All Things Relapses

You can watch the video of this podcast at: youtu.be/QFATm9hyLZI

[00:00:02] **Intro:** "ABCs of NMOSD" is an education podcast series to share knowledge about neuromyelitis optica spectrum disorder or NMOSD, a rare relapsing autoimmune disorder that preferentially causes inflammation in the optic nerve and spinal cord. "ABCs of NMOSD" podcast series is hosted by SRNA, the Siegel Rare Neuroimmune Association, and in collaboration with the Sumaira Foundation and Guthy-Jackson Charitable Foundation. This education series is made possible through a patient education grant from Horizon Therapeutics.

[00:00:51] **Krissy Dilger:** Hello, and welcome the "ABCs of NMOSD" podcast series. Today's podcast is titled "All Things Relapses." "ABCs of NMOSD" is an education podcast series to share knowledge about neuromyelitis optica spectrum disorder. My name is Krissy Dilger and I moderated this podcast. This podcast series is hosted by the Siegel Rare Neuroimmune Association in collaboration with the Sumaira Foundation for NMO, and Guthy-Jackson Charitable Foundation. ABCs of NMOSD is made possible through a patient education grant from Horizon Therapeutics. Horizon is focused on the discovery, development and commercialization of medicines that address critical needs for people impacted by rare autoimmune and severe inflammatory diseases. They apply scientific expertise and courage to bring clinically meaningful therapies to patients. Horizon believes science and compassion must work together to transform lives.

[00:01:52] For today's podcast, we are pleased to be joined by Dr. Hamza Coban. Dr. Coban is an assistant professor of neurology at University of Connecticut in Farmington, Connecticut. He is a neurologist specializing in neuroimmunology disorders including multiple sclerosis, neuromyelitis optica spectrum disorders and other rare autoimmune conditions affecting the central nervous system in adults and children. Dr. Coban received his medical degree from Hacettepe University School of Medicine in Ankara, Turkey. After medical school, he did a post-doctoral research fellowship at University of California, Los Angeles and University of California, San Diego where he studied neurodegeneration and neuroinflammation in the setting of Alzheimer's disease and HIV associated dementia. Then he completed his neurology residency at University of Connecticut in Farmington, Connecticut and served as chief resident in his last year of residency. After residency, he completed his fellowship training in neuroimmunology at University of Pennsylvania and Children's Hospital of Philadelphia. Dr. Coban's research focuses on the aging and transitional care of neuroinflammatory disorders from pediatrics to adulthood and adulthood to elderly.

[00:03:13] So thank you for joining me today. So to begin, can you just explain what a relapse is for someone who is diagnosed with neuromyelitis optica spectrum disorder?

[00:03:26] **Dr. Hamza Coban:** Of course. First of all, thanks for having me and giving me this opportunity to connect with you and with our patients. Regarding your question, in neuromyelitis optica spectrum disorder is somewhat similar to multiple sclerosis disorder patients too. First of all, there are a few things to consider before defining a relapse which sometimes can be confusing for us as providers as well as for our patients since we commonly use a couple of different terms synonymously. One of them is a relapse and we also

use an attack or flare-up or exacerbation. These terms, most of the time we use them synonymously. When we try to define a relapse, it's really a new or a worsening symptom, a neurological symptom. This symptom can be a focal symptom affecting only one neurologic system. This could be an eye involvement as in optic neuritis and visual change, this could be a weakness or numbness, tingling. This could be affecting only one of these areas or could be affecting multiple areas at the same time. But most of the time, they are new that our patients did not have before or they had some symptoms before, but they have gotten significantly worse. Another thing, these things, these episodes or symptoms should be happening in the absence of an infection or a fever and should be lasting at least more than 24 hours. That's how we define a relapse or an attack or a flare-up in NMOSD.

[00:05:26] **Krissy Dilger:** Okay. Great, thank you. And what is the difference between a relapse as you just defined it and a worsening of symptoms. For instance, how can someone who has NMOSD tell which one they are having?

[00:05:40] **Dr. Hamza Coban:** Yeah. In NMOSD, the relapse and the worsening of symptoms can be different. We may mean different things. First of all, as I explained earlier, the relapse, flare or an attack it's one aspect in our patients. The other aspect is pseudo relapse and another phenomenon commonly we come across with is Uhthoff's phenomenon. Maybe we can explain those first. A relapse as we discussed earlier, a new symptom that didn't happen before, lasts more than 24 hours in the absence of a fever or any other illness. A pseudo relapse is usually an old symptom that can feel a little worse in the setting of an infection or illness or a stress, this could be a physical stress or emotional stress, but they are old symptoms that they had before, just feeling a little worse. But as long as the illness is resolved and the fever is resolved, those symptoms should go back to baseline. That's pseudo relapse. And another phenomenon we deal with we see is we borrow this term from multiple sclerosis literature which is similar phenomenon called Uhthoff's phenomenon. In this case, what happens is some old symptoms again comes back or feels slightly worse in the setting of a physical activity or an exertion. For example, one of my patients mentioned that when she was doing outdoor activities, she was hiking, by the end of the hike, she felt weaker in her legs. But whenever she rested after 10 minutes or so, when she cooled down, her symptoms resolved and we call it Uhthoff's phenomenon.

[00:07:53] The other thing is worsening of symptoms can be misleading sometimes and can be confusing. Especially in our multiple sclerosis patients we talk a lot about progression or secondary progression or primary progression. This phenomenon is not as common in NMOSD. In NMOSD, the progression is usually dependent on the relapses. With every relapse, there [may be a lot] of symptoms over time, they may progress over time, but only with the relapses. We don't see progression independent of relapse as much. Still could happen, but much, much rarer. So that part is important. So we don't see that secondary progression as much with NMOSD. So if there is a worsening of symptoms, if something is feeling worse, an old symptom, then we should definitely start looking for any underlying infection and fever or any other stressors. Sometimes, these stressors can be silent meaning they may not cause an apparent symptom for example one of the common infection is urinary tract infection. Sometimes, we don't know about it until we test for it. So those are the important things to think about when we are dealing with symptom that is feeling worse than usual.

[00:09:31] **Krissy Dilger:** Okay. Great, thank you. That's a good explanation. So what is known about the cause of a relapse in NMOSD? Is it possible to pinpoint the cause or just what is known about it?

[00:09:48] **Dr. Hamza Coban:** So the cause of the relapse is an inflammation. Inflammation in the central nervous system and this inflammation even though we don't know that well what triggers that specific inflammation, inflammation nonetheless in the central nervous system affecting the brain, optic nerves, the brainstem portion and the spinal cord and this inflammation damaging the myelin and also other supportive

structures in the brain and spinal cord such as astrocytes and damaging the blood brain barrier and eventually can be damaging the neurons and axons. And when this happens, it causes new symptom most of the times and depending on the location, that symptom varies as in optic neuritis, visual symptoms, as in brain stem maybe hiccups or intractable nausea, vomiting or narcolepsy, excessive sleepiness or weakness in extremities. This could be again focal with one system is involved, one area of central nervous system is involved or can be multiple areas involved at the same time and they may have both visual symptoms as well as weakness or hiccups at the same time.

[00:11:22] **Krissy Dilger:** Got it. Thank you. So what should someone do if they think they may be experiencing a relapse?

[00:11:35] **Dr. Hamza Coban:** So in that case, I think it is very important to recognize those symptoms especially as we discussed earlier if there is a strong suspicion for a true relapse, a new symptom or worsening symptom in the absence of infection or illness and lasting more than 24 hours, definitely I would contact a neurologist right away and seek medical attention because especially in NMOSD and aquaporin-4 positive NMOSD, we know every attack comes and every attack can cause severe and debilitating symptoms and it is very important to recognize and diagnose early and treat early and definitely I would seek medical attention right away in that case.

[00:12:30] **Krissy Dilger:** Okay. Gotcha. So like possibly an emergency room if needed. Okay.

[00:12:37] **Dr. Hamza Coban:** Of course, definitely contact a neurologist office first if possible. If not reachable, going to an emergency room or admitting to the hospital is definitely reasonable.

[00:12:51] **Krissy Dilger:** Okay. Thank you. So speaking about treatment, how are relapses treated and by what type of medical professional would provide that treatment?

[00:13:04] **Dr. Hamza Coban:** I think at this point, the important thing is it should be treated by an experienced neurologist. The neurologist should be the leading provider, but it requires a multidisciplinary team approach and a comprehensive approach most of the times and it requires expertise for the most part and in case of an acute relapse, there has to be an experienced neurologist to make a diagnosis and guide the workup and treatment afterwards and an experienced nursing staff and sometimes the relapses can be severe and can require ICU admissions and there needs to be an experienced radiologist to read the imaging and give us a better idea about the process and depending on the treatment that we utilize, the experienced team with those treatment modalities are very important, but the main thing is prompt diagnosis and treatment effectively in a controlled environment in an experienced center.

[00:14:24] **Krissy Dilger:** Okay. Great, thank you. And which acute treatments are used in relapses?

[00:14:34] **Dr. Hamza Coban:** In acute treatment even though it may vary from center to center and depending on the symptom and severity of symptoms, most of the time our first line therapies after making the diagnosis, right after making sure this is an acute true relapse, the first line therapies are usually high dose steroids and depending on the severity and the response we usually quickly escalate the treatment especially in the case of aquaporin-4 NMOSD. It can be slightly different in MOG antibody related disease. Most of the time MOG antibody related disease are very responsive to high dose steroids and they recover quickly and they may not require further treatment but in aquaporin-4 positive NMO, most of the time we see more severe symptoms and more severe disability and exam findings for them. Most of the time we quickly escalate to plasma exchange right after steroids. Sometimes we do start with steroids and depending on response move forward to plasma exchange, sometimes we do it concurrently. And even plasma exchange may not

be sufficient in certain cases and it also requires some time every other day plasma exchange for about a week or longer. If we don't see significant response, we sometimes follow plasma exchange with either IVIG or more immunosuppressive treatments such as Rituximab or similar agents and that's how we treat at least in our center.

[00:16:33] **Krissy Dilger:** Okay. Thank you. So how long of a period must pass after a relapse before having another one? For instance, can a person relapse twice within the same week?

[00:16:49] **Dr. Hamza Coban:** It's an important question. Theoretically, I think we use an arbitrary number as 30 days. If there is a new symptom or a new attack, new MRI lesion within 30 days, we usually consider that within the same relapse, maybe the treatment wasn't as effective or maybe the treatment was delayed. If it happens in the first 30 days, we consider as one relapse. If it happened more than 30 days, consider it as a separate relapse.

[00:17:32] **Krissy Dilger:** Okay. Great, thank you. So you talked about some of the damaging effects a relapse can have on for instance vision or just in general symptoms of NMOSD. Is this damage permanent or is recovery of function possible?

[00:17:52] **Dr. Hamza Coban:** Again another very important question. The answer is potentially and probably more common than other demyelinating disorders such as multiple sclerosis and MOG antibody related disorders and compared to NMO. Most of the time with neuromyelitis optica spectrum disorder especially the aquaporin-4 positive NMO, the relapse resolves with or without treatment mostly partially as opposed in MS, especially earlier ages they tend to have almost full recovery. Again in MOG antibody related disorder, they tend to have almost full recovery but in aquaporin-4 NMO it is less common, however, it doesn't mean that's the rule especially if we are able to diagnose early enough and treat effectively early enough we can have great outcomes. A couple factors can be contributing that too in addition to early diagnosis and treatment. Maybe patient's age is an important factor, the younger the patient the better response they may get with effective treatment, but still even our older patients with effective and prompt diagnosis and treatment they have better outcomes.

[00:19:32] **Krissy Dilger:** Got it. Thank you. So we talked about acute treatments after a relapse. What are some of the therapies used to prevent relapses for people with NMOSD?

[00:19:48] **Dr. Hamza Coban:** Of course. At this point, I think it is important to understand the disease and the disease course and maybe the natural course. These disorders NMOSD, aquaporin-4 positive or MOG antibody positive or double negative NMOSD, they can be slightly different. If we have to start with MOG antibody related disease, it's usually most commonly monophasic disorder meaning after the first attack up to 50% of the time we don't see a recurrence or relapsing episodes. For them after the first event, most of the time after the treatment of the acute attack, we don't usually recommend preventive therapy right away unless they have another attack down the road. However, in aquaporin-4 positive NMO and double negative NMO to some extent, we know from natural history studies and experience they tend to have relapses and we also know each relapse counts and each relapse may not resolve completely and may cause permanent damage, permanent disability and that can build up. So for those patients, we most commonly recommend preventive treatment to prevent those attacks or relapses. For that thankfully nowadays we have FDA-approved medications with good effect, but we also utilized in the past before FDA approval, even now some off-label treatments and there are some ongoing studies and treatments under investigation. If we have to start with the FDA-approved ones, the first medication which was approved for NMO was eculizumab. It is a complement inhibitor, it's an IV infusion but one caveat is it has to be infused every two weeks and there

are some safety measures that needs to be taken. That's the first medication with good effect and which is approved by FDA.

[00:22:19] Another medication relatively recently approved is inebilizumab, another infusion therapy. It has a different mechanism of action. It is a monoclonal antibody targets some compartment of the B cell within the immune system. It's called anti-CD19 therapy. Again it's an infusion once every six months after the initial two doses in the beginning. And lastly another medication with different mechanism of action called satralizumab. It's an IL-6 inhibitor which is, the IL-6 is shown to be playing a key role in the pathogenesis of NMO in terms of blood brain barrier break and also further damage in the astrocytes and myelin and that medication works by blocking inhibiting to IL-6. It's a subcutaneous injection. In addition to these three FDA-approved medication, we utilize some other medications as off label. One of them, probably the common one is rituximab. It's also an IV treatment. Again has B cell depleting properties. Instead of CD19, it targets CD20 B cells and it is also an infusion every six months. And one advantage of Rituximab maybe it's probably more readily available in the acute hospital setting especially we can utilize in the acute treatment of NMO in the hospital setting.

[00:24:09] Besides that there are some relatively older treatments historically used. We still use sometimes maybe less although sometimes we use them in combination with other therapies such as azathioprine is one of them. It's an oral medication taken every day and another one is mycophenolate mofetil, again another oral medication with immunosuppressive properties and rarely, especially maybe not in the United States as much anymore but in other parts of the world lower doses of prednisone has been utilized. In addition to that, there are some other medications under investigation. Some of them completed the clinical trial period and shown to be effective. One particular one is ravulizumab which is second generation complement inhibitor similar to eculizumab with more extended interval infusions, instead of two weeks every eight weeks infusion. There are some additional treatments in early stages of investigation. It is a long list, but we are thankful that we have so many options with good effect for NMO patients nowadays.

[00:25:45] **Krissy Dilger:** Yeah. It's so true and thank you so much for going through each one of those. I know it is a lot but we appreciate it and I'm sure our community will as well. So, talking about therapies, when should someone consider switching therapies? Does a relapse mean their current therapy isn't working or would you try a little longer? Just curious to hear your thoughts.

[00:26:12] **Dr. Hamza Coban:** Of course, another important question. I think at this point, we have to consider a couple of things when we come across with this issue. One thing I think the timeline of events is important. And another important thing is even though all of these medications are quite effective, we are still dealing with significant and relapsing and remitting disorder which is a chronic disorder. Our ideal goal would be to stop relapses completely with zero relapse but it may not be the realistic goal at times. We may need to accept some relapses for some patients, but with that still it doesn't mean that we don't need to switch since we have other options and we try to find the right treatment for the right patient because one treatment may not work for everyone. So with that one important thing is the timeline as I mentioned earlier. Especially for some of the medications we have to look at when the relapse happened, how long after starting the treatment. If it happens every early on within 3 to 6 months after starting therapy, may not be considered as a true fail of that particular therapy. Most of the time, most of these medications takes a while to be fully effective especially the B cell therapies.

[00:28:07] And another thing especially it was shown with rituximab in observational studies even though we don't understand the reason behind this well, after starting rituximab within the first three months there was an uptake in recurrence of symptoms or relapses. Sometimes to mitigate that we may utilize a longer

prednisone taper or a concurrent immunosuppressive therapy but beyond that beyond 3 to 6 months, we usually see a better effect. So those are the other things to consider, but even with these considerations if someone is continuing to have relapses probably it's reasonable to think about switching to another therapy maybe a different mechanism of action. If you ask how many relapsed later, you would consider a switch. Probably there is a not great answer to that. It probably depends on the comfort level of the neurologist and the patient, also probably depends on the severity of the symptoms and the attacks but every attack, every relapse counts and most of the time we have a low threshold to switch therapies if we have to, but at this point again there are other considerations we need to look into especially around the immunizations, the vaccinations since some of these treatments especially complement inhibitors requires immunization for meningococcal bacteria to prevent meningitis.

[00:30:02] For example, if we are switching someone from rituximab or inebilizumab to one of these therapies, eculizumab or ravulizumab we have to think about that because we know vaccine response is attenuated with B cell therapies. So the timing of the vaccine becomes important and sometimes we utilize prophylactic antibiotics to some period of time until we are sure they have good response to vaccine or they are protected for this bacteria. Those are other important considerations during this process of switch.

[00:30:45] **Krissy Dilger:** Got it. Thank you. So, we get this question a lot in our community. Are there any non-medication or natural options for helping to prevent a relapse? Would for instance immune boosting vitamins help?

[00:31:05] **Dr. Hamza Coban:** That's a great question. I wish I had a better answer, but unfortunately we don't have great data about other interventions for example, diet or supplementations and so forth. One caveat with these interventions is very difficult to study a diet and there has been multiple studies ongoing with some good results but still it's a challenging area to study, but it doesn't mean that we don't have any recommendations based on experience and common sense. We definitely recommend a healthy and balanced diet. I personally don't recommend any specific particular diet or restrictions but heart healthy and a balanced diet would be my recommendation. The other thing we know from again multiple sclerosis literature more about this is the vitamin D supplementation. I still check for my patients their vitamin D status and if they are deficient, I recommend supplementing it. And another important consideration is vascular risk factors, such as smoking. Smoking has been shown to be an independent risk factor for MS and progression. It's probably true for NMOSD as well and since it is also a vascular risk factor and NMO also to some extent can cause similar problems, I definitely recommend to my patients to stop smoking and try their best to stop. And on top of that general common sense and general health considerations, overall wellbeing in terms of physical health as well as mental health, I think they are other important areas. Sometimes we may miss from time constraints, maybe some other reasons, maybe some personal factors, but the mental health, depression and anxiety is very common in our patients which contributes a lot to overall perception of wellbeing as well as perception of disease, disability, so it's very important to address those issues as well.

[00:33:51] **Krissy Dilger:** Got it. Thank you so much. That's the end of my questions, but I just wanted to open it up to you if there was anything else you would like to add on the subject of relapses in NMOSD.

[00:34:04] **Dr. Hamza Coban:** Of course. Thank you again for this opportunity. I think we had a great discussion. Beyond our discussion so far, I think I cannot stress enough that it's very important for us as providers and for our patients recognizing the signs and symptoms of an attack or a relapse in that sense and taking prompt measures to deal with that is very important. This could be in a patient with a known diagnosis or this could be someone who is having their first attack. Sometimes these symptoms can be ignored and missed especially this could be from our side, from patient's side because most of our patients are younger and they tend to ignore their symptoms because they are young and they don't expect any major medical

problem like that. And on our end as providers, we may miss some of the symptoms, some of the signs, so it is really important for us as a community to educate each other and recognize the early signs and guide the treatment accordingly. And again another important aspect as we discussed earlier especially for our patients taking care of ourselves as a community, as an individual in terms of overall wellbeing including mental health and physical health. I think those are the other things I want to add.

[00:35:57] **Krissy Dilger:** Great. Thank you so much. I think that's all very important and thank you for spending the time with me today. I and our community will really appreciate this resource.

[00:36:09] **Dr. Hamza Coban:** Thank you very much. Thanks for the opportunity. It's been great.