MIGRAINE WORLD SUMMIT

TRANSCRIPT

INTERVIEWS WITH WORLD-LEADING EXPERTS

COULD BIOMARKERS IMPROVE MIGRAINE DIAGNOSIS?

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Introduction (00:05): I am not sure how quickly all of this will move in time, but I'm quite sure, even if I don't see it in my professional career, that we will be able to biologically phenotype migraine attacks, and each patient more or less will know what peptides, and what genetics, and what epigenetics, and so on, are actually conditioning their disease and making it different from others. And then, from that, probably have precise medicine or more precise medicine for them.

Kellie Pokrifka (00:37): Biomarkers can help us not only diagnose diseases but [also] figure out what treatments work not only for the disease but also for individuals. As someone with chronic migraine, there is nothing I want more for myself and for our entire community than to be able to take a simple test to identify which treatments will actually work. We have today one of the leading experts on this topic, and she's going to go over how far away we are from these tests, what are biomarkers, and what are the differences in brains between people without migraine and people with episodic and chronic migraine. Dr. Pozo-Rosich, welcome back to the Migraine World Summit.

Dr. Pozo-Rosich (01:13): Thank you, thank you for having me back. It's a pleasure.

Kellie Pokrifka (01:17): All right, so what is a biomarker?

Dr. Pozo-Rosich (01:19): That's a very good question. It's a way of measuring a biological process or disease in a quantifiable way that is validated and that helps either diagnose, or predict evolution, or predict response — usually those are the three main things that biomarkers are used for — of a disease or of a treatment. So actually, it's a way of quantifying biology in a way, and that has to be linked to a disease. Then an ideal biomarker, you could also say, should be easily done — easily — so not too costly, you could say. So that's already when it gets to an industrial process that can be used in a generalized way.

Dr. Pozo-Rosich (02:10): You also have to think of practical. It has to be practical, applicable, easy to do in different setups of the world, and so on. But that's then the second step. We are still in the process of deciding which type of biomarkers could we eventually have for migraine, what type of information they would actually provide us, because, as I said, different functions or different ideas of the whole disease can be measured in different ways. So, we can get into details if you want later. So, first of all, we are in this first process, and then we need to see whether if it's applicable, and easy, and practical to use.

Kellie Pokrifka (02:58): When you say it could be easily done, what are some examples of the way biomarkers could be identified?

Dr. Pozo-Rosich (03:04): Well, it could be a blood test sometimes. So, you could have a molecular biomarker, maybe using genetic, epigenetic testing, or, for example, nowadays, kind of the big buzzword in treatment, but also perhaps even as a possible migraine biomarker, could be calcitonin gene-related peptides. So CGRP, which, as you know, we have now treatment by blocking or controlling the effect of CGRP, [is] clinically meaningful for many, not all, but many of our patients. So, the idea here would be to actually, perhaps — for example, think of whether if CGRP could become a biomarker. It is not yet a biomarker, first of all because we need to have a systematic way of measuring it that is validated in every center that could use it, for example.

Dr. Pozo-Rosich (04:01): So it's still not easily done. It's not like any blood test that we do on a systematic basis just to check glucose. Or, you know, glucose could become — imagine a biomarker? If it will be meaningful for us as a disease, in this case migraine, and it isn't. But what

I'm trying to say is that it has to be easily available in a way, and then you have to decide: what is it useful for? So, CGRP, what could we use it for? And perhaps you're aware of the research that we have been doing lately, and we, for example, found out that in saliva we could measure CGRP and that differentiated attacks.

Dr. Pozo-Rosich (04:43): So, some attacks — in some attacks that patients have, clinically they're all quite similar — but some of them have an extra release of CGRP and other attacks do not. And that already starts to tell you that not all of the attacks that clinically look alike are biologically the same. So maybe an opportunity for CGRP to become a biomarker could actually be to differentiate [between] types of attacks. And who knows, maybe [in] the future then, if you know that you have a majority of your attacks that are CGRP-mediated, then you can actually take CGRP drugs.

Kellie Pokrifka (05:19): Right, in that example, you said that there are differences in CGRP levels between attacks. Is that completely individualized, or would it be something like a hemiplegic migraine type, or one that has more nausea, or something like that?

Dr. Pozo-Rosich (05:33): Yeah, when we found those differences, we actually went into the very clinically detailed granulated data, and we saw that indeed, perhaps those that were CGRP-mediated attacks — photophobia and phonophobia, so being [bothered by] light or sound — was more present in CGRP-mediated attacks than those where CGRP was not as released. Instead in those CGRP-independent attacks, there was a bit more of nausea and dizziness. So those were the two signs that we could see, but it is a very small cohort, and I cannot be profoundly sure if that is kind of the case. And also, I mean, in many cases, you can have photophobia and nausea, so at the end, all of these symptoms are a bit all over the place in migraine attacks.

Dr. Pozo-Rosich (06:27): And that actually tells us that we need more profound biological data to actually really understand the types of migraine attacks that there can be, and CGRP is an example, but not the only one. So, I'm not sure how quickly all of this will move in time, but I'm quite sure, even if I don't see it in my professional career, that we will be able to biologically phenotype migraine attacks, and each patient more or less will know what peptides, and what genetics, and what epigenetics, and so on are actually conditioning their disease and making it different from others. And then, from [there], [they] probably have precise medicine or more precise medicine for them.

Kellie Pokrifka (07:13): I can't imagine how incredible that would be to walk in and be able to understand exactly what is causing, or not causing, but making sure that you have the correct diagnosis.

Dr. Pozo-Rosich (07:24): It's like having your — I would say fingerprint — so it's almost like your biological fingerprint that makes sense for you, at that time point at least. So, as I said, it will take a bit of time, but we are certainly working on it. And, I can envision or think that even in my professional career, I will probably see a diagnostic test for migraine at least; maybe even something that can help either diagnose or predict, maybe, risk for developing chronic migraine, so a more severe state of the disease, for now or for the future, and perhaps also some type of test that can actually let us know on which biological — I would say predict a bit of response to treatment. I'm not sure if response to treatment, but at least what type of treatment makes sense for that person a little bit, too.

Kellie Pokrifka (08:36): For people who may be still struggling to really understand what a biomarker is, are there any disease states with associated biomarkers that a lot of people would understand clearly?

Dr. Pozo-Rosich (08:46): Well, glucose is a biomarker for diabetes. At the end, you're actually — and if there's any person here who is diabetic will know that they look actually into glycosylated hemoglobin (HbA1c). So there [are] many types of quantifiable, you could say, biomarkers that can be, for example, used for diabetes. Yeah, I think also of Alzheimer's in the neurological space, where we are actually correlating the disease with the presence of amyloid and of tau proteins.

Kellie Pokrifka (09:25): All right, let's talk about brain imaging and your latest research that underwent that looking for biomarkers.

Dr. Pozo-Rosich (09:32): Neuroimaging is very interesting. It has given us a lot of information on the biological background of what migraine might be. We have actually been able to map how the brain, or what parts of the brain, get active or activated during certain phases of the migraine attack. So, in the prodromic state and initiation of the attack, you have the hypothalamus, which is very active, then you move forward towards pain, and then all the pain circuitry which involves the thalamus, and the cortex gets activated, and then you have the postdrome. So, at the end, we kind of understand. It's kind of interesting because, really, if you want to understand migraine, you have to understand many different pathways that are happening in the brain, and that actually gives you knowledge on how circuits and pathways in the brain work.

Dr. Pozo-Rosich (10:27): Then, in migraine, we're also working on what we call the functional outputs or outcomes of the disease, and that is measured through physiology or neurophysiology. So, we actually do what we call evoked potentials, [or] EEG [electroencephalogram]. So, we measure cortical activity brain waves in a way for people to understand and the electricity that goes around that. Also, the responses that the brain has towards different types of stimuli — so visual stimuli, acoustic stimuli, and so on — and we try to understand whether if that could also become a biomarker.

Dr. Pozo-Rosich (11:05): We actually wrote a paper that where we clearly see that all of these things that we're talking about are really different in chronic migraine than in episodic migraine or control patients. So it is clear in our minds that if you don't treat properly, migraine, once it becomes chronic there [are] many ways of measuring the impact of the disease in the brain using all of these techniques. The question that we don't yet know is whether if what we are seeing as a biomarker for chronic migraine is reversible or not.

Dr. Pozo-Rosich (11:39): So, we still don't know whether if what we are seeing is actually already there in that person before even becoming a chronic migraine patient, or if there are changes that are linked to just having a repetition of attacks one after the other one. So there are many interesting things going on, and longitudinal studies — those are studies where you follow the patient for a period of time and actually keep on repeating some tests — are needed and are currently starting to be done, I think, in our field. There's some that have been done, but not that many before, I mean.

Kellie Pokrifka (12:15): What are some of the differences between episodic and chronic migraine that you see in the brain-imaging studies?

Dr. Pozo-Rosich (12:20): In the imaging, what we saw was that, for example, amongst other things, the frontal lobe, so frontal here, what we have behind the forehead, was a bit thicker. So cortical thickness was a bit enlarged. Maybe who knows if it's because it's working a lot or not. So when we see something that is different, we still don't know the meaning that it has behind it. We see that it's different, but we don't know whether it's because it's overworking, because it's actually hypo-working. So we still don't understand sometimes the balances and then what translation that has in actual brain activity and function.

Kellie Pokrifka (13:05): Is it true that we've seen with patients with chronic migraine that their gray matter in their brain is actually shrinking?

Dr. Pozo-Rosich (13:11): So, the quick answer is no; I don't think so that in migraine we have a shrinkage of the gray matter. And there's gray matter a bit in different places of the brain. So maybe you're thinking of a study that I am not kind of thinking of it now. Maybe I'm forgetting a specific study, but at the global level, the answer would be no; gray matter shrinks really very much related to age.

Kellie Pokrifka (13:36): What about pain activation? So, with chronic migraine, our pain activation sites, I assume, are sort of always firing. Does that make us more vulnerable to other types of pain that aren't migraine-related?

Dr. Pozo-Rosich (13:50): That's a very good question. Somewhat difficult sometimes to fully answer. I would say that certainly the more pain you have then the easier for the system to not control pain, actually, to inhibit pain. It is because you sensitize — that's kind of the word — the whole sensory system, and it trains itself to actually trigger what you think is pain, so at a cortical level with lower thresholds … So that's one point. The second thing to take into consideration if you have inflammatory pain, which is partly what is going on in migraine, all of that inflammation sometimes, I think, also finishes up somewhere else. What I mean is that yes, I believe that depending on what type of cause is triggering pain, it can actually maybe create a pro-inflammatory brain state or a pro-inflammatory body state that can facilitate other types of pain.

Dr. Pozo-Rosich (15:03): It is clear at a clinical level that when you study at least clinical cohorts, so the people which are usually most severe patients that we see in our clinics that usually have chronic migraine, that is comorbid with other chronic pain conditions such as fibromyalgia or other symptoms, rheumatoid arthritis, just other types of pain which are not in the head or the brain — near the brain.

Kellie Pokrifka (15:36): Are these changes you see with people with chronic migraine? Have you been able to see whether they're reversible in episodic migraine if they're able to get out of that chronic state?

Dr. Pozo-Rosich (15:45): We are still, no, I mean the only positive data that I can think of that has been actually very recently published. Todd Schwedt and colleagues who work at the Mayo Clinic in Arizona actually followed the cohort of patients before and after treatment with anti-CGRP antibodies and they actually saw that brain improved a bit. What they mean by that is that yes, they were able to see that with a good treatment there are certain areas that were different, because here what you look into, neuroimaging, is you actually are trying to compare differences; so thickness, or, yeah, mostly a lot of cortical thickness.

Dr. Pozo-Rosich (16:28): So just looking at sizes you could say, and then you compare, you try to create a mean in your group, so group of patients versus group of controls, and you see whether that changes. And what they've seen or they saw was that initially, so before treatment, there were certain changes, and those changes minimize or decrease when you have treated patients. So there are still some little changes, but not as many as before treatment. So that's a way of trying to understand what or how we are doing this type of analysis.

Kellie Pokrifka (16:59): How far off do you think we are from having medications based upon PACAP [pituitary adenylate cyclase-activating polypeptide] and its role in migraine?

Dr. Pozo-Rosich (17:05): We already know; I mean, this is not new data. It's kind of data that comes from the 1990s. That when pain happens in the trigeminovascular system, that is mainly mediated by different types of neurotransmitters, peptides, you can call them whatever you prefer, kind of. Amongst them, you have CGRP, also PACAP, you also have VIP [vasoactive intestinal polypeptide], Substance P, nitric oxide, for example. So there are many types of neuropeptides or substances that are released by the system that actually are working to potentiate, and to not only potentiate, but for pain to happen. There [are] many things going on there. So PACAP is one of them, answering to what you were asking me.

Dr. Pozo-Rosich (17:58): So initially, we thought that maybe PACAP was there, but not too clinically meaningful, you could say. But lately actually coming, data coming from the Danish Center and others have shown that maybe not — so within the whole migraine attack there are different phases. So PACAP actually has more of an impact on the symptoms and probably the response to the treatment on symptoms that appear a bit, I would say, late in the attack, in the migraine attack, but not initially. So PACAP might have a role, for example, in prolonging attacks, in facilitating certain symptoms to appear.

Dr. Pozo-Rosich (18:46): So yes, PACAP is an interesting molecule for migraine, and hopefully we will find that by controlling it too, blocking it maybe with antibodies also. Maybe, hopefully, in the future we'll have new drugs that can help some patients because, as you know, with many of the drugs that we have nowadays, we help certain types of patients and not others. And that goes back to this biomarker question initially, which tells you that not all migraines are exactly alike.

Kellie Pokrifka (19:19): OK, so correct me if I'm wrong in interpreting this. So, if you were to inject a patient with CGRP, that could potentially initiate a migraine attack. But if you did the same thing with PACAP, it probably would not initiate an attack.

Dr. Pozo-Rosich (19:33): No, actually, as I said very recently, they proved that it could initiate an attack in some patients, like you're saying, [but] not in every patient. PACAP was actually triggering attacks, but in a delayed way. So yes, it can actually also happen and it doesn't happen in every patient, like with CGRP.

Kellie Pokrifka (19:54): You listed a lot of different neuropeptides, including CGRP and PACAP. Do you see any other promise in some of the other ones in potential targets for migraine?

Dr. Pozo-Rosich (20:04): Yes and no. So officially yes, which means that by blocking glutamate, or by blocking potassium, by blocking nitric oxide, I'm sure we would be successful in controlling migraine. The problem that we are facing nowadays — but maybe that could be maybe changed — is that when you block all of these substances that I was mentioning, you actually create a lot

of side effects to the system. So the body cannot tolerate [it] well if you stop its glutamate, or at least in the way that drugs have been developed until now. So we still have to better understand if we can actually viably, so in a comfortable way, block these substances, or if not, how could we do it. And sometimes you have to go downstream, which means that all of this in our biology, all of this is kind of a biochemical chain, and you can stop the process in different time points.

Kellie Pokrifka (21:05): How do epigenetics play into this?

Dr. Pozo-Rosich (21:08): Let's first understand that migraine is quite a genetically driven disease and that we have found already certain, we call them polymorphisms, that are differentially expressed in patients versus controls. Controls are people that do not have a family [history] or a personal history of migraine. So once that's said, the thing with our DNA is that not every part of our DNA is what we call active, or producing functions which are mediated through protein. Actually, parts of our DNA are silenced, and they only get activated if they're exposed to certain triggers in our bodies or the environment.

Dr. Pozo-Rosich (21:49): So that actually tells you that the relationship between, in this case, our brains or our bodies and our environment — which is a mixture of diet, of healthy, or lifestyle in general, hopefully healthy lifestyle, pollution, maybe even certain drugs or treatments — can actually activate or deactivate our DNA. And all of that is mediated — this activation — so to actually click a protein for it to activate and do its function or stop its function, you actually control this through what we call epigenetics. So all of that is very much linked to how we live, and that actually goes back to one also I think very important message, which is, not only I believe we have to get and look for treatment and an appropriate diagnosis because we don't want the disease to transform itself into all of these things that we were talking, that we can actually see in chronic migraine, which are not as clear in episodic migraine.

Dr. Pozo-Rosich (22:51): But also, we have to change mildly, at least our lifestyle, and have a healthy lifestyle. And I do believe that that's one of also the most powerful things that we can do for ourselves. Exercise, for example, is one of them, eating appropriately, drinking water. There [are] many things that, if you just don't do them right, they actually can facilitate a progression of the disease, trigger an attack. And I think we also have to remind ourselves of that and remember it, yeah.

Kellie Pokrifka (23:25): Yeah. I think that can feel really powerful that we actually have some kind of control over this disease, where so often it feels completely out of our control and we feel sort of powerless. So I really love that perspective on that.

Dr. Pozo-Rosich (23:38): Yeah, I think it has to be a mixture between lifestyle and understanding what the disease is about, but I would call it a friendship level. So I always highly recommend my patients to become — so make them understand that migraine is not their enemy, but their friend — friend in the sense that it actually helps you. First of all, have a connection with neurologists, and they explain if they're a good neurologist or, through your types of programs, what this brain is about, and it gives you a lot of insight on what are the needs of the brain, how it functions, and so on. I think it's quite interesting.

Kellie Pokrifka (24:16): I have never heard that perspective before. That is so cool. It may take me quite a while to become friends with my migraine, but I like that a lot.

Dr. Pozo-Rosich (24:26): Yeah, you have to think that migraine attacks are there to protect you, to actually help you survive, in maybe not the best way, but in the way that your brain knows how to do it or your body. You have to think that pain as a concept is thought to protect us. So if you break your arm, you have pain if you move it, so that you won't move it and actually help cure it by not moving it, or going to a physician, or so on, to the doctor. With pain in migraine and the whole attack, I truly believe it's a way that the brain has to shut down. It's a pity that it needs so much inflammation that actually creates so much pain. You have to understand this rhythm, the poses, and the needs that this brain has and not kind of fight against it because then the whole process actually is far more uncontrollable and it becomes really aggressive. Do not fight against your migraine.

Kellie Pokrifka (25:27): I love that advice so much. All right, how far off do you think we are from finding a biomarker that can diagnose migraine, that can determine what type migraine is, and determining what treatment types we have? And I assume they would probably be pretty far off from each other.

Dr. Pozo-Rosich (25:47): I think that diagnosing migraine might not be that far [off]. We'll have to understand what we are diagnosing, though. Migraine is nowadays complex and very — I mean homogeneous in some cases because you all have attacks that come in and out [of] patients – but heterogeneous at the same time. So, we're calling migraine a lot of things — biological things probably, or many different things — so we will have biomarkers to diagnose at least certain types of migraine. So, we will be able to say whether a patient has a genetic- based migraine kind of things; that doesn't mean that you might develop the disease, it means that you have a predisposition for the disease.

Dr. Pozo-Rosich (26:31): And then once you actually have the disease coming in and out with attacks, we might also be able to more or less give you, you could say this footprint or fingerprint in the sense of understanding what type of peptides of molecular aspects, or differentiate migraine at a molecular way, at least with the most-known prevalent peptides that we have nowadays. And I think probably that can be something that might happen in the future. And then we might also start to understand why certain patients respond to certain treatments or not. And that can also be something that might be happening in, you could say in the near future. The near future for you to understand, though, in science is at least a gap of five years. So, five to 10 years, what I'm talking about now might get to the market in five, 10 years.

Kellie Pokrifka (27:33): Do you feel like biomarkers actually help reduce stigma around diseases?

Dr. Pozo-Rosich (27:38): I think that the main thing that will happen with that is that we will reduce stigma a lot. So suddenly, this disease becomes real. It grounds itself in a way, we're able to measure it. I think already, by these new biological treatments, very disease-targeting treatments, I think there has been already an important change, but it will keep on going in this path if everything goes well as planned.

Kellie Pokrifka (28:08): Where can we learn more about your work? And specifically, I would love for you to talk about your work for translating some of this information into Spanish.

Dr. Pozo-Rosich (28:17): Yes. Well, we developed actually the whole — I can share with you how the whole thing came about. I've been doing headache medicine for 20 years now. And initially, especially the first, I would say 10 to 12 years, I was quite alone, which means that I was really handling a lot of patients with very short time. And I quickly realized that I didn't have the time

that I wanted to actually, first of all, educate enough, or — exactly — educate patients, so share with them some important information I believed that would help them manage their migraine better. So with all of this, I thought of a tool that could help me, and by helping me, I hope it has helped others.

Dr. Pozo-Rosich (29:06): We developed more than 10 years ago a website that we called Mi dolor de cabeza [midolordecabeza.org], which actually means "my headache," that is thought to be a place where all of these needs are connected, which means really giving tools for physicians and patients alike, I would say, on how, first of all, they can have information, so educate them about migraine. There's a fun test that you can do to actually diagnose — kind of self-diagnose. There [are] also different tools and diaries that can be used so that you're prepared when you go to a physician's visit. And yeah, there's a bunch of stuff that can be used by patients. And also, part of our mission, and goal, or initial vision even was also to help any type of physician that was treating patients, mainly, usually it's primary care physicians, but not only general neurologists too.

Kellie Pokrifka (30:13): And we need that so much. Dr. Pozo-Rosich, thank you so much for being on the Migraine World Summit.

Dr. Pozo-Rosich (30:19): Oh, thank you for the invitation. It's a pleasure to be participating in such a fun and educating event that happens around the world. Thank you.