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Gabrielle deFiebre: [00:00:00] Hello everyone and welcome to the SRNA Ask the Expert podcast series. Today's podcast is entitled Newly Diagnosed with a Rare Neuroimmune Disorder: What You Need to Know. My name is GG deFiebre, and I will be moderating this podcast. SRNA is a nonprofit focused on support, education, and research of rare neuroimmune disorders. You can learn more about us on our website at wearesrna.org.

[00:00:25] This podcast is being recorded and will be made available on the SRNA website and for download via iTunes. During the call. If you have any additional questions, you can send a message through the chat option available with GoToWebinar.

[00:00:39] Our 2020 Ask the Expert podcast series are sponsored in part by Alexion and Genentech. Alexion is a global biopharmaceutical company focused on serving patients with severe and rare disorders through the innovation, development, and commercialization of life-transforming therapeutic products. Their goal is to deliver medical breakthroughs where none currently exist, and they are committed to ensuring that patient perspective and community engagement is always at the forefront of their work.

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[00:01:29] For today's podcast, we are pleased to be joined by Dr. Ram Narayan and Dr. Olwen Murphy. Dr. Narayan is an Assistant Professor of Neurology, Division of Neuroimmunology at the Barrow Neurological Institute in Phoenix, Arizona. He also co-directs the Demyelinating Disorders Clinic at The Phoenix Children's Hospital, which offers patient care in the areas of multiple sclerosis and related neuroimmune disorders to children in the Southwest region. Dr. Narayan received his medical degree at PSG Institute of Medical Sciences and Research and completed a neurology residency at the University of Texas Southwestern Medical Center and a multi-institution neuroimmunology fellowship at UT Southwestern and The Johns Hopkins University.

[00:02:13] Olwen Murphy received her medical degree from University College Dublin in Dublin, Ireland and completed a neurology residency at The Royal College of Physicians in Ireland. Dr. Murphy was a James T. Lubin fellow at The Johns Hopkins Transverse Myelitis Center in Baltimore under the mentorship of Dr. Carlos Pardo. Dr. Murphy's research was on predicting outcomes after a diagnosis of transverse myelitis using current imaging techniques and spinal fluid analysis. The goal of the research project was to identify patterns or biomarkers that can be used in day-to-day clinical practice to identify benefits from therapies and help make better decisions about care.

[00:02:50] Welcome and thank you both so much for joining us today.

Dr. Olwen Murphy: [00:02:53] Thank you. I'm happy to be here.

Dr. Ram Narayan: [00:02:56] Yeah, thanks a lot for the SRNA for having us here.

Gabrielle deFiebre: [00:03:00] Great, thank you. So to start, Dr. Narayan, would you mind just kind of briefly just defining or describing, you know, what it is we mean when we say a rare neuroimmune disorder?

Dr. Ram Narayan: [00:03:11] Yeah, that's a very interesting question. So, I guess this is one of the first few podcasts after the TMA was renamed as the SRNA, and so I think it's very important to define and know what a rare neuroimmune disorder is. First of all, I tell you that I don't know if there is an actual definition.

[00:03:31] But we can define a rare neuroimmune disorder based on a few things. So first of all, these are rare autoimmune conditions that affect different components of the nervous system. And now, as a scale, to what we consider as rare, for instance, the incidence of MS. The prevalence of MS is about a hundred patients per 100,000 patients, 100,000 general individuals in the community, for example.

[00:04:03] So for every thousand individuals, you have one patient with MS. Whereas, on that scale, a rare neuroimmune disorder would be, the prevalence of that would be somewhere around one to ten in 100,000. So it is about a hundred times less common than multiple sclerosis, which is the classic neuroimmune disorder that, the more common, more classic neuroimmune disorder that is well known.

[00:04:34] And these disorders typically include conditions like acute disseminated encephalomyelitis, also called ADEM; there are some forms of optic neuritis; transverse myelitis; we would like to call them as myelopathies or immune-mediated myelopathies; neuromyelitis optica spectrum disorders, NMOSD; the more recently described, the MOG syndrome, the expanded form of that is myelin oligodendrocyte glycoprotein syndrome. And besides that, there are other conditions like neurosarcoidosis, Susac syndrome, CNS vasculitis, IgG-4 related disease, etc.

Gabrielle deFiebre: [00:05:17] Okay, great. Thank you. I think it was a really good overview. And then, you know, so if... What, for these disorders, you know, what are the most common initial symptoms someone might experience when they're having the initial attack of one of these disorders? Dr. Murphy?

Dr. Olwen Murphy: [00:05:36] Sure. Well, I think Ram summarized very well what these types of disorders are. And one of the commonalities between these disorders is that the symptoms can be quite similar even in these different disorders, whether it's MOG or neuromyelitis optica or transverse myelitis. And that's because the root problem really is inflammation occurring in the central nervous system.

[00:06:00] And so the symptoms that that causes really depends on the location of that inflammation. There's a couple of common areas affected. One would be the optic nerve. So that is the nerve that comes out of the brain and supplies the visual pathway to the eye. So this can be commonly affected in M.O.G. - MOG disorders - and neuromyelitis optica in particular.

[00:06:23] And that might manifest with impaired vision, blurring of vision, sometimes pain when moving the eye, or other visual symptoms. Other manifestations of inflammation in different parts of the central nervous system will vary as well. So inflammation in the spinal cord, which can occur with most of these disorders, is often called myelitis or transverse myelitis, and that often manifests

with symptoms in the arms and legs because the nerves from the brain come down through the spinal cord to supply all of the functions of the arms and legs, whether that's strength, whether that's sensation. So common symptoms that people might report with inflammation in the spinal cord would be numbness, tingling, pins and needles of their limbs or their torso, and sometimes weakness, balance problems, difficulty walking.

[00:07:18] Another common symptom that people often don't realize relates to the spinal cord is problems with bladder function and bowel function. And then the final area that can kind of be affected with these disorders is the brain. And the symptoms that can relate to inflammation of the veins of the brain are quite varied depending on the location within the brain and how severe that inflammation is. So sometimes they can affect things like eye movements.

[00:07:46] People might report double vision, difficulty swallowing, difficulty moving their face. So sort of symptoms around the face and the head and neck. Or else if the inflammation is deep within the brain itself, it can actually affect people's consciousness and their cognitive functions. So people might be confused or have seizures for example, or report difficulty with finding the words or memory.

[00:08:12] And all of these symptoms in rare neuroimmune disorders tend to follow a similar pattern in terms of their development as well because inflammation in the nervous system tends to brew up over days and weeks. So typically when people experience any of these kinds of symptoms, whether it's from the optic nerve, the spinal cord, or the brain itself, the symptoms tend to evolve over a couple of days to a couple of weeks. That's not a strict cutoff, though. Some patients can experience a much quicker evolution of the symptoms, and in some patients, it can be a little slower. But really these disorders are sort of defined clinically, which is the manifestations that people feel and experience with them by the location of the inflammation.

Gabrielle deFiebre: [00:09:00] Great. Thank you so much. It was a really great overview. So if someone is experiencing some of these symptoms, you know, where do they generally go or where should they go? Is it something like an emergency room, a neurologist, their general practitioner or an urgent care center? What have you typically seen? Doctor Narayan.

Dr. Ram Narayan: [00:09:20] So I'm going to say, so that really depends on where a patient is located and what kind of access, do they have to a healthcare facility. So I would say, I mean, by default it's very important to go to the emergency room as early as possible, because timely diagnosis and timely institution of the correct treatment makes a lot of difference in long-term outcomes.

[00:09:49] But that said, there are, there are some parts of the United States where patients may not have access to a neurologist through an emergency room. So, in such cases, it's at least important to touch base with the primary care physician and take it from there.

[00:10:08] But I would say that there are times when we experience a lot of symptoms, particularly with neurological symptoms in the setting of, for example, a migraine, which is a transient phenomenon, which we don't have to worry about too much. If a symptom lasts for more than 24 hours, I would take that pretty seriously and go to, then go to an emergency room as soon as possible.

Gabrielle deFiebre: [00:10:38] Okay, great. Thank you. And then, so once someone presents to either the emergency room or their neurologist with these symptoms, how are these disorders diagnosed? Who makes the diagnosis and if you could just walk me through the diagnostic process, that would be great. Dr. Murphy?

Dr. Olwen Murphy: [00:10:58] Sure. So again, some of this depends on what exactly the problem is and how it presents with individual people. But a common pattern would be that somebody would attend the emergency room, for example, with a new symptom such as weakness in their arms and legs, or possibly visual loss.

[00:11:16] The specialists that they would see would depend on the symptom. Most commonly it would be a neurologist, but sometimes we see when patients just have inflammation of the optic nerve and visual loss, may be seen directly by an eye specialist. Either way, whichever specialist sees them will have some experience with those kinds of symptoms and hopefully these kinds of disorders and should follow sort of a pretty typical pathway of investigations.

[00:11:43] Common things that people could expect to experience during the initial sort of evaluation of symptoms like this would be an MRI scan. And that can be of the brain or the spinal cord. And then blood tests are typically taken to look for markers of infection, because at the early stage it's very difficult sometimes to make a diagnosis of a neuroimmune disorder, and all the possibilities have to be considered. We also have blood tests available now for certain types of these disorders. For example, antibody tests, which are proteins in the bloodstream that can be detected in MOG or NMO disorders. In some patients, a spinal tap can be required, which is similar to the type of procedure a woman might undergo during the delivery of a baby, an epidural procedure. And the procedure basically is that a needle is inserted, and some fluid is taken away from the bottom of the back surrounding the spinal cord. Sometimes running tests on that fluid in the lab can be very helpful to us in differentiating whether there's inflammation there or whether there's not inflammation there.

[00:12:56] So typically the neurologist or whoever the specialist is dealing with the patient will look at a range of tests. So that's the MRI scan, the blood test, potentially the spinal fluid. And also of course, take into consideration the clinical picture. So that's the story that the patient tells them and the examination findings. And putting all those things together may point in the direction of the rare neuroimmune disorder.

Gabrielle deFiebre: [00:13:26] Great. Thank you. And then, Dr. Narayan, is there a difference in how children are diagnosed versus adults?

Dr. Ram Narayan: [00:13:32] Yeah, I'm fortunate to have a dedicated clinic here for children with rare neuroimmune disorders, in addition to having another clinic for adults, a separate clinic for adults.

[00:13:47] And so I'm able to appreciate differences in their clinical presentations, the workup they get, the treatments, and also the outcomes for pretty much the same disorder. There can be quite a bit of differences. By and large, just like Dr. Murphy mentioned, the way we make the diagnosis is more or less the same: getting a careful history, clinical exam, blood work, spinal fluid studies, MRI, et cetera. I'd like to just point out a few differences though. So for example, in children, many times,

the level of alertness gets altered. We call that as encephalopathy. That can be a frequent manifestation in children. Seizures can sometimes be their only symptom.

[00:14:40] They would just come in with the first seizure of their life. That can be the very first symptom of a rare neuroimmune disorder. The other thing, the other very important point to make here is that there are certain conditions per se. For example, the MOG syndrome and acute flaccid myelitis, ADEM - these are much more common in the pediatric population than in the adult population. Another very important point to recognize, and this is something which is a learning curve for myself, because I'm primarily an adult-trained neurologist. So, one very important factor to recognize with children is that a lot of symptoms can be underreported by children or are misinterpreted by children. For example, visual symptoms, sensory symptoms, so numbness or tingling - these kinds of symptoms can sometimes be underreported or quickly dismissed by parents as being something relating to some kind of sport or some kind of activity in school, et cetera.

[00:15:59] So, and then the other thing is when children grow older, teenagers, 16-year-olds, etc., many times there is a tendency for medical, for healthcare providers to consider functional etiologies, what we call as a stress-related or psychological manifestations or, bodily manifestations of psychological syndromes, and drug use, etc. So, a lot of healthcare providers can underestimate an underlying, or miss an underlying neuroimmune disorder in children. It's a little more common in children I would say than in adults.

Gabrielle deFiebre: [00:16:47] Okay. Great. Thank you. And then, what tests, I know Dr. Murphy, you talked a little bit about testing, but what tests should be done to make sure that someone receives a correct diagnosis, and who can perform these tests?

Dr. Olwen Murphy: [00:17:01] Sure. Well, I think we sort of covered the type of test that can be done. The question of what should be done in individual cases really varies, and that's going to depend on the patient involved, what disorders are suspected, and what the history is: was this a first event or was this something that's recurred over time? So the specific tests are going to be narrowed down a lot by what the suspected diagnosis is. For example, if neuromyelitis optica is suspected, then the providers are likely going to send blood tests to look for that disorder.

[00:17:39] In terms of who actually performs the test, it's again going to depend on the scenario, going to depend on where the patient is and what their healthcare system is. So some of these things can be done rapidly in the ER by any physician, and then some of the tests are more specialized and tend to be organized by neurologists, for example, who have expertise in the area.

[00:18:01] So, there's basically what we would consider levels of evaluation. There's the broad overview that's provided urgently, and then there's the more specific testing depending on the scenario for each individual patient.

Gabrielle deFiebre: [00:18:18] Thank you. And then if someone is getting an MRI, can brain or spine lesions be missed if they don't use something like gadolinium or special high-powered MRI equipment? Doctor Narayan?

Dr. Ram Narayan: [00:18:36] Yeah. I think the current imaging techniques are pretty good and very helpful in diagnosing and helping sort out between these various disorders. So let's first acknowledge that we really have good tools. That said, they do come with limitations.

[00:18:56] Now, for example, when a brain MRI is obtained, or when a spinal cord MRI is obtained for that matter, the MRI makes parts in slices. Like you could imagine that as making slices in a loaf of bread. You can obviously see that you're going to miss, you could miss lesions between those slices.

[00:19:18] So if there is a lesion within a slice within a slice of bread that can, that could be missed. So there is a small scope that lesions can be missed. Another thing is spinal cord MRIs - and Dr. Murphy has much more experience with this - are very prone to artifacts, what we call artifacts, meaning false signals, or false positive signals because of movement, because the spinal cord is floating in the spinal fluid, in the spinal canal.

[00:19:50] And so, it tends to create more false positive signals. And at the same time, there are some lesions which can also be missed. So just as we get false positive signals, we would also end up missing lesions in the spinal cord. The other thing is, with the brain MRI, we know now that with the advent of the seven-tesla MRI, which is the more advanced version of the MRI currently available in the United States, mostly for research purposes. The other version of MRIs, the commonly used, clinically used MRI is the three-tesla MRI. So the difference, main difference between this is that, with a seven-tesla MRI, you can identify lesions in the cerebral cortex, in the outermost part of the brain. We can see some lesions on a seven-tesla MRI which are otherwise usually missed on a three-tesla MRI. Finally, now outside the MRI, we have so many other imaging techniques, like diffusion tensor imaging and so many other novel techniques of imaging, which are still only being developed as research tools, where we do see lesions in an otherwise quote, unquote, healthy-appearing brain on MRI. So it is very important to recognize that all our tools for diagnosis do have limitations, and it is still, at the end of the day, the judgment that the neurologist makes that drives these diagnoses.

Gabrielle deFiebre: [00:21:28] Good. Thank you. I think that's a really good point.

[00:21:31] And so, for someone who is experiencing these symptoms or gets diagnosed with one of these conditions, is it important to make sure that they find the underlying cause of their inflammatory attack, and if it is, then how do physicians determine this cause and what if in some cases they aren't able to find one? Dr. Murphy?

Dr. Olwen Murphy: [00:21:54] Yeah, this is a very common scenario and something we deal with in the clinic all the time. So in a lot of circumstances, we are able to say, for example, that there has been some sort of inflammatory event within nervous system, whether that is, for example, in the spinal cord, we might call that a myelitis or an inflammatory myelopathy.

[00:22:14] Well, typically once an event like that is identified, we try and search for a specific underlying diagnosis and that would be something like neuromyelitis optica syndrome or M.O.G. - MOG antibody related syndrome. However, there's always going to be a proportion of patients in whom a specific underlying cause is not evident or can't be detected using the techniques we currently have available.

[00:22:41] And that can really mean one of the two things. That is simply that we don't have the tools available to currently detect what the specific cause is, or sometimes it means that an event like this could be a once-off kind of thing, with some sort of trigger. Sometimes we suspect a virus, for example.

[00:23:03] Maybe something that came into the nervous system and went away and is now gone. So it can be very difficult for us to say in an initial scenario what the diagnosis is and whether the person has a risk of developing a more long-term disorder. And in those kinds of situations, what we rely on really is our knowledge of these disorders: how they present clinically and how we interpret the test results - that's the MRI studies, the blood tests, the spinal fluid. We try and build up a picture and come as close to a specific diagnosis as we can but accepting that there are limitations to what we can do in medicine. And there will be cases and people in whom we cannot reach a specific diagnosis, and we have to be a little bit more broad.

Gabrielle deFiebre: [00:23:53] Okay, thank you. And then Dr. Narayan, I know when we were talking about where people go when they present with these symptoms, and you mentioned that timing is somewhat important. How important is timing in regard to diagnosing one of these disorders and then potentially also the underlying cause? Dr. Narayan.

Dr. Ram Narayan: [00:24:16] Yeah. So I mean, in short, time is brain. And, we also know, we now know that time is spinal cord. In a sense, every minute or every second that is lost, there are cells that are either dying or getting into the risk of dying. And so, it is important that we make an early diagnosis, intervene early.

But that said, it's important to understand that at least as of now, and I say that with caution because in the future, I could be proved wrong about this, so at least now, these conditions are not considered as medical emergencies, like stroke for example. Although now we know that there are strokes affecting the spinal cord which are mistaken as transverse myelitis. However, in short, time is critical. It does have an impact on immediate, intermediate, and long-term outcomes for a given patient for a given disorder.

Gabrielle deFiebre: [00:25:27] Okay, great. Thank you. And then, if someone's physician thinks that they might have a rare neuroimmune disorder such as ADEM, AFM, MOG antibody-associated disease, NMO, optic neuritis, or transverse myelitis, but they're not 100% certain, what can a patient do to advocate to make sure that they try to get to an accurate diagnosis? Dr. Murphy.

Dr. Olwen Murphy: [00:25:52] I think this is a really common question and an important scenario. So a lot of the disorders listed in this question, the diagnosis can be difficult to make. So sometimes it's as straightforward as a blood test. For example, in people who have aquaporin-4 antibodies in neuromyelitis optica. But a lot of the other disorders are a lot more tricky to diagnose, and it depends on recognizing a pattern of clinical symptoms and signs developing in a particular type of patient over time and with the, perhaps, MRI findings fitting with that disorder. So these are difficult disorders for physicians to make. I think what patients can do and what their families can do when they're in this scenario is to be as informed as they can about the possible diagnosis.

[00:26:42] And there's very good resources available on the SRNA website to point people towards the sort of typical symptoms and signs that can be seen with these disorders and what kind of tests can be completed. Many neurologists will have some experience with these disorders, but they can be rare.

[00:27:05] And depending on the particular area and healthcare system that the neurologist is working in, they may have had more or less exposure to patients with these types of disorders. So I

would say to patients that if they're concerned that they are in a healthcare system or haven't seen a specialist with a lot of expertise with these kinds of disorders, it's always a reasonable thing to do to discuss with your neurologist whether a second opinion might be helpful. And often patients might be hesitant to even mention that with their physician, but frequently it's something physicians think about themselves. And a neurologist, for example, working in a smaller hospital may have links with neurologists with more expertise in certain areas in larger hospital systems, maybe in the same state or region. So I would encourage patients that if they're wondering whether if a second opinion would be helpful, do discuss it with your own neurologist.

Gabrielle deFiebre: [00:28:06] Great. Thank you. And then, so, moving past the diagnostic process and the testing that might be done, once someone gets diagnosed with one of these conditions, what are the acute treatments that are used for rare neuroimmune disorders, and how does a physician decide which ones to use with a particular patient? Does it vary by diagnosis, by age, by severity of symptoms? Dr. Narayan?

Dr. Ram Narayan: [00:28:34] Yeah. I think that's very important for a patient to know what to expect when they've been diagnosed with a rare neuroimmune disorder and what treatments they're going to be started on. So I would like to conceptualize these, the acute treatment of these disorders in terms of in four steps.

[00:28:54] So usually, throughout the United States, steroids are usually used as first line treatment. And by steroids, I don't mean a low or moderate dose of steroids. These are high dose steroid treatments typically offered as intravenous treatments in the hospital. Sometimes there are patients who are able to obtain the same as outpatients.

[00:29:18] We can also do an equal dose of oral steroids, but it's still that same high dose of steroids. That's typically used as first line. There are rare times when we don't use steroids as first line, and I'll come back to that. Now, once we do steroids, we typically assess the response to that.

[00:29:38] And it's really important to remember that we typically don't wait for definitive answers before we start steroids on most of these conditions because the answers typically take a long time to get back. And so we have already started patients on treatment by this time. So as we are treating patients, we're also making changes in their treatment plan based on what labs and what workup we get back. So that's important. The second line of treatment typically involves either intravenous immunoglobulin, also called IVIG, or plasma exchange, also called plasmapheresis or PLEX. Now, when it comes to IVIG or plasma exchange, it really is dependent on an individual, a neurologist's experience.

[00:30:27] It depends on what is available in that healthcare setting. So certain hospitals may not have facilities to offer plasma exchange. It also really depends on, believe it or not, on what time of the week you go in into the hospital. There are times when, for example, I'll tell you this. So, right now we have a national shortage of intravenous immunoglobulin and we're getting notifications to minimize the use of IVIG unless absolutely needed.

[00:30:55] And so I'm now finding in my practice that we are using more plasma exchange than IVIG. With respect to plasma exchange, you typically need a large-bore central catheter in one of the large

veins, which is typically done by a critical care specialist or a surgeon, or an interventional radiologist.

[00:31:19] So, unlike for IVIG, all you need is a peripheral IV line, which can be done by a nurse. So, if it, depending on what time of the year or the week you go in, sometimes you may end up getting one treatment over the other. And it really does not, between IVIG and plasma exchange, for most of these disorders, it really does not matter which you go on first because they fairly have equal efficacies.

[00:31:48] Now, as third line, when you're talking about third line treatment, we talk about typically what we call chemotherapies, which we use to suppress the immune system or kill immune cells. So treatments for that are used are typically cyclophosphamide, also called Cytoxan, or rituximab, also called Rituxan.

[00:32:13] So these are IV treatments that can be offered in an acute setting if patients don't respond to any of the above treatments. And then rarely we end up, for very refractory patients, we end up going to the next or the fourth level by a level of treatment, which is typically all these experimental treatments. What we call Tocilizumab, Ocrelizumab. We use, Anakinra. So these are very, these are used on a very rare basis. And these are usually used in consultation with other experts and have only been tried in anecdotal case reports.

[00:32:58] Now going back to steroids. There are times when your doctor may feel that steroids are not first line. Now, so let me tell you a common clinical scenario. So if I have a patient who's coming in with a suspected rare neuroimmune disorder, and we get a brain MRI and there is also suspicion for a neoplasm or a tumor in the brain, then it's very important that we get a biopsy. Right? So if we are planning on a biopsy, or if your neurologist is planning on a biopsy, then they may hold on to steroids and rather prefer plasma exchange or IVIG because steroids can affect the outcome of the biopsy. It can affect the interpretation of the biopsy slides.

[00:33:44] Whereas IVIG or plasma exchange don't have as much of an influence on the biopsy. The other very important point to note is between IVIG and plasma exchange, if we are planning on doing one after the other, we'll typically do the plasma exchange first, followed by the IVIG.

[00:34:04] And the reason is very, it's very intuitive, very obvious, because if we gave the IVIG in the beginning and then followed it with plasma exchange, we may end up sucking out the IVIG using plasmapheresis. So, many centers, if they're sequentially doing IVIG and plasma exchange, they would first do plasma exchange and then do IVIG.

[00:34:29] The last thing to remember is you may not need all of these. You, when you go in and you get started on treatment with steroids or plasma exchange or IVIG, and if the neurologist is convinced about the improvement that you're making, and if it's significant, you may not graduate to the next level of treatment at that point. So, you would leave it to your system to heal on its own and then wait for the test results to come back to institute long-term treatment. If somebody has started on steroids and is not making any improvement, that's when they get started on... Or if they are not making satisfactory improvement, that's when they get started on IVIG, plasma exchange. And then if their improvement is not satisfactory with that, then they go up to the next level.

Dr. Olwen Murphy: [00:35:29] I would add as well, because I think this is something that we're so commonly asked at the clinic, that a lot of patients maybe come to us a couple of months after they've been diagnosed with one of these disorders and they ask us, "Oh, can I, should I have more steroids?" for example, or "Should I have plasma exchange?"

[00:35:52] But the timing of the treatment is important, as Dr. Narayan really carefully explained that these treatments are generally used in the acute setting. And typically, the inflammation with these kinds of disorders lasts days to weeks, or in some case months, but the window really for giving these kinds of treatments is typically in the first couple of weeks.

[00:36:16] So usually if somebody is thinking six months later, "Oh, should I be getting more steroids?", for example, it's not usually helpful at that point. Secondly, is that there's a lot of variation in different institutions and with different neurologists in exactly how these treatment protocols are approached.

[00:36:38] And that's really because we do have very little scientific evidence on which treatments should be given before another, and which treatments are even better than one or another. And we often see that patients come to us concerned that, was there a missed opportunity? Should I have gotten this treatment?

[00:36:58] Should I have gotten that treatment? And in most cases, we really say to patients that we would have done something very similar to what your local neurologist or your local hospital did, which is often a case of steroids or intravenous immunoglobulin. And the more aggressive treatments such as plasma exchange are the other things, they can be associated with risks as well. So it's not indicated in every scenario to consider the steroids with a higher risk or, sorry, not the steroids, consider the treatment associated with higher risk. And for many patients, the first line treatment, as Dr. Narayan explained, is enough.

[00:37:41] And my final comment would be because a lot of members of the SRNA now or parents or families of children with acute flaccid myelitis, and in case any of those are listening to this podcast, I would just add the caveat that acute flaccid myelitis is a slightly different ballgame from the other rare neuroimmune disorders we're talking about in terms of treatments.

[00:38:08] And that's because acute flaccid myelitis is really thought to be more of a direct viral infection of the nervous system with knock on inflammation rather than the inflammation itself being the primary inciting process. So there's really a lack of evidence or consensus at the moment as to which, if any, of these treatments are helpful in acute flaccid myelitis.

Dr. Ram Narayan: [00:38:34] Yeah, I agree with Dr. Murphy on all of that. Yep.

Gabrielle deFiebre: [00:38:38] Perfect. Thank you both so much. And just to follow up, Dr. Murphy, you did mention kind of the potential risks that might come with some of these treatments. Would you mind just discussing what the most common side effects are of these acute treatments, and how does someone generally decide whether the benefits of these outweigh the possible side effects?

[00:38:59] And do these side effects vary by patient? Dr. Murphy.

Dr. Olwen Murphy: [00:39:04] Absolutely. I think you're very correct in saying that potential side effects can vary in individual patients. The most commonly used treatment is probably steroids and things that people might experience in relation to steroids would be some insomnia.

[00:39:19] It'd be having difficulty sleeping, maybe feeling a little bit anxious or jittery or sort of pent up. And then another thing might be swelling, for example, of the ankles or high blood sugars, particularly if somebody is prone to diabetes. In terms of the other treatments, intravenous immunoglobulin is an infusion through the arm.

[00:39:42] It contains a high load of proteins. So there can be risks even associated with that, such as kidney dysfunction or a higher risk of clotting because it basically makes the blood a little bit thicker than it normally would be. The more advanced treatments then take another step up in terms of potential side effects.

[00:40:02] Plasma exchange is also done through an intravenous line. Sometimes a simple one in the arm or sometimes a central line going in through the neck. Basically, it's similar to your blood being filtered, sort of like a dialysis machine. And that can cause changes in your blood pressure, for example, dipping high and low, and that can have certain risks, particularly in older people with maybe other problems with their blood vessels.

[00:40:32] And then the other treatments that are, would be extremely rarely used would be things such as high powered anti-inflammatory drugs or chemotherapy drugs, which we rarely encounter, and they would have a very particular set of risks which would need to be discussed carefully with individual patients if they're being considered.

Gabrielle deFiebre: [00:40:56] Great. Thank you for that overview. And so, if someone has learned about these treatments, but their physician does not want to administer one or more of them, what are their options? Is this the time to get potentially a second opinion, or what would you recommend? Dr. Narayan.

Dr. Ram Narayan: [00:41:13] Yeah. And I've had that come up in inpatient encounters, and I think that is, that can be very frustrating. I should say that first. But there are a few things though, so I think Dr. Murphy pointed out to this very correctly. So there are times when we might expect that our neurologist treats us with plasma exchange or IVIG when we are out of the acute phase. So months out of the initial presentation. So that could be one scenario. The other scenario could be that could be an institutional preference or an institutional availability of one kind of treatment over the other. For example, certain places may not be able to do plasmapheresis, and certain places are unable to obtain IVIG these days.

[00:42:02] So it's also important to recognize why that particular treatment was not offered to them. And the third very important thing is for us to recognize that the neurologist may not feel obliged to start a treatment just because it exists. So if the patient is improving, so I would say I would typically tell my residents, you teach them, you treat the patient, not the disease, right?

[00:42:33] So if the patient is improving and making significant improvement and is coming close back close to baseline, there is not a need to institute plasma exchange or IVIG or any other forms of treatment unless it's deemed necessary for that particular condition. Then, lastly, I would say that there are times when I said when the neurologist may suspect a completely different disorder. Now

we may think because of certain biases that we have, that somebody has a rare neuroimmune disorder. It could be because of someone whom we recently saw getting affected with the neuroimmune disorder, etc.

[00:43:16] But in reality, there is, what we're probably dealing with is an infection of the brain or a neoplasm of the brain. And in which case your neurologist may not be convinced about using more and more of these immune treatments. So, well, I've just listed some common scenarios, there could be more. Now, if you definitely are convinced about a neuroimmune disorder in a given situation, and your neurologist does not seem reasonable about offering these treatments, then I think yes, you should try and get a second opinion. That does not hurt that.

[00:43:55] Again, as we just talked about recently, these disorders are rare. There's a very good chance that when we neurologists go through residency, we're not exposed to some of these disorders and to the treatments of these disorders, given the complexity of the diagnosis and treatment. So, yeah, I think it's important to recognize that lacking as well, and if needed, get a second opinion.

Gabrielle deFiebre: [00:44:21] Great. Thank you. And then we did get a question live now from someone asking about, that there have been some studies that they've read about adding gabapentinoids, in terms of helping with neural repair in the central nervous system. Is there any information about this, about how it might be used in the acute phase, if anything at all?

[00:44:43] Or if it's still in the kind of very early research phase? Dr. Murphy.

Dr. Olwen Murphy: [00:44:48] Sure. Well, in terms of the acute treatment of rare neuroimmune disorders, there's not currently any clinical trials suggesting that Gabapentin or gabapentinoids can help with actually treating the underlying disease, which is the inflammation.

[00:45:06] We commonly use them in the acute scenario for patients with pain or with sort of sensory symptoms such as burning, very troublesome pins and needles, or hypersensitivity. So that would be the most common use in the acute setting. I would add that there is a huge amount of research going on into various chemical products or molecules that may have what's called neuroprotective properties in terms of protecting the nerve cells more than others. But most of these studies, which have examined a wide range of chemical compounds, have failed to translate into making differences in clinical trials when they've reached that stage.

Gabrielle deFiebre: [00:45:53] Great, thank you. Okay. And then, so after someone has been diagnosed, they're in the hospital, they've received one or more of these acute treatments, what are the next steps? How do they, is the next step to go to, to do a rehabilitation program, or how is that decided? Dr. Narayan.

Dr. Ram Narayan: [00:46:15] So is this, this is after the acute treatment, is that what you're saying?

Gabrielle deFiebre: [00:46:20] Yes.

Dr. Ram Narayan: [00:46:22] Yeah. So, I'm able to think of a few scenarios. So once you get to the acute treatment in a hospital, it really depends on where you are with your abilities to ambulate,

where you are with your abilities to perform activities of daily living, where you are with cognitive abilities, etc.

[00:46:46] So this is where inpatient assessment, rehabilitation assessment becomes very important. And most academic centers, most hospitals in the U.S., including academic centers, have rehab assessment that happen to inpatients that are admitted for these disorders. So, then what happens is, the person who makes the assessment would usually be a physical therapist, it could be a psychiatrist, it could be any one of these. And then they would recommend dedicated rehabilitation for a select set of patients in whom it is deemed necessary. So, for example, if I go in with optic neuritis, all I had is just optic neuritis, and my vision is getting significantly better in the hospital, I may just get discharged home without any rehabilitation. I may just, slowly my vision may slowly improve, and I may just follow up as an outpatient. However, if I go in with transverse myelitis, where my legs are weak and I have difficulties with voiding and voiding urine, and I have, let's say my hands are also weak, and then those circumstances, I may need dedicated inpatient rehabilitation.

[00:48:05] And following that, there are people who may need continued outpatient rehabilitation as well. And in fact, I would say the longer and the more consistent you are with rehab, you're going to have better outcomes. And so, whether or not you're a good candidate for rehabilitation depends on what symptoms and what we call neurological deficits you have at presentation. And, more importantly, what you have at the end of your acute hospital stay.

Gabrielle deFiebre: [00:48:38] Okay. Thank you. And then, following up after that, so once someone is discharged from the hospital, what follow-up appointments should they make after leaving the hospital? So setting up care for the long-term to some extent, and how often should they contact their neurologist or general practitioner or other healthcare providers that might be involved in their care? Dr. Murphy.

Dr. Olwen Murphy: [00:49:03] Well, this would definitely be guided based on individual circumstances. So, for example, how severe the neurological problem was, whether further treatments are being considered, and whether the patient is thought to have a relapsing disorder such as neuromyelitis optica. So that being said, it would be typical to follow up with your main neurologist after something like this. And the frequency of the appointments is going to vary on an individual basis. I would say that, I think that something our patients often underappreciate is the value of having a good relationship with your primary care practitioner or your general practitioner.

[00:49:46] I think that it's really good to have a strong support who's not just good at assessing neurological problems, but that in the context of other things. For example, if somebody develops a urinary tract infection, things like this that commonly come up in regular day-to-day life and may or may not interact with the neurological problem.

[00:50:07] So I would say, in the long-term, it's really beneficial for patients both to have a neurologist and a primary care provider that they have a good working relationship with.

Gabrielle deFiebre: [00:50:21] Great. Thank you. And then, what are the chances of recovery after one of these disorders? If someone doesn't see any sort of recovery in the first few months, does this mean that nothing will ever happen?

[00:50:34] Or how is that determined? Dr. Narayan.

Dr. Ram Narayan: [00:50:38] That's a very interesting question. That's also a very frustrating question, both for doctors and for patients also, it's a frustrating concern, I would say. Not necessarily a question. So, the rates of recovery are very variable amongst all these disorders.

[00:50:59] I can tell you a few things. One, these disorders typically, with the right diagnosis and right treatment, they typically don't get worse, at least. Most patients, most of the times there is improvement. Now how much there is improvement and how long of an improvement, it depends on so many other factors.

[00:51:17] It depends on what kind of rehabilitation you get. It depends on how old is someone. So for example, children do far better with their recovery than adults. And it also depends on what long-term treatments are there to prevent further injury to the brain by the immune system. So, I get times when patients are told, "Oh, you know, you have this problem and you'll end up in a wheelchair all your life." First of all, I don't think this, I don't think it's professional even to say that. But what we're seeing is that that's not even correct because we do invariably see that these conditions do improve. The other thing, and so as I said, how much and/or how long the improvement is, is what we can't quantify at the beginning. And then the other thing is, I think when you're saying that "three months is when you have the best recovery" or "six months is when you have the best recovery," I think those statements should also not be taken as absolute statements. I think there are outliers, there are more outliers for that kind of a phenomenon than expected results. So, I would really not worry about the three-month mark or the six-month mark.

[00:52:58] I would just keep doing rehab and doing whatever treatment I'm supposed to be doing until I have attained a satisfactory level of improvement.

Gabrielle deFiebre: [00:53:11] Great. Thank you. And then, so after, if someone leaves the hospital and they get diagnosed with something that they've been told is likely to just be monophasic or just a one-time event, or even if they were diagnosed with something like NMO, if they start to experience what they think might be a relapse of symptoms, what would you generally recommend someone does?

[00:53:33] Dr. Murphy.

Dr. Olwen Murphy: [00:53:35] Well, I think it was very useful what Dr. Narayan mentioned earlier, that typically transient symptoms are not so worrying. So that might be things that last seconds or minutes or even hours. But symptoms that last for longer than twenty-four hours are typically more concerning. And then there's many, again, individual factors that come into this.

[00:54:01] So if someone, for example, has had weakness in their right arm before, and they get weakness in their right arm again, it can be hard for the doctors sometimes to differentiate whether that's something new or whether that's just recurrence of previous symptoms. But a general rule would be that if a patient experiences something that is either new or a clear worsening from their usual day-to-day sensation, and if that lasts for longer than twenty-four hours. Or if it's shorter than that, but it's very worrying or severe, it would be the scenarios in which it's important to seek medical advice. And again, the level of medical advice is going to depend on the scenario. And it's why it's good to have, as I mentioned previously, a good neurologist and a primary care provider,

just to ensure that if there is an emergency or troubling situation, that there're potentially multiple people that can help in accessing the health system.

[00:55:02] If symptoms are mild, a patient might select to go to their primary care provider first and be assessed there. If things are more worrying, they may go directly to the emergency department. Or, if they have another specific question that's not so urgent, they may try and contact their own urologists.

[00:55:21] But the general rule would be to seek medical advice and gauge that depending on how severe the symptoms are.

Gabrielle deFiebre: [00:55:30] Thank you. And then earlier at the beginning, Dr. Narayan, you mentioned how, when we were talking about what rare neuroimmune disorders are and how the not rare one is multiple sclerosis, how is the diagnosis of MS differentiated from one of these other neuroimmune disorders that are rare and maybe less likely to be seen by the treating physician? Dr. Narayan.

Dr. Ram Narayan: [00:55:53] Yeah. So first of all, MS is statistically more common. So in a situation where there is a suspected neuroimmune disorder, MS is statistically more common than any of these disorders.

[00:56:12] So that's one thing. The second thing is you definitely have clues. So for a diagnosis of MS, you need to meet the McDonald's criteria. The most recent iteration is as of 2017. Both with respect to symptoms and signs, and with respect to what we find on an MRI, the patient should meet dissemination in space and dissemination in time criteria.

[00:56:36] In other words, you should have had an immune attack in the past, meaning you should have had it at two different points in rough time, sometime and somewhere in the past and more recently for which the patient is actually seeing you for. And that's something which the patient may not be aware of.

[00:56:57] It could just be a silent attack, which we just recognize on MRI. So that's a very important thing to recognize. For multiple sclerosis, the immune system should have caused injury or caused an attack at two different points of time, and it should involve at least two different areas of the nervous system out of the five well-defined recognized areas. We typically call them as cortical, juxtacortical, periventricular, infratentorial, and spinal cord. So out of these five areas, it is important that the patient has lesions on MRI or symptoms pertaining to them in two of these areas.

[00:57:45] And in addition to that, there are some pointers in the spinal fluid that also favor multiple sclerosis versus other disorders. There are times when the diagnosis is sometimes vague and unclear. We now know that a lot of these rare neuroimmune disorders conventionally don't respond well to MS treatments, the conventional MS treatments. And so, if somebody is diagnosed with MS and is not responding to treatment and is getting worse, it is important to revisit the diagnosis and consider one of these rare neuroimmune disorders.

Gabrielle deFiebre: [00:58:23] Great. Thank you so much. And just, you know, we have just a few minutes left. I just wanted to open it up to both of you and see if there was anything else that you feel like we should add that we didn't really get a chance to talk about.

Dr. Olwen Murphy: [00:58:38] I think that we've covered a huge amount, and the questions sent in by patients and their family members are very helpful in terms of guiding the conversation. I would just add that, to end on a positive note, that while these disorders can be difficult to diagnose and difficult to treat, or challenging in terms of their manifestations, we see many patients do do very well after getting a diagnosis such as one of these. And that's been one of the most heartening experiences for me as a neurologist, is to see patients potentially diagnosed with a complicated disorder, but to recover well and to maybe adapt in their life and deal with that diagnosis over the years to come. And very important to stay active in terms of your physical health, being as physically active and exercising as much as you can, but also looking after your psychological health after a diagnosis such as this. Leaning on friends and family for support and identifying the things that you can do to improve your mental wellbeing.

Dr. Ram Narayan: [00:59:50] And if just to add on to that, I think it's also important for us to recognize, for both patients and for us to be humble about this and recognize that we, although we have named a few neuroimmune conditions, we know that this list is going to keep growing because we're learning more and more about these. The SRNA plays a huge role in supporting research in these disorders.

[01:00:18] And I urge patients and families to actively engage in research. You're not only helping yourself and your family, but you're helping a lot of people in the future as well. And in you're helping science in general, because this is a condition, these conditions are really, at this point of time, under-studied.

[01:00:44] And, so, yeah. So thanks. Thanks a lot for this opportunity.

Gabrielle deFiebre: [01:00:51] Thank you both so much. We really appreciate it.

Dr. Olwen Murphy: [01:00:54] Thank you.