Monophasic vs Recurrent Rare Neuroimmune Disorders

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[00:00:00] **Dr. Sydney Lee:** Hi everyone. Thank you so much for having me. I'm excited to talk with you all today. This talk is going to focus on the difference between monophasic and recurrent rare neuroimmune disorders. These are my disclosures and this is just a brief outline. We're gonna start first with talking about what a relapse is. We'll go through what that looks like in general, and then we'll spend some time getting more into the details of the different rare neuroimmune disorders, which ones are monophasic versus recurrent and what that might look like.

[00:00:41] And then at the end we'll spend some time going through what is a pseudo relapse and what might that look like. So, starting with relapse, what is a relapse? You might hear this called by some other terms as well. So sometimes it can be called an attack or an exacerbation. And basically, what this is it's an episode of new inflammation in the central nervous system.

[00:01:04] So that could be the optic nerves or anywhere in the brain or the spinal cord. And generally, for it to be a true relapse, we generally say that symptoms have to last at least 24 hours, often longer. And the symptoms really depend on what part of the nervous system is involved. If somebody had a prior attack and now, they have a new area of the nervous system affected, they'll probably experience new symptoms that are different from what they had with their initial attack.

[00:01:38] But you can have a new episode of inflammation affecting the old area of inflammation as well. You could also have worsening of prior symptoms with a relapse. An example of this would be a 21-year-old woman has a known diagnosis of neuromyelitis optica spectrum disorder or NMOSD. Let's say she had her initial attack many years ago and now she's waking up with new painful vision loss in the right eye.

[00:02:10] This vision loss persists until the next day, lasting at least 24 hours. That would be very concerning for a new relapse. What actually happens if you think you might be having a relapse? Often this requires contact with a physician or your care team. It depends on the relapse, but sometimes it requires hospital admission to get investigations done on a relatively quick basis and start any treatment that might be needed.

[00:02:41] And so this often involves a new neurologic examination comparing to the last examination. And then in a true relapse, MRI will often show a new area of inflammation. So, a new spot that's lighting up in

the brain or the spinal cord or the optic nerves. And then sometimes we might repeat a lumbar puncture as well to see if there's any evidence of active inflammation going on in the cerebral spinal fluid.

[00:03:11] And depending on the relapse someone might need what we call acute treatment. And the goal of that is really to calm down that active inflammation as fast as possible. And this is going to depend again on the underlying disorder or the severity of the relapse. It's gonna be a little bit different for every relapse, but it often involves some form of steroids, whether it's IVIG or oral.

[00:03:38] We might use plasma exchange, which we call plex or intravenous immune globulin or IVIG. And then again, depending on the relapse this can have some implications for preventive or long-term treatment as well. So sometimes a relapse might be an indication to start treatment if someone wasn't on treatment before.

[00:04:02] So that might be the case in somebody with myelin oligodendrocyte glycoprotein antibody disease or MOGAD. Or in the case of somebody who's already on treatment. For example, someone with NMOSD having a relapse might actually be an indication to switch the treatment that they're already on. And then what happens after that acute relapse phase, after the initial hospital admission and any treatment.

[00:04:33] So most relapses do have some form of recovery, but it's quite variable. And it can be difficult for us to predict exactly how much recovery somebody's going to have from a relapse. So again, this depends on the underlying disorder. And sometimes people can experience recovery months, even a couple of years after their relapse.

[00:04:57] So it can be quite a variable process, and every relapse is a little bit different. And often people might need to work with rehab whether that's in the inpatient or the outpatient setting. And then what do we mean when we say monophasic versus recurrent disorders? So monophasic is basically the opposite of recurrent or relapsing.

[00:05:22] If we say that there's a monophasic disorder, this means that there's a one-time single immune mediated attack on the central nervous system with no further episodes. So, no relapse versus when we say recurrent or relapsing. This means that there's also an initial immune mediated attack on the central nervous system, but there's now the potential to have further episodes or relapses in the future.

[00:05:51] And it's important to know that this classification, so whether you have monophasic or recurrent relapsing disease is really based on the natural course of the disorder. So even if you're on a really good treatment that prevents future relapses the disorder might still fall in the recurrent relapsing category.

[00:06:14] And let's dig in now to the more specific disorders that we're actually talking about. On the left here, we have those that fall in the monophasic category. That includes optic neuritis, transverse myelitis, and acute flaccid myelitis. MOGAD, ADEM, and autoimmune encephalitis can also fall in the monophasic category.

[00:06:37] And then on the right we have the recurrent relapsing category. The most classic kind of prototype for this would be multiple sclerosis, where you have the potential to have multiple relapses over the lifespan. We're not gonna talk specifically about multiple sclerosis today, but it does fall in that category.

[00:07:00] And then also in this category is NMOSD and then MOGAD, ADEM, and autoimmune encephalitis can also fall here. We're gonna go into all of these in some more detail and you can see that the bottom three, MOGAD, ADEM, and autoimmune encephalitis do fall into both categories. Sometimes that's where a little bit of confusion can arise.

[00:07:22] We'll do our best to go through those. Starting with optic neuritis and transverse myelitis, names often given when somebody comes in with optic neuritis or transverse myelitis. Despite extensive investigation, we don't necessarily find the underlying cause. There's no biomarker or neuronal antibody that we can detect.

[00:07:49] So that person's given a diagnosis of optic neuritis or transverse myelitis. And when this is the case it's generally monophasic. There's a single attack followed by a certain extent of recovery, but usually there's no subsequent relapses. And because there's no or felt to be very low risk or no risk for a future relapse, these people are generally not started on preventive treatment because we always have to weigh the risks and the benefits of starting our immunotherapy medications.

[00:08:27] That being said, people with optic neuritis and transverse myelitis can still experience daily fluctuations and pseudo relapses, which we'll get into at the end. Now there are some special cases where things can change over time. So very rarely somebody with an initial diagnosis of optic neuritis or transverse myelitis might actually have a relapse.

[00:08:54] And this should really prompt revision of the diagnosis. I have an example here. Let's say a 12-year-old girl develops numbness and weakness of both legs and difficulty emptying her bladder, and that comes on over the course of about two to three days. She goes into the hospital, and an MRI spinal cord shows a lesion spanning the thoracic cord or a good chunk of it from T four to T eight.

[00:09:20] She's got what we call a longitudinally extensive transverse myelitis. Her MRI brain is normal. She has lots of blood work done, she has a lumbar puncture, and there's no detection of antibodies that can be associated with spinal cord lesions. Overall, we know the clinical picture's not consistent with multiple sclerosis.

[00:09:42] Overall she's given a diagnosis of idiopathic transverse myelitis which we also just call transverse myelitis. And she goes on to do quite well for the next 10 years not on any preventive treatment, but then 10 years later, she develops vision loss in her right eye. So that's quite new for her.

[00:10:04] The spinal cord MRI shows no changes from previous, but when they look at the brain and the orbits this does show evidence of optic neuritis. And so, she goes back into the hospital, they repeat all of her blood work and her cerebral spinal fluid, and this time the blood returns positive for MOG antibody.

[00:10:24] And so with this, given her clinical picture and now this positive MOG antibody, her diagnosis is revised to MOGAD. So, this doesn't happen very often, but sometimes we do see it. And there can be a couple of reasons for this. We're always learning more about these disorders and so sometimes it's the case that someone's first attack happened many years ago and perhaps this antibody testing wasn't available or there wasn't enough awareness of the diagnosis.

[00:10:57] We know that sometimes antibodies can fluctuate, especially with MOG. Sometimes it can be negative when we first test it, and then over time or with a second attack or a relapse, that's when it can first become positive. Things can change and it can prompt going back and thinking about the diagnosis again.

[00:11:23] So now let's talk about acute flaccid myelitis. This also falls in the monophasic category. This is where you have a single attack with some extent of recovery. And it makes sense that this is monophasic, it's really felt to be related to an infectious trigger. You have that single attack and no subsequent relapses.

[00:11:47] We generally don't start preventive treatment for this. But still people can experience fluctuations in pseudo relapses. Now we'll talk about neuromyelitis optica spectrum disorder or NMOSD. By definition, NMOSD is relapsing. Again, that's based on the natural disease course without treatment.

[00:12:14] A person with NMOSD who is not on treatment the early studies showed that 92% of people will experience a relapse within the first two years after the initial attack. We know that the relapse rate is quite high, and in NMOSD the relapses can be quite severe. They often require hospital admission and treatment with IVIG steroids and possibly plasma exchange.

[00:12:41] We know that the response to acute treatment in NMOSD relapse might be incomplete. And then some special considerations are that the risk of relapse in NMOSD actually increases during pregnancy and the postpartum period. In people with NMOSD, with childbearing potential, it's just another thing to keep in mind.

[00:13:04] And we counsel people about this as well and really try to get their NMOSD under control if they're considering pregnancy. And really the mainstay of treatment for NMOSD is trying to prevent future relapse. So, the initial attack happens and that leads to the diagnosis after investigation.

[00:13:27] And then our goal is to start a preventive immunotherapy to prevent future relapse. And thankfully we have several effective medications for this now. So, we've got Rituximab, eculizumab, ravulizumab, inebilizumab, and Satralizumab. And we know that these work quite well. An example is that there's a 98.6% reduction of relapse with RAVULIZUMAB compared to placebo in the initial clinical trial.

[00:13:58] So that's a pretty good reduction of relapse. So, we're finding now that people with NMOSD tend to do quite well if we can get them on one of these treatments. That being said, very rarely somebody will have a breakthrough or a relapse while they're on one of these preventive treatments.

[00:14:16] And every clinician's practice might be a little bit different. At least at our center, if someone has a relapse on one of these treatments, we generally switch them to a different treatment within this same category. We'll talk now about MOGAD. So MOGAD is one that can fall in either category.

[00:14:38] So it can be relapsing in some people and monophasic in some people. Studies have shown that approximately 50% of adults with MOGAD will have a future relapse, and about 23% of children will have a relapse. There's quite a wide range for these numbers in the literature, 50% and 23% are the middle ground.

[00:15:01] And we know that if you are going to have a relapse with MOGAD, it's more likely to occur in that first six months after the initial attack. Not always, it can happen later than that. But that first six months is felt to be a higher risk period. And similar to NMOSD, the relapses with MOGAD do tend to be severe.

[00:15:23] Many people will need hospital admission and treatment with steroids or plex, sometimes IVIG. In contrast to NMOSD, MOGAD tends to respond really well to acute treatment. Then there's also been some evidence that a prolonged steroid taper over about three months after that acute treatment can be beneficial.

[00:15:50] And so this is one of the tricky parts about MOGAD is after somebody has their initial attack and they're diagnosed with MOGAD, we don't have a great way of knowing who will go on to have a relapse and who will stay in the monophasic category. And that's an area of active research now.

[00:16:10] And so there have been several studies that have looked at this, and a couple factors have come up. So, things that might predict that you could have a higher risk of relapse are if the MOG antibody is persistently positive on repeat testing, especially if that antibody titer or level remains high.

[00:16:32] Females tend to have a higher risk of relapse. People of Hispanic or Latino ethnicity, older children, and then people who have their first attack with optic neuritis. But again, these are not 100% predictors. There's a lot of variability. These have just been found to increase somebody's risk.

[00:16:53] And then what does this mean for preventive treatment in MOGAD? So right now, the evidence for starting a preventive treatment is lacking. In general, our practice after somebody has their initial attack would be to not start preventive immunotherapy because we don't know if that person is going to go on and have relapse.

[00:17:16] They could be monophasic. And then we've potentially started a medication that could have side effects or other risks. We're always weighing that risk and benefit. However, if somebody goes on and has their second attack or a relapse with MOGAD, then we start to consider starting them on a preventive therapy.

[00:17:36] However, we don't have concrete data for this. This is also an ongoing area of investigation and clinical trials are ongoing. Right now, what we're using in the clinic if somebody does have a relapse, is we think about starting something like rituximab or maintenance IVIG. Some people will use CellCept or azathioprine.

[00:17:58] There's a few different options. Then we'll talk about ADEM or acute disseminated encephalomyelitis. This is another one that can fall in that relapsing or monophasic category. It really depends. Some of you probably know that ADEM can be part of MOGAD. I find it helpful sometimes to think of ADEMas a syndrome or a presentation that could be a presentation of MOGAD.

[00:18:28] So some people, about 50% with ADEM will have the MOG antibody and then be classified as MOGAD. But in people with ADEM who do not have the MOG antibody, most of those people will have a monophasic course. So about 85%, and this is where you have no new symptoms, signs or MRI findings after three months from that initial ADEM attack, we see complete or near complete resolution of lesions and there's no further clinical or MRI evidence of active disease.

[00:19:03] But again, if you do test positive for the MOG antibody and fall under that MOGAD category, then the risk of relapse is then similar to what we just discussed with MOGAD. And then we'll talk briefly about autoimmune encephalitis. This is the last one. This can also be relapsing or monophasic. Autoimmune encephalitis is really an umbrella term for many different diseases.

[00:19:32] It's hard to say for sure. One kind of risk of relapse for all types of autoimmune encephalitis. It really depends on several factors. One of the more important factors is what type of autoimmune encephalitis. So what neuronal antibody is it associated with? Is this NMDA receptor encephalitis or LGI one?

[00:19:56] Each one is going to have a different risk of relapse. It also depends on whether or not it's associated with a cancer and the treatment for that cancer. We do know that for autoimmune encephalitis, early acute treatment can help to prevent future relapse. And unlike some of the other disorders, a relapse in autoimmune encephalitis tends to present in a similar manner to the first attack.

[00:20:23] People will come back with kind of the same constellation and pattern of progression that they had with their first attack. Similar symptoms, so this is in contrast to like NMOSD and MOGAD where your first attack could be optic neuritis. And then your second attack, if you have one, is completely different and it could affect a different part of the nervous system.

[00:20:51] And the relapses in autoimmune encephalitis can range from mild to severe. It can be highly variable. Again, there's no clear rule or guideline on starting preventive immunotherapy. It really depends on all these factors, the neuronal antibody and that person's individual risk of relapse going forward.

[00:21:16] So now let's take some time to talk about pseudo relapse. In contrast to a true relapse, a pseudo relapse is a temporary recurrence or an increase in old neurologic symptoms in the setting of infection, heat,

mental stress, physical stress, or lack of sleep. And so why does this happen? This is not a new attack of inflammation in the central nervous system, but the way that I like to think about it is, let's say somebody had an initial attack of transverse myelitis and with that attack they had right-sided numbness and weakness.

[00:22:00] And let's say they made a full recovery. On a good day, they feel back to their baseline. That pathway in the spinal cord has some prior damage. So that person is feeling well now, but there was previous damage in the spinal cord. And so now whenever there's any type of stress on the body, whether it's getting sick, going for surgery, not sleeping well, having a really stressful day at work.

[00:22:30] That threshold for old symptoms to come out is going to be reached more easily. You can think of that old area of damage as being like a vulnerable spot. The rest of the healthy brain tissue or spinal cord tissue is gonna do just fine handling that stress on the body, but that old area is just a little bit vulnerable.

[00:22:55] And so that person might not have a full repeat of their initial symptoms, but they might get like a little bit of tingling in the right arm. And often people tell us that it's almost like their barometer. Oh, today I'm getting a little bit of like my right arm is just feeling a little weak or my vision's going a little bit blurry again and when I think back, yeah, like I think I had a bad sleep last night or, yeah, actually I am feeling really stressed right now.

[00:23:27] So it's almost like it can sometimes be the first indicator that maybe something else is a little bit off. And this can be confusing because it can feel sometimes like a full relapse. So sometimes it can be quite severe. And other times it could be just in the form of like mild day-to-day fluctuations.

[00:23:49] Overall, this should not involve new symptoms. It's really old symptoms coming back. And sometimes we do see this on the neurologic exam but not always and there should be no new lesions on the MRI and no new elevation in the CSF inflammatory markers. And often pseudo relapse will require some different investigations because we really want to try to get to the root cause of the pseudo relapse.

[00:24:20] So we want to look for infection, we wanna talk with you about your stress or what might be going on. An example of that would be maybe we'll do a urinalysis to try to look for a urinary tract infection. And in terms of treatment for pseudo relapse this generally does not respond to immunotherapy.

[00:24:41] So we don't start acute treatment or change immunotherapies with a pseudo relapse. Really, we want to try to address the root cause. For example, if we found a UTI, the treatment for that would be antibiotics. That's all I have for today. Thank you so much.

[00:25:01] **Dr. GG deFiebre:** Thank you. We just had one question that came in. If you're answering, so are there gradations within recurrences, like people who have two or three and then others who seem to relapse regularly? Or differences between those who relapse on medication versus those who do not, or these associated with other outcomes.

[00:25:22] **Dr. Sydney Lee:** That's a really good question. There's no like definitive rule, but we tend to see that if someone has had one relapse or multiple relapses, they may be at increased risk of having more relapses. It's felt like maybe that dysregulation in the immune system is just a little bit harder to get under control.

[00:25:49] So an example of that would be somebody with NMOSD, let's say they're on rituximab. Most patients will do very well on rituximab without a relapse, but let's say somebody breaks through and has a relapse, it can be felt like maybe that person's immune system is just a little bit more aggressive and it's breaking through that treatment.

[00:26:16] And so that's where we'd have to consider switching treatment. It's hard to say. It's not that people with multiple relapses necessarily fall in a different category, but I think in that case we would definitely be watching very closely, monitoring that person very closely. And really adjusting treatments if we need to, going forward.

[00:26:40] **Dr. GG deFiebre:** Got it. Thank you so much, Dr. Lee. We really appreciate it.

[00:26:45] **Dr. Sydney Lee:** Great. Thank you. Take care.