

Immunology of Rare Neuroimmune Disorders

Part 2

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Krissy Dilger: [00:00] Hello and welcome to the SRNA "Ask the Expert" podcast series. This podcast is titled "Immunology of Rare Neuroimmune Disorders Part 2." My name is Krissy Dilger, 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 web site at wearesrna.org. Our 2022 "Ask the Expert" podcast series is sponsored in part by Horizon Therapeutics, Alexion AstraZeneca Rare Disease, and Genentech.

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Dr. Alexandra Simpson is currently a neuro-immunology fellow at Johns Hopkins in Baltimore, Maryland. She completed her medical school training at the University of Maryland School of Medicine in Baltimore, Maryland, and an adult neurology residency at Johns Hopkins. She has remained at Johns Hopkins for her fellowship training in neuro-immunology and neuroinfectious diseases. Her fellowship is funded via a Sylvia Laurie Physician Fellowship through the National Multiple Sclerosis Society, and she plans to continue in academia as a multiple sclerosis or MS physician, clinical researcher, and clinical trialist. Some of her research interests include developing better ways to identify and manage various symptoms that are difficult to treat in MS, studying the use of novel therapeutics for treatment of relapsing and progressive forms of MS, and incorporation of patient reported outcome measures into clinical trials. In addition to MS, she has clinical and research experience within neuromyelitis optica spectrum disorder, MOG antibody disease, and idiopathic transverse myelitis.

Dr. Paula Barreras is a neurologist, and neuroimmunology and neuroinfectious diseases fellow at Johns Hopkins University. Her clinical focus is on the diagnosis and management of rare neuroimmunological disorders with a special interest in neurosarcoidosis and myelopathies, including infectious, inflammatory,

and vascular myelopathies. She's involved in clinical and translational research focused on understanding viral host interactions leading to autoimmunity in the central nervous system, and on improving the diagnostic accuracy and our understanding of natural history and physiopathology of myelopathies and neurosarcoidosis. Dr. Barreras completed her medical school training at the University of the Andes in Colombia, followed by a research postdoctoral fellowship at Johns Hopkins in neuroimmunology and neuroinfectious diseases, where she focused on transverse myelitis and other causes of myelopathies including AFM. She also worked on understanding the neurological complications of arbovirus infections. She then completed her neurology residency training also at Johns Hopkins. She is currently a neuroimmunology fellow with an emphasis in neurosarcoidosis supported by the foundation for neurosarcoidosis research, working on identifying potential infectious triggers for neurosarcoidosis.

Welcome and thank you both for joining me today. So, to get started, can you just define what an autoimmune disease is?

Dr. Alex Simpson: [04:35] So, our immune system is primarily designed to recognize foreign materials like bacteria or viruses or fungal infections that could potentially be harmful to our body and eliminate these threats. If we sort of break down the word autoimmune, the auto prefix means self. Therefore, an autoimmune disease is a disorder in which an individual's immune system mistakenly identifies normal, healthy tissues or proteins as not belonging to that individual, and subsequently announce an inflammatory attack against those tissues.

Dr. Paula Barreras: [05:07] And the mistake that the immune system makes in recognizing these healthy tissues as foreign can affect any part of the body and specifically sometimes that attack is directed towards the nervous system including the brain, the spinal cord, or the optic nerves causing inflammation in those places. Now the immune system has different types of cells, the B cells that make antibodies, and I think most people learn what antibodies are this year after the COVID pandemic. But briefly, antibodies are proteins that normally recognize foreign material or organisms and flag them to be removed or destroyed by other components of the immune system.

And in some autoimmune diseases, some of which attack the nervous system, these vessels can make antibodies directed towards the normal tissues in the brain found for their optic nerves. In those disorders, these autoreactive antibodies can be measured and serve as a marker of disease. In other immuno-related diseases, there is no antibody we can identify and that could be, because we just don't have a test for that antibody or because other components of the immune system like T cells play a bigger role in the development of the disease. The T cells are other cells that also fight foreign substances in a different way independent of antibodies, and this can also be autoreactive and play a role in development of the disease.

Krissy Dilger: [06:38] Okay, thank you. And then for the next question, we know that steroids are often used to treat an acute attack for one of these disorders. So can you just explain how steroids work and what they do to the immune system?

Dr. Alex Simpson: [06:54] Sure, steroids which are also known as glucocorticoids, work by decreasing inflammation that's generated by our immune system. They actually act pretty broadly affecting both the innate and adaptive parts of our immune system and they regulate inflammation in a variety of ways including regulating gene expression in immune cells to reduce the production of signal proteins called inflammatory cytokines, which act to activate the immune system and produce inflammation. And at the same time, steroids can also stimulate the production of anti-inflammatory cytokines.

Dr. Paula Barreras: [07:30] The other way that steroids work is by producing swelling or edema. So, an inflammation that is a normal mechanism to dilate the blood vessels and bring fluid out of the blood vessels into the tissues, and that's the swelling that we see, and we can see this in the nervous system as well. The steroids induce the breakdown of some of the signals of the proteins that induce that dilation of blood vessels including some proteins called prostaglandins. The steroids also affect the migration of inflammatory cells of the immune system to prevent them from escaping the bloodstream into the tissues. And in that way, it sort of sequesters the immune cells and prevent them from causing additional damage and this is inflammatory attacks.

Krissy Dilger: [08:23] Got it, thank you. In a similar vein plasmapheresis or plex, also known as plasma exchange, as well as IVIG are both also treatments that are used for these disorders. So can you just explain how these treatments work and how they affect the immune system as well?

Dr. Alex Simpson: [08:45] So plex as you mentioned, it also goes by the names of plasma exchange and plasmapheresis is a medical procedure, and this is whereby a device filters a person's blood into the liquid portion or the plasma portion of the blood and then the cellular portion with all the various blood cells. With this procedure, a central line is placed in the neck and filters the blood to remove parts of the patient's blood that contain auto-antibodies or antibodies that mistakenly attack the healthy tissues of the human body.

Dr. Paula Barreras: [09:16] Now Dr. Simpson just explained very well what plasma exchange is. IVIG or intravenous immunoglobulin is the opposite in many ways of plasma exchange. In plasma exchange, we're removing antibodies. IVIG is an infusion of pooled antibodies from many donors, from many people. And these antibodies are presumably healthy antibodies that we give to our patients and IVIG acts in different ways. It's mechanisms of actions affect different branches of the immune system. So, it acts in different mechanisms. One way is that these healthy antibodies can actually bind and neutralize some of the, let's say, bad antibodies or auto-antibodies that mediate these neuroimmunological conditions.

IVIG can also neutralize part of the complement cascade. That's another part of the immune system where some proteins can directly cause destruction of cells and enhance the inflammatory process. So IVIG can also block those preventing that pathway from evolving. In addition, a lot of immune cells, B cells and T cells, but also cells of the innate immune system, have receptors for hemoglobin and this healthy hemoglobin combined to these receptors and modulate the immune response sort of like making it less inflammatory, decreasing the production of those pro-inflammatory cytokine kinds that Dr. Simpson was referring to.

Krissy Dilger: [10:57] Great, thank you so much for that explanation. Now can we go more specifically into the neuroimmune disorders, acute flaccid myelitis, acute disseminated encephalomyelitis, MOG antibody disease, neuromyelitis optica spectrum disorder, transverse myelitis, and optic neuritis. Can we kind of discuss how the immune system interacts with the neurological system to cause these disorders? What components of the immune system are involved with each of these and how do different treatments used for these disorders impact the immune system?

Dr. Alex Simpson: [11:36] Of course. So, to start off with how the immune system interacts with the various neurological disorders, the ones you listed are very diverse. So, when we're talking about specific disorders like MOGAD, MOG antibody disorder and NMO spectrum disorder, there are antibodies identified in the blood of people with these disorders that actually target particular proteins within the human body. These auto antibodies can bind those proteins in the optic nerve, in parts of the brain, and also in the spinal cord, and it can flag them to be attacked with inflammation by other components of the immune system. For other

disorders such as ADEM, transverse myelitis and optic neuritis that are not associated with MOGAD, NMOSD or multiple sclerosis, there is no identified antibody at this point that we have found.

Dr. Paula Barreras: [12:26] So, I think it's important to clarify the terminology a little bit, because for example the term TM or transverse myelitis is just a term that means inflammation of the spinal cord, but it's not telling you what the cause of that inflammation is. An inflammation can be secondary to many causes. For example, there is inflammation secondary to infections. So, there are cases of infectious TM and there is inflammation secondary to systemic or a multi-organ autoimmune or dermatological disorder that can involve the spinal cord, for example. And also, there is inflammation due to antibody mediated diseases like NMO or MOG. TM can be a manifestation of multiple sclerosis for example. And there are some cases where there is primary inflammation that we know that it's happening and we can measure, but we cannot identify the cause. And these are the cases that we refer to as idiopathic TM.

And the same happens with the terminology of optic neuritis or ON, or ADEM. These are terms that in a way are descriptive of what's happening, but it doesn't tell you the cause. All we know is that there is inflammation occurring in those sites of the nervous system. So, for those disorders where we cannot identify a specific antibody or a specific disease, we know there is inflammation and we suspect in many cases that there is a preceding factor, like a prior infection or a stress around the body that sets off a chain reaction of inflammatory events, like an initial stimulus that activates the immune system to cause inflammation. In some cases, this may be due to a protein or a part of a microorganism, like a virus or a bacterium that caused an infection that looks to the immune system like healthy tissue. And the immune system gets confused between the two and then triggers an immune attack by mistake. But in some cases, we don't really understand what the triggering factor was, but yet, we are able to detect inflammation in these places.

Krissy Dilger: [14:40] Okay, great, thank you. For our next question, after an acute attack, what does this mean for the immune system going forward? Is it different for the different disorders?

Dr. Paula Barreras: [14:58] Okay, so let's talk about AFM. Okay, so let's start by defining what AFM is. So, AFM means acute flaccid myelitis and that term is a descriptive term for inflammation of the spinal cord. That's Myelitis. And the acute and flaccid referred to, is happening very fast and the muscles being flaccid or floppy. And that's important, because that happens due to the involvement of the gray matter in the spinal cord, which is where the neurons live that control those muscles. There is still a lot of research going on to understand why AFM happens. We know that the clusters of this disease have been seen in children in areas and times of the year where specific types of enteroviruses were circulating. Most patients report fever and respiratory symptoms in the days before the AFM symptoms start and enterovirus, that's a specific type of virus, has been detected in several patients with this disease. Now there are animal models where they put enterovirus into animals that they will disease similar to what we see in children with AFM. So, all of this indicates that AFM, it's triggered by exposure to enterovirus, specifically enterovirus D68. But other types of enteroviruses, like A71 or other viruses like Coxsackie have been implicated.

There is research trying to understand if the neurological problems are due to the infection itself of the neurons or by the immune response to that infection getting out of control. However, most experts think that the main mechanism is direct neural invasion, direct infection by that virus and that's a little bit different than how we think about other causes of myelitis that are more autoimmune in nature. And that affects treatment, because treatment is mainly supportive and supportive means trying to protect the respiratory control, because a lot of patients lose the ability to breathe on their own, managing the complications of being immobile, and starting an aggressive plan of rehabilitation. Now when we think about immune therapies and how that interacts with AFM, the best treatment approach is not yet known and that's because we yet don't understand fully if the

main problem is direct infection or the immune response. And it's difficult because the immune response in an infection may be beneficial. Some inflammation may actually help control the infection.

So, experts have used immunoglobulin or IVIG, in cases of AFM and because this is a rare disorder there are no large clinical trials supporting the use of any of these interventions. But it's believed that, because IVIG has antibodies from many people, it can contain antibodies against enterovirus just because people in the community can be exposed to those viruses as well. So, it can have some antiviral effect. And also, because like we discussed before, IVIG can modulate the immune system. So, if there is a component of the immune system getting activated and the inflammation itself causing damage, then IVIG can regulate that. In the animal models of AFM, IVIG, seems to work, but we don't know yet if those results can be extrapolated to our patients. Other interventions like steroids or plasma exchange are a little bit more tricky in this situation because they can remove that immune response that can be beneficial to control the infection. And we don't yet know if these are helpful in any form.

Dr. Alex Simpson: [18:52] Excellent description, Dr. Barreras. So now moving from the AFM to ADEM. ADEM is an acronym that's short for acute disseminated encephalomyelitis. And essentially this encompasses a syndrome that's composed of many different neurological symptoms including encephalopathy with confusion and memory loss, with regard to the components of the immune system that are involved in ADEM, really our understanding is incomplete with the pathogenesis of ADEM, but in many cases ADEM occurs after an infection. We think this is possibly related to a similarity and structure of certain components of myelin which is kind of that insulation building block around the nerves and the infecting pathogen. Immune cells that Dr. Barreras talked about before that are T cells come into contact with this pathogen and become reactive to that antigen. Then when they encounter something similar looking in the central nervous system, often this myelin-base protein, this triggers an inflammatory cascade which involves components of both the innate and adaptive immune systems. Then resulting in injury to the myelin sheath and in some cases can damage the axons of the nerves themselves.

With the treatments that we use for ADEM, the standard of care is really to use high dose steroids. Oftentimes this is intravenously over several days followed by an oral steroid taper and steroids, as we mentioned before, act to really damp down the immune system. IVIG and plex can also be considered with poor response to steroids. Now, because ADEM often presents with symptoms of fever, headache, encephalopathy, or evidence of inflammation in certain labs while undergoing the work up, some people will require empirical antibiotics or antivirals with the work up that they're getting for the ADEM. And just a little bit of note with treatment for ADEM, often this is a monophasic event, so only occurs one time in a person's life, but some proportion of adults can have a relapse. Certain disorders like MOGAD can have recurrent ADEM-like presentations. And in that case when you're having more of a relapsing disorder, you should consider whether maintenance medication is needed to modulate or suppress the immune system.

Dr. Paula Barreras: [21:12] So, talking about MOGAD, since you mentioned that. So, in MOGAD, or MOG-associated disease that are autoreactive antibodies, auto-antibodies directed against myelin oligodendrocyte glycoproteins. So that's what MOG means. And MOG is a small component of that myelin sheets that Dr. Simpson was talking about, the wrapping around the axons in the central nervous system. And the study is looking into MOGAD development and why it happens do show that these autoantibodies against MOG lead to demyelination or the loss of that myelin, and that by itself exposes those axons to damage from the environment and axons end up dying off. The studies also show that T cells are involved. So, although we have a marker that is an antibody and antibodies are made by B cells, T cells are definitely important in MOGAD as well. And the trigger for these autoreactive B cells and T cells is not really clear in MOGAD, but in many cases, there is a story about an infection either a known infection that we can identify or infection like presentations with fever and respiratory symptoms before.

So, it's believed that there is an infection that activates the immune system and causes this cascade of inflammation and results in damage of these myelin by these B and T cells. Now interestingly when we think about treatment for MOG, you would think that treatments directed towards the antibody response would be the most effective, because we have an antibody that we can detect. And treatments like rituximab that's a monoclonal antibody that targets specifically B cells ends up killing the B cells that produce antibodies actually don't work as well as we would expect in diseases like MOG. And things like IVIG are more effective probably because they have a broader effect on the immune system and we've seen based on our studies, that is not all about the B cells in MOG, but T cells are also important.

Dr. Alex Simpson: [23:32] The next we'll touch on neuromyelitis optica spectrum disorder. We know that the presence of aquaporin-4 IgG in the blood is the main pathogenic factor of NMOSD and aquaporin-4 is a protein that's involved in water and homeostasis management in the central nervous system. Aquaporin-4 IgG can penetrate the blood-brain barrier which is that protective barrier between our blood and our brain and spinal cord and optic nerves and can reach these organs and attack the cells that express this aquaporin-4 protein, which is present in a specific cell type called an astrocyte. This results in an activation of the immune system causing cell damage to astrocytes that's mediated by antibodies, but also by the complement system. The damage of astrocytes itself can produce cytokines that attract other inflammatory cells which cause further damage causing injury to other cells called oligodendrocytes that produce myelin and to the axons of neurons leading to neurologic defects. With regard to the how treatments impact the immune system in NMOSD, so in the majority of people with this diagnosis they will have a relapsing force. So, if they have one event, they're very likely to have further events in the future, and this can be a very debilitating syndrome due to the location of attacks in the optic nerve and spinal cord.

So as a general rule these people should be on maintenance therapy with immunotherapy, with IV infusions including eculizumab, rituximab, and inebilizumab, a subcutaneous injection like satralizumab, or oral therapies such as azathioprine or mycophenolate. Some of these therapies target B cells and therefore the antibody production, whereas others modulate the complement cascade limiting the inflammatory damage induced by the antibodies. And then others such as mycophenolate inhibit the proliferation of various cells like the B cells and T cells. One final note about NMOSD is that these patients often require prolonged steroid tapers in their management.

Dr. Paula Barreras: [25:47] So that brings us to TM or transverse myelitis, and I think I touched a little bit on this before and how transverse myelitis is often thought of as a final diagnosis by some people in the community or by patients, but it's actually not. It's a term that describes a syndrome of inflammation in the spinal cord and that can be due to many causes. So, when we think about how treatments interact with the immune system in TM, we really need to be thinking about what is causing that inflammation in the spinal cord. So, if we think that the inflammation is due to an antibody mediated disease like in the case of NMO, then things like plasma exchange that remove those harmful antibodies makes sense.

However often, when somebody presents with a transverse myelitis episode for the first time, we don't know yet if that person is going to end up having NMO, or it's going to end up having MS, or if it's going to be one of those idiopathic cases where we don't really know the cause. So, the focus really when somebody presents with TM is try to exclude infection, because there can be infections that present like this and then the treatment would be completely different like antibiotics for example. But once infection is excluded and the workup is cooking for these antibodies and that usually takes several days to come back, then we want to give a treatment that is broad that affects the immune system at different points, because we don't know yet what the answer is going to be. If it's going to be a mainly an antibody mediated process and T cell mediated process or something else.

So, the broad treatment that we tend to use is the steroids, because like we said before, steroids really decrease the swelling that is happening in the spinal cord, and they decrease the presence of these cytokines that are the signal proteins that promote inflammation. And this is the standard of care every day in the acute period when the person first presents. Now, the caveat is that we don't know yet if this person is going to end up having an antibody mediated process. So, plasma exchange in the acute process also makes sense if there is a severe case if the suspicion is something like NMO, or if the person is just not responding to steroids, and that's with the rationale of removing those potential autoantibodies causing TM.

Optic neuritis is similar, right? This is inflammation of the optic nerve. The inflammation can be due to various causes and at the beginning we just don't know what the final diagnosis is going to end up being. And optic neuritis, this is a very common manifestation of demyelinating disorders. These are the disorders that affect primarily myelin, the most famous one being multiple sclerosis. It's a common first presentation of multiple sclerosis, but also, a common first presentation of NMOSD or MOG-associated disease. Some other disorders that can present with optic neuritis include sarcoidosis or other autoimmune and rheumatological conditions. And again, similar to TM when we cannot identify a cause and we call this idiopathic optic neuritis. So, the component of the immune system involved is going to depend on the cause of that optic neuritis. It can be an antibody-mediated process mediated by B cells mainly from the adaptive immune system, or it can be a T cell process or an interaction between B cells, T cells, and the innate immune system which happens in disorders like multiple sclerosis.

In MS and demyelinating disorders, the target of the immune attack is myelin and like we touch a little bit on before, myelin protects the axons from damage. So, when that's happening, when there's damage to the myelin, the signal transmission through that nerve is not efficient and if it stays unprotected eventually dies off and that's why it causes damage. However, in other disorders that cause optic neuritis like sarcoidosis, for example, also a rare disorder, the mechanism is completely different. There is a different type of inflammation called granulomas that is mediated by a different type of cell called macrophage. So really the component of the immune system depends on the final diagnosis. Similarly, since acutely we don't really know which one is going to be, we want to give a broad treatment and typically that brought treatment is steroids, high dose, intravenous methylprednisolone, and that Dr. Simpson is going to talk more on.

Dr. Alex Simpson: [30:53] Thank you, Dr. Barreras. So acutely, if optic neuritis is the first attack of inflammation or the first manifestation of these disorders as you mentioned, it's not often known what component of the immune system is the target, and steroids are used due to the broad action against the immune system. We also have some evidence that steroids can accelerate vision recovery. Most of our evidence comes from the optic neuritis treatment trial, and in that study, patients were given either intravenous methylprednisolone or a moderate dose of oral prednisolone. So, either IV or oral steroids followed by a steroid taper in the oral steroid case. The IV methylprednisolone accelerated the recovery of visual function and also reduced the risk of conversion to MS within the first two years in comparison with either placebo or those who had the oral prednisolone.

There were two randomized trials that studied the potential benefit of IVIG in optic neuritis, but neither study found a difference in visual outcomes at six months with this intervention. There is some evidence now suggesting that patients with optic neuritis due to NMOSD could be treated early with plasma exchange within 7 to 14 days of their symptom onset. Optic neuritis due to NMOSD is associated with poor disease outcomes and is often bilateral in presentation and some small case series have suggested earlier treatment with plasma exchange can help visual recovery in patients who don't respond to IV steroids. This is due to the same concept of plasma exchange removing antibodies that can be harmful in driving the immune response and diseases like NMOSD.

Krissy Dilger: [32:34] Wow, that was a really awesome, comprehensive overview of everything and thanks for going into detail like that. I think that will really help our community understand how the immune system impacts them. Going forward, what issues does someone with an immune mediated disease need to be aware of?

Dr. Paula Barreras: [32:53] The one thing to be aware of is that not all non-immunological conditions are relapsing and therefore not all conditions need long term immunosuppression. For example, some cases of ADEM happen and then we never see recurrence of that. The same happens with some cases of optic neuritis. So now that said, there is a non-zero risk of relapse in the future. So, I think what patients should be aware of is of what symptoms should prompt them to think that they're having a recurrence and seek medical attention. And those are symptoms that are similar to prior attacks that had resolved and now came back and are severe and persistent lasting more than 24 hours or new symptoms in other parts of the body that were not affected before. Things like weakness and numbness in the extremities, changes in vision and specifically loss of vision in one eye, if it's associated with pain in the eye, with eye movements and changes in bowel or bladder function.

Dr. Alex Simpson: [33:59] The other common misconception is that these diseases by themselves imply an immunosuppressed state and that's actually not the case. In these disorders, the immune system is actually overactive and so there's not an intrinsic higher risk of infections. However, once someone is on treatment with immunotherapy, including high-dose steroids, but also other therapies that suppress the immune system, there are other considerations.

Dr. Paula Barreras: [34:24] So once somebody is immunosuppressed, then there is an increased risk for infection. So, I think patients should be aware of that risk and also have a lower threshold to seek medical attention for what we would normally consider mild infections. So, it's good to keep your doctor aware of any urinary tract infections, flu, COVID just so your doctor and the patient also is monitoring for symptoms and be safe if things don't go in the right direction.

Dr. Alex Simpson: [34:59] Vaccinations are another important consideration for those who have immune mediated disorders. So many vaccines are dependent on the response of immune cells called B cells and certain immunotherapies as we've discussed before, deplete this B cell population. So, when people are on these medications, more thought really needs to go into the timing of vaccinations before after infusions and you may have to wait a little while. In addition, it's important to obtain all recommended vaccines while on immunotherapies. As mentioned before, immunosuppression from these medications can place you at greater risk of infection.

Dr. Paula Barreras: [35:37] Now, the other thing that I think is good for patients to be aware of is the concept of recrudescence. And what that is, is that with any stressor to the body like an infection, even a vaccination or being overheated, over-fatigued, sick with something else, then prior symptoms can reemerge and that is different from having a new attack. So, this concept of the old symptoms sort of acting up or patients feeling the symptoms again is very common and that's why we have the 24-hour rule, as we call it in neurology, and it's that if you are very fatigued and the stiffness in the weak leg became transiently worse, that's not worrisome by itself unless that's persistent beyond 24 hours, and usually accompanied by symptoms that either were not present before or symptoms that are more severe than baseline. So, this is very common, for example, in the setting of urinary tract infections, which we see often in patients with myelitis, either AFM or transverse myelitis from different causes, because there is a bladder dysfunction. Those patients get more common urinary tract infections and every time there's an infection, the old symptoms of the myelitis come out. And people may actually feel transiently weaker or more numb and these symptoms usually go away

with the treatment of the infection, and it doesn't necessarily mean that the immunosuppressive treatment they're on is failing.

Dr. Alex Simpson: [37:12] I feel that family planning is also an issue that is important to talk to people with immune-mediated disorders about, primarily if these people are on medications that would suppress the immune system. So, timing of medications may differ, or they might not be able to be on certain immunosuppressive medications. We always say to our patients in clinic, pregnancy should be planned if possible. We know that that's not always the case, but people who become pregnant or who are planning to become pregnant should keep their neurologists updated so that we can think ahead and make the necessary adjustments as needed. In addition, we also recommend that regular exercise and physical activity is important for all people with neuroimmunological disorders to help improve their strength and balance. And this can also be supplemented with physical therapy. We also recommend sticking to a healthy diet.

Krissy Dilger: [38:10] Great, thank you. Those are all great considerations for people with these disorders to consider because they may not be things that most people have on their mind. But it is important to know. So does having a neuroimmune disorder make a person more susceptible to other immune mediated diseases?

Dr. Alex Simpson: [38:32] I'd say that comorbidity with other autoimmune disorders is not uncommon, but that doesn't necessarily mean that every person with the neuroinflammatory disorder will develop another autoimmune disease. Common comorbid immune mediated disorders seen in MS, but also other neuroinflammatory disorders include lupus, psoriasis, asthma, type one diabetes, autoimmune thyroiditis, celiac disease, Sjogren's syndrome, inflammatory bowel disease, rheumatoid arthritis, and atopic dermatitis.

Dr. Paula Barreras: [39:05] And I think it's a good point to clarify is that it's not necessarily that the neuroimmunological disease by itself causes another immune disease or triggers another immune disease, but rather that for that individual that already developed an immunological condition, probably like their immune system is just susceptible to autoimmunity in general or a little bit more susceptible than the general population. And that's why we see emergence of multiple immune mediated disorders in some cases.

Krissy Dilger: [39:42] Got it. Great, thank you. My final question is, can you talk about the genetic component, if any, to rare neuroimmune disorders?

Dr. Paula Barreras: [39:53] Sure, I think this is touching a little bit on the on the prior topic. The new system may be prone to autoimmunity because there are genetic factors that influence the response of the immune system. So, the specifics of the genetics of each individual disorder is not completely understood and there is research going on to understand what genes specifically seem to be associated with genetic predisposition to certain disorders. But for example, we know that in multiple sclerosis, having a first degree relative with MS can increase the likelihood of developing MS, and this comes from studies of twins for example, but the risk is not 100%. So, it comes from other specific genetic factors like the major histocompatibility complex.

Dr. Alex Simpson: [40:48] The major histocompatibility complex, or MHC encompasses hundreds of genes that code for proteins that are involved in immune function. The human MHC is also referred to as the human leukocyte antigen or HLA complex, as many of these genes include proteins that are located on the surface of white blood cells, also known as leukocytes. For MS, in addition to rare neuroinflammatory disorders, variations or alleles in the HLA complex are linked to autoimmune disease. For example, the HLA DRB1*1501 allele is commonly associated with MS. NMOSD also appears to be a disease influenced by the HLA complex as it occurs more frequently in people who express certain alleles. For example, the DPB1*501 allele is a risk factor for development of this disorder in certain Asian populations, while the DRB1*0301 allele is associated

in Western populations. With that being said, there are certainly more factors at play than solely genetics that are linked to the development of neuroimmunological disorders and the interactions between genetics, epigenetic mechanisms, the environment, and other things definitely contribute.

Dr. Paula Barreras: [42:03] In other conditions like AFM, the role of genetics is less clear. There is probably a genetic component to the susceptibility to infection in the first place, but we don't know much about that just yet. And in other disorders like transverse myelitis or optic neuritis that are not associated with diseases like MS or NMO, there may still be a genetic susceptibility to autoimmunity more in general, but there's still a lot of research to be done to understand the specific genetic factors. I think the key message with the genetic disposition, and this is something that we are often asked by patients is, "Are my kids going to have this if I have it?" "Are my siblings going to have this?" And I think the answer is that these diseases are not hereditary in the classic sense that patients tend to understand hereditary disorders. So, it's not 100% probability that a first degree relative is going to have any of these conditions. There is probably a little bit of increased risk compared to the general population, but that risk is not nearly as much as what we would understand as a hereditary condition.

Krissy Dilger: [43:21] Got it. Thank you so much. That's the end of my questions. Is there anything either of you would like to add on this topic, or go into, or do you think we covered it all?

Dr. Paula Barreras: [43:35] Well, I think there's a lot of work to be done in these diseases still so this is a... We thank you for the invitation and we thank SRNA for the chance to participate and this motivates us more to keep studying and keep learning about these rare conditions. There are still a lot of questions to be answered here.

Krissy Dilger: [44:01] Great, thank you so much. I totally agree and hopefully research will keep progressing our understanding of these disorders and how the immune system is related. So, thank you both so much for your time. We really appreciate it.

Dr. Paula Barreras: [44:13] Thank you.

Dr. Alex Simpson: [44:14] Thank you.