



MIGRAINE WORLD SUMMIT

TRANSCRIPT

INTERVIEWS WITH WORLD-LEADING EXPERTS

IS MIGRAINE LINKED WITH COGNITIVE DECLINE OR DEMENTIA?

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Introduction (00:05): My view is the following: If you have migraine today and you use effective acute treatments, you change your lifestyle, use effective preventive treatments, you will certainly improve your life today. And you may well prevent trouble in the future, too, by reducing your risk of stroke, and reducing your risk of dementia, and reducing your risk of other negative health outcomes.

Carl Cincinnato (00:36): Many of the risk factors for migraine overlap with the risk factors for dementia. Is that where the links start and finish, or is there more to it? There's research that supports both sides of the debate. Does migraine increase the likelihood of cognitive decline and dementia later in life? If so, what can we do today to intervene? To help us navigate this controversial topic is Dr. Richard Lipton, one of the world's leading researchers in migraine and headache. Dr. Lipton, welcome back to the Migraine World Summit.

Dr. Lipton (01:03): Thank you so much. I'm thrilled to be here.

Carl Cincinnato (01:06): Let's start by reviewing: What is a risk factor?

Dr. Lipton (01:11): A risk factor is a characteristic that's associated with a higher likelihood of a negative health outcome. So a risk factor for migraine would be associated with a higher risk of having migraine. And examples of migraine risk factors include being a woman, being a person in midlife between the ages of 25 and 55, and so forth. Just because something is a risk factor, that doesn't mean that it's a cause of the disease. It could just be something associated with the disease and not a cause.

Carl Cincinnato (01:53): I like the example that you used in the debate that I saw at the medical conference recently, where you said matches and lighters are risk factors for smokers, but it doesn't necessarily cause cancer on their own.

Dr. Lipton (02:04): Right. So the idea there is: If you did a study where you identified people with lung cancer, you might find that people with lung cancer are more likely to carry matches, but of course we all know that matches are associated with lung cancer because smoking is the risk factor, and matches are just coincidentally associated with smoking.

Carl Cincinnato (02:34): What is dementia?

Dr. Lipton (02:36): Dementia is a clinical syndrome that's characterized by a loss of memory, or language function, or problem-solving ability, or other kinds of thinking abilities. And by definition, cognitive problems in dementia are severe enough to interfere with everyday life — with social functioning, with occupational functioning, or with maintaining independent living.

Carl Cincinnato (03:07): And what do we know causes dementia?

Dr. Lipton (03:10): So, the clinical syndrome dementia has many, many causes. In older adults, the most common and most feared cause is Alzheimer's disease. And the bottom line is that dementia is the overarching category and could be caused by Alzheimer's disease, by multiple strokes, by other disorders like Lewy body disease (LBD), or even vitamin B-12 deficiency or hypothyroidism.

Carl Cincinnato (03:45): And what has the research found between the links of dementia and migraine?



Dr. Lipton (03:51): So, there have been multiple studies now that identify people with migraine, follow them along, and ask the question: Do people who have migraine develop dementia at an increased rate? And there have been two large-scale summaries of the studies that examine migraine as a dementia risk factor. And broadly, what the studies find is that if you have migraine, you're about 33% more likely to develop dementia than if you don't have migraine.

Carl Cincinnato (04:31): Is that something that we should be alarmed about? What's the chances that we will develop dementia later in life?

Dr. Lipton (04:37): Yeah, well, so that 33% increase does sound frightening. I think it's worth pointing out that we know many, many risk factors for dementia, and the way I like to think about risk factors as this: I like to divide them into those that we can do something about and those that we can't really do much about. So for example, age is a risk factor for dementia, and risk of dementia goes up, doubling every five years after the age of 65, but age itself is not something we can do much about. The calendar marches on, no matter what we do.

Dr. Lipton (05:21): But high blood pressure, diabetes, obesity, spending too much time being sedentary, inflammatory disorders are among the many dementia risk factors that we can do a lot about, although my view is the following: If you have migraine today and you use effective acute treatments, you change your lifestyle, use effective preventive treatments, you will certainly improve your life today. And you may well prevent trouble in the future, too, by reducing your risk of stroke, and reducing your risk of dementia, and reducing your risk of other negative health outcomes.

Carl Cincinnato (06:11): And in fact, there was actually a study published that said the use of medication in migraine, regardless of the type of medication, actually reduced the dementia risk. Is that right?

Dr. Lipton (06:24): Yeah. So, there is some evidence that better migraine treatment reduces dementia risk. I think we need more studies evaluating the benefits of effective treatment on reducing dementia risk. But effective treatment of migraine — as this audience unfortunately knows, or [rather] fortunately knows — can have a very positive effect on your life today, and the benefits tomorrow are a fringe benefit.

Carl Cincinnato (07:00): And the two tips that I've been given that I've found really helpful and just simplify the whole diet question — because people ask what's the best diet and what should we be doing? The two tips that I've been given are the less processed food you eat, the better, universally. And then, the best research suggests that a diet higher in omega-3s and lower in omega-6s is also potentially helpful, specifically for migraine. It's also good for the brain. Is that what you've heard as well, Dr. Lipton?

Dr. Lipton (07:29): There is a diet pattern called the Mediterranean diet, and that's a diet that's based on plants, whole grains, fish, beans, nuts. And that diet is the best demonstrated diet to protect against dementia, but also perhaps the best diet you can follow if you want to reduce your risk of migraine as well.

Carl Cincinnato (07:55): Fantastic, very helpful. You were involved in a debate about this topic, migraine and dementia, at a recent medical conference, where one speaker said that there were 10 prospective studies that showed that migraine was not associated with dementia. They also



argued that some of the studies were of people in their 40s, which is way too young. How conclusive is the research?

Dr. Lipton (08:17): Studying the relationship between migraine and dementia is a little bit difficult. One reason for that is that migraine is most common between the ages of 25 and 55. And for dementia, risk doubles every five years after 65. So it goes from 1% at 65, to 2% at 70, to 4% at 75, and so forth. And the problem — from a research perspective — is that migraine often remits in later life. Now it doesn't remit in everybody, and I know that there are people with migraine who've had it as a lifelong disorder and continue to have it past menopause and into their 70s, and that is a real burden for sure. But the major pattern is that migraine remits as people get older. So in women, for example, in midlife, maybe 30% of women have migraine, and by the time you reach the age of 80, perhaps only 5% of people have migraine.

Dr. Lipton (09:27): And the problem is when you study migraine-dementia links people who had migraine earlier in life but haven't had it for 20 or 30 years, may well not remember the details of their migraine, and it may be difficult to determine whether or not they had migraine in the past. And that limits a study design called the case-control study, where you find people who are cognitively normal and people who are cognitively impaired, and you interview them about their lifelong history of migraine. In addition, of course, people who have cognitive decline may be more likely to forget that they have migraine. So I would say that there's no question that there are negative studies, but the summary data that I presented at the beginning is a summary of 12 or 13 studies that enrolled a very large sample. So I think the migraine-dementia connection is quite robust, even though not all studies are positive.

Carl Cincinnato (10:41): This is why it can be so challenging for a patient. You can find research, a published study, that confirms one argument and then another that contradicts it and says the other thing. And that's why it's so helpful speaking to you, Dr. Lipton. So, thank you.

Dr. Lipton (10:54): It may be worth saying, though, that there is a widely used methodology called meta-analysis. And when you do a meta-analysis, you identify a question you want to answer: Is migraine a risk factor for dementia? You systematically review all the relevant publications. You specify criteria for good studies, in terms of the way they measure migraine, in terms of the way they measure dementia, in terms of the study design. And then you take all the data from a large group of studies and you look at what's true on average across studies. And the meta-analysis I cited at the beginning included nearly 300,000 people — which is why I think the finding is robust — and that 33% increased risk was the weighted average across all the studies.

Carl Cincinnato (11:55): And that would be pretty exciting to be able to show that reducing migraine reduces risk of these cognitive issues later in life potentially.

Dr. Lipton (12:04): Yes, and it may be worth saying that people with migraine often have negative cycles, and we know that the more headaches you have, in many people, the more headaches you get. And we know that if you have effective acute treatment, that reduces your risk of having headaches worsen over time.

Carl Cincinnato (12:28): I remember you said a couple of years ago in the Migraine World Summit that pain begets pain. That's become somewhat of a famous quote of yours among our community, and that's so true.



Dr. Lipton (12:39): Well, it's terrible. People get into a pain trap, and then I work with my patients very hard to get them out of the pain trap.

Carl Cincinnato (12:51): Yeah, it's incredibly difficult. And I still tell people, when I'm asked at times, that crawling out of chronic migraine was the most difficult thing I've ever done. It's really, really difficult and not something to be underestimated. One of the things that you uncovered in the pathways that migraine and dementia share was cerebrovascular disease. Can you tell us what that is and some examples of those diseases that link migraine with dementia?

Dr. Lipton (13:18): Right. So, first, let me say that when we think about whether a risk factor actually contributes to the development of the disease, one of the things we look at is something called biological plausibility. Biological plausibility means: Does it make sense that migraine should be a risk factor for dementia? Is there a plausible mechanism that links migraine to dementia? And there [are] several plausible mechanisms for the linkage, which increases my belief that migraine really is a causal risk factor for dementia. So, one of them is stroke. We know that migraine, particularly migraine with aura, is a risk factor for stroke, and stroke is a family of cerebrovascular diseases. So "vascular" means of or pertaining to the blood vessels; "cerebro" means in the head; so "cerebrovascular" diseases are diseases of blood vessels in the head.

Dr. Lipton (14:32): And we know that migraine increases risk of clinical stroke, of subclinical stroke (meaning the patient is asymptomatic, but if you do an MRI, you can see the stroke), and also of a phenomenon called white matter hyperintensities, which are abnormalities in the parts of the brain that connect the regions that do information processing. We know migraine, particularly migraine with aura, is associated with all of those conditions, and we know that all of those conditions are associated with an increased risk of dementia.

Dr. Lipton (15:13): Now, it may be worth saying that the two most common causes of dementia in older adults are Alzheimer's disease and what's called vascular dementia. And when you examine the brains of older adults, you find that the two conditions — Alzheimer's disease and vascular dementia — co-occur with very high frequency. And it turns out they are mutually exacerbating, which is to say, at any given level of Alzheimer's disease in the brain, if you also have strokes, the impact on cognitive function is worse. And if you have strokes but you also have some Alzheimer's disease, the impact of stroke is worse, as well. So the idea here is that one of the mechanisms that may link migraine to dementia is that migraine causes an increased risk for stroke, which itself causes an increased risk for dementia.

Carl Cincinnato (16:19): Tell us about the glymphatic drainage and how that may be a component of migraine and a potential pathway to dementia.

Dr. Lipton (16:27): Sure. So, there is a system in the brain that helps remove toxic proteins and other toxic compounds from the brain, and it's called the glymphatic system. Its name is derived from "lymphatic," because the lymphatic system in the body is a system that we use to remove toxins or bacteria — you know, not from the head but from the rest of the body. So we know if the glymphatic system is not functioning well, certain toxic proteins accumulate in the brain, including amyloid and tau, which are the toxic proteins that cause Alzheimer's disease. And Rami Burstein's group has shown us that during headache attacks, the glymphatic system closes. So migraine attacks interfere with the system that is in the business of removing toxic proteins from the brain. If those toxic proteins accumulate, that increases dementia risk. Incidentally, the glymphatic system works best during sleep. So if sleep is disrupted, that can also interfere with



the clearance of amyloid and tau from the brain and may be one of the reasons that fragmented sleep is also a risk factor for dementia.

Carl Cincinnato (18:05): That's so interesting. I mean, that alone could be a reason why there's an association between migraine — because so many people we know have migraine and have sleep disorders — and its connection to dementia, which is also potentially associated, I would suspect, with people who have lifelong sleep disorders, as well.

Dr. Lipton (18:23): So, when people think about the association between migraine and sleep, well, one possibility is that migraine and depression occur together, and depression is a major disruptor of sleep. Another connection is through sleep apnea, which is that disrupted breathing pattern that you are most likely to find out about if someone you sleep with reports to you that you are snoring. But there is a third migraine-sleep connection, which we recently described, not at the most recent AHS [American Headache Society] meeting but at the meeting before that. And that is that many people have migraine at night that interferes with sleep. So pain itself can keep you from falling asleep or keep you from staying asleep. And something like a third of people with migraine experience sleep disruption due to headaches at night. And that's a neglected area, at least in my view.

Carl Cincinnato (19:28): Yeah, absolutely. I mean, it's hard to sleep when you've got a raging migraine attack. So, pain's obviously part of migraine, and part of dementia, and part of sleep disruption. Is stress and inflammation, as well?

Dr. Lipton (19:42): So part of the reason that a link between migraine and dementia is plausible is through mechanisms related to pain, stress, and inflammation.

Carl Cincinnato (19:54): That makes a lot of sense. So, pain, stress, inflammation: common in migraine; also common in dementia. And you mentioned depression, as well. That could be another — again, this comes back to that vicious cycle, right? You mentioned before that people as they get older tend to worry about cognitive decline and maybe that's being the early signs of dementia. Is there any evidence that migraine causes cognitive decline over the medium to long term?

Dr. Lipton (20:24): Yeah, so there is some evidence that migraine causes cognitive decline. Measuring cognitive decline is a little bit tricky because, to measure it, you need to administer serial cognitive tests. So you would need to bring people in once a year and give a cognitive battery over multiple years. But I would say that there is some evidence that migraine is a risk factor for cognitive decline. It may be worth saying that when we look at cognitive decline in older adults, it's traditional to divide the decline into what often is called normative and nonnormative decline. So normative decline is what happens to everybody as we get older. We process information more slowly, we learn more new information more slowly, and so forth.

Dr. Lipton (21:24): But then there's also what is called nonnormative cognitive decline, and that means decline related to diseases. And again, the diseases that contribute to cognitive decline are the same ones that cause dementia: everything from Alzheimer's to strokes to vitamin B12 deficiency to hyperlipidemia. There are multiple mechanisms that lead to cognitive decline. And one of the challenges in older adults is distinguishing the cognitive decline that's part and parcel of the normal aging process from the cognitive decline that is an early warning that dementia is impending. And one of the reasons that's difficult is that in many people, we don't have a baseline assessment. So, there's a condition called MCI (mild cognitive impairment), and that's



defined by performing below the mean of your age and education mates to a particular degree. But if you perform, say, two standard deviations below the mean on a cognitive test, one possibility is that you've lived there your whole life, and you're just fine, but your cognitive abilities are a little bit below average. But the other possibility is that you started with supremely good cognitive function, and where you are now represents a major decline.

Dr. Lipton (23:01): So, when we follow people over time, we mostly can detect change with that caveat about practice effects. But when someone comes in with cognitive complaints, it may be difficult to know where they started. So, years ago, I took care of a physics professor, and this was 10 years ago. She was 80 years old, and she literally performed at ceiling on every cognitive test I gave her, but she was certain that she was slipping. And it took five years before her real decline became measurable on my tests that were designed for people who weren't as brilliant as she was.

Carl Cincinnato (23:46): Yeah, wow. So there is some level of cognitive decline that's natural, and it's part of aging, and we shouldn't be overly concerned about it, but it's hard to tell. Depends where you're starting from. If you're brilliant like the physics professor, then you could still be sort of above the rest of the population but know that maybe something's coming. What about medications? That's the question we've had from our community. Can cognitive decline be accelerated by certain medications we're taking?

Dr. Lipton (24:13): Yes. And there's short-term effects and perhaps some long-term effects. So, it turns out that many of the medications that we use to treat migraine have some cognitive effects. Topiramate would be one example; amitriptyline and nortriptyline would be additional examples. And so, when a person with migraine has cognitive complaints, one of the first things I think about is: Are they on one of these drugs that causes cognitive impairment as a side effect? I mean, the other issue, though, is if you're in pain, if you're very stressed, then migraine itself may cause short-term cognitive impairment, as well. And so in people with migraine, it's desirable to test people between attacks so we're measuring — we're not measuring the effect of an acute attack — but also during an attack. Because then the question would be: "If I develop cognitive impairment during a migraine attack and I take an effective medication, will that effective medication reduce the cognitive burden?"

Carl Cincinnato (25:32): Can fear and anxiety exacerbate or accelerate cognitive decline?

Dr. Lipton (25:36): So, anxiety and stress are both risk factors for cognitive decline, and they're risk factors both on a short-term and a long-term basis. So if someone is in a period of increased stress, their cognitive performance may decline on a short-term basis. When the stress ends, they may fully recover. If someone is under chronic stress, that can be a risk factor for long-term cognitive decline. And many people in your audience know that cortisol is one of the body's major stress hormones. What many people don't know is that cortisol actually gets into the brain and acts on brain cells in the hippocampus, which is a region responsible for memory, and in a part of the frontal lobe, which is a region responsible for planning and executive function. And stress and high levels of cortisol actually lead to volume loss in those brain regions and can lead to long-term cognitive problems.

Carl Cincinnato (26:49): And then we've also spoken about the behavior and lifestyle factors — diet, sleep, movement, exercise — those other things that we can control that can give us the best chance of a longer health span.



Dr. Lipton (27:02): Right? So the distinction between health span and life span is an interesting one. I used to have a study of centenarians where I studied 100-year-olds and their offspring, and my mother at the age of 80 said to me, "You know, not everyone wants to live to be 100." And then she went on to say, "I would want to live to be 100 if I could do everything I'm doing now: if I could still play duplicate bridge, if I could enjoy the grandkids and maybe the great-grandkids. But if I'm going to lose the things that give my life meaning, then I don't want to live to be 100." And health span refers to life with all those things that make life worth living, and that's health span, and life span just refers to your age at death, which is not necessarily something we want to maximize.

Carl Cincinnato (28:04): Are there any final thoughts that you'd like to leave with the audience?

Dr. Lipton (28:08): So, I'd like to close with this thought: That migraine is sometimes viewed as a relatively trivial condition, as an episodic pain disorder — attacks come, people get better, and we don't need to do much about migraine because the attacks are all time-limited. But I do think it's really important to recognize that migraine is, for many people, I suspect including most of your audience, a chronic disorder where at minimum people can count on having recurrent attacks over long periods of time.

Dr. Lipton (28:48): And we shouldn't be surprised that people who have migraine as a chronic disorder have some chronic effects from their migraine. In some people, the migraine itself may progress. In a small proportion of people, they may develop strokes. Some people with migraine on a long-term basis have an increased risk of dementia, as well. And part of the value of viewing migraine from that long-term perspective is that it gives us the opportunity to treat it like a chronic disease and to intervene to relieve burden today and prevent long-term sequela tomorrow. And I would encourage your audience to view migraine from that perspective and to take advantage of the opportunities that arise from our ever-increasing understanding of the disorder.

Carl Cincinnato (29:48): Fantastic. Hopefully we can use this as motivation to take better care of ourselves and seek that quality of life. Where can we learn more about what you're doing and follow your work?

Dr. Lipton (30:01): Goodness. I actually don't have a huge web footprint. The one thing I've been doing for the last year that I really like is, I've been trying when I write papers to include with the papers user-friendly abstracts and sometimes visual abstracts. So if people who are not scientists or physicians want to know what a paper says, they have a user-friendly abstract that will allow them to understand the data.

Carl Cincinnato (30:40): Dr. Lipton, thank you so much for being so generous with your expertise and time today. We really appreciate you joining us again on the Migraine World Summit.

Dr. Lipton (30:48): It's a pleasure and an honor. Thank you.