INTERVIEW TRANSCRIPT

DISCUSSIONS WITH WORLD-LEADING EXPERTS

Our Evolving Understanding of What Causes Migraine

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Introduction (00:05): Many of us are here because we know the experience of living with migraine, but how exactly do we understand what migraine is? It's easy to think of migraine as a condition of the brain. After all, many of the symptoms seem to start there. But science tells us a bigger story: Migraine can involve the whole body, including the vascular system, hormones, the immune system, and the gut.

Introduction (cont.) (00:27): To help us explore this broader view of migraine as a systemic disease, we're joined by Dr. Vince Martin, director of the Headache and Facial Pain Center at the University of Cincinnati Gardner Neuroscience Institute. He'll guide us through what's really happening in the brain and the body during migraine, why it so often occurs with other conditions, and what this evolving science means for those living with migraine today. Dr. Martin, welcome to the Migraine World Summit.

Dr. Martin (00:53): A pleasure to be here.

Kate May (00:55): So firstly, I'd love to understand what this means as a systemic disease. What's the definition of a systemic disease?

Dr. Martin (01:03): So a systemic disease is a disease that affects other organ systems or the entire body. So there's this interplay between the disease and the rest of the body. I wanted to go over what are some of the old theories of migraine because many patients and persons with migraine have actually already heard of them. The first thing about migraine in terms of what was causing a migraine was it used to be thought to be a vascular disease.

Dr. Martin (01:31): So during an aura, which is usually where you get neurologic symptoms that precede a migraine — things like visual symptoms, flashing lights, zigzaggy lines, weakness or numbness on one side of your body. In the past, that was thought to be due to constriction of an artery.

Dr. Martin (01:48): And then the headache phase, which would occur after that — which is where usually you got your one-sided headache that throbbed and pulsated and got the nausea and sensitivity to light and noise — was thought to be due to vasoconstriction. And that was the prevailing theory. But some new theories now suggest that it's probably a lot more than that. Some of the prevailing genetic studies that have been recently done.

Kate May (02:13): Yeah, interesting. So it's come a long way from understanding it as a vascular condition to where we understand it now. So how is it different from understanding — some people may just understand migraine as a brain disorder or a brain issue. How is this understanding different from that?

Dr. Martin (02:29): Well, migraine has to involve the brain because the perception of pain in the head involves the brain. Currently, most neurologists and most headache doctors would tell you that migraine is a neuronal disease. And the data behind that was a lot of the early genetic studies of rare forms of migraine. There's one called familial hemiplegic migraine, which is where people get, as part of their aura, they get weak on one side of their body.

Dr. Martin (02:55): They found very specific mutations in genes of different calcium and neuronal channels or little pores in nerve cells that alter the ions in the neurons. So it would be things like sodium and calcium and so forth. So in that instance, it was thought, "Well, migraine, all of it must be a neuronal disease." And then later, they did some more genetic studies on more common variants because that rare form of migraine with paralysis is not your common migraine; that's extremely rare.

Dr. Martin (03:36): What they found was that most of the gene mutations early on were either involving nerve cells or the vasculature. So there were gene mutations causing abnormalities of the

blood vessels that go to the brain. So then the understanding evolved from this concept of migraine being a neurologic disease to a neurovascular disease. So one that could be neuronal or it could be vascular. But most recent studies have shown that there probably are other explanations for migraine as well.

Kate May (04:11): I have a question that has come from our community. Miranda and Karen from our community have asked: What's actually happening in the brain and body when migraine occurs?

Dr. Martin (04:20): Well, during a migraine attack, the trigeminal nerve becomes activated. So the trigeminal nerve is the main sensory nerve of the head and there are three divisions: There's the ophthalmic [branch], there's the maxillary [branch], and then the mandibular branch. There are three different divisions. And during a migraine attack, that nerve becomes activated. And when it becomes activated, it releases a protein called CGRP, calcitonin gene-related peptide. And then that peptide, that little protein, binds to other nerve cells and blood vessels as part of a cascade of events that occur with migraine.

Dr. Martin (04:56): And that's our current understanding. And many of the newer therapies that we have, that have come out over the last seven years basically either bind specifically to that protein or bind to the receptor — that place on cells or on blood vessels where the protein tends to bind — to block it. So a lot of the newer therapies block this whole process. So that part is neuronal and it also has a vascular component when you think of the cause of migraine.

Kate May (05:25): I'd love to move on to talking about some of the causes and comorbidities that occur with migraine. What do we know about what causes migraine?

Dr. Martin (05:34): Migraine is associated with a variety of other illnesses. Depression is more common in patients with migraine. Anxiety is more common. [Auto]immune diseases like rheumatoid arthritis and lupus are more common. And vascular diseases are more common in migraine. And pain disorders — things like neck pain, low back pain, fibromyalgia — all these disorders. In the past, no one has really understood why that actually occurs. I think a lot of the headache doctors are kind of like, “Yeah, that makes sense. Migraine's the center of the universe.”

Dr. Martin (06:13): But the reality is there has to be a reason why these diseases are overrepresented in persons with migraine. And I think many people in the audience will often have these different diseases. But there are very specific reasons why these diseases are more common. And there's some more recent studies that are called Mendelian randomization studies. And these have come out over the last three or four years. It's just kind of flooded this [area of research].

Dr. Martin (06:40): But the concept is that they'll find a disease and then they'll identify the gene mutations associated with that disease in a given population. And then they have to actually define who has migraine in that population. And because the genes were randomly distributed between individuals, it decreases a lot of the bias that can occur in studies. There's something called confounding, which is there could be other factors that might explain it rather than a cause and effect. But it allows you to actually assign a causative effect to a given disease for migraine.

Dr. Martin (07:17): And what they found is that there are lots of diseases that are associated with the development of migraine. So things like — one of the strongest ones is depression. Certain kinds of thyroid disease: High thyroid and low thyroid disease were associated with that. Certain GI [gastrointestinal] disorders: Things like celiac disease was associated with aura, and even peptic ulcer disease; so ulcers of your stomach were associated with migraine. And then some of the diseases of blood clotting. So some of these are very specific for migraine with or without aura.

Kate May (07:57): How are they able to sort of extract that out? Because I know people in our community might understand that migraine can co-occur with lots of conditions, but this is a step further saying that there's a causative effect. How are they able to find that?

Dr. Martin (08:09): Well, because in these Mendelian randomization studies, because the genes are assigned randomly to different people, they rule out the possibility of other factors, because all the other factors are going to be randomly distributed, at least theoretically, in the population as well. So it allows to assign a causative effect because of the randomization of these genes to individuals at birth. So it's a really fascinating concept.

Kate May (08:38): What are these diseases that can have a causative effect that were found in this study?

Dr. Martin (08:42): Things like deep venous thrombosis [DVT]; so that was found to be causative. Lupus was found to be causative for attacks of migraine with aura. Peptic ulcer disease was found to be causative for attacks of migraine without aura. And depression was found to be causative for attacks of migraine overall as well. So those are the common ones.

Dr. Martin (09:12): There were other ones as well, but those are … and then also high thyroid (hyperthyroidism), low thyroid (hypothyroidism), were also found to be causative for migraine as well. And then there are other things, too, like obstructive sleep apnea; there was one study that suggested that was positive. Vitamin D deficiency.

Dr. Martin (09:31): So these new studies are really changing the way that we think about migraine as being — it can be a neurologic disease; it is a neurologic disease, but the cause could either be neurologic, or it could be vascular, or in some instances, it could be from other illnesses. The latter part is totally novel. This is something completely new. And I think it makes sense to patients, too, that might have other disorders and want to know how they interrelate with migraine.

Kate May (10:03): What do we know about what causes migraine in relation to this new research that's come out?

Dr. Martin (10:09): It is very possible that — say take clotting disorders. We talked about that as a disease that might trigger attacks of aura. It's now thought that sometimes there can be tiny little blood clots that go up into the brain and actually trigger attacks of aura in some patients. So that's one mechanism. And then a lot of these inflammatory diseases, they release different proteins called cytokines as part of the disease. And it's thought that this inflammatory process, which is the release of these inflammatory proteins, can actually trigger attacks in given individuals.

Dr. Martin (10:49): And then in some cases, it's possible there could be some shared genetics. So the genes of one disorder could actually predispose to — like say for depression — maybe the genes that produce depression also produce or cause migraine. So there could be some combined genetic effect. Those are just some things.

Dr. Martin (11:11): If they've got obstructive sleep apnea — which is where you stop breathing at night — it's possible that the low oxygen levels that occur recurrently over time could produce migraine-like headaches. So there's a variety of different mechanisms, and it probably varies by the disease. Thyroid hormones, both high and low, can have neurologic effects as well. So in some of these things, we don't know the exact mechanisms. We just know that they probably are causative in some individuals.

Dr. Martin (11:41): And I don't want people to think that every migraine is triggered by another illness, because there could be neuronal genetic causes, neurovascular causes, and there could be other diseases that all trigger, or all cause, migraine.

Kate May (11:57): Would some of these conditions share some similarities with migraine? Do we know what's similar or what's happening with these comorbidities?

Dr. Martin (12:05): They would share things in the sense that they may be similar type illnesses that may have intermittent worsenings and fluctuations in disease activity and so forth. Probably the one that might most closely resemble migraine would be depression, which commonly occurs in migraine patients; they're both neurologic disorders with paroxysmal worsenings and so forth. But I'm not sure that there's a vast similarity between a lot of the diseases I've mentioned and migraine.

Kate May (12:42): So you mentioned genetics as a causal factor when it comes to migraine. How much of migraine is caused by genetics?

Dr. Martin (12:49): Only about half. So only about half of migraine can explain the presence or absence of migraine in a given individual, which means there also are probably environmental factors that play a role. So there could be — maybe you never had a history of migraine, and you take a blow to the head and you develop something called post-traumatic headaches that have migraine characteristics. So if you saw a headache doctor, they would probably say that you have migraine, but the reality was that you probably had post-traumatic headaches that led to migraine-like headaches.

Dr. Martin (13:21): So I think this concept that a migraine attack may not always be the endgame, which is kind of what the headache community currently thinks. It may just be a way the brain responds to many different things. It could be genetic. There could be genetic causes. There could be other diseases associated with it. Genes of blood vessels can cause it. And even environmental factors could play a role too, like head trauma and other environmental factors. Who knows? Maybe air pollution and other environmental factors could trigger migraine or headaches that have migraine characteristics. So it's looking at migraine in a much broader sense than what we've ever looked at before.

Kate May (14:06): Fascinating. And do you have anything else you'd like to share about what genetic studies tell us about migraine?

Dr. Martin (14:12): I think those are probably the big things. But one thing I would like to also cover with the audience is the difference between a cause and a trigger, because patients often get that confused. A cause is something that leads you to have migraines in general. So it causes you to start having migraines for the first time and so forth. A trigger implies more to a headache attack. So what triggers a migraine might trigger an attack.

Dr. Martin (14:41): Like, for example, if you get headaches around your menstrual cycle, it's probably the declining estrogen levels and other hormones that occur around the menstrual period that trigger that particular attack. Or if you get headaches with weather, for example, so a low-pressure system rolls in and you develop a headache when it rains — that's just triggering a given attack. Cause implies cause of the disease overall. So there's a big, big difference between that.

Dr. Martin (15:10): And what's interesting is that these diseases that people have can also increase the frequency and actually trigger headache attacks. It's either the disease itself or in some cases it might be the therapies that they're on. Like they may be on different medications for a given disease and it's possible that could trigger attacks. But we've been involved in some studies that have shown that if you have asthma, you're more likely to go on and develop more frequent headaches. If you have depression, you're more likely to go on and develop more frequent headaches. And then if you have other pain disorders like neck pain or low back pain, you can go on to develop other headaches.

Dr. Martin (15:54): But there are also a variety of other triggers, like stress can trigger a given attack and so forth. So that is really interesting — if you've got diseases and/or their treatments that will

actually make your headaches more frequent. To me, that's also another area that's very interesting to patients, is how these diseases make your headaches either more or less frequent.

Kate May (16:16): Yeah, fascinating. I think it sounds like there are so many things going on when it comes to causes or triggers of migraine that explain the complexity of migraine and why it's so hard to understand in our community or know what's potentially right for you. Because it sounds like there's so many different things going on; there's not one core answer. I'd love to follow up that with a question from our community: Mike has asked whether there's an underlying root cause to migraine. What does the evidence say about that?

Dr. Martin (16:43): Well, I think we've talked about that. I mean, we talked about the three different buckets: the genetics — that can either be neurologic disease, neurologic gene mutations, or vascular. We talked about the fact that other illnesses have most recently been found to be potentially causative for migraine. And we also talked about environmental factors. So I think that the idea of causality of migraine is a multifaceted question with multiple ways that you can generate migraine.

Dr. Martin (17:16): So in a way, the migraine attack is kind of just a way the brain responds to a variety of different things, whether it be a genetic cause or an environmental cause or even other illnesses. And so it may not be just specific to this very narrow thought of migraine in the past, which is that migraine is solely a genetic neurologic disorder. That probably is just not true.

Kate May (17:40): It does sound like there's so much that can feed into what migraine is and how this can present in different people with different conditions as well. I know there might be some people listening that know that they live with other comorbidities and it's hard to wrap your head around to understand how that might influence how your migraine presents and what's right for you. What could you say to listeners that might be listening along, concerned about comorbidities and these research findings, and what's right for them?

Dr. Martin (18:07): Well, I think that the main way you might be able to look at this is through the effect of these illnesses as a trigger factor. Because in terms of cause, I'm not sure that if you develop one of these diseases — if you're prone to those diseases and then those later cause migraine, I don't know of any way to necessarily interrupt that process. But the trigger part of it — where the diseases could trigger other illnesses — is very interesting. The way I approach seeing a migraine patient is, I'm looking at trigger factors.

Dr. Martin (18:45): So besides using all the migraine therapies that other people use, I'm looking at the patient saying, "All right, what could be driving the increased frequency of their headaches?" Do they have neck pain? So do they have disease of their neck that's causing migraine headaches that occur back here *[gestures to back of neck]*? Do they have TMJ? So a temporomandibular joint disease [TMD], where they get arthritis of this particular joint in the jaw, is triggering headaches here *[gestures to side of head]*. Do they have a sinus or allergic disease that seems to be flaring at the time? And is that causing headaches located in the forehead, between the eyes, and also in the maxillary sinus region? Or are they having depression, which could be moderating things? Do they have hormones that are moderating things?

Dr. Martin (19:30): So I'm looking for all these different trigger factors and then I might modify them. So we might go after their neck pain. We might go after their TMJ. We might go after treating their sinus disease. We might go after treating their depression. There are different things we can do for hormonal triggers. So I'm looking at how these things might be increasing the frequency of headaches in a given patient.

Kate May (19:54): Fantastic. So I guess by understanding that there might be other things going on, that could open up treatment options or understanding of what's going on and more options moving

forward. I wonder if migraine and other conditions are so connected, does treating one help improve the other?

Dr. Martin (20:10): We don't know the answer to that, for example. But we do know that treating with different nasal steroids or nasal sprays in the nose can reduce pressure in the sinus area, which I think in some cases might trigger headaches. We know that treating obstructive sleep apnea with something called CPAP [continuous positive airway pressure], where you have a mask, can reduce the frequency of morning headaches. And in some cases, I think that may actually trigger migraines. There are some data on treating neck causes — the neck pain and arthritis of the neck and herniated discs — in terms of referring pain up into the head that can trigger it. So we don't have a lot of data on treating other illnesses and the effect on migraine.

Dr. Martin (20:58): But at least in my practice, it seems like if you can get the neck pain under control; if you can get the hay fever and allergies and/or sinus disease under control; if you get the TMJ under control; or you can get the depression under control, that can make a big difference. We do know that if people are depressed with their migraines, they perceive the pain as much more severe than someone that's not depressed. And they also perceive it as much more disabling. So it has a much greater effect on their quality of life and also on what activities that they do.

Dr. Martin (21:33): So I think we need to consider these diseases being interrelated, and one disease can make another worse, and sometimes it can go the opposite way. We know that depression often occurs before migraine develops, and migraine can develop before depression occurs. So you don't really know what's the chicken and the egg. But the reality is it's probably bidirectional. It's probably both of these diseases are interacting with one another. And we also know that if you treat migraine well, that depressive symptoms can improve. So treating migraine can sometimes improve other diseases.

Kate May (22:10): I think that's a great message to send the folks listening at home — that there are some positive benefits that can come from disrupting that cycle or the interconnectedness of conditions and finding the right treatment for you. I'd love to follow up again: If migraine is systemic, how can that shape treatment approaches?

Dr. Martin (22:27): Well, I think that the treating clinician should think of treating other diseases outside of just migraine if they want to see maximal improvement in their patients, as we just discussed. It's treating the depression; treating the allergies and/or rhinitis; treating the TMJ; treating the neck pain; managing hormonal issues in women. All these things can trigger attacks and those conditions can be improved. And in some instances, at least in my experience, that seems to also decrease the frequency of migraine.

Kate May (23:05): We have another question from our community: Savanna is concerned about the long-term impacts of migraine, particularly as someone that's been living with migraine for a long time. What should people be aware of in terms of long-term effects?

Dr. Martin (23:18): Well, for the long term, there are a bunch of things — there are a lot of things we could talk about. One is that migraine patients can sometimes get these white spots in the brain called white matter disease. And in fact, that occurs probably, in my experience, in about 40% of all migraine patients. There are some data to suggest that the more frequent the headaches, the more likely you are to get these white spots.

Dr. Martin (23:43): And we're not sure exactly what these … it's called white matter disease. So we're not exactly sure what causes that. But one theory might be that the increased frequency of migraine may cause little areas of low blood flow into the brain — not strokes. But we don't know whether treating migraine and reducing frequency will reduce the likelihood of that.

Dr. Martin (24:06): Certainly, treating migraine can help depression in individuals that suffer from both of those conditions. And that can be a long-term side effect of migraine. And that's probably the best way I can answer that particular question. There probably are other diseases that might improve with treatment of migraine as well. Maybe anxiety would be another one.

Kate May (24:31): I'd love to ask you: For someone that's listening along living with migraine right now, what's a key takeaway from understanding migraine as a systemic disease?

Dr. Martin (24:40): The key takeaway is that you can't look at the brain in isolation. Just because you've got migraine and because at some point that neurologic system is activated, it doesn't mean that that's the only way that you manage migraine. You need to look at the whole body and develop treatment approaches in patients that might actually treat some of these other systemic illnesses, because it might actually improve your migraines.

Kate May (25:11): I'd love to ask you — you've been working in this space for such a long time — if you could design the next generation of migraine research with this systemic perspective, what would you prioritize? What would you like to see next?

Dr. Martin (25:22): I think that we're going to find that not every migraine is created equal. And I think that there very well could be trigger factor therapy. So like, for example, if you have a menstrual migraine — so a headache occurs around your menstrual period — that may have a different way that that is triggered. There may be specific treatments that just interrupt that particular process. The same is probably true with weather-triggered headaches.

Dr. Martin (25:56): I think in the future that as we understand more of how these — whether they be other illnesses or whether they be environmental factors — are actually increasing migraine frequency, that we'll be able to intervene specifically to actually improve migraine.

Dr. Martin (26:14): And the genetics is really interesting because there are so many different genes they're finding, and there might be — if there are many different ways, there are many different roads to Rome, if you want to think of it that way. So migraine can be — you can get there many, many different ways.

Dr. Martin (26:29): But once we find out the way that your migraines are being triggered or even caused, there might be very specific interventions that just pertain to your specific genetic defect or your specific environmental trigger or your specific internal trigger that causes the migraines. I think a lot of the therapies now just act globally on the trigeminal system. But I think that much more targeted therapies — that interrupt the process before it ever begins — to prevent migraine is where the money is going to be in terms of research going forward.

Kate May (27:03): Are there any other resources you'd like to recommend to our audience to learn a bit more about this topic?

Dr. Martin (27:08): Well, the National Headache Foundation has a variety of different videos and educational programs for persons with migraine. The American Migraine Foundation, likewise, has a lot of different handouts on migraine trigger factors and probably the causes. But a lot of this new stuff we're talking about — about migraine being a systemic disease — is just a new and evolving topic. So it's not one that even many headache doctors know much about.

Kate May (27:36): Fascinating. So perhaps keep an eye on this space and we can learn more and more in the future.

Dr. Martin (27:41): Exactly.

Kate May (27:42): Well, fantastic. Thank you so much, Dr. Martin. I know I've learned so much today and really valued this conversation and your expertise. It's fascinating to learn about the interconnectedness, the complexity, the causes, and all the other things going on in migraine beyond what we might initially think. So thank you for so eloquently breaking that down for us today. And thank you so much for your time.

Dr. Martin (28:03): My pleasure.