MIGRAINE WORLD SUMMIT

INTERVIEWS WITH WORLD-LEADING EXPERTS

TRANSCRIPT

MIGRAINE & HEADACHE RESEARCH FRONTIERS

MESSOUD ASHINA, MD
PROFESSOR OF NEUROLOGY
DANISH HEADACHE CENTER, RIGSHOSPITALET GLOSTRUP
UNIVERSITY OF COPENHAGEN

Introduction (00:05): It's not just a headache or you can just take the painkiller and it should go away: “It's nothing; it's not a disease.” We know about the burden, we know about the cost, and we know about specific medications developed to target migraine attacks — triptans. Now we have anti-CGRP medications acting both as an acute and preventive. So already, there, we have clear biomarkers in my opinion, so indirect biomarkers. But from the science point of view, to understand the pathophysiology of mechanisms of migraine, I think it's a great idea to study and to find the biomarkers of the disease.

Carl Cincinnato (00:46): Our next expert is a headache specialist and researcher who is the past president of the International Headache Society, the peak global body for headache and migraine clinicians. He's also the associate editor of three journals: *Cephalalgia*, *Brain*, and *The Journal of Headache and Pain*, which makes him very well placed to discuss new migraine and headache research with us today. Dr. Ashina, welcome back to the Migraine World Summit.

Dr. Ashina (01:10): Thank you. Thank you, Carl, for the invitation.

Carl Cincinnato (01:13): The new class of CGRP treatments have been a breakthrough in migraine treatment. For many people, these are well tolerated, effective, and, in some, they can experience a more than 80% reduction in migraine. However, they don't work for everyone. As you've pointed out in your own published work, the need for additional options is clear. Could PACAP be the next big innovation in the migraine space? Can you tell us what it is and why are so many headache researchers excited by it?

Dr. Ashina (01:40): Well, as you pointed out, not every patient responds to the new treatments. Roughly, approximately 60% of the patients, they report response to the monoclonal antibody — antibodies against CGRP or its receptor. About 40% of the patients either discontinued due to lack of efficacy, or side effects, or different reasons. But the point is that there [are] a number of patients who need new treatments. Right now, we can say that they tried all the old drugs. They also tried monoclonal antibodies against CGRP. They failed, and we must tell them that they are refractory, or resistant to the currently available treatment. This is a very unfortunate situation for the physician, and that's why we always say there is room for improvement. We need new targets to provide new medications to these patients not responding. There [are] also a number of patients who report partial response or poor response.

Dr. Ashina (02:49): Maybe they can also benefit from a combination of the monoclonal antibodies against CGRP and other molecules. PACAP is a very interesting molecule. It is expressed in all migraine-relevant structures — its receptors and [the] molecule itself. When we give PACAP infusion to migraine patients, we can provoke migraine attacks, suggesting that PACAP can be a target — whether it is PACAP itself, or what we call a ligand is a target — or PACAP's receptor. It's a big question. One of the receptors has been tested some years ago, and unfortunately, monoclonal antibodies against this receptor failed for migraine prevention.

Dr. Ashina (03:36): Two currently running programs on anti-PACAP monoclonal antibodies will show us next year, hopefully, whether this target is relevant for migraine, meaning that we can prevent migraine attacks. And in the future, it'll be interesting to study whether this medication, if the trial is positive, can work on those who failed to respond to monoclonal antibodies against CGRP. We can also try in the patients that never tried other monoclonal antibodies to see whether it works in this group in the real world. Plus also, the prospect of combining those two medications will be also very interesting to see in the future.

Carl Cincinnato (04:25): Do you think PACAP could be the next class of CGRPs if the research is successful that's currently underway?

Dr. Ashina (04:32): Yes, the PACAP could be another success story, which starts from preclinical studies showing the expression of this peptide and its receptors in the migraine-relevant structures — such as [the] trigeminal nerve, blood vessels, cranial blood vessels — in particular infusion studies, showing that this molecule can induce migraine. Very similar story to the CGRP. So, we can repeat the same story with CGRP, hopefully. But of course, there is no guarantee. Science is full of surprises.

Carl Cincinnato (05:06): Absolutely. And if we are let down by the studies that are currently underway, are there any other potential drug targets that could launch a whole new class of treatment? Adenosine, for example, is one that has been mentioned?

Dr. Ashina (05:21): Yes, adenosine was mentioned, in fact, over many years. And recently, we showed that adenosine infusion causes headache, but not really a migraine. In very few patients — migraine. And what was interesting [was] that induced headache was associated [with] a short-lasting vasodilation — the dilation of the extracerebral arteries, extracranial arteries. Well, it is very difficult about adenosine because adenosine acts on two receptors — not two, actually, in fact, on four receptors, and maybe there are many other receptors also not really discovered yet — but acting on some receptors, it may act pronociceptive, meaning that it can cause pain; and in some receptors, it acts as an antinociceptive. That's why this dual effect of adenosine is very difficult to study in humans. And so far, we have only one provocation study showing that it's not really inducing. Very few patients reported migraine attacks, but it was not statistically significant for placebo.

Dr. Ashina (06:35): And one example is about coffee: You know, coffee's effect is also an adenosine effect. And what is interesting is that when we drink coffee, we can in fact treat our migraines, especially when we combine the coffee with aspirin or other painkillers, and many combination drugs contain caffeine. But on another hand, we also know if we do it too much, we can also induce headache. So, this is also an example of the dual action of adenosine.

Carl Cincinnato (07:02): Does that suggest that you could — adenosine is one of those treatments that could be ... not abused, but overused — you could have rebound headaches from?

Dr. Ashina (07:12): Yes, my point is that you can get a rebound headache, but probably it's because of the multiple receptor effect of adenosine. And in this study that I mentioned with adenosine infusion, we suggested that further studies with the selective modulators are needed to elucidate whether the adenosine's A2A receptors could be a potential target for the treatment of migraine. But this is something in the future — not in the near future.

Dr. Ashina (07:50): Another interesting target that we discovered — potential target we discovered — is the KATP channels. The KATP channels — it's ATP potassium-dependent channels, and when we open these channels we can in fact induce migraine attacks in almost all patients. And it'll be interesting to study the blockers of these channels.

Dr. Ashina (08:20): The problem is that these channels are located everywhere in our body, and if we start blocking all the channels, it could cause potential serious adverse events. That's why our task is to find the selective channels, preferentially located at migraine-selective structures,

and to see whether the blocking of these channels can provide another new target for the acute or preventive treatment of migraine. The reason that I'm so interested about these channels is that we consider them the downstream of the current mechanisms that we're targeting now. And by targeting the downstream mechanisms, further down in the cascade of the signaling pathways, we might achieve better response.

Carl Cincinnato (09:13): Is that AKP channels that you're referring to? Have I got that right?

Dr. Ashina (09:17): It's KATP channels. It's KATP. They are ATP-potassium-dependent. Yes.

Carl Cincinnato (09:24): So, moving now to a different potential target. I wanted to talk about the psychedelics such as psilocybin or LSD. Are these treatments — there's a lot of controversy around them; historically, these are banned, highly scheduled substances. Is there any medicinal merit to these?

Dr. Ashina (09:42): Yes, psychedelics — it is not a new story; it's an old story, but now it's kind of reviving and it's coming back. I'm very cautious about that for two reasons: One is that we need more evidence because anecdotal evidence is not sufficient. We need systematic and validated studies focusing on this particular mechanism. And the second is that the side effects, potential of the side effects, of these, let's say, drugs or medications. I wouldn't exclude it entirely. So we can use it in our practice, but I think my belief is that if we do that, it'll be very limited.

Carl Cincinnato (10:34): And what about medicinal cannabis?

Dr. Ashina (10:36): Yes, cannabis is also something — a very popular topic — and the cannabis and cannabinoid receptors are located in the migraine-relevant structures. And the question is whether the efficacy of cannabinoids — potential efficacy of cannabinoids — is something specific for migraine or it's just universal for all kinds of pain? It's very difficult to say. There are a lot of studies, but so far, to my knowledge, we don't have firm evidence of this class of medications working in migraine.

Carl Cincinnato (11:13): A recent study published in *Cephalalgia* took saliva from patients measuring levels of CGRP during a migraine attack, and the results showed that there were two types of migraine attacks depending on whether the CGRP levels increased or not during the acute phase of the migraine. Does this open the door to predicting response to treatment and perhaps personalized medicine in migraine?

Dr. Ashina (11:35): Yes, there is an ongoing search for so-called biomarkers which can predict efficacy of anti-migraine medications. This is intuitively, a very, very elegant thought — that you can, in fact, predict, you can take a sample, and you can say, "Well you have a 90% chance that this drug will work." We see something like that happening in cancer treatment, and we are all excited about that, but it is also complicated. It's not so easy. You need a simple biomarker, right? And this study was one of the first attempts to find a single biomarker measuring in saliva CGRP. Well, it is an interesting observation, but what this observation needs is to be reproduced by other groups — it's very important — and maybe in a large sample size. I think it's a first step, this study measuring the CGRP in saliva, but I would wait. I would like to see more studies from other groups, either reproducing or showing something different.

Carl Cincinnato (12:55): You mentioned a biomarker to be able to tell which patients might respond and which may not. How close are we to finding a biomarker for migraine diagnosis and why might the discovery of a biomarker be a good thing for people with migraine?

Dr. Ashina (13:11): I think that the biomarker for migraine is important to show something specific for this disease. It could be important also to recognize it as a disease. It could be also important that in some patients — few patients, I would say — that you are not sure whether it's migraine or something else. You can say, "Well, it is a migraine based on this biomarker." But recognition of migraine as a disease is important, but I don't think it is so important if we find this biomarker. Already now, we have indirect biomarkers for migraine. How many diseases have specific receptors — molecules involved in their pathogenesis — and the drugs acting on these receptors, on these molecules, in fact, abort or prevent migraine? This is already the case in migraine: OK, so it's not just a headache or you can just take, you know, the painkiller and it should go away: “It's nothing; it's not a disease.” We know about the burden, we know about the cost, and we know about specific medications developed to target migraine attacks — triptans. Now, we have anti-CGRP medications acting both as an acute and preventive. So already there, we have clear biomarkers in my opinion, so indirect biomarkers.

Dr. Ashina (14:43): But from the science point of view, to understand the pathophysiology of mechanisms of migraine, I think it's a great idea to study and to find the biomarkers of the disease. And this is basically what we are doing. You know, when we do the imaging studies, when we do the provocation studies, when we do the biochemical studies, all of them are focusing to find something specific, unique for migraine, different from other primary headaches.

Carl Cincinnato (15:13): I think you raised a really good point about the CGRPs being a migraine-specific treatment, and I think in a way that that has helped legitimize migraine itself as a diagnosis because it's a specific treatment that only works for people with migraine in that sense.

Dr. Ashina (15:29): Already in triptans, back in the '90s, we showed that when the triptans were introduced in our clinical practice, that was a huge game changer because everybody said, "Well, we now have something which is specific to treat migraine." And the patients were so happy.

Carl Cincinnato (15:48): Yes, absolutely. There was research recently published in *The Journal of Headache and Pain* that suggested there might be a slight increase in the risk of dementia in those who have migraine. Is this any cause for alarm among migraine patients?

Dr. Ashina (16:04): I would be very careful in the interpretation of association status because ... just because migraine is associated with something doesn't mean that there is a directional association between these two conditions. Number two, migraine is so prevalent, so the likelihood that the migraine can overlap with something is quite high, OK? So, I can give you one example. Also, one of the important associations is with depression, right? And the question is whether the symptoms the patients report are really depression or anxiety, for instance, or just a reaction [from] the multiple attacks. And a successful treatment of those attacks, in fact, reduces the symptoms. So in this case, those are only symptoms, OK? This is not a B diagnosis, another diagnosis, you know, depression or anxiety. And as a clinician, I've never seen in my life, patients coming to my office who successfully treated their depression and telling me, "You know, Messoud, I'm migraine-free." I've never seen it in my life. OK, so there are two different

conditions, but in epidemiological or registry status, they can overlap. And they can suggest this association and increased risk of this and that. But I'm very cautious in interpretation of this association status in particular with dementia. I personally don't believe in that.

Carl Cincinnato (17:42): It is the first study. I mean, up until this point, there's been no evidence that I'm aware of that suggests that there is any causal relationship whatsoever.

Dr. Ashina (17:52): No.

Carl Cincinnato (17:54): You mentioned before, mental health and how a lot of people with migraine may also have mental health issues. I think if you have chronic pain, that's not a particularly pleasant experience — that can be depressing. And if you have acute attacks that are disruptive and unpredictable, well that can cause anxiety, as well. It's interesting that you mentioned that could be considered a symptom of migraine because it's a direct result of the migraine itself, rather than a discrete mental health issue or disorder.

Dr. Ashina (18:23): You are absolutely correct. Many of my patients, they also suffer anxiety of having an attack, you know, anticipation that attacks might come — cephalalgiaphobia, you can call it: the phobia of the migraine or headache will come. And this by itself, it is a burden — an interictal burden. It's a very popular topic right now, so interictal burden [of] migraine. And by successful treatment, you can, in fact, also measure how can you reduce this interictal burden.

Dr. Ashina (18:58): One example is that one of my patients told me, "Well, you know, Messoud, now I can go to the party and I can have a glass of wine. I don't have this anxiety that if I go there, if I touch alcohol, you know, I can get a migraine." Or just going out with too many people, too many interactions sometimes by itself could be very stressful for patients, and that's why they avoid social gatherings. And in this case, when the treatment is successful, they can participate. So this functionality, that you can function normally and you don't have to be afraid of that between the attacks, it is very, very important.

Carl Cincinnato (19:41): What developments have we seen in the last year about the CGRP monoclonal antibodies? I know they've been out now for a couple of years. Have there been any developments or new comparisons or potential new side effects that have emerged or improved understanding that you can speak to?

Dr. Ashina (19:57): I can tell you that real-world experience and my clinical experience is quite positive. What I also learned now with the new medications is that some of the patients might also develop some adverse events, maybe because they have also other comorbidities, and these comorbidities, some way around, they can influence their tolerability of this medication. So, that's why I always say that real-world studies are very important because we need to study that in the real population, not the population only from the clinical trials when we always include patients with no other comorbidities, with no other problems.

Dr. Ashina (20:44): But there is also room for improvement — we need to study these new medications in children to see whether they work, and they're safe, and they're well tolerated — it's very, very important. We also need to study [them] in elderly adults because, unfortunately, they're discriminated [against] in the clinical trials; they're not included, and we need to study this special population. We need to learn more about the possible side effects or any kind of danger for the pregnant women of taking these medications, because some of them

get pregnant while they're taking these medications and they have a long half-life. So we need to gather all these data in order to guide our patients better.

Carl Cincinnato (21:35): Speaking of that: Gepants — these have been available now in the U.S. for some time. In Europe, I know that they're sort of on their way. What have you seen over the last year regarding the gepants?

Dr. Ashina (21:49): What is interesting about the gepants is that you can administer them orally; so, they are the tablets. And we will also see one of the gepants coming out as a nasal spray, pretty similar to what we have with the triptans — tablets and nasal spray. Hopefully, we'll also have a gepant as an injectable — the subcutaneous, like we have with the sumatriptan. Why not? This is all, in fact, that I wish we would have it. And for the tablets that so far are introduced and used, I can say it's very interesting — two aspects are very interesting: One is that the gepants can be used both acutely and preventively. So it's kind of an all-in-one, right? It's a quite unique situation. You know, all the time, this concern or anxiety of developing the medication overuse — it's highly problematic for these high-frequency patients. So, if we can offer to these high-frequency patients something new without risking getting into the medication overuse, having an acute and preventive effect, that is great, I think. So it just expands the armamentarium of the medications we have. So we have so many things we can offer to our patients right now. So it's really good.

Carl Cincinnato (23:12): Can you take triptans and gepants at the same time? Like, can the same patient be given them — use triptans on some days, when they get to their quota, transition across to gepants?

Dr. Ashina (23:22): Taking triptans with the gepants, in terms of the safety, shouldn't be any problem. I mean, I don't see any biological reason not to do that, and I think the patients are also doing that. More logical would be if patients [are] taking the gepants as a preventive, and then when they get attacks, they can take triptans if they like to – if they think that the triptans are working better as an acute medication than gepants. So this could be a case, one scenario. Another scenario could be that the patients taking gepants for prevention, and once in a while, they take also a gepant for the acute treatment.

Carl Cincinnato (24:09): You mentioned that you'd like to have a gepant that's an injectable. Why is that? Are you looking for non-oral options there, or is there another reason?

Dr. Ashina (24:17): It'll be really good if you have something fast-acting, let's say acting in a matter of 15 minutes or 30 minutes and then going back to normal function without being tired, without being sleepy; this is important. And also the prospect of having [an] injectable also for patients with a cluster headache — it'll be also interesting to study, but this needs to be shown whether it is working or not.

Carl Cincinnato (24:45): We mentioned before how injectables avoid the gut, and recent research has emerged around the gut and brain, and speaks about the gut-brain axis. Could the gut and the gut flora be playing a role in migraine? Is there research that shows potential in that space that could be helpful for people living with migraine?

Dr. Ashina (25:08): Well, it's a very interesting topic, but unfortunately very few data, mostly speculative data — not the data is speculative, you know, opinions or point of view about this. It's [an] interesting axis, [a] very interesting axis. We do see some associations also, for

physiological status, suggesting that migraine patients have a higher incidence, or complaints of gastrointestinal tract problems. Also, the drugs that we're targeting, in fact, you know, the CGRP are also expressed, located in the gastrointestinal tract. So we are also targeting them. Whether it has any effect on the outcome, nobody knows about that. This is very, very interesting, and this is something that we will hear more [about] in the future. And I find this fascinating, this topic, but unfortunately I cannot tell you of any major breakthrough in this field right now that gives us hope that it could be a potential, not target, but potential major player in the migraine pathophysiology.

Carl Cincinnato (26:32): Last question: Thank you so much for your time, and you've been very generous with sharing your knowledge and expertise. What new treatments are you excited about that are coming soon or are likely to be recently released?

Dr. Ashina (26:45): I cannot say about recently released. I can just say that in Europe, we will see some introduction of the gepants. I'm all excited about that — already in Denmark, one of the gepants is approved. I also can't wait to see another gepant approved. I want more options. This is my dream as a physician, as a specialist in this field, to have more options [for] our patients. I cannot tell you that there is one particular one that is bulletproof [that's] coming. I'm excited about the PACAP — antibody against PACAP. Fingers crossed it works. If it [doesn't] work, then we have to figure out what's not working and what are the mechanisms underlying PACAP-induced migraine. Maybe we'll see something with amylin — this is another interesting peptide from the same family as CGRP. As I mentioned before, the prospect in the future with the role of the ATP-sensitive potassium channels in migraine pathophysiology is very, very interesting. Can these channels be a new potential target for migraine? Well, we will see in the future.

Carl Cincinnato (27:58): And we'll be watching. Dr. Messoud Ashina, thank you so much for joining us on the Migraine World Summit.

Dr. Ashina (28:04): Thank you for inviting me.