MIGRAINE WORLD SUMMIT

TRANSCRIPT

INTERVIEWS WITH WORLD-LEADING EXPERTS

THE GUT FACTOR: EXPLORING THE ROLE OF DIGESTIVE HEALTH IN MIGRAINE

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Introduction (00:05): I've always been interested in the gut and migraine, but there seems to be this very intricate association between the brain and the gut. And that relates to the autonomic nervous system, particularly the vagus nerve, that comes from the brain and goes down into the gastrointestinal tract. It relates to the fact that a lot of the same neurochemicals that are involved in migraine are also found in nerve cells in the gut. You don't really think about the gut, but the gut is richly innervated by nerve cells. And chemicals like serotonin, which we know is important in migraine; glutamate; CGRP (calcitonin gene- related peptide), which is the new peptide that's important in migraine; is richly found in the gut.

Carl Cincinnato (00:50): It's increasingly recognized that migraine can have systemic effects on the body, including the gastrointestinal system (GI), otherwise known as the gut. In this interview with Dr. Vince Martin, president of the National Headache Foundation, we explore the different ways in which migraine can affect the gut and why. Dr. Martin, welcome back to the Migraine World Summit.

Dr. Martin (01:10): Pleasure to be here.

Carl Cincinnato (01:13): Nausea and vomiting are so common in migraine that these symptoms help doctors diagnose the condition. But Migraine World Summit viewer Geoff asked: How does something that is considered to be a neurological disease affect our gut in such a way?

Dr. Martin (01:28): Well, it is very interesting. There basically are neurologic connections between the trigeminal system, which is the main nerve involved in migraine, and the center in the brain that controls nausea. And when that center in the brain that controls nausea gets activated, there's nerves that go to the stomach to cause it to basically stop contracting, and that gives you the sense of nausea.

Carl Cincinnato (01:50): What are other GI symptoms that are commonly reported during a migraine attack?

Dr. Martin (01:55): Well, there can be a bunch. Some patients will report diarrhea, which is almost like the opposite of nausea, where the gut actually hyperfunctions and leads to watery bowel movements. Some people can get some loss of appetite, as well. Some people can get full much quicker when they eat. It's called early satiety. So there [are] a number of gastrointestinal symptoms that can accompany a migraine attack, which is really interesting. Because when you think about this connection between the brain and the gut, I mean, you would think that they're not really that close in location, that they can have profound influences on one another.

Carl Cincinnato (02:35): Is there such a thing as abdominal migraine?

Dr. Martin (02:38): Yes, there's one form of migraine called abdominal migraine where people will get pain in their epigastrium, which is just beneath the sternum in the abdomen, and they can have recurrent bouts of abdominal pain with or without migraine symptoms. And this can occur repetitively and sometimes it can stump even gastroenterologists in terms of what the diagnosis may be. They look for a lot of other pathology like gallstones and so forth, and they don't find anything. And really, it's a diagnosis of exclusion. What that means is that once you've done your full gastrointestinal evaluation, and particularly if they've got a history of migraine and they're having these bouts with or without migraine, then they could be called abdominal migraine.

Carl Cincinnato (03:20): Is this type of abdominal migraine something that's typically associated with children or adolescents versus adults, or can it occur in both?

Dr. Martin (03:29): Well, it can occur in both, but it's much more common in children and adolescents, but it's being more commonly recognized in adults, as well. But it's certainly more common in a younger population.

Carl Cincinnato (03:40): So if a parent, or two parents that have migraine have a child that starts complaining of these symptoms of gut — or pain in the stomach — without necessarily all these other symptoms, should they be on alert that this could be migraine, given the genetic link?

Dr. Martin (03:57): Particularly if the child might've had a migraine in the past, or maybe they don't have any past history of that, but there's a real strong family history of migraine. It's a distinct possibility.

Carl Cincinnato (04:08): What is gastroparesis?

Dr. Martin (04:11): Gastroparesis is something that occurs within the context of a migraine attack. And that's basically where the stomach stops contracting. I mean, you may not realize it, but when you eat a meal, there's some contraction of the stomach that kind of propels the food into the small intestine. But when patients have migraine, those contractions may stop, and the stomach just kind of sits there and can lead to gastroparesis, which can lead to a number of different things. It can lead to problems with nausea, but it can also lead to some difficulties with drug absorption. So some of the oral pills that migraine patients take, if the patient were to have gastroparesis, may not actually be absorbed. The other interesting thing about the gastroparesis is there have been studies that have shown that the gastroparesis, or the lack of contraction in the stomach, may occur not only during the migraine attack but can occur during other times when they don't have migraine. So it's possible that these symptoms could manifest even outside of a migraine attack, where people may feel full easily; they may have a little bit of epigastric pain, pain in their stomach region; and nausea.

Carl Cincinnato (05:22): What is the telltale sign of gastroparesis?

Dr. Martin (05:26): Well, it would be a diagnosis that's made on imaging. So, they give a radioactive substance; sometimes they put it in eggs. And they can ingest that, and you can actually see how quickly that radioactive substance goes from the stomach into the small intestine. And they have certain normative data to determine what constitutes gastroparesis.

Carl Cincinnato (05:49): And from a practical perspective, if we have nausea or stomach pain and we feel a migraine attack coming on with that, if we take an oral tablet at the time that we have gastroparesis, does that mean that the absorption of that tablet would be stalled or delayed significantly, such that the treatment may not be nearly as effective as it otherwise would be if we didn't have it?

Dr. Martin (06:12): It probably varies between individuals. Some individuals may be more prone to gastroparesis than others, and different attacks may have more gastroparesis than others. And I think that's demonstrated by the fact that vomiting occurs in a minority of patients. And vomiting is almost certainly related to the fact the stomach is not contracting and, as a result of gastroparesis. But there could be some people who have moderate to severe gastroparesis

where the drugs just aren't absorbed well. And in those situations, you may need to consider intranasal routes like nasal sprays, or subcutaneous injections.

Carl Cincinnato (06:50): Are devices potentially helpful in that situation, as well?

Dr. Martin (06:53): Devices could be used as well, so anything that bypasses the gastrointestinal tract, the oral gastrointestinal tract, could be effective, including devices.

Carl Cincinnato (07:03): We had two other people from our community ask: What is the gut-brain axis and its significance in understanding the relationship between migraine and gut health?

Dr. Martin (07:15): That's a great question. To me, it's just fascinating. I'm always interested in how migraine affects other organ systems because, not only being a headache doctor, I'm an internist, so I've always been interested in the gut and migraine. But there seems to be this very intricate association between the brain and the gut. And that relates to the autonomic nervous system, particularly the vagus nerve, that comes from the brain and goes down into the gastrointestinal tract. It relates to the fact that a lot of the same neurochemicals that are involved in migraine are also found in nerve cells in the gut. You don't really think about the gut, but the gut is richly innervated by nerve cells. And chemicals like serotonin, which we know is important in migraine; glutamate; CGRP (calcitonin gene-related peptide), which is the new peptide that's important in migraine; is richly found in the gut.

Dr. Martin (08:13): And in addition, a lot of the hormones that are produced by the pituitary gland that is inside the skull — maybe we wouldn't consider that necessarily part of the brain — but those hormones, particularly cortisol, can have profound influences on the gastrointestinal tract. So there are a number of different ways. And inflammation can occur in the gut, and we'll talk about that later, probably when we talk about probiotics and the microbiome. But certain bacteria, or certain bad bacteria, can release inflammatory markers like TNF-alpha [tumor necrosis factor] and other chemicals that produce inflammation not only in the gut but that can actually have neurologic effects on the brain.

Carl Cincinnato (08:56): What is leaky gut and how might that be related to migraine?

Dr. Martin (09:00): Leaky gut implies that when there's inflammation in the gut that the gut allows substances to more readily traverse the gut, and that would include a lot of bad things, like those markers and chemicals related to inflammation. And those can have effects in what we call the blood-brain barrier — that's the barrier between the bloodstream and the brain — and create leakiness of that, as well. So, if you want to think of it as, you get a leaky gut, but it could also cause almost a leaky brain where more substances and more inflammation can actually be involved in the brain itself.

Carl Cincinnato (09:37): So, we have a protective lining in our gut that stops certain substances from traversing into our bloodstream. But if we have holes or leaks in that, that's — maybe that's the colloquial term "leaky gut" refers to — and that means that chemicals can, not just traverse into our bloodstream from our gut but also, you're saying into the brain, as well.

Dr. Martin (09:58): They can go into the brain, or they can modulate the nerve cells that are in the dura, the lining of the brain, and that can have a profound effect on migraine, as well. At least that's a hypothesis.

Carl Cincinnato (10:08): How would someone know whether they have a leaky gut or not?

Dr. Martin (10:11): There are some research studies that have been done looking at that phenomenon, particularly in animal models and so forth, but the average person could never know for sure if they have a leaky gut. They may suspect it and may hypothesize about it, but to my knowledge, there's no scientific tests that diagnose that in humans.

Carl Cincinnato (10:33): And are there ways to, if you suspect that you may have one or you're having potential symptoms of a leaky gut, are there ways to manage that?

Dr. Martin (10:42): There's something called the microbiome, and that's basically a bunch of bacteria that are in your gut. And the microbiome changes on a daily basis. It relates to your diet; it relates to whether you've had recent antibiotics that may kill off certain bacteria in your gut; and so forth. So it creates a group of bacteria, some of which can be anti-inflammatory and some of which can be pro-inflammatory. So, it's that ratio between the good and the bad bacteria and the substances that they produce that may promote or may inhibit inflammation in the gut. But also, what happens in the gut can also influence the brain, as well. So it's this balance between good and bad bacteria in the gut that's very important.

Dr. Martin (11:28): And what's really interesting is that a lot of healthy lifestyles — so if you eat a healthy diet rich in fruit, vegetables, fibers — this promotes the healthy bacteria in your gut. And if you eat a poor diet that has lots of sugar in it, lots of carbohydrates, and lots of other things, processed foods, and so forth, that creates an unhealthy environment. Or if you've been on antibiotics for a long period of time, particularly broad-spectrum antibiotics: So, there are antibiotics that — there's narrow-spectrum where they just kill just a few bacteria, but there's broad-spectrum ones that can kill a lot of bacteria in your gut. Those can really wreak havoc on someone's gastrointestinal tract and their microbiome, and it may throw them into a bad pro-inflammatory state for a long period of time.

Carl Cincinnato (12:19): We've spoken before on the Migraine World Summit about how foods can be inflammatory. Is this a potential link in how what we eat can influence the level of inflammation in our gut and therefore potentially influence our migraine condition?

Dr. Martin (12:34): Well, that is a possibility. We know that there [are] certain kinds of diets. One is a high omega-3, low omega-6 fatty acid diet. And that's been shown in two clinical trials to actually reduce migraine frequency. And the omega-3s are thought to be good fatty acids. So, they produce fats that are less likely to promote pain. And the omega-6s are found to actually promote inflammation. So you want to have the high omega-3s and low omega-6 fatty acids. And these are diets that are very high in things like flaxseed, but you don't want to consume a regular flaxseed because that's very poorly absorbed in your gut. I don't know if you've ever eaten flaxseed bread, but it actually comes out the opposite end, so it's not absorbed. So you have to use flaxseed meal. And I'll put that in a smoothie in the morning where I have blueberries, and I put in sometimes strawberries, and I put in some cocoa, and some coconut milk, and so forth, and I'll create this smoothie, but I'll also put a couple of scoops of the flaxseed meal. Finned fish — things like salmon, swordfish, tuna, and so forth. Bluefish are very, very healthy. Those chia seeds also are high in omega-3s. And healthy oils like olive oil are also very helpful.

Dr. Martin (14:05): So creating a diet that's very healthy, or high in these omega-3s and low in omega-6s, is very important, and that actually will help improve your microbiome. And then, in

addition to that, low-fat diets have also been shown to do that, as well. So if you minimize the fats in your diet, your red meats, and your bacons, and other foods that have high fat content, then that can help the microbiome as well.

Carl Cincinnato (14:32): Rena, from our community, wanted to know specifically about gluten and sugar. You mentioned carbohydrates and sugar as things to try to minimize. What's the link there with migraine and inflammation?

Dr. Martin (14:44): Well, gluten, for people who have either a gluten enteropathy or something called celiac disease, what happens is the wheat proteins in the foods actually create an inflammatory response within the gut, mostly within the small bowel. And that can cause malabsorption of vitamins, for example. And there is an association with migraine, as well. There have not been any really well-controlled studies looking at restricting gluten or a gluten-free diet in terms of reducing migraine attacks. There's one blood test called a transglutaminase, which — it's the IgA variety, not the IgG — can be tested as a simple screening test for celiac disease. And if that's positive, it would drastically increase the risk of celiac disease. I probably picked up maybe 20 or 25 people over the years that had no diagnosis of celiac disease, but actually they had some diarrhea, or they had one of these other diseases that we talked about, that the diarrhea was intermittent, that I picked up celiac disease. And I can't say that in every instance that a gluten-free diet was helpful for their headaches, but there's some for whom it was almost a cure.

Carl Cincinnato (16:03): Yeah, wow. I mean, I've been tested for celiac disease and it came out negative. But I do find that the less starchy white bread, for example, that I have, the better I do. And you may just have a milder intolerance, and that can be sort of also helpful in just reducing that or switching to alternatives. Because I love bread!

Dr. Martin (16:28): It's very difficult to avoid. And I would say one other thing: It is very difficult to completely eliminate gluten from your diet. It's found in so many different foods, and you have to be really diligent to eliminate gluten from your diet. So even people that think they've eliminated all of it, in many instances, they really haven't.

Carl Cincinnato (16:48): Yeah, and I think sugar is similar, but I've actually found dramatically reducing the level of sugar I have to be easier than reducing gluten. Because I can, first of all, just remove any use of the sugar — the white sugar, the brown sugar, the honey and sort of monitor the sweet things that I do consume. And actually, once I've done that, I don't miss it nearly as much as I find with gluten, with bread.

Dr. Martin (17:13): Well, there are studies looking at foods that have a low glycemic index. Those are the foods that don't release glucose into the system as much. And it wasn't a great study, but there was one study that suggested that a low-glycemic-index diet was actually effective in reducing the frequency of migraine attacks. And I found that personally myself, because if sometimes where I'll be — have no headache at all — and I'll eat a piece of chocolate cake or some other sweet and immediately I get a headache; it's very interesting. It must have something to do with the spike of glucose that occurs after you eat one of these foods that release glucose very readily.

Carl Cincinnato (17:52): And as someone who has migraine, it's kind of like, that's my barometer versus my gut. I can trust my response. And as you said, it's immediate when you consume it.

Dr. Martin (18:02): Other things, like processed foods, foods that contain glutamate, and there are some people that tend to be very sensitive to monosodium glutamate (MSG). So basically, a healthy migraine diet is one where you eat lots of fresh fruits, probably more of the fruits that don't spike the blood sugar. Things like blueberries, and raspberries, and blackberries, and so forth, as opposed to the real citrusy fruits that have lots of sugar. And then eating a high-fiber diet is very helpful. So a lot of whole grains, and so forth. And then, avoiding processed foods, you exercise appropriately, and you live a healthy lifestyle, that will help. That may not always be the panacea for every patient that has migraine, but it makes a huge difference.

Carl Cincinnato (18:47): How do we sort of make those decisions judiciously so that we can still enjoy life to some extent but also find the right balance and not compromise in a significant way our overall health and well-being and exacerbate migraine?

Dr. Martin (19:01): Well, I mean, it doesn't mean that you have to be perfect all the time. I mean, I think that you can get carried away with anything, and you can get carried away with diet where you decide you can only eat — I've had people that say, "Well, I can only eat potatoes, chicken soup, and one other thing."

Carl Cincinnato (19:18): Stress is a common trigger for migraine and gastrointestinal issues (GI issues). Can you discuss the physiological changes that occur in response to stress and how they may exacerbate both conditions?

Dr. Martin (19:30): Basically, there's glucocorticoid steroids, things like cortisol, that get released by the adrenal gland. So, there's basically a gland in the brain, called the pituitary gland, that releases a hormone called ACTH [adrenocorticotropic hormone], that then affects the adrenal gland to secrete cortisol. So basically, when you're under stress, it basically releases these steroids that have an effect on inflammation in your body. And that can have a pretty profound influence on the gut, too. In fact, they have found that patients with abdominal migraine have an exaggerated stress response, and they predict — and they oftentimes worsen during periods of stress. So, as you said before, it more commonly occurs in young kids. So whether they're under stress at school, or some sort of family or social issue at home, that will often worsen the symptoms of abdominal migraine.

Dr. Martin (20:27): And the same is true with migraine, if it isn't abdominal migraine. One of those common triggers for migraine is stress. And what's interesting about stress is that the migraine can occur either at the onset of the stress or sometimes when the stress is being relieved. The so-called "letdown headaches" can occur. So the one thing about the migraine brain is, it can often adjust to some physical state, but it's during these periods of transition, whether it be a weather change or whether it be a change in the levels of stress, where migraine becomes more common and more prevalent.

Carl Cincinnato (21:05): The migraine brain likes routine [and] consistency.

Dr. Martin (21:09): Likes routine, and also the steroids have an effect on your microbiome. So it's like this orchestra of things. You've got hormonal influences, and you've got chemicals produced by bacteria in the gut, and then you've got the vagus nerve, which is a nerve that goes directly from the brain to the gut. They're all influencing the gut.

Carl Cincinnato (21:29): We spoke about the microbiome before and the gut bacteria; can that influence migraine onset and severity?

Dr. Martin (21:38): We don't know. But there have been animal studies. And what they found is that once you give those antibiotics and change the microbiome, then all of a sudden they're sensitive to pain enhancements. And they also found that if they block certain kinds of chemicals that they think are involved in the inflammatory process, like TNF-alpha, for example, that that goes away. So they think that, you know, that you alter the microbiome; you alter the inflammation, but you block the inflammation. And then the other thing about it is that they've looked at the microbiome of patients with migraine versus patients that don't have migraine, and there are differences in the microbiome. Now you can't necessarily say that that's the reason why they have migraine per se, because it may just be occurring as a kind of an incidental bystander. Maybe there's something about gastroparesis that influences the bacterial content of the gut, and maybe it's not related at all, but I think there is some experimental evidence to suggest that the microbiome can influence pain.

Carl Cincinnato (22:42): And so, would it be plausible then if we took things like probiotics and improved our diets, that we could assist with migraine? And certainly, it doesn't seem like it could hurt.

Dr. Martin (22:53): There is some evidence in randomized controlled trials that probiotics may help. Now the problem is in each of these studies, they use different probiotics. And each of these probiotics have different concentrations of bacteria — the good bacteria and the bad — and they postulate what are good bacteria. There's one bacterium called Lactobacillus that they say is anti-inflammatory, and there was another one called Bifidobacterium. So there's a lot of different bacteria that actually can be helpful, at least we think, but there's not uniformity from one probiotic to another. So I can't give you an example of one probiotic that I would definitely recommend it for migraine patients, but it's a burgeoning field and one that's evolving. And I wouldn't be surprised if we could get a couple of randomized controlled trials with one specific probiotic. I wouldn't be surprised if that's something that we try as a therapy in some patients with migraine in the future.

Carl Cincinnato (23:52): One of the other things that people with migraine and gut issues also might consider is medication side effects. What are some of the most common side effects of migraine medications in the gut, and how might they be managed or mitigated?

Dr. Martin (24:07): Well, I mean any medication that causes nausea, or some actually cause constipation. For example, some of the new meds, like the gepants, can cause nausea. And there's even one of them called atogepant [Qulipta], and actually Ubrelvy (ubrogepant), that can cause constipation, as well. Some of the monoclonal antibodies, like particularly Aimovig [erenumab], have been associated with constipation in patients. And then there are other meds that actually can actually help that. Some anti-nausea meds like prochlorperazine, which is — the trade name for that is Compazine in the United States, and Reglan, which is metoclopramide. So, drugs that treat nausea — they actually affect the dopamine pathways, which is another chemical that we think is important in migraine — can actually be very beneficial in treating migraine attacks. And then other preventive meds like tricyclic antidepressants, things like amitriptyline (the trade name for that is Elavil), and nortriptyline (the trade name for that is Pamelor), can cause constipation, as well. And anti-inflammatories can cause ulcers of the stomach; they can also cause nausea; and they can cause gastritis, as well. So there are a number of different effects that medications can have on the GI tract.

Carl Cincinnato (25:32): We spoke about how inflammation is bad in the gut and can lead to leaky gut, but you take these anti-inflammatories and they can cause things like ulcers, and it sounds like more inflammation in the gut. Is that right?

Dr. Martin (25:41): It can. It can cause gastritis. And the other thing that's interesting, and we haven't talked about this yet, but there is some preliminary data that a bacteria called H. pylori [Helicobacter pylori], which is a bacteria that causes inflammation of the stomach, or is called gastritis in medical terms, that that is more common in migraine patients. So, I wouldn't say that's a definite, but there's some early preliminary data suggesting that a bacterial infection in the stomach can be associated with migraine, as well.

Carl Cincinnato (26:10): There's a type of migraine called cyclical vomiting syndrome. Traci from our community wanted to know more about this type of migraine. Is this something that could be occurring as a result of our microbiome or something happening in our gut?

Dr. Martin (26:22): I'm not aware of research that connects the two, but cyclic vomiting syndrome is a syndrome where usually patients have some past history of migraine and they'll have these bouts where they will vomit, vomit, vomit, vomit for days, and sometimes even weeks, consecutively in attack periods. And it is thought to be a variant of migraine. That, too, occurs more commonly in young kids. But I've seen that in adults, too. And sometimes that will respond to migraine-specific medications — both acute therapies like triptans, like sumatriptan (a trade name for that is Imitrex in the United States anyway) — or it can respond to preventive meds — things like amitriptyline and other preventive medications that we commonly use for migraine. So, it's a very interesting syndrome. That, too, is a diagnosis of exclusion, meaning that if you have these people who are having these bouts of vomiting, they usually get a gastrointestinal evaluation, they'll get their stomach scoped, they'll get certain hormone levels checked and so forth, to make sure there aren't other alternate explanations for these bouts of vomiting.

Carl Cincinnato (27:35): Kirsten said that she was a colicky baby. What do we know about the connection between colic in infants and the development of migraine later in life?

Dr. Martin (27:44): Well, there's definitely an association. So, patients who have migraine are much more likely to have colic as a baby. And there's several studies that have demonstrated that. And that may relate to this predisposition to develop gastroparesis, or maybe they develop some gastric distension because their stomach, and maybe their small bowel, just aren't functioning normally. But there's definitely an association there.

Carl Cincinnato (28:06): Do you think colic could be migraine expressed in an infant?

Dr. Martin (28:11): It's possible. I mean, we'll never know that until the little kids can tell us they're having pain.

Carl Cincinnato (28:19): Are there any final thoughts that you'd like to leave with the audience?

Dr. Martin (28:23): I think that the final thoughts would be that the gut's an important part of migraine, not only in this association between the gut and the inflammation and the microbiome and all the things that we talked about, but in treatment. Because it can influence what drugs you use, how they're absorbed, and how medications' side effects affect the gut, as well. So, I would say: healthy gut, healthy brain. And that if you can maintain a healthy

microbiome and do all the right things — and I'm not saying that that's going to work for every patient — but it certainly will help in many patients that have migraine.

Carl Cincinnato (29:07): Where can people learn more about you and your work?

Dr. Martin (29:10): You can get on www.headaches.org, which is the NHF website, and there's a lot of important information. We have a lot of educational programs. We have an educational program called NHF Migraine [University], which is probably one of the most comprehensive migraine educational programs ever developed. That's completely free to people. And that was something I helped write, as well. And if you're a physician, for example, we have something called Primary Care Migraine. It also can be accessed through the NHF website, www.headaches.org, that you can actually download a free app that has educational videos on migraine, has all the migraine meds with all their doses, and recommendations for titration if it's a preventive med. So, there's lots of resources we have. If you're interested in some publications I've written, I'm sure you can access that through your library. But I wrote a two-part series on "Diet and Headache" back in 2016 published in the journal *Headache*, so you might have access to that through a library locally.

Carl Cincinnato (30:14): You've certainly been very busy, and we appreciate all the work and advocacy that you've been doing through the National Headache Foundation. Dr. Martin, thank you so much for joining us again on the Migraine World Summit.

Dr. Martin (30:25): My pleasure.