MIGRAINE WORLD SUMMIT

TRANSCRIPT

INTERVIEWS WITH WORLD-LEADING EXPERTS

BEYOND 50: INSIGHTS INTO MIGRAINE THAT AGES WITH US

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Introduction (00:05): It seems that they are as good responders as people with the age group under 60, and [with] no safety issues and no tolerability issues. But this is a very selective group of patients that we include in the clinical trials. And we know that in clinical trials, most of the people included in clinical trials have almost no other comorbidities. But in real life, in clinical practice, we know that in people over 60, they have some comorbidities. And the question is: When we have multiple comorbidities, what is the safety and tolerability of these medications that we're going to use in this population?

Paula K. Dumas (00:48): Does migraine ever just go away on its own? If you're under 50, you may have heard that migraine often improves with age. Yet that's not true for everyone, says a new study published this year by our next guest. It can become even trickier to manage in older age due to changing hormones, comorbidities, and age itself. Dr. Messoud Ashina is the past president of the International Headache Society and one of the most prolific migraine researchers on the planet. We are honored to share his groundbreaking insights with you here today. Dr. Ashina, welcome back to the Migraine World Summit.

Dr. Ashina (01:25): Thank you, Paula. Thank you for inviting me.

Paula K. Dumas (01:28): So, what is the typical pattern for migraine onset and peak?

Dr. Ashina (01:32): Migraine typically onsets as an early adult. And it usually peaks in middle life and quite often in most of the cases, becoming less severe in later years.

Paula K. Dumas (01:49): So why should somebody in their 20s, 30s, and 40s understand this pattern?

Dr. Ashina (01:55): Well, because understanding the pattern early, as you said, that during the 20s and 40s usually enables effective management. And in this way, we can minimize the migraine's impact on one's quality of life and also [on their] career. And we know that the migraine is a disease which is associated with disability. That's why it's important.

Paula K. Dumas (02:24): The study that I had read that I wanted to ask you about said that if migraine started before the age of 18, there was a higher prevalence of migraine in old age. That 1 in 3 people who had migraine before the age of 18, it persisted into old age. Is that consistent? Has that been proven elsewhere?

Dr. Ashina (02:47): Yeah, I mean, if we look at the prevalence, especially when we talk about the children in this age group, we see no real difference between boys and girls. So the prevalence is the same. But then, during puberty you see this shift; the difference, the more women affected compared to men. And this becomes more and more progressive with age; the prevalence increases in the women population compared to the men. So age-related and sex-related changes are very important. They're coming; let's put it that way, in tandem, together. And what we see that, again, going back to the burden of migraine, it really strikes during the most productive age of people's life, something like between 20 and 50 years old. So that's why this age-related and sex- related changes during life — the migraine evolution is important.

Dr. Ashina (03:54): And that's why we try to bring more attention to this aspect also in our paper about these mechanisms, the possible mechanisms. There are many things we don't understand about the migraine — the migraine pathophysiology. And one of the things we don't understand is this natural evolution of migraine; why for some people it goes this way and for

other people it goes in a more progressive way? Why some people transform from episodic to high frequency and then to chronic or vice versa? We don't know exactly the reason for that.

Paula K. Dumas (04:27): Yeah, it is fascinating that the patterns change so much. There was a 2019 study that showed that the elderly and disabled population have a relatively high burden of migraine, 16% or so, which is almost as high as the 18- to 44-year-olds. And that blew me away. How can that be?

Dr. Ashina (04:49): Yeah, this is a good question, Paula. I wish I could answer this question, but things are quite complicated. Again, it would go back to the migraine pathophysiology. One of the conditions that I can compare migraine with is asthma. We would usually see that asthma is very prominent in young age — again, the most productive years of life. But then it kind of gradually evolves and goes away with age. You can also talk about the hay fever when you have an allergy. It also [gets] better with age. So in most of the cases of migraine, fortunately, it goes — I mean, it is not progressive in this context. But again, going back to the main message of our paper is that we also have this population, older adults, which is important to study because we do see some people keep coming to our clinics with migraine at this age, over 60. And the management of these patients — this is what becomes complicated and challenging for many clinicians, including myself.

Paula K. Dumas (06:00): So there's a silver tsunami that's coming, and there's a disproportionate percentage of the population that's over 60, and this creates a big public health issue, right? Has this segment been well-studied in clinical trials?

Dr. Ashina (06:12): Unfortunately, this segment [has] never been studied properly in clinical trials. And this is a problem. We have some post-hoc analysis with some of the people who were included in the clinical trials, the age [group] over 60. They've been extracted from this material and looked [at] in terms of the efficacy and safety. It seems that they are as good responders as people with the age group under 60, and [with] no safety issues and no tolerability issues. But this is a very selective group of patients that we include in the clinical trials. And we know that in clinical trials, most of the people included in clinical trials, they have almost no other comorbidities. But in real life, in clinical practice, we know that in people over 60, they have some comorbidities. And the question is: When we have multiple comorbidities, what is the safety and tolerability of these medications that we're going to use in this population?

Dr. Ashina (07:15): And because, in my opinion, the clinical trials discriminate [against] these people, the lack of the data creates also some challenges for us. Because the patients ask us, "OK, if I have this and this disease, is it safe for me to take this?" And another aspect we also forget is that the people with comorbidities also take some other medications. And we don't know whether there [are] any interactions between these medications and the new medications, especially with the new biologics that we are now using — widely using — in clinical practice. So all these aspects are important, and that's why we think that the clinical trials, they should include the patient group with age over 60 and study them specifically, maybe also as a separate population.

Paula K. Dumas (08:04): So, let's get to the landmark study that you recently published in *Lancet Neurology.* Did this study follow individuals over time or examine epidemiological patterns?

Dr. Ashina (08:15): This article or the study was a comprehensive review about the aspect of migraine in older adults. We carefully reviewed the literature about epidemiology patterns

among the older adults. We focused on prevalence; we focused on characteristics and treatment approaches. We found some differences also that … because what we found that episodic migraines occur infrequently and may have less predictable patterns, while [with] chronic migraine, they may exhibit more stable patterns in this. And this is a typical patient group that we see in clinical practice — this age group over 60 — that the people in this group, they have more, let's say, high-frequency or chronic migraine rather than episodic migraine. It could be less intense, maybe, in some patients, but still very frequent.

Dr. Ashina (09:21): And another aspect of this paper was, Paula, that we looked at the possible pathophysiological mechanisms related to aging and changes in pattern. Because we do know, we do recognize that the migraine becomes, let's say, less frequent and less intense in most of the patients, fortunately. But many people, they still suffer. But we discuss these mechanisms, and it could be that the possible explanation that some people still suffer from migraine [over the] age [of] 60, and maybe frequent migraine. For some, there are some biological, let's say, underlying mechanisms for that. So we try to bring some multiple mechanisms explaining the evolution of migraine with the age in context to pathophysiology and try to explain this aspect. The problem is, again, by reviewing all this literature, we found that there are very, very few, let's say, research and articles focusing on these aspects.

Dr. Ashina (10:28): And this is also one of the objectives of this paper: to provide the comprehensive review of the topic and encourage people interested in migraine research, epidemiology, or pathophysiology. And also, people interested in the treatment management, people advocating for clinical trials in this group of patients. We want to bring focus on this topic, and that was a main objective of this article. So that's why we consider that very important and timely. But the problem was that we kind of struggled to find the new literature over the past five years to put something like advanced, some advances in this field. So that was a problem for us, but I think it's also very sad for our field that we don't have so much focus on that.

Paula K. Dumas (11:27): Well, I'm really glad that you are shining a spotlight on this segment because we've got so many people in our community who are like, "Yes! Finally, someone's paying attention to those who are over 55 or 60 and still struggling with this, still suffering." Aura can be more prevalent as we age. How else does the clinical presentation of migraine change as we age?

Dr. Ashina (11:50): Yeah, this is a very good question about the aura, Paula. Because usually, when we see patients in the age group between 20 and 50, we do not see so many people suffering from frequent auras, frequent auras in clinical practice. Most of the people with migraine, they report migraine without aura and coexisting migraine with aura, which is infrequent. And maybe some of them they had only two to four attacks during their whole life, or some of them, they maybe have one or two attacks per year. But we do see some people with the frequent auras every month or each migraine attack associated with aura. But with age, something different happens. What happens is that people having auras associated or followed by the migraine headache with all associated symptoms suddenly change the pattern. People start having auras without headache and what happens also [is] frequent auras without headache.

Dr. Ashina (13:03): So there [are] some age-related changes. In particular, when we talk about aura mechanisms, it's very interesting. We don't have a good explanation for that. But if you have frequent auras, believe me, this is a clinical — and in terms of management — challenge. I

mean, it's a real challenge because we don't have specific medications, specific medications to stop auras because they're pretty short-lasting. We all know that they're usually something like between 20 and 30 minutes. And another problem is that we don't have specific medications that we know that they might target the mechanisms underlying aura. We do hope that the medications that we usually use for patients without aura, they can be also used, applied for people with aura, even people with aura without migraine headache. But we don't have any data for that.

Paula K. Dumas (14:03): Yeah, I've talked to a number of people who have said that the presentation of their symptoms has changed dramatically over the course of their lives, and now that they are over 50 or over 60, as the case may be, they might have all of the other symptoms minus the headache and the nausea, which are less frequent. But as you say, aura, photophobia, phonophobia, just all that sensitivity that we experience, and of course cognition — we don't know whether to attribute that to normal aging or not. But I'll come back to that in a second.

Dr. Ashina (14:40): Another thing in regard to aura, Paula, I'd like to mention also that some people with migraine, they report onset of migraine after age 50 or sometimes 60, which is quite unusual. This is something like we usually consider as a red flag. Because it's late onset, right? We always think about the secondary cause for that, but fortunately, in most of the cases it is a primary headache. But what is interesting, they start having auras. So the usual debut, what you see in this age group over 50, over 60, is the first onset of aura — not so much first onset of migraine with headache, but migraine with aura. And we don't know about that. So why you see this, let's say, late onset specifically with this subtype of migraine.

Paula K. Dumas (15:41): Clearly, more research needs to be done with that population and with that pattern. So, speaking of patterns, many people in our community have chronic migraine. What factors make chronic migraine more likely to persist in later life?

Dr. Ashina (15:57): Yeah, but there are different factors. There are some factors that we call modifiable factors and some factors nonmodifiable, so unmodifiable. So, something that we cannot really change — the genetics, right? Or disposition, susceptibility for migraine, your individual threshold. Some people, they develop chronic migraine, some people they do not develop chronic migraine. As I mentioned before, many people in this age [group], when they report to the clinics, they report more high-frequency or chronic migraine. What is the reason for that? How the age [and] how this evolution plays a role? The underlying exact mechanisms, we don't know. Some of the modifiable risk factors — we know about the medication overuse, right? And if, let's say, attacks stay frequent and not really severe like it used to be, still people might take too much medications. And we know that the triptan, specifically triptan overuse, is associated with a transformation from episodic into chronic migraine. So, this is something that is generally accepted and we know how to manage that.

Dr. Ashina (17:12): There are also different factors, other factors that we know that they're associated with chronic migraine, and they considered to be as risk factors for development of chronic migraine. I can mention like obesity; I can mention chronic diseases in general; the smoking can also be in this context. But if we are going, again, to age-related aspects or factors, then we can see with age we also have development of metabolic syndromes, which we call it as an umbrella of the different conditions such as diabetes, obesity, hypertension, cardiovascular diseases. You can treat them, and we don't know how the successful treatment of these conditions will affect migraine. In my clinical practice, not too much, unfortunately. Regarding

obesity, we don't know yet because we don't have a good trial showing that, well, in fact, that if you really reduce the weight, you can improve the migraine. We don't have data on that.

Paula K. Dumas (18:21): It's so difficult. I know so many people who are over 50 and are just continuing to struggle because they have more than one thing that they're trying to manage — migraine plus these comorbidities. So we do have another talk on menopause this year, but I wanted to ask you how changing hormones like lower estrogen and testosterone affect our migraine experience.

Dr. Ashina (18:44): Well, this is also a very interesting question about the hormonal fluctuations. And what is important to note here is that during menopause for women and also for the andropause for men, all these factors, they can really alter the migraine frequency, intensity, but also the symptoms: They're not maybe as pronounced [as they] used to be before. But you also see sometimes an increase [in attacks] after menopause. It is — for most of the cases we see — improvement with age. But we cannot put it exactly for the menopause because we do see many patients coming back, and they have been in menopause for years, but they still have frequent migraine attacks. So, this is [an] important aspect, but there is no doubt that the hormonal changes and migraine experience, they're coming together. And we do see that, like a cycle-related migraine before and after menopause. There are many aspects also related for that. For men, we see the same when they go to this age — andropause. So we also see that there are some changes, but for some people, you see that it goes up, it becomes more frequent.

Paula K. Dumas (20:09): It certainly seems like a good reason to go back and see your physician regarding migraine. If you're using some of the same treatments that you used when you were younger, when your hormones were different, and now your body is reacting differently, you might have comorbidities, changing hormones. Seems like a good idea to go back and just reestablish with your headache specialist or neurologist and, "Should I be on the same plan, or should I be taking something different or trying something different?"

Dr. Ashina (20:39): Absolutely, I agree. So, what is important here is that we also provide some kind of consensus guidelines also for this specific age because we do have some consensus or guidelines for the age group under 18. It's about the migraine in general in adults. But we don't have a specific [guideline for] older adults. So we came up with some suggestions in this paper, but again, this is based on the consensus. By the way, I have to also acknowledge all my co-authors in this paper because it's not a paper coming from Denmark. It is an international consortium of people coming from the different countries. And we did have a consensus of everything that we wrote in this paper, including the recommendations for the treatment. And we all agreed in this paper that we need to bring more attention to this group — in older adults, migraine in older adults — in order to improve our assessment of these patients. And also most importantly, [the] treatment of these patients.

Paula K. Dumas (22:00): I would love to see guidelines for people over the age of 50, 55, or 60. That would be amazing, and I bet we could get a lot of patient advocates willing to help with the development of those. So, if a person over 50 is struggling with memory issues, as we do sometimes, how can we determine if it's normal cognitive aging, migraine brain fog, or early dementia?

Dr. Ashina (22:28): I don't want to say early dementia. The question is, when we talk about the cognitive problems, are they related to pain? Are they related to the head pain? Because in any

kind of pain, your performance, your cognition cannot be compared when you are asymptomatic. But some people claim that maybe patients with migraine, they have some impairment — cognitive impairment. But the good news, Paula, is that there have been a number of studies, including very good population-based studies, showing that there is no difference between migraine patients and people without history of migraine. So when you compare these two populations, there was no difference. In addition, there was a study — I don't remember, that was many years ago — that looked specifically at patients with aura also and compared them again to the background population. And they found that they had better performance — cognitive performance — than the background population.

Dr. Ashina (23:29): So, I'm a migraineur myself, so I'm very happy about my cognition. But of course, during the attacks, my performance is not the same. So we can all recognize that. There are some studies suggesting that [there] could be associations with dementia [and] with other conditions. But the problem is, Paula, when we talk about [this] very, very prevalent disease, the likelihood that it can overlap with any other diseases, any other conditions, it's quite high. We do see sometimes, a paper coming up saying that, well, there is association with Parkinson's, there is association with epilepsy, with depression, with anxiety, with dementia. I think we have to be very careful when we interpret these studies. Even with the depression and anxiety, because in my opinion there was some backlash, there was some negative side of that because people created stigma around the migraine, that it's all about the depression and anxiety, which is not true. So I consider them two independent conditions.

Dr. Ashina (24:35): And that's why, when we talk about the cognitive disturbances, I usually explain to people with migraine coming to clinics — to my clinic — that this is something that we usually relate to high-frequency migraine. Because when you are suffering from migraine every week, what you would expect and what we see that when we give new medications — specifically new medications — and when we see how they improve the quality of life, we also see that some of the symptoms that we call depression, anxiety — that goes away. And the same in terms of the cognition, the cognitive performance. I do see patients now coming back to me and saying, "Wow, I have now so much energy. This migraine fog, like you said before, it's gone." So it says something about the migraine biology.

Dr. Ashina (25:36): So, this is just a consequence because our system, our limbic system, our memory, our performance [are] affected when we suffer all the time of this repetitive condition. Fortunately, for most of the people with a very episodic migraine, it is not a problem. But with the population that we see with frequent migraine attacks, they do have this problem. But I relate this problem to migraine, but not, let's say, the brain disease or something else that associated with migraine. No, for me, it is just consequence of migraine.

Paula K. Dumas (26:18): Well, that's very encouraging. And I just want to restate that what you've said is that migraine and memory issues might travel together, but they're not necessarily correlated. Kind of like migraine and depression and anxiety travel together, but they're not necessarily correlated. And when you focus on treating the migraine as you can with some of the new therapies that are available, then the cognition issues often get better as well, correct?

Dr. Ashina (26:48): Absolutely correct.

Paula K. Dumas (26:50): Wonderful. So, for people who have current chronic migraine or former chronic migraine, what kind of proactive steps can we take to reduce the impact of migraine as we age?

Dr. Ashina (27:03): I mean, there are some — many factors. I would say we can engage with the different strategies, like stress reduction. And sometimes also maintaining a headache diary can also help to see how frequent migraine is. And again, this will induce contact [with] a physician, so you can bring it. It's kind of a patient engagement in this context, very important. Because we don't expect the physicians asking all the questions when we go and talk to our family doctors. So that's why if it's a problem, it's important to document that and confront that, you know, this problem, and your physician should take care of that. And we also need to, in my opinion, stay updated. We advise them to stay updated with the new therapeutic approaches and also the different health aspects, such as — we talked before about — lifestyle modifications. They can also be very important, a priority to mitigate the migraine impact with age. So it's very, very important.

Paula K. Dumas (28:25): Well, you might just have some people flying into Copenhagen to meet with you after this interview because you've shared so many brilliant nuggets of insight with us that I think will encourage many people who are continuing to struggle with migraine in their 50s and 60s and beyond. So, anything else that you'd like to add about this study or this topic that we haven't covered?

Dr. Ashina (28:49): I just want to encourage people to read this paper that if they're interested about that. And I would also like to say thank you also for the Migraine World Summit because this is [an] important forum, which in my opinion, brings many interesting aspects of migraine and primary headaches and creates awareness about this topic, such as migraine related to age is very, very important. So I'm happy to be part of this conversation today, and I hope that the people find our conversation also interesting.

Paula K. Dumas (29:25): Well, I know they will, and we absolutely couldn't produce it without your brilliance and that of many of your colleagues. So, thank you so much for your generosity for being here with us today. Where can people learn more about what you're doing or follow your work?

Dr. Ashina (29:39): Well, my work, usually what I do is I post all our articles and papers coming from my group on my Twitter (now it's X). So this is the place that you can follow my work, primarily. We do have also a Danish website, but I think it'll be difficult to read in Danish. But nowadays, with Google Translate you can do it. Internationally, my colleagues are following me on PubMed. They can always see in the databases all the articles coming from my group, but otherwise we post them in our Twitter, my own Twitter, my name, or we have a Human Migraine Research Unit Twitter, and all the new stuff is always there. And we do have a link to all the papers, so all the people, they can follow my research there.

Paula K. Dumas (30:34): Well, Dr. Ashina, thank you so much for your incredible body of research that is giving us new light on this condition called migraine that we all live with. We deeply appreciate that. And thank you for joining us on the Migraine World Summit.

Dr. Ashina (30:49): Thank you. Thank you for inviting me, Paula.