



# INTERVIEW TRANSCRIPT

DISCUSSIONS WITH WORLD-LEADING EXPERTS

## **How Early Life Stress Affects Migraine Risk**

Serena Laura Orr, MD, MSc

Associate Professor of Pediatrics | Pediatric Neurologist

University of Calgary | Alberta Children's Hospital

Calgary, Alberta



**Introduction** (00:05): Many of us have heard of adverse childhood experiences (ACEs), and their link to chronic health issues. But it's time to get curious about a broader question. If ACEs like neglect, abuse, or other major traumas can impact headache and migraine risk, what about other early life stressors? Dr. Serena Laura Orr is a pediatric neurologist and headache specialist who also leads research, including foundational work on the relationship between early life stress and headache.

**Introduction** (cont.) (00:34): We'll explore how factors beyond the standard ACEs checklist can shape a person's headache and migraine risk, and what that means for management. Dr. Orr, welcome to the Migraine World Summit.

**Dr. Orr** (00:45): Thank you very much. It's such a pleasure and honor to be here.

**Elizabeth DeStefano** (00:49): Let's begin by defining the core concepts that we'll be discussing. Could you first define adverse childhood experiences, or ACEs?

**Dr. Orr** (00:58): Yes, so the traditional definition of ACEs comes from a study that was done a few decades ago, where ACEs are defined according to three categories. So we have abuse — that could be physical, sexual, or emotional; neglect; and exposure to adverse household environments, so household dysfunction.

**Dr. Orr** (01:22): So that includes things like experiencing a divorce within the family, living with someone who's been incarcerated, living with someone who has mental illness, or exposure to domestic violence in the home. So that's the traditional definition of adverse childhood experiences.

**Elizabeth DeStefano** (01:41): And there has been recent professional discussion of expanding the definition of trauma. Why and how has the definition evolved as a result?

**Dr. Orr** (01:52): Yeah, I think that the scientific community and the patient community are really questioning this unique focus on the household that we've had for decades. And looking at — every person lives in a broader context than their household, of course that's our core exposure — but looking at things like community-level exposures that can be traumatic, and even environmental-level exposures.

**Dr. Orr** (02:18): So what I mean by that: If we look at the community, many things in the community that we live in can impact us, like not having access to drinking water, not having access to good employment opportunities, being exposed to systemic racism within the community and outside of the community.

**Dr. Orr** (02:36): And then we're living in interesting times from a climate perspective, and so there's been a call to look at environmental factors as well, like exposure to climate change emergencies and natural disasters that can be very traumatic, like living through an earthquake and seeing people die.

**Dr. Orr** (02:54): So I think we're trying to look at it more broadly to encompass things outside of the household that can be traumatic as well. But I have to say that that approach hasn't really been adopted universally into the research yet, mostly because the tools that we have to measure ACEs are still the older tools that focus on the household exposures.



**Elizabeth DeStefano (03:17):** Before we get into your research specifically, let's talk about what is known generally about the relationship between ACEs and adults with migraine or headache disorders. What is the increased risk in the presence of trauma in early years?

**Dr. Orr (03:32):** There've been quite a few studies that were recently pooled together in a 2023 type of study that we call a systematic review and meta-analysis. So what they did is they looked at all studies of people that reported exposure to ACEs in childhood and that had headache disorders measured in adulthood.

**Dr. Orr (03:54):** So it included — most of the studies were looking at migraine. At least half of them were looking at migraine, but other headache disorders were included as well, like cluster headache and tension-type headache. And what they found is that across all of the different studies, there is a consistent elevated risk to develop a headache disorder if you've had exposure to ACEs as a child.

**Dr. Orr (04:18):** And the risk level depends on what exactly you're looking at. So there are differences between the types of exposures and the risk, but overall, if you've had exposure to an adverse childhood experience, you have 50% higher odds of developing a headache disorder, including migraine. And we don't understand as much the link between specific types and the risk of headache disorders and migraine, but it seems from this study that neglect and emotional abuse may be the most potent risk factors.

**Dr. Orr (04:52):** The other thing that was interesting about this 2023 study is that they looked at how many ACEs you were exposed to and the risk of developing a headache disorder. And they found something that we call in the research world a dose-response relationship.

**Dr. Orr (05:08):** So that's where you look at how many ACEs, and then the risk, and we see that with increasing numbers of ACEs, the risk of developing a headache disorder becomes higher. So that if you have had exposure to one ACE, your risk is about 25% higher in terms of the odds. But if you're in the highest category where you have three or more ACE exposures, your odds may be doubled.

**Dr. Orr (05:34):** So what that tells us — I come from some epidemiology training in my master's degree — is that there's a higher chance that there is causality there. So that means that if we can show that with increasing exposure the risk of developing migraine is higher, we are more confident that this may actually be a cause of developing migraine.

**Elizabeth DeStefano (05:56):** So you're speaking really with this dose-response relationship to a cumulative effect of multiple ACEs on risk. And I'd love to come back to that, actually, and talk a little bit more about what that means is happening in the body and brain of someone who experiences that in a moment. I'd love to get into your research specifically, if we can. Your work has obviously been instrumental in exploring the link between early life stress and migraine in children.

**Elizabeth DeStefano (06:24):** Your 2019 study, “Early Life Stress in Adolescent Migraine,” found a direct link between family stress and the onset of migraine. And it was determined that that was through stress's ability to increase anxiety and depression. Then your 2022 review and meta-analysis on ACEs and migraine found the association was not definitively explained by the same mental health symptoms. Can you break these down for us and help us understand the difference?



**Dr. Orr (06:55):** Both of those studies were done on a population-based Canadian dataset. So what that means is that there's an effort to make that dataset representative of all Canadian youth outside of residential care, which is important to say because a lot of the research that has been done on ACEs has been done in clinical populations, and that may not represent everybody living with migraine.

**Dr. Orr (07:16):** And both of these studies followed youth anywhere from birth to age 1, when they were first recruited to the study, all the way out to 14 to 15 years. So it's a really beautiful dataset that allows us to measure ACEs when we think they're highest risk, so in the first seven years of life, and then look at the development of migraine in adolescents. So that was measured at 14 to 15.

**Dr. Orr (07:44):** So the first study in 2019 — the two studies are actually quite different. The first study looked at, like you said, the household-level stress. So these were not ACEs. So this was in the first few years of life, lower-level stress exposures like household dysfunction, maybe just fighting in the house, but not maybe the full extent of domestic violence; living with a parent who has depression; and punitive or aversive parenting. So more harsh parenting styles, but these are not traditionally thought of as ACEs. They are stressful to live with.

**Dr. Orr (08:21):** So in that particular study, we found in the first few years of life that having exposure to lower-level stressors in the home was associated with developing migraine as an adolescent, but not actually directly.

**Dr. Orr (08:35):** So it was driven through the child having higher anxiety and depression in middle childhood, so that perhaps living in a stressful environment, but not full ACE level, drives more mental health symptoms in middle childhood, and that that is associated with elevated risk of migraine as an adolescent.

**Dr. Orr (08:55):** The second study was with the same dataset, but this time, we looked at traditional ACEs in the first seven years of life. And then we thought that we would see a similar pattern where we'd see an association between ACEs and developing migraine as an adolescent, but that it would be what we call mediated through, so explained through, the mental health in middle childhood.

**Dr. Orr (09:20):** But actually, in that study, when we looked at the high-level stressors, the traditional ACEs, we did not find any driving through mental health, but we found a direct relationship between ACEs in the first seven years and developing migraine as an adolescent.

**Dr. Orr (09:36):** And like the other study I was talking to you about, that big meta-analysis, we found a dose-response relationship. So that the more ACEs the child was exposed to in those first seven years, the higher their risk of developing migraine in adolescence. Which again, it's the only study that I'm aware of in kids that measured exposure longitudinally, meaning we don't go back and ask them, "Did you have any ACEs?" But we actually measure them as they're happening.

**Dr. Orr (10:07):** So it's very powerful, again, from looking at causality, because you don't have any bias in what people can remember. They're measured as the child develops. And then it's also the only pediatric study with that design that's looked at that dose-response relationship that's been shown in studies that ask people to remember back about their ACEs.



**Dr. Orr** (10:29): But I think it was a really important study, I think. Not to toot my own horn, but we were able to use this Canadian dataset to show in a very powerful way that there's probably a real causal relationship there in kids. And that's kind of replicating what's been seen in adults.

**Elizabeth DeStefano** (10:51): So from that analysis, it sounds like you're able to add to what was already known in saying that it is, in fact, these specific ACEs. And impacted in the dose-response relationship perspective to amount of risk of the actual ACEs themselves that's contributing to the incidence of migraine or headache disorder.

**Dr. Orr** (11:15): Exactly. And that it's not that we can say that this is driven through mental health for these high-level traumatic exposures, that there is some direct relationship from that to developing migraine, which was very unexpected and interesting.

**Elizabeth DeStefano** (11:32): So does this mean, then, that it's very possible, or likely, that ACEs are having a nonpsychological impact, then, on the neurodevelopment that then predisposes a child to development of migraine? And if so, what kind of biological pathways could be at play?

**Dr. Orr** (11:53): That's an excellent question. And yes, that's what we are starting to think, is that there's a nonpsychological driver that goes through changes in brain development. And just to speak to that, I think it's complex, and I don't think that we fully understand. But we think there's probably, in a very oversimplified way of looking at this, two pathways that go from ACEs through brain development, potentially, to different neurological outcomes, including migraine.

**Dr. Orr** (12:29): So if we look at ACEs, they're quite different, right? They're not all the same. And we can kind of categorize them. This is based on, I will say, the work from Sikorski et al., from that 2023 paper we were talking about earlier. In that meta-analysis, they categorize them as either threat — so things like sexual abuse, emotional abuse, physical abuse; and then neglect ACEs — so not having any attention, not having access to food and water.

**Dr. Orr** (12:59): And that those two are probably different in terms of how they impact brain development. So when we think of being in a threatening environment, that is thought to activate our stress systems in the brain. So these are things like our sympathetic nervous system, our fight-or-flight system, and our hypothalamic-pituitary-adrenal axis. (We call it the HPA axis.) It's our cognitive stress response system in the brain that produces stress hormones like cortisol.

**Dr. Orr** (13:30): And so there's some data to suggest — again, we need to study it more, and there's nothing specifically linking this to migraine — but just broadly, if a young person is exposed to a very threatening environment, their stress systems in the brain are going to be turned on more. Obviously, that's an adaptive response.

**Dr. Orr** (13:47): And that being chronically in a state of high stress where your stress hormones are going and your epinephrine, your adrenaline system, is going, skews the brain towards responding more to threat because that's what the brain has to do in that environment. And that over time, that chronic stress activation primes the brain to be more reactive to stress. So that's what we think is happening on the threat ACEs side.

**Dr. Orr** (14:16): And we can theorize after, about how that may link back to migraine. Then in terms of the neglect ACEs, there's some data to show that youth in a very neglected environment, so youth in care settings, youth that were severely neglected, there's parts of their brain that don't



develop to the same extent as somebody who's not in a neglect environment. And this we think is driven through something called synaptic pruning.

**Dr. Orr** (14:44): So when we're born, we have many more connections between brain cells than we do now at our age. So the young brain is born to develop to the environment that it's in. And so over time, as the brain learns what it needs to survive, the connections between neurons — cells in the brain — get pruned. So pruning is just another word for cut or deleted. So that the brain can become more adapted, and more specialized, and more rapidly responsive to the environment it's in.

**Dr. Orr** (15:18): So if a child is put in a really deprived environment where they're not stimulated enough, they're not fed enough, the brain develops in that low-complexity environment and tends to actually be underdeveloped in certain areas. So that's a very long answer. How all of this connects back to migraine is still a bit unclear.

**Dr. Orr** (15:41): One theory that I have, and this is really theoretical because it's not been shown: If we look at the threat side, if the brain is in a threatening environment, is it an adaptive response to develop migraine? So if you're in a dangerous place, what is a way to better survive? Being withdrawn, going to a quiet area and retreating from the threat. So is there something about developing migraine that actually biologically makes a lot of sense if you're in a threatening situation?

**Dr. Orr** (16:16): I actually think that the answer is yes. And I think framing this as: This is your brain's way of protecting you from the environment that you grew up in, is actually very trauma-informed in a way because we are all developed to survive. Our brain develops to survive. It doesn't develop to make us happy or healthy. It develops so that we can survive the environment that we're born into. And so there may be something actually very adaptive of developing migraine if you've been exposed to trauma.

**Elizabeth DeStefano** (16:49): What a fascinating perspective on the idea of living with migraine to view it as potentially an adaptive response.

**Dr. Orr** (16:59): Yeah, I think so. I mean, I have no exact proof of that, but I've thought about this a lot and I think it makes sense. And I've talked to other headache specialists. And when we talk about this, it's always a very enriching conversation. And others tend to nod and say that makes a lot of sense.

**Elizabeth DeStefano** (17:15): Yeah, it's very intriguing. So to recap, when we're talking about ACEs and their potential for a direct — a nonpsychological impact via changes in neurodevelopment, we are talking about the possibility of two pathways and looking at that as a differentiation in ACEs of those that are threat-type ACEs and those that are deprivation-related ACEs. The threat-type ACEs may impact, essentially, nervous system regulation, right?

**Elizabeth DeStefano** (17:45): And the deprivation-related ACEs may have an underdevelopment impact through their effect on synaptic pruning. What do we know, Dr. Orr, about what timing in a child or adolescent's life poses the greatest susceptibility to impact on headache or migraine risk as a result of an ACE?

**Dr. Orr** (18:12): Yeah, I think that's a very good question. Just looking broadly at environmental impacts on brain development, we know that the first five years are a really high-risk period for the brain to respond and develop differently based on its environment. And that makes sense



because this is a time of massive changes in the brain. I mean, you can just look at a child grow in the first five years and see it in front of you.

**Dr. Orr (18:36):** But biologically, that's driven by differences in how the brain develops with its myelination. So in the brain, we have gray matter, where the cells live; and white matter, where the wires to help the cells talk to each other live. And they have something wrapped around them called the myelin sheath, which is kind of like the insulation around electrical cords. And in the first four years is when you see the most rapid change in brain myelin patterns.

**Dr. Orr (19:05):** The other thing that we talked about a couple minutes ago that's really changing a lot in the first five years is that idea of how many synapses are there, the connections between the brain cells. And there's a lot of pruning that — deleting those synapses and cutting and specializing the brain in the first five years. So just based on basic principles of brain development, we know the first five years are a big time of opportunity for the brain to respond to its environment.

**Dr. Orr (19:34):** But there's actually some really interesting data that came out of the U.K. a couple of years ago where they had a birth cohort study, and they followed thousands of kids, again, up until adolescence from birth. And they actually took blood samples throughout their life. And they measured ACEs. So what they looked at in the blood were what we call epigenetic patterns. So we all have our genes, which are like the recipe for our body. And, you know, you inherit your genes.

**Dr. Orr (20:03):** But there's also ways that the genes can be turned on or off that are impacted by the environment. So like little markers that can say, "Yes, you should make protein from this gene," or "No, you shouldn't." Or ways that the genes can be folded or unfolded to make it easier to make or not make the protein. So those are called epigenetics. And so they're a way that the environment can impact the expression of genes.

**Dr. Orr (20:31):** So they took blood samples from these kids repeatedly to look at epigenetic changes. And then they looked at ACEs throughout childhood. And at 15, the epigenetic markers in the blood were looked — they looked back to see, "Are any of these changes we're seeing in the expression of genes related to ACEs in childhood? And if so, at what time are the ACEs most potent to cause these changes in gene expression?"

**Dr. Orr (21:00):** And so, yes, they found, I think 40 or so, 50 — don't quote me on the exact number — epigenetic changes, most of which were related to brain pathways like the oxytocin pathway, certain neurotransmitter pathways. They found a relationship between those genetic markers and trauma in childhood. But when they looked at the timing of trauma, they found that ages 3 to 5 had the most epigenetic changes related to trauma.

**Dr. Orr (21:32):** So again, validating that idea that the first five years of life, and maybe in particular the toddler/early childhood years, may be a really potent time for trauma to cause changes in brain development.

**Elizabeth DeStefano (21:46):** So that critical timeframe, either up to 5, or 3 to 5, as the case may be, may be when those genes can be most susceptible to being turned on or affected in how they function based on epigenetic, or external to a person's own genes, factors.

**Dr. Orr (22:06):** Exactly. Yes.



**Elizabeth DeStefano (22:08):** Your work has also delved into the intergenerational aspect of pain and family mental health. How might a parent's own history of either chronic pain or mental health issues impact their child's own migraine risk?

**Dr. Orr (22:25):** Yeah, we haven't specifically gotten to looking at this in migraine yet, but there are plans to. But we do know from the broader chronic pain and ACEs literature that a parent's exposure to trauma unfortunately has an intergenerational impact, like you say, and increases their risk of poor mental health outcomes, difficulties that the child may have in their socio-emotional development, and more issues with substance use, as well as some chronic diseases.

**Dr. Orr (23:00):** We believe and hypothesize that there's probably an association there, if a parent's been exposed to trauma, that there may be a higher risk of the child having migraine. But we haven't looked at that yet. We have plans and protocols to do that. So hopefully in the next few years we'll have an answer to that. And how that happens, again, biologically, is very unclear. But we do know — we were just talking about epigenetics in that study looking at the critical periods for ACE exposure.

**Dr. Orr (23:32):** We do know that parents can transmit not only their genes, but parents can transmit epigenetic changes to their children. So if a parent has lived in a high-trauma environment and has developed epigenetic changes in response to that — let's say, again, I'm stretching this — that skews them to developing migraine. Those epigenetic changes can be passed on to the child. We know that from basic science studies in animals and other fields of work.

**Dr. Orr (24:02):** So again, we think that may be one mechanism that explains how trauma in the parent's childhood could lead to different mental health and physical health outcomes in the child.

**Elizabeth DeStefano (24:16):** So a parent whose genes and the function of their genes are impacted by external circumstances, those alterations to that parent's gene function can be passed on in terms of passing the same alterations to gene function onto their child.

**Dr. Orr (24:34):** That's correct. And that's where — here's a biological reason why we need to look beyond the direct household exposures in the child. Because if you think of communities like the Indigenous community in Canada that have been — there's a genocidal history here with that community.

**Dr. Orr (24:54):** You think of those widespread impacts of systemic racism and historical trauma on the community and how those things can be passed on quite literally in genetic changes from generation to generation.

**Elizabeth DeStefano (25:09):** Even though you share that that has been well established in a lot of science, I don't think that a lot of the public is truly aware of how proven that is, that genetic changes in one generation can be passed on. Genetic changes as a result of environmental or community-based impacts can be passed on genetically. Thank you for sharing that.

**Elizabeth DeStefano (25:34):** So you mentioned, and we know, that the early ACEs research is a benchmark for having established what have historically been considered ACEs. And as you mentioned, though there are many other life stressors that may be at play here in what's being explored. Based on what you know through your own research, other research you've been a part of, and research you've studied, how would you like to see the definition of ACEs expanded to include, for instance, what events?



**Dr. Orr (26:07):** Yeah, I'm a big proponent of patient engagement in research, and involving people with lived experience in research. And actually, when we look at the idea of trauma-informed care, just in the clinic, one core concept is that engaging the person in their treatment decision-making to empower them and give them a voice is a very trauma-informed approach. But I think historically, we haven't taken that approach enough in research.

**Dr. Orr (26:35):** We decide that we're the experts, and we know what the best study is to do, and we're going to study this, and use this definition of ACEs. But actually, we need to empower people with lived experience of migraine disease to come into our research teams and help us with this type of thing. So I don't think that I have the best answer to that.

**Dr. Orr (26:56):** But I think the best approach to expanding the definition of ACEs is to get together a big team, including people with lived experience of migraine and trauma, and diverse people as well, from different communities. We've talked about natural disasters and exposure to community-level trauma. These are things that are not evenly distributed geographically or across different groups.

**Dr. Orr (27:20):** So engaging with lots of different people who have different life experiences to make sure that we have a comprehensive list of potentially traumatic exposures, I think, would be the best way to go about it, before we develop the next tool for ACE measurement, right. because we're still all using this Felitti tool from the 1980s with these household-level ACE exposures.

**Dr. Orr (27:45):** But I think to develop the next best next-generation tool that's more comprehensive, we should work together on the research side, and with people with lived experience from different communities, to make sure that we capture everything. Because having lived in a certain environment myself, I may think much more of one type of exposure than another. And I think that's true for all of us.

**Elizabeth DeStefano (28:07):** Well, let's dive into what all of this means in clinical practice, both in pediatrics and for adults living with migraine. So in a busy clinical practice, what does an effective and sensitive screening process for stressors look like?

**Dr. Orr (28:24):** Yeah, that's a very good question. And I think, unfortunately, a lot of clinicians, because we weren't necessarily taught about this in medical school, or how to screen for trauma, a lot of clinicians are afraid to even open up any questions because they don't feel equipped to ask the questions properly. They don't feel like they know what to do if trauma comes out.

**Dr. Orr (28:49):** So I think the first thing for clinicians is to educate themselves a bit, and also just come from a humble perspective that you do not need to be an expert on trauma-informed care to do it. You need to start. You need to try. You need to recognize it and try to implement it in your practice. But it's not — you don't need perfection and endless amounts of hours of reading.

**Dr. Orr (29:13):** So coming from a humble perspective is important, and coming from a perspective where you want to avoid retraumatization is important, too. So one thing is having just a broad question that you ask your patients about trauma without pushing them to go into every nitty-gritty detail is a good way to frame this and to open up the conversation. So asking something like, "Have you lived through anything particularly difficult or traumatic in your life?" And then just seeing what comes out.



**Dr. Orr (29:46):** And some people want to talk about it at the first visit or at a follow-up visit. And some people don't. And so then you go and see how the patient leads the conversation. So, they may say yes.

**Dr. Orr (30:02):** And my follow-up question to yes would be, "You don't need to tell me any details. I appreciate you sharing that. If you'd like to tell me a bit more about it, you can. If not, I'm just going to make note of that, because we know there's a relationship between trauma and chronic pain, including headache disorders." And then, yeah, so I think the important thing is you need to recognize that trauma is there. You need to open up the conversation, but not push them to every nth of detail to make them relive their traumatic experience.

**Dr. Orr (30:34):** And then if there's a yes, then I think, making sure that you screen for current dangerous situations like domestic abuse, because that's something that you want to make sure that you can act on, and current mental health as well. And then also just validating. I like to validate why I'm asking that question, like I said, because we know there's a relationship between chronic pain and migraine and trauma.

**Dr. Orr (30:59):** So, and also how to support you if you're still living with any symptoms of trauma. So then it can open the conversation to symptoms of trauma and make sure that you develop a plan for that. The other piece is just looking at what can empower people in the clinical relationship if they've had trauma. So, I mean, I think everybody should get a trauma-informed clinical encounter because if you look at the data, it's probably around 60% of people that have had at least one ACE.

**Dr. Orr (31:31):** So you can assume that most of us have had some exposure. And then, doing things like listening properly, which I know is hard sometimes in a busy practice, but really important. Empowering people through their treatment decisions, and engaging them in informed decision-making, and shared decision-making is really important. Giving people time to trust you is a key thing. And then validating what the person's strengths are is a very trauma-informed approach.

**Dr. Orr (32:02):** So, yes, you may be living with migraine, you may have headache all of the time or every day but look at how well you're doing at this part of your life — just empowering them with what is going well and what their strengths are. And then looking at supporting peer relationships that are really healthy.

**Dr. Orr (32:19):** This is where things like the Migraine World Summit and patient communities are really important, because we know that people who have lived through trauma, who are living with chronic pain, migraine, other chronic diseases, can be very empowered by positive peer relationships with other people who have lived experience of the disease and trauma. So that's a long answer. And there's other pieces to this that I'm not talking about, but just some little pieces of how we can implement trauma-informed care.

**Elizabeth DeStefano (32:46):** So it sounds like some critical elements in practicing from a trauma-informed care perspective are to, first of all, as you are asking questions, also doing so in a way that educates the person living with migraine on the fact that there is a connection between trauma and migraine or headache disorders, which in and of itself can be eye-opening.

**Elizabeth DeStefano (33:11):** Offering support for living with that experience, either in the past or potentially even still currently, and screening for any particular safety or support necessary



there. Offering empowerment in that person's strengths, and also highlighting the benefits of peer support, are all critical elements when an experience is identified as relevant.

**Dr. Orr (33:38):** That's right. And just to add, as I hear your summary, I think another really important thing that's easy to do in clinical practice is validation. And this goes outside of just the trauma-specific lens, but validating people's lived experience is really powerful.

**Dr. Orr (33:55):** And actually, there's some data from my collaborator, Dr. Noel, in a pediatric chronic pain clinic that looked at how much a clinician used validating language in their encounter, and how much the parents did, and how the child did with their chronic pain. And there seems to be an association between validating the experience of chronic pain and trauma or whatever it might be and having better outcomes.

**Dr. Orr (34:17):** And so what I mean by that is, if somebody says, let's say, just take an example, "I was sexually abused and then my headaches became a lot worse." You can, rather than just moving on from that, you can say something like, "That makes a lot of sense. When the brain is exposed to a massive stressor like that, it actually can skew towards more sensitization to pain. And so that makes sense. Your brain's adaptation to this is valid."

**Dr. Orr (34:49):** "Your experience of this is valid." It is really powerful to take a trauma-informed approach and can help develop a stronger, more trusting relationship, which is also part of trauma-informed care.

**Elizabeth DeStefano (35:01):** So that validation piece sounds like it's very important, not only for clinicians to know, but also potentially parents of children living with migraine or headache disorders. Are there any other ways that you guide parents or caregivers about mitigating effects of early-life stressors on children's health?

**Dr. Orr (35:21):** Yeah, well, I think the first thing is validating that there's a link between pain and trauma based on differences in how the brain develops. And then looking at what the child is currently living with, symptom-wise from the trauma, outside of migraine as well, right? So some children have had that exposure, but they've already kind of worked through it, either with someone in their family that supported them or a therapist or whatnot.

**Dr. Orr (35:52):** And some children may not even really recognize or have thought about their current issues with sleep, or hypervigilance, or anxiety that may relate back to the trauma. And so helping them see a link between whether there's any current symptoms other than the pain and the trauma, developing a plan to support them with that, validating it, and making sure that they have a trusted adult that they can open up to. So that may be a therapist, it may be a parent, it may be a teacher.

**Dr. Orr (36:29):** From the mental health literature — this is a bit of a divergence, but I think it's very relevant here — there's a lot of emerging data to show that we have this youth mental health crisis, and what can we do to buffer that. And that one of the most consistent and strong buffers to youth mental health issues is actually just having an adult in their life that they trust and can talk to.

**Dr. Orr (36:55):** So, again, we don't know if that relates back to migraine, but we know in the mental health literature that that is a very positive thing. And mental health and migraine are linked. Mental health does not cause migraine, but they can travel together. And so I think that idea of trying to help them identify a trusted adult in their life is helpful.



**Elizabeth DeStefano (37:17):** So for adults or children with migraine, when ACEs are a part of a person's lived experience, are there any important clinical actions that are important to take beyond what we've spoken about that are relevant to that experience?

**Dr. Orr (37:38):** Yeah, so I think if you have identified that there's a trauma history, first that awareness that there's not only a link between having trauma and developing migraine — there are a few studies, not a lot, we need more research in this area — but a few that have looked at also if you have trauma, does that mean that your migraine outcomes are different? So there are some studies that show that people with migraine and trauma are more likely to also have depression.

**Dr. Orr (38:06):** That they may have more sensory hypersensitivity than other people with migraine, and that they may have higher headache frequency and more migraine-related disability. So once trauma is identified, the clinician should think that this is a person that may need a little bit more support and aggressive treatment, because they may not only have developed migraine in part related to trauma, but they may be at risk of more severe outcomes. So that's one thing.

**Dr. Orr (38:35):** And then the other piece is screening for current symptoms of trauma, like trauma and stressor-related symptoms like hypervigilance, sleep issues, flashbacks, because they may need additional support to help regulate their nervous system in this context. And then I think — we actually just recently wrote an article on trauma-informed care for migraine.

**Dr. Orr (39:00):** And this idea of actually maybe explaining some of this to the patient in front of you as part of that piece of acknowledging and validating that: “You've had this trauma exposure. We know that the brain develops differently in that setting and that may explain a lot of what you're going through. And this is, rather than looking at it as, this is a deficit-based approach and you're broken.

**Dr. Orr (39:25):** Actually, your brain did what it needed to do to survive your environment. And this is where things are at. But there's a lot of hope. There's a lot that we can do to help you. And this is just — your brain was being smart in the environment that it was in, and we can help you with this. So first, that validation that you're not broken; this was your survival mechanism, and we can help you,” I think, is a really important message.

**Elizabeth DeStefano (39:52):** Looking ahead, what are the most critical unanswered questions in this field? What research do you hope to see in the next, let's say, decade to help us better understand these links between early adversity and migraine?

**Dr. Orr (40:08):** Yeah, that's a great question. I think we kind of weaved it in a little bit. But, number one, I think we need to redefine what we're looking at for ACEs, and do engagement of people with lived experience to look more broadly outside of the household at other factors that may be relevant, because I think we're only seeing the tip of the iceberg and we're ignoring a lot of other pieces that may be relevant. So that's number one.

**Dr. Orr (40:34):** Number two — and I'm not putting these in any order of importance because I think they're all really important — is the idea of taking a strengths-based approach. I kind of just alluded to that in my last answer. But so far, most, or if not, yes, all of the research on ACEs and migraine specifically has been from that deficit lens. And it's not wrong. It's our place to start. Yes, having ACEs increases the risk of migraine and worse outcomes, dose-responsive relationship, all of that piece is important to know.



**Dr. Orr (41:06):** But now what? Is that helpful? Not really, because it doesn't give us a way to help patients. So first of all, what treatment approaches will help this subset of patients who have both trauma and migraine? But even maybe more importantly, from a preventive perspective, what are the buffers?

**Dr. Orr (41:27):** Because not every person in every traumatic experience — we know people put in the exact same earthquake, or flood, or whatnot will have very different responses to that. So what are the individual factors that increase the risk? But even more interestingly, what are the buffers? So what is it about a particular person, the family they live in, the community they live in, the country they live in, and the social supports that are available, that can buffer against the impacts of trauma?

**Dr. Orr (41:55):** If 60% of us are going to have exposure to at least one ACE, how can we invest in early childhood environments that are healthy and that can buffer against this inevitable part of being human? I think this is a really exciting avenue for future research. And then third is the mechanism. So we talked about some of what we know in terms of threat and what it does to the brain, and what neglect does to the brain. But there's still a lot that's not understood broadly about that, and then nothing really to link mechanisms back to migraine.

**Dr. Orr (42:30):** And so there's a lot of potential, really impactful work that can be done there, because I think that, if we have this one environmental exposure — and I could be wrong, but I'm going to say that I think ACEs are probably the clearest environmental factor that can lead to migraine. Migraine is not just caused by one thing. There's genetics, there's different environmental things.

**Dr. Orr (42:51):** But I think ACEs are at the top of what we know in the environment can lead to migraine. If we can understand how you get from there to migraine, I think we can understand migraine disease and biology a lot better than we currently do, because we don't have it all worked out. So I think that's also a really fascinating area for research.

**Elizabeth DeStefano (43:12):** Absolutely. What you have shared here today is so enlightening and eye-opening, and I think also very hopeful for what it highlights about what we can learn to better support people with migraine who have been impacted in some way through an ACE or another early life stressor, but also, as you've said, what understanding all of this better could teach us in general about migraine itself. So, Dr. Orr, where can we learn more about you or follow the work that you do?

**Dr. Orr (43:46):** Oh, thanks for asking. We have a website where I call our group the Pediatric Headache Research Lab. And so we have a website where you can read about the work that we're doing. We need to update it because it moves so quickly. But we are at [pehrl.ca](http://pehrl.ca). So that's probably a good place to get an idea of some of the things that are going on. It reminds me to update the website as well.

**Dr. Orr (44:12):** I'm also on Blue Sky. I'm not on a lot of social media, but I do share occasional research updates from our lab or other really interesting stuff that's going on in the field there. And I have a page for the University of Calgary website with some details there as well. But yeah, thanks for asking.

**Elizabeth DeStefano (44:30):** Absolutely. And are there any other resources that you'd like to recommend to those that are watching and listening to this?



**Dr. Orr (44:38):** There's some very interesting high-level information about ACEs on the CDC website that goes over what the association is between ACEs and a variety of different health outcomes. And I think it's really compelling to look at what's going on between ACEs and migraine, but also step back and see the broad variety of health outcomes that are associated, just to give some perspective.

**Dr. Orr (45:04):** And again, to drive home that idea that if we can make societies that are better for young children and young families, the amount of disease that we can prevent — not just for migraine disease, but for a broad variety of health outcomes — is really fascinating. So that's a good place to look if you're trying to educate yourself a little bit more about ACEs.

**Elizabeth DeStefano (45:23):** So we will link to all of the resources and websites, as well as your studies, in the show notes so that people can easily find them. Thank you, Dr. Orr, so much for the time you've shared with us today, sharing just absolutely incredibly fascinating and important information in terms of early life stressors, adverse childhood experiences, and more on the risk of migraine and headache disorders. And thank you so much to you for the work that you and your colleagues do. We greatly appreciate you.

**Dr. Orr (45:57):** Oh, that's so kind. It's my pleasure to be here to talk about this. I think it's a fascinating area and there's a lot of opportunity to help a lot of people in better understanding this. So it's a pleasure, and I appreciate you identifying this topic and inviting me to talk about it.

**Elizabeth DeStefano (46:12):** Thank you.