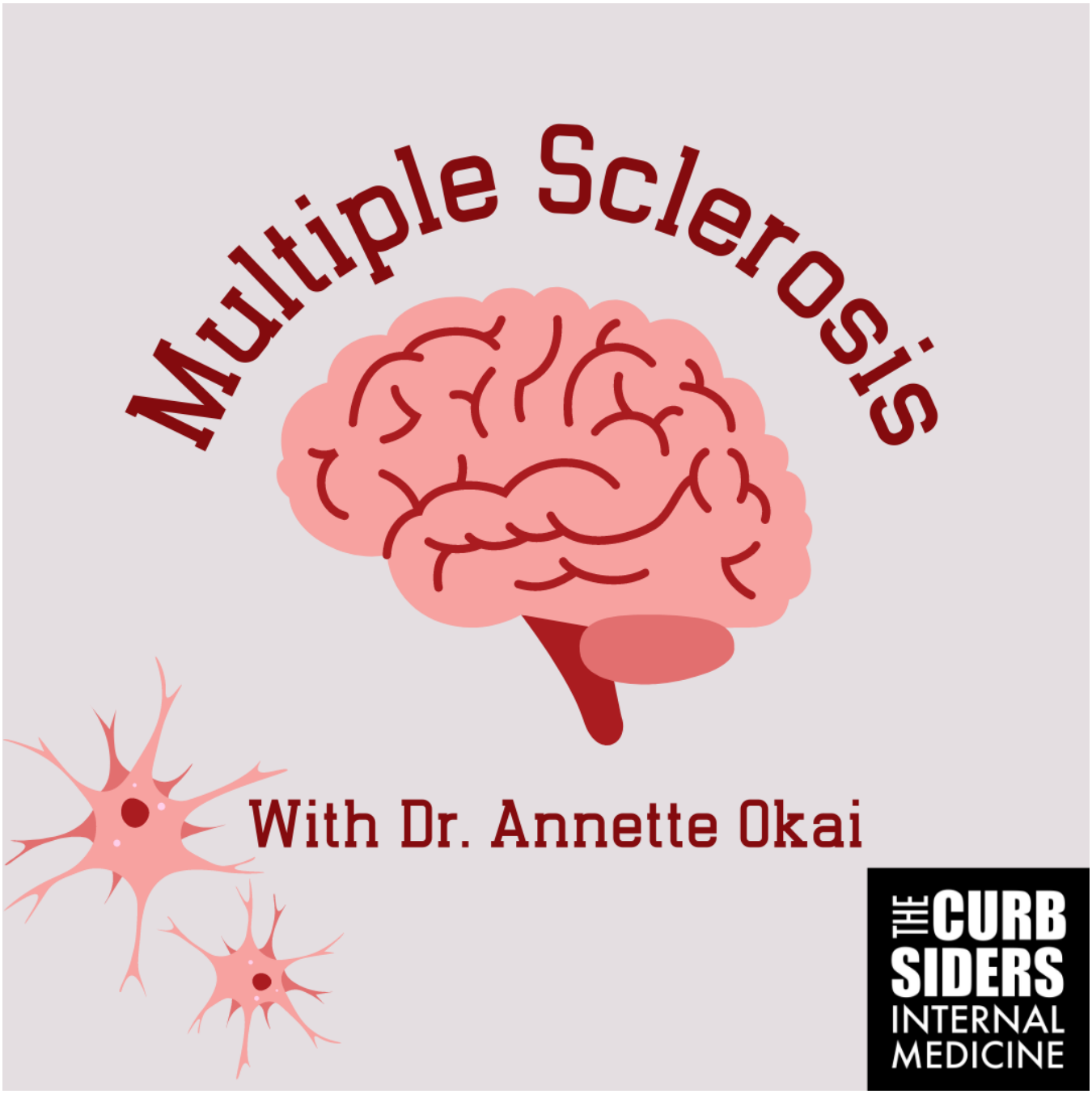
#344 Multiple Sclerosis with Dr. Annette Okai



[The Curbsiders theme]

Matthew: Welcome back to The Curbsiders. I'm Dr. Matthew Watto, here with my great friend, Dr. Paul Nelson Williams. As always, Paul, I'll tell the audience first that we're going to be talking about multiple sclerosis tonight with a fantastic guest, Dr. Annette Okai. And Paul, then I'll ask you, how was my energy coming into the show? How'd you like it?

Paul: [laughs] No, you came in real hot tonight. That's okay. I can tell you're amped up. It's good.

Matthew: [laughs] All right, Paul. Well, before we move on, would you remind the audience, what is it that we do on this episode or on this episode, on this show, Paul? What do we do on this show? It's late.

Paul: [laughs] Yeah.

Matthew: Audience, it's late.

Paul: Sure is.

Matthew: It's 10 o'clock on a weeknight. As usual, Paul and I recording a podcast.

Paul: What else am I going to do on a Monday night? But as a reminder, we are The Internal Medicine Podcast. We use expert interviews to bring your clinical pearls and practice changing knowledge. And Matt, as you alluded to tonight, we had a terrific episode with Dr. Annette Okai to talk just through the diagnosis and management of multiple sclerosis. So, a lot of high yield stuff tonight.

Matthew: Yeah, and we should thank Dr. Deb Gorth, a Curbsider extraordinaire, who is working tonight, probably in the intensive care unit, something, something heavy. She is, unfortunately couldn't be here tonight, but she did write and produce this episode. So, thank you to Dr. Deb Gorth. And on this episode, we talk a lot about the initial diagnosis because I think our guest even admits that's a tough thing to do. We talk about what initial workup we should get in primary care, all the different things that would be our role in this, and then we talk about treatment in broad strokes, because Paul there're 23 treatments. So, we had to stay broad on that.

But we do talk about how as primary care we will partner with Dr. Okai, as the neurologist or with whoever our local neurologist is. And Paul, she actually really-- When we asked her intro, she really gives her full bio almost. I'm almost thinking here, we should just go to the pun and let Dr. Okai introduce herself. But maybe you could give her title and then I'll give you the pun.

Paul: [laughs] I may forestall the pun as long as possible, but Dr. Okai is the Director of Clinical Neuroimmunology and Multiple Sclerosis Research at North Texas Institute of Neurology and Headache in Plano, Texas and she's a Clinical Associate Professor of Neurology at Texas Tech University Health Science Center. So, do what you got to do, buddy.

Matthew: Paul, I really had trouble and I would like to upfront here. I would like to thank *faculty.washington.edu/juggler/jokes.html* for these puns or jokes, which I'd like to submit. So, Paul, what I like about this first one is it doesn't really work on an audio podcast, but I'm going to do it anyway.

Paul: Right.

Matthew: So, Paul, what do you call a brain connected to three eyes?

Paul: I don't know, Matt. What do you call that?

Matthew: A brain. And so, Paul, if I were to write that out for you-

[laughter]

Matthew: -it'd be brain spelled with three i's. I really like that one, Paul.

Paul: Oh, there reminds me-- Can I tell you joke real quick?

Matthew: Sure.

Paul: What is a pirate's favorite letter?

Matthew: I'll let you say it, Paul. I don't know.

Paul: No, No, it's important that you answer it. So, what is a pirate's favorite letter?

Matthew: R? Is that right? [laughs]

Paul: You'd think it'd be R, but it'd be the C that he loves.

[laughter]

Matthew: All right.

Paul: We will cut that part out. [chuckles]

Matthew: Nope, Keep it in. I think we need to keep it in. All right, that's great. A reminder that this and most episodes are available for free CME through VCU Health at *curbsiders.vcuhealth.org.* Annette, thank you for joining us and the first question we're going to ask you as always is, can you tell the audience a little bit about yourself and give them a hobby or interest that you have outside of medicine?

Annette: Thank you for having me. I am Annette Okai. I am a fellowship trained multiple sclerosis expert. I did my training in the Philadelphia area. I went to, now, Drexel University School of Medicine. I did my residency and fellowship at Thomas Jefferson Hospital and moved to the Dallas area to practice. I'm currently Director of Clinical Neuroimmunology and Multiple Sclerosis Research at North Texas Institute of Neurology and Headache. I hold an academic position as associate clinical professor at Texas Tech University in Lubbock.

Outside of medicine, I love to travel. Traveling is my passion. I go to various places, new places, I travel at least once a quarter, that's my de-stressor, that's my relief. Most people may not understand this, but

I get my best rest on the plane, because there are no phones, pagers, emails, or anything that I have to deal with. So, that's what I do love.

Paul: And what place have you liked best in the past five years that you traveled to, where have you found the most restorative or maybe even the most surprising place that you visited?

Annette: I will say, in the past five years, the memorable, the most memorable place I will say is Barcelona. Now, I've been to Barcelona several times, but I think this city is just so amazing. Every time I go there's something new to discover and I really love the food.

Paul: Oh, yeah. Seriously, so, when I plan travel that is solely the thing I'm interested in. So, yeah, we'll have to talk-

[laughter]

Annette: Yeah.

Paul: -speak off air, I am speaking to myself.

Annette: Food has to be on the top of the list. [laughs]

Paul: Sure. Architecture, history, blah, blah, blah. But yeah, how are the tapas is the important question here.

Matthew: My favorite thing to ask guests is, as you were coming through in your career to get to where you are, what is some of the greatest advice you had and you could pick the level, whether it was when you were in med school, or when you were still in training, or now that you're out practicing? What's some of your favorite advice you've received? It doesn't have to be the best. Just any favorite advice you'd like to pass on.

Annette: I think coming up as a physician or physician in training, we're very consumed with the whole practice, we're consumed with the profession. It's hard to really focus on yourself when you're focusing on patients. Along the way, one thing I think as a medical student, there was an attending, who always said, “Make time to eat” and that was important. That was very important. It may seem very trivial, but very important, make time to eat. And then as I went along, there was another attending who said, “Take time for yourself.” That's where I picked up this habit of every quarter, I take a break.

Some people, they take two weeks in the year, and go for a long vacation, and that's good enough for them. But for me, what I found very refreshing or taking care of myself is to break it up in little spurts. Every quarter, I take time off, even if it's just a long weekend of five days to take care of myself. And then patient wise is always listen to the patient. Even though, we are the experts in the field, we always have to listen to what patients are telling us, because that's where you get what you need to make the best of it and take care of the patient the best that they need.

Paul: Let's start with our case from Kashlak. We're going to be talking, let's say, we'll call this person, Mrs. Smith. She's a 34-year-old elementary school teacher. She's presenting to her primary care doctor, because she noticed a headache and painful eye movements over the past day that had then progressed to blurred vision in the right eye, and this has made it difficult for her to drive. She reports that she has pain behind her eye and a mild headache. There has been no associated dizziness or aura, and her pain and blurred vision have lasted for the past two days. So, apparently, she got a pretty quick doctor's visit with their PCP.

She had been treated in the past with Toradol for migraines, but this did not provide relief of her current symptoms or change her vision for the better. While her pain could be assisted with migraines. Her PCP apparently, realizes that we're recording an episode tonight on MS and was thinking more along the lines of optic neuritis. This being the case in front of us, we have a patient who has these relatively acute vision changes and pain behind the right eye. We're thinking maybe optic neuritis, which means we read the episode title and probably thinking about multiple sclerosis. I think as a framework, maybe you could just talk us broadly about how we should think about multiple sclerosis, then obviously, we can get more granular as we progress through. So, just give us your broad framework for how you think about MS.

Annette: Multiple sclerosis can present in many different ways. It's hard to just choose one symptom and say this is classic for it, but there are a few common symptoms, common threads along the way. Vision change is one in optic neuritis, where division change is associated mostly with pain that could be one presenting symptom and a common presenting symptom of MS, weakness, numbness. I think what is important to realize is, if the symptoms are consistent and lasting for more than 24 to 48 hours that's something that should raise a flag that we're dealing with an inflammatory process such as multiple sclerosis.

This case that you just presented is something that's very common and it could go either way. Some physicians may say, “Well, she has headaches and the headaches are causing vision changes, let's try a headache medication before anything else.” But fortunately, they listened to the episode and say, “Wow, let's think about something else since it has been ongoing for the past two days,” optic neuritis could be a possibility. But I think the key in this case was this symptom persisted for more than 24 hours. It interfered with a function, and that was enough to get her to the doctor, and that should start the process of saying, “Let's look at what we have here if this could be optic neuritis.”

Matthew: It seems, Paul, this would trip me up, because with the history of migraines, I'd be maybe reassured. I don't know about you, Paul. Do you find that a scary [chuckles] road to go down?

Paul: Actually, I was scared in a different way just because I can always one up you for anxiety. I can hear myself, talking to myself and is thinking like, “This is an elementary school teacher. So, are they in front of a computer, are they creating tests all day long, is this eyestrain that's causing a headache? I might send them to an eye doctor.” I guess, this might be a good time to talk through about potential mimics here that we should be concerned about or other things that might belong in the differential as we're talking through this patient.

Annette: Great point. Let's talk about the most common things first. Like you said, Paul, eyestrain, she has been sitting in front of the computer most of the time, but the red flag here to rule that out is that it's only one eye. If we're thinking eyestrain, then we will expect both eyes to be involved. Matt, to your point where she has a history of migraines, yes, we know migraines can present with vision change, with pain, and headache like things. So, it is one of the things that we have to be aware of.

Certainly, that can mimic some symptoms of MS when we're talking about this. But differential still include a lot of things. Given that she's 34-year-old, I haven't heard any history of any vascular disorders such as hypertension, or diabetes, or anything to that effect. But if she did have that then we would consider those as well in the differential for multiple sclerosis. But given her relatively young age at 34, given that is one eye and not both eyes, so, okay, this can just be computer strain that we are talking about. Then we have to bring optic neuritis or the possibility of multiple sclerosis into the differential.

Migraines are still in there, because she has the headache. But because it's persisting for, as I said more than 24 to 48 hours and she has tried an analgesic in the past without significant relief and I must point out that Toradol does a pretty good job for headaches as well. Then with that being said, we have done the migraine part, so now, we move on what else could it be? Optic neuritis will be one. As I said, all the other vascular things have been ruled out. Now, we say, okay. Paul, to your point, probably she should see ophthalmologist given that she has problem driving. That is an appropriate referral as well because the ophthalmologist can dilate her eyes and see if there's inflammation in back of her eye to say this is optic neuritis or the neurologist could be the other referral. So, either way either points of referral will be appropriate for this patient.

Matthew: Yeah, I'm wondering with the history with migraines, part of what I was getting at is, patients say, maybe they've had a migraine, maybe the migraine that they thought they had was another symptom of MS that happened years ago. Probably, I would want to dig into that make sure this had been a repetitive pattern over time and no lasting symptoms. But what other things should we ask about. We're going to ask you about what exam and what other testing we might do at this initial visit aside from maybe refer her to an ophthalmologist? But what other things should we want to make, ask about that might help us move towards more of multiple sclerosis as a diagnosis here?

Annette: Great question. First, like you mentioned [unintelligible [00:15:12], is this a repetitive thing? So, for people who have had migraines and develop this eye symptom and eye pain, I would say this is quite different from my migraines I usually have. You want to elicit that history. Have they ever had loss of vision in the past not associated with headache? That's one thing you want to ask about them. Are they having any other symptom? Because while this teacher is focused on her eye, because it has now affected her driving, she may have dismissed that she has numbness or tingling in her hand or in her feet. There's something that, “Oh, this isn't important, it's just numb and tingling,” but it's been numb and tingling for two days, but it hasn't impacted her function, so, that may not have been disclosed in the past.

In terms of past medical history, things I tend to do when I try to elicit this, there are certain questions that I ask. Bell's palsy is common. If they had that in the past, that could be a sign of demyelination.

Have you had any numbness or tingling more one side than the other that have lasted for days or four weeks? Have you had any weakness, have you had vertigo? So, those associated symptoms will lead me to say, “Okay, this is something that in constellation will make me think that I'm dealing with an ongoing inflammatory process overall.”

Matthew: From what I was reading to narrow it down, because Paul and I see a lot of patients with all these symptoms. But I know context is key. It seemed there's a common age range for people to at least initially present is something like the teens to the 50-year-old range, before 10 and after 50, I was reading it's uncommon. Can that help us narrow down because Paul and I see lots of patients with vertigo, weakness, tingling?

Annette: Definitely.

Paul: God pins the needles. Oh, God helped me. Yeah.

Annette: I know and the pinky finger. If they're tingling on the pinky finger or the big toe. The median age of diagnosis is between 20 to 50 years or so. But of course, there are people on opposite end of the bell curve, but young adults are the most common people that multiple sclerosis affect. This lady is 34 years old and as I said, she doesn't have any other significant history that will lead us to think that it could be some vascular process. The age of presentation is important and sometimes, what we tend to dismiss is that a stressful event can bring on symptoms, especially if they are prime for multiple sclerosis. What do I mean by that? She's 34-year-old, it could be the end of the year or the beginning of the year, and she's getting into school and all of that. If she is primed for multiple sclerosis, she can start presenting symptoms at that point.

That brings me to another differential because if she comes in and say, I've been under a lot of stress recently, I often see that, “Oh, you have been under a lot of stress, let's bring your anxiety down a little and probably, this will improve symptom.” That is something that also occurs and we have to take care and not to fall into that trap that you are stressed, so, this is making your vision worse over two days. But it has happened and overall multiple sclerosis is a difficult diagnosis to make. If you haven't done an MRI or anything else, just getting the clinical history may lead you to believe that, “Oh, there's a lot of things anxiety going on or it could be migraine.” So, it takes being a good detective to really put the pieces together.

Matthew: Paul, I don't know about you, it's reassuring to me to hear her say it's a difficult diagnosis, because I feel that way. If you feel that way that I imagine, it's okay for Paul and I to feel that way, but Paul, you were looking like you were going to say something?

Annette: It's quite okay to feel that way.

Paul: I feel that way about most things all the time.

Annette: [chuckles]

Paul: I was going to ask, Miss Smith say has a facilitative visit and makes it into your office and you're doing your physical examination, we don't have a diagnosis yet, but you have suspicion. I imagine you're going to do an exam that is much better than mine and not using a stethoscope or a reflex hammer and you actually do sensation testing and that kind of stuff. But what are the especially high yield examination maneuvers or what are the things that you pay the most attention to, if you have a clinical suspicion for MS?

Annette: In terms of the neurological exam, if I have a clinical suspicion for MS and yes, I understand that as primary care doctors, the neuro exam is not as in depth for you guys as it is for me. But the eyes are important. Looking at pupil dilation and non-dilation is important looking in the eye doing a fundoscopic exam. In this case, if Miss Smith, I had seen her in consultation, I would have looked into her eye to see if there's any papilledema, so, swelling up the back of the eye, that will indicate inflammation to me. I want to see if her pupils dilate equally or one is sluggish in dilation versus the other. So, there's a rapid afferent pupillary defect, something that we see.

I will also like to see how her eye movements are depending on where the lesion is. Sometimes, eye movement can be restricted with her presentation of optic neuritis and see if I can elicit double vision as well. And then, look at reflexes, brisk reflexes is something that tells me that the communication between the spinal cord and all of that is somehow impaired. As I said, even though, she hasn't mentioned anything else, but what her motor exam looks like in her sensory exam, but if she came to me with this and I did a consultation, I'll concentrate on the eyes, I'll concentrate on her reflexes, and then all the other parts of the neurological exam, obviously, but that will be it.

Matthew: And it seems with optic neuritis, it could be both eyes, but most of the time, it's one eye affected, I guess, you would test vision in each eye to try to figure out if it truly has a difference in vision in one eye versus the other.

Paul: Exactly. Thank you for that, Matt. Yes, I will say that the handheld eye chart can help you determine visual acuity. Sometimes, they can be severe as they are unable to see. I can only count fingers in that eye. But something you just said, well, I'm going to take us back to what would be included in the differential. Usually, it is present in one eye, but sometimes you can have both eyes involved, sometimes one more than the other. But if we see bilateral involvement with decreased visual acuity and impairment of function, one differential of MS that we will consider will be neuromyelitis optica, which is NMO and we have a blood test for that. So, that's just a little nugget of information for us to keep in the differential when they come present with optic neuritis.

Matthew: Annette, this is take two here on this, because I had a misunderstanding of what the APD is, the afferent pupillary defect. So, if you could explain it to the audience about how we test for it and how you think about that, like how you explain it to early learners like Paul and I are early learners when it comes to this.

Paul: [laughs]

Annette: This is something that can be done in the office very quickly to determine which eye is affected. It's best done in a dimly lit room. Make sure the lights are off and give both eyes the time to dilate appropriately and then we do the swing flashlight test, where you shine a bright light into each eye. What happens is that with the healthy eye, you have very brisk constriction of the pupils when the light is flashed in the eye. And in the affected eye, you have poor constriction. So, it looks more dilated and not constricting as well as the healthy eye.

Matthew: Yeah, this sounds like it'll take some practice, but it does sound it's definitely doable and something that we should be able to recognize. I'm going to be terrified if I see this Paul in a patient.

[laughter]

Paul: I'll be impressed.

Matthew: [laughs]

Annette: Once you see it, it is easy to recognize afterwards.

Matthew: It is easy. Yeah.

Annette: Yes.

Paul: So far, we've been mostly focusing on a presentation consistent with optic neuritis. I'm wondering if you couldn't talk about other potential typical presentations of MS, are there any classic, I don't know, motor, or sensory presentations, or anything else we should be mindful of as patients come into our office?

Annette: Definitely. Optic neuritis, we have over 40% and it ranges from 40% to 70% of patients as their presenting symptoms. But there are other common presentations that occur such as transverse myelitis. There's inflammation in the spinal cord and that can produce symptoms such as weakness or sensory symptom on one side more than the other, difficulty walking. We have brainstem syndrome and what does that include? They can have vertigo, or dysarthria, or slurred speech, or difficulty with balance, keeping in mind that most of the symptoms will be continuous for more than 24 hours in a way. So, those are some of the other presenting signs that will lead us to think about multiple sclerosis as a possible diagnosis. Yeah.

Matthew: That's great. Yeah. Well, not necessarily transverse myelitis, but some of those things like the speech and the vertigo, the walking difficulty, those are in my very primitive illness script for multiple sclerosis. Those are some of the ones that would hit for me in addition to the eye. So, we've talked a lot about a lot of things so far. Optic neuritis, usually one eye, it's going to be painful, vision changes, but it could be both eyes.

Annette: Mostly painful. Sometimes, you may have painless, but mostly painful. Yeah.

Matthew: And some other things just to recap. When we're initially taking the history, we're going to ask about vascular risk factors to think about, could this be a vascular issue or stroke? We're going to ask about history of migraines, history of Bell's palsy. Our physical exam is going to be a very complete neurologic exam focusing on the eye and we're going to test reflexes, balance, all those things. Probably, a more thorough exam that we would normally do in primary care, at least neurologic exam. And then I think now it'd be good to move on a little bit and talk about, if we're the primary care doc seeing this Miss Smith at the first visit worried about optic neuritis, what else should we do? She's going to get a referral to you probably to ophthalmology or neuro-ophthalmology, what other testing should we order, what else should we do before we send her to you? Yeah, let's take it from there.

Annette: If possible, and I say, if possible, because sometimes, based on several things, it's easier for a specialist to get an MRI. But I've had primary care doctors who order the initial MRI of the brain, if a brain or orbits depending on what the patient is presenting with, if it's a weakness or something, if they need spinal MRIs. If possible, the primary care doctor can order that to get it started. But what is easy to do for the primary care doctors also look at inflammatory labs? We want to look at things like the ANA, ESR, CRP, those labs that indicate that there's increased inflammation in the body, that's something that can start the process going for the patient, and then other mimics of MS, so, other inflammatory disorder that can look like MS.

We also want to look at rheumatoid factor, ACE level, because rheumatoid arthritis, sarcoidosis, and lupus, they are all inflammatory disorders that can have symptoms similar to MS. It's important that we cross our Ts and that are our eyes to say we have looked at all those other inflammatory disorders and they are not contributing to the vision symptom that the patient is experiencing or the numbness and tingling that they have. The easiest thing for the primary care doctor to do will be to order the labs. Some go the extra mile and do the initial order, the initial MRI to see if that can be done, but if they cannot that's not an issue. It can always be done when they get to us or the ophthalmology.

Paul: And the internal question is that, with contrast, with and without, let's say, we're feeling [unintelligible [00:30:00], so we actually want to order him imaging, what is the best way to order the MRI for you?

Annette: It's best to order it with contrast, because contrast tell us if there is active inflammation at the time. With Miss Smith, this began two days ago. We think there's active inflammation. We want that confirmation if we see inflammation of her optic nerve. The contrast will light up the lesion as we call it as our jargon. We'll see enhancement or some would say active signal on the MRI. So, it's best to get it with contrast, if that's what we're thinking. Then it gives us dissemination in time for the patient.

Paul: I feel I often see, especially when my neurology colleagues are working this up. They actually order a brain and cervical spine, is that typical practice or should we just be doing the brain in my dumb-dumb primary care setting?

Annette: That is best practice for a neurologist. Coming from a primary care doctor, if we get the brain MRI, we will really appreciate that. If you're feeling very generous and you can get both of them approved, that will be awesome. But we're being practical here, most insurance company will want to

see brain lesions before they consider paying for cervical spine lesion if you don't have any other symptoms. Best practice is both brain and cervical spine MRI, but it can be a logistical nightmare for the primary care physician if they keep getting denials, whereas once we have certain things documented and what we're looking for, it may be a easier road.

Matthew: That's nice of you to say. You're just like, “Yeah, it's easier for me to get.”

Paul: Exactly.

Matthew: The insurance companies don't fight me as much as MRIs, because you, as a neurologist, that's probably appropriate. I do just want to comment on the labs, because we on the show, our audience, they’re go getters, they want to send you this patient wrapped up with a bow, they want to have a lot of testing, so you could ever-- [crosstalk]

Paul: Doing the LP in the office, they're looking for oligoclonal bands, the whole thing.

Matthew: Yeah, that’s right. That's right.

Annette: Yeah.

Matthew: Our audience above average clinicians.

Paul: [laughs]

Matthew: But I would say, as far as like, ANA, ESR, CRP, maybe an ANA, certainly, ESR, CRP, I would probably get just based some basic more primary care labs. Sometimes, the ANA can just be like, once you get somebody with a positive ANA, then you're down this road. If I'm not thinking there's any other things of lupus, I might leave that to my neurologist colleague to decide if we need to do that. Sarcoidosis as well, is there any other symptom that I'm thinking about sarcoid, whether I'm going to look at the chest or whatever. I'm not sure, Paul, if you think how you feel about that as well. I'm always scared to order these giant panels if I'm not sure what I'm going to do with all the results.

Annette: [laughs] As what I will narrow it down to is vitamin B12, thyroid, ESR, CRP, those are things that, oh, if you see them being abnormal, you're comfortable with, correct?

Matthew: Yeah. If I'm worried someone has lupus or rheumatoid arthritis, I'm very comfortable ordering those.

Annette: Yeah.

Matthew: I think that would just be my practice not to indiscriminately order some of those other tests where if you get a false positive, the patient's like-- You know what I mean?

Annette: Yeah.

Matthew: That's my thing. But I think this is a great list you've given us.

Annette: Yeah, for MS, we will see mildly increased ANA in most cases, not all of them.

Paul: Oh, no.

Annette: But we will see a low titer, anything below one to 161, one to 80, you will see that in multiple sclerosis. I think the reason why we ordered those things, because if someone has the tendency to have an autoimmune disorder such as multiple sclerosis, their chances of a secondary autoimmune disorder increases. It's not uncommon for us to have lupus and MS in the same patient. It is not uncommon for us to have rheumatoid in MS in the same patient, because the risk increases with just having one, you buy yourself another one, basically. So, that's why we do all those testing and we have to differentiate that this isn't lupus that we're seeing. Because lupus can cause vision changes as well, optic neuritis as well. But sending the patient to the specialist, if we can get the standard ESR, CRP, B12, vitamin, folate, TSH that's a good place to start and we can take it from there.

Matthew: I think maybe now's a good time to talk about, what is it, the 2017 McDonald criteria for-- When do we know we've made a diagnosis? I guess, if this was just a onetime thing she had, we would maybe call this a clinically isolated syndrome, if I'm trying to sound cool to in front of a neurologist but--[crosstalk]

Annette: You're sounding very cool right now. [laughs]

Matthew: Can you tell us, what is a clinically isolated syndrome and then how do we get to a full diagnosis of MS?

Annette: The classical definition of MS is dissemination in time and space, where you have two separate clinical events in different systems and now, you have multiple lesions in multiple places. Multiple sclerosis, you've had dissemination in time to different events and space with all the lesions. But the 2017 McDonald criteria really try to help us make the diagnosis with all the tools that we have and to risk stratify patients. What we found is that patients will have one episode, but when you do look at all the other testing like the MRIs, and you look at CSF results, and you see oligoclonal bands, everything falls in line with MS, but they haven't had a second event. We're holding off on treating those patients.

They coined the phrase clinically isolated syndrome, you had one event and you had to wait for a second event to make it definite MS. While we know that waiting is not the best thing, we need to treat these patients and treat them early. What the McDonald criteria did was bring these early patients, these clinically isolated patients into the fold if they met all these other criteria by using MRIs, by using CSF, so doing a lumbar puncture to now make the criteria. If you have had one event and you have oligoclonal bands in your CSF, you have met dissemination in time and space. If you have had one event, and you had enhancing lesion and non-enhancing lesion on MRI, you have fulfilled dissemination in time and space and now, we can treat you early instead of waiting for more damage to

occur to then make the diagnosis. So, clinically isolated syndrome was really called early MS early on, but now is considered MS, if you met all the other paraclinical testing with that.

Matthew: My understanding the reason this is important is because you want to get people on these disease-modifying therapies as early as possible. When they have that early inflammation, we think maybe that delays progression or just is going to be beneficial. Is that how you think about? Is that the biggest reason why they did this?

Annette: Yes. Starting patients early on on disease-modifying therapy, we found in clinically isolated syndrome delayed a second relapse for about a year in our early therapies that we have. By delaying a set of relapse for a year, you have actually saved the brain tissue. And so, when someone does have this second attack, then there are in the relapsing remitting multiple sclerosis phase. Relapsing MS as we now call it is the most common category that we have of MS and this is where people have a relapse, they recover either completely or partially, and they're stable for a period of time, and then they have another episode. And so, they have these fluctuations over time. So, that is relapsing MS. With secondary progressive MS that comes after relapsing MS after a certain period of time, where patients aren't having frequent relapses or they may be having shallow relapses over time and develop in more disability.

And then the last category that we have is primary progressive MS, where they have an attack, and then never fully recover, and it can just continue to develop disability over time. It's just a steep slope as opposed to a staggered slope over time. The categories just to review is clinically isolated syndrome, relapsing multiple sclerosis, secondary progressive multiple sclerosis, and primary progressive multiple sclerosis. Primary progressive is in a category of its own. The other three all falls under relapsing.

Matthew: Annette, I was surprised to read because I didn't realize, they said that relapsing MS oftentimes, they eventually stop relapsing and then they just slide into secondary progressive, because I guess, after certain relapses, you don't necessarily always fully recover, you don't fully regain all the function after a relapse, and then over time, they just accrue so many hits that they have more disability and they start to just progress slowly. Is that how it goes?

Annette: Yeah, so, that's a good understanding of it. If you have so many relapses over time, you tend to lose your neurological reserve. You have a fixed amount of neurons and if you keep damaging them, you don't have the reserve to then recover and say, “Okay, I can still get back some function and all of that.” You lose neurological reserve and then degeneration starts to occur, and that's where you slide into the secondary progressive phase. And so, it's important that we start treatment and continue treatment early to preserve as much as we can.

Matthew: Yeah, and it seemed there was no way to predict early on who was going to progress rapidly and who wasn't. Because I guess, there are some people who just have a relatively benign course and it never causes really severe disability, but other people eventually become progressively more disabled.

Annette: Correct.

Paul: Well, it sounds we're drifting towards treatment, which I'm excited to hear about, but I feel we would be remiss if we didn't talk about pathophysiology, because there was groundbreaking, earth-shattering Twitter on fire article that came out relatively recently that touched on the pathophysiology. I would love to hear how you break this down for patients or even your primary care colleagues as to what's going on here. Maybe you could talk about Epstein-Barr while you're at it, that would be even better.

[laughter]

Annette: All right, so pathophysiology of MS. We do not have one known cause of MS. We know there are several risk factors and the immune system has to be primed for this to occur. One thing I like to remind patients and probably my primary care colleagues is that MS really is an immunological disease, it is an immunological dysfunction affecting the nervous system, as opposed to the other way around. The immune system is dysfunctional and that can be due to different factors. When that happens, then it attacks the central nervous system causing MS. What are some of the risk factors that we know of? Well, low vitamin D level is a risk for MS, the further away from the equator you live is a risk for MS, you also have family history of autoimmune disorder, that's a small part that comes along with it, and then other environmental factors.

Every month or so, we come up with a new risk factor for MS. Childhood obesity, exposure to certain viruses, and then this year, a landmark paper was published about EBV. EBV, also known as mono in in teenagers has been listed as a very common risk factor for MS. It's important to point out here that EBV doesn't cause MS. EBV has been found in majority of MS. We look at it as a risk factor, not a causal factor for MS. We have looked at many viruses in the past, EBV, CMV, HTLV looking for any infectious cause that will trigger the immune system. But this was a longitudinal study so far by 20 years to follow this group and we must say that this group was very limited, mostly veterans and what they found that the virus that was common in everyone that developed MS was EBV. What's the implication for this? That's the question.

For those who already have MS, not a whole lot we can do, but do we look towards what we can do if we identify other risk factor? Can we vaccinate against EBV to reduce this? The thing about EBV is that it's an ubiquitous virus. Something is very ubiquitous, but not everyone who has EBV gets MS, but 99% of MS patients get EBV. So, now we have to look at the implications and see what we can do in terms of reducing the risk factors for those who are prone to this disease.

Matthew: The other and this is just a primary care thing. I wanted to mention there was an article I saw in Journal Watch, it was Rogers, et. al., it was in the Journal Brain in 2021 just looking at the impact of smoking cessation on disease progression, and it just seems not surprisingly current and former smokers had worse outcomes with multiple sclerosis and that quitting seems to help with the client. I think in primary care we're always looking for ways to get our patients to quit smoking. I guess this would be another way. Do you talk to your patients about that as well?

Annette: I do talk to them all the time about that. And a line I'd like to use is that, “Lung transplant has been perfected and people do it commonly, but we haven't been able to transplant the brain.”

Paul: [laughs]

Annette: [laughs] You need to stop smoking. But the pathophysiology behind that is the same because smoking really reduces the elasticity of the blood vessels. When those blood vessels and blood walls become very weak that allows those inflammatory cells to then enter the brain more freely. And so, as a smoker, you have more severe relapses, you have more weakening of your blood vessel causing more degeneration over time, and then your disease just progresses with certain things that smoking does to the body. So, yes, we counsel them all the time. That is important not only for their lungs and overall function, but for their brain health as well.

Matthew: I think we should definitely move to talking about treatment a little bit. I'd be curious to hear how you tackle this or how you talk to patients about what treatment they might give. Maybe I can just to keep our case coming along with us. Let's ground it in the case here. Miss Smith, we got an MRI of her brain, and we did see some inflammation, we got the MRI, we also included the orbit, so, we did see evidence of optic neuritis there, and then we saw an old lesion that was not enhancing that we thought was maybe evidence of a prior episode. So, I guess, we've shown dissemination in space and time and now, we're going to talk to her about treatment. How might you talk to Miss Smith about treatment?

Annette: Okay. We have MRI that shows nonactive lesion and [unintelligible [00:48:59] MRI that shows an enhancing lesion. And so, she fulfills dissemination in time and space. For her acute symptom for what she presented with right away, we always have the thing about preserving the organ. It has impacted her driving. The first thing we want to do is treat acutely. And usually for relapses or attacks as some patients call it, we use high-dose oral steroids. I've had a few of my primary care colleagues when I tell them the dose, they're like, “What? I have not used that before.” But it's essential that we reduce inflammation as much as possible. We use high-dose steroids which is one gram methylprednisolone IV for three to five days. Sometimes, we modify because patients can get to the hospital on time and we give them a ton of oral steroids.

Matthew: I thought this was a typo, Paul. I think I saw 1,250 milligrams of prednisone. Is that [crosstalk] ballpark?

Paul: [laughs]

Annette: Yeah. Well, 1,250 milligrams of prednisone.

Matthew: How many tablets is that?

Paul: [laughs]

Annette: To help the patient along, I gave them 15 milligram tablets, not the 20, so 15 milligram tablets and that's 12 in the morning, 12 at night, but three days with omeprazole for their stomach. Even the pharmacists call and say, "Are you sure you're not tearing this patient's gut lining?" I'm like, "I'm sure, because aspirin can do the same thing." So, yes. But if you will, we want to treat in a timely manner. Think about it. It is Friday afternoon and this patient comes in, they've had an optic neuritis attack, and you can—first in the time of COVID sending them to the ER is not the best thing sometime. So being practical, you call in it into the pharmacy, 12 tablets twice a day with Pepcid, omeprazole, or whatever is needed to reduce that inflammation as soon as possible. Or, if you can get them wherever in normal times, I would like to say they go to the infusion center, the ER and get IV 1 gram Solu-Medrol for three to five days, the best standard treatment of MS relapses.

Now, in terms of long-term treatment, those we call disease-modifying therapy and they're called that because we have learned over time that they really change the course of the disease. They really reduce relapses. The three goals of disease-modifying therapy are to reduce relapses, reduce MRI activity, and reduce disability progression, which they have been shown to do over time. You want them on long-term therapy because Miss Smith, she wants to drive and she doesn't want this to happen to her again. She doesn't want to be in classroom and not be able to see her students, or see the board, or something of that kind. Based on her MRI, she has met criteria, then we talk about treatment options.

There are different treatment options. I always like to tell them how far we have come. MS has been around for over 150 plus years, but therapy was only approved in 1993. Since then, there has been an explosion of growth in the amount of treatment options that we can offer to patients. They all have very unique mechanism of action. We first started with self-injectable therapies, interferons and glatiramer acetate was our standard therapy for years. And then about 10 years later, we had an infusion come about, and then we had oral therapies, and that has just been improving over time, and we now have about 21 FDA-approved therapy for MS. Because MS is so heterogeneous, it's also important to look at the whole patient when you're making the decision on what to start the patient on. What does the MRI look like? Have they have full or partial recovery from their relapse? Do they have any residual disability? We also look at comorbidities.

That's something I also collaborate with my primary care colleagues on, because if there are other comorbidities, we want to monitor for drug-drug interaction. We also want to monitor for certain side effects that certain things may be exacerbated with the patient. There are other things that I will rely on my primary care colleagues to follow up on. So, for an example, several oral therapies, we have to make sure that certain medication such as heart medication, beta blockers, or ACE inhibitors, calcium channel blockers that may not be the best person for certain oral medication.

Why am I saying this? Let's look at Mrs. Smith for an example. She's 34 years old, and she does not have any history of hypertension or diabetes, but she has a history of migraines. Beta blockers are used for migraines and certain other antihypertensives are used for migraines. We have to make sure that we do not have that overlap, if I do decide to put her on an oral therapy. Or, for another patient who I may decide to do an infusible therapy, I may need mammogram, or Pap smear, or a certain skin exam prior to starting in as they are on treatment, that's something as a neurologist. I will not feel comfortable

ordering a mammogram for my patient. Now, I'll have the primary care doctor do that. The collaboration when it comes to therapy is key, as well.

Matthew: And timing vaccines, can you talk about that a little bit?

Annette: Yes. Especially now in the era of COVID, where we're getting vaccine, we're getting the flu shot that's something that's important. Several of our therapies are immunosuppressive therapy. We are suppressing the immune system, because that is a dysfunction that is occurring and we need that to be in the lower range. But because of the mechanism of action, the immunosuppressive properties of certain therapies, the patient may have a blunted response to certain vaccines. We have to be careful in timing of the dosing of the medication, and when the patient gets vaccinated. And so, that's also important that we keep in contact with the primary care doctor who is administering the vaccination to say, no, the patient may get the vaccination after a certain period of time or we may decide to hold the therapy while they get vaccinated and require usually for vaccine we want to wait at least, we want them vaccinated a month before we do most of our dosing.

But if that is not the case and we really have to treat that patient, then we set a time schedule for them to get the vaccine. I'm speaking mostly of attenuated or inactivated vaccine, or mRNA vaccine. Because for MS patients, we do not recommend live vaccine because that may stimulate the immune system. And sometimes, there are lots of studies on this and it's 50-50, it may lead to increase in immunologic activity, and result in a relapse. But there are other studies that say not necessarily, but just as a general rule of thumb, we avoid live vaccines in MS patients.

Matthew: Can I ask about the--? Because Paul, we've talked about IBD, we've talked about rheumatoid arthritis. I know in inflammatory bowel, they tend to just hit them with the immunosuppression and just keep it running, because if you let up on it, they tend to flare. With MS, is it one of those things where you can hit it hard, and then back off over time, and maybe decrease the intensity of the immune suppression or the therapy? Is there any broad treatment approach to it?

Annette: It's a great question. MS is a lifelong disease. Right now, we treat people lifelong. I say that cautiously because right now, we have studies going to say as people age and what happens naturally as humans age is that their immune systems tend to go down naturally. Do we need to continue with these immunosuppressants, if they're aging and they're having an aging immunosuppressant? that question has not been answered yet. We're doing the study to come up with the answer. There have been several small studies that show that when you stop immunologic treatment or disease-modifying treatment, there are some patients who tend to relapse and there are some patients who tend to do well.

With this wide multicenter study going on, we may have a better answer. But at this time, we continue to treat until we have that answer, because patients can be in their 60s and still having relapses when we expect them to be on a decline in an immune system. And then there are some people who have been stable for a long time and don't need anything before. But we have no way of telling who those people are at this time. We'll wait for that study to read out but in the meantime, we continue to treat.

But that being said, though, there are few treatments that we hit hard as you said. The way their dose is that we treat them and their full treatment may take one or two years, and then they do not need any further treatment for a few more years after that. They're not being treated continuously, but their immune system has already been primed to remain low for years that they are being treated that the effect of the medication can last that long.

Paul: I was going to ask just in terms of again, working collaboratively. In the primary care setting, are there labs that we should be checking routinely that would be helpful? For instance, are you following inflammatory markers to monitor treatments? Should we be getting serial CRPs or ESRs or should we be checking other labs for medication side effects? What's helpful and typically done for these patients after they're started on treatment?

Annette: Typically, the labs that we check are liver function, blood count, and vitamin D, those are the three main things. We do not do serial ESR, CRP that does not provide us a whole lot of information, whether they increase or decrease over time. Vitamin D, we want to make sure that the patient is in normal range and not deficient over time and liver function because most of our medications are metabolized through the liver, so we do that every three months as a matter of fact. For some patient, it's easier to go to their primary care doctor to get that done, than coming to the neurologist.

More word of caution I have for my primary care colleagues is that when you do the CBC, because we are immunosuppressing the patient, there may be a shock when they see the white blood cell count or the lymphocyte count and is practically very low, and we have to say, “No, you do not need to send them to the hematologist to be worked up for anything. This is what we are doing to them.” The blood cell count is something that with most of our therapies, which are immunosuppressant, maybe mostly abnormal, especially the white blood cell count and the lymphocyte count, but that's where we want them to be. But basically, the three main things are the CBC, CMP and vitamin D levels.

Paul: And the vitamin D, are we more aggressive about repletion just giving the correlation there? Is there a higher reference range? I'm always agnostic about the first place, but it seems this patient population, I actually have to pay attention to it. So, what are we doing with those numbers, specifically?

Annette: Yes, we won them in mid to high range as much as possible. One of my safe prescription is the weekly ergocalciferol for months, because we need to keep them mid to high level range over time. We have to be very aggressive with replacement over time, because vitamin D is a soluble vitamin. If they take daily vitamins, they may hang around. I don't know what the range for most laboratory, but 30 is what I see here mostly and 30 that's still very low. We want them 50 or above if that’s the range of what we are using.

Paul: Oh, wow.

Annette: Yes.

Matthew: I wanted to refer the audience, the [unintelligible [01:03:54] had in the clinic article on multiple sclerosis in 2021 that really has a list of all the medications and really nicely says like, what some of their side effects are and interactions and things. So, that would be a good thing, because I think we're going through in broad strokes here, because there's just too many to talk about on the podcast, but I like the fact what I'm hearing here is, we're going to need to look up the individual agents probably be in contact with the neurologist, at least to know what to look out for especially the first time we see some of these, and then we're going to be monitoring the blood counts, the comprehensive metabolic panel, so we can see the LFTs, making sure they're vaccinated, screened for cancer, this kind of stuff that we can do in primary care.

Miss Smith, just to bring it back for a second. We treated her very promptly, we got in touch with you, we were worried about this optic neuritis. We hit her with high-dose steroids because we wanted to do that quickly, because we want to preserve organ function as you said. Let's say now, she' seeing you, things have calmed down a little bit, and she's talking to you about disease-modifying therapy, but she just wants to know like, "What's my prognosis, how is this going to affect my life? I'm 34, I'm hoping to have kids." How do you talk to her about that? I imagine you have that conversation a lot.

Annette: I do have that conversation a lot. First, I try to reassure her that and I think most people when they hear the diagnosis of multiple sclerosis, the first thing that comes to mind is disability, is wheelchair. I try to assure patients. This disability is not an outcome anymore if we start treatment early and stay on treatment. And then I gave a list of pros and cons, what's working, what's favorable, and what we're concerned about that we need to work towards. We talk about how does she recover from her initial relapse. A good recovery is a good sign, partial recovery not so good. What her MRI looks like and how we can reduce inflammation over time for her to lead a complete life.

I try to reassure patients that with proper treatment disability is not an outcome, but what we know that if we don't treat properly and there's high disability rates in someone that can reduce their lifespan, because then complications of MS then affect how long they live. But with the therapies that we have right now, they're very effective in reducing disability that people can live whole lives once they start and stay on treatment. For Miss Smith, she is concerned about having children in the future and this is very doable for her for most of our therapies. Yes, we have to be cautious about her being on treatment. Most of them, we do not recommend that patients get pregnant while on treatment. But with proper cleaning and timing, it has to be a planned pregnancy. They can have [unintelligible [01:07:38] pregnancy.

I must point out that having multiple sclerosis does not put someone at high risk, for a high-risk pregnancy. It does not result in fetal retardation, and it does not result in premature birth. Just the disease as its own, but our disease-modifying therapy can be teratogenic if they get pregnant. So, that's why it has to be planned. There are only one or two of our disease-modifying therapy that sometimes, we allow patients to stay on, but the majority is we have to plan it. It can still be done and it has been done successfully in multiple cases.

Matthew: There's a bunch of other stuff we could potentially talk about. Again, I I'll refer the audience to this in the clinic article because they talk about symptom management for things like spasticity,

neuropathic pain, depression, some of the bowel and bladder symptoms, and heat intolerance, things like that.

Annette: I think we should talk about that a little bit.

Matthew: Okay.

Annette: Yeah. Why do I think we should talk about that? Because what I like to tell patient is that MS comes with baggage. You don't just have MS, and you take your disease-modifying therapy, and that's fine. MS comes with a whole lot of things because of these systems that are effective. In terms of weakness, in terms of spasticity, in terms of bowel and bladder dysfunction, those are things that even if we give our best treatment as we like to say and decrease inflammation over time, because the damage has already been done, those symptoms are still going to occur, so you will need symptom management. What predicts quality of life is, if you treat the symptoms that the patient is experiencing at that time. So, for improved quality of life, we need to treat symptoms as best as we can.

And so, depending on what is effective, we treat with disease-modifying therapy and then we treat the symptom. If they're having bowel and bladder symptoms, we treat for neurogenic bladder and sometimes bringing a urologist if needed. If they're having motor symptoms, we'll make sure rehab is part of their treatment plan. If they're having sensory symptoms, we have medication for that spasticity, sleep issues. If someone isn't sleeping well, because of symptoms, they get fatigued during the day, that impact their daily function and then you just have that circle going and we need to break that.

Matthew: It is. Yeah, the range of symptoms, of course, it can affect lots of different organs. But looking at this list of symptoms in this table, it's table number three in the clinic article. It's a lot of medications that I'm comfortable prescribing, a lot of conditions that I'm comfortable at least tackling initially. So, I think in primary care some of this symptom management and stuff that it should be within our wheelhouse. Paul, I'm not sure if you feel the same way, but it’s stuff we deal with maybe not all at once like you might with someone who has multiple sclerosis, but we deal with some of these things.

Paul, we've talked a lot here. I'm wondering if you think there's any holes in what we're talking here, I mean, we've gotten Mrs. Smith to the point where we're talking to her about long-term planning and we're doing the good primary care stuff we're getting around disease-modifying therapy. Anything else you think we need to put Mrs. Smith through before we letting that go?

Paul: I hate to do it, but we've touched on it. But I feel we have not talked directly about flares and talking about mitigation of symptoms, how to recognize them, are there any particular triggers we should be counseling patients for? I feel that's one area, at least for us to recognize, if not directly manage. I feel that might be helpful.

Annette: Yeah, I think it's good, because sometimes they may present to your office first. Let's talk about relapses and flares. One thing MS is characterized by relapses and while the goal of disease-modifying therapy is to reduce relapses, sometimes, we have breakthrough. Let's define what a relapse is. A relapse is either one, a new neurological symptom that the patient has not experienced

before and is continuous for more than 24 to 48 hours in the absence of fever, fatigue, chill, or any kind of extreme stressor. So, that's one definition of a relapse.

The second definition is the old symptom, which had been stable for a long period of time increases significantly not stable, but constant for more than 24 to 48 hours in the absence and this is important of infection, fatigue, stress. Now, I keep saying infection. Why do I say that? It's that if there is an infection, you have lots of inflammatory cells in the body fighting off the infection and those inflammatory cells are the same cells that irritate the nerve and damage the nerve. The most common things I see with my MS patients is either they have a urinary tract infection or sinus infection, and the vision starts to go blurred or they start to be numb and tingling and they call and say, "I'm having a relapse just like the first time around." Well, if anyone calls my office, the first thing my staff does is to make sure we check CBC, urinalysis because the top three causes of patients calling for a relapse is infection, infection, infection.

Matthew: [chuckles]

Annette: [chuckles] Why do I do a urinalysis? Because their symptoms may not be apparent. They may not have the back pain, they may not have other classic sign of a urinary tract infection. But when you do the urine, you see a urinary tract infection right there. Or they have a sinus infection, or if they are here in Texas, they went out in the 97-degree heat at Six Flags, and the next day they are weak and unable to walk. Well, that's not a relapse. If it's caused by an infection, if it's caused by extremes of temperature or they have a fever or chill, we call it a pseudo-relapse. Once we rule out no signs of infection, no signs of fatigue, or death in the family two or three times over, then it's a true relapse and then that's when we bring in the relapse treatment protocol of steroids again.

Matthew: The 24 tablets of 50 milligram prednisone, Paul.

Paul: [laughs]

Annette: Or IV one-gram Solu-Medrol daily. [laughs]

Matthew: Okay. And we want to start that as soon as possible once we're convinced it's a true relapse and they're not having some of these phenomena that are caused by hot weather exposure, or fever, infection that sort of thing.

Annette: Correct.

Matthew: Okay, which is the pseudo-relapse.

Annette: Yeah.

Matthew: Yeah, I think I'm definitely going to want some hand holding the first time I tried to pull the trigger on this very, very high-dose steroid for a relapse, but this has been great and I know there's more ground to cover but, Paul, I think we've done hero's work here or Annette has done.

Paul: As per ush.

Matthew: Annette has done hero's work. We're just [crosstalk] asking questions.

[laughter]

Annette: This is great.

Matthew: Annette, at this point, I think we should ask you for some take home points. If there's maybe two or three things you really want the audience to remember from this discussion tonight, what would those be and then we'll let you go. We have to let you get on with your evening, but this has been so much fun hanging out.

Annette: I think what I would like the audience to do is to get the patient early enough to the neurologist, so refer early on. That is key. We know that preserving brain function is something that is important and that we need to do. Early referral is important. Second, collaborate with your friendly neurologist or MS specialist in providing comprehensive care to the patient in terms of monitoring their liver function, monitoring for malignancies, or comorbidities, making sure that drug interactions or increase in side effects are managed appropriately. And also, if there is a hint of a relapse and you need the neurologist onboard, call them early enough so that they can provide you with either advice or take on the care of the patient. But I as a MS specialist am always available to my referring physicians and whoever needs to, so I'm sure there are others who are willing to do the same.

[music]

Paul: This has been another episode of the Curbsiders bringing you a little knowledge food for your brain whole.

Matthew: Yummy.

Paul: [laughs] Yeah, I thought it was going to happen. Get your show notes at *thecurbsiders.com*. While you're there, sign up for our mailing list to get our weekly show notes in your inbox, plus twice each month you'll get our new Curbsiders Digest, recapping the latest practice changing articles, guidelines, and news in Internal Medicine.

Matthew: And we're committed to high value practice changing knowledge. So, we want your feedback. Please subscribe, rate, and review the show on Apple Podcasts or on Spotify. You can also contact us at *thecurbsiders@gmail.com*. A special thanks to our producer for this episode, Dr. Deb Gorth, who unfortunately couldn't be here tonight because she's literally saving lives. I also wanted to thank the team at Pod Paste, who helps with production and editing. Elizabeth Proto runs our social media, Stuart Brigham composed our theme music. A reminder that this and most episodes are available through VCU Health at *curbsiders.vcuhealth.org,* if you want to collect CME credit. And then, Paul, with all that until next time, I've been Dr. Matthew Frank Watto.

Paul: And as always, I remain Dr. Paul Nelson Williams. Thank you and goodbye.

[Transcript provided by SpeechDocs Podcast Transcription]