exist. Positive RT-PCR testing for COVID-19 has been described after recovery[6,7,8]. Most common explanation besides inaccuracy of testing could be persistent shedding of virus or true re-infection.

Genetic material of viruses can persist in the host even after clearance of live virus and resolution of the disease process[9,10], thus detection of genetic material by RT-PCR does not necessarily mean re-infection. Current literature suggests that patient suffering from COVID-19 can have a positive RT-PCR test due to prolonged viral shedding even after complete symptomatic recovery[7,8,10]. Li J. et al, reported a positive RT-PCR test positive in a patient with severe COVID-19 after 36 days of symptom resolution and 60 days after symptom onset. Although the presence of antibodies to SARS-CoV-2 in serum significantly reduced risk of re-infection, protection is less robust in patients aged 65 and above[14,15,16].

Our patient had milder COVID-19 disease, possibly had prolonged viral shedding for over 2 months resulting in a positive RT-PCR test.

Another interesting finding in our patient is the presence of tender cervical lymphadenopathy. Although the CDC does not list lymphadenopathy as common signs and symptoms of COVID-19[11], there are reported cases of lymphadenopathy in severe COVID-19 disease[12,13].

Conclusion

Here, we present a case of a positive RT-PCR test due to prolonged viral shedding after 2 months of initial SARS-CoV2 infection. Another possibility is symptomatic COVID-19 re-infection although development of lymphadenopathy is not common in COVID 19.

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Myasthenia Gravis Exacerbation Following Second Dose of mRNA-1273 Vaccine

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Introduction

A wide spectrum of central and peripheral neurological manifestations associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been reported in the literature. Neuromuscular complications of SARS-CoV-2 infection resulting in coronavirus disease 2019 (Covid-19) range from the emergence of new findings to the exacerbation of existing neuromuscular disorders like myasthenia gravis. [1, 2] Interim analysis by a physician-reported registry, COVID-19 Associated Risks and Effects in Myasthenia Gravis (CARE-MG), demonstrated that, of reported myasthenia gravis patients with COVID-19, 40% of patients relapsed or experienced crisis requiring rescue therapy and 24% died due to COVID-19. [3] To the best of our knowledge, however, exacerbation of myasthenia gravis has not been reported following currently available COVID-19 vaccinations. Here we report a case of myasthenia gravis exacerbation requiring hospitalization and rescue therapy following a second dose of the mRNA-1273 vaccination.

Case Report

A 69-year-old female with a history of Myasthenia Gravis (MG) [by abnormal electrophysiological studies of single fiber electromyography suggestive of a postsynaptic neuromuscular junction disorder, binding AchR Ab: 0.44 nmol/L level (Athena Diagnostics), Abnormal binding of MGT-30 epitope of Titin (Washington University lab) and significantly elevated Antistriational Ab at 1:15360)] was in her usual state of health. However, she developed an acute onset of shortness of breath and generalized weakness with difficulty ambulating following the second COVID-19 vaccination (Moderna). Later in the evening of receiving vaccination she felt fatigued but remained afebrile. However, she woke up the next day with respiratory distress, had difficulty raising from bed and was seen in the emergency department. On arrival, she was tachypneic with a respiratory rate in the 20s and tachycardic with HR of 110. Her examination showed use of accessory muscles of respiration and moderate proximal weakness. She was only able to count to 6 on a single breath. Her pulmonary function tests showed negative inspiratory force at -40 cm of H20. Chest x-ray showed no acute processes. She denied any other recent medication dose adjustments other than withholding her Pyridostigmine 48 hours for an SFEMG the day before she received the vaccination, which she had already resumed 20 hours prior to the vaccination. She was treated with plasma exchange, did not require intubation and continued on choline esterase inhibitors. She improved in her respiratory status with NIF at -52. She gained strength enough to ambulate and climb stairs with assistance. Prior to this episode, her myasthenia gravis was managed with IVIG and choline esterase inhibitors. She was not yet on any other immunosuppressant as she had been unable to tolerate Mycophenolate Mofetil and was reluctant to take Azathioprine. Her insurance had declined coverage for Eculizumab. Her initial presentation was shortness of breath at rest in early 2019 with an initial MG ADL (MG Activities of Living Scale) of 10 and the most recent ADL prior to hospitalization was 2.

Discussion

Currently, three Coronavirus Disease 2019 (COVID-19) vaccines have been granted emergency use and marketing authorization by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to combat the COVID-19 pandemic. Our patient received SARS-CoV-2 mRNA-1273 (Moderna) which is a messenger RNA vaccine. This vaccine encodes a stabilized version of the SARS-CoV-2 full-length spike glycoprotein trimer called S-2P. It is modified to include two proline substitutions at the top of the central helix in this S2 subunit. The mRNA is encapsulated in lipid nanoparticles at a concentration of 0.5 mg per milliliter and diluted with normal saline for target vaccine concentration. In a phase 3 placebo-controlled trial enrolling 30,420 volunteers, the mRNA-1273 vaccine showed 94.1% efficacy at preventing Covid-19 illness, including severe disease. Aside from transient local and systemic reactions, no safety concerns were identified during that study. [4] In a study focusing on the subpopulation of adult patients specifically stratified according to age (56 to 70 years or ≥71 years), which was a dose-escalation, open-label trial of mRNA-1273, adverse events were predominantly mild or moderate in severity and most frequently included fatigue, chills, headache, myalgia, and pain at the injection site. Such adverse events were dose-dependent and were more common after the second immunization. [5] However, it should be noted that in both the Pfizer-BioNTech COVID-19 Vaccine and Moderna COVID-19 Vaccine clinical trials, incidents of Bell's palsy were cited as medically attended adverse events (MAAE). Because of that, considering the biological plausibility, FDA recommends surveillance for cases of Bell's palsy with the deployment of the Moderna COVID-19 Vaccine

into larger populations. [6] However, it is imperative that such observations are cautiously widened to include other neurological comorbidities. The temporal relationship of MG exacerbation in our patient strongly suggests that it was related to the mRNA-1273 vaccination. Given the surveillance importance of emerging data, we believe that this case should be shared with the scientific community in a timely fashion.

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Infectious Myositis

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Introduction

Infectious myositis (IM), is the infection of the skeletal muscle tissue (particularly voluntary muscle), which is characterized by swelling, pain, tenderness, and/or weakness. Infection of the skeletal muscle is atypical and is caused by various agents like bacteria, mycobacteria, viruses, parasitic, and fungal organisms. Among all the agents, the most common cause of infectious myositis is bacteria (frequently by staphylococcal and streptococcal species).[1-4]

Myositis is of different causes and non-infectious causes of myositis are shown below in Table 1.[5-7] This review does not cover the topic of noninfectious myositis. Infectious myositis is caused by various pathogens like bacteria, viruses, fungi, and parasites. Different causative agents of infective myositis are shown below in Table 2.[4,6,8,9] The following section will further discuss bacterial myositis.

Table 1. Non-infectious myositis causes[5,6]

Idiopathic inflammatory myopathies
- Polymyositis
- Dermatomyositis
- Inclusion body myositis
- Myositis associated with collagen vascular diseases
    - Polyarteritis nodosum
    - Wegener's granulomatosis
    - Systemic lupus erythematosus
    - Sjogren's syndrome
    - Rheumatoid arthritis
    - Scleroderma
    - Polymyalgia rheumatica
    - Mixed connective tissue disease
    - Adult Still's disease
    - Vasculitis - leukocytoclastic, hypersensitivity
- Myositis associated with malignancies

Other forms of inflammatory myopathies
- Myositis associated with eosinophilia
- Myositis ossificans
- Giant-cell myositis

Myopathies caused by medications and toxins

Metabolic myopathies
- Inborn errors of metabolism
    - Disorders in glycogen metabolism
    - Lipid storage disorders
    - Mitochondrial myopathies

Endocrine disorders
- Hypo- and hyperthyroidism
- Acromegaly
- Addison's disease
- Cushing syndrome
- Hyperaldosteronism
- Hyperparathyroidism

Electrolyte abnormalities

Nutritional deficiency

Diseases that may cause myopathic symptoms
- Neuropathic disorders
- Muscular dystrophies
- Other diseases of the neuromuscular junction

Medication-related adverse effects

Other causes
- Sarcoidosis
- Amyloidosis
- Behcet's disease
- Atherosclerotic emboli

Table 2: Causes of infectious myositis[4,6,8,9]

Infectious organism group	*Organisms*
Gram-positive bacteria	*Staphylococcus aureus* *Group A Streptococcus* *Streptococcus (groups A, B, C and G, S. pneumonia, S. anginosus)*
Gram-negative bacteria	*Aeromonas hydrophila* *Burkholderia mallei, B. pseudomallei* *Citrobacter freundii* *Enterobacter SPP* *Haemophilus influenzae* *Klebsiella oxytoca, K. pneumoniae* *Morganella morganii* *Neisseria gonorrhoeae* *Pasteurella spp* *Proteus spp* *Pseudomonas spp* *Salmonella spp* *Serratia marcescens* *Vibrio vulnificus* *Yersinia enterocolitica*
Anaerobic bacteria	*Bacteroides spp* *Clostridium spp* *Fusobacterium necrophorum and F. nucleatum* *Streptococcus spp (anaerobic, e.g., Peptostreptococcus)* *Veillonella spp*
Mycobacterium spp	*Mycobacterium avium complex* *Mycobacterium bovis* *Mycobacterium haemophilum* *Mycobacterium leprae* *Mycobacterium tuberculosis*
Atypical bacteria	*Actinomyces spp* *Bacillus spp* *Bartonella spp* *Borrelia burdorferi* *Brucella spp* *Coxiella burnetti* *Francisella tularensis* *Legionella pneumophila* *Leptospira spp* *Mycoplasma pneumoniae* *Nocardia spp* *Rickettsia and R. conorii* *Treponema pallidum*
Viruses	*Adenovirus* *Cytomegalovirus* *Dengue virus* *Enteroviruses (Coxsackie B virus and ECHO virus)* *Epstein-Barr virus* *Hepatitis A, B, and C viruses* *Herpes simplex virus* *HIV* *HTLV-1* *Influenza A and B viruses* *Mumps virus* *Parainfluenza virus* *Parvovirus B19* *SARS-Coronavirus (COVID-19)* *Varicella-zoster virus* *West Nile virus*
Fungi	*Aspergillus spp* *Blastomyces dermatitidis* *Candida spp* *Coccidioides spp* *Cryptococcus neoformans* *Fusarium spp* *Histoplasma capsulatum* *Mucormycosis* *Pneumocystis jirovecii* *Sporothrix schenckii*
Parasites	*Entamoeba histolytica* *Echinococcus spp* *Haycocknema perplexum* *Microspordia spp (Annicaliia, Trachipleistophora, Pleistophora)* *Onchocerca volvulus* *Plasmodium spp* *Sarcocystis spp* *Schistosoma spp* *Spirometra mansonoides* *Taenia solium* *Toxocara canis* *Toxoplasma gondii* *Trichinella spp* *Trypanosoma cruzi*

COVID-19, coronavirus-19; ECHO, enteric cytopathogenic human orphan viruses; HIV, human immunodeficiency virus; HTLV-1, human T-cell leukemia-lymphoma virus type 1; SARS severe acute respiratory syndrome.

Bacterial infections of the musculature

Bacterial myositis is rather uncommon. Various routes of infection include a contiguous site of infection, vascular insufficiency, penetrating trauma, and hematogenous dissemination. Acute bacterial myositis is most commonly caused by *Staphylococcus aureus*. Myositis cause (bacterial or other forms) should be established before initiating the management of cases. Various categories of bacterial pyogenic infections of the musculature are shown below in Table 3.[1,4,6]

Table 3: Various categories of bacterial pyogenic infections of the musculature[6]

Type of infection	Causative agents
Pyomyositis	*Staphylococcus aureus* (most common cause)
Psoas abscess	*S. aureus*, mixed gram-positive organisms, gram-negative aerobic and anaerobic organisms, *Mycobacterium* species
Staphylococcus aureus myositis	*S. aureus*
Group A streptococcal myositis	*Streptococcus pyogenes*
Group B streptococcal myositis	*Streptococcus agalactiae*
Clostridium species myositis, gas gangrene	Usually *C. Perfringens*, but in spontaneous cases *C. septicum*
Non-clostridial myositis • Anaerobic streptococcal myonecrosis • Synergistic non-clostridial myonecrosis • *Aeromonas* myonecrosis • Vascular gangrene	• *Peptostreptococcus; S. aureus, group A streptococci* • *Streptococci* and mix of other organisms • *Aeromonas hydrophila* • *Proteus, Bacillus, Bacteroides,* and others

Purulent Infectious Myositis (PIM or Pyomyositis)

Purulent infectious myositis (PIM) is a subacute infection of the axial skeletal muscles which is neither a contiguous infection of the bone or soft tissue nor due to a penetrating injury.[6,10] Even though, pyomyositis was considered a "tropical disease" earlier, the cases are well reported in temperate regions.[3,11]

Recent theory in the pathogenesis of PIM suggested transient bacteremia in the presence of muscle injury. As the healthy muscle is resistant to infection, bacteremia without associated muscle damage is improbable.[6,12] Less than 0.5% of the cases of staphylococcal bacteremia developed PIM, demonstrating that muscular damage or other pathology should be present to develop PIM.[6,13]

Young males in their second to the fourth decade of life are most susceptible to work injuries. Most of the patients also have a history of excessive exercise (especially in young athletes), carried out a couple of days or hours, before developing PIM.[10,14] Predisposing factors for PIM are shown below in Table 4.[10]

Table 4: Predisposing factors for purulent infectious myositis[10]

Conditions	Predisposing factors
General conditions	• Cancer • Chronic liver/renal disease/failure • Diabetes mellitus • IV drug abuse • Malnutrition • Organ transplantation • Postpartum/post-abortion • Skin conditions (eczema, varicella, etc.) • Trauma (overuse in athletes)
Rheumatologic conditions	• Dermatomyositis • Polyangiitis • Progressive systemic sclerosis • Rheumatoid arthritis • Systemic lupus erythematosus
Immunodeficiency conditions	• Agammaglobulinemia • Chronic granulomatous disease • Cyclic neutropenia • Drug-induced pancytopenia • HIV infection / AIDS • HTLV 1/2 infection • Myeloperoxidase deficiency
Hematologic conditions	• ALL, AML, CML, PmL • Aplastic anemia • ß Thalassemia • Felty's syndrome • Myelodysplastic syndrome • Multiple myeloma • Non-Hodgkin lymphoma • Sickle cell disease • Sub-clinical leukemia
Medications	• Anabolic steroids, Glucocorticoids (chronically) • Certolizumab pegol • Chemotherapy • Infliximab • Leflunomide • Tocilizumab

ALL, Acute lymphoblastic leukemia; AML, Acute myeloblastic leukemia; CML, Chronic myeloblastic leukemia; PmL, Promyelocytic leukemia; HIV, Human immunodeficiency virus; AIDS, Acquired immunodeficiency syndrome; HTLV, Human T-cell lympho-trophic virus; IV, Intravenous.

Table 5: Purulent infectious myositis clinical stages and management[10,20]

Stage of disease	Clinical characteristics	Management plan
Stage 1 – Invasive	• Typically lasts 10-21 days • Insidious onset of dull muscle pain, low-grade fever, myalgia, malaise, cramps, anorexia • Localized edema (woody induration) • Little or no muscular tenderness • Only a small portion of patients present at this stage	Antimicrobial treatment
Stage 2 – Purulent or Suppurative	• Duration from 24 h to 12 days • Fever and chills • Abscess formation, muscular mass/swelling is visible with diagnostic techniques • Tender muscles • Most patients present in this stage	Antimicrobial therapy + drainage of intramuscular collections or incipient abscesses (drainage through percutaneous route or open surgery)
Stage 3 – Late stage	• High fever, severe pain, infection signs locally, and systemic symptoms of sepsis • Progressed to septicemia, metastatic abscesses, and multi-organ dysfunction which can lead to mortality • Few patients present at this stage	Antimicrobial therapy + intramuscular abscess excision (open surgery)

Different PIM classification methods were recommended. Based on the area of the world as tropical vs non-tropical. Based on the route of infection, as primary or secondary. Primary PIM includes cases developing from bacteremia, while secondary PIM involves cases through continuous spread from either bone or soft tissue.[10, 15-17] PIM is categorized based on the muscle groups involved as cervical, para-spinal, thoraco-abdominal, pelvic, and lower extremities, further as multifocal or generalized myositis.[10,18,19]

PIM staging is based on the progression of the infection from the early stages of bacterial seeding in the muscle to the late stages. PIM clinical stages and their management are shown below in Table 5.[10,20] Diagnosis of PIM in the early stages might be difficult because of subtle skin and other systemic examination findings and has a high chance of misdiagnosing the condition.[10]

For osteoarticular complications, radiographs are used in making the diagnosis of PIM. Intramuscular collections are diagnosed by ultrasound, contrast computed tomography (CT), and magnetic resonance imaging (MRI), for deep infections of the thorax, abdomen, and pelvis.[10,21]

Antimicrobials treatment should include a combination therapy to target gram-positive, gram-negative aerobe, and anaerobic microorganisms like third or fourth-generation cephalosporins (ceftazidime or cefepime) along with anaerobic coverage (metronidazole), beta-lactams (piperacillin/tazobactam) or carbapenem and clindamycin in toxic shock (Group A Streptococci).[10,20,22]

Psoas Abscess

Psoas abscess is caused by a purulent infectious collection in the psoas muscle, either unilaterally or bilaterally. Psoas abscess is called primary when it is due to an occult hematogenous spread (S. aureus) and secondary when it is due to a contiguous spread from other locations.[6,23]

The main cause of psoas abscess used to be Mycobacterium tuberculosis (Pott's disease) infections, which were spreading between vertebrae and psoas muscles. Recently, these are mainly seen in immunocompromised patients (chemotherapy or HIV). Secondary psoas abscesses are due to the spread of gastrointestinal and genitourinary infections. The most common age group affected are from 30 to 50 years of age.[6,24,25]

Recently, primary psoas abscess is caused by community-acquired MRSA and other pathogens like S. pneumoniae, S. milleri, and group A streptococcus. Gram-negative organisms like Escherichia coli, Pseudomonas, Haemophilus, Proteus, and Pasteurella species rarely cause the primary psoas abscess. Risk factors include diabetic patients, alcoholics, the elderly, and the immunocompromised.[6,26,27]

High vigilance is required while diagnosing a psoas abscess. The classical triad of pain, fever, and limp is often absent. Other symptoms that are commonly seen are back pain, flank pain, groin mass or fullness, limp, malaise, anorexia, and weight loss.[6,26,27] Lab testing shows leukocytosis, anemia, and elevated erythrocyte sedimentation rate. CT or MRI are used in diagnosing the

psoas abscess.[6]

Management includes intravenous antibiotics and surgical drainage. Open surgical drainage or CT-guided percutaneous drainage is done based on the volume and number of the abscesses.[6,28] For secondary psoas abscesses, combined management of gastrointestinal or genitourinary infections along with debridement and drainage abscess prevents the recurrence of the infection.[6,29]

Psoas abscess along with spinal infection should get a spinal surgery to prevent spinal instability, spinal cord compression, and other neurological deficits. Antibiotic therapy should include agents against enteric gram-negative and anaerobes, along with beta-lactams (piperacillin-tazobactam, carbapenem). Vancomycin should be used for community-acquired MRSA. Antibiotics are ideally given for 3 weeks after drainage, often continued for 4 to 6 weeks. For M. tuberculosis, therapy with four-drug anti-tuberculosis drugs should be continued for 6 months. Primary psoas abscess has a good prognosis and a mortality rate of 2%, while secondary psoas abscess has a mortality rate of 20%.[6,28,30,31]

Bacterial myositis

Acute bacterial myositis is the diffuse infection of the muscle without an intramuscular abscess. It is commonly seen in adults and is reported less frequently than PIM and psoas abscess. Gram-positive organisms (*Streptococcus*), are the most frequent cause of myositis.[6,32]

Staphylococcus aureus *myositis*

Staphylococcus aureus often causes diffuse myositis along with rhabdomyolysis. Creatine kinase levels will be elevated (unlike PIM), along with CRP levels. Vancomycin or Daptomycin should be included in the management plan to target MRSA. Abscess and dead tissue are removed through surgical debridement and vacuum-assisted closure (VAC) of the wound is employed when is debrided area is large.[6,33]

Group A streptococcal necrotizing myositis

Group A streptococcus (GAS) is the most common cause of cellulitis and various muscular infections like pyomyositis, subacute myositis, acute myositis, and malignant myositis. A severe or fatal form of the infection is called GAS necrotizing myositis or streptococcal myonecrosis or spontaneous streptococcal gangrenous myositis.[5,6,8]

Typically, young men are commonly affected, without a history of trauma or immunocompromised conditions. Although the route of infection is not known, it often starts as a sore throat, pharyngitis thus leading to bacteremia and spreading to the muscles. Nonsteroidal anti-inflammatory drugs act as a risk factor for the infection.[5,6,34,35]

Clinical features involve early stage flu-like symptoms, myalgia, and rash, which later on develop into severe pain of the muscle, fever, and local tense swelling. GAS necrotizing myositis might have multiple sites of infection, which progresses within 1 to 4 days to bacteremia, toxic shock syndrome, and multiorgan failure. As the intramuscular pressure increases in the infected muscle, it would lead to the development of compartment syndrome.[5,6]

Lab findings typically show leukocytosis along with elevated muscle enzymes. Muscle biopsy shows muscle necrosis and gram-positive cocci between the muscle bundles.[5,6,32] Diagnosis of GAS necrotizing myositis depends on blood cultures and MRI; MRI is used to differentiate between fasciitis and necrotizing myositis.[6,36]

Immediate surgical exploration and debridement along with fasciotomy are required to reduce the increased compartment pressure. More often surgical excision should be repeated to remove the necrotic tissue and more frequently amputation is necessary.[5,6,37]

Intravenous antibiotic therapy with penicillin along with clindamycin has shown higher efficacy in reducing the bacterial burden during the stationary growth phase (Eagle effect), by inhibiting the toxin and other virulence factors production via blocking the protein synthesis.[6,38] IV immunoglobulin neutralizes the streptococcal exotoxins when used in patients with streptococcal toxic shock syndrome. GAS myositis has a mortality rate of nearly 85%.[6,32,35,36]

Group B streptococcal myositis

S. agalactiae can cause either PIM or myositis. The risk factors for group B streptococcal musculature infections include peripheral vascular disease, diabetes mellitus, alcoholism, malignancy, and immunocompromising conditions. Infection generally spreads from other body parts (foot ulcer, endocarditis). Treatment generally comprises penicillin and surgical debridement of the infected and necrotic muscles.[6,39-41]

Clostridium species myositis

Clostridium perfringens infection causes clostridial myonecrosis or gas gangrene. Infection occurs through various routes, which are traumatic wounds with soil contamination, vascular insufficiency involving the extremities, surgeries of bowel and biliary system, septic abortions, unhygienic injections of medications and illicit drugs.[6,42]

The presence of a foreign body and low oxygen concentrations promote anaerobic conditions that help the

clostridium to convert from spore form to vegetative form, which releases the toxins for tissue damage and produces other systemic symptoms.[6]

Spontaneous clostridial myonecrosis can occur without a wound, because of C. septicum bacteremia caused by occult colon cancer, bowel infarction, and neutrophilic enterocolitis.[6,43] Other species of Clostridium which are known to cause gas gangrene are *C. novyi. C. histolyticum, C. sordellii*. Clinical features include severe pain, edema, sweet odor discharge from the injured area (6 h to 3 days). The wound might turn from pale to bronze color due to hemorrhagic bullae. The presence of gas can be detected on radiographs of the infected tissues.[6]

Lab examination shows leukocytosis along with hemolytic anemia because of clostridial alpha-toxin and bacteremia is seen in 15% of the cases. Gram stain of the wound exudate usually shows numerous gram-positive bacilli with blunt ends and typically lacks neutrophils. Differential diagnosis should include fulminant myositis (GAS necrotizing myositis) and non-clostridial myositis. Crepitant cellulitis is commonly seen more superficially but should be considered while diagnosing clostridial myositis.[6]

Treatment consists of emergency surgical exploration along with the debridement and excision of the infected muscles and fasciotomies to relieve the pressure. Antibiotics should cover GAS necrotizing myositis and should be a combination of penicillin and clindamycin.[6,44]

Hyperbaric oxygen might have some benefit, as high oxygen concentrations inhibit the clostridial growth and thus reducing the alpha-toxin production. Hyperbaric oxygen can be used when there is incomplete surgical excision at paraspinal and abdominal areas. The mortality rate of clostridial myositis is between 20-25%, often the survivors have disfiguring wounds.[6,45,46]

Non-clostridial (Crepitant) myositis

Non-clostridial myositis includes four categories, which are:[1,4,6,46]

- Anaerobic streptococcal myositis
- Synergistic non-clostridial myonecrosis
- Aeromonas hydrophila myonecrosis
- Infected vascular gangrene

Anaerobic streptococcal myositis

Anaerobic streptococcal myositis has similar characteristics to clostridial myonecrosis, which are considerable necrosis of the muscles, gas, and foul exudate from the infected muscles. Anaerobic streptococcal myositis can be differentiated from another myositis, by its slower evolution of infection over 1-4 days, overlying erythema, muscle contraction on stimulation along with numerous neutrophils in the exudate. Most common causative organisms include anaerobic *streptococci* (*Peptostreptococcus*), GAS, and *S. aureus*. Treatment includes gram-positive covering antibiotics (Penicillin, Vancomycin for *staphylococcus*) and surgical exploration and debridement.[5,6,46]

Syngergistic non-clostridial myonecrosis

Synergistic non-clostridial myonecrosis is the infection of the subcutaneous tissues and fascia, which might extend into the muscle and skin. The infection is often polymicrobial, including both aerobic and anaerobic organisms, like *streptococci, Peptostreptococcus, E. coli, Klebsiella, Enterobacter, Bacillus cereus*, and *Bacteroides*. Risk factors include diabetic patients, immunocompromised states like chemotherapy patients with neutropenia. Treatment includes complete surgical debridement of the infected tissues and broad-spectrum antibiotics. The mortality rate is high for patients with this infection.[6,46]

Aeromonas hydrophila *myonecrosis*

Aeromonas hydrophila, is an anaerobic gram-negative bacillus, which causes a rapid, progressive myonecrosis, after a penetrating trauma in a freshwater environment and is associated with fish or other aquatic animals. Myonecrosis has similarities to clostridial gas gangrene, due to its rapid onset (24 to 48 h) and progression after trauma.[6,46]

Clinical features include pain, serosanguineous bullae, marked edema, gas in the fascial planes, and toxicity along with the history of exposure to freshwater directs towards *Aeromonas* diagnosis. Treatment comprises surgical debridement and antibiotic therapy. Antimicrobials like gentamicin, tobramycin, carbapenems, and ciprofloxacin are most effective against *Aeromonas*. *Vibrio vulnificus,* causes myositis and is associated with exposure to saltwater.[6,46] As per literature review done by Koth et al., (2012) of *Aeromonas hydrophila* soft tissue infections has found that these infections occur following motor vehicle crashes, farmyard injuries, puncture injuries, and mud football injuries involving wound contamination from aquatic and non-aquatic environments.[47]

Infected vascular gangrene

Infected vascular gangrene is a mixed infection in a muscle group or a limb that has arterial insufficiency, frequently seen in diabetes mellitus. The most commonly seen bacterial species are *Proteus*, *Bacteroides*, and anaerobic *streptococci*. Even though the infection does not spread beyond the vascular gangrene, foul-smelling pus and gas formation are notable. *Bacillus cereus* causes myonecrosis due to thrombosis of the arterial grafts

with *crepitus*, along with aggressive post-traumatic infections.[6,46,48]

Other forms of bacterial myositis

Some of the other bacteria not discussed above can sporadically cause myalgias, myositis, myopathy, and rhabdomyolysis. Although endocarditis might cause diffuse myalgias, diagnosis is established by blood cultures and echocardiography. Syphilis might also be associated with myalgias and should be confirmed by micro-hemagglutination - *Treponema pallidum* test.[6,49]

Other causes of myalgias are *Rickettsia rickettsii* (Rocky Mountain spotted fever), *Francisella tularensis* (Tularemia), *Borrelia burgdorferi* (Lyme disease), and diagnosis is based on serological tests.[6,50,51] Muscle involvement in Mycobacterium infections is seen in < 1% of the cases. Myositis develops slowly and is insidious, physical exam shows a mass or swelling in the muscle and adenopathy is often absent.[6,52,53]

Acute rhabdomyolysis during bacterial infections occurs less commonly. Legionella is the most common bacteria associated with rhabdomyolysis development. Less often bacteria like *staphylococci, streptococci, Salmonella, Leptospira, Neisseria meningitides*, and *Mycoplasma pneumoniae* are also involved in rhabdomyolysis.[6,54-57]

Viral myositis

The viral agents are the most common cause of nonbacterial infectious myositis. Clinical symptoms involve myalgia's, polymyositis, and rhabdomyolysis. Among viruses, influenza is the most frequent causative agent reported to cause viral myositis. Other viruses that are widely involved in myositis are shown in Table 2.[3,6]

Influenza

Influenza usually presents with cough, fever, rhinorrhea, and myalgia's (diffuse, self-limiting). In the late stage of the infection, patients develop "acute benign myositis", with typical symptoms like pain, tenderness, and swelling (gastrocnemius and soleus muscles); difficulty in walking is also noted. Influenza-associated myositis is seen more often in children as the immature muscle cells are more prone to infection.[3,58,59]

Among children, boys are more affected than girls (2:1). It has a mean presentation on day 3 and influenza type B is commonly seen than type A, due to the presence of a glycoprotein in Type B strains. Diagnosis is confirmed by the clinical history, detection of virus by polymerase chain reaction (PCR) test of the nasopharyngeal secretions. Symptoms usually resolve in one week but may last till one month. Treatment includes symptomatic care and often may develop into life-threatening rhabdomyolysis, with an increase in creatine phosphokinase and myoglobin-induced acute renal failure which is commonly seen with influenza A.[3,46,58]

Coxsackievirus

Pleurodynia is caused by group B coxsackievirus (rarely by group A) and less often by enteric cytopathogenic human orphan (ECHO 1, 6,9, 16, and 19) viruses. The symptoms include acute onset of sharp chest pain over the sternum or lower ribs, fever, muscle tenderness, and abdominal pain might be present. Coxsackie A9, B2, B6, and echoviruses 9,11 can also cause myositis in skeletal muscles and might develop into rhabdomyolysis with elevated muscle enzymes and myoglobinuria. Diagnosis is based on clinical features, serologic evaluation, and culture of the virus from either pharyngeal or fecal samples. Treatment is symptomatic.[3,46,59,60]

Human immunodeficiency virus

Clinical features of HIV infection are polymyositis, weakness, myalgia's, and elevated muscle enzyme levels. Patients with HIV might initially present with polymyositis, which will lead to the diagnosis. Patients with immunocompromised and low CD4+ T lymphocytes are more prone to develop several other forms of myopathies like inclusion-body myositis, wasting, vasculitis, infiltrative lymphocytosis syndrome, antiretroviral medications (mitochondrial myopathy), myasthenia syndrome, and skeletal muscle malignancy.[3,46,61]

While doing work-up for viral myositis, HIV testing should be included. Serum creatine phosphokinase is increased, muscle biopsy and electromyographic changes might aid in making a diagnosis. Management includes supportive care and treating the underlying myositis causative agent. Antiretroviral therapy should be initiated if the patient is diagnosed for the first time. Few cases of myositis might develop into rhabdomyolysis.[3,46,62]

Coronaviruses

Coronavirus disease-2019 (COVID-19), is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Although it is known to cause life-threatening respiratory illnesses, there is increasing evidence of multisystem involvement in neurological, gastrointestinal, and cardiac systems. Although myalgia's are common in COVID-19 patients, elevated creatine kinase levels are reported in SARS patients. Zhang et al. reported a case of COVID-19 associated myositis involving a proximal limb, bulbar, and facial muscles, which was treated with 1000 mg intravenous methylprednisolone for 5 days.[63]

Mehan et. al. reported that 78% (7 out of 9) COVID-19 patients who had MRI of the spine showed evidence of paraspinal (only in the lumbar spine) myositis featuring intramuscular edema and enhancement. The study concluded that a high frequency of myositis in COVID-19 patients reported myalgia in a small series.[64] Beydon et al. demonstrated that the association of myositis with interstitial pneumonitis can be seen in COVID-19 patients or autoimmune myositis.[65]

Other viruses

Human T-cell lymphotropic virus type (HTLV-1) causes "adult T-cell leukemia/lymphoma and tropical spastic paraparesis/HTLV-1 associated myelopathy". Hepatitis B and C viruses are also implicated in the development of polymyositis. Adenovirus is involved in causing myositis, myocarditis and rhabdomyolysis. Parvovirus B19 leads to myositis along with fever, diffuse rash which involves cheeks. West Nile virus also causes myositis along with neurological symptoms. Other viral agents that are involved in the myositis are shown in Table 2. Diagnosis is usually based on the clinical picture, serological studies, and cultures of the nasopharyngeal and stool samples. Muscle biopsies, immunofluorescent or PCR studies, electron microscopy are often used in the diagnosis of the causative virus.[3,46,66-68]

Fungal Myositis

Fungal infections of the musculature are relatively uncommon. Most of the cases are seen in immunocompromised patients and the diagnosis is established through biopsy and culture of the specimens.[3]

Candidiasis

The most common cause of fungal myositis is candida and is usually seen in immunosuppressive patients (chemotherapy and broad-spectrum antibiotic usage). *C. tropicalis, C. albicans, C. krusei* are the involved species in infecting the musculature. Clinical features include fever, rash, muscle tenderness, diffuse, micro-abscesses or focal, and fungal abscesses of the muscles might also occur. Diagnosis is established by imaging (CT, MRI, ultrasound), muscle biopsy, histopathology and fungal cultures. Management is with amphotericin B, azoles, or echinocandin and surgical drainage for large collections in the muscles.[3,8]

Cryptococcosis

Cryptococcus neoformans causes myositis through the dissemination of the inhaled organisms. Most of the cases are seen in transplant recipients and HIV patients. Clinical features include pain and swelling of the muscles in the lower limbs. Diagnosis involves muscle biopsy, lumbar puncture for CNS involvement, positive cryptococcal serum antigen, and blood cultures. Treatment is with amphotericin B, flucytosine for multifocal disease, fluconazole for localized disease, and surgical drainage for purulent collections.[3,69]

Histoplasmosis

Histoplasma capsulatum is dimorphic fungi and causes myositis through dissemination in HIV and immunocompromised patients. Diagnosis is established through biopsy, histopathology cultures of the fungus, and antigen testing. Treatment is with amphotericin B and surgical drainage for collections.[3,70]

Aspergillosis and other fungi

Aspergillus spp causes myositis in immuno-compromised patients, similar to other fungal causative agents. Diagnosis is with biopsy and fungal culture, fungal antigen testing. Treatment is with voriconazole or amphotericin B and surgical debridement for necrotic tissue. Other causes of fungal myositis are shown in Table 2.[3,6,71]

Parasitic agents

Various parasites encyst in the muscles, thus causing myositis. Travel history is important in diagnosing the parasitic infections that are acquired abroad. History of food ingestion along with eosinophilia points towards a parasitic causative agent. Different parasitic agents that are involved in causing myositis are shown in Table 2.[3,6]

Trichinosis

Trichinella spp, especially *T. spiralis*, infects humans through undercooked meat, like pork, bear, cougar, and wild boar, thus the larvae encyst in the striated muscles. Clinical features include gastrointestinal symptoms, fever, myalgia's, muscle weakness and swelling (extraocular muscles, head, and neck muscles). Although the infection is self-limiting, complications like myocarditis can occur due to encysted larvae. Diagnosis is through detailed dietary history, eosinophilia, raised muscle-related enzymes, serological testing for antibodies, radiographs for encysted larvae, and muscle biopsy. Treatment involves albendazole or mebendazole, severe myositis should include the addition of corticosteroids.[3,72,73]

Cysticercosis

Taenia solium, pork tapeworm infects humans through contaminated food and water, thus leading to cysticercosis. Eggs develop into invasive larvae, which move through the intestinal wall and move to CNS, subcutaneous tissues and

muscles. Symptoms may include seizures, myalgias, myositis, and weakness due to inflammatory reactions from the dying cysts. Imaging (MRI, CT or ultrasound), shows scolex in a clear cyst, thus aiding in the diagnosis. Radiographs of the cysts have a "puffed rice" or "spindle-shaped" appearance. Serological testing of the cerebrospinal fluid or blood is also used in making the diagnosis. Treatment is with albendazole or praziquantel and surgical excision for large intramuscular lesions.[3,74]

Toxoplasmosis

Toxoplasma gondii, is acquired through ingestion of undercooked meat (pork or lamb), containing tissue cysts or oocysts from cat feces. An acute infection might be asymptomatic or may develop into a fever, malaise, myalgia's and cervical adenopathy. Immunocompromised patients, T-cell deficiencies, therapy with corticosteroids and AIDS patients might develop polymyositis and myocarditis. Severe infection symptoms include wasting, fasciculation's, fever, encephalitis and multiorgan failure. Diagnosis is with clinical history, serologic testing, muscle biopsy along with immunocytochemistry, and microscopy, and isolating organisms from tissue culture. Therapy is with sulfadiazine and pyrimethamine, in early stages of myositis, and steroids should be included in the late stages of the disease.[3,75]

Microsporidiosis

Microsporidia spp, route of infection is not clear, might be through insect bites, contaminated water, or undercooked meat. Immunosuppressive states, therapy with corticosteroids and tumor necrosis factor antagonists, and AIDS patients increases the risk for microsporidiosis. Clinical features include fever, muscle pain, wasting, and weakness along with elevated creatine kinase. Diagnosis is based on muscle biopsy along with light and electron microscopy. Treatment is with albendazole and itraconazole is added for *Annicaliia vesicularum* myositis.[3,76]

Conclusions

Infectious myositis is caused by bacterial, viral, fungal and parasitic organisms. Pathogenesis of myositis is either via direct infection of the muscle or immune-mediated injury. Bacterial and fungal myositis is usually confined to a muscle group, while viral myositis is diffuse and parasitic myositis often has a travel history along with eosinophilia. Diagnosis is with clinical features, laboratory, serology, cultures, and imaging. Treatment is with appropriate antibiotics and involves a holistic approach from various specialties.

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The Early History of Arimoclomol for Inclusion Body Myositis

Mazen M. Dimachkie, Pedro M. Machado, Claus Sundgreen, Thomas Blaettler, Jeffrey Statland, Laura Herbelin, Andrew Heim, Linda Greensmith, Michael G. Hanna and Richard J. Barohn

Background

The early history of arimoclomol involves two parallel lines in exploration, one in the USA and the other in the UK. In the mid- 2000s, Dr. Rick Barohn was asked to be a site in a Phase 2 study of arimoclomol in Amyotrophic Lateral Sclerosis (ALS). This was a Northeast ALS Consortium (NEALS) study that was funded by the drug company CytRx, which owned the compound. CytRx was interested in the possibility that arimoclomol could slow down the progression of neurodegenerative diseases that involved protein misfolding.[1] This hypothesis was based on the 2004 findings from Dr. Linda Greensmith's lab in the UK, which showed that arimoclomol was effective at delaying disease progression and extending lifespan in the $SOD1^{G93A}$ mouse model of ALS.[2] Dr. Barohn attended the investigators meeting, learned about the drug, and had the idea that it should also be tried in sporadic inclusion body myositis (IBM). He discussed this with the CytRx representatives. They had not heard of IBM but were interested, and Dr. Barohn sent them information about the disease including the Muscle Study Group (MSG) publications.

Targeting Protein Homeostasis in Sporadic Inclusion Body Myositis — A KU & UK Collaboration

In the fall of 2006, Dr. Barohn and his research assistant, Dr. Jeffrey Statland (who had just begun the internship), presented the concept of using arimoclomol for IBM at the annual MSG meeting in Beaver Hollow, N.Y. They explained the rational of using the drug for IBM. He was asking if the MSG would consider becoming involved in a multicenter trial (see Appendix). They proposed a 70 patient, one-year trial of 300 mg/day and proposed the primary outcome would be quantitative muscle testing (maximum voluntary isometric contraction testing [MVICT]) with secondary outcomes of IBM Functional Rating Scale (IBMFRS), time to walk 15 feet, manual muscle testing (MMT), Purdue peg placement, 36-Item Short Form Survey (SF-36), and Individualized Neuromuscular Quality of Life Questionnaire (INQoL). They proposed that the known natural history of IBM is that the MVICT scores will decline by an average of 4% or Z score of 0.28 over 6 months. They extrapolated a Z score for 12 months of 0.6 units and stated that to halt progression they would need a sample size of 35 subjects per group to detect a difference between the 2 groups, with 80% power. They suggested an optional muscle biopsy sub-group to examine Heat Shock Protein 70 (HSP70) levels, inflammation, vacuoles, and amyloid inclusions. Unfortunately, the feedback from the MSG was disappointing. There was little enthusiasm for the project moving forward at that time as a multicenter trial. It was suggested a single site trial should be the initial step.

Dr. Barohn then applied to CytRx for an investigator-initiated grant so that the company would supply the University of Kansas Medical Center (KUMC) team with enough drug and placebo to study 12 patients with IBM in a pilot trial to study tolerability in this patient population. Dr. Barohn created the protocol with several investigators at KUMC including Dr. Jeff Statland, Dr. Yunxia Wang, and Laura Herbelin. Dr. Wang obtained internal pilot funding from the General Clinical Research Center (GCRC) National Institutes of Health (NIH) pilot grant program for junior investigators to perform the study on the GCRC at KUMC. Dr. Barohn applied to the Food and Drug Administration (FDA) to get an Investigational New Drug (IND) designation (FDA-IND # 76,773) and he was able to cross-file on the CytRx IND. He asked the FDA if a 12-month trial could be accomplished. The FDA at the time only had human data from ALS patients receiving the drug for 3 months, so they would not give him the 12-month study. The FDA would only agree to a 4-month drug study. Therefore, a protocol was designed whereby the patient received drug or placebo for 4 months, but they were followed on the protocol for another 8 months, or a total of a year. Patients had monthly evaluations. In addition to looking for safety signals they also proposed to do pre- and post-muscle biopsies to measure HSP70 levels and histologic features as noted above. The biopsies were to be obtained at baseline and after Month 4.

A parallel interest in the drug for IBM was occurring in the UK. The only individual who was enthusiastic about the Barohn and Statland presentation at the MSG in 2006 was Dr. Michael Hanna, who had heard about the drug from his colleague Dr. Greensmith. She had been working with arimoclomol and its derivatives for several years in collaboration with Biorex, the original Hungarian company that made arimoclomol, testing its neuroprotective properties in a number of mouse modes of motor neuron degeneration, including the $SOD1^{G93A}$ mouse of ALS. It was these findings in $SOD1^{G93A}$ mice that led CytRx to acquire arimoclomol and set up the first trials of the drug in ALS patients. Dr. Greensmith's findings in ALS led her also to test the effect of arimoclomol in models of other protein misfolding disorders, including models of IBM. Her findings showed that arimoclomol was able to decrease levels

of abnormally folded proteins and prevent cytoplasmic mislocalisation of TDP-43 in primary rat muscle cell cultures transfected with beta amyloid precursor protein or exposed to inflammatory mediators. Furthermore, arimoclomol was also found to ameliorate the disease phenotype of mice expressing mutant Valosin Containing Protein (VCP), in which skeletal muscles show an inclusion body myopathy-like phenotype, including accumulation of misfolded proteins as well as muscle atrophy and weakness. Dr. Hanna approached CytRx to obtain some arimoclomol for a small clinical trial at the UCL Queen Square Institute of Neurology. Dr. Barohn, however, had already approached the company and had an agreement with them to receive the drug and do a pilot trial in Kansas. Since Drs. Barohn and Hanna were both leaders in the MSG, they decided to join forces and do a 24 patient IBM study, 12 in London and 12 in Kansas City with a 2-to-1 randomization of active drug to placebo. CytRx was willing to expand the size of the study if it was going through one protocol and one IND, held by Dr. Barohn.

Dr. Hanna found national funding from Arthritis Research UK (merged in 2018 with Arthritis Care to form Versus Arthritis) to perform the study in London at the UCL Queen Square Institute of Neurology. In 2007, Drs. Barohn and Statland obtained an R13 NIH grant to have an international meeting on nondystrophic myotonias in Kansas City. Dr. Hanna's group was also part of that project and they attended the meeting. This allowed both doctors to finalize the protocol so that each site was enrolling patients by the fall of 2007 on both continents. Dr. Dimachkie also met with Dr. Barohn and Dr. Hanna; he was introduced to the study as he was moving to Kansas City to start his new position at the KUMC. Once Dr. Dimachkie formally joined Dr. Barohn at KUMC that summer, he became involved in the study. Dr. Adrian Miller and subsequently Dr. Pedro Machado became involved in the study at Queen Square assisting Dr. Hanna.

Meanwhile, Dr. Greensmith continued to obtain promising data in her laboratory using arimoclomol in the VCP model and in cell culture. Patients were entered into the study and completed the study over two years. The data from both sites was analyzed in London and it was determined the drug was well tolerated in this population. It was also shown there may have been a small trend at 8 months in some of the clinical endpoint measures, namely the IBMFRS,[3] mean right grip strength hand grip MVICT score, and the mean MMT score. Unfortunately, the muscle biopsy measures did not show the anticipated change over time, but there were a host of reasons for that including transportation issues of the muscle tissue from the USA to UK, which may have accounted for this. After extensive discussion, it was decided to merge the clinical data and the pre-clinical data into one manuscript. This manuscript was published in Science Translational Medicine in 2016.[4]

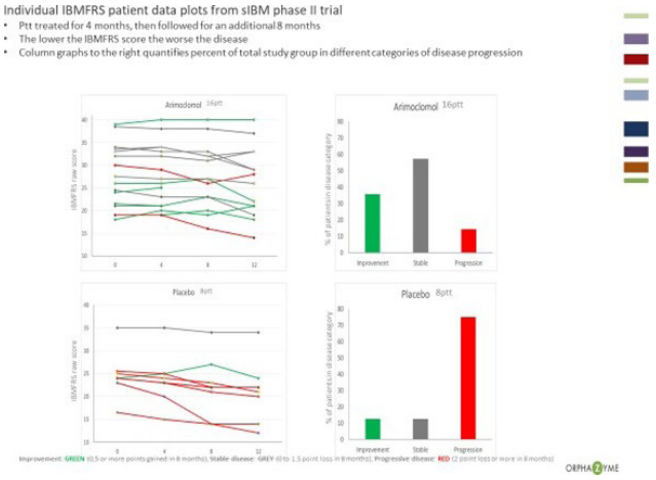
The IBM4809 Path Forward — A Randomized Controlled International Efficacy Study

As the group decided to publish the combined results of the preliminary data, the group moved to apply for a federal grant to fund a larger multi-center international randomized controlled study. When the data was presented at the MSG there was growing enthusiasm to move forward. A protocol was designed using the IBMFRS as the primary endpoint instead of MVCIT for the large trial, and the sample size was increased to 150 subjects in a 1-to-1 randomization. The protocol was approved by the MSG executive committee and it became an official MSG study. The project was presented to the NIH NeuroNext consortium and was rejected for a full grant application. Dr. Dimachkie had become the overall PI of the project by this time with Dr. Machado as the multiple PI and Drs. Hanna and Barohn in senior leadership roles. Dr. Dimachkie then applied to the FDA Orphan Products Development (OOPD) program for funding. The application was funded on the third try, and Dr. Dimachkie received notice of the grant award in 2015 (RO1FD004809), which we named IBM4809. The trial is registered as NCT02753530.[5]

In the meantime, CytRx sold the rights to the drug to the Danish company Orphazyme. The 4 trial leaders began meeting regularly with Orphazyme to explain the nature of the IBM project and to get assurance that they could get both drug and placebo for the project. This relationship developed well, and the company was interested in the preliminary data from the pilot study. Orphazyme performed a post hoc responder analysis of the efficacy data from the pilot study (Figure) based on the yearly average rate of decline of the IBMFRS by 3 points. This demonstrated that 14/16 in the arimoclomol 100 mg PO T.I.D. group did not progress (n = 9) or improve (n = 5) at 8 months, which was 4 months after the last randomized dose. However, 2/16 progressed as assessed by a loss of 2 or more points on the IBMFRS at 8 months. In the placebo group, 2/8 were stable (1) or improved (1) at 8 months; 6/8 progressed. This encouraging post hoc analysis furthered the already existing strong enthusiasm of this collaborative group.

Ultimately, and as detailed later in this report, Orphazyme became interested to the point that the company suggested this become a joint industry-academia study moving forward, and the investigators agreed. Dr. Barohn transferred the IND to Orphazyme. Orphazyme and Dr. Dimachkie had interactions with the FDA regulatory agency. One outcome from these meetings is that the FDA

Figure 1. Post hoc analysis of pilot study data.



accepted the IBMFRS as a clinically relevant primary outcome measure for this study.

Despite receiving FDA-OOPD notice of award to start June 1, 2015, Dr. Dimachkie did not initiate enrollment as several important next steps needed to be addressed. Given the limits on maximum FDA-OOPD funding dollar amounts at that time, this study of arimoclomol in IBM did not yet contain the "bells and whistles" to fulfill a strict regulatory agency's approval pathway. If this study were to be positive, it would be very important to have a more rigorous structure such as Code of Federal Regulations (CFR) Part 11 compliant database or on-site monitoring. On July 17, 2015, Dr. Dimachkie met with the Orphazyme leadership team in Boston and was joined via teleconference by Dr. Barohn and Dr. Hanna to share the good news. Dr. Dimachkie presented the study data and shared news about the FDA-OOPD grant award. As part of the grant application to FDA-OOPD, Orphazyme had already made a commitment to manufacture matching capsules of arimoclomol and placebo to be released to the trial through several campaigns. However, the goal of the Boston meeting was also to discuss with Orphazyme the possibility of expanding the scope of this academia-industry collaboration.

Intense communication with Orphazyme followed this meeting through the rest of 2015. This culminated in the collaboration of the study team with Orphazyme to support the Type C filing with the FDA regulatory division. On March 18, 2016, Dr. Dimachkie and Laura Herbelin met in New Jersey with Orphazyme and B&H Consulting Services, Inc. The Type C file was finalized shortly thereafter and submitted by B&H, requesting a meeting with US Regulators for the middle of 2016. Later that year, the collaborative group exchanged correspondence with the FDA regulatory division and adjusted the protocol according to their feedback. As an example, we were encouraged to seek a higher dosage of arimoclomol. We evaluated the current safety data of arimocolomol. Based on that analysis, we informed the FDA regulatory agency that we were increasing the dosage to 400 mg PO TID. The protocol was adjusted to match requirements of section 6 of the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) rules. All along the way, Dr. Dimachkie was in close communication with the FDA-OOPD program manager to keep the FDA-OOPD funding agency informed of ongoing work and to make sure that any proposed changes do not compromise existing study funding. By late 2016, Orphazyme provided more study support by funding a CFR Part 11 compliant database and hiring a Clinical Research Organization (CRO) to perform on-site monitoring.

The next challenge was to get the drug delivered from Europe to the US. The study drug was manufactured in France and packaged in Germany for shipment. To that point, Dr. Dimachkie got the support of the KUMC Research Institute, Inc (RI). To become the Importer of Record and after seeking guidance from experienced importers, Dr. Dimachkie and the KUMC RI submitted the application to allow investigational medical product entry into the US in order to enroll the first study subject. In the summer of 2017, the study drug shipment cleared customs and arrived in Kansas. KUMC remained the Importer of Record until Orphazyme took over IND sponsorship in late 2017 and managed drug entry into the US and UK for the remainder of the study. By mid to late 2018, all participating sites were activated. To further support the 2014 orphan designation by the FDA OOPD, Orphazyme received in December 2019 FDA Fast Track designation for arimoclomol in IBM. Orphan designation (EU/3/16/1659) had also been granted by the European Commission/European Medicines Agency (EMA) on May 30, 2016, following an application and physical meeting with the EMA on April 19, attended by Dr. Pedro Machado, Dr. Linda Greensmith, and Orphazyme representatives.

Conclusions

In summary, this strong academia-industry collaborative partnership with Orphazyme is fundamental not only for providing an experimental drug, but also securing robust operational trial conduct and GCP compliance. This strong partnership drove regulatory interactions and processes and allowed for the implementation of add-on studies to investigate pharmacokinetics, introduce clinician and patient global impression scales, a muscle MRI sub-study, and most importantly, an open-label extension

opportunity for the 4809 participants. All along the way, the ultimate goal has been to move forward the field of IBM with strong communication that promotes lasting and trusting partnership. If the IBM4809 study results are positive, this strong partnership is positioned to support filing for regulatory approval in the US and Europe, with the possibility to offer the first effective therapy for people with IBM.

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Acknowledgments

We acknowledge funding support from the Neurology Department Ziegler Research Fund and the NIH Funded General Clinical Research Center for the pilot study conduct at the KUMC. We also recognize funding from the FDA-OOPD (RO1FD004809) and support for Ophazyme for the IBM4809. PMM and MGH are supported by the National Institute for Health Research (NIHR), University College London Hospitals (UCLH), Biomedical Research Centre (BRC). We thank patients with IBM who have participated in the pilot study and in IBM4809 and all of those who have expressed interest in the studies.

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5. Study of Arimoclomol in Inclusion Body Myositis. Trial details publicly available at: https://clinicaltrials.gov/ct2/show/NCT02753530

Appendix

PowerPoint slides presented by Drs. Jeffrey Statland and Richard Barohn at the 2006 Muscle Study Group meeting.

Arimoclomol Therapy for IBM

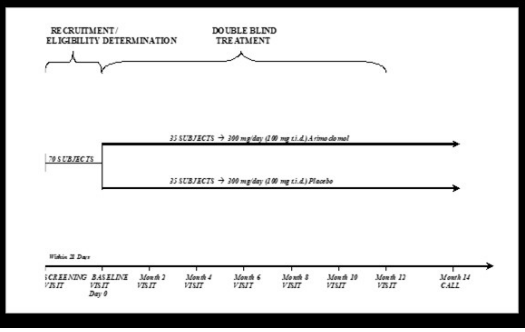
Richard J Barohn, MD
Jeffrey Statland, MD
Department of Neurology
University of Kansas Medical Center

Arimoclomol Therapy for IBM

- IBM was thought to be an immune mediated myopathy
- IBM does not respond to Immuno-mudulatory therapy
- IBM is increasingly thought to be a disease of myodegeneration
- Protein misfolding may play a role in the pathology of IBM
- Arimoclomol is a potent co-inducer of Heat Shock Proteins
- Heat Shock Proteins protect the cell from protein misfolding

We Propose

- A 12-month placebo controlled double blind trial of Arimoclomol 300mg/day versus placebo in 70 patients with IBM



Primary Outcome Measure

- Quantitative Muscle Testing
  - ❑ Composite MVICT

Secondary Outcome Measures

- Manual Muscle Testing
- Purdue Peg Placement
- Time to walk 15 feet
- IBM-FRS
- SF-36 v2
- Functional Disability Scale
- Will add INQoL to protocol

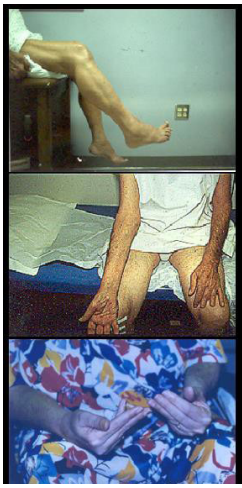
Statistical Considerations

- Natural history and Avonex studies suggest MVICT scores will decline by an average of 4%, or 0.28 Z score units over 6 months (SD 0.88)
- Extrapolating to 12 months, we expect a decrease of 0.6 Z score units
- To halt progression need sample size of 35 subjects per group
- This will provide 80% power to detect a difference in the mean response of 0.6 Z score units between the two groups, using a two-tailed two-sample t-test at the 0.05 level of significance

Muscle Biopsy Sub-Study

- Optional study in 35 volunteers
- Month 12 versus Baseline, drug versus placebo
- Will examine:
  - ❑ HSP 70 levels (Gallagher)
  - ❑ Inflammation
  - ❑ Vacuoles
  - ❑ Amyloid inclusions
  - ❑ Gene expression profiles (Greenberg)

Background and Preliminary Studies

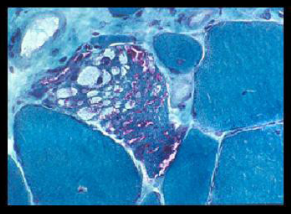


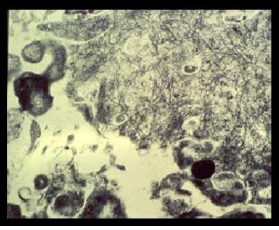
IBM

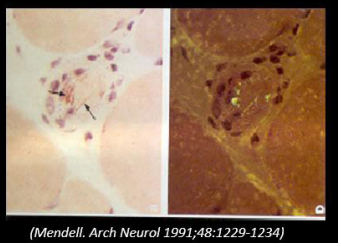
- Most common progressive debilitating muscle disease in persons >50 y.o.
- Predominately affects finger flexors, and quadriceps
- Often leads to severe disability and confinement to wheelchair or scooter
- Although originally considered an inflammatory myopathy, does not respond to immuno-modulatory agents

IBM Pathology

- Inflammatory cells
- Vacuoles
- Amyloid inclusions
- Paired helical filaments







(Mendell. Arch Neurol 1991;48:1229-1234)

IBM may be a Myodegenerative Disorder

- Muscle Biopsies show:
  - Amyloid fibrils containing Aβ 40/42
  - Paired helical filaments containing p-tau
  - These inclusions co-localize with other proteins also found in Alzheimer's disease
    - Presenelin-1
    - Apo E
    - Ubiquitin, etc
- *In vitro* models overexpressing Aβ Precursor Protein mimic IBM pathology
  - *Askansas. Neuroreport. 1997; 8: 2155-2158.*
- Animal models overexpressing Aβ Precursor Protein mimic IBM pathology
  - *Fukuchi. Am J Pathol. 1998; 153: 1687-1693.*
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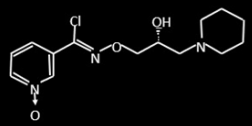
Arimoclomol



- Derivative of Bimoclomol, developed by CytRx, a potent co-inducer of Heat Shock Proteins
- Stabilizes Heat Shock Transcription Factor-1 (HSF-1)
  - This increases levels of HSP70 and HSP90
- Interacts with acidic membrane lipids to stabilize plasma membranes
- Interacts with cardiolipin in mitochondria
  - May stabilize membrane
  - May inhibit apoptosis

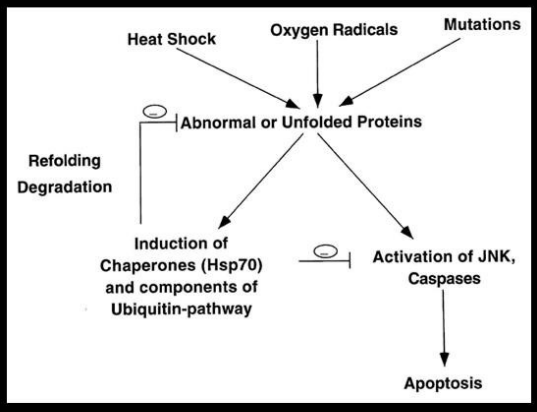
(Kieran. Nature Med. 2004; 10: 402-405; Torok. PNAS. 2003; 100: 3131-3136)

Heat Shock Proteins

- Prevent aggregation of mutant and damaged proteins
- Catalyze protein folding and multimer assembly
- Solubilize aggregated proteins
- Promote ubiquitination and degradation of abnormal proteins
- Promote proper folding and glycosylation of membrane and secreted proteins
- Suppress apoptotic program
- Regulate own expression in cytosol and ER

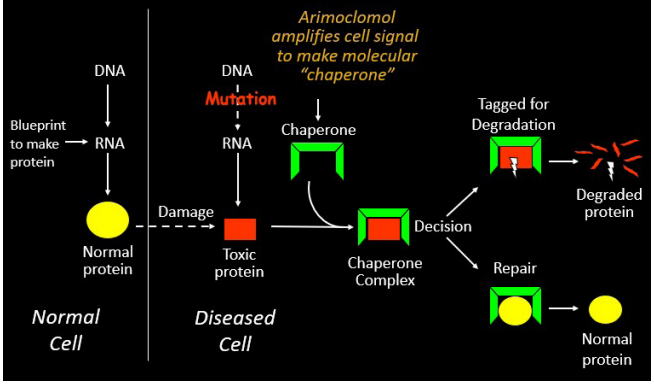
(Sherman. Neuron. 2001; 29: 15-32)

Heat Shock Pathway

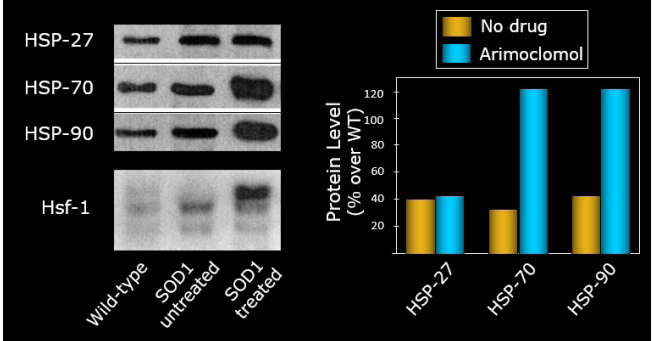


(Sherman. Neuron. 2001; 29: 15-32)

Repair or Degradation of Toxic Proteins: *The Cellular Stress Response*

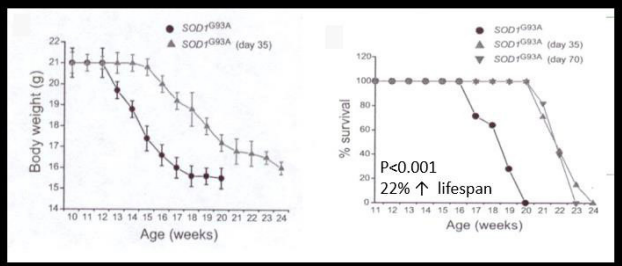


Arimoclomol Increases Spinal Chaperone Expression in SOD1 Mice: *Hsf-1 hyper-phosphorylation*



From Nature (Med), Volume 10(4), 402-5 (April 2004)

Arimoclomol Increases Lifespan in SOD1 Mice



Arimoclomol: *Drug Characteristics*

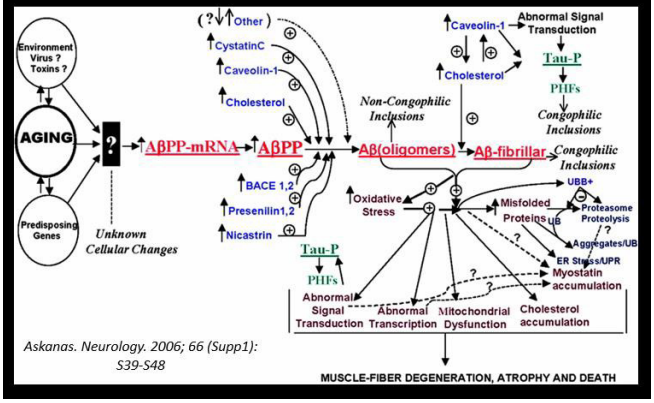
- Chemically stable
  - Bulk API stable for at least 4 years, light sensitive
  - Stable in solution for at least 1 week at pH 1-13
  - 2-year stability as capsules (50, 100, 200 mg)
- Extensive preclinical evaluation
  - Safety tested in multiple species
  - Good oral bioavailability, distribution, and metabolism
- Shown to be well-tolerated in two Phase I clinical trials
  - 30 total volunteers
  - Well absorbed, distributed and cleared
- Currently in Phase II trial in ALS

Why Propose Arimoclomol for IBM?

- HSP70 co-localizes with amyloid inclusions in IBM biopsies
- HSP70 levels are increased (~4.5 X) in IBM biopsies
- Protein misfolding is considered part of the pathological mechanism
- Mitochondrial defects are associated with IBM

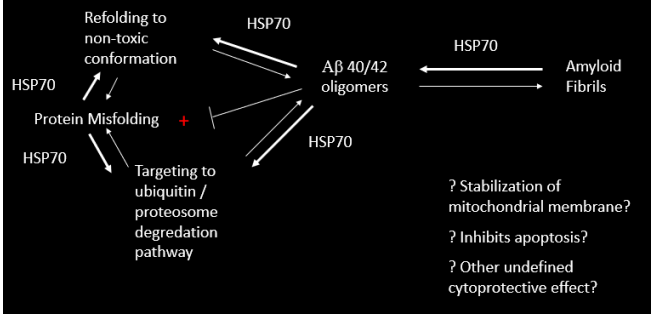
(Askanas. Neurology. 2006; 66: S39-S48.; Oldfors. Neurology. 2006; 66:S49-55)

Proposed Pathological Mechanism for IBM



Askanas. Neurology. 2006; 66 (Supp1): S39-S48

Possible Protective Role of Arimoclomol in IBM



*Department of Biochemistry, and †Research Laboratory of Neuromorphology, Institute of Neurology, University of Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

Abstract

Amyloid β (Aβ) is a 40- to 42-residue peptide that is implicated in the pathogenesis of Alzheimer's Disease (AD). As a result of conformational changes, Aβ assembles into neurotoxic fibrils deposited as 'plaques' in the diseased brain. In AD brains, the small heat shock proteins (sHsps) αB-crystallin and Hsp27 occur at increased levels and colocalize with these plaques. *In vitro,* sHsps act as molecular chaperones that recognize unfolding peptides and prevent their aggregation. The presence of sHsps in AD brains may thus reflect an attempt to prevent amyloid fibril formation and toxicity. **Here we report that αB-crystallin does indeed prevent *in vitro* fibril formation of Aβ1–40. However, rather than protecting cultured neurons against Aβ1–40 toxicity, αB-crystallin increases the toxic effect. This indicates that the interaction of αB-crystallin with conformationally altering Aβ1–40 may keep the latter in a nonfibrillar, yet highly toxic form.**

The Molecular Chaperone αB-crystallin Enhances Amyloid β Neurotoxicity

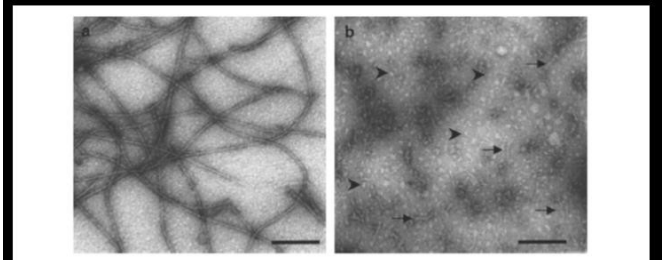
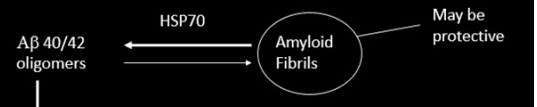


FIG. 3. Effect of αB-crystallin on amyloid fibril formation by $A\beta_{1-40}$ as observed by electron microscopy. $A\beta_{1-40}$ (10 μg) was incubated for 5 days in the absence (a) or presence (b) of bovine αB-crystallin (10 μg) in 100 μl PB, pH 7.4 at 37°C. Arrows, protofiber structures; arrowheads, αB-crystallin complexes. Scale bar is 200 nm.

Possible Pathological Enhancement of Arimoclomol in IBM

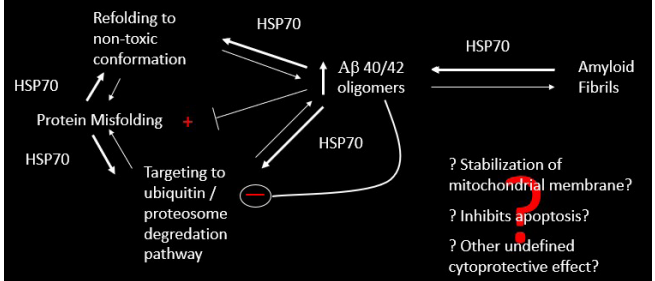


- Inhibition of ubiquitin/ proteasome degredation pathway
- Phosphorylation of tau
- Mitochondrial abnormalities
- Protein misfolding

Or . . .

Early in pathological process HSP70 is protective

But then



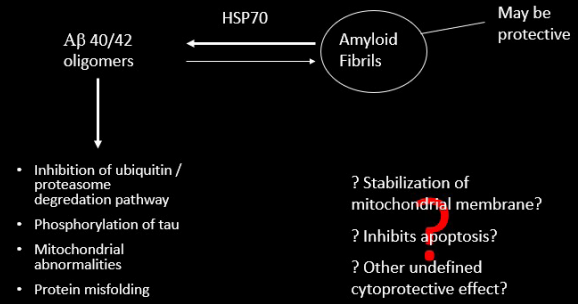
Implications for Arimoclomol in IBM

- Arimoclomol may be cytoprotective
- Arimoclomol may be cytotoxic
- For muscle fibers early in the pathological process Arimoclomol may be protective
- For muscle fibers late in the pathological process Arimoclomol may accelerate cell death

Future Directions

- Design and submit protocol grant to the NIH for an efficacy/safety/tolerability study
- May need animal or in vitro data to support grant
- NIH translational cooperation grant
  - Get funding for in vitro and animal studies

Leading to . . .



Eyelid Myotonia and Face Stiffness in Skeletal Muscle Sodium Channelopathy

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Keywords: *myotonia, paramyotonia congenita, non-dystrophic myotonia, eyelid myotonia, skeletal muscle sodium channelopathy, skeletal muscle chloride channelopathy*

A 70-year-old man presented with lifelong muscle stiffness and pain. This improved with repetitive muscle activity consistent with a warmup phenomenon and worsened with exposure to cold leading to painful facial cramping, paroxysmal attacks of leg stiffness with falls and throat spasms following a cold drink.

The neurologic examination showed well-developed muscles (Herculean musculature), grip myotonia and prominent delayed relaxation of the eyelids after forced eye closure (eyelid myotonia, video 1). Genetic testing revealed a heterozygous known pathogenic variant (p. Arg1448Cys) in the *SCN4A* gene diagnostic of a skeletal muscle sodium channelopathy, a non-dystrophic myotonic disorder.

Myotonia is the clinical phenomenon of delayed skeletal muscle relaxation following voluntary contraction or percussion. It is seen in the dystrophic myotonic disorders (myotonic dystrophy type 1 and 2) which are disorders of progressive weakness and multisystem involvement notable for early cataract formation and potential cardiac involvement. Myotonia is also seen in non-dystrophic myotonic disorders, as in this patient. These are characterized by exclusive skeletal muscle involvement with features of delayed muscle relaxation and stiffness, muscle pain, fatigue and sometimes weakness.[1]

Non-dystrophic myotonias are caused by mutations in two skeletal muscle voltage-gated ion channels that lead to muscle membrane hyperexcitability: (1) gain-of-function mutations in the voltage-gated sodium ion channel (*SCN4A),* and (2) loss-of-function mutations in the chloride ion channel (*CLCN1*).

In sodium skeletal muscle channelopathies, eyelid myotonia, facial stiffness, and exacerbation of symptoms in cold weather are more common than in chloride channelopathies.[1] This constellation of symptoms is seen in this patient and illustrates how aspects of the myotonia syndrome and examination finding of eyelid myotonia can suggest *SCN4A* as the more likely causative gene on clinical grounds alone.

Historically, patients with non-dystrophic myotonia exhibiting unexpected or "paradoxical" worsening of myotonia with exertion have been described as having paramyotonia congenita—a subtype of muscle channelopathy later linked specifically to the *SCN4A* gene.[2,3] The patient reported here also has an *SCN4A* pathogenic sequence change but does not fit the disease description for paramyotonia congenita due to consistently reported attenuation of stiffness with muscle exertion or a warm-up phenomenon. Notably, while the warm-up phenomenon is more common in chloride channelopathy it is not exclusive to chloride channel disease and has been reported in 35% of subjects with *SCN4A* mutations in a prospective observational study of 34 subjects.[4-6]

Video 1 highlights the patient's personal experience with skeletal muscle sodium channelopathy. Here, the worsening of symptoms with cold exposure was sufficiently severe to prompt the patient to maintain a full beard in an effort to lessen the burden of face stiffness and pain that are most severe in cold weather.

The management of sodium and chloride skeletal muscle channelopathies is symptomatic. Mexiletine, a sodium channel blocking class IB antiarrhythmic, is a first-line agent for the management of myotonia in non-dystrophic myotonias and has the most evidence of effectiveness.[7] Other sodium channel blockers, lamotrigine, ranolazine

Figure 1. Still from video example of delayed relaxation of the eyelids after forced eye closure (eyelid myotonia).

and the carbonic anhydrase inhibitor, acetazolamide, have also shown clinical benefit and may also be used.[7]

In addition, this patient should be informed about the potential of severe generalized muscle stiffness or myotonic crisis that can occur with the use of the depolarizing muscle relaxant succinylcholine during general anesthesia.[8] Having a medical warning card or wrist band that displays the non-dystrophic myotonia diagnosis and drug contraindications may further help mitigate perioperative risk.

Video 1. Eyelid Myotonia

Video 1.

The media clip captures a pronounced example of delayed relaxation of the eyelids after forced eye closure (eyelid myotonia). Also, note the full facial hair that the patient cites as a helpful measure for mitigating facial muscle stiffening and pain in cold weather.

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