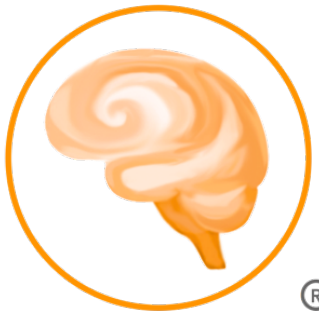

MIGRAINE WORLD SUMMIT

INTERVIEWS WITH WORLD-LEADING EXPERTS

TRANSCRIPT

THE GUT-BRAIN CONNECTION IN MIGRAINE

JAY PASRICHA, MD, MBBS
CHAIR OF MEDICINE
MAYO CLINIC, ARIZONA

Introduction (00:04): The theme that I'm going to emphasize again and again is: disorders of the enteric nervous system. The nerves that control the gut, whether it's the lower esophageal sphincter, which regulates how much acid goes back into the esophagus; whether it's the stomach; the small bowel; or the colon, they are in a very intimate manner linked to disorders of the vagus nerve and possibly migraine. So none of this should be surprising; that migraine is associated with any one of these chronic GI symptoms. The exact mechanisms have yet to be worked out, I will grant you that, but the phenomenon is well known.

Carl Cincinnato (00:45): Emerging research reveals a complex bidirectional communication system between the gut and the brain. The impact on the gut and what it contains reaches farther than many of us appreciate. It goes beyond digestion and immunity and into areas such as cognitive function and mood. Disruptions or imbalances have been implicated in a wide range of disorders, including irritable bowel syndrome, irritable bowel disease, obesity, and even mental health issues. To help us answer questions about the link between the gut and migraine is Dr. Jay Pasricha. Dr. Pasricha, welcome to the Migraine World Summit.

Dr. Pasricha (01:22): Thank you, Carl. It's my pleasure.

Carl Cincinnato (01:25): So, what parts of the body are we talking about when we mention the gut?

Dr. Pasricha (01:30): The gut is a semi-colloquial way to talk about what is formally known as the gastrointestinal tract, and that includes all the organs involved from the ingestion of food to the passage of waste materials. So, formally it begins with the esophagus, which is the food pipe or gullet, and ends in the rectum and anal area. Traditionally, we've separated the mouth from the esophagus, but in reality, the mouth is where food first enters.

Carl Cincinnato (02:04): And how is the gut and the brain connected?

Dr. Pasricha (02:09): The gut and the brain are connected very intimately, and they've been connected for eons through the evolutionary process. The gut serves a very critical function without which the organism cannot survive, and that is the processing of materials from the environment to generate energy. And that process is called digestion. And that's really what the gut does. And in order for the gut to be able to do that, it has to be not only finely controlled by the brain — because remember, the brain consumes 20% of the body's energy while only being about 2% of its weight. So the brain in our head is an energy-hungry beast, and it has to make sure that the apparatus for generating energy, i.e., the gut and its associated links with metabolism, are always in good shape. Now, that method of control and command takes many different ways, but it involves hormones for sure.

Dr. Pasricha (03:15): The gut is also an endocrine organ. So just like the thyroid or other organs, it produces a variety of hormones, and these hormones can signal to the brain directly or indirectly. But perhaps the most well-known and well-studied way by which the gut communicates with the brain is through what we call the superhighway, and that's the vagus nerve. So, the vagus is one of the so-called cranial nerves. That means these are the nerves that the brain developed to send out to the periphery. And the vagus nerve monitors functions in all those organs that generally are below conscious recognition or conscious understanding. So, these are the so-called visceral organs: the heart, the lungs, and most importantly the gut. So about 90% of the vagus is sensory. Its role is to monitor the environment, monitor the function of these organs, and convey that information back to the brain. The brain receives that function.

It receives that signal, and then by feedback mechanisms provides some regulation of those organs through what we call motor nerves; it's about 10 or 20% off the vagus system. So there's a feedback loop.

Carl Cincinnato (04:27): And what's the enteric nervous system referring to?

Dr. Pasricha (04:31): So, let's start with the brain, right? The brain is classically what we call the central nervous system. So, the central nervous system is the brain and the spinal cord. And then there are a variety of peripheral nervous systems. One of them is the autonomic nervous system. The autonomic nervous system is what controls functions such as heart rate, blood pressure, stress responses, temperature regulation, all the things that you're not supposed to be aware of but are vital for your health. And then there is the enteric nervous system, which is also a stand-alone, relatively autonomous nervous system that is contained entirely within the wall of the gut.

Carl Cincinnato (05:11): Yeah, I think for a lot of people, myself included, you think about the brain and you think about neurotransmitters, but there's actually a huge number, something like an estimated 100 million neurons in the gut. And neurotransmitters are produced in the gut. And two chemicals that come up time and time again in migraine is serotonin, which is very well known, but also GABA [gamma-aminobutyric acid]. Can you talk about the production of serotonin and GABA in the gut?

Dr. Pasricha (05:38): Yeah. So, you know, it's estimated that 80 to 90% of the entire body's serotonin originates in the gut. And the serotonin is actually produced by the lining — or most of the serotonin is produced by the lining of the gut that's interfacing with the food, the microbiota, or anything else that's inside the gut itself. And what serotonin does, at least one of many things it does, it triggers what we call peristalsis, which is an orderly sequence of events that causes the gut to push food down. GABA's a very interesting drug in the gut. It's one of those drugs, unlike serotonin, that has been relatively poorly studied, even though we've known for a long time that the concentrations of GABA in the gut are extremely high. We don't fully understand what GABA does in the gut. There are some clues that it is an important neurotransmitter for motility and secretion, but exactly what goes wrong when GABA is not produced in enough concentrations or produced excessively, we don't fully know.

Carl Cincinnato (06:54): You mentioned before the microbiota, and if anyone's doing some research about the gut and migraine, the gut microbiome comes up quite quickly in the explanations. Can you discuss what the relationship is between those two and what they are?

Dr. Pasricha (07:11): So, the microbiome is another way to talk about the bacteria in different organs of the body, right? So, when it comes to the gut microbiome, we mostly are referring to the trillions of bacteria that live in our colon, which is where they normally reside in greatest abundance, although there are bacteria in the stomach, and to a much smaller extent in the small intestine. Clearly there are bacteria in the mouth: That's the oral microbiome. The bacteria on the skin: That's the skin microbiome. So anywhere where bacteria — and actually if you want to broaden that, it's not just bacteria, it could be viruses, certain kinds of fungi — anywhere that they live in what we call a commensal relationship, which is a relationship that is of mutual benefit, that's the microbiome. So, with respect to gastrointestinal-related disorders and the gut-brain axis, we usually talk about the gut microbiome, and typically we're referring to the bacteria in our colon.

Carl Cincinnato (08:11): So, talking now about the impact on health from the gut, how does that sort of play a role? How does the gut affect our overall health?

Dr. Pasricha (08:20): So, the gut is like the skin, it's an external organ. Now it's hard to conceptualize that, but you know, you swallow something, whatever, it's going right into your gut. And so, the gut is actually a major interface between the inside of your body and the environment. So it is always going to be vulnerable to environmental insults, injuries, and predators. And that's why the gut has evolved not only for digestion, but also to maintain the barrier and mount an appropriate immune response. All of these are vital components of the gastrointestinal tract. So if everybody — and it seems to be that everybody's confident that the microbiome affects our systemic health — you have to ask the question, how does it do that? These bacteria are not jumping inside our bloodstream and doing what they're doing. They're staying in the colon, and somehow they are sending signals to the rest of our body to maintain our health, or in cases where things go awry, to produce ill health.

Dr. Pasricha (09:37): But how do those signals get there? And this goes back to what I said initially, it's a combination of hormones. In large part I think it's nerves, and we talked about the vagus, and I'll get back to that. And sometimes perhaps it's the products of the bacteria, you know, small molecules, peptides that get absorbed just like drugs that you take for a condition get absorbed. So you can think of the microbiota as sort of your own little pharmacy producing good stuff. And sometimes when things go wrong, producing bad stuff. But we know in a lot of instances that this signaling between the gut and brain when it doesn't work properly, things break down.

Dr. Pasricha (10:21): When we irritate the stomach, for instance — this is the paper we published a couple of years ago — it sets [off] a chain of events that include sensitization of the vagus nerve. So the vagus nerve is now generating a lot more noise at higher frequencies than it would have in health. And that is reaching the brain and causing changes in the brain, not just in terms of the behavior of the anxiety and depression, but when you look for molecular changes or pathological changes, you can find that. So these connections, these intimate connections between the gut and the brain, which have been designed so that the brain maintains control of the energy production, are also its weak spot. Because if things go wrong, then it can have untoward effects. And that's kind of what we are discovering. So, there may be forms of depression and anxiety that originate in the gut. Lots of patients with gut disorders — irritable bowel syndrome is a classic example — have anxiety and depression. For a long time, doctors assumed it's the other way around — they had anxiety and depression to begin with and it's manifesting itself as gut symptoms. But now we've shown that the opposite can also be true; it is bidirectional, as you said in your opening statement. And there's some human evidence that's coming out that you could start with a gut disorder and then over a period of years develop depression and anxiety at a higher risk. But these paradigms may also apply to other disorders beyond depression and anxiety.

Carl Cincinnato (11:51): And a lot of people that are watching this have chronic pain, and obviously migraine. But how does the role of the gut influence pain?

Dr. Pasricha (12:01): So, chronic pain is a very broad term. There are patients who have very specific causes for the pain, right? If you have an injured joint — shoulder joint, knee joint — you can develop changes that cause chronic pain, and that's localized to that. And that's generally not difficult to understand. And there are others where they have had nerve injuries and you get chronic pain from that, and that's not difficult to understand. Or patients who've

had prolapsed discs and chronic back pain. But then there's another category of patients where the pain is more generalized. It's not necessarily limited to one specific region. And these are what we call general examples of neuropathic pain syndromes, where we believe the pain is coming not from the organ itself, although it appears to be coming from the organ. But the problem is not that there's anything wrong with the organ, but there is something wrong with the nerve.

Dr. Pasricha (13:01): So it's like having a faulty fire alarm, right? Most often when the fire alarm goes off, you are right in thinking that there's a fire or smoke. But when the fire alarm itself is faulty, the signal that it generates is the same. And your brain thinks there's pain, there's injury to that organ, because it can't tell whether it's the fire alarm or the organ itself. So that's called neuropathic pain. And it's a very wide spectrum of disorders, but there's a lot of overlap. Patients who have widespread fibromyalgia, for instance, which is a kind of somatic pain that we think is neuropathic in nature; patients who have irritable bowel syndrome, which we think is a form of neuropathic pain emanating from the bowels; and patients who have migraine. There's a lot of overlap. If you take any one of these — you take a hundred patients with migraine, half or more will have irritable bowel syndrome kind of pain or irritable bowel syndrome; half or more will have fibromyalgia. Conversely, [if] you take a hundred patients with fibromyalgia, you'll find a significant number have migraine, and IBS, etc., etc. So people have traditionally gone to different specialists and been siloed into saying: This is fibromyalgia, this is migraine, this is IBS. But actually, if you take the big picture, we're dealing with a more widespread and more unifying diagnosis, which is neuropathic pain, right? So one way to explain how the gut is connected to migraine is to understand it as part of this more widespread neuropathic problem.

Dr. Pasricha (14:45): Now, having said that, with respect to migraine, there are actually even more deeper connections. So, we know as an example that vagal nerve stimulation — some forms at least — has been approved by the FDA for migraine. And as we've talked about earlier, the vagus is the highway from the gut to the brain.

Dr. Pasricha (15:10): So it makes sense that perhaps the neuropathy that we are talking about is affecting the vagus nerve itself. And what is the origin of that, whether it was some neonatal or early-life injury to the gut that resulted in sensitization of the vagus nerve? We don't know that. We can speculate, and we have some animal models that suggest that. But clearly this axis, the gut-brain axis, is affected in migraine. We know a lot of patients with migraine get nausea, a lot of patients get GI upset, they can have diarrhea. Conversely, eating the wrong things triggers migraine, having gastroenteritis triggers migraine. So that connection is real, and we believe that part of that connection is through the vagus nerve, and this is why vagal nerve modulation may work in a subset of these patients. So that's the second sort of connection with migraine and the gut.

Dr. Pasricha (16:08): And then of course the third connection is … now with these new drugs that we have, the CGRP antagonists — or the CGRP-signaling antagonists, I should say, because there are different forms — can have effects or side effects on the gut. Now we know that some patients on certain kinds of these drugs have more constipation than others, and than other drugs. And we don't quite understand what the basis of why one drug causes more constipation than the other. But we do know that part of it may depend on the fact whether you're using a drug that acts against the CGRP receptor or against the CGRP neurotransmitter itself.

Carl Cincinnato (16:51): So, for a patient who is listening to this and has had some signs of gut issues, maybe they're thinking, "Oh, you know, that could be IBS." Or that, you know, "I

definitely have fibromyalgia. I've certainly got allodynia with migraine. I've got nausea." What are the implications now? When you take that step back, you look at the broader picture treating the whole person, I think which you are alluding to, what's your approach when someone comes to you with some of these symptoms and they've got migraine?

Dr. Pasricha (17:21): So, I think there is a spectrum. The spectrum we see is more complex, lots more overlap. And we are trying to find the patterns. And I think we are finding the patterns. One of them is the autoimmunity — in a subset of these patients, there may be an autoimmune basis. But clearly all of them are united by one thing: The nerves are not working well; they're sending a lot of noise. And so we focus on neuromodulators. And fortunately, we have now a couple of dozen different kinds of neuromodulators that are available and that we can try in patients. And generally, a combination or one of these significantly helps their symptoms.

Carl Cincinnato (18:07): When you talk about neuromodulators, are you talking about devices? I mean, that's the first thing I go to.

Dr. Pasricha (18:12): No, I'm talking about drugs.

Carl Cincinnato (18:13): Right. So there's medicinal treatments that are neuromodulators, not just the devices that ...

Dr. Pasricha (18:20): It's very gratifying actually to see the wide range of neuromodulators that have been developed. And not all of them were developed for the purpose of neuromodulation. There's a classical example: tricyclic antidepressants. They were developed in the '70s for treating depression, but we now know them as very powerful neuromodulators, and we use them for that much more than we use them for depression or anxiety. These are drugs that they are using already. We're talking about nortriptyline, we're talking about gabapentin, we're talking about topiramate. These are all different neuromodulators. We have half a dozen or more different mechanisms and classes of these that can be used in combination.

Carl Cincinnato (18:55): And they have [an] impact on the gut?

Dr. Pasricha (18:57): They have impacts on gut pain for sure. Yes. And gut motility.

Carl Cincinnato (19:03): Let's discuss some common gut symptoms that people with migraine experience. Nausea, and even vomiting, is a big problem for a lot of people with migraine, especially during a migraine attack itself. Is this purely because of the migraine, or is there something more happening in the gut?

Dr. Pasricha (19:17): That's a great question. I don't think we fully understand the answer. But clearly the pathways in the brain that respond to signaling, that correspond to the nerves serving the migraine pathway, overlap with that serving the nausea pathway. So how that actually works, we don't know, but clearly the vagus nerve appears to be involved. We know the vagus does signal nausea, and we know that vagal nerve modulation is helpful for migraine. So that's a likely candidate. Now, nausea and vomiting are not the only symptoms that patients with migraine suffer from in terms of their GI symptoms. Many patients will have diarrhea, some patients will have chronic GI problems, not just during the migraine attacks. And I can talk about that later if you'd like.

Carl Cincinnato (20:07): Yeah, I'd love to go into some of those. One that Amber and Claire asked, who are members of our community, they spoke about gastroparesis. They wanted to know: What is this and how is it linked with migraine?

Dr. Pasricha (20:20): Again, we think that the vagus is a common thread, the vagus nerve, because the vagus conveys sensation from the stomach. And in the cases of gastroparesis, it conveys nausea signals to the brain. But the vagus also controls stomach motility to some extent. And if you cut the vagus, stomach motility or the ability to empty food, may be impaired. So that's one of the ways that we can start thinking about how migraine and gastroparesis are linked. So, this theme that I was talking about earlier, that migraine is part of some kind of generalized neuropathy, may be true. Again, it's a hypothesis, somewhat speculative, but I think with further investigation by others, including our group, perhaps we can come closer to finding out the truth and what really lies behind that connection.

Carl Cincinnato (21:12): So, coming back to other symptoms, we've got a viewer from our community, Liz, who spoke about acid reflux and bloating. Is that something that you hear a lot of people with migraine complaining about as well?

Dr. Pasricha (21:24): Yes. So acid reflux is very common in the general population, right? Ten, 20% of the population will have some kind of reflux. And in a large number of patients that reflux can be chronic and not trivial. That's why drugs that treat reflux such as the ones that you see on TV are so popular. But it is again, part of the spectrum of GI disorders. So I think the theme that I'm going to emphasize again and again is: disorders of the enteric nervous system. The nerves that control the gut, whether it's the lower esophageal sphincter, which regulates how much acid goes back into the esophagus; whether it's the stomach; the small bowel; or the colon, they are in a very intimate manner linked to disorders of the vagus nerve and possibly migraine. So none of this should be surprising that migraine is associated with any one of these chronic GI symptoms. The exact mechanisms have yet to be worked out, I will grant you that, but the phenomenon is well known.

Carl Cincinnato (22:33): We've got a patient called Janet from our community who has IBS, and she says that she's using these newer migraine medications, which are helping reduce the pain and frequency, but it's making her IBS — her irritable bowel syndrome symptoms— worse. In that scenario, do you look to switch that patient off a medication that's antagonizing IBS and try to find something else that helps with both?

Dr. Pasricha (22:56): So, I suspect, although I don't know, she's using one of the newer anti-CGRP signaling drugs. I think it's very much worthwhile switching agents within that class. There is now, thankfully, a large choice of those drugs, and switching that around is worth trying. But again, I cannot tell your viewer what the exact mechanism is — why her IBS got worse. Possibly it's constipation getting worse, because we know some drugs cause worsening constipation. In general though, we'd like to think of CGRP as a common factor in a lot of pain syndromes. So you would think, based on just logical reasoning, that if you have pain in one syndrome like migraine and CGRP works on that — CGRP-acting drugs work on that — they should work on the pain in IBS. So it again, depends whether the pain got worse, or the constipation got worse. If the constipation got worse, the pain will naturally get worse as a consequence of that. But these are complicated questions and nobody really has the answers yet.

Carl Cincinnato (24:05): But it's good to know that even within a treatment class like the antibodies, or the gepants, or others, that it might be worth rotating within that class, not changing entire categories of treatment, so that there are options there.

Dr. Pasricha (24:17): That's correct.

Carl Cincinnato (24:19): We've spoken about harmony between the gut and the brain and this axis that connects them. Let's shift the conversation now to actually restoring the gut. What are some things that we can do to do that?

Dr. Pasricha (24:32): So, I start off by saying we don't have a lot of drugs, and we don't have very effective drugs for the most part. Now we talked about the brain in the gut as being the second-largest nervous system outside of the brain in your skull, right? Hundreds of millions of nerve cells and neurons. Now, if you think about how many drugs there are to treat anxiety and depression — between 50 to 100 drugs that are used and approved for anxiety and depression. And that's just anxiety and depression. That doesn't include all the other disorders of the CNS. You can count on the fingers of two hands, all the drugs that are approved for gastrointestinal. I'm not talking about liver diseases. I'm talking about — I'm not talking about inflammatory bowel disease. I'm talking about this group of disorders affecting the second-largest brain. So, if patients are frustrated when they come to gastroenterologists to get treatment for these disorders, they're justified because there isn't enough choice.

Carl Cincinnato (25:44): Right. And what about — coming back to inflammation — what about stress? You know, stress in the job, life stresses. We know that stress is linked with a certain amount of inflammation, or can produce a certain amount of inflammation, in the body. And you've mentioned that inflammation, almost like background inflammation in the gut, can also be playing a role. Do you think there's links there?

Dr. Pasricha (26:07): If the brain wasn't linked to the rest of the body, it wouldn't be doing its job. So, the brain is in this unfortunate position that every sensation, every obvious sensation, like a pinprick — but every signal that you don't even perceive, which is probably 99%, that's happening in the background, the brain is receiving those signals and responding to that. And in turn it's sending back signals to constantly fine-tune the function of those organs that it's receiving signals from. So of course, if the brain itself gets ramped up, as in stress, you can imagine that those feedback loops will be affected, sometimes adversely.

Carl Cincinnato (26:49): Yeah, yeah. So, what about exercise and/or more regular movement? Is that something that you've seen any merits for or worth trying for some people?

Dr. Pasricha (27:00): Exercise does help ... so these are gentle measures, right? Healthy diet, exercise, avoiding smoking, avoiding drinking too much, you know, trying to maintain our body weight within a range. These are general lifestyle measures that have consequences for our well-being ... many ways beyond the gut, right? But yes, the gut itself — clearly if you're a healthy person, you want to increase your fiber so that your bowels move regularly, you prevent diverticula, and you promote a good microbiota. Exercise also helps with bowel movements. So we tell patients who are constipated, you know, without any other obvious cause: Increase your fiber, increase your fluid intake, and exercise. These are all things that are helpful measures. Are they "magic bullets" for any of that? And if you have [a] serious disease, is that going to help? Probably not.

Carl Cincinnato (27:54): What's your view on probiotics?

Dr. Pasricha (27:57): I think probiotics are a very important pathway to improving our health, but they remain in the potential rather than the real space, as of today. And that's because probiotics that are being used today have generally not been developed in a rational way. What do I mean by rational? Let me use the analogy to rational drug development, right? What is rational drug development? Rational drug development is: You take a disease that you want to treat, you figure out what are the molecules that are important in causing that disease. And then you target those molecules, either ramp them up, or ramp them down. That's rational drug development. Empirical, or you know, just by observation alone is: "I don't know why it works, but maybe it will; let's try something." And sometimes it does work, sometimes it doesn't. Most probiotics … have been developed to date without a clear idea of what is it that they are targeting — it's a broad sweep. You don't know what you're actually changing in terms of the product of the microbiome. You actually don't even know how effective they are in even populating your colon. It's — there's a lot of leaps of faith here.

Carl Cincinnato (29:26): So, let's talk lastly about antibiotics. What impact do they have on the gut? How can they influence our gut well-being?

Dr. Pasricha (29:35): Antibiotics, clearly by definition, will have an effect on the microbiota. You give mice a course of amoxicillin, and then you examine the enteric nervous system, and after 10 days the numbers are diminished by up to 60% or more. You have a loss of neurons. And when you stop it, eventually it comes back. But it goes to show the link between the microbiota and everything that's happening in the gut, including in the deeper layers of the gut, such as the nerve cells. So there's a lot more to be learned, but we know that excessive use of antibiotics is a problem. And excessive use of antibiotics in childhood may potentially explain some of these changes in the microbiome that would translate into adverse effects on health as adults.

Carl Cincinnato (30:33): Well, this has been a fantastic conversation about migraine and the gut. I've certainly learned a lot. Dr. Pasricha, I want to thank you very much for your time and your expertise today on the Migraine World Summit.

Dr. Pasricha (30:44): That's my pleasure. Bye-bye.