PEDIAPOD OCTOBER 2023 TRANSCRIPT

Geoff Marsh
Hello and welcome to Pediapod for October 2023. This month, we look at the association between placental pathology and neurodevelopmental outcomes in patients with neonatal encephalopathy.
Hypoxic-ischaemic encephalopathy, a subset of neonatal encephalopathy, is the most common neurological condition in term born infants. Despite widespread implementation of therapeutic hypothermia- the mainstay of treatment for HIE- many neonates experience persistent neurological deficits.
It is known that a range of acute and chronic placental pathologies are more common in infants with HIE, however little is known about how differences in utero-placental function might contribute to varied outcomes after HIE.
In this episode of Pediapod, we speak to Early Career Investigator Jeffrey Russ from Duke University Medical Center, who retrospectively analyzed whether acute versus chronic placental pathology were differentially associated with outcomes in patients with presumed HIE.

Jeffrey Russ
I'm Dr. Jeffrey Russ. I'm now a fetal and neonatal neurologist, Assistant Professor of Pediatrics at Duke University. I majored in neuroscience at the University of Pennsylvania as an undergraduate and then wanted to do both clinical medicine and lab-based science and it turns out that an MD-PhD Program is a really great way to hedge and keep both options open for a decade or so of training. I was sort of debating what niche area of neuroscience I wanted to really focus on and I happened to find a really great mentor, Dr Julia Kaltschmidt, who at the time was at Sloan Kettering, and now is at Stanford, who was studying spinal cord development. Flash forward then to returning to medical school and I just hadn't quite found something in my rotations that really felt like it clicked and that it was something I wanted to do on a daily basis until my very last required rotation, which was pediatrics. All of a sudden, I just found myself really enjoying the clinical aspect of Pediatrics. I remember saying to my wife, you know, I really like this but I want to do neurology, if only there was a way to do both of those things. And it turns out that child neurology is exactly the way to do both of those things. As a child neurology resident, I was at UCSF, which has one of the more established Neurologic Intensive Care Nurseries. And by the end of residency, I realized that I really enjoyed the breadth of pathophysiology in neonatal neurology and fetal neurology for that matter and brain development. But neonatal encephalopathy is one of the most common things that we see. It's the most common brain injury in term infants. And it's important to clarify that neonatal encephalopathy or presumed hypoxic-ischaemic encephalopathy which is a subcategory, is really describing an injury in the term neonatal brain as opposed to the preterm brain. And because it's so common and it's such a common cause of downstream symptoms that I manage in the clinic like seizures, cerebral palsy, developmental delay, cortical visual impairment or

cortical blindness, that's why I wanted to focus on it as a research topic.

Geoff Marsh

And so just getting a definitions straight, hypoxic-ischaemic encephalopathy is when you have neonatal encephalopathy that's thought to be because of a lack of oxygen or blood getting to the brain.

Jeffrey Russ

Correct, yeah. I think traditionally that term was thrown around a lot and it was problematic because it implies that you know that there was some event leading to poor oxygen delivery or poor blood flow to the neonatal brain. And it also, I think, was used very narrowly with kind of a subtext that maybe this was caused during the delivery and that maybe there was some fault by providers that led to this. And so now I think we've adjusted our language to be much more agnostic to the underlying etiology. So the precise terminology now is ‘neonatal encephalopathy with presumed hypoxic-ischaemic encephalopathy’, if you think that this was resulting from some kind of impaired blood flow to the neonatal brain.

Geoff Marsh

But even though it's a specific subcategory of neonatal encephalopathy, HIE isn't just one uniform pathophysiology is it? There are all sorts of fetal and placental factors that can affect the blood flow and oxygen getting to the fetal brain.

Jeffrey Russ

Correct. It's really a heterogeneous disorder. There have been studies looking at how often presumed HIE is associated with a sentinel event like placental abruption or uterine rupture or something like that. And, you know, depending what study you're looking at, that's maybe clearly associated in about 15 to maybe 20% of cases, which leaves a good, you know, 80% or so that don't have an obvious sentinel event leading to presumed HIE. So that's why my research interests and really the field in general has started to focus on placental pathophysiology because the placenta is a record of the in utero environment, and there are a lot of heterogeneous disorders that can impact the placenta.

Geoff Marsh

Broadly, what sorts of placental pathologies are we talking about?

Jeffrey Russ

A lot of studies look at chronic pathology versus acute pathology in the placenta. Broadly speaking, chronic placental pathology has to do with abnormal vasculature in the placenta. So maternal vascular malperfusion and fetal vascular malperfusion. Essentially, the maternal side of the placenta or the fetal side of the placenta has abnormal vasculature that impairs blood flow and oxygen exchange. There's another chronic condition, villitis of unknown etiology, and that's essentially an aseptic inflammatory placental disorder. So for whatever reason, that we still don't fully understand, the maternal side of the placenta becomes inflamed and not because there's

an infection there but sort of an abnormally ramped up immune reaction. Those are some of the more common things that we refer to as chronic placental pathology. On the acute side are things that a lot of pediatricians and neonatologists may be more familiar with. So certainly something like placental abruption would be an acute placental event. Chorioamnionitis, that's a very common pathology right around the perinatal period. Other things would be meconium staining of the placenta, it's often a clue that there was meconium in the amniotic fluid and that a neonate may have some meconium aspiration. So acute versus chronic is one common axis for splitting these.

Geoff Marsh
Is the idea that those acute and chronic placental pathologies are well documented as being more common in infants with HIE but we don't necessarily know how those different pathologies differentially impact the type of brain injury and their outcomes?

Jeffrey Russ
That's exactly correct. It seems to be that these are more commonly associated with HIE. And then it starts to become an interesting question of, well, these are very diverse pathologies, you know, some are acute, some are chronic, some are vascular, and some are inflammatory. And if you start to look at these subcategories, do they have a differential impact on outcomes in neonates with presumed HIE?

Geoff Marsh
And in terms of your rationale for asking this question, are you saying that the placenta could actually be a good source of information for prognosticating about infants who've had this presumed HIE?

Jeffrey Russ
Yeah. The helpful information that could come with this is that the placenta is really a record of what the in utero environment was like for three trimesters. And especially because neonatal encephalopathy and HIE are sort of vague and heterogeneous, we often find ourselves speaking in sort of broad and vague terms and prognosticating to families about how a neonate is going to do. So anything that we can do to uncover other biomarkers or other potential placental information that may help us prognosticate about how a neonate will do could be really invaluable.

Geoff Marsh
It must have been quite hard to get your hands on the right data because you needed to find these instances where there was data on the mother and the placenta and the infant as a triad.

Jeffrey Russ
For all the reasons you said, it's hard to find the full triad. So what we needed were maternal medical information, neonatal medical information and banked placental specimens. And when

we set those inclusion criteria looking over the last five years we did at least have 50 triads that we could include, which we felt was decently powered to begin to ask these questions. And we also have benefited from having a pathologist, Kyle Strickland, here at Duke who had special expertise in placental pathology. So we had banked placental tissue and a pathologist who could review these in a very standardized way. So our primary outcome was how did they do neurodevelopmentally over the next 18 to 24 months? Then we also were interested in how nursery outcomes changed. Were there differences in the need for a G-Tube? Were there differences in the rates of death before discharge? Were there differences in the rates of the length and duration of intubation? And then were there any differences in patterns of injury on MRI? And were there any differences in EEG findings that might suggest something about their seizure risk, because essentially all of these kids get EEG monitoring for the full course of therapeutic hypothermia.

Geoff Marsh
So did the categorization of that placental pathology have any bearing on how those neonates did before and after discharge?

Jeffrey Russ
So the grand punchline from all of this is that no, it didn't seem to have a difference, at least in our sort of small subject number.

Geoff Marsh
There was an interesting result, when you reanalyzed some of the data specifically for the presence of chorioamnionitis.

Jeffrey Russ
Right. So when we went back and started to think maybe acute versus chronic isn't the most informative dimension of placental pathology, we started to look back at some of these other methods for separating placental pathology. We really honed in on the presence or absence of chorioamnionitis and interestingly enough that did seem to have some bearing on the EEG outcomes, in particular on the rates of postneonatal epilepsy. Not seizures that happened in the very acute period after presumed HIE from the insult to the brain itself, but neonates who go on to continue to have epilepsy after the acute period, after their discharge from the nursery.

Geoff Marsh
Have you got any mechanistic insight into how one might lead to the other?

Jeffrey Russ
I can give you the hand-waving answer which is certainly inflammatory states in the developing brain will impact brain circuitry. And so there's some kind of crosstalk between the immune system and the developing brain that leads to sort of aberrant circuit development and higher excitability and seizures. But at a cell and circuit level I think we just don't know and that's really

at the forefront of neurology and neuroscience right now.

Geoff Marsh
Do you think there would be value in more routinely keeping hold of placental tissues for analysis in these infants?

Jeffrey Russ
Yeah, absolutely. I mean, that would be one of my big, take home messages to any neonatologist or obstetricians that happen to hear this. Because there seems to be increasing evidence for the value of looking at placental tissue, I think in order to begin to validate the findings of our study with a much higher sample size, it would be important to start to hold on to this placental tissue more. And I would add to that that one of the other important subtleties of our findings was that of all of the mothers who had chorioamnionitis, half of them were diagnosed on placental pathology alone. And so all the more reason to hold on to these placentas. If a neonate has outcomes that are more severe than you would expect, if you go back and look at the placental pathology a couple of days later and see microscopic evidence of chorioamnionitis that may support that those neonates are potentially at a longer term risk of epilepsy.