MIGRAINE WORLD SUMMIT

INTERVIEWS WITH WORLD-LEADING EXPERTS

TRANSCRIPT

INFLAMMATION CONTROL AS MIGRAINE CONTROL

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Introduction (00:05): They're finally getting down to understanding and having ways to look at inflammation within the body better, depending on the disease. So, I think it's something that we've suspected in many conditions — like migraine, for instance — for a long time. I've seen elevated markers in the blood — of inflammation — but not really being able to visualize it, per se.

Carl Cincinnato (00:32): According to the prestigious medical journal *Nature*, systemic and chronic inflammation has been recognized as the most significant cause of disease today. It plays a role in cardiovascular disease, cancer, diabetes, kidney disease, liver disease, and autoimmune and neurodegenerative disorders. Migraine is no exception. And most of us with chronic migraine also have one or more other chronic health conditions. Is inflammation the missing link? To help us understand inflammation's role in migraine — and most importantly, how we can manage it — is Dr. Gretchen Tietjen. Dr. Tietjen, welcome back to the Migraine World Summit.

Dr. Tietjen (01:10): Well, thank you very much for having me.

Carl Cincinnato (01:12): Is there such a thing as good inflammation? Like, does it serve a purpose?

Dr. Tietjen (01:16): Yeah, I would say ... I would equate good inflammation with acute inflammation. If you have something ... And typically, the things that we'd be talking about that we'd notice as inflammation would be things we could see. So, let's say it was something on the body — in a joint or on the skin — and you see redness, and you have pain, and you have some swelling, and it's warm or it hurts to use a joint, you know — that might be what happens in acute inflammation. But if in a few days it goes away and gets better, then we would consider that good inflammation — the body did what it was supposed to, through the inflammatory response and all that goes with that, to heal itself. But inside the body, when we're talking about chronic inflammation, a lot of times it's things you can't just look at, see, and monitor visually. It's more like some of the sick behaviors. And that would be if you just felt fatigued or maybe sort of depressed, or you didn't want to eat, or you just weren't feeling ... feeling out of sorts, feeling a little depressed, feeling like nothing sort of was right, couldn't sleep well. Those all might be signs, potentially, of chronic inflammation.

Carl Cincinnato (02:40): So, it seems like inflammation has gotten a lot of attention lately. Is this focus on inflammation justified? Is there ... is it all just a bit of hype? Or is this genuinely something we should be aware of and conscious of?

Dr. Tietjen (02:56): No, I think that they're finally getting down to understanding and having ways to look at inflammation within the body better, depending on the disease. So, I think it's something that we've suspected in many conditions — like migraine, for instance — for a long time. I've seen elevated markers in the blood — of inflammation — but not really being able to visualize it, per se. So, I think that there's probably ... And you know, some inflammation is really severe. But other inflammation is just very insidious — low-grade — but still important. I've done some work in the biomarkers of inflammation and hypercoagulation and things that we see with endothelial dysfunction. But even though we see ... If you compare the migraine group to the nonmigraine group, you see elevations in migraine in something like c-reactive protein, which is one of the most common markers of inflammation. But yet, it may not be that elevated, you know. So, it's one of those things where if you're comparing them and statistically, you're seeing a difference, you're probably onto something. But on the other hand, it's not something

where I could just draw a blood test. It's so nonspecific. It could be elevated, but it could be because [you're] getting a sinus infection. I mean, there are a lot of things that can acutely increase that.

Dr. Tietjen (04:29): And that's why having all these different studies that people have done, and if they tend to show the same things, it's very helpful — meaning there's something there. But it may not be an overwhelming reaction like you might see if the person had something like a vasculitis or cancer or ... Some kinds of diseases might really increase the inflammation to a point where you know it's abnormal just by looking at the blood tests. The other one just might be a little out of range, or maybe at the upper limits of range, but not really that abnormal. And so, they're helpful when you're trying to study it and study the mechanisms; they may not be that helpful on a day-to-day basis when you're treating a patient in some conditions, like irritable bowel [syndrome] and migraine. So, they're not things that are typically done outside of studies.

Carl Cincinnato (05:21): There's a lot in that response which I want to make sure I can break down. And so ...

Dr. Tietjen (05:25): OK.

Carl Cincinnato (05:26): One of the first things you mentioned was the inflammatory marker c-reactive protein, and that the level of c-reactive protein in someone who has chronic inflammation may only be subtly higher than in an otherwise healthy subject.

Dr. Tietjen (05:40): Yeah.

Carl Cincinnato (05:41): Are there other markers that you can use? Or do you do multiple tests for c-reactive protein? Because, I mean, we've heard about how inflammation connects to some of the most devastating diseases that affect the population.

Dr. Tietjen (05:53): There are other markers of inflammation. Like when I did some of my studies, we did inflammatory cytokines; those are interleukin beta, interleukin 6, I think interleukin 10. You know, there's a number of those ... There's transforming growth factor beta, there's TNF [tumor necrosis factor] alpha. You know, these are inflammatory cytokines that we've also looked at in disease or conditions like migraine, comparing them to healthy subjects without migraine, and see that they are elevated. We know, also, that some of those are — and those cytokines, in particular — are elevated during the attack. So, that's really good information to have.

Dr. Tietjen (06:41): And there were also some studies that were done that showed other inflammatory substances — most important of which was the calcitonin gene-related peptide or CGRP, which is now ... I mean, it's been known about for probably 20 years or so, but that knowledge hasn't just stood still. When people realized that, they started trying to develop drugs where they could use that information — block it — and then see if that actually helps the migraine; either prevent it or treat an acute attack. And what we know now, just in the last few years since these drugs have been on the market, and the clinical trials showed that they were effective ... That we have things like monoclonal antibodies — against calcitonin gene-related peptide or CGRP, which is an inflammatory neurotransmitter — that that helps prevent migraine. And people get monthly shots or every-three-month shots — and that can be very helpful. But then they just more recently came out with the gepants drugs, which are the small

molecule c-reactive — or excuse me, calcitonin gene-related peptide antagonists — in that if a person takes that acutely for an attack, it will help abate the attack very quickly. And they've just recently approved a couple of these drugs for daily use and prevention of migraines. So, the same drug might be used both acutely and for prevention. But that was from knowledge of these studies of looking at some of these factors of inflammation, that they got from these blood tests.

Carl Cincinnato (08:30): So, to recap some of what you just said: People with migraine seem to have higher levels of inflammation — both at baseline, when we don't have a current attack, and also at elevated levels during an actual attack. And that may be due to something like CGRP, the calcitonin gene-related peptide — which is released during a migraine attack — which is known to be an inflammatory neuropeptide.

Dr. Tietjen (08:56): Yes. It might be related to that or to the inflammatory cytokines that also play a role during an attack. There's another thing that happens with inflammation: When people have aura, which about 30% of people with migraine do, it's been shown in animal studies that the cortical spreading depression that occurs, which is part of the aura — it's sort of an electrical activity of, first, activation, followed by a sort of a period of rest electrically in the brain — that when that occurs, there's a release of inflammatory cytokines. And those can be found in the circulation at some points, but they can also ... these are happening in the brain parenchyma — this inflammation — but it can also potentially get into the meningeal circulation, as well and cause some problems there. So, there's a lot going on inflammation-wise. But it is thought by a lot of very prominent researchers in this area that when inflammation becomes chronic, that leads to chronic migraine. You know that the more migraine you have, the more likely you are to have elevation of inflammatory markers and actually more inflammation going on in the body. In people that have aura, they may actually even have ... We noticed in our study that it did seem that the inflammatory markers were higher in [migraine with] aura than they were in migraine without aura. But it occurred in both conditions.

Carl Cincinnato (10:50): And which comes first? Is it the inflammation that brings migraine? Or is it the migraine that brings the inflammation or causes the inflammation? Or do they feed off each other?

Dr. Tietjen (10:59): I think they feed off each other. One came first — obviously something had to start it. And we know that migraine is ... probably 50% of migraine is an inheritable condition: that people who have first-degree relatives, they're about twice as likely to have migraine without aura; and if the relative has migraine with aura, they're about four times as likely to have migraine with aura — that seems to have a little bit more heritability, although we haven't identified the genes as well in these big genome-wide association studies. So, part of it is you have a predisposition, or some people call it a liability — I read in one article "genetic liability" — but you have a predisposition to getting migraine if you've inherited it from a parent. But there are other things in the environment — and those can be things that can cause a lot of conditions and inflammation — but things like stress, things like lack of sleep, things like poor diet, things like having some kind of an infection or something. You know, it may make you more likely ...

Dr. Tietjen (12:12): Because you can think of migraine as … there's a threshold for it. We have a lot of bacteria and other microbiota — you know, microbes within our gut. And those are really thought to have, maybe, a very big role. And if the gut gets out of balance — the type of

bacteria in it aren't the most favorable ones — you can get a lot more inflammation, and that sends messages to the brain. And that might make somebody who's predisposed to migraine be more likely to get migraines; they're more likely to have chronic inflammation. And so, I think that's the thing ... There are ways to control that without taking anti-inflammatory drugs — that's probably not the thing that's going to help the microbiome. But it's like, having a better diet is probably the best thing you can do since the diet really changes the microbiome. But stress management can make a difference, as well. Getting a lot of sleep, those things. But we know that when the gut microbiome is out of balance, that people do have problems with sleep. Their stress may get worse, they may get more migraines; that kind of thing is thought to be likely what's happened.

Carl Cincinnato (13:29): I'd love to come back to the gut and the link with inflammation and implications for treatments. We have a few questions from our community that I'd love to share with you. So, the first is from Rae, who's a viewer from our community. And she said that managing internal inflammation seems to be the treatment now for virtually all health conditions, including autoimmune, migraine, cardiac. What is known about the cause of high levels of internal inflammation? And what specific techniques can be used to fight this type of inflammation?

Dr. Tietjen (13:59): Unless it's due to something like an infection, it's not the kind of thing that you'd normally treat with antibiotics. But there are a lot of things that can help, probably. And a lot of them are, you know, the type of things that I mentioned, where you're basically trying to create a more homeostatic environment. You know, you eat meals regularly; you eat good, healthy foods; you avoid foods that have inflammatory likelihood — and those would be things like processed foods, red meats, some of these things that are high in the omega-6's. So, that's one thing. But I think that you can't really underrate things like good sleep, having decreased emotional stress and physical stress. So, people that have taken up things, and do it effectively, like meditation or yoga or tai chi or all these things that are kind of moving meditations ... They've done studies on inflammatory markers in people that start doing these things, and it does lower them. So, we know that those things are good for you. So, that's hard to do, so it's not as easy as just taking something. But I think diet is something that is definitely, really, something that we can all participate in and make a difference in our health.

Carl Cincinnato (15:36): OK. So, we've got a couple more questions. We might go through these a little quicker ...

Dr. Tietjen (15:40): OK.

Carl Cincinnato (15:40): Joan has chronic migraine, which has progressed to the point where she's been told by a rheumatologist that her blood work indicated she has high levels of inflammation circulating in her body, and neuropathic pain. Can uncontrolled migraine lead to this situation?

Dr. Tietjen (15:56): No, I don't think so. It's a little bit different than, sort of, the osteoarthritis that most of us end up with, where there's aches and pains in the joints. And, you know, sometimes that can be due to too much wear and tear on the joints that come with age, but also that come with age and being overweight.

Carl Cincinnato (16:15): So, let's get into some of the treatments that you mentioned. And one of the things that came up was diet. Is there any science to support a specific anti-inflammatory diet to reduce inflammation?

Dr. Tietjen (16:27): Yes. And I think the study came out probably just earlier this year or last year. It was in the *British Medical Journal*, where they took, I believe it was, about less than 200, but maybe 188 or something, people with migraine. And they had three arms to the study where one group, they didn't change the diet particularly — they had the same level of omega-3 and omega-6 that they had before they started. And they were recording daily headache diaries. And they were also doing some blood tests to look for markers — they weren't of inflammation so much; they called them, like, antinociceptive markers — but some kind of a blood marker. And they also did a thing for, sort of, "How disabled were you by your migraines?" We call it the Headache Impact Test; they use a score on that. But anyway, they had a ... That was sort of the control group that didn't really alter their diet much. And then they had one group where they just told them to start eating more of those omega-3's, the anti-inflammatory foods — those were the ones that I had mentioned, like fruits, nuts, olive oil, leafy vegetables, onions, garlic, that kind of thing — but not to change their omega-6 diet. Then they had the third group where they told them to increase the omega-3's and decrease the omega-6's. And that's where we saw in those ... that's where we saw the most improvement in the headache frequency.

Carl Cincinnato (18:01): This is a pretty groundbreaking study ...

Dr. Tietjen (18:02): I think so.

Carl Cincinnato (18:04): ... that shows, like finally, out of a lot of studies that have been conducted — in a randomized controlled trial; so, a credible research study ...

Dr. Tietjen (18:12): Yes.

Carl Cincinnato (18:13): ... that there actually is a diet where you increase your omega-3's and you lower your omega-6's and you can improve your migraine condition.

Dr. Tietjen (18:19): Right. And even just increasing your omega-3's still helps some. So, anything you can do to your diet like that seems to definitely make a difference.

Carl Cincinnato (18:31): So, omega-3's — are these things like deep, cold-water, fatty fishes, like salmon and sardines and krill and mackerel, etc.?

Dr. Tietjen (18:40): Yes. Those are what [have] the omega-3's. And so that, I think, is ... And, you see omega-3 in some of these other things — so nuts, and you know, some of that type of thing.

Carl Cincinnato (18:53): Do you think that diet's the best way to treat inflammation in the body?

Dr. Tietjen (18:57): Well, I think it goes back to the whole heart of the matter. I think you can improve your gut health — that, I think, in turn, can help you improve your brain health. And I think that taking things like supplements can be very helpful. We don't have ... Some supplements have quite a bit of data; on other ones, not so much. But a lot of times people can get what they need in a more healthful diet and without actually going to supplements. But I think getting a lot of ... I don't think you can underestimate how important it is to get enough sleep and get the right kind of sleep. But they all kind of tie into each other. Because if you're

not healthy, you just may find getting to sleep more difficult or getting restful sleep. And I think it becomes a vicious cycle sometimes.

Dr. Tietjen (19:53): And so, I think stress management is a huge thing. You know, I had done some of my work in early-life stress, which can sort of set up the body for having increased responses or abnormal responses to stress as adults — even if they've psychologically processed what happened to them when they were younger and all the adversity they had. It's sort of like it changes how you process things for the rest of your life, somewhat, physiologically. And being able to really take control and learn stress management techniques so that stresses of everyday life don't cause a lot of imbalance in your system — which might lead to more inflammation — I think is important, as well. So, that's sometimes things that people ignore. But that's where I think meditation has become so ... yoga, you know, those things have really become popular on their own — not with necessarily doctors telling people to do them — because, I think, people realize they feel better and that may be part of why.

Carl Cincinnato (21:00): I think inflammation provides a couple of clues as to why migraine can be so complicated and so difficult —particularly chronic migraine — to break. Because migraine itself can cause inflammation; migraine is known to be comorbid with other sleep disorders and mood disorders; and there's medications for migraine that cause you to gain weight. All of these things just fuel off each other to cause more and more inflammation, and so it can build up to create like this rolling snowball that can be incredibly hard to stop.

Dr. Tietjen (21:34): Yes, and I think particularly when you have depression and anxiety thrown into that, which I think are certainly comorbid with migraine, but ... they've been tied to a lot of the things that have been tied to migraine. You know, there are reactions to stress both in youth and adulthood that interfere with sleep. And we know there's a lot of inflammation in depression. And it's thought that, actually, inflammation might cause depression, as well as depression causing more inflammation.

Carl Cincinnato (22:10): Exercise, we know, is great for migraine, if you're able to do it — and particularly aerobic exercise that's low-impact. But exercise, I thought, was also inflammatory in some respects. Can you talk about that?

Dr. Tietjen (22:22): Well, I think it can be inflammatory if you do exercise that can — and I'm certainly not an exercise expert – but I mean, if you do things that could hurt your joints or that type of thing, you might have inflammation of that afterwards. We know from doing certain exercises ... If you had a job on the house and you had to do a lot of hammering and sawing or something where you're lifting up and then you get a sore back — that kind of thing. So, definitely you can get inflammation from, sort of, wear and tear. But if a person is conditioned or slowly conditions themselves so that they're not actually causing injury to their body ... But doing things like aerobic — I personally find, being somebody with arthritis, that bike riding is great exercise if you do it and you do it as best you can, go as far as you can, as fast as you can, with as much resistance as you can take. And I think it's very good exercise. Or people that use stationary bikes and do high-intensity training and that kind of thing, where you exercise real fast for a minute or two and then rest for a minute and then do it again and again.

Carl Cincinnato (23:39): So, anti-inflammatory treatments are really commonly used — NSAIDs, nonsteroidal anti-inflammatories — are one example, such as ibuprofen, and there's many others. Do these work to address inflammation in the body? And would daily use of these be recommended?

Dr. Tietjen (23:56): Thirty years ago ... When I started practicing 35 years ago, we were using things like naproxen sodium. And we'd tell people: "Take this twice a day for about a week around your menstrual period and see if it helps." And it would help. I think the problem with doing that long term, if you don't need to, is that there's a risk. There's a certain percentage of the population — it's not a real small percentage — that is going to get some reaction from their kidneys, and I think that that makes it where if we can find safer drugs than that, that's probably better. So, I don't really know that it would help someone that much with migraine to totally keep it away. We don't normally recommend it.

Carl Cincinnato (24:45): And I guess there's a risk ...

Dr. Tietjen (24:47): Yeah.

Carl Cincinnato (24:47): ... as well, of medication overuse over time in some people.

Dr. Tietjen (24:50): Yeah. And how much some of those would cause, it is hard. But there have been things that have shown that even nonsteroidals, even acetaminophen, in some people cause medication overuse headaches, so that the headache just sort of keeps coming back. We know caffeine can do that. So, I think that, you know, try to use things that are a little safer, that aren't going to be predisposed to the medication overuse. When there's anything that you usually think of as an acute drug ... We know that corticosteroids can help, sort of, get rid of a bad bout of migraine attacks, but you don't want to do that regularly because those have a whole host of side effects.

Carl Cincinnato (25:32): So, speaking of steroids, Hilary asked that — she gets a short course of prednisone ...

Dr. Tietjen (25:39): Prednisone.

Carl Cincinnato (25:41): Yeah. And it's the only thing that completely takes away her migraine. And so, it seems to her that there must be an inflammatory aspect to migraine. Can you explain if there's any other way that she can treat migraine besides taking this treatment? Because ...

Dr. Tietjen (26:00): So, it sounds like she's taking it acutely when she gets her headaches. So, one thing I'd say ... one thing, a couple things that I can think of. One is — and I'm not talking about her specifically; I'm going to say for anyone that finds that it really works — I think there are a lot of people that steroids, like prednisone, don't really help them that much, unfortunately. There are some people that it does. And a lot of times if they're having a really bad headache that they can't break, they try it. But I have known that there are a number of people where they work really well when, you know, we take the history better or the headaches morph a little bit. But they really are experiencing maybe more of a cluster-type headache or a paroxysmal hemicrania or another headache type that really could be treated with another medication that might be safer, and that would cut down on the need for taking the corticosteroids.

Dr. Tietjen (26:59): When I had patients that needed those occasionally, I'd be very careful. I'd keep track in their chart, and I didn't like to use them more than every few months, just because of the fact that they can have bad side effects. But you don't want them to interfere with the adrenal function because that would be really very serious. So, I would say to someone like that: "Have they really tried everything?" If they had tried everything that was available a few years

ago, have they tried some of the things that are available now? Because with ditans and the gepants, you know, new drugs out there ... even an old drug like DHE is now FDA-approved for inhalation or nasal spray therapy or whatever — that's supposed to be very effective and not have the side effects it had before — that to try some of those things for the acute attack. Or some of the neuromodulatory devices out there now. So, I think that there's a lot of things, that if a person hadn't tried, that they might find that there are some things that work very well for them. If they just had tried the triptans and had tried all of them and said, "Well, they just didn't work for me," maybe those aren't going to work for her. But something else that has a different mechanism may be very effective. So ...

Carl Cincinnato (28:19): Excellent. So, it sounds like low-grade inflammation is actually behind a lot of modern-day diseases that we see. And the signs of this inflammation — chronic low-grade inflammation — can be subtle. And sometimes they're expressed in conditions that we might be facing, or other times we just might be, sort of, a little bit sluggish, be a little bit fatigued, which a lot of those things — those signs and symptoms — are part of migraine itself. So, addressing this through dietary factors, lifestyle, stress management, and working with your clinician for treatment sounds like the solution that hopefully will come to a sustainable improvement.

Dr. Tietjen (29:05): Yeah. I think it really needs to be an integrated approach. I think you can't just, sort of, do one thing. I mean, if you can, that's great. It's hard to argue against all the, sort of, lifestyle changes that just [are] what we really should recommend to every single person at length, every visit, because those are the things that ... You know, they go to their primary care doctor to be aware of those things, and they're a little bit harder and you have to, sort of, keep at them. But medications have a role — sometimes a very important one. But if you [do] not need the medications to start with ... because every medication has a potential side effect, and you may not even be aware of what some of the side effects are. Not talking about even the migraine ones per se, but you think of all these proton-pump inhibitors and the nonsteroidal anti-inflammatories and all these things that people take that aren't just working on one part of the body — they have a systemic effect. And as few drugs as a person can get away with taking, the better it is.

Carl Cincinnato (30:13): Fantastic. OK. Well, Dr. Tietjen, this has been wonderful. I've taken some mental notes about changes that I can make to improve my own health and well-being and lower my inflammation. Thank you so much for joining us again on the Migraine World Summit.

Dr. Tietjen (30:30): Oh, well, thank you so much for having me. I've enjoyed talking with you, and I hope your audience finds the things we talked about helpful for them.