



Episode 239: Is Migraine a Systemic Disease?

Lindsay Weitzel, PhD:

Hello everyone, and welcome to HeadWise, the videocast and podcast of the National Headache Foundation. I'm Dr. Lindsay Weitzel, founder of MigraineNation, and I have a history of chronic and daily migraine that began at the age of four. I am excited to be here today with Dr. Vincent Martin. Hello, Dr. Martin, how are you?

Vincent Martin, MD:

Good. How are you?

Lindsay Weitzel, PhD:

I am good. Dr. Martin is a headache specialist, and he is the director of the Headache and Facial Pain Center at the University of Cincinnati. He is also the [past] president of the National Headache Foundation. I am super excited to hear what he has to say today on our topic which is, is migraine a systemic disease. I think most of us who experience migraine are aware that it can come with a whole lot of different symptoms. So, let's begin by defining what it means for something to be categorized as a systemic disease, Dr. Martin.

Vincent Martin, MD:

Well, a systemic disease is one that affects not just one organ system, but multiple organ systems or in some cases the entire body. That's probably the simplest definition I can give you.

Lindsay Weitzel, PhD:

We're going to investigate, we're going to ask some questions, and go over some data to talk about this hypothesis about whether or not migraine is considered a systemic disease. So, let's start off, maybe talk to us about what is migraine, what causes it. All these things that I think people, often the pain so bad, but we don't know what it is or why. Can you talk to us about that?

Vincent Martin, MD:

Well, there's two different types of migraine. There's migraine with aura and migraine without aura. Migraine with aura involves usually a neurologic event that occurs prior to the headache of migraine. So, you might have visual symptoms where you see flashing lights or zigzaggy lines. You might have numbness that maybe starts in the face and marches down to the arm. That's called a sensory aura. You might have a motor aura. Fortunately, this is extremely unlikely, but some people can get actually weak on one side of their body and that almost kind of mimics a stroke. But at any rate, the aura tends

to be reversible, so it only lasts anywhere from 5 to 60 minutes and generally precedes the headache phase of migraine. Fortunately, the aura only occurs in about 15 to 30% of those that have migraine.

And then migraine without aura does not have the preceding neurologic symptoms but has the classic headaches where usually you see there a 1- or 2-sided headache with nausea, sensitivity to light or noise. Usually, it's moderate to severe and usually can have a pretty profound impact on a person's life. So those are the two different types of migraine, with and without aura.

And in terms of what causes it has taken a real evolution over time. There was a theory called the vascular theory of migraine that was advanced a long time ago, like about 80 years ago by Harold Wolff that suggested that the aura phase of migraine was when the arteries going to the brain constricted, and then the headache phase of migraine is when the arteries dilated. And that was the prevailing theory of what caused migraine that went from anywhere from 1940 up into the 1980s when this theory was largely disproven.

And then it was thought basically that migraine was a neurologic disorder at that point. And later genetics came into play and they found those people that had some rare forms of migraine, particularly where they got weak on one side, had very specific mutations of these things called ion channels, like little pores in cells where sodium and calcium and potassium can go across and go into nerve cells and cause the nerve cell to either be more active or less active.

So that kind of supported this theory that migraine was solely a neurologic disorder. But then when they started looking at it in other more common forms of migraine, and they found there were also some genes involving the blood vessels, so the vascular cause. So, I think for a long time it was migraine, particularly with the genetic studies, was a neurologic and a vascular disorder. And I think most neurologists would probably say it's primarily a neurologic disorder.

Lindsay Weitzel, PhD:

If I understand correctly, please correct me if I'm wrong, could it perhaps not be the exact same in every person? Can some people have a more vascular type of migraine, and some people have a more neurological type of migraine?

Vincent Martin, MD:

One thing that people don't really realize is that migraine is probably not just one disorder. There probably are certain types of migraine that are solely involving the neurologic system with mutations causing defects in nerve cells. And there are some that actually involve the blood vessels. And we're going to talk later about some other potential causes of migraine as well that might involve other organ systems and other diseases. I think that this can vary from person to person.

Lindsay Weitzel, PhD:

We all know that there are a lot of comorbidities or diseases that are associated with migraine that seem to come along with migraine. Let's talk about those. What are some of those diseases?

Vincent Martin, MD:

Besides being a headache doctor, I'm a general internist, so for me this is like one of the most fascinating things, is it's why is migraine associated with so many other diseases. Things like depression, anxiety are more common in those with migraine. Some allergic and respiratory disorders, like we had done some studies looking at the hay fever and rhinitis being associated with migraine. Asthma is associated with migraine. So are certain autoimmune diseases, things like lupus and psoriasis and so forth are associated with migraine as well. And a lot of GI disorders, things like, irritable bowel syndrome, celiac disease and so forth.

So, there's just this myriad of diseases and frankly in the headache field we really haven't come up with a good explanation until now, I think, of why these disorders are associated with migraine. I think we just said, well migraine is kind of the center of the universe anyway, so I guess it makes sense that all these diseases are associated with it. But until now, we really haven't had an explanation for that.

Lindsay Weitzel, PhD:

We hear so much about migraine triggers. Are triggers considered to be a cause of our migraine disease?

Vincent Martin, MD:

Well, I think this is one of the most common misconceptions of patients because they'll come into my office and say, Dr. Martin, what causes my headaches? And what they're really saying is why are my headaches increasing at this time. So, a cause is something that leads to the overall disease. So, a cause would cause you to have migraine itself. And a trigger would be something that might actually instigate or start a migraine attack.

So, they're like different things. Trigger factors are things like hormonal changes around your menstrual period or a weather change or stress. And a cause, at least this is kind of what we've been talking about before, things that actually cause you at the very start to have your very first migraine, why you have migraines overall. It's a totally different thing, and I think that patients need to understand that. I think in most cases they're asking about what is triggering or precipitating a given migraine attack.

Lindsay Weitzel, PhD:

I always like to think of it this way. And I'm actually not sure how you're going to answer this, so I'm curious. If I were to somehow miraculously be able to eliminate all triggers from my life, would I still have migraine disease?

Vincent Martin, MD:

Probably, because not all attacks are going to be triggered, have a finite trigger. And you have to remember that there could be triggers that we don't even recognize now. So, I would think that you still would have migraines, but if you have a trigger and you're being exposed to it on a continual basis, you will have more frequent headaches with exposure to that trigger than if that trigger was totally non-existent. So, I would say, yes, you probably would still have it because you still have migraines. They

may not be occurring because you're not exposed to an environmental trigger or an internal trigger for that matter.

Lindsay Weitzel, PhD:

I'm always fixated on the genetics of migraine because in my family it begins at a very young age. Do we know how much of migraine can be attributed to our genetics?

Vincent Martin, MD:

I think that's a great question. Only about half of migraine is attributed to genetics. And I think this is something else that's kind of lost amongst many headache physicians is, if it's only half genetic, then you have to figure out well what are the environmental factors that may actually not just be triggering an attack but may actually be causing you to have that migraine predisposition.

So, there could be environmental factors. We really haven't well defined what those environmental triggers might be, but I could hypothesize what some could be. It could be that maybe you never had migraines your whole life, and you took a blow to your head, had some trauma to your head, and all of a sudden you start having migraine like headaches. In the headache world, we call them post-traumatic. So, you had some sort of trauma to your head, but the headaches have migraine characteristics. So that would be just one example of an environmental cause potentially.

Lindsay Weitzel, PhD:

Let's talk about some of these studies that have come out lately on Mendelian randomization and migraine. So first probably tell us what Mendelian randomization is and why these studies are important for us.

Vincent Martin, MD:

Well Mendelian randomization allows us to assign a causative effect to a given disease on another. And the way they do it, let's say that you're looking at a disease and let's just take say lupus for example. So what they do is they basically identify the gene mutations or we actually call them SNPs [single nucleotide polymorphisms] but for the for the public, it's probably easier to think of a mutation, a bunch of mutations that are associated with that disease. And then they have to then take this target population and they will define whether they have migraine or not. So, in most cases, they've sent them questionnaires that have been validated and they can determine if they've got migraine.

And because the genes are randomly allocated for that disease randomly, it's almost like a randomized controlled trial. It's like an experiment. So, it makes it much less likely that there are other factors outside of the disease itself that might explain the association between two different diseases. And so, it's a very powerful technique and one that we're seeing in many, many different studies now.

But there have been a flurry of studies in the last four years looking at can other diseases cause migraine. And that's pretty powerful if you think about it. Are other diseases causing migraine? And the answer is yes, but they're very specific ones. So, depression was found to be causative for migraine. In addition, some of the autoimmune diseases, things like lupus, at least in some studies, was found to be causative. There was one study on psoriatic arthritis, so psoriasis that has arthritis. There are some GI

causes. Irritable bowel syndrome was thought to be causative for migraine. There was one study suggested that celiac disease was causative for migraine with aura. And a lot of diseases of clotting, they looked at gene mutations for clotting and found that those were not predictive for migraine without aura, but they were very predictive for migraine with aura. So, there may be differences in whether someone has migraine with or without that aura in terms of a given disease being causative for migraine.

Lindsay Weitzel, PhD:

Does it ever go the other way around? Does migraine cause any other diseases that we're aware of?

Vincent Martin, MD:

Well, and I don't want people to be overly alarmed at this, but there was one study that looked at migraine causing Alzheimer's disease. But mind you, that would be something that probably wouldn't happen extremely commonly. But there was one study that suggested that there was an interrelationship there.

Lindsay Weitzel, PhD:

We've discussed the difference between a cause and a trigger. And we've talked about diseases and comorbidities that are related to migraine. Can any of these diseases trigger migraine, bring on an attack, make our migraine worse?

Vincent Martin, MD:

Well, I've been involved in a number of different studies. We looked mostly at immunologic diseases, so diseases of the immune system, things like hay fever and rhinitis, which is an inflammation of the nose. And people that have rhinitis and migraine have more frequent headaches. In addition, asthma, we looked at asthma in terms of its ability to predict someone to go from episodic, which is an infrequent migraine pattern, to chronic migraine where they have 15 or more days per month with headache, of which eight or more meet migraine criteria.

So people with asthma were more likely to evolve into the more frequent headaches, which kind of implies that they're actually triggering it in some way, either the disease or its treatment. And that's something we haven't really talked about, is it could be that a medication used to treat the disease could actually then trigger migraine attacks. That's another possibility.

Pain disorders, so if you have like neck pain and low back pain and TMJ and other things, have been associated with more frequent attacks of migraine, in fact, the progression from episodic to chronic as well. And depression is no different. So, depression is also associated with a higher likelihood of developing more frequent headaches, suggesting that there could be some effect of either the disease itself or its treatment.

Lindsay Weitzel, PhD:

This is all been very interesting. We've talked about various angles, different diseases, the genetics, etc. So now I'm curious if we can bring it back to our title and the reason that we're here. Do you feel that migraine meets the criteria to be categorized as a systemic disease?

Vincent Martin, MD:

I think the answer to that is yes in some instances. So, I think that can migraine solely be a neurologic disease? Yes. Can migraine solely be a vascular disease? Yes. And can migraine be a consequence of other systemic diseases that we talked about? The answer is yes.

So, I think that that's the evolving concept, is that we have different causes for migraine, including other diseases. And you might say, well, why is it even important that we recognize that other diseases could actually cause some of that migraine for the very first time or if they're present cause more frequent attacks of migraine.

So, it basically means that as clinicians, we should be looking at the whole patient and recognizing that other diseases may cause migraine. They may moderate the frequency of migraines. What we don't know is whether treatment of the systemic illness, the illness that may cause migraine, if you treat that, we don't know whether that makes you less likely to have migraine attacks. But I think we do have some suggestive data that might suggest that in some instances that might be true. Like depression, for example, is often treated with antidepressants. And migraine too can be treated with antidepressants. So, you could argue that maybe there could be some dual effect there.

If people have rhinitis, so if their nose is blocked, they're more likely to snore. And what can they get? They're more likely to get obstructive sleep apnea and have periods where they don't breathe at night. And there could be other examples as well. I can envision other scenarios where if people are overusing opioid pain medications for chronic pain, that that might lead to more frequent headaches.

So, there could be multiple mechanisms at play here. But clearly, I think that we're finding that at least a subgroup of those with migraine probably do indeed have a systemic illness.

Lindsay Weitzel, PhD:

I think this is one of the most interesting episodes we've done, because I think that a lot of us who experience this in our bodies have felt this in our sensations, in our bodies and wondered about it, but didn't know how to put it into words. And so, I find this very interesting and I think our audience will too. I hope everyone enjoyed this episode. Please tune in again for the next episode of HeadWise. Bye bye.