

Is it a relapse or recurrence?

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[00:00:05] **Dr. Benjamin Greenberg:** I have the distinct pleasure of introducing our next speaker, Dr. Lauren Tardo. Lauren completed her medical school at University of Mississippi and then migrated over here to Texas. She was a neurology resident with us here at UT Southwestern, served as chief resident for the neurology program. Then did her fellowship with us and came on faculty now three, four years ago.

[00:00:30] She's risen to be the Clinical Director of the Neuroimmunology Clinic at UT Southwestern and the co-director of our Parkland neuroimmunology program and has a particular interest and focus in anti-MOG associated disorders while still seeing obviously patients with all these conditions. And we asked her to give probably what I would consider one of the most important talks of the day. And that is how do you know if you're having a relapse or not when symptoms flare? So with no further ado, I will turn things over to Dr. Tardo.

[00:01:12] **Dr. Lauren Tardo:** Thanks, Ben. And I see a lot of familiar faces in the audience. So, hello. As Ben said, my name is Lauren Tardo. I'm one of the Neuroimmunology Faculty here at UT Southwestern and see patients at both UT Southwestern and Parkland. And I agree that this is a very important topic. I think I've had - on Wednesday, I had a full day of clinic and in the afternoon pretty much every single patient asked me this question at the end of the visit. And so I told them all, okay would you like the full presentation or the two minutes spiel? Because I told them I was giving this talk today and most of them opted for the two minutes spiel. But this is a very important topic and something that we are commonly asked in our clinic, is how do I know if it's a relapse or how do I know if it's just an old symptom recurring? And so let's jump in.

[00:01:59] So a little bit of background. So many of these rare neuroimmune disorders can be relapsing in nature. So specifically our NMO patients and some of our MOG patients as well, but some of these disorders may also be monophasic meaning they really just have one attack. And these include things like our idiopathic transverse myelitis patients, our idiopathic optic neuritis patients, some of our ADEM patients, and even some of our MOG patients fall into this monophasic category. And so it's really important to recognize what is a relapse because it changes things because typically this represents or it does represent disease breakthrough and generally is an indication that we need to be making a long-term treatment change.

[00:02:45] And the other important point and probably one of the biggest hang ups for my patients is that not all of the symptoms that a patient experiences after having one of these events represents a relapse.

And so just briefly, what is a relapse? And so the simple definition is that it's new symptoms or worsening neurological symptoms that you may have experienced in the past that indicate a new area of inflammation. And that's the key point in a relapse is that really what it means is that we're having a new area where the immune system has broken through and caused damage.

[00:03:23] Typically these symptoms are going to progress over hours to days. And they're what we call sometimes focal symptoms, meaning less non-specific. So not likely just fatigue or just headache, it's generally going to be accompanied by one side of a weakness or one side of sensory loss or visual disturbances or new bowel bladder symptoms. Certainly, those other things can happen in combination with that, but typically we want to see the what we call focal symptoms. And usually, we'll see new active lesions on MRI if we get an MRI in the setting of that acute episode.

[00:04:03] The terminology that you may hear us use in the clinic is important, but it's also extremely confusing because many of us call these events different things. And so these are just a few of the terms that we sometimes use. So we may call it a relapse, we may call it an exacerbation, we may call it an attack. I've heard people call it an event before. And so there's multiple different names that can be used to equal relapse. But the important thing to recognize is that regardless of the terminology or regardless of what we call it, it's a new inflammatory event within the central nervous system.

[00:04:43] It's also really common to have recurrence of prior symptoms and this is a lot of times where this gets confusing is, are these old symptoms a relapse? And so the way to think about this is, when you had your original attack, whether it was optic neuritis or transverse neuritis or one of these other conditions, a scar formed. And so whenever we have recurrence of old symptoms or temporary worsening, a lot of times it's that scar misbehaving is how I simplify it for my patients is that scar is acting up today for some reason or another. And the signal that needs to go from eye to brain or foot to brain is going through a more tangled network that day. And so it manifest sometimes as more symptoms or recurrence of symptoms.

[00:05:31] Again, like I said, it's typically those old symptoms, it's typically less than 24 hours. You'll notice that I put an Astra cure, because if it's related to something like an infection or an ongoing stressor to the system, it can technically persist beyond 24 hours while that stressor is still on your system. And typically we can find an identifiable cause which is important and we'll talk about some of those here in a minute. In terms of the terminology here, there are many terms that we use to classify these as well that you may hear us say in the clinic. One is pseudo-exacerbation. Another one is pseudo relapse. Another, we may just say this is recurrence of symptoms. And sometimes we use the terminology of recrudescence just another way of saying that we're having old symptoms that come back.

[00:06:26] And both this slide and my prior slide with all of these different terms on it are very confusing and I think we as healthcare providers need to do better when talking with our patients. So sometimes we're very rushed in our visits and so we'll throw out these big terms that can be very, very confusing to patients. And so we need to do better. And it's always okay to ask if I say something to my patients, I want them to ask and say, what does that mean? Can you break that down for me, Dr. Tardo? Because it's very confusing.

[00:06:57] And so I'm going to spend the next few minutes jumping through this slide looking at what symptoms are more likely to be relapsed. And so on the - it's on the right side of the screen. On your left side, there's a green box and these are our symptoms that we would typically classify as most likely or more likely to indicate that a patient may be having a relapse. In the middle, we have the yellow box, which are on the fence sometimes hard to decide. And then in the red box, we have our symptoms that are typically less likely to be representative of a relapse. I find the green box to be the easiest. And so these are patients who typically have new typical symptoms in a new area.

[00:07:42] And so what do we mean by new? So new meaning a symptom that you've never had before. So if your original event was transverse myelitis, and suddenly we have new vision loss, that's pretty telling that this is likely going to be a true relapse, and also in a new area, so the same thing. Previously, let's say the right side of your body was impacted. And two years later, we have an episode on the left side of your body generally that tells us, okay they've never experienced this, this is likely going to be a relapse. The other one on this one is new typical symptoms in an old area. And so this means that let's say that a patient has always had right leg sensory changes. But suddenly they have right leg weakness and they never had weakness in that right leg before. Generally, that tells us, okay this is likely a relapse.

[00:08:38] Again, the yellow box is a little bit difficult and gives us all pause. But this is whenever we have patients who have an old symptom that's worsening and it lasts greater than 24 hours. I struggle the most with this box when someone calls into the clinic. So this is generally the box that I'm going to be getting, I want an MRI, I want to find objective evidence that there's new inflammation going on in that old area where we previously had seen a scar. And then in the red box, these are the symptoms that you've had before. So let's say you had sensory symptoms on the right side of your body and these come back intermittently, but they last less than 24 hours. These are typically the things that whenever a patient calls into the clinic, we're not going to be as concerned about as a true relapse.

[00:09:28] Again, there are always exceptions to these rules, but this is a broad view of where we would classify your symptoms if you called into our clinic and our nurses are well versed in this as well. And know each of our preferences in terms of if one of my patients calls, what am I going to want them to do? And so I think this can be really helpful. It's simplified and so it's still confusing. In terms of some of the symptoms you may experience if you were to have a new relapse and it was transverse myelitis. So typically, patients will experience either weakness in an arm or a leg that was not previously impacted or both legs or both arms.

[00:10:16] And this can include weakness, loss of sensation. Sometimes patients with transverse myelitis will initially just have new bowel or bladder issues that they'd never experienced before. Or if you had transverse myelitis in the past, it can be old symptoms that progressively worsen. Again, that's the key that these are progressively worsening and that they're over this 24-hour period. That's when we would be more concerned that maybe we're having a relapse of transverse myelitis specifically if you'd had it before.

[00:10:48] Similarly, with optic neuritis, a lot of times patients will have eye pain with loss of vision in the previously unaffected eye. So if you had it on the right side and you develop new symptoms on the left side, that's going to be telling us that this most likely is representative of relapse. Or if you'd had optic neuritis in the past and both eyes or one eye and we have recurrent vision loss in that eye. If it's progressively worsening, not getting better over 24 hours, generally, we're going to be looking for, okay, are we having another episode specifically of optic neuritis?

[00:11:28] So why is this important? The first point is that true relapses require us to act, whether we put a patient into the hospital or we don't put them into the hospital, we're going to be giving them steroids typically either in the IV or by mouth. We may be doing plasmapheresis or we may be doing IVIG depending on what your specific disease process is and how bad the relapse is. But even more important is if we have a patient who has a relapsing condition at baseline. So let's say for our NMO patients who are on a long-term treatment and we have a true relapse. This is important because that tells us that your immune system has found a way around that medication and has been able to sneak back into the nervous system and cause problems again. And so that tells us that that medication is not working for you and that we need to make a treatment change. And so it's really important that we determine this, because we would want to get you on a treatment that worked better for you.

[00:12:33] And on the opposite side, pseudo relapses are also important. You'll notice that it says does not require acute treatments and has an asterisk beside it, it does not require acute treatments in the sense of we're not going to be doing steroids. We're not going to be doing IVIG. We're not going to be doing plasmapheresis, but we will be looking for that underlying cause and potentially trying to do an acute treatment for whatever that may be, which I'll jump into a little bit later. And it doesn't typically require a long-term treatment change. So those patients who have NMO and have a pseudo relapse with recurrence of symptoms related to their prior optic neuritis, if we can confidently say that it's a pseudo relapse, then typically we're not making a treatment change. And so this is really important.

[00:13:19] This is also really important for our patients to have had a monophasic process or that one attack and they're left with issues related to that. Because if we think something is a relapse in those monophasic disease processes, we need to act, because again, it's telling us that immune system is actually coming back and we probably now need to get you on a preventative medication. Versus if it's a pseudo relapse, we don't necessarily need to commit you to a long-term treatment that may suppress your immune system. If we still think this is a monophasic process again, one attack. And so what are some of those root causes that could potentially cause a pseudo relapse or a pseudo exacerbation? The most common one is infection, specifically urinary tract infections.

[00:14:10] And so my nurse Ala and Sarah know that if a patient calls into clinic with new symptoms or old symptoms, the first thing I'm going to do typically is I'm going to do a urinalysis. I'm going to do a blood count. I'm going to check liver and kidney function to see if there's an identifiable cause for why those symptoms may be recurring. Lab abnormalities can do it as well. So if a patient is diabetic and has significant fluctuations in like their glucose level or their blood sugar level, sometimes that's enough to tip you over into having some recurrence of old symptoms. Overheating is a big one, especially this summer. I feel like this summer was worse than past in Texas. And I had many patients over the months of July and August who were noticing that their fatigue was worse or that their vision was becoming blurry intermittently. And the only thing we could pinpoint was the heat.

[00:15:09] And I feel like I had that conversation a lot more this year than I have in the past. I don't know if Dr. Greenberg or anyone else in our clinic had that conversation a lot, but I feel like the past few months have been really, really tough. So I was very excited when I walked outside this morning and it was 55 degrees. I think we finally have made it. But this is a big one for our patient population. The same thing can happen if you're doing an intense workout or something like that. So let's say you overdo it at the gym, you may notice that that previously impacted eye, the vision of the lip blurry or your foot drop may become a little bit worse after overdo it at the gym. And again, generally think back to those original slides, it's temporary. So as we remove that stressor, as the core body temperature comes down, we should see that start to go back to baseline.

[00:15:57] High stress can do it. And typically these are big events, big, big life events, like losing a job or losing a loved one. But sometimes just having a high period of stress, multiple days in a row can do it. So I saw a patient this week who'd had a big board meeting the past week and they'd spent the week leading up to it, preparing for it, had pulled a lot of all-nighters, and then they just crashed after that meeting. And were having some worsening intermittent blurry vision and things like that and that's what it was, it was the stress. And so we talked about how do we compensate for that. What do we do if we know that we've got these demanding events coming up how do we prepare ourselves to be able to still be successful but also not crash afterwards?

[00:16:40] Surgery can do it. So if a patient is undergoing a big procedure, something like that is a stress on the system and that can do it as well. And the other thing is poor sleep. And I think we don't realize how

important sleep is. If a patient has insomnia or if a patient is getting up multiple times at night to urinate, it can certainly correlate with a recurrence of old symptoms. This one's easier said than done. So I have two very large dogs, Hank and Duke. Duke is 88 pounds and Hank, I think is 60 pounds and Hank likes to sleep right between me and my husband and he is a mover.

[00:17:18] Some nights I don't sleep well and it's my fault. One of the things that I will do with my patients is if we're having a lot of these episodes where we're having a lot of bad days, in addition to our good days mixed in is try to identify the cause and a lot of times sleep is not good. And sleep is low-hanging fruit. Sometimes if it is something that we can modify. If there's a pet in the room that's waking up multiple times per night, let's come up with a different plan. If you're on your computer right before bedtime, if you're on your phone right before bedtime, easy things that we can potentially modify that may help sleep, which in turn may reduce the number of those "bad days" where we're having recurrence of old symptoms can be really helpful.

[00:18:07] So what do we do if we think we may be having a relapse? And so the first thing again, like we talked about typically is that we're going to work on ruling out those secondary causes. However, there are some things in that green box that if I know a patient has never experienced those symptoms before, a lot of times what we'll do is we'll go ahead and start the treatment while we work on getting MRIs, getting labs. If it's a slam dunk, this is a relapse, but a lot of times it's not that slam dunk and a lot of times it's in that yellow box that I pulled up initially. And it's a little bit more difficult to determine.

[00:18:40] And so we start looking, we start doing the labs that we talked about. All while in the same time, we're getting urgent outpatient MRIs to try to expedite this workup to determine if it is indeed a new inflammatory event within the central nervous system. And then if it is, then typically we're going to do those treatments that I discussed previously. So steroids, plasma exchange or IVIG and then we'll have a conversation once we get through that acute phase of what do we do now? So if we were on a medication and I broke through, what is the next treatment that we move to? Or if I wasn't on a medication, because we didn't think I had a relapsing disease, what do we do in terms of going on to a preventative strategy? So there's two phases of what we do once we confirm that someone has a relapse.

[00:19:30] So what can you do as a patient? I think the biggest thing is to communicate with your medical team. I always tell my patients, I would rather know about something in the moment and not six months later because I have some patients who won't call and I tell them that is what it's there for. That is what the phone is for is to call us. That's why we have urgent lines is because I would like to walk you through what to do if we're having these symptoms, because it can be really confusing, especially for my patients who are just newly diagnosed, learning what's normal for them can take a while. Sometimes I tell my patients give yourself a year to map out what is your good day? What is your bad day? What triggers those bad days? And so in that first year I tell them, call me, I'd rather be overly cautious and have you call me too many times, so we can work through this together to help you learn what's normal for you.

[00:20:24] The other thing is to track your symptoms. So track the duration of them, track the pattern so that when you were having the phone call or the visit, we can try to place you into a green, a yellow or a red in terms of what this may be. And again, the biggest thing is to not be afraid to ask for assistance. So this is difficult for us even. So if it's not a slam dunk new symptom, new area of the body, this is something that we struggle with too in terms of knowing and that's how we rely on some of these other ancillary things like labs and MRIs to help us confirm if a patient is truly having a relapse. And so please, please don't be afraid to ask.

[00:21:03] And so in conclusion, relapses represent disease breakthrough. That's the biggest thing. A true relapse is disease breakthrough. It is an inflammatory event. It is the immune system coming in and causing

damage. Again, not all symptoms like we talked about indicate that a patient is having a relapse. One of the most important things you can do like I said, is keep track of your symptoms. I think very early in your diagnosis, start keeping track of your symptoms. Map your good days, map your bad days. So as this evolved you can know, oh, that's just one of my bad days. And a lot of times patients can look back and say, oh, it was related to this. I know what I did. I was at a baseball game on the weekend and I overdid it and now it makes sense why Monday I felt the way I felt. And that's hard to do that. And so I think if you keep a journal and track that it makes it a lot easier to look back and decide that.

[00:21:57] Again, it's really important to communicate with your care team. So please do. I always tell my patients to call if it's an acute concern because depending on where you're seeing my chart or our messaging portal can sometimes back up. So if you have a true concern and you need an answer, call us. And again, relapses may indicate that we need a new treatment or that we need to go on to treatment. And I know I went through that fast, because I really wanted to rely on questions from the audience because I think again, this is probably one of the most difficult topics. And so I added a lot of time for questions to work through some of this with you guys. So any questions?

[00:22:47] **Audience Member 1:** How often when a person has a relapse, do you do the new treatment?

[00:22:53] **Dr. Lauren Tardo:** So if it's a true relapse where we're seeing that a patient has had a new event. So let's say if you were in the yellow box and it was a little difficult for us to determine. But we did the MRI and we saw that there was a new area of inflammation or that there was an old area that is now inflamed again. Generally, every time we see that we're going to have a conversation of, we probably need to be making a treatment change and the hope would be that we find a treatment that we're not breaking through on, that we're not seeing that.

[00:23:29] **Audience Member 2:** My question is long and short. My husband was struck July as we're being loaded to go to the rehab facility. They walk in the room and say you have transverse myelitis. We've spent 7, 8 weeks in the Baylor system. Apologies if anybody here is in the Baylor system, I'm not going to rag on them. I'm just here to say and to ask what everything you just described in 30 minutes he had, they've completely misdiagnosed him. We were in the emergency room all last night and they're like, wait till Monday, call your doctor. My question is how can I get my husband into this program?

[00:24:08] **Dr. Lauren Tardo:** So we take self-referrals. And so you can go on the website and you can refer him that way. Have them reach out to Dr. Tardo if they call you or you try it again and just say, saw Dr. Tardo at a talk, she said to put another self-referral in and that may work. And we can chat afterwards too and I can get your name and look for the referral. It does not. No you can do it right now on the self-referral side.

[00:24:41] **Audience Member 3:** You had mentioned that there are labs that you can check that would indicate a possible relapse or recurrence. What labs are those?

[00:24:55] **Dr. Lauren Tardo:** So I was specifically referring to looking for a secondary cause. So blood counts, urinary analysis, liver kidney function, but you bring up a good point and there is some suggestions in some of the clinical trials specifically for NMO that there are potentially some serum tests that we could send. We don't do it clinically, because we don't have it validated, but potentially in the future, there may be some blood test available. But right now, there's not a blood test that says yes, you're having a relapse. So really, I was relying more on those labs to determine if there's a cause that would explain recurrence of old symptoms. But it's a great question and I think, and I hope in the future we will have a blood test that could tell us in some of these disorders specifically NMO if a patient may or may not be having a relapse. Does that answer your question that?

[00:26:00] **Audience Member 3:** Yeah.

[00:26:01] **Dr. Lauren Tardo:** And again, we're not doing it clinically yet. It's only in the clinical trials that they're looking at this and trying to determine if it is something that can be validated, but it potentially could come in the future.

[00:26:15] **Audience Member 4:** Hi. Thank you so much for the talk. So recently I got both like a flu and a COVID booster on the same day and then a few days later, I was experiencing a lot of fatigue and arm weakness and my transverse myelitis occurred in the cervical spine. So my symptoms were mainly loss of use in my arm. So I was wondering one, if you've observed that vaccines can cause recurrences and two, do you think there's a big difference in whether you only get one vaccine at a time or whether you get two vaccines in one visit?

[00:26:58] **Dr. Lauren Tardo:** So it's a good question. And so when you get a vaccine, the vaccine is triggering your immune system. And so sometimes in the same way as if you got a cold or got the flu itself or COVID itself, your immune system is amped up. And so similar to if you had an infection, whenever your system is amped up, trying to make antibodies or respond to a virus or something, you can have the same thing like a pseudo relapse, a pseudo exacerbation. Typically that does not represent disease breakthrough. And especially if it's recurrence of those old symptoms that can be reassuring to you. And so as you get over that inflammatory response that your body is appropriately having to respond to the vaccine, generally, we see that go away.

[00:27:37] It's a good question, especially now. And then in terms of the one versus two, so it's a personal preference. And so I have some patients who get both of them at one time and do great. I have some patients who know every time I get the flu vaccine, I have a bad day the next day. And so in those patients, I generally say, okay, let's separate yours by two weeks just so we don't have a double whammy. But in general, most patients do really well and it's a temporary impact if that does happen. It's a really good question though. Any other questions?

[00:28:10] **Audience Member 2:** I just had a question. If you have a confirmed relapse and you've gone through steroids and plasmapheresis, how do you tell if it could possibly happen again or you just don't know?

[00:28:22] **Dr. Lauren Tardo:** So that is a great question. And so again, typically, if this is a relapsing condition and we're on an immunotherapy, then we're going to change immunotherapies. Unfortunately, they're not all perfect, but the hope would be that we're going to transition to one that's going to work better. Or let's say this is a patient who was in that category where they've only had one event and we don't have them on a preventative medication, at that point, we're going to start a preventative medication. A lot of times again, if we can confirm that it really is a second attack. And again, we don't have a way to know for sure. It really just depends on the underlying etiology, the risk factors. Some of the screening for the medications, that's how we pick a medication, but we don't have a way to really say we know for sure that this is the right one for you. And hopefully, one day we can get there with our medications and knowing how to better break down patients into this is the right drug for you and this is the right drug for you. We just don't have that information right now. It's a good question though. Anything else? Oh, wait, there's one more.

[00:29:25] **Audience Member 5:** What is the advisable time frame in between the two?

[00:29:36] **Dr. Lauren Tardo:** I generally, say about two weeks, between them, I don't know if you have a different recommendation in terms of if you're going to separate them and not get them at the same time, I generally say two weeks.

[00:29:47] **Dr. Benjamin Greenberg:** Yeah. I think Dr. Carter's answer at the beginning is right. When it's personal preference. If you know it's going to make you feel bad, would you rather have 2-3 days and really bad or two separate days bad? I'm a just get punched in the face and go for three days, emerge, feeling better guy. But, from a safety perspective, it doesn't matter. So it's just a tolerability in how you feel.

[00:30:16] **Dr. Lauren Tardo:** I generally say two weeks, I separate mine by two weeks because, after my COVID vaccine, I always was run down a little bit. And so I wasn't brave enough to get both of them at the same time. So I personally separate mine by two weeks, because I'm the opposite. I'd rather just have a semi-bad day and another semi-bad day versus one really, really bad day. And so again, it's personal preference.

[00:30:40] **Audience Member 6:** If the patient has ongoing, more of the vague symptoms that never resolve. I mean, the really acute symptom that drove them to the emergency room thing that is resolved, but the ongoing, more vague symptoms never resolve. How do you ever determine then when should you become concerned that this could be elevated to a relapse?

[00:31:07] **Dr. Lauren Tardo:** It's a great question and that's that yellow box that I was talking about. If it's the same symptoms that they had from the get-go outside of the severe symptoms that got better, but it's their new baseline, generally less concerned versus if this was a new thing at pop-up. But it's difficult. And so sometimes in those patients, those are patients that I keep on surveillance imaging monitoring where we're making sure that because there's so much still going on in the background that we're not seeing silent disease breakthrough. And so I tend to individualize it based on what my patients are telling me, but it's typically more reassuring that it's the same thing, the baseline. Does that make sense?

[00:31:45] **Audience Member 6:** My question is, I guess on the medication side to manage the symptoms, how do you know - when you have the same recurring symptoms for several years, how do you determine whether your medication is really helping or is there something that could work better? Is that just communication with you to say - I don't know, I mean, is that like -

[00:32:12] **Dr. Lauren Tardo:** Yeah, the biggest thing you said it is to communicate with the care team in terms of I'm still experiencing this, I'm still having a lot more bad days than good days. Should we try to different medication or should we adjust your dosage? And so it's just communicating with the team. And I think there's a whole talk later today on the symptom management for those background baseline symptoms that you may experience outside of your attack. Great question though. Awesome. Thank y'all.