MIGRAINE WORLD SUMMIT

TRANSCRIPT

INTERVIEWS WITH WORLD-LEADING EXPERTS

INFLAMMATION & CHRONIC MIGRAINE

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Introduction (00:05): Exercise plays a role in that; weight loss if needed. I don't mean people that have normal weight should lose weight, but with obesity comes increased inflammation. Getting good sleep and maintaining normal circadian rhythms, managing stress, if a person has elevated blood glucose, getting that under better control. I think all those things are important.

Carl Cincinnato (00:31): In our previous interview with Dr. Gretchen Tietjen, we discovered that systemic and chronic inflammation is recognized as the most significant cause of disease today. One research study found that 88% of people with chronic migraine have at least one comorbid condition, while 39% have four or more comorbid conditions. Today we go deeper to understand the role of inflammation in chronic migraine, its links to other diseases, and explore options to reduce inflammation. Our hope is to better understand how to reduce our risk of related diseases today and in the future. Dr. Tietjen, welcome back to the Migraine World Summit.

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

Carl Cincinnato (01:13): It's been two years since we discussed inflammation and its relation to migraine. What have researchers learned since then about the inflammatory response and its relation not just to migraine but to other systemic diseases?

Dr. Tietjen (01:24): At the national meetings and also in the literature, there's been a lot of research presented and debate about the role of inflammation in migraine. It is something that has been prompted by studies of cytokines, biomarkers in the blood, other things related to migraine to see what role inflammation actually plays. And I think the main question is: We know that inflammation in migraine — at least neurogenic inflammation, and we can go over what the differences are — but that it may occur during migraine; but is it actually a cause of migraine or of the headache, or is it sort of an innocent bystander or what we sometimes refer to as an epiphenomenon? And that cytokines and chemokines are released, but they may or may not play a role in causing the actual headache or having anything to do with cortical spreading depression.

Carl Cincinnato (02:37): So, there is some debate amongst researchers and clinicians about the role of inflammation in migraine?

Dr. Tietjen (02:44): Oh yeah, definitely. I would say that in fact there was an actual — oftentimes at the American Headache Society, they will do debates just because they're an interesting way to engage the audience on a variety of different topics. And last year, at the Denver meeting, two researchers — Andrew Charles, who's also a clinician, and Dan Levy, who is a PhD researcher on inflammation — debated the facts as to whether or not they felt that inflammation was playing a big role in migraine.

Carl Cincinnato (03:23): Let's shift now to autoimmune disorders. What is an autoimmune disorder for those who may not be familiar?

Dr. Tietjen (03:29): If you look at what's a normal immune response, if you get some kind of an invader in your body, like you get a virus, what happens is your immune cells, primarily your lymphocytes, they create antibodies, and then that fights the invader. But what happens in autoimmune is when the immune system creates antibodies that then attack the body's own cells. So there's probably different things that can happen that can lead to autoimmune

difficulties, but it's basically when the body's getting attacked by its own antibodies made by its own lymphocytes.

Carl Cincinnato (04:17): What do we know about the increased rate of migraine disease in other autoimmune disorders related to inflammation?

Dr. Tietjen (04:23): There [are] over a hundred different autoimmune conditions, and many or most have at least some component of neuroinflammation. From looking at those that have been most frequently questioned or researched about whether they were comorbid with migraine, you can find that, for instance, multiple sclerosis (MS), which is an autoimmune condition, seems to look like it definitely has an association with migraine, being about twice as common in … migraine about twice as common in people with MS. There [are] other ones as well, some of the rheumatoid arthritis (RA) or other rheumatological disorders. Those also seem to have a bidirectional relationship to migraine, meaning migraine seems to look like it is associated with rheumatoid disorders and vice versa. Inflammatory bowel disease (IBD) is also one that has been associated with migraine.

Dr. Tietjen (05:35): But if we look at others like lupus — lupus is pretty widespread with regards to the different organs that it can affect — skin, lungs, brain, kidneys — but that's a very controversial literature. There have been studies that have shown associations; other ones that have not. But I think when you have an underlying autoimmune disease, there's always a chance that your headache is related to the inflammation of the autoimmune disease. But for people who have migraine and autoimmune disease, when they have a flare-up of their autoimmune disease, it certainly makes their migraine more likely to come out. So, they can be amplified by the inflammation of the autoimmune disease, but it doesn't necessarily mean that it's causing the primary headache; it may be causing the secondary headache. So, it can get a little bit complicated there.

Carl Cincinnato (06:33): That's something that we hear a lot as well, that when you have a cold or a flu and you've got this kind of inflammation from an infection or something similar that you're more vulnerable to a migraine attack, and likewise with allergies; is that kind of the mechanism at play?

Dr. Tietjen (06:46): It's hard to know exactly what the mechanism is, but it definitely does seem like if you have a condition that is causing you difficulty and you have underlying migraine, your migraine will be worse. And you can, I think, infer that because there's inflammation in that condition, that maybe that is part of what's triggering it. The one actual autoimmune condition, diabetes type 1, was one thing that was associated with migraine, but in an inverse reaction, like if people had type 1 diabetes, they were actually *less* likely to have migraine. There was a negative association with that one, for whatever reason. So for all the autoimmune diseases, it's really hard to say that there's been enough research on associations with migraine per se, but in those that have done it, we certainly have found some that seem to be consistently associated with migraine.

Carl Cincinnato (07:55): Well, it's nice to hear that migraine might be a protective factor against a certain type of diabetes. We're certainly welcoming of any good news as a result of having migraine. Let's take a quick step back and provide an overview for those who may not have seen your interview on inflammation two years ago on the Migraine World Summit. What is inflammation?

Dr. Tietjen (08:15): If you look at regular inflammation that we talk about, it's usually in response to an acute injury or an infection. That's sort of the traditional way that we think about inflammation — some swelling, some pain, loss of function — certainly think of that in terms of rheumatological disease like arthritis. But neurogenic inflammation, which is what we oftentimes are referring to when we talk about migraine, is just a little bit more complicated because we can't really actually see it. I mean, you get release of neuropeptides and other inflammatory mediators, and there we're talking about [peptides] like Substance P, CGRP, Neurokinin A, PACAP — you know, from the peripheral nerve endings. And those can lead to some changes like vascular: increased vascular permeability, vasodilation, mast cell degranulation, and maybe some edema. And you can think of this as sort of a sterile inflammation; it's not a reflection of any kind of underlying infection.

Dr. Tietjen (09:34): And then the neurogenic inflammation response we think is primarily from the Substance P, but the question is: That may occur, but is that what's being sensed and being relayed back to the brain as pain? Or does it have more to do with more of a neurogenic type of stimulation of nociceptors that are not related to inflammation? And I think that that's the question that comes up as to, yeah, you can say there's release of cytokines because of the role of the neuropeptides and neurotransmitters, but [does] that really have anything to do with the actual migraine headache per se? When you look at this in animals, you really do seem to have a pretty good role of inflammation in many different kinds of animal studies, but then it's always hard to say, "Well, that's what we'd see in a person [with] migraine." But it's certainly food for thought, and I think animal models have some usefulness, certainly.

Carl Cincinnato (10:56): So what you're describing is what may be happening during a migraine attack from an inflammatory perspective.

Dr. Tietjen (11:02): Yeah, I think that most people would agree that there is some probably neurogenic inflammation that occurs in migraine, and I think the question is, just what is the role of that in the actual migraine process? Is it something that is happening but really isn't pertinent to the head pain and the symptoms that people get with nausea, sensitivity to lights and noise, the postdrome that they have?

Carl Cincinnato (11:33): Do you think that inflammation is one of those factors that may be responsible for why an autoimmune disorder generally is more common in those with migraine?

Dr. Tietjen (11:44): The amount of inflammation associated with autoimmune diseases varies on the disease, but I do think that it's something that's kind of tied through most autoimmune diseases. And I think that when you think about why now not all autoimmune diseases are elevated in migraine — and some we don't know about but some that have been looked at — really the evidence isn't very good, or at least not consistently good that we would say it. So I think it's a little bit hard to say if it all comes down to inflammation, but it certainly seems to be the thing that rises to the top of the list that makes you think that maybe that's a reason for a connection. It's not like we're talking about just one condition.

Carl Cincinnato (12:36): And one of the things that we see from feedback in our community is that a lot of autoimmune disorders have headache. Sometimes it's just regular tension headache, or it's migraine as part of the expression of their autoimmune disorder. So I guess it's not surprising that we have a lot of questions asking about the relationship between migraine and an autoimmune disorder.

Dr. Tietjen (12:55): I mean, they're really great questions, and it's just that the answers aren't always very satisfying. I think the question is, is it always migraine or is it something else? I always sort of refer to that as symptomatic migraine. It looks like migraine; is it really migraine or is it just a headache that resembles it? I think that that is unclear, and I think the literature, for instance, on multiple sclerosis and the way that they did the studies make it look like there certainly was. It doesn't mean there's a causality there, but there certainly was a relationship and association between migraine and multiple sclerosis that was stronger than we saw in those other diseases.

Carl Cincinnato (13:45): With the description of an autoimmune disorder being something that — it's an overreaction from the immune system attacking itself, in that sense, could migraine be considered as an autoimmune disorder? I mean, we're overreacting to external stimuli, and the body seems to be attacking itself. We have this awful pain that's self-inflicted in some sense.

Dr. Tietjen (14:03): I think I'd be hesitant, based on what we — the knowledge that we have to really pinpoint it as an autoimmune disorder — at least not yet, when we know what we have to find in other diseases to call them autoimmune. There's a lot of — even when you look at some of these inflammatory cytokine data and you try to study that in the blood of people with chronic headache, it's not really that consistent from study to study or which marker is actually elevated and is it elevated during the attacks more than it is between attacks. A lot of that kind of data we just don't really have.

Carl Cincinnato (14:57): Right. So it sounds like it's quite inconsistent. These inflammatory mediators, like cytokines and others, aren't being picked up consistently through research in the most severe population of those who have chronic migraine.

Dr. Tietjen (15:08): Right. And I think some of it has to do with, you know, different populations of people, different exclusion criteria. So, and one thing that I think is particularly interesting is that some studies that were done in about 2004, 2006 — I know by some Italian researchers, I think [Sarchielli] was the name of the first author in those — I always thought were very intriguing because they took venous blood from the jugular, so emptying down from the brain during and between attacks, and saw that some of these inflammatory mediators and cytokines were elevated in patients with migraine. But when you look at cerebrospinal fluid in migraine and you look at those same mediators, it's not as clear-cut. One study that's gotten, I think, a lot of interest was one by Robert Cowan at Stanford, and they looked at a lot of different mediators and actually quite a few different biomarkers, and they … did find increase in some other markers but not those of inflammation. So it's kind of like that's probably the best data set for migraine that's come out there so far, and they couldn't really substantiate that. So that was kind of a little disconcerting.

Carl Cincinnato (16:41): So if you have chronic migraine and central sensitization, it doesn't necessarily mean that you have systemic inflammation.

Dr. Tietjen (16:50): Central sensitization is kind of a hypersensitivity in the nervous system. It's kind of an abnormal processing, and you feel sort of a hypersensitization and an allodynia, meaning a nonpainful stimulus actually feels painful. Now the question is: that's not inflammation per se. There is information that suggests that inflammation can maybe lead to central sensitization. It's probably not the only thing that causes it, but that it can be a cause of it.

Carl Cincinnato (17:20): And we know that there [are] those things that in our daily life that contribute to inflammation, like our diet, chronic stress, hormonal fluctuations, infections, like we spoke about COVID and having a cold or flu, arthritis, obesity. Do you think our genes play a role as well?

Dr. Tietjen (17:37): Yes, I do think that they play a role. I think that I would say it's not clear how big a role — like you can have genes that have been associated with a few autoimmune disorders, for instance. You could have those, but if you don't have other things going on as well, they may not really manifest themselves as an autoimmune or an inflammatory disorder. But add something onto it, add another few triggers onto it, and then you may end up with a condition. Because a lot of things that we look at as triggers of inflammation also are triggers of autoimmune disorders, and inflammation can be a trigger of an autoimmune disorder. So, you know, I think there's certainly a connection there.

Carl Cincinnato (18:25): From a dietary perspective, gluten and sugar seem to be major contributors, according to a viewer of ours, Rena, who gets migraine attacks. Is there a connection between these foods and inflammation?

Dr. Tietjen (18:36): Yes, diets, if you are trying to decrease inflammation. What are ones that cause it? What are things that are thought to limit it or decrease inflammation? And refined carbohydrates — things like white bread, pastries, things with sugar — those certainly are associated with inflammation. Gluten, I think, is a real problem for some people more than others. The inflammatory things tend to be predominantly, but not exclusively, in the gut. And the Mediterranean diet is one way that they kind of summarize; that's supposed to be a good anti-inflammatory diet.

Carl Cincinnato (19:22): Do we know if things like artificial sweeteners are better or worse for us than the sugar it's trying to replace in the first place?

Dr. Tietjen (19:30): Well, I think they're worse, from some of the things I've read about them recently, but it wasn't necessarily clear exactly if it had all to do with inflammation. But I would say I think people shouldn't just replace sodas with diet sodas because I think that's very unhealthy as well. But the other things, though, that are anti-inflammatory: Exercise plays a role in that; weight loss if needed. I don't mean people that have normal weight should lose weight, but with obesity comes increased inflammation. Getting good sleep and maintaining normal circadian rhythms, managing stress if a person has elevated blood glucose, getting that under better control. I think all those things are important.

Carl Cincinnato (20:22): And I think we underestimate diet as well, right? There [are] few things that can affect our health more than what we eat, and we kind of know this sort of vaguely, but I don't think it gets enough airtime when it comes to disease management and quality of health.

Dr. Tietjen (20:37): I think it does, and it's hard — I mean, it's hard to alter diets. Some people can't just because they live in a food desert and there's not much good produce and that type of thing. And some people just grew up, unfortunately, on these ultra-processed foods. And I know that one of your readers, from the notes that you sent me, had asked about effective medications for inflammation if you can't tolerate things like indomethacin, which can have some pretty bad side effects for some people. And you know, I don't really personally know of any, but I was thinking some people have thought that using omega-3 fatty acid — things which can decrease inflammation — may be helpful. Now I think the question is — there's been more

data on that they may actually help for migraine. So if you're a migraine person asking that question, as probably most of your listeners are for the Summit, that might be something to try, or eating the foods that contain omega-3 fatty acids, and those would be things like fatty fish like salmon, mackerel, trout, tuna, those types of things.

Carl Cincinnato (21:52): Is the rationale for using ice caps or ice packs on the head to reduce inflammation? Is ice anti-inflammatory?

Dr. Tietjen (22:00): Ice is anti-inflammatory. It can vasoconstrict, cause less fluid, so less edema — whether that's why it works for people — I know it worked well when I had a swollen knee recently. Ice was great for a short period of time in decreasing inflammation; whether that's how it works when people use ice things on their head, it's less clear.

Carl Cincinnato (22:24): So you mentioned indomethacin is a treatment that's used for inflammation. Ice is something that is perhaps one of the go-tos for so many of us to try to take the edge off a migraine attack. And we spoke about reducing unhelpful inflammation in the body through potentially dietary and lifestyle factors like exercise and avoiding processed foods, and having foods high in omega-3s and fatty acids, which we've actually spoken about on the Migraine World Summit before. And we were thrilled to see that there's some evidence now that really supports that this may be one of the few options that has some evidence to support migraine reduction just through dietary factors.

Dr. Tietjen (23:01): I think that is important to point out, and there are some other anti-inflammatory drugs besides — indomethacin is used a lot for certain types of headaches, the trigeminal cephalalgias. Many people take ibuprofen for migraine, Aleve for migraine. I mean, those have been tested for treatment of migraine acutely, and sometimes certain people find them very helpful. I think a lot of people that are probably listeners to a program like this are people that maybe have more severe migraine and, of course, haven't found those to be as useful. The problem is with those drugs, whether you take them a lot or a little — I mean, even a person who takes it rarely — could potentially get a side effect from a nonsteroidal anti-inflammatory drug, so they're not totally safe.

Carl Cincinnato (23:55): And the other option from those drugs or the other alternative might be neuromodulation, which I didn't know that they were sort of anti-inflammatory.

Dr. Tietjen (24:02): Yeah, I mean, I had just sort of found that recently as to, was there any evidence that there had anything to do with inflammation, and it looked at — there had been a couple of studies that had been done — vagal nerve stimulation and also in acupuncture and it looked like it decreased inflammation.

Carl Cincinnato (24:24): If someone is worried about their inflammation levels, can they be tested? Are there any kind of clear biomarkers?

Dr. Tietjen (24:30): Those would be things, like the most common ones are probably sedimentation rate — sometimes called an ESR — that's a rather inexpensive test. There's also an antinuclear antibody (ANA) [that] can be helpful in sometimes an autoimmune disease. But I guess high-sensitivity c-reactive protein, or [hs]-CRP, that's another common one to look at. So there [are] a number of different blood tests that can be looked at to look for inflammation.

Dr. Tietjen (25:06): The cytokines — those were done, and maybe things have changed in some places — but those are done primarily through research studies and research labs and usually aren't a routine test. But I'm sure in things like rheumatological practices and stuff, maybe those kinds of things are checked more commonly than they are in a migraine practice. The hard part is, though: What do you do with that data? If you have an autoimmune disease and you have migraine, you may find that if you get tested, if things are bad and it's high that you could try treating your autoimmune disease differently. Does it really change how we would treat migraine? I think the [answer] is, we really don't know. And that, other than the things that we talked about — ways to sort of decrease it through sort of nonmedication things [like] neuromodulation and some of these lifestyle changes. I think that that's what probably people with just migraine would mostly end up turning to.

Carl Cincinnato (26:06): And it might give you an added impetus to act on if you can see a clear result saying that your lifestyle is contributing to inflammation, which is contributing to your health issues. It might give you enough of a nudge to sort of make changes in the right direction.

Dr. Tietjen (26:21): I think that if a person has migraine though that's not under good control and they don't have an autoimmune disease, sometimes when we check those things, we actually find things that make us say, "This is higher than I would expect to see in migraine." It's not just a tiny bit elevated, it's a lot elevated and maybe start looking at some of those other autoimmune tests that are done.

Dr. Tietjen (26:43): But anybody that I've talked to who is an autoimmune specialist, they say that it is not easy in anyone to really make a diagnosis. But if you have a headache and pain is your main problem, it makes it a little bit harder to know where to get started. But sometimes I have — because mostly because I've been very interested from a research point of view — I have looked at those things, and sometimes it definitely points me in a direction, or another doctor to refer to that might be able to help sort of pinpoint that down. "Do they have that? Do they have a different autoimmune thing? What's the most proper treatment?" And I'll tell you that treating those certainly can help with getting the headaches under control, particularly if there's a secondary component that's sort of maybe exacerbating an underlying migraine disorder.

Carl Cincinnato (27:38): So, who would you encourage to go get tested for some inflammatory markers or potentially for an autoimmune condition that may not be diagnosed?

Dr. Tietjen (27:48): I would say that if they have migraine though and they've noticed things like sometimes GI distress, if they've noticed arthritis. I mean, arthritis is really common, and it's a really common migraine comorbidity. But in a very high percentage of people that have osteoarthritis, at least, I would say that those are people who I think that testing certainly makes some sense to discuss it. And as I said, getting just some routine labs, they're able to diagnose for a lot of things that are considered autoimmune conditions. You know, you want to make sure you don't have diabetes that you're not aware of. And I think the question is, [are there] people [who] are not getting their headaches under control: The headaches are getting worse; they've tried all the migraine drugs? Then I always think you've got to start looking at comorbidities, and maybe this is something that if they have some other symptoms, it can point you in the right direction.

Carl Cincinnato (28:50): That's a great suggestion. If your symptoms are getting worse and you're doing everything to manage your migraine condition, think about getting tested for something else that may be sort of adding fuel to the fire that you're not aware of.

Dr. Tietjen (29:02): Oh yeah. I mean sometimes just drawing some lab tests that are considered actually pretty routine or available everywhere and probably would be covered by their insurance for somebody who is ill and not getting better.

Carl Cincinnato (29:17): Great! Well, thank you so much, Dr. Tietjen for joining us. Thank you so much, and we appreciate you once again on the Migraine World Summit. Thank you, Dr. Tietjen.

Dr. Tietjen (29:25): Oh, thank you for having me, Carl.