

PEDIAPOD MAY 2021 TRANSCRIPT

Geoff Marsh

Hello and welcome back to PediaPod for May 2021. This month we're looking at a potential new biomarker for white matter injury in preterm infants.

Extremely preterm infants are at a high risk for brain injury. And this risk is most severe in children with intraventricular hemorrhage, followed by post-hemorrhagic ventricular dilation. This is because the dilation of the lateral ventricles compromises the developing white matter tracts around the ventricles. Bedside cranial ultrasound allows clinicians to identify the progressive dilation of the lateral ventricles. However, there's currently no consensus on how to quantitatively estimate the dilation and at what point to intervene. In this episode we meet Dr. Rawad Obeid, a pediatric neurologist at the Oakland University School of Medicine in Detroit, Michigan. He and his team investigated a new parameter for estimating lateral ventricular dilation called the frontal-temporal horn ratio in an effort to define normative values, and to correlate this parameter with white matter injury at term-age equivalent. Rawad is also this month's highlighted early career investigator, and he started off by telling me how his love for pediatrics began as a child in Syria.

Dr Rawad Obeid

I initially did my medical school and Damascus University in Syria. My dad is a pediatrician and I got the chance to work with him, even as a child and that really influenced me to decide to go into pediatrics. Also working with a lot of disadvantaged children back home was really eye opening to how much is needed, especially the children who have brain diseases or are handicapped. So I came here to the United States, and did my training in the Children's Hospital of Michigan, Wayne State University in Detroit. After that continued to do pediatric neurology in the Children's Hospital of Pittsburgh. Then I got the great opportunity to be accepted in a neonatal neurology fellowship that was at the Children's National Medical Center in Washington DC. Right now I'm the director of the neonatal neurology program at the Beaumont health system in Detroit, Michigan.

Geoff Marsh

So it sounds like you've maintained this interest in pediatric neurology and brain injury since you were a child, almost. Why is it that premature infants are more susceptible to brain injury and things like cerebral palsy?

Dr Rawad Obeid

We all know that the brain is very fragile in the last trimester of pregnancy. It is a time when the brain is still building resilience to fight the stress that can happen either during that last trimester of pregnancy or after birth. The white matter is very susceptible to injury. Not only that, but also their other systems are immature, systems that are important for the brain health, like for example, the lungs, the heart, lots of these babies are born with a immature lungs that cannot provide enough oxygen to the brain, which is adding to the risk that they're born with.

Geoff Marsh

What does the progression to the white matter injury look like?

Dr Rawad Obeid

The white matter itself is very fragile and can easily get damaged with hypoxia. So a lack of oxygen in general in the body can affect the white matter very directly. And then the fragility of the blood vessels inside the white matter, more so the germinal matrix, as we call it- a collection of blood vessels that are very fragile and actually should go away in term babies, but they're still present in premature babies. So the fragility of these blood vessels with the stress of labor can lead to a bleed or hemorrhages in this germinal matrix and that hemorrhage can affect the white matter, because it's very close to the white matter and this is why we see commonly, white matter infarcts, as we call them, because of these hemorrhages from the germinal matrix. That hemorrhage also can lead to blockage of the drainage of the cerebral spinal fluid and that can cause more problems, which is the accumulation of that cerebral spinal fluid in the ventricles. The pressure of the fluid pushing on the white matter nearby, we think can also lead to further damage to the white matter,

Geoff Marsh

As a clinician, if you spot this intraventricular hemorrhage progressing on through to that situation of post-hemorrhagic ventricular dilation, there are interventions available to you in order to try and stop that white matter injury, right?

Dr Rawad Obeid

That's correct. The solution is to remove the fluid from the ventricles. The procedures that we have right now, there are two types: There's temporizing measures, they're not very invasive, we remove some fluid but we know that this fluid may accumulate again so we may need to repeat these temporizing measures, versus more permanent measures where we put a device inside the ventricle that drains the fluid all the time- what we call ventriculoperitoneal shunt.

Geoff Marsh

That sounds highly invasive and it sounds like something that you don't want to do unless you really need to do, and that gets at the heart of this paper doesn't it. You're interested in what's the best way to spot this ventricular dilation and at what point do you intervene with such drastic measures?

Dr Rawad Obeid

And that is always a big debate between the neonatologist, the neurologist, the neurosurgeons. The paper is really addressing one part which is the way we look at the ultrasound of the head, which is a common procedure we do in these premature babies. Some people may address it in very qualitative terms, like for example, we may say the ventricles are 'mildly big' or 'moderately big'. There are also some more numeric parameters that have been used. We met with our neurosurgeons at our hospital, and we discussed what is the best parameter that they feel comfortable with. And they actually recommended that we use the frontal-temporal horn ratio, which is a parameter that they are very familiar with and they use commonly in older children to measure the size of the ventricles. The second aim was to use our parameter that we are describing here to find a reasonable number that we think after this number, you probably are going to run into problems in terms of more brain injury caused by the post-hemorrhagic ventricular dilation itself. So we ended up actually with about 750 head ultrasounds for

the whole sample of extremely premature babies for that time period between 2011- 2014. Some of them actually were normal premature infants with no intraventricular hemorrhage, so we use these relatively as controls. The whole cohort got a term-equivalent brain MRI so we had also this data to evaluate the outcome for these premature infants.

Geoff Marsh

So how accurate was your new parameter, this frontal-temporal horn ratio, at predicting white matter injury in these infants?

Dr Rawad Obeid

So the frontal-temporal horn ratio was very associated with a high degree of white matter injury. Not only that, but we were also interested in looking at the change in that frontal-temporal horn ratio. So not just the value, because some people may say, if you have high value but it's not changing, is that the same as if the high value is continuing to change and increase? And we did actually find that the trajectory of the frontal-temporal horn ratio correlated with further white matter injury- the faster the ventricle was growing, the more injury we noticed on the brain MRI and also the long term outcome was also worse in terms of the diagnosis of cerebral palsy.

Geoff Marsh

So it sounds like frontal-temporal horn ratio could be used as a sensitive biomarker of white matter injury. But the fact that the trajectory seemed to be more important for predicting white matter injury- does that tell you anything about how regularly cranial ultrasounds should be being performed in extremely premature infants?

Dr Rawad Obeid

That's a very good question. When you are doing these serial ultrasounds, you're able to pick up that change in the size of the lateral ventricle. You're able to possibly intervene early because you're picking it up early. Sometimes, when you're intervening early, you're not just improving the long term outcome, but also by doing these temporizing interventions early, we may actually avoid going to a more permanent device that will stay in the body of this child for his whole life, which is the ventriculoperitoneal shunt.

Geoff Marsh

And earlier on you discussed the desire for a standardized, quantified number for when to intervene. Do you have one, based on this study?

Dr Rawad Obeid

We found that a frontal-temporal horn ratio value of point five one is the cut point that had the highest sensitivity and specificity. So it was 89% specific to determine that this child will most likely have a moderate to severe injury on the brain MRI.

Geoff Marsh

Is it an easy thing to measure? Are their guidelines or does it take real specialists to assess this number that you've put forward?

Dr Rawad Obeid

One of the reasons we like the frontal-temporal horn ratio is that the point of interest on the ultrasounds are very easy to identify. Radiologists are used to measuring these distances. And then what is most important here with the frontal-temporal horn ratio is that you also measure the distance between the skull bones and you account not only for the size of the lateral ventricle- by measuring the biparietal diameter, you're accounting also for the size of the brain, which is also unique about this parameter compared to other parameters that look only at the size of the ventricle and don't account for the size of the brain, because those are premature babies and their heads are very small. So you have to be careful because the brain overall is small and a lot of them are also born even smaller, because they're a twin, or they have intrauterine growth restriction. So the brain could be very tiny. So all these, in my opinion, make this parameter very interesting. Also, it's a parameter that technically is desired by neurosurgeons. They're very familiar with it. So we're really hoping that this will improve the communication between the physician, clinicians and the surgeons.

Geoff Marsh

So what's next for you then? Have you got any trials planned for this?

Dr Rawad Obeid

So our next step is we're trying to now test this parameter in a prospective manner. We tried to control for a lot of variables that always are very problematic in this population like the degree of the hemorrhage, the other neonatal comorbidities... So the plan is to try to control as much as we can for these variables. And also try to use this parameter as part of a protocol to treat these infants for their post-haemorrhagic ventricular dilation. So possibly to use this cut off that we found as a time to intervene, hopefully so that we can get a better outcome. That way that we can prove that this parameter is actually not only good retrospectively, but also it's good to use in a prospective fashion as part of a treatment protocol that will lead hopefully to a better outcome in this population.

Geoff Marsh

That was Dr. Robert Obeid from the Oakland University School of Medicine, Detroit, Michigan. And that wraps up another episode of PEDIPOD. Please do join us again next month. I'm Geoff Marsh. Thanks for listening.