



MIGRAINE WORLD SUMMIT

INTERVIEWS WITH WORLD LEADING EXPERTS



TRANSCRIPT

WHAT CAUSES MIGRAINE AND ITS SYMPTOMS

CATHERINE STARK, M.D.



Introduction (00:04): I would conceptualize it as you're born with your migraine threshold at a certain point, and you can shift that threshold by lifestyle interventions: so by eating regularly, by drinking lots of water, by getting a consistent amount of sleep every night, and being on medications if necessary. All of that is going to increase your threshold — so increase your tolerance to those triggers. Likewise, you can drop that threshold down: If you sleep really erratic hours, get on a plane, all of those things can lower that threshold. So absolutely, while you do have a genetically predetermined position for your threshold, you can move it.

Carl Cincinnato (00:04): A question that most people with migraine want to have answered is, "How did I get migraine?" It's something that we often try to answer ourselves, searching for a reason for our suffering. But could understanding the causes and our painful symptoms help us understand our brain and the disease better? Joining us to explore the causes and symptoms of migraine is Dr. Catherine Stark. Welcome to the Migraine World Summit, Dr. Stark.

Dr. Stark (01:12): Thank you very much.

Carl Cincinnato (01:13): Let's start off with what causes migraine.

Dr. Stark (01:17): So, migraine is a collection of symptoms that a person experiences in response to abnormalities of neurochemicals within the brain itself, particularly affecting the part of brain that processes pain. We know that once that process gets started, there's a multitude of downstream effects that affects nearly all the parts of the brain, that accounts for the wide variety of symptoms that patients with migraine will experience. What actually causes the abnormal brain activity is not well understood. Once it's started, we know quite a lot about the process of migraine evolution; but as to what actually lights the match that starts the migraine attack, we don't have a great understanding of that.

Carl Cincinnato (02:06): Why is it the case that we don't fully understand the picture of migraine after so much time and research and advancement within medicine?

Dr. Stark (02:13): So, part of the reason is because migraine is such an intermittent phenomenon. It's really difficult to catch people in a spontaneous migraine attack while we've got them in the lab and while they're being studied. On top of that, the brain's quite inaccessible. We can't chop bits out of it with impunity. We can't easily access the neurochemical environment around the brain directly.

Carl Cincinnato (02:36): What are some signs of abnormal brain activity that's associated with migraine?

Dr. Stark (02:41): So some of the things that we know do change during a migraine attack in individuals with a susceptibility to migraine — between attacks in some cases — are some of those neurochemical levels. So, one that your listeners may well have heard of is calcitonin gene-related peptide or CGRP. We know that those levels will increase in an attack. Other physical changes are often seen, such as vessels will dilate and contract during various phases of a migraine event. And functional imaging studies, such as functional MRI and PET scans, will light up in various areas of the brain during different phases of a migraine attack. For example, in the prodrome, the hypothalamus is often active; during the pain phase, multiple areas of the brain will light up; and during the postdrome, it is often the brain stem.



Carl Cincinnato (03:34): And what causes this abnormal brain activity to occur in the first place?

Dr. Stark (03:38): So, there's really two questions: There's, "Why does an individual have the susceptibility to develop migraine?" and, "Why does that individual who does get migraine have a migraine today?" We think the susceptibility to migraine is largely genetic, but there are some environmental factors that will impact that, as well. And as for a migraine today, there's often been a stress of some sort to the brain that will bring that on, such as a poor night's sleep.

Carl Cincinnato (04:11): If you have someone in your family that has migraine, does that make you more likely to have it?

Dr. Stark (04:15): It absolutely does. So, there's a strong genetic factor as a cause of migraine. There's some that are quite clear cut. So in hemiplegic migraine, for example, we know some of the genes that cause that, and it's a straightforward inheritance. You get the gene or you don't, you get the migraine or you don't. But [for] the vast majority of migraines, both with or without aura, it's more complex than that — it's about 40 different genes that will increase your susceptibility to migraine. And it's not the individual genes, but the interaction between them that will change that susceptibility. So conversely, a patient who does not have a family history of migraine might inherit a handful of genes that weren't enough to cause migraine from Dad, a handful of genes weren't enough to cause migraine from Mum, but that combination can be enough to increase that patient's susceptibility to migraine. So they can still have a genetic cause for their migraine in the face of a lack of a family history.

Carl Cincinnato (05:17): Can you tell us what's meant by environmental factors? We're not talking about, necessarily, pollution or the environment per se, it's something else.

Dr. Stark (05:25): That's right. So, the environmental factors that we would typically think of would be things like exposure to stress in early life, or exposure to physical stress — a head injury, in particular. And that can really cover the whole gamut from a significant acquired brain injury, such as in a motor vehicle accident; repetitive head injuries from sports; or even a single, quite minor head injury looks like it can contribute to a patient developing a susceptibility to migraine.

Carl Cincinnato (05:59): So, if you have more people in your family with migraine, does it make you more likely to have more severe migraine symptoms yourself?

Dr. Stark (06:05): It certainly does. So, we know people who've got a strong family history — so more than one family member with migraine — you're more likely to have a younger age of onset of migraine, and migraine is likely to be more severe, more frequent, and [with] higher levels of acute medication use.

Carl Cincinnato (06:22): And it can be quite difficult to ascertain exactly who in your family has migraine. Because it seems like it's not well diagnosed, and there might be a father, for example, who's always had these sinus issues or sinus headaches, but it turns out that that could have been migraine?



Dr. Stark (06:39): Yeah, so historically, migraine was poorly diagnosed and also a little bit taboo. So you'll often find families where there was a suggestion that Grandma or Grandpa had headaches, but it was never much talked about. I think our tendency to be open with our health conditions is very much a modern phenomenon.

Carl Cincinnato (07:03): And if your family member just put up with it and couldn't necessarily get a good quality of life despite their condition, does that mean that that will be the case for you, as well?

Dr. Stark (07:13): That is a 100% "no." Migraine treatments have evolved so significantly over time. So, even in the last 10 years, we've had a huge explosion in the way that migraine can be treated. So do not despair. If you've had a family member with terrible migraines, there is absolutely hope that your migraines could be well treated.

Carl Cincinnato (07:35): Are there other risk factors, such as underlying conditions that could also predetermine your vulnerability or susceptibility to migraine? And where this question's coming from is, we have a viewer, Jessica, who wants to know if her family history of extreme ear, nose, and throat issues could be a factor in migraine in her family.

Dr. Stark (07:55): So, we know that migraine does tend to coexist with a lot of other conditions, and that's really right across the spectrum. Other neurological conditions have been associated with migraine: things like epilepsy; Tourette syndrome; psychiatric conditions such as depression and anxiety; and even seemingly unrelated systems, like for example, a patent foramen ovale, which is a heart condition; Raynaud's phenomenon, which is a rheumatological condition; sleep disorders. All of these things have been associated with migraine. And what that means is, if you have migraine, you're more likely than the average person to have those conditions, and vice versa. What has not been established is a causative relationship between a lot of those comorbidities. So what may be occurring is a genetic predisposition to both conditions [that] may exist close by on the genome so they tend to get inherited together. Or possibly, there might be an underlying causative factor that contributes to both conditions, rather than one that hasn't been identified yet.

Dr. Stark (09:12): So, then the ENT question, in particular, is an interesting one. We know that a person who's got a predisposition to migraine who develops any pain in their head or neck — and that might be from a bacterial sinusitis, that might be from a toothache, and might be from a wry neck — that pain will feed into the same pain areas that are involved in the migraine process. It can trigger off that train of neurochemical events that is experienced as migraine; and so that unrelated pain can trigger a migraine and cause problems in patients who have ENT problems, in particular.

Carl Cincinnato (09:55): Can you tell us a little bit about the trigeminal system?

Dr. Stark (09:58): So, the trigeminal system, in particular, is involved with the face. Any pain around the face can trigger that system off.

Carl Cincinnato (10:09): Just coming back to environmental conditions like the climate and air quality and bright sunlight — do they cause migraine or do they trigger migraine?

Dr. Stark (10:20): So, trigger would be more accurate there. We don't have really big high-quality epidemiological data on triggers, but there are some triggers that are routinely



reported in all different places of the world as bringing migraine attacks on, in people who are susceptible to migraine. And some of these are weather-related. So, high altitude is a reliable trigger. Changes in weather, particularly changes in barometric pressure or in humidity, can definitely be a trigger. Air travel seems to be a consistent trigger. Smells are often cited as a trigger. It's often more sort of noxious, volatile substances like perfumes and deodorants, but cigarette smoke and air pollution have been reported as triggers for events — for example, our recent bush fires in Australia, there was a lot of migraine that was triggered around that time. And bright lights, including sunlight, can certainly be a trigger for some patients.

Carl Cincinnato (11:27): So how would you define or describe the difference between a cause of migraine and a trigger?

Dr. Stark (11:33): So, cause is the big picture. It's why an individual has the susceptibility to develop migraine attacks: So, that might be their genetic makeup, combined with early life experiences, combined with a physical trauma. Whereas a trigger is why one of those individuals has a migraine today: So that might be a poor night's sleep or big change in the weather.

Carl Cincinnato (12:03): Can medication cause or trigger migraine?

Dr. Stark (12:08): So, medication probably isn't implicated as a cause for migraine, but certainly can be a trigger. The most common way that this would occur would be in the setting of medication overuse headache, which is a trap that a lot of people with migraine will fall into. If you're overusing your acute medications, this will increase your likelihood for a migraine attack to start. And after a particular migraine event treated by an acute medication, rebound headache can occur as a result of that, as well.

Carl Cincinnato (12:46): So as it relates to triggers, some people are told about this concept of the migraine threshold. Can you tell us a little bit about that?

Dr. Stark (12:54): So, the migraine threshold is really describing how easy it is for you to be tripped into a migraine. Probably any person in the world could have a migraine induced if their brain was put under enough stress. So if I were to put you on an airplane for three days, feed you 12 bottles of red wine, and not let you sleep, it's very likely that you would experience a migraine attack. The person who has a susceptibility to migraine, or gets migraine a lot, will be tripped over into migraine much more easily. So the same exposure would definitely cause a migraine in someone who has that susceptibility, and even quite a minor trigger — exposure to cigarette smoke, for example — may be enough to trip that person. So it's really how much of a hair trigger you're sitting on to have a migraine event triggered.

Carl Cincinnato (13:55): So, one thing I've noticed personally is that when I get a good night's sleep and I'm exercising and eating well, my threshold actually changes. Do you have the sense that migraine thresholds are genetically predetermined or is there some room for movement based on, maybe, some behavioral lifestyle factors and even some medication and treatment that you're receiving?

Dr. Stark (14:20): Absolutely. So, I would conceptualize it as you're born with your migraine threshold at a certain point, and you can shift that threshold by lifestyle interventions: so by



eating regularly, by drinking lots of water, by getting a consistent amount of sleep every night, and being on medications if necessary. All of that is going to increase your threshold — so increase your tolerance to those triggers. Likewise, you can drop that threshold down: If you sleep really erratic hours, get on a plane, all of those things can lower that threshold. So absolutely, while you do have a genetically predetermined position for your threshold, you can move it.

Carl Cincinnato (15:06): And I get the sense as well, that you can develop both, sort of, positive and negative feedback loops.

Dr. Stark (15:13): Absolutely. Migraine does tend to breed migraine. So when you've had a lot of migraines recently, those networks are primed. They're on more of a hair trigger than they would be otherwise. Likewise, if you've had a bit of a break, that you've backed off on that trigger a little bit.

Carl Cincinnato (15:31): Can you tell us a little bit about the phases of migraine that distinguish it from other types of headache?

Dr. Stark (15:35): Sure. And so, there's four main phases of a migraine, and not all patients will experience all of these phases. The first is the prodrome, which can last from a few hours up to even a couple of days before the rest of the migraine gets going. And this is characterized by mood changes such as depression, irritability, yawning, increased need to urinate, sensitivity to light and sound, difficulties with concentrating, and nausea are some of the things that might be experienced during that phase. Some people are able to identify this and know that a migraine is on its way. And other people can only really identify it in retrospect.

Dr. Stark (16:20): The next phase is the aura, which of course not all people with migraine will experience. The most frequent or the classic aura is a visual aura and this can have both positive and negative features. So what I mean by that is, a positive phenomenon is extra things: new vision that might be spots or sparkles or geometric shapes, which are typically black-and-white or silver and evolve over time. And negative phenomenon is loss of vision, which can either affect a part, a corner of vision, half of the field, or even your entire field of vision, which can be really frightening. Sensory symptoms are another aura, which is reasonably common. This will typically be positive: So, tingling or pins and needles which will start in one body part and will typically move over the body to involve other body parts over the course of minutes. And more rarely, weakness can accompany that phase, as well. And that lasts 5 to 60 minutes.

Dr. Stark (17:24): Then the headache phase, which is often but not always the most problematic phase for patients. This classically will be a unilateral pain, so affecting one side of the head or the other, and not always the same side. Classically it's a throbbing pain, but it can also be tight or dull or quite sharp, have a drilling quality to it. And associated with the pain, there's often nausea or vomiting. There's sensitivity to light, sound, and smell. Mood is often really low. There can be insomnia or increased need to sleep, and neck pain and stiffness can often accompany this phase, as well. This can last from 4 hours up to 72 hours.

Dr. Stark (18:16): And then the last stage is the postdrome, and this is really dominated by cognitive problems. So, low mood, difficulty concentrating, fatigue, just feeling washed out or hung over, is often the way that patients will describe this phase.



Carl Cincinnato (18:34): Tension-type headache, which is a headache that 95% of the population experiences, is just essentially like a tension around the head — a band of, sort of, pressure around the head. And that's very different than the four phases that you've just described.

Dr. Stark (18:50): It certainly is. So the biggest difference between migraine and tension-type headache would be the severity. So it's a very rare to be incapacitated by a tension-type headache. But all of the associated nonpain phenomena are really rare to occur in a garden variety or tension-type headache. And that's one of the clues that you aren't dealing with migraine.

Carl Cincinnato (19:17): How strictly do patients tend to follow that pattern? So we were talking about certain phases lasting like the aura, for example, from 5 to 60 minutes — can that kind of overlap with the head pain? Is it a neat, sort of, discrete phase of the attack, or can it be a blurry mess at the time for the patient?

Dr. Stark (19:36): It can 100% be a blurry mess. So, a lot of the less specific symptoms really can spill over all four phases of a migraine. Nausea, in particular, can be seen all the way through. A good-going visual aura — so, clear-cut spots, sparkles, or shapes usually follow the rules — so it usually precedes your headache, and it goes away before your pain starts. But more nonspecific visual changes, such as blurriness or strange depth perception, can really lead into the phases on either side.

Carl Cincinnato (20:18): And why is it so different for different people?

Dr. Stark (20:20): Because everyone's brain is unique; we're all unique snowflakes. We've all got our own genetic makeup, we've got our own early life experiences, we've got our own soup of neurochemicals and hormones that are affecting our brains. And as a result of that, the symptoms that are experienced are really different between individuals.

Carl Cincinnato (20:43): And then even within individuals, you can have different symptoms with different attacks. Is that true?

Dr. Stark (20:48): One-hundred percent. So, in any complex system that has multiple variables impacting on it, you can present that system with the exact same triggering event and the outcomes can be wildly varied and really difficult to predict. Weather systems would be a good example of that. The brain is basically the ultimate complex system and in that way, even an identical-seeming trigger — "I drank three scotches last week and didn't have a problem. I drank three scotches last night and have the worst migraine in my life," — is really common. So your brain, although it's the same brain, is not in the same state from one day to the next.

Carl Cincinnato (21:35): As patients, can our symptoms help diagnose the cause of our migraine disease?

Dr. Stark (21:40): So, the classic example of that would be motor weakness as an aura. So, that can quite clearly indicate hemiplegic migraine as a cause. And that's one of the ones that we do understand the best.



Carl Cincinnato (21:55): If I've got continued light sensitivity in between migraine attacks, after I've had one, would that be considered part of the migraine? Would that be considered a symptom of just migraine condition generally? Or is that something I need to see the clinician, the doctor, about?

Dr. Stark (22:11): So, sensory sensitivities are probably almost certainly related to migraine. So people will often report that they are really sensitive to light in between times, not just during a migraine event. It's usually heightened during an event. And there are some very interesting theories about that sensory sensitivity, in particular. People often wonder: Why have the genes for migraine been passed down when they're horrible? They cause a really nasty hit; they're incapacitating. And one thought is that this heightened sensory sensitivity actually used to convey an advantage to, not necessarily the individual, but to the tribe.

Carl Cincinnato (22:58): I mean, migraine is an awful, awful thing — I mean, I wouldn't wish it on my worst enemy — but in saying that, at the same time, it's made me a much healthier person. I'm much more grateful for my health since I've experienced losing it. And the quality of my diet, my sleep routine, the amount of exercise I do — I don't think would be anywhere near where it is at the moment if I didn't have migraine keeping me constantly in check.

Dr. Stark (23:31): There's a really interesting point. I would certainly say my migraine patients have some of the healthiest lifestyles of lots of my other patient groups because they're getting such immediate feedback on any transgressions they make from a lifestyle point of view.

Carl Cincinnato (23:48): Tell me about the timing of symptoms and the fact that it's so variable, not only between patients, but also within the same individual. How do you know when you should seek help? Because often we're told as patients that if things change, see the doctor. So where do you kind of draw the line between what's something significant that you should really go to the doctor, even ER — to the hospital, to the emergency department about — versus something that could be just part of the typical pathology of migraine or evolution of migraine as you get older?

Dr. Stark (24:20): So, the main triggers for seeking medical attention during a specific migraine event would be if you're not coping: So if your acute medication that you would typically use is not getting on top of your pain and you are struggling — and that is definitely a precipitant for going to see someone. If you are getting really dehydrated — so unable to keep down fluids — it's going to slow down getting out of that particular migraine event. Or if there's something really different about your migraine. So, just because you get a migraine, it doesn't mean that all headaches that you experience are going to be migraine. For example, I had a patient the other day with classic migraine, always the same — well, always roughly the same — and then she suddenly got a thunderclap headache where she went from zero to 10 out of 10 pain. And that had never happened before. She quite rightly presented to the emergency department and it was quite a different cause for headache that was unrelated to her migraine. So if things are really different, if you've got something that's brand new for you, or if you're not coping, then you should absolutely seek medical attention

Carl Cincinnato (25:38): Irritability, anxiety, depression, these are all things that you mentioned can often be common with migraine. Why is that?



Dr. Stark (25:47): So, there are a lot of interactions between mood and migraine. So, through the phases of a migraine attack, all phases can be associated with low mood or irritability. But in between migraine attacks as well, there's lots of ways that migraine can impact on your mood. Firstly, it can be a really rational response to having migraine messing with your life: You know, "Am I going to miss work again? Is my boss going to fire me? Am I going to have to miss yet another social occasion? People are going to stop asking me soon." All of these things are really anxiety-provoking thoughts. Likewise, a low mood can be induced by missing out on things that you used to find pleasurable: "I used to love going to the football [games] and loved going fishing, and I can't because it might trigger a migraine." So there's sort of a direct impact on your mood from the limitations that migraine can place on your life. But on top of that, there is an association between depression and anxiety and migraine, as we talked about earlier with the comorbidities. So they tend to go together. Perhaps they're inherited together, perhaps there's a root cause — early childhood trauma or something — that's contributed to both phenomena. And lastly, it's important to think about tablets. So the migraine medications, both preventives and acute treatments, can impact your mood, and vice versa. Some antidepressants and anti-anxiety agents can impact migraine, as well. So there are lots of ways that the two can interact.

Carl Cincinnato (27:24): Yawning is something that a lot of people seem to experience in the prodrome phase. Is it true that yawning can help relax the brain and that it occurs due to a lack of oxygen?

Dr. Stark (27:35): So, researchers used to think that oxygen was the real driver behind yawning, but we don't think that so much now. I think it's our response to reduced mental alertness. And we know that a yawn will transiently increase arousal or alertness, so it's possible that this is what's happening. We know that you're less alert during the prodrome phase of a migraine and that yawn can stimulate hormonal changes by stimulating the carotid body up in the neck, and the physical changes of sucking cool air into the lungs, and cool blood going up to the brain in higher volumes may be contributing to that increased alertness as well.

Carl Cincinnato (28:22): You've published a study about sleep and migraine. Can you tell us what you discovered?

Dr. Stark (28:25): Yeah. Sleep is important in migraine for a lot of different reasons. So as you mentioned, changes in sleep habits are a really potent trigger for migraine — so either oversleeping or undersleeping. And the oversleeping can be a surprise to people — it's your classic Saturday morning migraine when people sleep in and get a migraine that day. And shift workers, as well, are really susceptible to having migraines triggered. During a migraine attack, fatigue and insomnia are both really common features. So your sleep can be impacted by this migraine attack today. But on top of that, sleep disorders are often comorbid with migraine. So insomnia is probably the most common sleep disorder that will go along with migraine. Sleep-disordered breathing, such as obstructive sleep apnea and snoring, are really strongly associated with headache, but it's more frequently a morning headache rather than migraine, per se, that people wake up with in the morning. Not necessarily associated with oxygen levels, interestingly enough — so it was postulated that low oxygen overnight may be a trigger, but that doesn't seem to correlate with risk of headache the next day. If you treat that sleep-disordered breathing, say sleep apnea or snoring, it probably does help with morning headache, but impact on associated migraine is less clear cut.



Dr. Stark (30:07): Are there any final thoughts that you'd like to leave [with] the audience regarding the causes, triggers, and symptoms of migraine?

Dr. Stark (30:14): So, your migraine causes are fascinating, but there's not a lot that you can do about them. However, there's a lot that you can do in terms of managing triggers. So I'd really encourage your listeners to try and take ownership of their migraine, and do everything they can from a lifestyle point of view to try and reduce their chance of triggering a migraine event, given that it's something that they can control.

Carl Cincinnato (30:43): Dr. Stark, thank you very much for joining us on the Migraine World Summit.

Dr. Stark (30:46): It's my pleasure.