



MIGRAINE WORLD SUMMIT

INTERVIEWS WITH WORLD-LEADING EXPERTS

TRANSCRIPT



BEYOND THE PAIN: OTHER MIGRAINE SYMPTOMS

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Introduction (00:05): It may seem obvious, but migraine is a brain disorder and a neurological condition. And I think because it's always thought of as a head pain condition, you can quite easily forget that it's just so much more than headache. And the brain is obviously the controller of our whole body. And ourselves and other teams have demonstrated this very widespread brain dysfunction during those symptoms before headache has even started.

Lisa Horwitz (00:36): We all know that migraine attacks can cause debilitating pain, but many people experience additional symptoms that are equally disabling. Nausea, light sensitivity, vertigo, mood swings, and allodynia are just a few symptoms that can accompany a migraine attack. What causes these additional migraine symptoms? Should we be treating each of these conditions separately? Dr. Nazia Karsan is a postdoctoral clinical fellow whose research examines the pain-free symptoms of migraine and their impacts on patients. Dr. Karsan, welcome to the Migraine World Summit.

Dr. Karsan (01:12): Thank you. Thank you for having me.

Lisa Horwitz (01:14): Yeah, I'm really excited. So, I know your research is dealing with all of the other parts of migraine that aren't just head pain. What are the most common migraine symptoms that people experience?

Dr. Karsan (01:30): So, there've been several studies for over several decades looking at this, and it's well recognized that many patients will report symptoms that start what we call in the premonitory or prodromal phase of migraine — so up to 48 hours prior to headache onset — that can warn of impending headache and can be quite reliable at predicting that headache is coming. If you look across the studies, the most common symptoms that come up consistently are tiredness, and that's a sort of overwhelming fatigue and being quite somnolent; mood change, so that can vary from irritability to very depressed to actually elated and quite hyperactive; and then yawning, neck stiffness come up a lot. And then the final one that seems to consistently come up is this cognitive change: so, this real inability to focus, to concentrate; some patients report difficulties reading and writing, difficulty speaking and formulating words, but not in a speech disorder kind of way, but in a cognitive way.

Dr. Karsan (02:37): And then less commonly, we do see patients who report cravings — and that could be cravings for savory or cravings for sweet — and a kind of general sense of altered eating habits. So be that anorexia or hyperphagia — so, eating too much or eating too little — feeling very, very thirsty and consuming more. And then other things like sensory sensitivities that are more generally identified with the headache phase of the migraine attack but can actually start quite early. So, things like light and sound sensitivity, smell sensitivity, movement sensitivity, touch sensitivity of the head and other areas. So a really broad range of symptoms, but there are definitely a few that kind of come up very consistently in both adult and children studies that do seem to really dominate the phenotype of that phase.

Lisa Horwitz (03:30): I'm so glad you went through this extensive list, because I think a lot of people don't realize that these symptoms are tied to their migraine attacks. Especially things like aphasia — being unable to find the words that you want to say — I never would've thought that was part of this entire process of a migraine. You say that these usually start during the prodrome phase?

Dr. Karsan (03:57): Yes, that's right. In the lead-up to headache before headache starts, the brain is already abnormal.



Lisa Horwitz (04:04): Why do you think migraine affects so many different parts of the body? So many different systems, from pain to words to mood changes?

Dr. Karsan (04:14): It may seem obvious, but migraine is a brain disorder and a neurological condition. And I think because it's always thought of as a head pain condition, you can quite easily forget that it's just so much more than headache. And the brain is obviously the controller of our whole body. And ourselves and other teams have demonstrated this very widespread brain dysfunction during those symptoms before headache has even started. And that can affect areas like the hypothalamus, which is our body's internal clock and regulates things like sleep-wake cycle: when we eat, when we feel hungry, when we feel thirsty, how we regulate our body water content, how we regulate our arousal, and when we're awake and when we're asleep. And regulates yawning and things like that, as well as other brain areas that control mood, that control concentration.

Dr. Karsan (05:12): And so, you can imagine that if all of those brain networks are abnormal before headache, then why would you not get all these symptoms that seem to almost be coming from the gut sometimes? Or be completely unrelated to headache things like yawning? But actually, they all are from the brain and there's a neural substrate for all of those symptoms.

Dr. Karsan (05:33): And it's so interesting that you can speak to somebody and then map those symptoms really onto this, these changes in functional brain imaging that we see during that phase.

Lisa Horwitz (05:45): It's so, so extremely complex and I'm so glad that people like you are out there researching this, because for so long, so many of us just felt alone experiencing all of these different parts of migraine. Some of the things you described like appetite changes, cravings — a lot of people think of these as triggers, like, "I'm craving chocolate — I ate the chocolate, I got a headache." Are some of these still considered triggers or is the thinking now that really this is just the start of the attack?

Dr. Karsan (06:19): If you look at what patients report as triggers and what the premonitory symptoms are, you can see an association. For example, patients often report that light — bright light — is a trigger or sunlight is a trigger for their migraines. And then you can look, as I said in the first question, that light sensitivity can be a feature in the premonitory phase. So you think, oh, OK, so they think light triggers them but they're sensitive to light. And you can kind of make those same associations with things like, as you said, chocolate cravings or other foods, cheese, for example, and things that patients have historically reported as being migraine triggers. And if you look at the experimental evidence, it's actually very disappointing from a patient perspective when you look at triggers. So, teams that have tried to systematically study this by exposing people who say that a consistent trigger triggers their migraine attacks, and exposing them to that in an experimental fashion, haven't really been able to trigger attacks very successfully.

Dr. Karsan (07:23): And with that, I mean things like light, exertion, chocolate, which has been looked at in a randomized study. So, the evidence for that is disappointing. And so that led us to look at these associations, and other teams have done that, too. And I mean, I don't think it would be right for me to say that no triggers exist, but certainly, for some of them we did identify significant associations with the corresponding premonitory symptom that patients were reporting. So, things like light and hunger and cravings triggering headache — or certain foods rather — but actually it was those patients that had premonitory cravings. And it was



those patients that had premonitory light sensitivity that reported light. So, you can start seeing how actually maybe some of these triggers — that when patients avoid them, it doesn't actually help their headache too much or help the onset of their headache — are actually early brain changes and premonitory manifestations that are being misinterpreted.

Lisa Horwitz (08:30): In general, would you say that these start a few days before the pain? What is the window of time people might start to experience these?

Dr. Karsan (08:38): There does seem to be a range of times, you know, between a few hours before the headache all the way back to a couple of days before. And that fits with neurophysiological studies and our imaging work that's shown that the brain, you know, can be abnormal before the headache. And the neurophysiological studies suggest that that can be, you know, 24-48 hours before. And some of the imaging work that other teams have done in spontaneous attacks suggests that that sort of 48-hour window is when things are kicking off in the brain before headache starts.

Lisa Horwitz (09:10): How long after the headache is resolved can some of these symptoms last?

Dr. Karsan (09:17): Yeah, so that resolution phase after headache has improved is called the postdrome. And that is really made up of very, very similar symptoms to the premonitory phase. But perhaps more than the yawning, the neck stiffness, it's much more dominant in phenotype with this fatigue and real inability to concentrate — this sort of hangover feeling, like you've consumed a lot of alcohol and you just need to sleep and then wake up and things will be better — that sort of malaise rather than this sort of hypersomnolence.

Dr. Karsan (09:52): And you know, studies have shown that that can also last variable periods of time. Recently I saw a study that suggested for some patients a couple of hours before they're back to normal, for some patients up to 24 hours. You know, if you speak to patients in clinic, some of them say a couple of days. Again, quite a variable window before people feel like they can return to normal function.

Lisa Horwitz (10:18): So one person experiencing an attack can really feel not like themselves for two to five days if you take in account the prodrome, the pain phase, and the postdrome.

Dr. Karsan (10:33): Absolutely. And I think it's why it's so important to understand these symptoms because they contribute so much to the morbidity of an attack. You know, so much of the disability of the attack can be outside of the headache phase.

Lisa Horwitz (10:49): Oh yeah. I often find that the accompanying symptoms are far more disabling than any pain, because you can get used to the pain, but it's hard when you're cognitively not at your best and you still have to work or parent or drive a car. In terms of treatments, we know there are acute meds that target the pain, the head pain of a migraine. Are there specific treatments that you recommend for these additional symptoms?

Dr. Karsan (11:16): No. So, unfortunately, that's a real area that needs development and is so relatively unexplored in migraine. And we're in such an exciting era of novel treatments, but actually, we have this very unexplored niche in that, of: Is it possible to treat these symptoms? And perhaps even more interestingly: Is it possible to actually stop pain coming on at all by treating during those symptoms and just preventing headache at all? Which, obviously would be a very exciting option.



Dr. Karsan (11:49): Some interesting work has come out of the CGRP work, where clinical trials have started looking at the effects of these drugs on additional disabling symptomatology, outside of what we call the canonical migraine symptoms of ... that being light and sound and nausea, etc., and have looked at things like cognitive function and return to functional ability after a migraine attack, and have shown promising results. So, I think incorporating those bothersome symptoms outside of headache, and perhaps outside of what we recognize as canonical migraine symptoms, will really take us forward in understanding how these drugs may work in that process. And give us ideas about how we can perhaps use that knowledge to think about drugs that work before the process really escalates into pain.

Lisa Horwitz (12:45): Yeah, a way to calm our brains down would be an amazing development for the future. I want to take a moment to ask you specifically about your research with King's College. You're focusing on imaging the brain during attacks, is that correct?

Dr. Karsan (13:01): Yes.

Lisa Horwitz (13:02): And what are you looking for when you are viewing these images?

Dr. Karsan (13:06): We take a substance that's known to consistently trigger migraine symptoms in a proportion of people with migraine and watch the attack. And what happens is that you compress the timeline. So how a normal attack, a spontaneous attack, in someone with migraine may be 12 hours of premonitory symptoms, seven hours of headache, and then a two-day postdrome — you just squash that into one day. And it gives us — not for patients, but from an experimental perspective — gives us a really unique opportunity to actually view these attacks in front of us, to bring them on, and then at the appropriate time, to image and capture different phases.

Dr. Karsan (13:51): And in that way we get the imaging and we also get the correlation with the symptoms. And I think that's really important, because I think you can image anything. But you need to understand what's being experienced at the time that that imaging is taken, because then you can start thinking about if there's a correlator for these symptoms and if there's a substrate in the brain that's driving particular symptoms.

Dr. Karsan (14:11): And so that's what we've tried to do. And we've taken imaging during the premonitory phase, imaging during headache, and imaging after headache has gone, after treatment with a triptan or with aspirin. And then compared that to baseline imaging and done very statistical tests with the scans to look at differences over the different phases really, with a particular interest in these early symptoms. Thankfully, due to so many really lovely and altruistic migraine patients and volunteers, we've managed to do that with around 25 patients and show that there's different areas activated, or presumed to be activated, and involved in mediating these different phases. And that the imaging looks very different in the premonitory phase to the postdrome and to the headache phase.

Lisa Horwitz (15:10): You're getting brave migraine patients to come in and volunteer to put themselves in pain and in an MRI machine to study this. So, you're finding that different parts of the brain are lighting up in the prodrome as opposed to during the attack or pain phase?

Dr. Karsan (15:26): So, some of the areas are quite common in both. So, things like the cingulate cortex, which is involved in mood and cognition — it's quite a vital part of sensory processing — that seems to be active in both. And there are other areas that are active in both, which is



unsurprising, because those symptoms don't just stop and headache starts. You know, they often continue but they presumably become less noticeable in the presence of headache. But if you look at phenotypic studies, things like cognitive dysfunction and neck pain peak during headache rather than in the premonitory phase. They just start earlier. So, it's not surprising that the same area is active. But then you start seeing lower-down brain stem regions in the pons and in the medulla, which obviously must drive the pain aspect of migraine and have been shown in other studies to be active during the pain part. And it's this sort of evolution of imaging findings I think is really interesting, because it just, I think, helps show that it's so much more than pain.

Lisa Horwitz (16:35): Exactly. It is so much more than pain. And what patient doesn't want to have their experience validated by a scan? I think so many of us want to know exactly what's going on in our brain and why is it doing this to me? So having someone be able to see it and tell them about it is so huge. After you have seen so many of these scans, and seen from the whole phase of the attack, has that changed the way that you prescribe treatments to your patients?

Dr. Karsan (17:07): So, I don't think it's changed my prescribing. I think it's definitely changed my understanding of the impact of even episodic migraine on people with migraine. Because I think it's so common, and it's almost more common to have it than not to have it. But it's only when you speak to people that have it and understand what they have that you realize the impact that it can have. And I think watching prospective attacks in the research and just, the more and more patients you talk to, you just understand more and more that the experience is so different for everyone. And it's not the kind of condition that you can just generalize and say: migraine. It's such an umbrella term for such a complex, complex condition. And like I said, seeing the most naive of it in children is just fascinating because they obviously display things so differently.

Lisa Horwitz (18:14): There's no filter; they don't have that filter that adults have. You say that your research focuses on observing the brain during an attack, is that correct?

Dr. Karsan (18:25): Yes.

Lisa Horwitz (18:26): What is the most surprising thing that you have learned in these observations?

Dr. Karsan (18:34): I think now having seen so many patients have an attack in front of me — which sounds almost silly to say as a doctor — but obviously, usually, when you see a patient they're not in the midst of an attack, and they're reporting to you what's happened to them retrospectively. And I think there's a lot to learn from actually watching prospectively what patients go through. And I think it really gives you a different understanding of how bad things can be for some patients.

Dr. Karsan (19:04): And having done that with experimental provocation, I've been really shocked at how somebody who will come in and be very friendly and calm and perhaps, you know, even a colleague or a researcher who will volunteer. And you provoke this migraine and their entire personality changes into very irritable, very angry, very moody, and just almost a completely different person to the person that you consented at the beginning of the study. And also, I think, for me, the thing that really stands out is this cognitive dysfunction. You know, these people that are highly intelligent and driven, and really this process really plays with their thinking and they just become very different.



Lisa Horwitz (19:53): I'm so glad you're researching that because I am definitely one of those people who — my cognitive abilities greatly diminish during an attack. For patients like me who may not realize they're in an attack because their brain is already processing information differently, do you have any tips for them to recognize their attack so they can begin a treatment?

Dr. Karsan (20:16): So, that's another really difficult one, because we don't really have, at least modern-day treatment studies of the effects of treating early before pain. We don't really have up-to-date data in randomized control trials to look at that. So, if you recognize your premonitory phase or your prodrome, does treating at that time prevent headache onset or at least improve the symptoms that come thereafter? We don't really have that data. But I think from just an understanding perspective and a patient insight perspective, I always encourage patients to diary consistently what they're experiencing and when, because it's only really when you see a pattern that you then recognize that these are consistently things that are happening before every attack.

Dr. Karsan (21:11): And studies have shown that, you know, the main symptoms are fairly consistent across different attacks and then become quite reliable predictors. And then if we were to hopefully one day be in a position that we could offer treatment, then you know when to treat because you've identified where you are at in that cycle, and it's consistent for you.

Lisa Horwitz (21:33): Are there any symptoms that someone might experience during an attack that may not actually be related to the migraine and indicate that they should get immediate medical attention?

Dr. Karsan (21:47): So, the way I think about it is if patients — I think the onset is very important. So, if it's like a very sudden one minute I'm fine, the next minute I have a symptom, that's always of concern. I think the evolution of those symptoms is really important. So, do they just come and then stay fixed, or do they sort of move around and spread? Aura is much more likely to have this sort of spreading phenomenon where, for example, tingling can start in one area and then spread up the arm and down the leg, for example, over some minutes. That's less likely to happen with a stroke than it is with aura. But I would say generally my rule is if you have something that's new and focal that you've not had before, you should seek attention. And if you have something that you think is aura but you've never had aura before and you are over 50, that's something that should seek attention.

Dr. Karsan (22:40): So, it's been published by, actually, Dr. Dodick's group, this SNOOP four criteria, which are the sort of red flags of headache and when you should be concerned. So, any sort of sudden thunderclap-onset headache, any new focal neurological deficit, anybody that develops a new headache or new symptoms over the age of 50, just things that are more likely to be something serious rather than just attributable to migraine.

Dr. Karsan (23:07): And I think it can be really difficult, because a lot of what patients may experience may not be recognized as being part of migraine. It's really only when you understand the condition that you understand that so much other stuff can come with it. But you do also have to err on the side of caution because you don't want to attribute everything to the attack. And that's why I think [keeping a diary] is so useful, because if patients can understand exactly what happens to them with each attack, I think patterns make life a lot easier than sudden new things happening.



Lisa Horwitz (23:40): Yes, patterns help. And I find that sharing my information with the people I live with so that they are aware — like, "Hey, when I get a migraine I'm going to be confused, I'm going to struggle to find my words, I'm going to make mistakes" — it just helps them knowing that I'm safe or not safe, too. And then maybe the people you're with can see when you've crossed a line and need additional medical attention before you do.

Dr. Karsan (24:05): I think from a — the biggest concern always being stroke or something of that kind — if you look at a hyperacute stroke unit, the commonest, what they call "stroke mimics," are migraine and epilepsy. So, you know, the things that can look very similar to stroke. So, a post-seizure weakness, or a partial seizure causing speech trouble or something like that, or one-limb weakness or something like that. And migraine, obviously, because patients can just get such a range of symptoms. And I would really urge anybody that gets a new symptom that they've not had before, that they get checked. Because you just don't know. And I think it's easy to assume, but then hindsight is a great thing, isn't it? And it's always better to be safe and have the imaging to know that there's nothing else going on, particularly, as you say, if people are having quite a lot of speech disturbance and weakness and things like that which can look very much like a stroke.

Lisa Horwitz (25:08): From your research and your work as a physician, what in your opinion is the most misunderstood symptom of migraine?

Dr. Karsan (25:19): Yeah, so for me it would be the cognitive aspect. So, I think this more global cognitive dysfunction, which we know can start before, can occur during headache, and then can persist afterward, is just so poorly understood. And it's so disabling, and it's just something that's so difficult to convey to employers, to schools, you know, for the children. And I think that's really something that we need to understand better and need to understand the effects on treatment better. Because often, to relay to somebody else, they don't understand why you can't just be normal again if your headache's gone.

Dr. Karsan (26:00): And I'm sure you've experienced that. And I think that's like the really hard thing. And I think it's hard as well because, from a time-off-work and sick-note perspective, if the first-line primary care practitioners don't understand that, then you end up in a sort of cycle where actually some of these patients are much more disabled by non-headache symptomatology, but they don't have the resources or the means to really be able to treat that or explain that to anybody. And I think that is really one area in particular that I think is massively under-recognized and people almost think of as almost being a kind of nonorganic or functional symptom. You know, like it's, "Oh, they're just saying they can't think," or not attributing it to actual brain dysfunction and actually being quite a prominent part of the attack.

Lisa Horwitz (26:55): And it's even hard for patients to fully describe how disabling it is. I'm glad that you are promoting that this is a real thing — that it is disabling — and are working to hopefully give us more information about it for the future. I have one last question for you before I let you go. Do you experience migraine? And if you do, what are some of your favorite tools in your migraine kit?

Dr. Karsan (27:24): So yes, I do experience migraine, thankfully not too frequently, but when I do, I know about it. I would say — and I say this to my patients, too — that I think it's always good to have options. So, I have three options in my little migraine kit. So, I'll try and start low with paracetamol or acetaminophen, and if that doesn't work, then I move on to naproxen or another nonsteroidal anti-inflammatory.



Dr. Karsan (27:57): And then I have a triptan in there. And I personally try to avoid the triptan, because I get a lot of this somnolence and fatigue afterward, which just exacerbates the postdrome. But at least then I've got three options. And then if I think it's gonna be a bad one, I can take the triptan and the nonsteroidal together, which can often prolong the effect of the two. I guess the best thing is having, you know, some flexibility in your lifestyle that allows you to stop and do what you need to during that time. It would be that from an employer perspective or childcare perspective, which I think is often a challenge.

Dr. Karsan (28:36): But I do a children's clinic, as well, once a week, and it's interesting because it's almost the most pure phenotype of an attack when you talk to a child. And just that ability to remove them from school and go to a sick room and be picked up and taken home is often enough to get them back into school the next day, whereas obviously as adults we often don't have that luxury.

Lisa Horwitz (29:04): No, we really don't. It's hard to rest as much as your body wants to during an attack. Where can we learn more about what you're doing or follow your work?

Dr. Karsan (29:16): So, there's a lot of resources that are available to sufferers of migraine and headache in the U.K. and internationally. The Migraine Trust is a big patient charity and advocate for patients with migraine, and so they often have a lot of work that comes through our teams and other teams published on their website and e-bulletins to keep patients up to date with really what's going on from a research perspective. Then from a King's College perspective, we have our work on our headache group webpage and with what we're sort of doing as a team and individually. So lots to learn and lots of resources available for patients, and hopefully, further understanding of their condition and treatments going forward.

Lisa Horwitz (30:07): Thank you, Dr. Karsan, for all of that useful information on the pain-free symptoms of migraine and how debilitating they can be for people suffering an attack.

Dr. Karsan (30:17): Thank you for having me.