Q&A Panel

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Dr. GG deFiebre: [00:00:05] Hi, everyone. Welcome to the Q & A panel for the pre-RNDS. I'm very pleased to be joined by Drs. Pardo, Flanagan, Michael, and Smith for this session. So, thank you for joining us and for your talks earlier today. We really appreciate it. So yeah, thank you. To jump into questions, we've gotten a lot of questions today. Dr. Flanagan how common is it to have only sensory changes in transverse myelitis? This person has lesions between C5 and C6. And mainly just has sensory changes. Is this something we see frequently?

Dr. Eoin P. Flanagan: [00:00:43] Well, yeah it is something we can see particularly with myelitis from multiple sclerosis. We will see where they just have numbness and tingling but don't get as much weakness, so bowel and bladder impairment. So sometimes you can have milder cases of myelitis just involving the sensory tracks. So, we can see that. We see it less frequently with the aquaporin-4 MOG antibodies where usually patients are weak and have bowel and bladder impairment too.

Dr. GG deFiebre: [00:01:10] Got it. And then Dr. Pardo, do you mind talking a little bit about myelitis of paraneoplastic origin? This person was told that it's very, very rare. Just interested more about how and why tumors would cause issues in the central nervous system.

Dr. Carlos A. Pardo: [00:01:30] Yeah, that's a very interesting question. In the past 10 years or more, we have been paying more and more attention to the long-term consequence of cancer in the brain and spinal cord and among those, myelitis associated with cancer. Paraneoplastic disorders are basically remote effects of cancer that produced manifestations in brain and spinal cord because the new response that the cancer may trigger, and sometimes that response may produce injury damage of the brain or spinal cord is mostly frequently seen in brain problems. Mostly paraneoplastic disorder that produce problems like encephalitis or other type of manifestations. It's very rare in the spinal cord. In my experience, we have seen only few cases of remote effect of cancer in the spinal cord as a paraneoplastic disorder. And again, we always need to pay attention to that, but that is unfortunately it's a very frequent problem associated with cancer. In women, cancer associated with breast carcinomas and in men testicular carcinomas and monster carcinomas frequently produce paraneoplastic disorders. Probably my colleague, Dr. Flanagan, who is in a center who

sees a lot of paraneoplastic disorder because they have a very good system to tracking down paraneoplastic disorders in the spinal cord. I'm not sure if your experience with paraneoplastic disorders is the same or is different to what we see here at John Hopkins.

Dr. Eoin P. Flanagan: [00:03:23] Now, I think it's similar. Yeah, it's very rare compared to sarcoidosis or aquaporin-4 MOG much, much less common, but it does occur, and when it occurs it's usually pretty severe and can be difficult to treat. The problem is a lot of times the patients present initially with the symptoms of myelitis or spinal cord dysfunction with paralysis and sensory symptoms, and they don't know they have the cancer. And sometimes the neurologists need to think to order those antibody tests or to look in the body for cancer. So, it's important if a patient has a myelitis and nobody knows what the cause is, it's an important one to look for. But still very rare so similar experience.

Dr. GG deFiebre: [00:04:03] And that as a follow up, would this type of myelitis be treated with anti-relapse medications or if once the kind of cancer is treated, is it then safe to assume that there wouldn't be a relapse?

Dr. Carlos A. Pardo: [00:04:15] The rule of thumb in paraneoplastic disorders is to treat the cancer. If you are able to identify the cancer obviously, either chemotherapy, radiation therapy or surgical resection is the way to go. And obviously other immunological avenues are, annual to treat this type of disorder. I don't know Eoin, what do you think about other treatments?

Dr. Eoin P. Flanagan: [00:04:43] Yeah, I think we use similar. We'll use them steroids or plasma exchange sometimes acutely in these patients. We don't tend to use as much long-term preventative treatment because sometimes they're just a one off and we treat the cancer, but they are difficult to treat. So, we don't get as good a response with those as we do with some of the other conditions to treatment.

Dr. GG deFiebre: [00:05:07] Thank you. And then Dr. Smith, someone asked during a MOG attack they had a seizure and were given a diagnosis of meningitis. Is there likelihood that this might be autoimmune encephalitis instead. And what's the difference between these two?

Dr. Tammy Smith: [00:05:24] I'm sorry, your sound actually cut out for a second. But what I understood was that they had a seizure during a MOG attack and that there was a question about whether this could also be a sign of autoimmune encephalitis, is that right?

Dr. GG deFiebre: [00:05:37] Yes. So, they got a diagnosis of aseptic meningitis and so they're wondering about autoimmune encephalitis potentially being a diagnosis instead. And what the differences between them.

Dr. Tammy Smith: [00:05:47] Yeah. I would say in our experience MOG attacks can often come with seizures, especially if there's a large amount of like an HM type involvement. If it was just an optic myelitis or transverse myelitis less so. So aseptic meningitis in this case just means an inflammation of the tissue around the brain that's not caused by something that's infectious. So that's why it's a septic. And so, an antibody mediated process could be consistent with an aseptic meningitis as well. I would say it's certainly reasonable if there was no inflammation seen in the brain on imaging at that time, despite the MOG antibody and the seizures being new to look for any other causes that could be autoimmune mediated. But if there was inflammation seen in the brain on imaging in association with the MOG attack then it seems fairly consistent with a MOG attack.

Dr. GG deFiebre: [00:06:48] Thank you. And then Dr. Levy, we had a question about if we know this the main causes of premature death in those who have recovered from one of these rare neuroimmune disorders. Their

increased risk of certain things like cancer or increased risk of infection due to something like a pressure sore. Is there any ongoing monitoring that so much to do to kind of prevent this?

Dr. Michael Levy: [00:07:14] Yeah. I think the most severe of the neuro immunological diseases is neuromyelitis optica and we profiled this specific disease population among patients who live in the mid-Atlantic from New York to Washington DC. And we profiled and characterized the cause of death in 30 patients over the previous seven years or so. And there were 30 deaths. Nearly all of them were due to a severe recent attack in the cervical cord or in the lower brain stem in areas that control swallowing and breathing. And those were the major issues because people even after they recovered from that one lesion in the next year or so, they were at very high risk of some sort of infection from that previous attack. Usually related to swallowing and inhaling swallowed contents, things like that. From transverse myelitis, the only complications I've seen recently are related to blood clots from immobility and that can also be a cause of death and MOG they're very, very few deaths. And I don't have a good sense yet of what people are at risk for.

Dr. GG deFiebre: [00:08:31] Thank you. And then Dr. Flanagan kind of related back to cancer again. Does using immunosuppressant treatment make someone more susceptible to developing cancer because of the suppression of the immune system?

Dr. Eoin P. Flanagan: [00:08:44] And that's a good question and a theoretical question. There are certain cancers that we know or some certain medications that can increase the risk of blood cell cancers. So, for example mycophenolate and if you use them for a long time like 5, 10 years they can result in blood cell cancers. So, we get a little bit concerned when we're using them for long periods of time. With the other immune medications, there's some theoretical risk because your immune system is interesting in that it fights off infections, but it also goes around your body and make sure that there's no abnormally growing cells or cancer is forming, and it helps clear those out. So, there's a theoretical risk. But most of the time the immunosuppressants really the benefit far outweighs the risk. So, it's not really a reason not to treat some of these conditions which can be very severe, but it is something we monitor particularly for the mycophenolate and azathioprine.

Dr. GG deFiebre: [00:09:44] And then Dr. Pardo. So, we got a question that given that HM or transverse myelitis with encephalopathy is very rare in adults. What is that a smaller kind of non-specialty medical center could get consultation without having to travel there? Is there things that patients can do to kind of get a consult in that way?

Dr. Carlos A. Pardo: [00:10:08] Yeah, actually it's an interesting question. During the pandemic, we learned to do all of these remote consultations and telemedicine assessment. Unfortunately, that is actually very difficult now because there are the restrictions that we were experiencing pre-pandemic are already re-implemented. So, in other words legally, there are very few opportunities to do telemedicine across the States. If you are in a state it's like Massachusetts you are very lucky to be very close to Dr. Levy or if you are near to all of places near to the major clinic it's very easy to go there but unfortunately you are at the mercy of other centers that have more expertise on this and I strongly recommend that you go to the SRNA website where there is a list state by state of all providers that are around the country that may provide consultations about encephalopathy myelitis, transverse myelitis, etcetera.

[00:11:17] So that's a very good resource but just to be more specific and more practical at least for giving you advice is when patients are dealing with a combination of encephalopathy or encephalitis plus myelitis, the clinician particularly the neurologist needs to be extremely careful to characterize what is going on. For example, during the summer we deal with viruses particularly West Nile virus for example that may have

the potential to produce that combination of problems. Again, so it depends in what state you are located and if you have difficulties finding a good provider actually, please feel free of sending information to the SRNA and they can give you some guidance where to find providers that may provide remote consultation. Remember sometimes in the medical practice we are subject to legal aspects of that legal practice and that unfortunately limit the possibility to provide specific advice. But we are able to help you and give some guidance if you contact the SRNA website.

Dr. GG deFiebre: [00:12:26] Yes, thank you Dr. Pardo. If you need help finding a provider you can certainly reach out, we can try to point them in the right direction. And then Dr. Smith got a question about this person tested negative for aquaporin-4 both there after a lumbar puncture and there's spinal fluid and also in their blood test. Can someone still have NMO even if they are negative for this antibody and if their clinical features match and what is kind of thinking about treatments and the causes of double negative NMO. Hopefully I've not been cut out.

Dr. Tammy Smith: [00:13:04] No, that was great. Sorry. Thank you for that question. Yeah, so there are clinical criteria for the diagnosis of NMO, NMOSD in the absence of a positive antibody for aquaporin-4 so those are called the Wingerchuk criteria. And clinicians can use those to diagnose someone with NMOSD even in the absence of a positive aquaporin-4 test. One other thing that's important to keep in mind whenever an antibody test is ordered, is that not all antibody tests for aquaporin-4 are the same. So, some reference laboratories will still run a specific kind of test called an Eliza. That's not a very good test for aquaporin-4 and aquaporin-4 should really always be tested using a cell-based assay. So, it's important to know what kind of testing was done on your samples but you can absolutely be diagnosed with NMOSD in the absence of a positive aquaporin-4 antibody. Now the clinical trials for NMOSD, different trials for those FDA approved medications, some of them allowed for aquaporin-4 positive and negative patients and others allowed only for aquaporin-4 positive patients, but we often employ very similar medications and treatments as we would for a seropositive patient in those cases.

Dr. GG deFiebre: [00:14:34] Thank you for that overview. And then Dr. Levy do we know if people are born MOG and or aquaporin-4 positive or is this something that is thought to develop over someone's lifetime? And why do we think this might happen as a genetic, environmental a combination?

Dr. Michael Levy: [00:14:53] I don't think people are born with it, but I think people maybe predisposed to it genetically. And that's especially true with aquaporin-4 where we see auto immunity that runs not only in the families but coexisting auto immunity within the patient. So, I think that there is some risk factor there, but I can't quantify it. I don't know what it is. We've looked for a long time. The truth is you can find NMO in many, many different populations around the world even in many disparate genetic groups. So, there's no single gene that predisposes to it, but it does seem to run in auto immunity in general. Now, MOG is a little bit different in that regard because we don't see a lot of overlapping auto immunity. And so, I don't know what causes that either. We still don't even have patient families with two or more people affected with MOG. We're running tests in the lab to look at reactivity dependent on background genetics and so far, it doesn't seem to be dependent on genetics, there's still more work to be done but that's at least my preliminary hypothesis.

Dr. GG deFiebre: [00:16:16] Great thank you. And then Dr. Flanagan acute attack, why do some people make a spontaneous recovery while others do not? Do we know why that happens?

Dr. Eoin P. Flanagan: [00:16:30] It's hard to know. Yeah, we don't know why. We know what the different diseases that cause myelitis that there can be differences in outcome. For example, the aquaporin-4 antibody, positive NMOSD tends to have a worse outcome and it may also depend on what type of treatment you

get. In general, what we're seeing more and more with the aquaporin-4 antibody myelitis is that the plasma exchange seems to be very effective and the earlier the better. If you do have an acute attack, you really want to be pushing to see if you can potentially get this plasma exchange treatment because it can really impact the recovery. So, there are some factors like that and with the MOG antibody the recovery tends to be a little bit better and then with MS it tends to be milder with better recovery too. So, it depends a little bit on the type of disease. There may also be other factors like racial factors. I know Dr. Levy has done some studies showing that African Americans can have a worse outcome and we don't know the exact reasons behind that. But it does highlight the importance of really trying to treat those patients and aggressively too.

Dr. GG deFiebre: [00:17:37] Thank you. And then Dr. Pardo what causes or influences someone with seropositive NMO to then turn into seronegative after the attack or sometime after treatments?

Dr. Carlos A. Pardo: [00:17:50] I'm sorry, I missed the last part of the question. So, do you mind repeating again?

Dr. GG deFiebre: [00:17:58] What causes or influences someone who might be seropositive, so they have the aquaporin-4 antibody then becomes seronegative? Does this happen after events after time or when do we see this happening?

Dr. Carlos A. Pardo: [00:18:14] Let me see if I understood correctly the question is patients that are seropositive and then turn to seronegative. So, I assume that is mostly because the treatment that was implemented and obviously either plasma change or interventions with immunosuppressive medication probably will decrease the reactivity of those antibodies. But I don't know Dr. Levy may have more experience on this, Michael.

Dr. Michael Levy: [00:18:45] Yeah. With aquaporin-4 it's very rare to lose seropositivity. We've seen it a couple of times and I'm always skeptical when patients say it to me and then they show it to me and I'm like, "I still don't know if I believe that or not." But with MOG, we do see it quite a bit. We tend to see it when the disease remains quiet for years, maybe 3, 4, 5 years and no relapses even with treatment, as long as there's no disease activity, then the MOG antibody tends to go away, and we think that that's associated with a lower risk of relapse.

Dr. Carlos A. Pardo: [00:19:24] So, there is one important aspect, and this question actually is bringing a very important question that I will ask every participant in this round table is in the neurology is very infrequent to follow antibody tires as an outcome measure of the disease activity. I think that as neurologists probably we relate mostly on the clinical situation where the antibody tires and I will open the door for Tammy, Michael, and Eoin to give their opinion about this because this is important for patients and family to understand.

Dr. Tammy Smith: [00:20:04] Yeah, I totally agree that following the titers doesn't routinely make sense. I think clinicians sometimes do it to try to reassure themselves that they're having some kind of an outcome but with the treatments that they're pursuing but really the antibody tighter does not necessarily match the clinical picture. And so, it can be very misleading.

Dr. Michael Levy: [00:20:26] Yeah, I only use it in a supportive role. If patients are truly in remission for years and years, they want to come off of treatment. It's worth looking to just get that confirmation that things really have quieted down and then I feel more comfortable taking them off medications.

Dr. Eoin P. Flanagan: [00:20:41] Yeah, I agree completely with all of that. And I think all the studies that have been done that have looked to follow the antibodies, it's very variable how it goes over time. So, I think you're much better off following clinically.

Dr. GG deFiebre: [00:20:55] Thank you. And so, we're at the end of our time. I just wanted to open up any kind of last thoughts or comments before we end.

Dr. Eoin P. Flanagan: [00:21:04] I would say thank you to all the participants who are involved in research who have really helped us learn a lot about these diseases and we really have a lot of good treatments coming. So, I think the future is bright for all of them.

Dr. Michael Levy: [00:21:16] Thanks to the SRNA for enabling that research.

Dr. Tammy Smith: [00:21:22] Thanks for inviting me and it's great to see patients who are interested in learning more about their disease and participating in their care. It's really a great thing to be a part of. Thank you.

Dr. Carlos A. Pardo: [00:21:33] And I will say thank you to all families and patients every time that you agree on participating in research you are contributing only to our understanding of the disease, but you are helping many many, dozens of people with all of these diseases. And participation research is extremely critical for understanding a disease and obviously for creating and establishing new treatment. So, thank you for participating in research.

Dr. GG deFiebre: [00:22:00] And thank all of you so much for your talks today and for joining for the Q & A. We really appreciate it. So, thank you.