

PEDIAPOD FEBRUARY 2021 TRANSCRIPT

Geoff Marsh

Hello and welcome back to PediaPod for February 2021. This month we discuss autonomic nervous system maturation in premature newborns.

The latter half of gestation and early neonatal life are critical periods for the maturation of the autonomic nervous system. Premature infants are born with underdeveloped autonomic maturation, and must undergo their developmental changes in a vastly different setting to the natural, *in utero* environment. A number of studies have shown autonomic dysmaturation in premature infants, although these have mainly looked at cohorts of children from high morbidity NICUs.

Dr. Sarah Mulkey, a fetal neonatal neurologist at Children's National Hospital in Washington DC tracked the sympathetic and parasympathetic maturation of a cohort of preterm infants with low medical morbidity in a large community NICU to assess how birth gestational age affected their autonomic maturation. Here she is.

Dr Sarah Mulkey

The autonomic nervous system is part of the nervous system that's developing throughout fetal life. It's really important when a baby is born because it is responsible for the baby making that transition, being able to regulate the respiratory functions, the blood pressure, the heart rate, and then also to start that emotional engagement with the parent or caregiver. All of this is, in part, by the autonomic nervous system and its development.

Geoff Marsh

What are the consequences of premature birth on the development of the autonomic nervous system?

Dr Sarah Mulkey

When a baby is born premature the autonomic nervous system also is immature. There are different components of the autonomic nervous system. So we have our sympathetic system - the fight or flight system - and the parasympathetic system which is more the relaxed, calming part of our nervous system. During fetal life, the sympathetic system actually is onboard first and showing earlier maturation and it's the parasympathetic system that kind of gets triggered to mature later in gestational age, more towards term. So when a baby is born preterm, the relative component of the sympathetic system, or that fight part is higher than the parasympathetic system, which is that more calming part. So, when a baby is born preterm, the system may be unprepared to really help the baby transition properly and it may put the baby at risk for having blood pressure issues, problems with heart rate, respiratory regulation, and so ensuring that the system develops properly for babies born preterm is very important.

Geoff Marsh

And so if a preterm baby is born with a not fully developed autonomic nervous system, then the rest of their development has to happen in this completely unnatural environment...

Dr Sarah Mulkey

Yes, exactly. In the title of my paper, we call it the 'extra-uterine milieu'. If you think about the inside of the womb, the baby is in a nice, dark, warm place. They hear their mother's heartbeat and their gastric motility, and so it's just this calm environment where their nutrition is being provided for them and then when they're born prematurely, this baby is then whisked from this dark, warm, calm environment to the environment of a neonatal intensive care unit, which is vastly different. Their skin is exposed to the outside world and it's not as warm, there are lights, there's noise, there's beeping sounds of monitors, so it's very different. And now they need to develop that autonomic nervous system that is reacting to all of the things that it is exposed to but it's then developing in a very different environment than the intrauterine environment.

Geoff Marsh

And so could you bring us up to speed on the current thinking in the field about the evidence for how the autonomic nervous system development is different in premature infants?

Dr Sarah Mulkey

There have been previous studies looking at babies that are born preterm showing that their autonomic nervous system may not show much development in that time period from preterm birth to discharge from the NICU. In a previous study that we did, prior to this one, we looked at babies born at more extreme prematurity only, at 28 weeks or less, that needed care at a high-level NICU, and those babies, by the time that they were discharged, their autonomic nervous system was still underdeveloped compared to a term newborn.

Geoff Marsh

I wonder then, if you could justify the existence of this new study, how is it different to those previous studies and what exactly were you trying to get at?

Dr Sarah Mulkey

We had the opportunity to study preterm newborns at a delivery hospital, a high volume delivery hospital in a community that delivers about 10,000 babies per year. What we thought we were going to find in this study was that those babies that were born more preterm would have slower rates of development of their autonomic nervous system compared to other preterm babies that were born closer to their due date. What was so exciting to us was that we found that even those babies born really in the more preterm gestational age group - so under 28 weeks compared to those born more mid preterm or later preterm - they all showed a good rate of development of their autonomic nervous system in the NICU environment that we studied.

Geoff Marsh

So at the beginning they had this less mature nervous system, but you're saying that by the time they were discharged, that had sort of evened out, contrary to your predictions?

Dr Sarah Mulkey

Correct. Yes, so those babies born more preterm, their sympathetic tone and their parasympathetic tone was lowest. But yes, while they were in the NICU we saw that the slope of the development of

their autonomic tone, both sympathetic and parasympathetic, was actually very similar between all of the groups of our babies and that by the time they went home, even those most preterm babies in our study had similar autonomic tone to those preterm babies that were born in the later preterm group.

Geoff Marsh

I suppose the interesting thing about this study is to ask the question, why did these findings contradict those of previous studies? You mentioned that previous studies had more prematurity-associated systemic morbidities. I was really interested to read in your paper about the fact that you guys had adopted this kinder, gentler practice in your NICU.

Dr Sarah Mulkey

Yes, so I think it probably has to do with several different reasons. One is that if we look overall at the babies in this cohort, they were able to be cared for in this very good level 4 community NICU but they did not have to be transferred to other hospitals for neonatal surgeries or other very complex conditions. They really had a pretty low level of what we call prematurity-related morbidity. So I think that's part of why we saw their autonomic nervous system develop so well between all of the groups. The other thing that we really think has something to do with these good findings is that the NICU that we evaluated these studies in really has adopted a lot of the newer, more gentler approaches to neonatal intensive care that are happening in a lot of NICUs around the country and around the world, including private rooms where it's quieter, there's less light, more regulation of the sounds that the baby experiences. For babies that are born under 28 weeks at this NICU, they have an IVH bundle, or intraventricular hemorrhage bundle to try and limit IVH, which has been very successful for them. In that bundle they really have limited touch of the baby for three days, they do not do a head ultrasound for three days, do not weigh the baby, and bundle the care so that that baby is disturbed, for whatever cares are needed, at very limited time points. The other thing is that the parents of these babies live in the community and for the most part were very present during their babies neonatal intensive care unit stay and so often we would be coming in to evaluate the babies and the mother is there holding the baby, they do early skin-to-skin contact. They also try and limit invasive mechanical ventilation. So we have to speculate that all of these different approaches that are more gentle in the way that these babies were cared for, probably also promoted the autonomic nervous system development that we saw in these babies.

Geoff Marsh

I don't want to be completely non-scientific, but it makes intuitive sense, doesn't it, that an environment closer to the *in utero* environment, which is more natural, would promote the normal maturation of the autonomic nervous system?

Dr Sarah Mulkey

Yes, I think it does make a lot of sense that we want to have that baby in as calm of a NICU environment as possible to help promote this part of our nervous system that's learning how to react to its external world.

Geoff Marsh

Does that suggest that perhaps it's prematurity-associated morbidities which affect the autonomic nervous system maturation as opposed to the other way round?

Dr Sarah Mulkey

Yeah, so that's what we think. Obviously, being born preterm does deliver you into the world with a more immature autonomic nervous system, but that in the absence of having prematurity related morbidities and being in an environment that is supportive to your autonomic nervous system, the autonomic nervous system can develop quite well during the neonatal intensive care unit stay, and so we're actually working on another study comparing this cohort of babies that had the low level of prematurity related morbidities to preterm babies that were transferred in from their birth hospitals to our quaternary children's hospital and looking at the difference in their autonomic nervous system development during the NICU stay. And we do see that it's different. I think we need to take it further, so I only looked until these babies went home from the NICU. So after they go home from the NICU, are they as similar to a term born baby? It would be important to know. I'd also be very interested to delve into more about whether those babies whose mothers were present more, if they did more skin to skin contact, breastfeeding versus bottle feeding, and those kinds of interventions that we know are good for babies, to really try and study whether those are the features of this NICU that made the big difference for these babies. And then also to compare them to those babies with more morbidities to really understand whether it's the morbidities of prematurity that affect the autonomic development along with the birth gestational age, or is it really just the morbidities by themselves.

Geoff Marsh

That was fetal neonatal neurologist, Dr. Sarah Mulkey from the Children's National Hospital in Washington DC. And with that, we've reached the end of the episode. I hope you'll join us again next month. I'm Geoff Marsh. Thanks for listening.