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What's In This Issue?

Letter from the founding facilitator for issue 5

It is a pleasure to publish Volume 1, Issue 5 of the RRNMF Neuromuscular Journal. Once again we have many interesting articles in our new issue and some are in categories that are a bit different from our first 4 issues. In addition to this brief introduction, we have three other pieces in the "What's on Your Mind?" Category. The first is another outstanding article by my good friend Dr. Josh Freeman on the topic of how the Covid-19 pandemic disproportionately strikes the most vulnerable members of our society and how this in part can be attributed to longstanding health care disparities on our system. As I said in the last issue, Josh has had a blog site for years and I thought we should allow him to publish his some of his great pieces in our new journal. The next editorial is by Dr. Raghav Govindarajan, my neuromuscular partner at the University of Missouri. Dr. G has written a wonderful piece about the millennial generation and how as they come to age they will have an impact on everything, including our profession of neurology. The final piece in this section is something really different for a neurology journal. It is my list and accompanying explanation of Rick Barohn's Ranking List of the North American Art Museums. Art is one of my hobbies and over the years I have had the immense privilege of traveling around the world to attend medical and neurology meetings. I always made it a point to visit the local art museum and I developed an "NIH style" ranking system for the ones in the USA and Canada. I won't say any more in these comments and you can learn more about how the list evolved in the article. When I launched this journal I made a point that we welcomed articles outside of the world of neuromuscular disease, neurology, and medicine, so here is the first one. Hopefully we will receive more.

In the original neuromuscular section, beginning with the "New Stuff" we have a terrific article by the Cleveland Clinic neuromuscular group authored by Drs. Tiffany Pike-Lee and Yuebing Li describing three cases of CIDP that also had another underlying autoimmune disorder. I recall we had a number of cases in our 1989 CIDP paper in which a variety of other diseases were associated including Hodgkin's, inflammatory bowel disease, and chronic hepatitis, and we introduced the concept of "concurrent diseases" with CIDP (Barohn RJ et. al Archives of Neurology 1989; 46:878-884). Here the authors have a case of primary sclerosing cholangitis (not previously reported with CIDP), a case of ITP, and a case with a very high ANA. We then have four interesting single case reports: Sjögren's syndrome and a sensory motor autonomic neuropathy (Farheen et al); GBS after a Shingrix vaccine (Zafar et al); motor neuron disease in an HIV patient who stopped taking antiretroviral therapy (de Bruin et al); and a CIDP case with IgG tubular antibodies that was difficult to treat (Giacobbe et al). These are all welcome contributions to the neuromuscular literature. In the Visual Stuff category, Dr. Govindarajan describes how ptosis improved rapidly after initiation of plasmapheresis and he makes the point that this may be the first objective sign of improvement after the initiation of plasmapheresis. In looking at his figures I noted in addition to upper lid ptosis there is what I call lower lid reverse ptosis where the lower lid sags downward. This also improved with the plasmapheresis.

Finally, I am reprinting a paper I published in 1997 in a rather obscure annual neurology review publication from India called Advances in Clinical Neurosciences. Since I doubt anyone outside of India has seen it, and I always liked this paper, I asked the editors and publishers of the original annual if I could republish the paper in the RRNMF Neuromuscular Journal and they gave me permission to do so. It is a project I did as a neurology resident in which I collected a dozen cases of what we called then reflex sympathetic dystrophy (now referred to as complex regional pain syndrome) and all of the cases had an underlying peripheral neuropathy. In addition, all had abnormal radionuclide three-phase bone scans.

Recently two University of Missouri medical students began assisting in the editorial process of this journal. Jiji Oufattole is currently an MS2, and Breanna Tuhlei is an MD/PhD student (in neuroimmunology!) and she is in the MS3 year of her training. They have been assisting in copy editing and as we move forward they will be Co-Managing Editors of the journal. Thank you Jiji and Breanna! I still get an enormous amount of help and support from Marianne Reed and Pam LeRow in the digital publishing unit at KU. I could not get these issues out without them. Thank you Marianne and Pam! I also am thankful for the constant assistance of Amanda Sebok who is the senior executive administrative assistant in the EVC of Health Affairs office at the University of Missouri. I could not function professionally without her.

I believe the RRNMF Neuromuscular Journal readership will enjoy these publications. Please continue to send in articles for upcoming issues. Be thankful every day. I know I am. Have a happy minimalistic Thanksgiving and please be safe and wear your masks!

Rick

Structural racism, structural violence and COVID-19: We must fight both epidemics

Joshua Freeman, MD

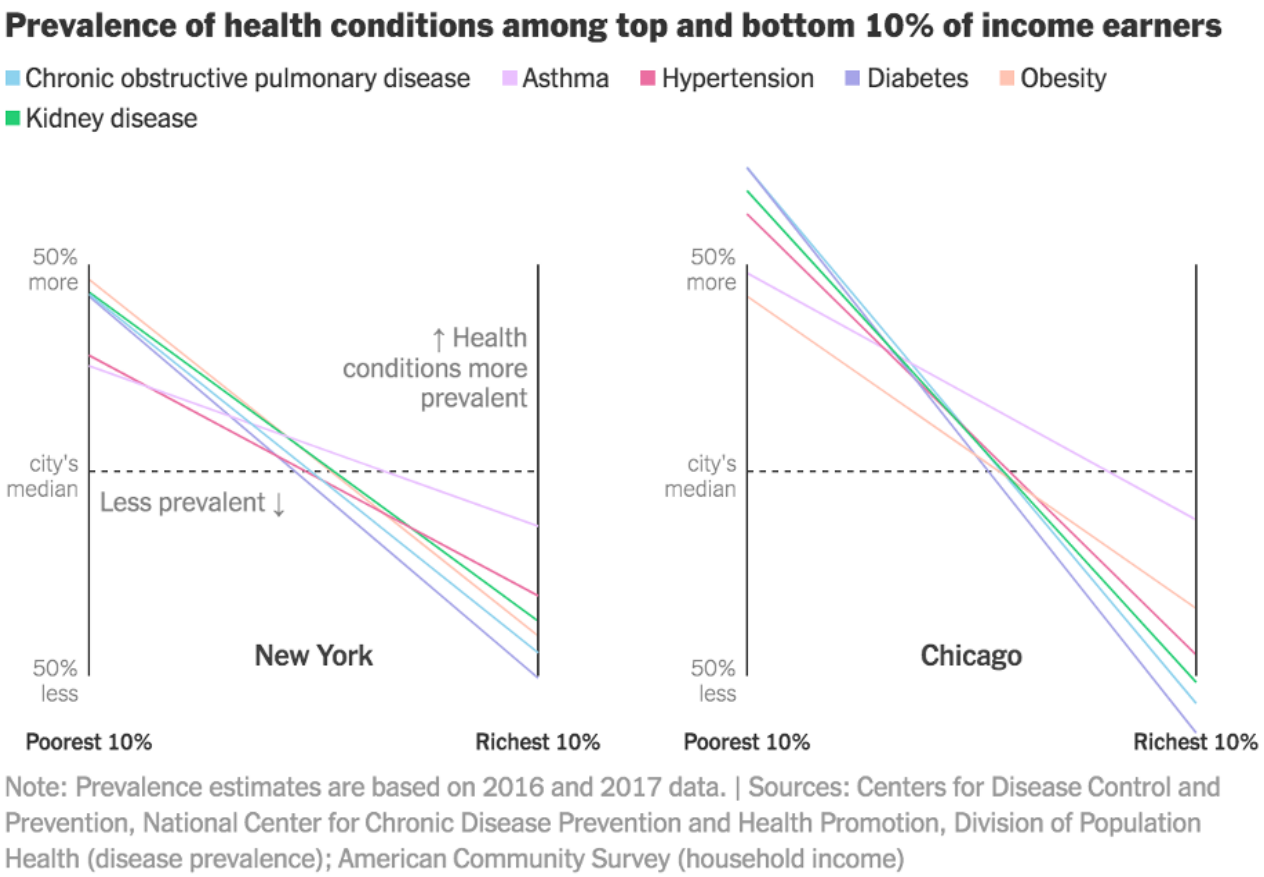
Originally published in the *Medicine and Social Justice* blog, https://medicinesocialjustice.blogspot.com/2020/06/structural-racism-structural-violence.html

The novel coronavirus which causes COVID-19 does not discriminate. Despite the common human error of teleologically imputing motivation to organisms – or even inanimate objects – this virus, like other viruses, like other microorganisms, does not choose its victims by conscious intention. Like other microorganisms, it is opportunistic, attacking people who are available and do not mount an immune resistance against it. In the case of COVID-19, that was, at least initially, everyone who was exposed, so that while it began in China it was brought to other countries by international air travelers, generally among the more economically privileged.

But it didn't stay that way. While the virus does not discriminate, human societies do, and poor people always suffer more. In many countries, including the US, the UK and Brazil it is minority populations, people of color, and especially Black people who have borne the brunt of the epidemic. This disparity is particularly dramatic in countries with long histories of racism that have vicious right wing leaders.

The *Guardian* describes Enormous disparities': coronavirus death rates expose Brazil's deep racial inequalities. In the US, another country with these two characteristics, the disparities are so large that they should be shocking, except we are used to them now. This graph from the *NY Times* shows the disparity in COVID cases based on income, (the graphic shows NYC and Chicago, and clicking on the interactive link lets you look at the specific but similar patterns in many major cities), but the disparity based upon race is layered on top of that.

Study after study demonstrates this disparity. They are revealed in hearings in the House of Representatives, and have been demonstrated for many chronic diseases. The cause is Structural Racism, which systemically has placed



Black people in lower-paying jobs with much less hope for advancement and the accumulation of wealth, more blighted and polluted neighborhoods where access to basic services (food, transportation, recreation) is worse, segregation of schools either by law (*de jure*) or *de facto* in which education is worse, and more limited, and the incredible chronic stress of racist practices in society. This clearly manifests in the fantastically high rate of police brutality against Black and other people of color in the US, as has been demonstrated again and again, and with the murder of George Floyd has led to what (we hope) will be sustained and sustainable demands for change, and in the psychological stress that the ever-present danger of such acts along with less lethal racist treatment wreaks on the people experiencing it. All of us are worn and depleted by acute stress situations ("fight or flight", with the exhausting secretion of adrenergic hormones) and need to rest to recover, but the *chronic* condition of stress experienced by oppressed and repressed people leaves no room for recovery, weakens resistance, increases chronic disease and shortens lives. Medical students (at least that large majority who are white) sometimes find this the "soft" stuff, not like the cellular level biochemistry and physiology, that sounds more "real", but this is not so. There are studies that demonstrate, concretely, cellular level indicators of longevity (leukocyte telomere length) are shortened in people undergoing chronic stress, overall,[1] and in many specific conditions, including PTSD, chronic lung disease, Alzheimer's disease, and chronic racism.

Our healthcare system is responding, but much of it not in a way that will help stem the epidemic. Recently, I wrote about 'Rich hospitals get the bulk of government bailouts: It's the American way!' (May 26, 2020), and more recently information comes to light that shows many systems are doing even less to help America confront the virus, laying off thousands of actual healthcare workers, and more to line the pockets of their C-suite executives! While these egregious and unforgiveable abuses are worst in for-profit hospital systems such as HCA, they are also occurring in many large and prosperous "non-profit" systems.

The *NY Times* comments on Anthony Fauci, the NIH's top virologist:

> He described the pandemic as "shining a very bright light on something we've known for a very long time" – the health disparities and the harder impact of many illnesses on people of color, particularly African-Americans.
>
> The coronavirus has been a "double whammy" for black people, he said, first because they are more likely to be exposed to the disease by way of their employment in jobs that cannot be done remotely. Second, they are more vulnerable to severe illness from the coronavirus because they have higher rates of underlying conditions like diabetes, high blood pressure, obesity and chronic lung disease.

Philip Ozuah, the CEO of Montefiore Medical Center in the Bronx, very hard hit by the virus, writes of the deadly combination of racism and COVID-19 writes that "I fought two plagues and beat only one",

> America has changed its behavior in such profound and fundamental ways to mitigate the coronavirus, from self-quarantining and working from home to wearing masks and literally risking our lives to care for the sick. As our streets fill every night with protesters demanding a change that has been too long in coming, I dare to hope that we as a people can summon the same selfless courage and determination to change our behavior to address the endemic racism and brutality that plagues our country.
>
> Then finally we may rid ourselves of that deadly virus as well.

For a clear, angry, and cogent description of the roots, causes, current manifestations of, and discussion of what we might do, a recent entire episode of John Oliver's 'Last Week Tonight' is a must-view. He starts with the horrific and (finally) increasingly known statistics – such as that in Minneapolis, people of color are 7 times as likely to be arrested as whites, and the incredible fact that in the US 1 in 1000 Black men can expect to be killed by the police! Toward the end he quotes Kenneth Clark commenting on uprisings in the 1960s. Clark describes how after each previous crisis, from 1919 on, the powers-that-be say the same things and nothing really changed. The stark reality that this is still true 50 years later is unavoidable. Oliver insists that things must change, that we need to direct address and change the way that police to their jobs, and indeed redefine what the role of the police should be. He states that *'It's about a structure*

[1]Olveira BS, et al., Systematic Review of the Association Between Chronic Social Stress and Telomere Length: A Life Course Perspective, Aging Res Rev. 2016 Mar;26:37-52. doi: 10.1016/j.arr.2015.12.006. Epub 2015 Dec 28.

built on systemic racism that this country built intentionally and now needs to dismantle intentionally.'

Some have suggested that the risk of spreading the coronavirus from people gathering in mass demonstrations is high. These demonstrations have even been compared to the right-wing "anti-mask" demonstrations. The risk of infection is likely heightened, but care can be taken; the important point is that whatever is necessary to finally confront and end racist violence in this country, particularly by the police, must happen and must happen now. Bassett, Buckee, and Krieger from the Harvard T.H. Chan School of Public Health take this on directly and strongly in a recent Op-Ed in the *NY Daily News*, 'Racism is a deadly virus too: a public health defense of these mass protests'. They contrast the risk of COVID-19 infection by demonstrators consciously and purposely not wearing masks to the anti-racist demonstrators who are doing their best to wear masks and practice physical distancing. They conclude that:

> Protesters are in the streets demonstrating against police brutality and white supremacy not because they are indifferent to the risk of COVID-19. They are doing what they can to protect themselves and their communities precisely because the institutions that are supposed to protect and serve them have been killing black people in this country far longer than the coronavirus has.

The evidence is in and is clear. Indeed, it has been in and clear for many generations. Racism exists, not merely in the beliefs and attitudes of some or many people, but in the intrinsic structure of American society. It is structural racism and structural violence. It continues to kill and harm people at intolerable rates. In the midst of a terrible global pandemic caused by the SARS-CoV-2 virus, we finally and thoroughly must fight and erase the epidemic of structural racism in the US.

Millennials and Their Impact on Practice of Neurology

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Who are millennials?

Neil Howe and William Strauss, authors of the 1991 book Generations: The History of America's Future, 1584 to 2069, are often credited with coining the term 'Millennial'. Howe and Strauss define the millennials as consisting of individuals born between 1982 and 2004. Millennials are the first generation to come of age in the new millennium and thus the name. Sometimes referred to as generation 'Y', the US census bureau does not officially recognize this terminology or the generation (only baby boomer generation is recognized). There has been wide variations in defining the limits of the millennial cohorts with some including even those born in 1980 or 1981 and some limiting them to only those born before 1996. However, all of them share common characteristics, the chief of which is their embrace of technology.

Why are they important?

Millennials currently account for the largest living generation, surpassing the 74.9-million baby boomers. Further, millennials now constitute about one-third of the American workforce exceeding both the Generation X and the baby boomers. About 155,000 physicians, (15% of the total active physicians) come under the category of millennial physicians. Similarly, one-fourth of the American Osteopathic Association's membership can be defined as millennial. The share of workforce in medicine and neurology who can be identified as millennial neurologists is only going to increase in the coming years. Given these staggering numbers and their particular set of values, millennial neurologists will have a direct and significant impact on the way neurology is practiced in future.

What are their values and attributes?

Millennials often get the scorn as entitled brats and are sometimes referred to as 'trophy kids' (term that reflects a trend in sports, as well as in life, where mere participation is frequently enough for a reward) or even 'Peter Pan' generation for their habit of delaying rites of passage.

Strauss and Howe have in addition identified 7 traits of millennials:

1. Special
2. Sheltered
3. Confident
4. Team-Oriented
5. Achieving
6. Pressured
7. Conventional

More so in medicine and neurology, there is a subtle underlying theme that millennial neurologists are 'country club doctors' limited in their duty hours (not enough time in the trenches as my professor used to say) due to mandatory ACGME work –hour restrictions and have thus not earned their bona fides like prior generations. Despite these negative attributes and at the risk of generalizing an entire generation to which there will be many exceptions, the following are some common values and attributes that millennials across the spectrum might share:

- Proficiency and familiarity with technology
- Desire for flexibility in work schedule, high priority on achieving work-life balance and an emphasis on teamwork
- Working towards achieving social justice including racial diversity, respect for individual rights (of patients and themselves) and a willingness to question imposed hierarchies and standard practice if needed

How is this going to impact the practice of neurology?

These unique attributes and social values (some negative but many positive) along with their sheer number in workforce is likely to have a greater impact on practice of neurology as well as the way AAN might interact with its members in the coming decades. Of course, every generation had their own unique attributes and value system (some of which the millennials have continued from their preceding generation) and have left indelible mark on our cherished field. But the perfect mix of technological advances, importance of work-life balance and break down of social hierarchies has created the possibility of having a significant impact on the practice of neurology. These include:

Impact of technology on practice

Millennial neurologists are technologically savvy due to ubiquitous use and presence of technology in their day to day lives. This can translate into relative ease and comfort with electronic medical records and many millennial neu-

rologists have rarely used paper charts. Many of these electronic medical records are even accessible by tablets and smart phones which can be carried into the patient's room to show charts and images and used to put in quick orders with the use of speech recognition software embedded in them; documentation has become easy, templated and even on-the-go. The clunky desktops and laptops which were viewed as a barrier to physician patient interaction are going away fast and practices are increasingly under pressure to catch up on new technology. Technology for millennials thus might be a tool to build physician-patient relationship rather than a barrier and practices can save space and money by not investing in desktop workstations.

Teleneurology, with its promise of improving access to care and breaking the traditional face to face physician patient interaction, has emerged as an alternative practice model to many millennial neurologists who may be much more at ease with navigating the technology. With the rapid technological advances that are happening in telemedicine, millennial neurologists and patients may find it more comfortable interacting through telemedicine and it may become the dominant or even the sole mode of practice for millennial neurologists replacing the brick and mortar clinic.

Millennial neurologists are also more likely to have accounts on social networking sites and are likely to use it for networking as well as for job hunting rendering the traditional marketing ads, especially print based ones, redundant. This is something practices and academy might need to invest in to target the millennial neurologists.

On the flip side these technological advances including over reliance on technology for diagnosis and treatment can adversely affect the development of neuro clinical skills which are highly valued by other specialists and patients alike. The master clinician who had shown us the tricks of clinical exam and introduced us to fancy new neurology tools from his bag might be at risk of becoming obsolete.

Impact of work-life balance on practice

Millennial neurologists place high value on work-life balance. It is not that millennials are lazy or don't want to take care of patients but rather they have seen first-hand the effects of poor work-life balance on marriages and families in their parent's generation in addition to burn out of promising neurologists and don't want to repeat these mistakes. Millennial neurologists have also worked and trained in shifts mandated by ACGME. While this can affect continuity of care and learning, it has forced millennial neurologists to work and collaborate in large teams (often with advanced practice providers) which they have come to appreciate and value.

Many millennial neurologists prefer to go into large practices (academic or private) where they lose autonomy but gain flexibility in their work schedules. All these changes and the ever-increasing burden of paper work placed on physicians has sounded the death knell for solo private practitioners. In addition, there is a real risk that the ever-increasing need of flexibility by millennial neurologists might affect our patient's access to care especially now that many of them have gotten insurance for the first time. Practices may choose to hire more advanced practice providers to prevent this and millennial neurologist are perfectly poised to develop a collaborative team-based approach with them.

Impact of social mores on practice

Millennial neurologists have broken the traditional patriarchal physician-patient relationship and have becomes advocates for patient centered, patient partnered care. Further the current millennial neurologists form the most racially diverse group in the history of American neurology and with it they have a deep understanding of diversity and racial equality which in turn translates into greater respect for patients and colleagues of diverse culture. Millennials also espouse pragmatic idealism as defined by David Burstein (author of Fast Future) which is a 'deep desire to make the world a better place combined with an understanding that doing so requires building new institutions while working inside and outside existing institutions'. This sometimes is misunderstood as millennials questioning authority and hierarchy which is deep seated in medicine and could lead to unnecessary friction within the practice. It is more likely millennial neurologists want to seek clarification and explanation rather than accept status quo so as to make positive changes to the practice.

Conclusion

Millennial neurologists are poised to have significant impact on the practice of neurology but it remains to be seen whether the greater emphasis on work life balance causes issues with access to neurological care or will technological advances and team based approaches favored by millennials compensate for that.

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Rick's North American Art Museum Ranking List

Richard J. Barohn, MD

In the pre- Covid era, we all did a lot more traveling! I estimate I was traveling 3 to 4 times a month for various academic events and meetings. I was able to visit many cities over my academic career... some over and over and over. I must admit one of the things I am enjoying in this difficult time of the covid pandemic is that I am not traveling now. I like it. Sometimes I wonder "what was I thinking over the last 40 years doing all of that travel??"

But one advantage to all of the academic travels was that I was able to visit many art museums and I was able to feed my deep interest in viewing art. I am not an artist and have no artistic ability. But I enjoy looking at art enormously and it has been a big part of my life. I have a bit of an art collection but of course most of it is not museum quality art. To see that level of art you need to view it in museums. I started making it a habit that each time I visited a city I tried to find a bit of time, even if it was a couple of hours (sometimes even an hour!) , to visit the local art museum. I got to know many of these museums well, and the museums and the art in their walls became good friends that I would go back to view over and over.

About five years ago I got the idea to begin ranking the art museums i was visiting. I think this was when we began doing our traveling Neuromuscular CME course and we would go to one or two cities a month, covering up to 10 cities a year. We (Mazen Dimachkie, Todd Levine, Jon Katz and I) did these courses on Saturday's so I would find time on Friday afternoon or Sunday morning to get to the local museum.

We rank things all the time in our academic lives, be it reviewing grants, or journal articles, or resident and fellow applicants. We are used to ranking things. Now it may be very presumptuous for a neurologist to think he can rank art museums →and I acknowledge that fact and that I am surely an amateur. Nevertheless... I started ranking museums. I decided to stick with art museums in North America. Why?

The museums in France, United Kingdom, Spain, Italy are phenomenal. and we probably have one or maybe two art museums in the USA that can compete with the Louvre, the National Art Gallery of England, the Prado and the Ufizi and the Vatican museum. Maybe one day I will try to do that ranking, but it would be a challenge. So i stuck with North American museums and that was hard enough.

I came up with a scoring system on a 1 to 5 scale with 1 being wors/ 5 best. And I came up with 5 categories. The first two are somewhat self-explanatory:

Quality: This sort of speaks for itself. On average what is the quality of the art?

Quantity: How much art is in the museum?

The next two may take some explanation:

Depth: how much art is there in the various areas of the collection? For example, do they have just one Rembrandt or 5? One or two pieces of art from the Italian renaissance or a dozen? One Monet or several? A few impressionist works of art or 20?

Range: does the museum just collect American art? Or does it collect art from around the world? For example, the Metropolitan Museum of Art (the MET) in New York City collects just about everything. On the other hand, the Museum of Modern art (MOMA) in New York City collects just modern art, essentially since the turn of the century and most since world war 2. So while the MOMA is a fabulous art museum that ranks very high in quality, quantity, and depth in what they collect, in the range category it ranks low. I have had arguments with an art Curator friend of mine who was aghast that I did not have the MOMA in the top 5. I tried to explain why but she would not hear it. For her quality trumped all! Nevertheless, I have stuck with this approach. Maybe it's an amateur approach but its Rick's approach :)

Then I have a final category that I call: Building and Environment. I decided, after visiting so many museums, that I could weigh in on:

How good was the building?,

If it was old, had it been kept up physically? If it was new, was it an improvement?

How was the art laid out for viewing? Did I get lost easily?

Was the temperature ok?

How good were the bathrooms? Where they hard to find?

Was it hard to read the labels about the art?

Did they go above and beyond to give extra information about the art pieces and the collection? Did they make an attempt to provide an educational program?

How good was the food service area? How good was the museum store?

Each time I went to the museum I would try to rank it and write down my numbers immediately after the visit. If I had visited it and ranked it before, I updated my rankings and noted the date. I put all of this on an excel spread sheet. I decided to have two averages for each museum: the average of the 4 art categories (Quality, Quantity, Range, Depth) and then a column with the average of all 5 categories, that included the Building and Environment.

Whenever I tell folks I have this Rick's North American Museum Rankings data, they of course want to know two things:

What are the top/best museums?
How did my local museum rank?

Regarding the top ranked, the MET and the National Gallery in wash DC ranked the highest....both all 10s in the four art categories. However, if we add the building/environment category the National Gallery wins due to its wonderful buildings and facilities, both east and west structures that are connected underground. While the art in the MET is just extraordinary, I cringe every time I go in the old, confusing building. I get lost every time I visit it. Where can you eat/drink in peace? And where are the bathrooms? I really don't like that building. The Art Instutute of Chicago comes in at a solid 3. For years I had the Philadelphia museum of Art as number 4 but then I finally got to the Detroit Art Museum in 2018 and what an amazing collection and building! So Phili got bumped down a notch. The other sleeper that broke into the top 10 was the Cleveland Museum of Art, which I finally got to when I attended a family wedding (can't miss the opportunity!). And Boston Museum of Fine Art was consistently in the top 5 until I visited the Detroit and Cleveland museums. But BMFA is still in the top 10, as is the MOMA. Again, it made the top 10 but only got a 5 in range.

Other sleepers that should get mentioned are the Indiana Museum of Art in Indianapolis on the old Lilly estate, the Minnesota Institute of Art, and the Speed Museum in Louisville. When I visited them I was amazed at the quality and breath of the collections. These museums, like the Detroit and Cleveland museums, are not walkable from downtown hotels. So you have to really want to get to these. They are at least a good half day visit as its unlikely you can just pop in and out of them when you are in the city like you can in New York, Wash DC, Boston, Phili, and Chicago.

And where does MY local art museum(s) rank? The Nelson-Atkins art museum is a jewel in the Midwest. I rank it at 17 with an art score of 6.5 and overall score of 6.8. My other local great art museum is the St. Louis Museum of Art which was the first art museum I visited as a teenager and probably got me hooked on art. I ranked St Louis at 20.

A couple of other points: I did not start putting dates of my last visit down until 2017. So some of the dates prior to that are estimates. I did visit all of the museums on the list except one: the Madison Museum of Contemporary Art in Madison, Wisconsin. My cousin Mark Wallis visited that one and I trust his impeccable art taste. He provided the rankings for that one. He tells me it's a gem.

Then there are the ones I have not visited yet. My bucket list. I list them at the bottom of the table. Who knows given the covid situation when I will get to these museums. If any of you want to weigh in on these and write a "what's on your mind" letter to the journal and fill us in on these art museums, please do that.

My next idea was to list the top five or 10 art pieces from each museum on the list. →another project and maybe another article....

Rick's North America Museum Rankings

updated 11.10.20

RANK	4 PARAMETERS	RANGE	QUALITY	DEPTH	QUANTITY	ART AVG	BLD/ENV	OVERALL AVG	LAST VISITED
1	National Gallery, Smithsonian, Wash DC	10	10	10	10	10	9	9.8	10/24/2018
2	The Metropolitan Museum of Art, NYC	10	10	10	10	10	3	8.6	11/10/2019
3	The Art Institute of Chicago	10	10	10	9	9.75	7	9.2	10/11/2018
4	Detroit Institute of Arts	10	9	8	8	8.75	10	9	8/12/2018
5	Norton Simon Museum-Pasadena, CA	8	10	9	6	8.25	10	8.6	3/13/2016
6	Philadelphia Museum of Art	8	9	8	8	8.25	4	7.4	2014
7	The Getty, Los Angeles, CA	7	10	8	8	8.25	5	7.6	4/26/2018
8	The Cleveland Museum of Art	8	8	8	8	8	10	8.4	5/26/2017
9	Museum of Fine Arts, Boston	8	8	8	8	8	5	7.4	2018
10	MOMA-The Museum of Modern Art-NYC	5	10	10	7	8	4	7.2	12/23/2018
11	Indianapolis Museum of Art, Indiana	8	9	7	8	8	5	7.4	2018
12	Barnes Foundation-Philadelphia, PA	6	10	10	5	7.75	8	7.8	2014
13	Minneapolis Institute of Art, Minnesota	8	7	7	8	7.5	5	7	5/14/2016
14	The Museum of Fine Arts, Houston	7	8	7	7	7.25	5	6.8	11/16/2019
15	The Broad, Los Angeles, CA	3	9	10	7	7.25	5	6.9	4/27/2018
16	Kimbell Art Museum-Ft. Worth, TX	7	10	5	5	6.75	10	7.4	2017
17	The Nelson-Atkins Museum of Art, Kansas City, MO	7	7	6	6	6.5	8	6.8	9/1/2019
18	Art Gallery of Ontario, Toronto, ON	7	7	6	6	6.5	5	6.2	7/29/2017
19	Yale Center For British Art, New Haven, CT	1	9	10	6	6.5	8	6.8	2017
20	Saint Louis Art Museum	7	7	6	6	6.5	7	6.6	7/11/1905
21	Baltimore Museum of Art	6	7	7	6	6.5	5	6.2	8/5/2017
22	Los Angeles County Museum of Art	6	6	6	7	6.25	7	6.4	2017
23	Joslyn Art Museum - Omaha, NE	7	7	5	6	6.25	8	6.6	11/13/2016
24	National Portrait Gallery/Smithsonian Art Musum, D	4	7	7	7	6.25	8	6.6	9/25/2018
25	The Speed Art Museum-Louisville, KY	7	6	6	6	6.25	9	6.7	9/8/2018
26	Crystal Bridges Museum of American Art-Bentonvill	4	8	7	6	6.25	10	7	11/2/2019
27	The Frick Collection-New York	5	10	5	4	6	10	6.8	11/8/2019
28	Isabella Stewart Gardner Museum, Boston	5	9	6	4	6	9	6.6	2018
29	The Phillips Collection,Wash DC	6	9	4	4	5.75	9	6.4	3/7/2018
30	McNay Art Museum, San Antonio	7	7	5	4	5.75	8	6.2	2015
31	Timken Museum of Art-San Diego, CA	5	6	6	6	5.75	7	6	2015

Rick's North America Museum Rankings

updated 11.10.20

RANK	4 PARAMETERS	RANGE	QUALITY	DEPTH	QUANTITY	ART AVG	BLD/ENV	OVERALL AVG	LAST VISITED
32	Wadsworth Atheneum Museum of Art, Hartford, CT	6	6	5	5	5.5	4	5.2	10/8/2017
33	de Young / Legion of Honor Fine Arts Museums of San Francisco	6	5	4	7	5.5	7	5.8	2017
34	Amon Carter Museum of American Art-Fort Worth,	4	6	5	6	5.25	7	5.6	2017
35	Norton Museum of Art, West Palm Beach, Florida	4	7	5	5	5.25	9	6	3/10/2019
36	Meadows Museum-Dallas, TX	3	7	7	3	5	8	5.6	2018
37	Phoenix Art Museum	5	5	5	5	5	6	5.2	2017
38	High Museum of Art, Atlanta, GA	6	5	4	4	4.75	4	4.6	10.19.18
39	Honolulu Museum of Art	7	5	3	4	4.75	5	4.8	11/3/2018
40	Whitney Museum of American Art- New York	2	8	5	4	4.75	9	5.5	1/20/2018
41	Dallas Museum of Art	6	4	4	5	4.75	5	4.8	2017
42	The Walters Art Museum, Baltimore, MD	1	7	7	4	4.75	5	4.8	8/6/2017
43	Philbrook Museum of Art, Tulsa, OK	6	5	4	4	4.75	7	5.2	3/23/2019
44	Blanton Museum of Art-Austin, TX	5	5	5	4	4.75	6	5	8/18/2019
45	Rothko Chapel-Houston, TX	1	8	8	1	4.5	10	5.4	4/17/2018
46	Hirshhorn Museum-Washington DC	4	6	4	4	4.5	6	4.8	2017
47	Madison Museum of Contemporary Art, Madison, WI	4	7	4	3	4.5	8	5.1	*M.Wallis 11.2018*
48	Solomon R. Guggenheim Museum-NYC	4	5	4	4	4.25	5	4.4	2017
49	New Orleans Museum of Art	6	4	2	5	4.25	8	5	1/28/2018
50	Wichita Art Museum	4	5	4	4	4.25	6	4.6	8/24/2019
51	San Antonio Museum of Art (SANA)	4	4	4	4	4	7	4.6	2018
52	Modern Art Museum of Fort Worth	2	7	3	4	4	10	5	2017
53	Seattle Art Museum (SAM)	4	4	4	4	4	6	4.4	7/27/2019
54	Albright-Knox Art Gallery, Buffalo	4	4	4	4	4	5	4.2	2017
55	Portland Art Museum	4	4	4	4	4	5	4.2	2017
56	San Francisco Museum of Modern Art	4	4	4	4	4		4	
57	Denver Art Museum	6	4	2	4	4	4	4	2017
58	Spencer Museum of Art, Lawrence, KS	5	6	2	3	4	6	4.4	10/10/2017
59	Rhode Island School of Design (RISD)Providence, RI	5	5	3	3	4	1	3.5	7/20/2019
60	Dia Beacon, Beacon, NY	2	6	4	3	3.75	8	4.6	2015

Rick's North America Museum Rankings

updated 11.10.20

RANK	4 PARAMETERS	RANGE	QUALITY	DEPTH	QUANTITY	ART AVG	BLD/ENV	OVERALL AVG	LAST VISITED
61	The Menil Collection - Houston, TX	3	5	4	3	3.75	8	4.6	2016
62	Nerman Museum of Contemporary Art; Johnson County Community College,Overland Park, KS	3	3	3	4	3.25	6	3.8	2019
63	The Montreal Museum of Fine Arts	3	3	4	3	3.25	3	3.2	2017
64	Oklahoma City Museum of Art	3	3	3	3	3	7	3.7	11/10/2017
65	The Art Museum of South Texas-Corpus Christi, TX	3	3	3	3	3	6	3.6	2015
66	Yale University Art Gallery, New Haven, CT	4	4	2	2	3	8	4	
67	Kemper Museum of Contemporary Art-Kansas City, MO	3	3	3	2	2.75	8	3.8	2019
68	Vancouver Art Gallery	2	2	4	2	2.5	1	2.3	2017
69	Orlando Museum of Art	3	4	2	1	2.5	3	2.6	4/13/2018
70	Boise Art Museum	2	3	2	2	2.25	5	2.8	8/12/2017
71	The Mennello Museum of American Art Orlando	1	4	2	1	2	3	2.2	4/15/2018
72	Perez Art Museum Miami	1	2	2	2	1.75	6	2.6	2017
73	The Bass, Miami, FL	1	2	0	1	1	2	1.7	2/2/2018
	BUCKET LIST:								
	Columbus Museum of Art, OH								
	Walker Art Center - Minneapolis, MN								
	Cincinnati Art Museum, OH								
	Contemporary Arts Center, Cincinnati, OH								
	Milwaukee Art Museum, WI								
	Clark Art Institute, Williamstown, MA								
	Muscarelle Museum of Art - Williamsburg, VA								
	Daum Museum of Contemporary Art Sedalia, MO								
	Albrecht-Kemper Museum of Art, St. Joseph, MO								
	Marianna Kistler Beach Museum of Art Manhattan, KS								
	Glenstone Museum-Potomac, MD								
	National Gallery of Canada-Ottawa								

Rick's North America Museum Rankings

updated 11.10.20

RANK	4 PARAMETERS	RANGE	QUALITY	DEPTH	QUANTITY	ART AVG	BLD/ENV	OVERALL AVG	LAST VISITED
	The Wallach Art Gallery at Columbia University Lenfest Center of the Arts, NYC								
	Toledo Museum of Art , OH								
	American Visionary Art Museum, Baltimore, MD								
	Penn Museum, Philidelphia, PA								
	Harvard Art Museums, Cambridge, MA								
	North Carolina Museum of Art, Raleigh, NC								

Chronic Inflammatory Demyelinating Polyradiculoneuropathy Associated with Rare Autoimmune Conditions

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Keywords: *Autoimmune disease, chronic inflammatory demyelinating polyradiculoneuropathy, primary sclerosing cholangitis, thrombocytopenia, postpartum.*

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune mediated disorder affecting nerve roots and peripheral nerves. Patients usually present with symmetric proximal and distal weakness, large-fiber sensory deficits and diffusely reduced reflexes. While the disease progression usually lasts for at least eight weeks, CIDP course can be relapsing-remitting, chronic progressive, or stepwise progressive.[1-2] The immunopathogenesis of CIDP includes abnormalities in the innate and adaptive immune systems including cellular and humoral responses but the triggering events and precise interaction between these systems are still not entirely elucidated.[2-3] There have been many case reports of polyautoimmunity in CIDP patients including concurrent myasthenia gravis, systemic lupus erythematosus, autoimmune hepatitis, and many others.[3-10] The identification of polyautoimmunity in some CIDP patients suggests a possible common immunopathogenic mechanism.[11] Here we report three cases of CIDP that were associated with autoimmune conditions including primary sclerosing cholangitis, immune mediated thrombocytopenia, and postpartum with positive antinuclear antibody (ANA).

Patient 1

A 63-year-old male with a remote history of primary sclerosing cholangitis (PSC) and ulcerative colitis status post colon resection presented with subacute onset of numbness and tingling in his face, hands and feet, and bilateral hand weakness. Muscle strength testing was graded as follows (right/left, Medical Research Council grade): first dorsal interossei 4/4, abductor digiti minimi 4/4, and abductor pollicis brevis 4/4. Strength examination of the remaining muscle groups was normal. Sensory nerve conduction studies (NCS) revealed absent bilateral median and ulnar sensory nerve action potentials (SNAPs) and intact right sural SNAP. Motor NCS showed compound muscle action potentials (CMAPs) with reduced amplitudes and prolonged distal latencies in the right peroneal (fibular), right tibial, bilateral median and bilateral ulnar nerves, and prolonged F-wave latencies. No clear conduction block or temporal dispersion was observed. On needle electromyography (EMG), scattered fibrillations and long-duration motor unit potentials were observed in muscles from the right upper and lower extremities. The study was interpreted as an acute to subacute sensorimotor polyneuropathy with predominantly demyelinating features. Over the next two months, his weakness and paresthesia worsened, with the development of significant weakness in his bilateral facial muscles, and muscles in the bilateral proximal upper and lower extremities. His speech became dysarthric and he was unable to ambulate. Cerebrospinal fluid (CSF) showed elevated protein at 122 mg/dL (normal 15-45 mg/dL) with 1/μL mononuclear cell (normal 0-5/μL). A right sural nerve biopsy showed loss of myelinated axons without inflammation, amyloid deposit or granuloma formation.

Laboratory analysis revealed elevated sedimentation rate at 95 mm/hr (normal <15 mm/hr) and C reactive protein (CRP) at 5 mg/dL (normal <0.9 mg/dL). The following abnormal liver function results were observed: aspartate aminotransferase (AST) of 132 U/L (normal 14-40 U/L), alanine aminotransferase (ALT) of 87 U/L (normal 10-54 U/L), alkaline phosphatase of 378 U/L (normal 38-113 U/L) and total bilirubin of 6.7 mg/dL (normal 0.2-1.3 mg/dL). Finding of active PSC were confirmed via computed tomography of the abdomen and endoscopic retrograde cholangio-pancreatography (ERCP).

Intravenous immunoglobulin (IVIG) was administered, leading to minimal improvement. Oral prednisone at 40mg daily was initiated, and he also received 5 sessions of plasma exchange. His common biliary ducts were dilated via ERCP. These treatments led to significant improvement in all of his symptoms, signs and serological findings. At month five, his speech became normal, and he ambulated independently. Muscle strength exam showed no weakness. Repeat sedimentation rate and liver function tests were all normal. Prednisone dosage was reduced to 10 mg daily.

Patient 2

A 76 year-old-male presented with subacute onset of numbness and tingling of hands and feet, and weakness

of bilateral lower extremities. He had been hospitalized a few weeks prior to presentation for acute cholecystitis and pneumonia. During that admission he was found to have newly developed thrombocytopenia with platelet count of $39x10^3/\mu L$ (normal $150\text{-}450x10^3/\mu L$) and anemia with a hemoglobin of 8.8g/dL (normal 14-18g/dL). Muscle strength examination revealed the following (right/left): shoulder abductors 4/4, elbow flexors 4/5, elbow extensors 4/4, wrist extensors 3/4, first dorsal interossi 3/3, abductor digiti minimi 3/3, abductor pollicis brevis 3/3, hip flexors 3/2, knee flexors 2/2, knee extensors 3/3, dorsiflexors 3/2, and plantar flexors 3/3. Reflexes were diffusely absent. Sensory exam showed absent pinprick up to the distal shins and reduced vibration sensation up to the knees. On sensory NCS, the left sural, superficial peroneal, median, ulnar and radial SNAPs were absent. Motor NCS showed slow conduction velocities in the left peroneal, tibial, median and ulnar nerves, prolonged distal latencies in the left median and ulnar nerves, and presence of conduction block in the left ulnar nerve. CSF showed elevated protein at 68mg/dL and mononuclear cell count at 3/μL. MRI of the lumbar spine showed mild cauda equine root enhancement.

Hematology was consulted for further workup of anemia and thrombocytopenia. Hemoglobulin quickly improved, but platelet count further reduced to $17x10^3/\mu L$. There was no evidence of hemolysis. A bone marrow biopsy showed no evidence of lymphoproliferative disorder. A skeletal survey was negative for lytic lesions. Computed tomography (CT) chest, abdomen and pelvis showed no evidence of malignancy or organomegaly. There was no evidence for POEMS, immune thrombocytopenic purpura (ITP) or Evans syndrome. No clear etiology for thrombocytopenia was found despite extensive workup.

He was treated with monthly IVIG and oral prednisone which led to steady improvement in his neuromuscular status. At month 48, his strength examination was normal while on prednisone monotherapy of 5 mg daily. In parallel with the improvement in muscle strength, there was a steady improvement in the platelet count which became gradually normalized at month 35. It was thought that he suffered from a combination of CIDP and immune-mediated thrombocytopenia.

Patient 3

A 39-year-old female presented with progressive numbness and tingling of hands and feet, radicular leg pain, and difficulty with gait requiring assistance at two months after an uncomplicated cesarean section. Muscle strength exam revealed the following: shoulder abductors 4/3, elbow flexors 3/3, elbow extensors 3/3, wrist flexors 3/3, wrist extensors 4/4, abductor digiti minimi 4/4, first dorsal interossi 4/4, abductor pollicis brevis 4/4, hip flexors 2/2, knee flexors 2/2, knee extensors 1/ 2, dorsiflexors 2/3, and plantar flexors 2/2. A sensory exam revealed reduced pinprick up to distal legs and vibration sensation at the toes. Laboratory results showed a positive ANA at 1:2560 that was normalized two months later. CSF studies showed elevated protein at 409mg/dL with mononuclear cell count at 6/μL. An MRI of the cervical and lumbar spine showed diffuse nerve root enhancement, more prominent in the lumbar than the cervical region. Sensory NCS revealed reduced right sural but intact right median and right ulnar SNAPs. On motor NCS, the right peroneal and right tibial CMAP amplitudes were reduced, the right tibial H-reflex was absent, and the right tibial, median and ulnar F-waves all had prolonged latencies. EMG revealed scattered presence of fibrillation potentials and neurogenic recruitment of normal appearing motor unit potentials. A right sural nerve biopsy showed mild loss of axons without clear evidence of inflammation or demyelination. A salivary gland biopsy was essentially normal. The patient was evaluated by rheumatology, and no evidence of a connective tissue disorder was found.

She was treated with intravenous methylprednisolone at 1 gram per day for five days, IVIG at 2 gram per kilogram of body weight, and seven sessions of plasma exchange with no improvement. At week nine, her muscle strength continued to deteriorate, and she became bedridden. She was started on oral prednisone at 60mg daily which led to noticeable improvement in her strength in one week. For the subsequent five months, she was treated with repeated monthly IVIG and prednisone at weaning dosages, which led to steady and significant improvement in her strength and sensory exam, and she regained ambulatory status. Subsequently she was treated with oral prednisone alone. Repeat MRI of lumbar and cervical at month seven showed reduction in nerve root enhancement. A repeat electrodiagnostic study at month 14 showed normal nerve conduction studies except an absent right tibial H-reflex. At month 48, the patient had a normal neurological exam off immunosuppression.

Discussion

The co-occurrence of CIDP with other autoimmune diseases has been previously described in several case reports.[3] Here we described three patients presenting with CIDP with rare autoimmune conditions. The first patient

had a remote history of primary sclerosing cholangitis and ulcerative colitis status post colon resection. He had not received medical treatment for either condition, furthermore, his liver function tests were normal for the prior few years. Coinciding with the onset of CIDP, there was a recurrence of his PSC.

To date, there have been no prior reports of co-occurring CIDP and PSC. Murata et al. described a 36-year-old woman with an 18-month history of progressive numbness and clumsiness of the limbs who was diagnosed with CIDP as well as primary biliary cirrhosis (PBC). PBC is clinically similar to PSC, however, PBC causes inflammation and destruction of only septal and intralobular bile ducts and spares extrahepatic ducts.[12] One proposed mechanism for co-occurrence of CIDP and PSC is that there may be common antigens associated with biliary epithelial cells and Schwann cells.[13] Prior studies have shown myelinated fibers in CIDP express the major histocompatibility complex II along with B7 family of co-stimulatory molecules which are also expressed on biliary epithelial cells.[13-14]

Patient two had a combination of CIDP and thrombocytopenia. There have been a few prior reported cases of CIDP in association with ITP or Evans syndrome.[15-18] However, hematological evaluation of our patient did not suggest a diagnosis of either ITP or Evans syndrome which manifests as a combination of hemolytic anemia and thrombocytopenia. The thrombocytopenia noted in our patient worsened and improved in parallel with his CIDP which suggested an immune-mediated mechanism. Platelets have also been implicated in a variety of active immune functions, thus suppression of platelet function could potentially stimulate the development of other autoimmune conditions.[19]

The onset of CIDP in patient three occurred two months postpartum with transient, but significant, elevation of ANA. There have been few reported cases of CIDP worsening during the postpartum period, but new onset CIDP in the postpartum period has not been described.[20] Pregnancy creates a relative immunosuppressed state in which T helper type 2 (Th2) and Th3 cells are increased and Th1 cytokines are suppressed.[21] During the postpartum period there is a shift towards Th1 cytokines which may heighten the proinflammatory response leading to development or exacerbation of other autoimmune conditions.[21] Prior studies have shown that active and remitting CIDP have a higher percentage of Th1 cells in CSF with upregulation of type I cytokines compared to other noninflammatory neurologic diseases.[22]

Conclusion

Other autoimmune diseases, even rare autoimmune conditions, can co-occur with CIDP, and the presence of such coexisting conditions can help make a diagnosis of CIDP. The identification of polyautoimmunity in some CIDP patients supports the idea of a common immunopathogenic mechanism.[3,11]

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Shingrix Vaccine and Guillain-Barre Syndrome: A Case Report

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Keywords: *Shingrix vaccine, Guillain-Barre syndrome, Autoimmunity, Herpes Zoster.*

Introduction

Herpes zoster (HZ), also known as Shingles, is caused by Varicella Zoster Virus (VZV), a member of the α-herpes virus family. There are an estimated 1 million cases of HZ each year in the United States, and almost 1 out of every 3rd person will develop HZ in their lifetime.[1] VZV is usually acquired during childhood and remains latent in the dorsal root ganglion and becomes reactivated in advanced age or an immune-compromised state. If left untreated, HZ can cause complications such as post-herpetic neuralgia, meningoencephalitis, and permanent nerve damage.

To combat this increased incidence of the disease, primary prevention with the vaccination is the mainstay of treatment. Shingrix is a non-live recombinant vaccine that has recently been approved by CDC-Center for Disease Control and Prevention for HZ. It consists of glycoprotein E (gE) and an adjuvant component called AS01B. AS01B enhances the potency, quality, and longevity of the immune response.[2] gE is usually present on the surface of cells infected by the varicella-zoster virus.[2] gE is vital for viral replication and is also capable of inducing cellular and humoral immunity. Some components of the vaccine, such as gE or the AS01B may be associated with the development of some autoimmune diseases through the process of molecular mimicry, epitope spreading, reactivation of memory T cells, or super antigenic T cell activation.

This report presents a case of Guillain- Barre syndrome that developed after the administration of the Shingrix Vaccine.

The Shingrix, a non-live recombinant vaccine, utilized to prevent herpes zoster infection. Some components of the vaccine may be associated with the development of some autoimmune diseases. We report a case of Guillain-Barre syndrome that developed after the administration of the Shingrix Vaccine.

Case report

A 79-year old male with a past medical history of clinically diagnosed neuropathy by his PCP, initially presented with symptoms of progressive tingling and numbness in his feet for over a week to the urgent care clinic. At the baseline, the patient was very active, and the history was negative for any other relevant symptoms. The neurological examination at the urgent care was reported unremarkable (no further details available). However, the patient reported receiving the Shingrix vaccine ten days before the onset of symptoms. Due to the patient's history of outdoor activities, he got empirically treated with doxycycline, and blood drawn for tick-borne serologies came back negative. He returned with worsening paresthesia and weakness in his legs, which culminated in a fall. A neurological examination done on this visit showed diminished pinprick and vibration bilaterally from the toes to the knees with areflexia at biceps, brachioradialis, patella, and Achilles despite Jendrassik maneuver. Romberg was positive, with no dysmetria on finger to nose test. His gait was broad-based. There was no loss of sensation in the upper limbs. Motor examination showed a weakness with foot dorsiflexion and medical research council- MRC grading of 4/5 for bilateral hip flexion and knee extension.

Lumbar puncture showed elevated CSF Protein: 195 mg/dl, with a normal corrected WBC count. Electrodiagnostic study revealed demyelinating polyneuropathy (Table 1).

MRI of the lumbar spine with contrast showed enhancement of the ventral roots (Figure 1). The patient was

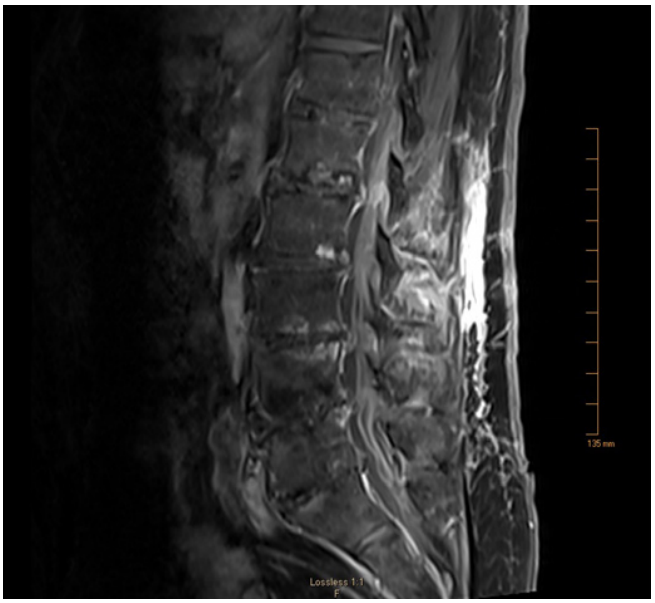

Figure 1 : MRI Lumbar Spine with and without contrast, T1 –Post contrast shows enlarged and enhancing nerve roots involving L1 through S1.

Table 1: Nerve Conduction Study (NCS) showing the evidence of a demyelinating polyneuropathy. The motor NCS shows prolonged latency and slowed conduction velocity in addition to reduced compound muscle action potential amplitudes in some nerves due to pre-existing neuropathy. NR=not recordable

Nerve / Site	Latency (m/s)	CMAP Amplitude (mV)	Conduction Velocity (m/s)
Left Median			
Wrist	7.7	4.0	
Ref.	<4.2	>4.0	
Elbow	14.3	3.6	37.5
Ref.			50
Right Ulnar			
*Wrist	4.2	7.2	
Ref.	<3.6	>5.0	
Below Elbow	10.3	6.0	41.3
Ref.			
Above Elbow	13.0	5.7	36.6
Ref.			50
Left Peroneal			
Ankle	NR	NR	NR
Ref.	<6.0	>2.5	
Right Peroneal			
Ankle	NR	NR	NR
Ref.	<6.0	>2.5	
Left tibial			
Ankle	15.6	0.9	
Ref.	<6.6	>2.0	
Knee	32.2	0.3	27.1
Ref.			
Right tibial			
Ankle	9.1	1.9	
Ref.	<6.6	>2.0	
Knee	27.1	1.1	25.2
Ref.			40
Left Peroneal Tibialis Anterior			
Fibular head	4.0	4.0	
Ref.	<4.0	>4.0	
Knee	6.9	3.9	33.7
Ref.			40
Right Peroneal Tibialis anterior			
Fibular head	12.4	2.5	
Ref.	<4.0	>4.0	
Knee	14.4	2.2	48.3
Ref.			40

started on IVIg (2g/kg body weight over 5 days), resulting in improvement of strength with residual pinprick sensation deficit only in the toes and reduced vibration in his feet from his previous neuropathy two months after treatment.

Discussion

Guillain-Barre syndrome (GBS) is the most common acute inflammatory demyelinating polyneuropathy preceded by infection with bacteria or viruses. It is worth noting that over 50 cases of GBS were reported until today, secondary to only Herpes Zoster infection.[3] In a study by Parra et al., the association of GBS with Zika Virus infection was established. The role of cross-reactive immunogenicity and molecular mimicry plays a vital role in the development of the disease.[4]

The temporal association of the development of autoimmune neuromuscular disorders and vaccine administration is well documented. Several vaccines, although beneficial, have proposed to be implicated in the development of autoimmune disorders, especially GBS. The precise mechanism is unknown, but one probable cause could be the vaccine components eliciting an exaggerated immune response. As stated earlier, the Shingrix vaccine consists of the glycoprotein E and adjuvant AS01B. Adjuvants, by definition, are substances that augment antigen-specific immune response.[5]

However, studies reported the role of adjuvants in causing autoimmunity by molecular mimicry and simulating an immune reaction in animal models or humans similar to the bacterial or viral infections.[5] Recently, Yadav et al. reported the first case of GBS presented ten days after the Shingrix vaccination in a 76-year-old female, as seen in our case.[3]

The flu vaccine, Tetanus toxoid, BCG, Rabies, Smallpox, Hepatitis B, MMR, Diphtheria, and Poliovirus vaccines are attributed to GBS's development.[3,5] Boe et al. described the case of a 14-year-old who developed GBS within two weeks after the human diploid cell rabies vaccine.[6] Khamaisi et al. reported a 52- year-old woman who developed GBS after her second injection of hepatitis B vaccine.[7] However, there are controversies in terms of establishing the causality of GBS secondary to vaccine administration. Chen et al., in their study on the role of the vaccine in causing GBS, they reported that there is no increased risk of GBS development after vaccinations in both adult and pediatric population groups. Their results are contrary to three meta-analyses that established the association between GBS and influenza vaccination.[8]

Although hypothesized that the Shingrix vaccine may have led to GBS in our patient, the exact pathogenesis is still not clear. In addition to the adjuvants, immune responses directed against the Glycoprotein E can also result in autoantibodies or T-cell activation that cross-react with ganglioside GM1 in the myelin resulting in immunological damage to the peripheral nerve sheaths. Further in vitro studies will be required to assess this relationship.

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Treatment-resistant CIDP in an IgG Tubulin Autoantibody Positive Patient: Case Report and Review of the Literature

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ABSTRACT

Objectives. To describe a case of rapidly relapsing chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in the setting of positive serum IgG tubulin autoantibodies.

Methods. We wrote a case report and performed a literature review of IgG tubulin autoantibodies and the use of rituximab in treatment resistant CIDP.

Results. Our case report describes a 29-year-old woman with CIDP that was resistant to treatment with steroids, intravenous immunoglobulin, and plasma exchange. An extensive workup of her rapidly relapsing CIDP was negative, with the exception of positive serum IgG tubulin autoantibodies. She ultimately stabilized on oral steroids, plasma exchange and rituximab, with a regular recurrence of weakness occurring approximately every month that led to rehospitalization.

Conclusions. Anti-tubulin antibodies could be a marker of a subtype of CIDP that is treatment resistant. We detail her clinical course to serve as an example for other cases of IgG tubulin autoantibody positive CIDP patients that could be described in the future.

Keywords: *CIDP, IgG tubulin autoantibodies, rituximab, demyelinating neuropathy.*

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a heterogeneous disease caused by autoimmune destruction of the peripheral nerve myelin sheaths. Numerous antibodies felt to play a role in the underlying pathophysiology of this disease have been isolated in an attempt to better understand it.

In the literature, there is disagreement about whether anti-tubulin antibodies are markers for a subset of patient's with CIDP. In 1993, Connolly et al published a paper on the detection of IgG and IgM tubulin autoantibodies in the sera of CIDP patients. Using ELISA, selective high-titer serum anti-B-tubulin antibodies occurred in up to 42% of patients with CIDP.[1] In 1995, Van Schaik et al questioned their diagnostic value when only 3 of their 43 patients had positive antibodies using Western Blot.[2] Manfredini et al found similar results using an immunoblot technique, with high serum tubulin IgM titers in only 10.5% of CIDP patients.[3] While the more recent studies indicate that anti-tubulin may not have good diagnostic value,[2,3] one could also infer that anti-tubulin CIDP may represent a rare form of the disease and could even warrant a different treatment approach.

Here we describe a patient with positive anti-tubulin antibodies, whose diagnosis followed a somewhat atypical clinical and electrodiagnostic pattern for CIDP; resistant to treatment with steroids and IVIG.

Case Presentation

A 29-year-old woman presented with two months of progressive upper and lower extremity weakness with inability to walk, as well as numbness and tingling in the hands. On examination, she had diffuse muscle weakness, most prominent in the proximal upper extremities. Bulbar and respiratory muscles were spared. She was areflexic. Nerve conduction studies (NCS) showed a severe generalized sensorimotor polyneuropathy with axonal and demyelinating features (Table 1). Needle-EMG showed active denervation in the proximal more than distal upper extremities, and to a lesser degree in the proximal and distal lower extremities. EMG suggested an acute to subacute process, with minimal chronic features. The working diagnosis was CIDP. She completed five days of intravenous immunoglobulin (IVIG) and was discharged with improved strength in all extremities, however she remained areflexic. Figure 1 shows her MRC sum scores and treatments for each admission.[4]

Four weeks later, she experienced worsening paresthesias and weakness in upper extremities and was readmitted. Cerebrospinal fluid (CSF) showed protein of 78 mg/dL and cell count of 17 WBCs/mcL with 100% lymphocytes. She received four days of IVIG but failed to respond to the treatment, and her examination at discharge was unchanged.

Five days after discharge, she returned with profound weakness in all extremities and continued areflexia. NCS showed a primary demyelinating polyneuropathy. EMG

Figure 1: MRC Sum Scores with Corresponding Treatments

Admissions and days between each admission	1	(30 days between)	2	(5 days between)	3	(18 days between)	4	(10 days between)	5
MRC admission	36		44		34		44		23
MRC discharge	48		44		46		32		54
Treatment	IVIG 2g/kg		IVIG 2g/kg		Plex x5 1 g Solumedrol		Plex x5 Prednisone 80mg QD		Plex x5 Rituximab 900 mg/m^2

MRC= Medical Research Council sum score (grades the sum of motor strength from 0 to 5 in bilateral deltoid, biceps, wrist extensor, iliopsoas, quadriceps femoris, and tibialis anterior for total score of 60 in patients with normal strength).

showed many muscles with markedly reduced recruitment, with absent or sparse active denervation, suggestive of interval reinnervation since the prior study (Table 1). Workup for reversible, infectious, paraproteinemic and common autoimmune conditions were unrevealing. Repeat lumbar puncture demonstrated elevated CSF protein (61 mg/dL) and cell count (30 WBCs/mcL, with 99% lymphocytes). CSF testing for neurotropic viruses were negative. CSF cytology and flow cytometry studies showed no evidence of malignancy. Pan-CT and transvaginal ultrasound were negative for malignancy. MRI brain and spine imaging showed only minimal enhancement in the upper cauda equina. A demyelinating polyneuropathy panel (Washington University in St. Louis) revealed elevated IgG anti-tubulin antibodies (20,000, ref range <2500). The IgM anti-tubulin titer was zero. Neurofascin 140 and 155, anti-ganglioside and contactin-1 antibodies were negative. She received three days of IV solumedrol and five days of plasma exchange (PLEX). She clinically improved, with only residual numbness and tingling of her hands.

Another relapse occurred eighteen days later. Her MRC sum score on admission was 44. On day three of admission, she worsened to an all-time low MRC sum of 8. She then received PLEX, was started on an oral course of high-dose prednisone, and clinically improved to an MRC score of 32, albeit still not back to her strength on admission.

She returned ten days later for recurring weakness, and the decision was made to administer IV rituximab 900mg (2nd dose 2 weeks later) in addition to PLEX. Upon discharge, she regained her strength and was discharged home on 80mg per day of prednisone. Over the next six months she presented monthly with weakness in her arms > legs which improved with PLEX sessions to roughly 5/5 strength everywhere. Rituximab was administered again six months after the last infusion.

Discussion

Our patient meets the EFNS/PNS clinical and electrodiagnostic criteria for typical CIDP, based on her recurrent symmetric proximal and distal muscle weakness, sensory impairment, and areflexia in all extremities for more than two months,[5] reduced motor nerve conduction velocities of >30% below the lower limit of normal in more than two nerves, increased motor distal latency of >50% above the upper limit of normal in two nerves, and absent F-waves in two nerves.

Based on the EFNS/PNS criteria, CSF with elevated protein and absent pleocytosis (leukocytes <10 cells/μL) is supportive of CIDP. Our patient had elevated lymphocytes in both lumbar punctures, which could be because she received IVIG prior to both as IVIG has been linked to CSF pleocytosis.[6] The CSF pleocytosis from IVIG is associated with symptomatic aseptic meningitis in the literature, which our patient did not have.[6] Additionally, prior studies suggest that a mild to moderate pleocytosis in the CSF does not exclude the diagnosis of CIDP. Lucke et al found that of 273 patients with CIDP based on the EFNS/PNS criteria, 14 of them had >10 leukocytes in the CSF. Most patients with CSF pleocyto-

Table 1: Serial NCS and Needle EMG Data

		1st Admission	3rd admission
R median	motor NCS: DML (ms)	**5.05**	
	CMAP amplitude (distal/proximal), μV	**5.3/3.6**	
	CV (m/s)	**33**	
	sensory NCS: amplitude (μV)	**12.9**	
	F wave latency (ms)	**NR**	
L median	Motor NCS: DML (ms)	**6.35**	**6.88**
	CMAP amplitude (distal/proximal), μV	**2.8/2.3**	**2.2/1.3**
	CV (m/s)	43	**32**
	Sensory NCS: amplitude (μV)	**4.9**	**NR**
	F wave latency (ms)	**NR**	**42.9**
R ulnar	Motor NCS: DML (ms)	4.43	
	CMAP amplitude (distal/proximal), μV	**2.1/1.5**	
	CV (m/s)	**34**	
	Sensory NCS: amplitude (μV)	**5.0**	
	F wave latency (ms)	31.3	
L ulnar	Motor NCS: DML (ms)	3.49	3.18
	CMAP amplitude (distal/proximal), μV	**5.1/4.3**	**4.4**/3.4
	CV (m/s)	**39**	**37**
	Sensory NCS: amplitude (μV)	23.7	**11.5**
	F wave latency (ms)	**NR**	
L tibial	Motor NCS: DML (ms)		**6.72**
	CMAP amplitude (distal/proximal), μV		**2.7**/2.8
	CV (m/s)		42
	F wave latency (ms)		**58.3**
R peroneal	Motor NCS: DML (ms)	5.89	
	CMAP amplitude (ankle/fib head/pop), μV	7.8/6.0/5.3	
	CV (fib head, pop) m/s	40/**26**	
	F wave latency (ms)	**NR**	
L peroneal	Motor NCS: DML (ms)		6.15
	CMAP amplitude (ankle/fib head/pop), μV		4.9/4.2/3.9
	CV (fib head, pop) m/s		41/**28**
	F wave latency (ms)		**60.5**

NCS = nerve conduction study, EMG = electromyography, NR = no response, L = left, R = right, fib head= fibular head, pop = popliteal fossa, blank rows = not done. Abnormal values are bolded.

sis had an acute to subacute presentation and responded to therapy with steroids and/or IVIG after six months.[7]

The assessment of this patient's response to therapy has been guided by the clinical picture and treatment time to efficacy as documented in the existing literature. However, there is subjectivity in our patient's examinations as they were performed by different neurologists. The findings were consistent with the patient's own subjective reports of wors-

ening muscle weakness on admission and improved muscle weakness upon discharge.

Additionally, we classified our patient's disease process as "treatment-resistant," because of her multiple relapses into recurrent inflammatory demyelinating disease despite standard therapies of corticosteroids, IVIG, and PLEX.

Our decision to start rituximab was based on a randomized controlled trial by Roux et al, which showed that rituximab administration in patients within a shorter duration of disease was associated with a better clinical response. The median time to response was six months, and 75% of the patients in that study responded to rituximab.[8] It is notable, that most of those patients had an associated hematologic or autoimmune condition, which were absent in our patient.

A second study of 13 patients with CIDP refractory to standard treatments found that on average, the response duration to rituximab was only two months. Of the five patients without a coexisting hematologic disease in this study, two responded to rituximab within two months and three did not respond at all. Three patients were able to stop their IVIG or plasmapheresis after starting rituximab.[9] Another study showed similar findings.[10]

In a study looking at treatment-resistant patients with antibodies against Node of Ranvier proteins, disease duration in both patients that responded was less than one year at the time of initiation of rituximab.[11]

Compared to IgM anti-tubulin antibodies, the spectrum of clinical disorders associated with IgG anti-tubulin antibodies is even less well-defined. In Connolly's original 1993 paper out of 70 CIDP patients, there were twice as many IgM protein positive patients than IgG protein positive patients.[1] This is different from van Schaik's study, where 2 of the 43 patients had detectable IgG anti-tubulin antibodies and 1 had IgM anti-tubulin antibodies.[2] Our patient would have been excluded from van Schaik's study because they only included patients with a CSF cell count of < 10/mm.[3] Our study also differs from van Schaik's study because our patient's IgG anti-tubulin antibodies were detected using ELISA, the same method used in Connolly's paper. In van Schaik's study they used Western Blot, which is not as sensitive but has greater specificity.

Of the 10 CIDP cases with anti-tubulin antibodies mentioned in the literature, the average age of onset was 60. The weakness pattern was variable (proximal, distal, symmetric, asymmetric) and only 2 of them had positive IgG anti-tubulin antibodies.[2,3,12,13] A case by Stubbs et al described an IgM anti- tubulin antibody positive patient with a sensory-predominant polyneuropathy.[12] No details about treatment outcome have been described in these cases.

This may be the first detailed case report of the clinical course of an IgG anti-tubulin positive patient with CIDP. With the paucity of prior data about this CIDP variant, we are unsure if the tubulin autoantibodies are associated with the treatment-resistant nature of this disease or if the positive antibodies are an incidental finding. We hope that this report will inspire more research that can lead to faster recognition and treatment of refractory CIDP patients.

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Sjögren's Syndrome Related Sensory Motor Neuropathy and Autonomic Neuropathy: A Case Report

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Introduction

Neurologic involvement has been reported in primary Sjögren's syndrome (SS) in approximately 10–25% of cases.[1,2,3] Peripheral neuropathy is a major neurological manifestation of Sjögren's syndrome[4] and its etiology has been considered to be vasculitis in the peripheral nerves.[2] While neuropathic symptoms of SS can be varied, it is unusual to have two different types of neuropathic presentations simultaneously in a patient. We describe a case of Sjögren's syndrome presenting with autonomic symptoms who was noted to have large fiber neuropathy on EMG and inflammatory changes on nerve biopsy.

Case report

A 65 year old man presented with eight-month history of presyncopal and syncopal episodes lasting few seconds associated with change in position, mostly on standing up. He was hospitalized for multiple syncopal episodes. He denied any aura or prodromal symptoms, urinary incontinence, tongue biting, confusion, dysarthria, dysphagia, focal weakness, numbness. He had unintentional weight loss of about 40 lbs in one year. Patient had dry eyes and dry mouth and was diagnosed with Sjögren's syndrome about five years ago based on serology (SS-A positive, SS-B negative). Plaquenil was tried for his SS but was not effective, hence stopped. He failed Fludrocortisone for his syncopal episodes. Other significant past medical history included anemia, hip replacement, and depression. Patient had history of smoking and he denied heavy alcohol use. His medications included albuterol, metoclopramide, midodrine 10 mg 3 times a day, pantoprazole 40 mg daily, pyridostigmine 60 mg 4 times a day, and Spiriva.

Examination showed positive orthostatic vitals (blood pressure lying down 103/68 with a pulse of 65, sitting 92/63 with a pulse of 70, standing 62/40 with a pulse of 75) and weight of 57 kg. Neurological examination patient showed normal speech, memory, attention, concentration. Cranial nerve examination was normal. Motor examination showed full strength throughout with no atrophy and normal tone. Reflexes were 2 throughout. Sensory examination showed decreased pinprick distal to mid-shin level bilaterally. Position and vibration sense were intact at the toes. Coordination was normal. The patient was able to get up from seated position, although slowly due to fear of passing out.

Work up showed normal cardiac enzymes, normal cortisol, lactate level, HBA1c was 5.6. Patient had a spinal tap that was normal for cerebrospinal fluid analysis except for high protein of 63, no oligoclonal bands, negative for malignant cells. Invitae cardiomyopathy panel, transthyretin amyloid panel, comprehensive neuropathy panel were negative. MRI brain showed chronic left posterior cerebellar stroke with ischemic white matter changes, which were minimal. Work up for malignancy was negative: CT chest, abdomen, and pelvis showed emphysematous changes and bilateral renal cysts. Testicular ultrasound noted no malignancy. Gastric endoscopy showed mild gastritis. Cardiac work up was included; electrocardiogram (EKG) showed normal sinus rhythm, left axis deviation, poor R-wave progression concerning for possible anterior septal infarct, and nonspecific ST-segment changes in the anterior precordium. Echocardiogram showed small to normal LV cavity size with normal systolic function, ejection fraction of 65%, mild mitral regurgitation, and mild tricuspid regurgitation.

An electrodiagnostic study from an outside facility showed mild generalized sensory motor peripheral polyneuropathy.

He had a left sural nerve biopsy done which showed moderate loss of large and small myelin axons and focal moderate perivascular chronic inflammation in the epineurium (Figure 1 and 2). Congo red-positive amyloid and onion-bulb formation were not seen.

Patient was started on Prednisone 50 mg daily for three months that was tapered slowly over several months. He was on lansoprazole for gastric prophylaxis. He had failed fludrocortisone at outside facility, so he was started on midodrine instead, which did not help either. A follow up visit few months later showed reduced frequency of dizzy spells when changing position and weight gain of about 5 pounds.

Table 1. Nerve conduction studies in a patient with Sjögren's syndrome-related neuropathy

Nerve	Sensory Distal Latency (ms)	Sensory Distal Amplitude (MicroV)	Motor Distal Latency (ms)	Motor Distal Amplitude (mV)	Motor Conduction Velocity (m/s)	F Wave Latency (ms)
Median*	NR(<4.3)	NR (>10)	3.6 (<4.5)	7.7 (>4.0)	49.7 (>49.0)	39.6 (<31)
Ulnar*	NR (<4.1)	NR (>8.0)	3.0 (<3.8)	12.0 (>5.0)	47.5 (>49.0)	39.0 (<32)
Radial**	3.3 (<2.9)	23.2 (>15)				
Peroneal^			6.9 (<6.1)	0.4 (>1.5)	30.8 (>35)	NR
Tibial^^			7.2 (<6.6)	0.2 (>3.0)	38.4 (>38)	NR
Sural	NR (<5.10)	NR (>4.0)				
Superficial Peroneal	NR	NR				

NR = no response. Normal values in parentheses.

*Stimulating wrist, recording digits 2 or 5 (sensory) or recording abductor pollicis brevis or abductor digiti minimi muscle (motor).

**Stimulating forearm, recording anatomical snuff box.

^Stimulating ankle, recording extensor digitorum brevis muscle.

^^Stimulating ankle, recording abductor hallucis muscle.

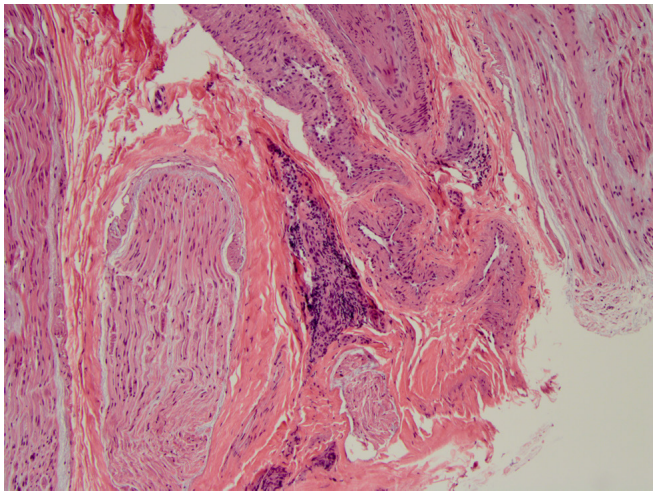

Figure 1. H &E (Hematoxylin and Eosin) stained section (10 X objective) shows focal moderate chronic inflammation near a vessel in the epineurium.

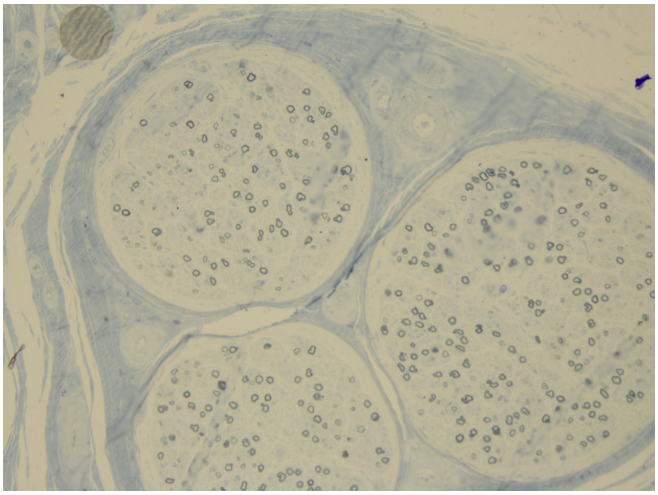

Figure 2. Toluidine blue stained section (20 X) shows moderate loss of large and small myelinated axons with rare regenerative axonal clusters.

Discussion

Sjögren's syndrome is a systemic autoimmune disease characterized by xerophthalmia and xerostomia; it is associated with widespread systemic visceral involvement.[5] The neurologic manifestations of primary Sjögren's syndrome are varied and can be divided anatomically into two categories: peripheral neuropathies and central nervous system (CNS) conditions.[6] Peripheral neuropathy is a major neurological manifestation.[5] The reported neuropathies in primary Sjögren's syndrome include distal sensory polyneuropathy, axonal sensorimotor polyneuropathy, chronic inflammatory demyelinating polyneuropathy (CIDP), multiple mononeuropathy, sensory neuronopathy and small fibre neuropathy.[7] Sensory symptoms without substantial motor involvement are observed predominantly in sensory ataxic, painful sensory, trigeminal, and autonomic neuropathies.[5] Motor impairment is apparent in multiple mononeuropathy, multiple cranial neuropathy, and radiculoneuropathy. Auto-

nomic symptoms such as abnormal pupils and orthostatic hypotension are particularly noted in patients with sensory ataxic, painful, trigeminal, and autonomic neuropathies.[5]

Our patient demonstrated autonomic symptoms along with sensory motor neuropathy findings on electrodiagnostic testing. The old stroke noted on MRI in the absence of vascular risk factors in our patient could be one of the central nervous system manifestations of Sjögren's syndrome.

The broad range of symptoms is in part derived from the varied pathophysiology of the disease. Central pathology can reveal direct infiltration of monocytes into the CNS versus indirect vascular compromise via autoimmune attack of the large and/or small vessels.[8] Similarly, peripheral involvement can include either peripheral infiltration of autoimmune cells vs vascular disruption of the different structures eliciting varied effects, however direct antibodies against type 3 muscarinic receptors have also been described.[9] Given the diverse pathology found in SS, electromyographic (EMG) findings would be equally assorted, fitting the associated structures damaged. Gøransson discovered 55% of the SS patients studied revealed EMG abnormalities with 27% showing axonal polyneuropathy, but sensory only and motor only findings were also reported.[10] The standard serological tests (anti-SS-A, SS-B) are less sensitive compared to minor salivary gland biopsy in the diagnosis of SS.[11]

For the therapy of neuropathy associated with Sjögren's syndrome, corticosteroids[3,4] immunosuppressants,[3] plasmapheresis,[13] and immunoglobulin[14,15,16] administration have been reported anecdotally and suggest a favorable therapeutic response.[2] Several reports have documented success with rituximab for sensory ataxic neuropathy.[17,18] Treatment of small-fiber neuropathy is aimed initially at symptomatic relief of the associated pain.[12] In the long-term follow-up, these patients ultimately showed progression of symptoms.[2]

Our case highlights the need to recognize autonomic signs in patients with Sjögren's syndrome and consider a broad differential. The nerve findings of moderate perivascular inflammation of the epineurium helped solidify the diagnosis, as well as the quick response to steroids. The EMG findings show classic form of a sensorimotor axonal polyneuropathy that can occur in SS in addition to the focal neuropathies that happen secondary to the perivascular inflammation. Immune suppression is the mainstay treatment and can result in improvement of symptoms.

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Ten-Year Plateau Phase in Human Immunodeficiency Virus Induced Motor Neuron Disease upon Antiretroviral Therapy: A First Case from Eastern Africa

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ABSTRACT

We report an individual with rapidly progressive motor neuron disease (MND), phenotypically compatible with amyotrophic lateral sclerosis (ALS). The patient described in this case report proved positive for human immunodeficiency virus (HIV) and was initiated on antiretroviral therapy (ART). Following ART he clinically stabilised over 10 years and deteriorated again due to noncompliance or ART resistance. HIV infection can give rise to an MND mimic, HIV-ALS. The improvement in response to ART supports the notion that HIV-ALS is a treatable entity also in Africa. This is the first case report of a patient with HIV-ALS and long term follow up in Sub-Saharan Africa. The report raises the suggestion that an additional (retro)virus can play a role in the aetiology of ALS.

Introduction

Patterns of neurological morbidity and mortality in low-income countries, like the Sub-Saharan African (SSA) country of Tanzania, differ in comparison to high income countries, because of a greater burden of communicable diseases.[1,2] In SSA, the epidemiology and phenotypes of non-communicable neurological conditions like neuromuscular diseases are likely comparable to other populations across the world, although underdiagnosed and -reported.[1-3] While motor neuron disease (MND) has been reported from SSA since the nineteen seventies, there have been few recent publications.[3-7]

Human immunodeficiency virus (HIV) infection is still one of the leading causes of morbidity and mortality in the world and its neurological manifestations are manifold.[8,9] Since early on in the HIV epidemic, multiple cases of HIV-ALS have been described.[10-16] HIV-ALS can cause a clinical presentation compatible with sporadic ALS (sALS). [15] HIV-ALS tends to occur at younger age, with a more severe and progressive phenotype.[7,10-15] The occurrence of HIV-ALS is not related to the duration or stage of the HIV infection.[14]

SSA accounts for over 70% of the global HIV epidemic. There has been no literature on HIV-ALS from SSA apart from a recent study from South Africa, a country with higher socioeconomic level and a multi-ethnic patient population.[7] An association of HIV and MND was suggested in a large cohort of MND patients from Northern Tanzania.[4] One patient from the same series with HIV-ALS is described in this report. He was treated with ART and clinically stabilised over 10 years.

In patients with HIV-ALS a response to ART has been described in previous case reports.[7,10-15] The diagnostic consideration of HIV-ALS is important since treatment with ART can affect the course of the disease.

Case report

In June 2007, a 41 year old male was admitted to Kilimanjaro Christian Medical Centre (KCMC), a tertiary referral centre in Northern Tanzania. He had a nine month history of a nasal speech, progressive difficulty chewing and swallowing for seven months and difficulty walking for six months. Around the same time he had developed a seizure disorder characterized by tonic-clonic seizures which were suppressed on phenytoin. His past medical history was remarkable for the diagnosis of HIV in May 2005. In October 2006 his CD4 count was 250 cells/cmm and he was started on ART (stavudine (d4T), lamivudine (3TC) and nevirapine (NVP)).

In June 2007, neurological examination showed reduced gag reflex, brisk jaw jerk, positive snout and palmomental reflexes. The tongue was atrophic with fasciculations, decreased range of movement and there was pseudobulbar speech. The upper limbs showed symmetrical claw like hand deformity with marked wasting and fasciculations of the forearm and hand muscles. Power was symmetrically reduced to Medical Research Council grades 3-4/5 with a proximodistal gradient and more in extensor than flexor–musculature. The lower limbs were affected with marked wasting and slightly reduced power distally. All tendon reflexes were pathologically brisk with bilateral extensor plantar reflexes and Hoffman's sign. Gait was spastic

with the need for assistance to mobilize. Sensory examination was normal. (Figure 1)

Full blood count, erythrocyte sedimentation rate (ESR) and renal and liver function tests were normal with a negative VDRL test and a CD4 count of 697 cells/cmm. Chest

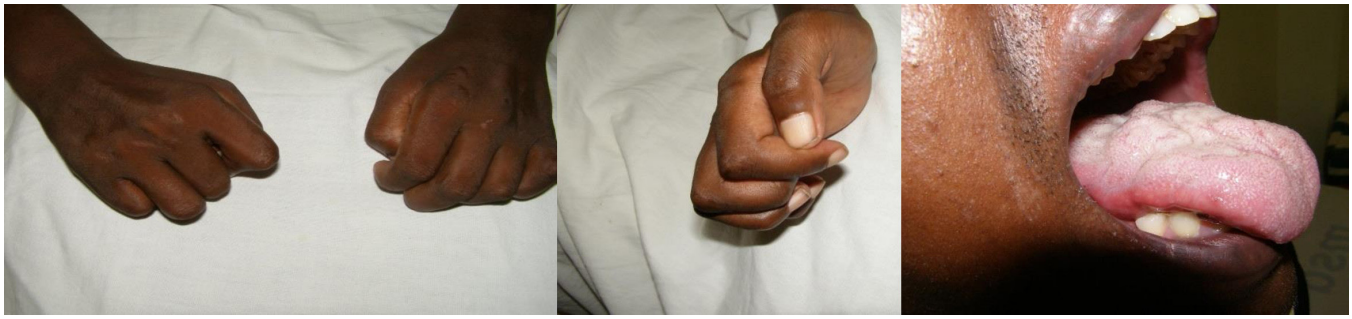

Figure 1: photos of the hands from 2008 show wasting of hand muscles and clawing. Photo of the tongue from 2008 showing atrophy.

X-ray and CT brain were normal. Cerebrospinal fluid (CSF) had normal biochemistry and cell count, and an undetectable HIV ribonucleic acid (RNA) viral load. No other cause was found for his new onset seizure disorder. There was no EMG or MRI facility in Northern Tanzania in 2007/8.

A diagnosis of HIV-ALS was made and his ART regime was changed to abacavir (ABC), didanosine (ddl) and lopinavir/ritonavir (LPV/r) for better central nervous system (CNS) penetration. He developed distal sensory neuropathy and changed ART again in December 2007 (Zidovudine (AZT), 3TC and LPV/r). He was observed with three-monthly visits, with stable symptoms until January 2008, when he was lost to follow-up.

November 2017, the patient was readmitted to KCMC with symptoms of congestive cardiac failure. He was reviewed by the same neurologist (WPH) as on his first admission. After 2008 his symptoms had improved such that he could walk and function independently. His swallowing had also improved though his speech remained unchanged. From two years before the admission in 2017 he required assistance when walking. Neurological examination in 2017 was largely comparable to 2007 apart from slightly more pronounced upper motor neuron signs (spasticity) in his upper limbs. (Figure 2)

Over the previous 10-year period the patient said to be compliant with his ART. During the admission in 2017 plasma HIV RNA copies were 7919/ml suggesting lack of ART compliance or the emergence of ART resistance. Electromyography supported the presence of lower motor neuron degeneration in the cranial, cervical, thoracic and lumbosacral segments, based on the Awaji criteria.

Based on the history and physical examination the clinical diagnosis was 'definite' ALS. It had stabilised on ART for a decade but deteriorated with signs of therapy failure as a possible explanation. (Figure 3)

Discussion

This is the first case report of a patient in SSA, outside South Africa, with HIV-ALS. The first tentative report of

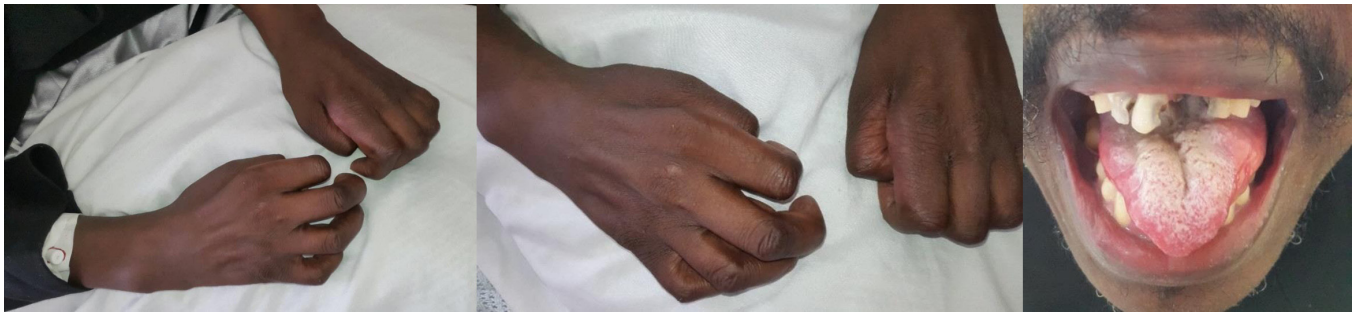

Figure 2: photos of the hands from 2017 show wasting of hand muscles and clawing. Photo of the tongue from 2017 showing atrophy.

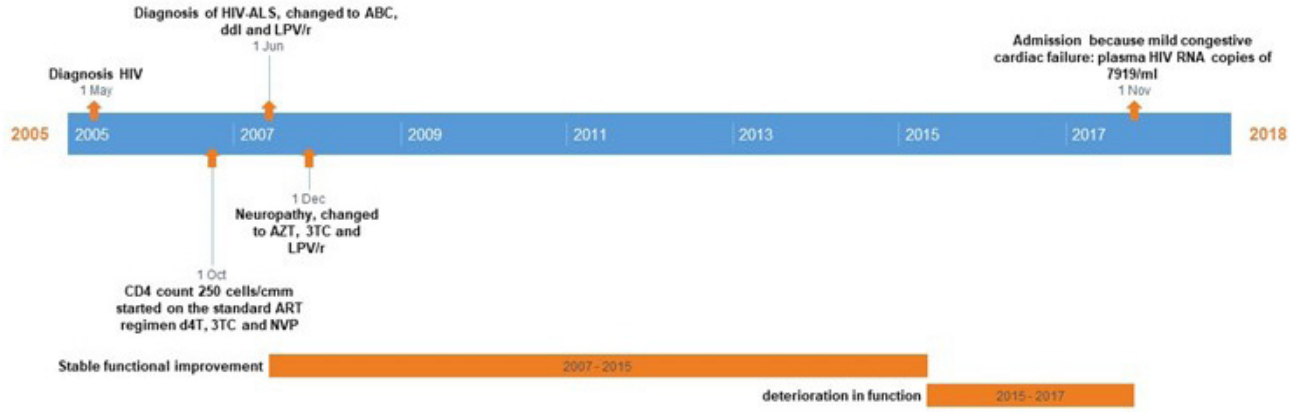

Figure 3: timeline. 3TC: lamivudine. ABC: abacavir. ALS: amyotrophic lateral sclerosis. ART: antiretroviral therapy. CD4: cluster of differentiation 4. d4T: stavudine. ddI: didanosine. HIV: Human immunodeficiency virus. LPV/r: lopinavir/ritonavir

an association between HIV and MND was of a HIV infected patient, who developed classic ALS in 1985.[16] From 1985 to 2018 there have been over 30 cases described in case reports and series of HIV-associated MND.[10-16] A recent retrospective study from South Africa describes 35 patients with HIV-associated motor neuron syndrome compared to 101 HIV-uninfected MND patients.[7]

The estimated HIV prevalence rate in adults in Tanzania is 4.6%.[17] The global incidence of ALS is 1-2 per 100,000 persons each year with a prevalence of 4-6 cases per 100,000.[18] The reported MND prevalence rates among Black African HIV-infected and HIV-uninfected patients are respectively 2.4 and 0.44 cases per 100,000.[7,19] HIV was suggested to be a causal confounder.[7,19]

Clinically, HIV-ALS is identical to sALS in HIV-negative patients but occurs younger, is more severe and progressive. It can be arrested or (partially) reversed by initiation or optimisation of ART.[7,10-15]

In our patient neurological symptoms developed on the standard ART regimen despite virological suppression. He had started ART when the CD4 count went below 250 cells/cmm, as was usual at the time. June 2007 he changed to ART with good CNS penetration, on which there was no progression of symptoms during 8 months. He was lost to follow-up for almost 10 years during which he describes a long period (7 years) of gradual improvement. From 2015 there was deterioration in function and on re-evaluation in late 2017 he was found to have a high viral load in plasma. This suggests treatment failure due to noncompliance or ART resistance. Of clinical interest was the nearly identical pattern of neurological signs over the 10-year period of observation.

Partial to full clinical improvement after starting ART has also been reported in a number of studies on MND in HIV.[7,10-15] In a South African study, 17 of 35 patients with HIV-associated motor neuron syndrome survived longer than 10 years after starting ART.[7] Early ART initiation or optimisation (≤6 months) and use of ART with CNS penetration improve outcome.[7,10,14]

The described patient developed a seizure disorder (generalised) around the same time as he started his MND symptoms, no cause was found. While the occurrence of seizures is increased significantly in patients with HIV, they are usually secondary to opportunistic processes or vascular in origin, neither of which were present in this case. Possibly there is a relation and to reclassify the diagnosis to ALS-plus is very reasonable.

A (retro)viral aetiology in sALS has been hypothesized.[19-22] Motor neuron cells are vulnerable to certain viruses, illustrated by poliomyelitis virus which targets anterior horn cells. HIV can occur in the microglial cells of the CNS but is not identified to invade motor neurons. Therefore the pathophysiology of HIV-ALS might be explained by a secondary inflammatory response or an unknown opportunistic virus infecting the motor neurons.[21] In some patients with sALS an increased HERV-K expression has been found in cortical neurons and anterior horn cells suggesting that this endogenous retrovirus might play a role in the aetiology.[10,11,20,22] The serum of this patient could unfortunately not be tested for HERV-K.

Our first report from Tanzania supports the notion that HIV-ALS can be a treatable entity also in Africa.[7,19]

Teaching points

- HIV infection can give rise to motor neuron disease including HIV-ALS.
- HIV should routinely be tested in patients with ALS.
- Antiretroviral therapy can potentially reverse and treat HIV-ALS making it a treatable entity, also in Africa.
- Retroviruses might play a role in the aetiology of motor neuron disease.

Acknowledgements

We would like to thank the family for their participation and informed consent for the photographs, EMG and publication of this case report. We would also like to thank Kilimanjaro Christian Medical Centre for allowing us to work closely with patient and family.

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Re-publication of my RSD Peripheral Neuropathy Three-Phase Bone Scan Paper

Richard J. Barohn, MD

I hope the RRNMF readership will indulge me in re-publishing this old paper of mine which I love for many reasons, but alas I do not believe anyone outside of India has seen it. When I was a neurology resident at Wilford Hall U.S. Air Force Medical Center in San Antonio (1983 to 1986), I saw a number of cases of what we then called Reflex Sympathetic Dystrophy. Now we refer to this as Complex Regional Pain Syndrome. All of the patients had an underlying peripheral neuropathy or nerve damage of some sort and I suspect that's why they were referred to neurology. I had done some reading on the three-phase bone scan and RSD and I ordered the scans on all of these patients, and to my surprise all were positive showing increased activity in the flow, tissue, and bone phases, as had been reported in the literature. I collected all of the cases and I recall presenting them at the annual all-military neurology conference that was called AMED in either Washington DC at Walter Reed or Letterman Army Medical Center in San Francisco. This was a great forum of Army, Air Force and sometimes Navy neurologists and residents in which we heard lectures from well-known academic neurologists. Residents also had the opportunity to present "research" data, usually a single or series of case reports. I presented from the platform at this conference each year of my residency and I know it prepared me for so many future scientific presentations.

I believe I did the RSD presentation at the military neurology meeting in my last year of residency, in the spring before I went to Ohio State University to do a neuromuscular fellowship under Jerry Mendell, John Kissel, Zarife Sahenk, and Jack Warmolts, an experience which changed my life. In the OSU fellowship everyone got ready to present posters or platforms at neurology meetings all year round: AAN in the spring, ANA in the fall and any other specialty conference that would come up. As a resident at Wilford Hall I submitted my RSD abstract to the ANA and amazingly it was accepted. I had to put together the poster the old-fashioned way at OSU and the team helped me do that. It was my first poster at a national meeting. At the time actually typed the information for the poster and then our secretary Nancy Hodges would enlarge the printed version on a copy machine, and we would paste these onto cardboard for the poster. I had brought multiple copies of the three-phase bone scan images with me. I was very proud of this poster and I still have most of it (I never throw anything away). I went on to work on the projects Jerry and the team had for me during that fellowship year and left the RSD TPBS information unattended for a while. There was a lot of pressure to get the big CIDP project done (see my reference to this in the Letter from the Founding Facilitator in this issue) and along the way I picked up other projects involving diabetic lumbosacral radiculoplexopathy, congenital myopathy with small Type 1 fibers, testosterone and muscle stimulation for myotonic dystrophy; mitochondrial myopathy and respiratory depression; a ragged red fiber case with autopsy, evoked potentials in CIDP, delayed gastric emptying in Duchenne muscular dystrophy. All resulted in a publication eventually except for the myotonic dystrophy one, but I still have that manuscript and plan to submit it to the RRNMF Neuromuscular Journal next year (never never let a paper go unpublished).

I did see one dramatic case of RSD while a fellow with Jerry. It was a 17-year-old who tried to commit suicide from a drug overdose, fortunately unsuccessfully. But he was found down and had been in one position for a day or so. He had a compressive sciatic neuropathy. The strength component improved but he was left with a raging RSD. I recall he limped in holding a bucket. I asked him what the bucket was for and he said he has to take it everywhere to and fill it with cold water and immerse his painful foot in the water for pain relief. This was the only thing that helped. The foot and distal leg was red and warm. His three-phase-bone scan was of course abnormal in all three phases. Jerry and the OSU team considered me their resident expert in this condition. It was the only thing I ever taught them. We put the young man on high-dose prednisone, analgesics, and sent him for a lumbar sympathetic block and he did well over time.

When I returned to Texas after the fellowship I was still writing fellowship papers and it was not until several years later that I got to the RSD-TPBS paper. I sent it to several journals but could not get anyone to publish it. The paper was long and had a lot of photographs of three-phase bone scans. I almost gave up and then in 1996 Drs. KK Sinha and P Chandra asked me if I wanted to contribute an article to their annual Advances in Clinical Neurosciences volume. I immediately thought of the RSD-TPBS paper and they willingly accepted it. I went on to publish several other articles in Advances in Clinical Neurosciences over the next several years. But the only neuromuscular one that had information that I never subsequently published was this paper (Michael

Collins and I did publish the longest case report ever on primary progressive aphasia in one volume. It was a case we saw at Wilford Hall Medical Center together and it may be worth republishing that one at some point! A classic Collins "brief report").

So now we have launched this new journal and it occurred to me that now is my opportunity to share this old paper with the world. It took me a while to find a way to contact the editors. I had very old email addresses of the editors and all I had was an address for the Catholic Press on Karbala Road in Ranchi, India. Fortunately, with the help of Jayashree Sundarajan, one of my former neurology residents, I got an updated email address from Dr. Chandra, was able to contact him and ask if I could reprint the paper in this publication. He graciously agreed on August 12, 2020:

> Dear Dr. Barohn,
>
> On behalf of the publishers and editors of Advances in Clinical Neurosciences, I am happy to grant permission to reprint the following paper in the RRNMF Neuromuscular Journal:
>
> Barohn RJ. Reflex sympathetic dystrophy due to peripheral neuropathy and the Three-Phase- Bone Scan: Case Series and Review. 1997;vol7,pages 129-150.
>
> Unfortunately, we don't have an electronic copy.
>
> Thank you for the link to the new journal. I look forward to reading it. With best wishes,
>
> Prakash Chandra

I had asked Dr. Chandra if they had an electronic copy which would make reprinting it easier but alas this was before the age of electronic copies, I think. So Marianne Reed in the digital publishing unit at KU has a high quality scanner. I still had glossy paper preprints of the paper (I said I never throw anything away) and I mailed it so she could have the original paper scanned. And that is what appears in this issue.

I would like to thank Dr Chandra for allowing me to reprint/republish this old paper which has a lot of sentimental value to me. And I still think the TPBS is a good tool although few use it now.

I hope you enjoy my neurology residency paper.

Advances in Clinical Neurosciences, 1997; **7**: 129-150

REFLEX SYMPATHETIC DYSTROPHY DUE TO PERIPHERAL NEUROPATHY AND THE THREE-PHASE BONE SCAN : CASE SERIES AND REVIEW

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Introduction

Reflex sympathetic dystrophy (RSD) is a disorder characterized by a painful, tender, often edematous extremity, with varying degrees of color, temperature, and dystrophic skin changes (Table 1)[1-4]. A number of different terms have been used to describe the same syndrome over the years (Table 2). The clinical manifestations of RSD can be confusing, and a patient may not exhibit all of the classic features, making the diagnosis difficult. Although poorly understood, RSD may represent local dysfunction of the autonomic nervous system and is most often seen in the setting of trauma to an extremity, with or without associated nerve injury (Table 3), While the first reported cases of RSD occurred after significant trauma to a peripheral nerve[5], RSD has been described infrequently in association with peripheral neuropathies in which there has not been trauma[6-9]. Some authors believe that RSD cases can be assigned a clinical stage, depending on symptoms and signs and temporal course[2,10]. In addition, the use of the three-phase bone scan has been reported to be useful in establishing the diagnosis of RSD[6,11-21], although its sensitivity has been debated by others[22-25]. We report twelve cases in which asymmetric neuropathies at various sites along peripheral nerves were associated with RSD. Our goal was to determine how often the TPBS was abnormal in patients with a neuropathy who were also suspected of having RSD, and whether or not an abnormality on the TPBS correlated with the clinical stage of RSD.

Case Selection

All patients were referred to the neurology service for either a suspected neuropathy or extremity pain. In addition to clinical examination for localization

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Table 1 — RSD - Signs and Symptoms

Pain (usually burning)
Tenderness
Swelling
Joint stiffness
Discoloration
    pale or red
Sudomotor changes
    increased or decreased sweating
Temperature changes
    cool or warm
Dystrophic changes
    thin, tight, smooth skin
    hair loss
    subcutaneous tissue atrophy
    nail changes - brittle, ridging

Table 2 — RSD Synonyms

Causalgia and major traumatic dystrophy
Minor causalgia and minor traumatic dystrophy
Sudeck's atrophy
Shoulder-hand syndrome
Posttraumatic painful osteoporosis
Posttraumatic pain syndrome
Posttraumatic angiospasm or vasospasm
Algoneurodystrophy
Oligodystrophy
Reflex neurovascular dystrophy
Sympathetic - maintained pain syndrome

Table 3 — Events that can cause RSD

I. Trauma
    Sprains, dislocations, fractures, minor contusions, crush injuries, burns, knife and gunshot wounds
    Iatrogenic
    Postsurgical, tight casts, needle injection into nerves, aortofemoral bypass.

II. Diseases

Visceral diseases	myocardial infarction
Arthritic diseases:	rheumatoid arthritis
Infectious diseases	cellulitis, herpes zoster
Neurologic diseases	
Central nervous system	strokes ("posthemiplegic dystrophy")
	tumors, posttraumatic
Peripheral nervous system	radiculopathy
	plexopathy
	mononeuropathy
	mononeuropathy multiplex

III. Idiopathic

of the nerve lesion(s), patients were questioned and examined for evidence of tenderness, color, skin temperature, sweating, dystrophic skin or nail changes, and edema compared to the contralateral extremity. In order to fulfill criteria for *symptoms* of RSD, patients had to have complained of a severe burning pain in the involved extremity. In order to fulfill criteria for *signs* of RSD, patients must have had tenderness and abnormalities in at least one of the following three areas compared to the contralateral extremity: temperature, color change, sweating change. Clinical evidence for edema and dystrophic skin changes were not mandatory but were noted to be present or absent. Dystrophic changes consisted of smooth, glossy, taught skin or brittle, grooved, discolored nails. Temperature measurements of the involved extremity was compared with that of the contralateral extremity using a skin thermistor. Temperature was measured over the dorsal surface of the hand or foot, respectively. A surface skin temperature difference of greater than 1°C was considered to indicate a significant asymmetry. The involved extremity was considered to be "colder" or "warmer" than the unaffected limb if its skin temperature was 1° below or above the contralateral extremity, respectively.

We attempted to place our patients into the diagnostic criteria scheme proposed by Kozin and colleagues[14,15]. In their scheme, definite and probable RSD patients must have pain and tenderness. Definite RSD patients have vasomotor instability changes (temperature or color change) and edema; probable RSD patients have vasomotor changes or edema. Possible RSD patients had only pain without vasomotor changes or edema, or only vasomotor changes and edema without pain.

We attempted to categorize patients as to the stage of RSD using a modification of the staging system described by Bonica[2]. In our staging system, patients were categorized as having either stage 1 or stage 2 RSD. To be considered for stage 1 RSD, patients would have to have had at least two of these three features: redness, increased sweating, and a warm extremity that had pain and tenderness. In stage 2 RSD, the painful tender extremity would have to have had at least two of these three features: a pale or grey or cyanotic color; decreased sweating or dryness; and a cool extremity. If a painful extremity had a mixture of features from the stage 1 and 2 criteria, the stage was considered indeterminate. We did not utilize what has been called stage 3, which Bonica considers the "atrophic" stage, as the color, temperature, and sweating abnormalities of stage 3 are reported to be the same as in stage 2[2]. Temporal factors (time since onset of pain) were not considered into our classification scheme, but the time elapsed since onset of symptoms and our evaluations was documented.

All patients had electrophysiologic testing in which conventional needle electromyography (EMG) and nerve conduction study (NCS) techniques were

utilized. In all patients, the EMG/NCS findings were abnormal and supported the diagnosis of either a radiculopathy, plexopathy, or peripheral neuropathy.

Radionuclide Studies

Three phase bone scans (TPBS) were performed using technetium-99 methylene diphosphate (Table 4). A 20 mCi bolus injection was made via an antecubital vein. If the painful extremity was the arm/hand, then the injection was made in the contralateral antecubital vein. The phase-1 radionuclide angiogram (RNA), an indirect assay of blood flow, consisted of sequential rapid sequence images 5 seconds apart for 40 seconds. Immediately afterward, a 500,000 count phase-2 blood pool image was obtained, delineating the early extracellular-fluid distribution of the radionuclide tracer. Three hours after injection, the phase-3 delayed static image was made, assessing in the technetium uptake into bone. The studies were considered to be positive if all three phases demonstrated asymmetric radionuclide activity in the involved extremity compared to the contralateral extremity. In phase 1, we looked for both early flow to one of the extremities as well as the intensity of the radionuclide activity. In phases 2 and 3, the intensity of radionuclide activity was examined. These were qualitative assessments made by inspection of the films.

Table 4 — The three-phase bone scan (TPBS)

Intravenous 20 mCi Technetium - 99 methylene diphosphate	
Phase I:	Radionuclide angiogram flow study Sequential images every 3-5 seconds X 30-60 sec
Phase II:	Blood pool or tissue phase image 500,000 count blood pool image obtained immediately after Phase I
Phase III:	Delayed/static image 500,000 count image obtained 3 hours after injection

Summary of Cases

A summary of the 12 cases of neuropathy with RSD is given in Table 5. The ages ranged from 18 to 65. In eight cases, the neuropathy involved a unilateral painful upper extremity, and in four the lower extremity was involved. The peripheral neuropathies consisted of: mononeuritis multiplx[2], carpal tunnel syndrome[2], ulnar neuropathy[1], brachial plexopathy[4], lumbar plexopathy[1], lumbar radiculopathy[1].

Both cases of mononeuritis multiplex (MM) (cases 1 and 2) had a more widespread generalized neuropathy found on neurologic examination and with

Table 5 — Reflex sympathetic dystrophy with peripheral neuropathy — summary of cases

Patient	Age/ Sex	Neuro-pathy	Etio-logy	Dura-tion of symptoms (months)	Pain	Tender-ness	Color change	Temp change	Swea-ting change	Edema	Dystro-phic changes	Stage	Kozin crit-eria°	Ab-normal TPBS	Rx	Pain Res-ponse
1	60/F	MM:Predom. Median/ Ulnar/ Peroneal	Vascu-litis	1.0	+	+	—	Dec	Dec	+	+	ID	Def	+	PR,CY, SGB,PT	Dec
2	62/F	MM:Predom. Sciatic	Un-known	1.0	+	+	Pale	Dec	None	+	—	2	Def	+	PR,PT	Dec
3	65/F	Brachial Plexopathy	Tumor	6	+	+	Pale	Dec	Dec	—	+	ID	Prob	+	PR,SGB, PT	Dec
4	18/F	Lumbar Plexopathy	Idiopathic	6	+	+	Pale	Dec	None	+	+	2	Def	+	PR,LSGB, PT,NSAIA, TRI	No
5	30/M	Brachial Plexopathy	Idoipathic	5	+	+	Red	Inc	Inc	—	+	ID	Prob	+	PR,TRI, PT	Dec
6	60/M	Brachial Plexopathy	?Diabetes or Idiopathic	5	+	+	Red	Inc	None	+	+	1	Def	+	NSAIA,PT	Dec
7	53/F	Brachial Plexopathy	Idiopathic	5	+	+	Pale	Dec	None	+	+	2	Def	+	PR,SGB, PT	Dec

—Contd

Table 5 — Reflex sympathetic dystrophy with peripheral neuropathy — summary of cases — Contd

Patient	Age/ Sex	Neuro-pathy	Etio-logy	Dura-tion of symptoms (months)	Pain	Tender-ness	Color change	Temp change	Swea-ting change	Edema	Dystro-phic changes	Stage	Kozin crit-eria°	Ab-normal TPBS	Rx	Pain Res-ponse
8	36/M	Sciatic	Ischemic	1	+	+	Red	Inc	Dec	—	+	1	Prob	+	SGB	Dec
9	60/M	Lumbar(L5)	L4-5 Disc Herniation	2	+	+	—	Dec	Inc	+	+	2	Def	+	PR, Bed rest	Dec
10	63/F	Ulnar	Ischemia	3	+	+	Pale	Dec	None	—	—	2	Prob	+	SGB,PT	Dec
11	40/F	CTS	Rheuma-toid Arthritis	1	+	+	Pale	Inc	Inc	+	+	ID	Def	+	Splint, NSAIA	Dec
12	60/F	CTS	Idiopathic	2	+	+	Pale	Dec	None	+	—	2	Def	+	Splint, NSAIA	Dec

F Female; M = Mate;

MM = mononeuritis multiplex; CTS = carpal tunnel syndrome; Predom = predominately; Dec = decrease; Inc = increase;

+ = present; - = absent

TPBS-three-phase bone scan; ID = indeterminate; Def = definite; Prob = probable; Rx = treatment

PR = prednisone; CY = cyclosphosphamide; SGB = sympathetic ganglion block; PT = physical therapy; NSAIA = non-steroidal anti-inflammatory agent;

TRI-tricyclic anti-depressant

°Kozin criteria = see Kozin, *et al.*[14]

EMG/NCS testing (so-called "over-lapping" mononeuritis multiplex[27]. The two MM cases had sural nerve biopsies. In case 1, the MM was dominated by involvement of the left peroneal and left median and ulnar nerves. The sural nerve biopsy had pathologic evidence of a necrotizing vasculitis (see case 1 summary below). The nerve biopsy in case 2 revealed a severe axonal neuropathy but no evidence for vasculitis. Of the four cases of brachial plexopathy (cases 3, 5, 6, 7), three were idiopathic, or the Parsonage-Turner syndrome[28], although one patient (case 6) had diabetes mellitus. One of the brachial plexopathy patients (case 3) had tumor invasion of the plexus (see case 3 summary below). In the patient with a lumbar plexopathy (case 4), no cause could be found and therefore it was presumed to be idiopathic[29,30]. Case 8 developed a sciatic neuropathy following aorto-femoral bypass surgery (see case summary below)[31] Case 9 had a lumbar radiculopathy due to a herniated disc between the fourth and fifth lumbar vertebral bodies (see case summary below). Case 10 developed an acute ulnar neuropathy when her left arm became transiently ischemic due to an embolus originating from severe atherosclerotic disease of the subclavian artery (i.e., an ischemic monomelic neuropathy 6). The transient ischemia lasted only one hour, after which time the circulation to the arm spontaneously improved, but she was left with a residual ulnar neuropathy. The final two cases (cases 11 and 12) had carpal tunnel syndrome (see summary of case 12 below).

All twelve of the cases had severe burning pain and tenderness and some combination of vasomotor changes (temperature, color, sweating) and edema as part of our entry criteria for RSD. Eight fulfilled the Kozin criteria for "definite" RSD and four fulfilled these criteria for "probable" RSD[14,15].

Seven of the twelve (58%) had a pale hand or foot, in three (25%) it was erythematous and in two (16%) there was no color change. In eight (66.6%), the surface temperature was clinically reduced, and in two (16%) it was increased. Only three (25%) were felt to have increased sweating and in three (25%) the involved hand or foot was dry. Edema occurred in seven (58%) patients and dystrophic skin and nail changes occurred in nine (66.6%) patients.

We were able to categorize two cases as RSD stage 1, six cases as stage 2, and four cases were indeterminate.

All of the twelve patients had an abnormal TPBS in each of the three phases compared to the contralateral extremity. The abnormalities consisted of early and increased flow on to the involved extremity on the phase I angiogram image, increased radionuclide activity on the phase 2 tissue pool image, and increased activity in bone on the delayed phase 3 static image. As all of the 12 cases had abnormal TPBS, there was no relationship between the RSD diagnostic category

or stage and the finding of increased radionuclide activity. In other words, all of the stage 1, stage 2, and indeterminate stage patients and all of the "definite" or "probable" patients had an abnormal TPBS in all three of the phases. The time elapsed between symptom onset and TPBS evaluation was 1 to 6 months (mean 3.2 months).

Of the 12 RSD cases, eight patients' skin temperature was decreased compared to the contralateral limb, while in four cases the temperature was increased. However, as all 12 patients had an increase in radionuclide activity in phases 1 and 2, there was no tendency for an abnormal TPBS (i.e., increased radionuclide activity in the affected extremity) to be seen more often in patients with increased skin temperature.

Six of our patients had a series of temporary sympathetic ganglion blocks, and four of these also had a two to three week course of prednisone (60 to 80 mg/day, with rapid taper over two to three weeks). Tricyclic anti-depressant and nonsteroidal anti-inflammatory drugs were also used in these cases if indicated. The remaining six patients who did not have a ganglionic block received prednisone [3], or a non-steroidal anti-inflammatory drug [3], occasionally in association with a tricyclic anti-depressant medication [2]. All of the cases had vigorous physical therapy as well. Although these cases were not uniformly treated, 11 of 12 had a reduction or resolution of the symptoms and signs or RSD. Three-phase bone scans were not repeated.

Selected Cases

Case 1 — This 50 year old black female noted diminished sensation in her feet bilaterally, followed two months later by a left foot drop, and two weeks later by the sudden onset of burning pain, paresthesia, swelling, and weakness in the left hand. When examined one month after the left arm pain began, profound weakness and sensory loss was present in the distribution of the left median, ulnar, and peroneal nerves as well as a symmetrical distal sensory polyneuropathy. The left hand was cool, dry, edematous, and tender, and the skin was shiny and taut. It could not be determined if there were skin color changes. EMG/NCV confirmed the clinical diagnosis of a mononeuritis multiplex involving the left median, ulnar, and left peroneal nerves, superimposed on a diffuse distal polyneuropathy. A left sural nerve biopsy demonstrated a necrotizing vasculitis of medium-sized arteries, consistent with polyarteritis nodosa. Increased radionuclide activity to the left hand was present in all phases of the TPBS. The patient was treated with prednisone and cyclophosphamide, and she had a slow improvement in strength. However, four temporary left stellate blocks were required within the first month of therapy for pain relief. A repeat TPBS one year later was normal.

Case 3 — A 65 year old female who had a right mastectomy for infiltrating ductal carcinoma (no radiotherapy), presented five years later with a six month history of severe pain, tenderness, and weakness in the right arm and hand. The hand was cool, pale, and extremely tender, with normal pulses. The skin over the dorsal hand was smooth, shiny, and dry. Neurologic exam and EMG/NCV indicated a lower and middle trunk brachial plexopathy. A CT of the chest and axilla and a cervical myelogram were normal. TPBS (Fig. 1a, b, c) demonstrated increased tracer flow and bone uptake in the right hand. No definitive etiology for the brachial plexopathy was established, although metastasis was suspected. A series of four right stellate ganglion blocks, physical therapy, and a 14 day course of steroids resulted in dramatic pain relief and increased mobility of the right arm and hand, although weakness persisted. Two months later, enlarged right cervical lymph nodes were biopsied that revealed metastatic carcinoma.

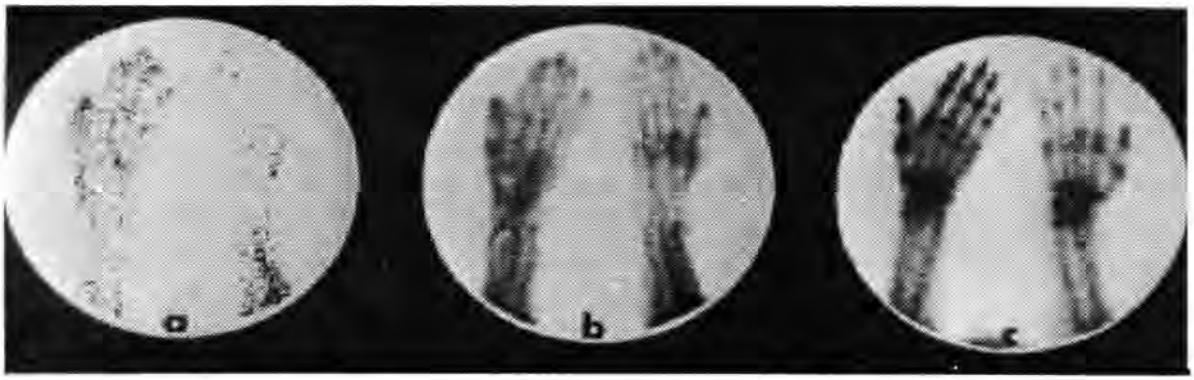


Fig. 1 — Case 3 - Increased flow to the right hand and increased radionuclide uptake in the juxta-articular aspects of all hand and wrist bones on the right (a = RNA, b = blood pool, c = delayed static image). On this figure and all of the following figures, the right limb is on the right of the photographic image (the readers left), and the left limb is on the left of the photographic image (the readers right). Thumbs are lateral on all images. Only one RNA image is shown for brevity.

Case 5 — This 30 year old male developed severe left scapular pain, followed by left upper extremity paresthesia, weakness and burning hand pain. He reported the left hand was edematous and would change colors. At an evaluation at another hospital, an idiopathic brachial plexitis was diagnosed. Two short courses of prednisone significantly diminished the burning pain. The patient was referred to our hospital seven months later for re-evaluation due to persistent profound left arm weakness and atrophy, and moderate pain. The left forearm and hand were warm, erythematous, with increased palmer sweating, and thin, shiny, skin over the dorsal hand surface. The hand and forearm were tender. The left arm muscles from the shoulder to the hand had only minimal motor function, with loss of touch and pin sensation to the shoulder. The left arm was areflexic. An EMG/NCS study was consistent with a severe brachial plexitis effecting all levels of the plexus. Numerous fibrillation potentials were

present in muscles innervated from nerve segments from the upper, middle, and lower plexus trunks. Motor and sensory potentials on NCS had low amplitudes. The TPBS (Fig. 2a, b) showed early asymmetric tracer flow to the left arm and hand, increased activity on the blood pool image, and a marked increase in carpal bone and juxta-articular region uptake in the static images. He received an oral tricyclic medication and physical therapy. The pain continued to slowly improve, but no significant return in arm or hand motor function occurred. The TPBS was not repeated.

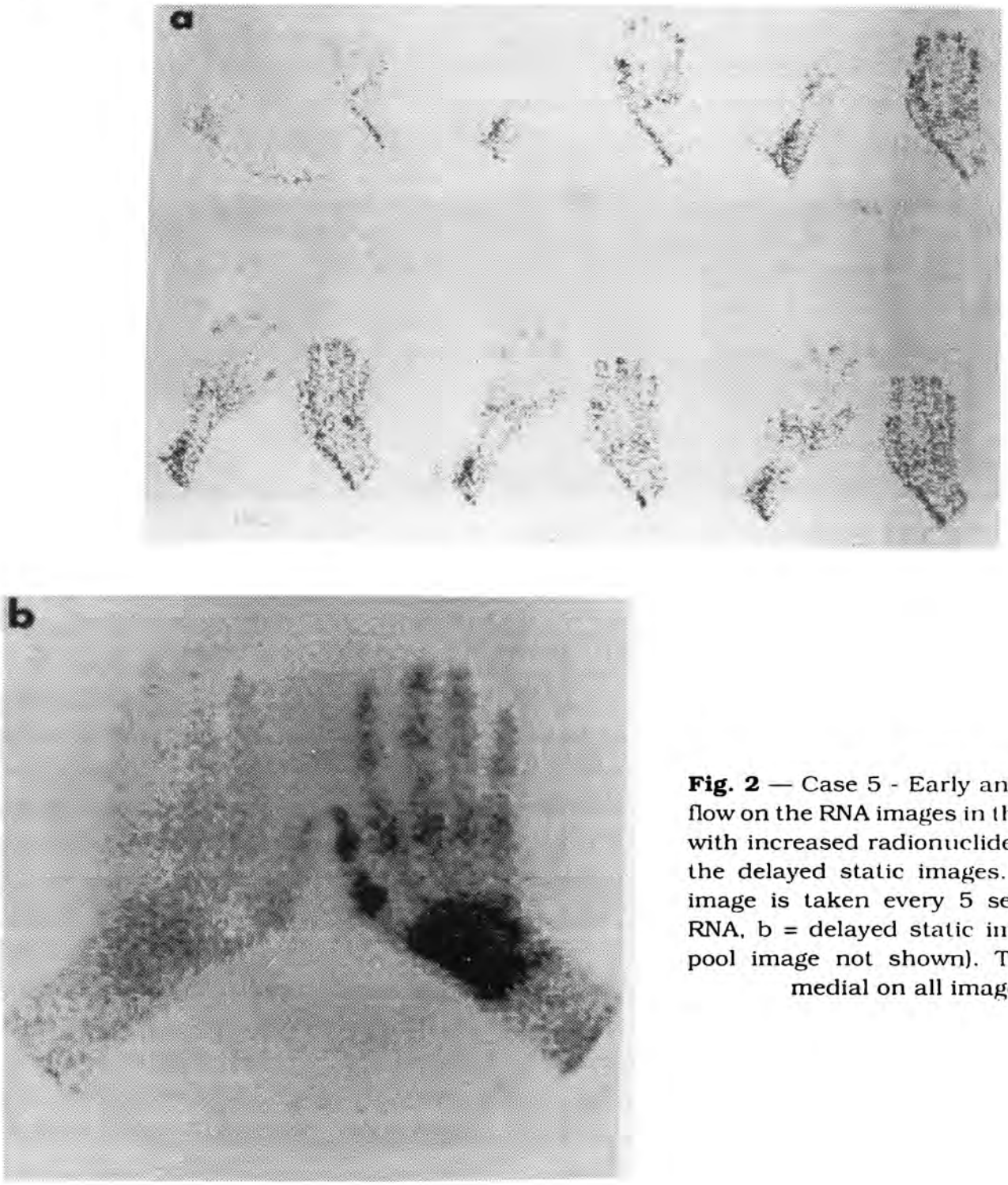


Fig. 2 — Case 5 - Early and increased flow on the RNA images in the left hand, with increased radionuclide activity on the delayed static images. Each RNA image is taken every 5 seconds (a = RNA, b = delayed static image) (blood pool image not shown). Thumbs are medial on all images.

Case 8 — This 36 year old male underwent right aortofemoral bypass surgery for severe atherosclerotic disease with vascular claudication. Several days after surgery, he began complaining of severe burning pain throughout the right foot with numbness and weakness. The vascular grafts were determined to be patent. On examination one month later, the right foot was tender, warm, and red, with good distal pulses. The skin over the dorsum of the right foot was dry and scaly. All sensory modalities except vibration were decreased throughout the right foot, and the right ankle jerk was absent. Motor strength was difficult to assess due to the tenderness. An EMG/NCS was consistent with a right sciatic neuropathy. The TPBS (Fig. 3a, b, c) showed increased radionuclide activity in all three phases. Several temporary right lumbar sympathetic blocks abolished the burning pain. The sciatic neuropathy was most likely due to intra-operative ischemia. The TPBS was not repeated.

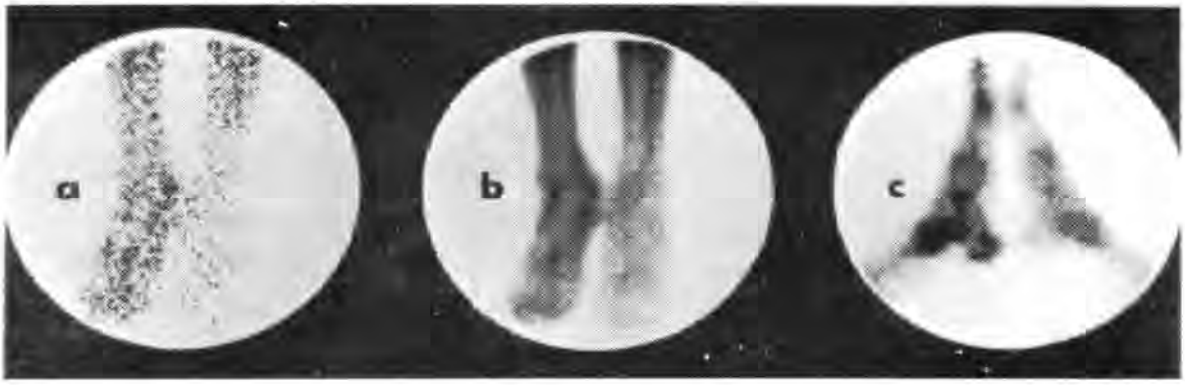


Fig. 3 — Case 8 - Asymmetric increase of radionuclide in all three phases on the right foot (a = RNA, b = blood pool image, c = delayed static image). Only one RNA image is shown for brevity.

Case 9 — A 60 year old male had symptoms, signs, EMG, and myelogram evidence of a left L-5 radiculopathy due to a herniated L4-5 disc. In addition, the left foot was edematous, cooler than the right, exquisitely tender, and moist. TPBS indicated increased tracer activity in all phases in the left foot (Fig. 4a, b, c). A two week course of prednisone and bed rest resulted in marked improvement of the sciatica and the RSD symptoms and signs. The TPBS was not repeated.

Case 12 — This 60 year old female developed paresthesia in the right median nerve distribution as well as constant pain and tenderness over the wrist and thenar region. Mild edema of the right hand was present, and the hand was cool and pale, without a detectable change in sweating compared to the left hand. Nerve conduction studies were consistent with a right carpal tunnel syndrome. The EMG showed no denervation in the abductor pollicis brevis. The TPBS revealed increased activity in all three phases (Fig. 5a, b, c). The increased radionuclide activity appeared to be more prominent in the region of the hand

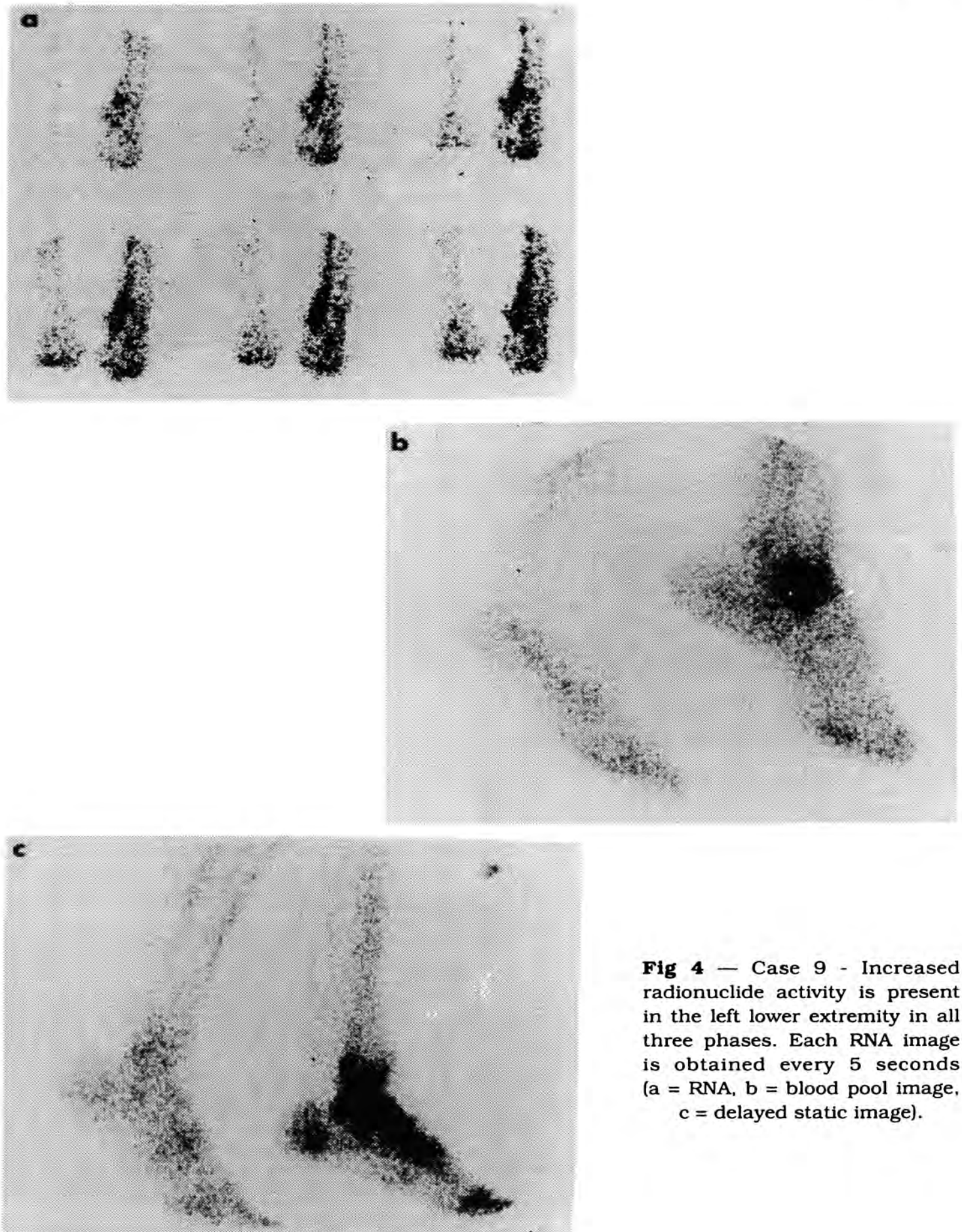
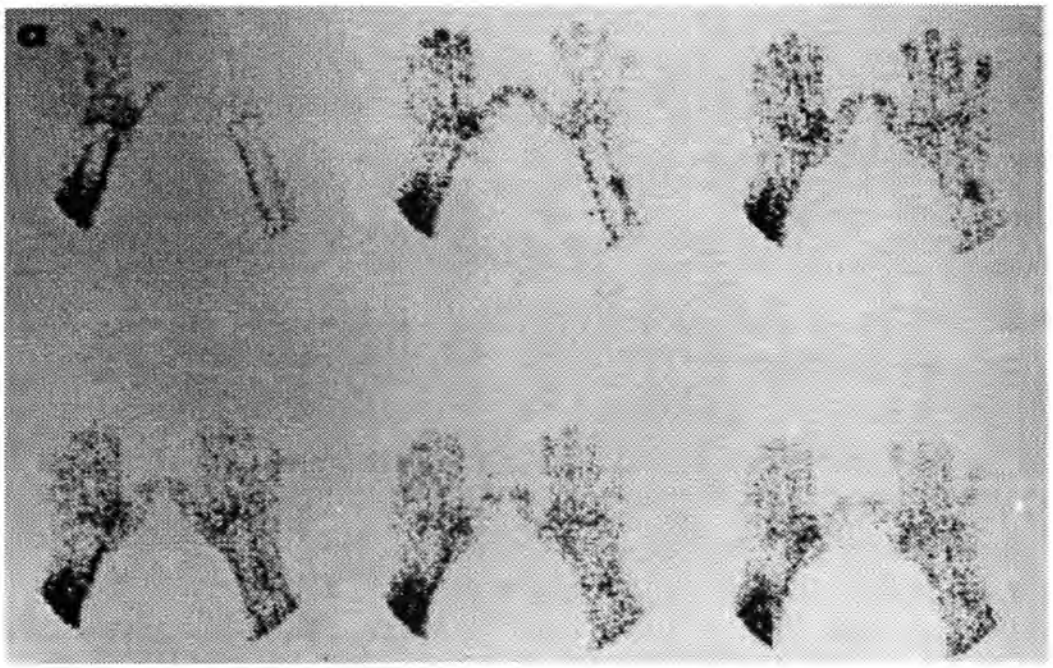
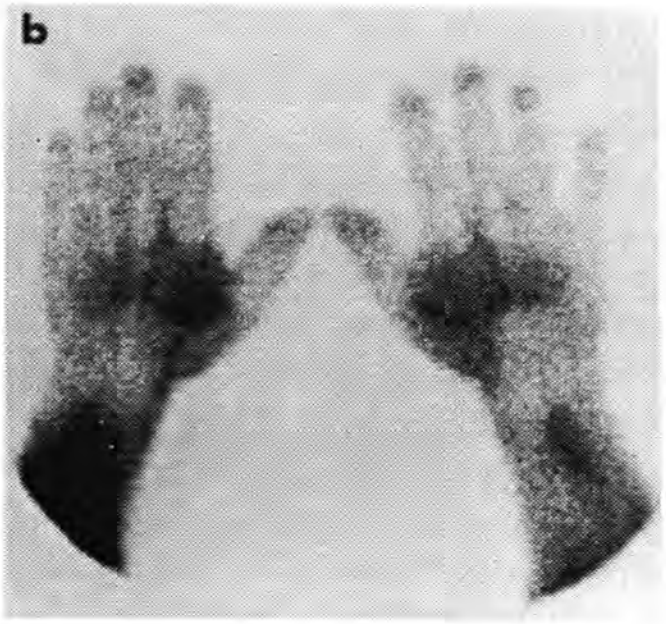


Fig 4 — Case 9 - Increased radionuclide activity is present in the left lower extremity in all three phases. Each RNA image is obtained every 5 seconds (a = RNA, b = blood pool image, c = delayed static image).





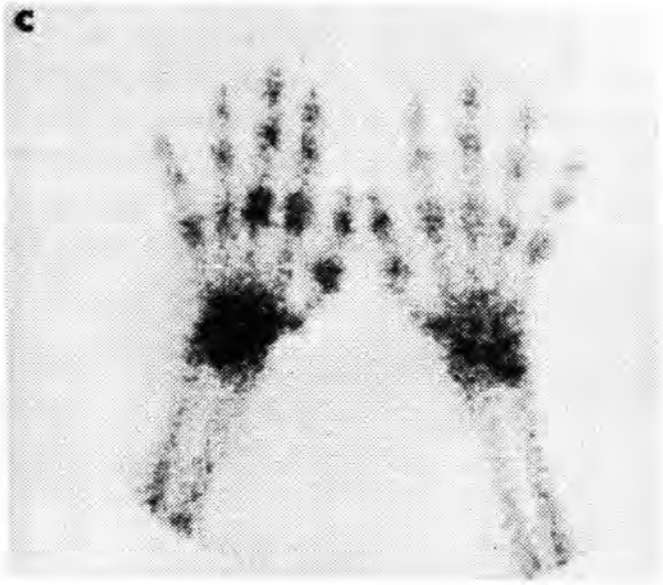


Fig. 5 — Case 12 - Increased radionuclide activity in all three phases on the right hand. Each RNA image is taken every 5 seconds (a = RNA, b = blood pool image, c = delayed static image). Thumbs are medial on all images.

approximating the median nerve distribution (especially in RNA images). With the use of a volar wrist splint and non-steroidal anti-inflammatory agents, the symptoms and signs improved significantly, and surgery was not required. Six months later, a repeat TPBS was normal.

Discussion

Weir Mitchell provided the first detailed description of causalgia following major traumatic nerve injury[5]. Over the years, a number of terms have been used to describe a similar syndrome that is seen in association with less severe forms of limb trauma or in various disease states (Table 2). These share in common the findings of severe pain (usually burning in character), vasomotor, sudomotor, dystrophic skin and nail changes. Currently, the term reflex sympathetic dystrophy is the most frequently used term to describe these condition[3]. Some authors feel one can distinguish between causalgia and RSD, in that causalgia only follows major trauma to a large peripheral nerve; in the absence of such trauma, the term RSD is use[1,2]. We and others[32,33] believe this distinction is somewhat artificial and in our clinic the terms are used interchangeably.

The diagnosis of RSD is sometimes overlooked, especially if all of the symptoms and signs are not present. The TPBS has been shown to be a helpful tool in substantiating the diagnosis of RSD[11-21]. In these earlier descriptions of the TPBS in RSD, the inciting cause is often not mentioned[11,18,19,21]. When the presumed etiology is described, the most common causes are trauma, fracture, idiopathic, or cerebral vascular accident[12,15-17].

Our cases indicate that RSD can occur in the setting of non-traumatic peripheral neuropathies including mononeuropathy, mononeuritis multiplex, plexopathy, and radiculopathy. While it may seem surprising, only a few prior reports have addressed the association of RSD due to abnormalities of the peripheral nerves or roots not due to trauma[6-9,13]. There have only been two well described cases of RSD with an abnormal TPBS in which the cause of RSD was presumed to be a peripheral nerve injury not due to a traumatic event[6,13]. In both of these cases, the RSD was due to lumbosacral root compression. Kozin and colleagues refer to several patients who had RSD with nerve injury secondary to fractures[14], but no details are provided.

In each of our 12 cases, all phases of the TPBS were abnormal, revealing increased blood flow and bone uptake of the technetium radionuclide in the involved extremity. Previous studies have indicated that the TPBS is not always abnormal in RSD[14,15,18,19,22-25]. In these studies, the sensitivity of the TPBS ranged from as low as 24%[23] to as high as 96%[19]. However, what distinguishes our cases is that all had significant peripheral nerve or root damage, presumably the

precipitant for the RSD. Indeed, in the series with the lowest sensitivity for the TPBS of 50%, Werner and colleagues retrospectively reviewed the records of patients who had been evaluated for "nonspecific upper extremity pain"[24]. Our population of patients was much more selective.

The other feature all of our patients had in common was that the TPBSs were done from 1 to 6 months after the onset of RSD, which is relatively early in the course.

Therefore, we feel that an abnormal TPBS is a useful test for confirming the clinical diagnosis of RSD which has occurred in the setting of an underlying peripheral neuropathy when the RSD symptoms have been present for six months or less. Some physicians are reluctant to make the diagnosis of RSD in incomplete cases, in which there are not abnormalities in all three aspects of color, temperature, and sweating change. Only four of our cases had abnormalities in all three of these clinical areas (Table 5). In the series by Kozin and coworkers, patients with "definite" RSD were more likely to have an abnormal TPBS than "probable" RSD patients[14]. All of our "definite" and "probable" patients had an abnormal TPBS, and again, this may be due to the fact that all had a significant peripheral nerve injury, documented by EMG/NCS. Thus, the TPBS can be a useful tool to support the diagnosis of RSD in "incomplete" cases, especially when there is documented damage to peripheral nerves.

It is also important to note that the TPBS is a procedure that can be easily performed in any hospital with a division of nuclear medicine. Indeed, when a standard technetium bone scan is done, the same techniques are used. The only difference is that images are taken immediately in order to obtain the phase 1 and 2 images. When a standard bone scan is performed in order to detect bone metastatic tumor, after a patient is injected with technetium the RNA and blood pool images are not obtained and only the delayed static (phase 3) image is taken several hours later. Thus, no new technology needs to be obtained in order to perform the TPBS. Recent studies from the Mayo Clinic have demonstrated that resting sweat output and the quantitative submotor axon reflex test are both frequently abnormal in RSD[23]. However, these sophisticated tests of autonomic dysfunction are not routinely available to most physicians.

With regard to classifying RSD cases by stage, traditionally it is taught that in the early stages of RSD (stage 1 of Bonica) the involved extremity is red, dry, and warm, presumably due to under-activity of the sympathetic nervous system. In this paradigm, after a period of time, usually months, the extremity becomes cool, pale or grey or cyanotic, and sweaty, consistent with sympathetic nervous system over-activity. In this second stage, "dystrophic" skin and nail changes may occur, with hair loss and brittle, grooved nails. In the third "atrophic" RSD

stage which occurs months or years later, there is significant atrophy of muscle and subcutaneous fat, and the skin becomes smooth, glossy and shiny. The signs of sympathetic nervous system over-activity remain present.

Our cases defy these evolutionary changes. A patient with features of stage 2 RSD was seen after only one month (case 2) of symptoms, and a patient had stage 1 RSD signs when examined after five months (case 5). In addition, often the change in sweating did not correlate with the color or temperature changes, making the stage indeterminate. Thus, in case 1, the temperature was decreased (suggesting stage 2), and the sweating was decreased (suggesting stage 1). Likewise, in case 5, the color and temperature suggested stage 1 RSD, but the increased sweating suggested stage 2. Such inconsistencies in skin blood flow and temperature, and lack of correlation between length of symptoms and temperature, have been documented by others[4,34,35]. In addition, we found it quite difficult and very subjective to determine when the patient entered the atrophic stage 3, and therefore we did not use this in our staging criteria.

It has been suggested that increased blood flow activity when measured with a technetium tracer or doppler laser flowmetry may be observed more often early in RSD[10,24,26], presumably correlating with decreased sympathetic activity and thus increased blood flow. While all of our patients had the TPBS within six months of symptom onset, the TPBS changes did not readily correspond to the clinical features. All seven of our patients with stage 2 RSD had abnormalities in all three phases of the TPBS, and eight patients with decreased skin temperature also had an abnormal TPBS. Thus, while all patients may have had early RSD based on the time course and TPBS findings, the clinical findings did not necessarily reflect early RSD. For all of these reasons, we no longer find it useful to classify patients according to clinical stages.

A diagnosis of RSD in association with a neuropathy may influence therapy. An attempt should first be made to treat the underlying neuropathy if the cause is known. In a recent report by Grundberg and Reagan[9], RSD was reported in the setting of carpal tunnel syndrome, cubital tunnel syndrome, and cervical radiculopathy. Then the appropriate nerve or root was surgically decompressed, the RSD resolved or improved significantly. Fitzcharles and Esdaile[8] described three cases of carpal tunnel syndrome and RSD: two improved with oral steroid therapy, and one improved after surgical decompression. Cases of lumbar radiculopathy and RSD have improved after surgical decompression[6,13]. Our cases of RSD with carpal tunnel syndrome and lumbar radiculopathy improved with more conservative therapy and surgery was not needed.

If directly treating the cause for the neuropathy is unsuccessful, or if the cause is not known, therapy directed toward the RSD should be addressed.

Therapy can involve sympatholytic or non-specific approaches (Table 6). The standard form of therapy for severe RSD has been the use of temporary or permanent sympathetic ganglion blocks[36-38]. A variety of intravenous sympatholytic medications have also been reported to be useful including regional guanethidine or reserpine[37,39], or intravenous phentolamine[40]. Oral drugs such as propranolol[41], nifedipine[42], prednisone[14], phenoxybenzamine[43], and prazosin[44] are all reported to improve the pain. In addition, clonidine skin patches[45] and intranasal calcitonin have been beneficial in some patients[46]. Kozin and co-workers reported that if the TPBS is abnormal in clinically suspected RSD, the patients are more likely to respond to treatment with a short course of prednisone[14]. All of our patients who received this steroid regimen and intravenous regional bretylium and lidocaine[47] had at least partial pain relief. Ganglion blocks were used initially with steroids if the pain was particularly severe, or used later if the response to steroids was incomplete. Six of our twelve patients received a temporary sympathetic ganglion block and five had a reduction in pain, although often a series of 3 to 4 blocks was necessary. No permanent chemical or surgical sympathetic ablations were done. Recently, intrathecal morphine was shown to benefit some patients with intractable chronic RSD[48].

Table 6 — Therapies for RSD

Specific sympatholytic therapies:
Sympatholytic ganglion block
Paravertebral epidural
Regional guanethidine or reserpine
Intravenous phentolamine
Surgical sympathectomy
Propranolol
Phenoxybenzamine
Clonidine
Other therapies:
Prednisone
Intravenous regional bretylium and lidocaine
Non-steroidal anti-inflammatory medications
Nifedipine
Tricyclic antidepressants
Calcitonin
Narcotics
Transcutaneous nerve stimulation
Physical therapy

Although helpful in establishing a diagnosis, the TPBS results leave many unanswered questions as to the etiology and pathogenesis of RSD. Increased blood flow to the involved extremity was present in all of our cases, whether or not the extremity was cool and pale, or warm and red. RSD, especially those cases with features of stage 2 and 3, is thought to be due to sympathetic over-activity, and this is based largely on the therapeutic response to sympathetic blocks[2]. A number of peripheral[1,3,26,36,37,49-52] and central[3,37,50,52-55] mechanisms have been hypothesized to explain this presumed increased sympathetic activity, which results in an increased alpha-adrenergic output and vasoconstriction. However, the increased blood flow on TPBS would seem to be at variance with the concept of increased sympathetic activity. Perhaps the increased blood flow and bone uptake is due to the action of local hormonal or chemical factors, such as prostaglandins, substance P, calcitonin gene-related peptide, or histamine, all which can be found at the site of tissue injury[26,56,57], and can exacerbate pain. On the other hand, the increased technetium activity seen on the initial 2 phases of the TPBS may not be reflective of the sympathetic activity at the superficial skin level, and may reflect increased flow to deeper vasculature in the muscles and bone. While this could explain why a patient with a cool, pale extremity could have increased flow on the early TPBS images, it still would not explain why flow to deeper structures would be increased in a presumed hyperadrenergic state unless other factors were involved.

Indeed, the frequent inconsistency between the clinical findings of color, temperature, and sweating changes puts into question whether RSD is in fact due to an over-active sympathetic nervous system. Such speculation has been raised by others as well[26,32,33]. Some patients with RSD do not improve with sympathetic ganglionic blocks[32], other patients obtain pain relief independent of sympathetic nervous system interruption[58], and the degree of pain relief does not correlate with the extent of sympathetic blockade[59]. Bej and Schwartzman[60] found that RSD affected limbs actually had increased blood flow compared to the contralateral extremity during the Valsalva maneuver and cold pressor test. More recently, Drummond and co-workers[35] found that plasma concentration of noradrenaline was actually lower in the painful affected extremity with RSD compared to the contralateral side. These investigators hypothesized that their findings could imply a supersensitivity to sympathetic neurotransmitters, but this has yet to be confirmed. However, their biochemical findings would be consistent with the increased activity of the TPBS in our patients. Interestingly, in a novel animal model that may simulate RSD, Wakisaka and colleagues[61] found that after nerve constriction injury, at a time when skin temperature was decreased, catecholamine levels were absent. Findings such as these in both human and animal models raise questions about the role of an over-active sympathetic nervous system in RSD and other neuropathic pain syndromes.

It may be that in patients with the clinical presentation of "reflex sympathetic dystrophy", the pathophysiology may be sympathetically-mediated in some, and sympathetically-independent in others[33]. In this regard, a recently established consensus definition of RSD clearly avoids implicating pathophysiologic mechanisms, but is primarily descriptive and operational[62].

Conclusions

1. The RSD syndrome can occur in the setting of non-traumatic diseases of the peripheral nervous system at the root, plexus, and peripheral nerve level.

2. The three-phase bone scan will be abnormal in such cases when performed within six months of pain onset and will show an increased technetium flow to the limb and uptake in the bone in all three phases.

3. It is difficult to classify patients into RSD stages based on time course, color, temperature, and sweating change, as these features often do not correlate with one another. In addition, these factors do not correlate with the finding of increased flow on the TPBS. Therefore, we do not believe that attempting to categorize patients into RSD "stages" is clinically useful.

4. Since the TPBS in our patients all showed increased activity, this puts into question the role of an over-active peripheral sympathetic nervous system in the pathophysiology of RSD, and supports the findings by others of decreased plasma catecholamine concentration in RSD affected limbs as reported recently in both human RSD 31 and animal models of painful nerve injuries[61].

5. While the mechanism underlying RSD still requires further elucidation, in clinical practice, an abnormal TPBS can be of great value in supporting the diagnosis of RSD in the setting of an underlying peripheral neuropathy.

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Early Responsiveness of Ocular Symptoms of Myasthenia Gravis with Plasma Exchange

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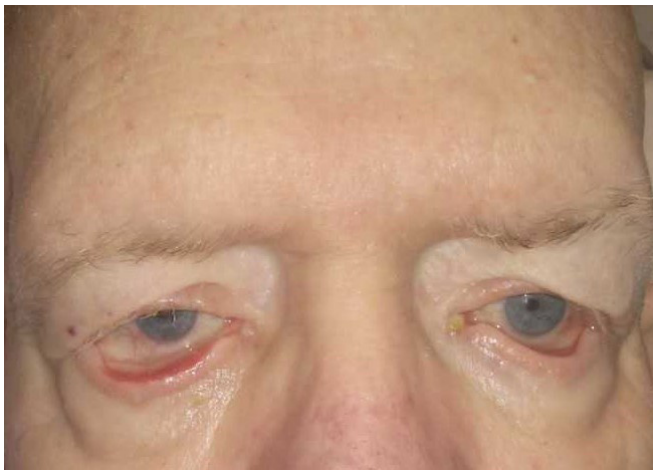
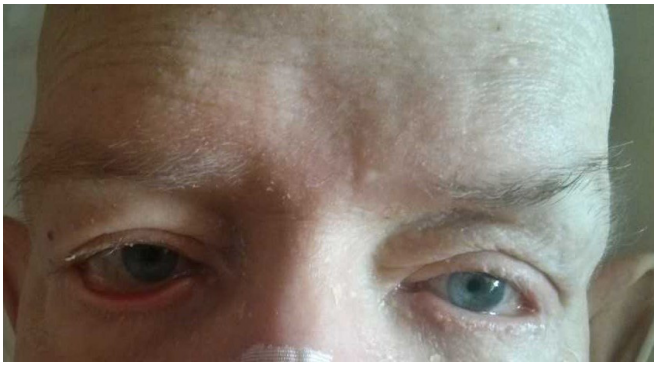
70-year-old male presented with generalized weakness, fatigue, ptosis with dysphagia and slurred speech. On exam patient had fatigable ptosis (figure 1), positive Cogan's sign, and fatigable arm weakness. Low frequency repetitive nerve stimulation of the ulnar nerve showed significant decrement. His acetylcholine receptor binding antibody was elevated (not available at the time of treatment, patients' value was 0.5nmol/L, normal less than 0.02nmol/L). He was started on plasma exchange with significant improvement in ptosis with the third exchange (day 5) although he continued to have fatigable arm weakness, dysphagia and slurred speech. Eye signs are the earliest to respond early to plasma exchange especially among older seropositive patients and can be an indicator for treatment responsiveness.[1]





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