Pediatric RESEARCH

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COMMENT

Placenta and perinatal brain injury: the gateway to individualized therapeutics and precision neonatal medicine

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Wu and colleagues analyzed the placental pathology from a subset of the neonates in the NEATO trial who had reports available and correlated the placental pathology findings with outcomes. This study highlights the importance of placental pathology, and its potential to bring precision medicine to critically-ill neonates. Placental pathology will likely aid stratification of neonates for clinical trials and accelerate progress for neurorepair.

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Wu et al.[1] analyzed the contribution of placental pathology to outcomes in the NEATO trial, a phase II, randomized, double-blind, placebo-controlled trial that tested the efficacy of erythropoietin (EPO), in addition to hypothermia, for term infants with hypoxic–ischemic encephalopathy. The primary results of the NEATO trial demonstrated that high doses of EPO plus hypothermia reduces brain injury, when compared to hypothermia alone.[2] While the analyses in this new report had the typical weaknesses of ancillary studies, essential information is provided on the importance of placental pathology. In particular, the contribution of the intrauterine environment in all infants with perinatal brain injury is emphasized, as is the necessity to retain placentae for essential clinical information. Specifically, this study highlights: (1) brain health in the context of the course of the entire pregnancy; (2) how the placenta is representative of intrauterine microenvironmental pathophysiology; (3) and the need for perinatal medicine to move towards the precision medicine methodologies. Precision approaches are now widely accepted and practiced in other areas of pediatrics, such as childhood cancer, where enormous inroads in efficacy and long-term outcomes have been achieved.

The authors relied on 35 available pathology reports rather than central review of actual histology in all 50 babies. The small sample size limited the strength of the analyses. However, the data highlight the need to bring the era of precision medicine to the care of fragile neonates. Sick newborns have very short lifespans from which to draw clues for stratification in clinical trials. As such, many neonatal intervention trials to improve neurological outcomes have resorted to broad inclusion criteria. This may be, however, an ineffective strategy, as it has now become clear that we need to consider the spectrum of insults that lead babies to suffer neonatal encephalopathy and other forms of perinatal brain injury.

For neonates, one source of significant individual and precise information on maternal, fetal, and intrauterine health is the placenta. In this study, 54% of placentae showed abnormalities. Infants who did not have placenta pathology available for review did not differ from those who did, except the placenta was less likely to be available for babies born by spontaneous unassisted vaginal delivery. Based on pathology reports, 13 (37%) were classified as "chronic" changes, while 9 (26%) exhibited "acute" chorioamnionitis, and 3 (9%) had signs of both acute and chronic abnormalities. Chronic placental abnormalities were defined as maternal vascular malperfusion, fetal vascular malperfusion, and villitis of unknown etiology. Notably, the babies with an acute or chronic placental abnormality had a lower mean head circumference, a surrogate for brain growth, which emphasizes the importance of a healthy placenta to support neurodevelopment. Despite the small sample size, these data highlight the role of placental health and neurodevelopment, consistent with numerous prior reports.[3,4]

The data presented in this trial underscore the importance of a cellular and molecular cascade of microenvironmental disruption commencing in utero prior to term delivery. It also emphasizes the importance of placental vascular issues, as well as infection. Indeed, placental hypoxia–ischemia is not benign in the context of the evolving brain injury in term birth, as has been noted in prior studies.[5–7] In the present study, acute pathological placental abnormalities were defined as histological signs of chorioamnionitis. Notably, only one of the nine women diagnosed with pathological chorioamnionitis, but no signs of chronic abnormalities, received a clinical diagnosis of chorioamnionitis. By contrast, only one of three women who had the clinical diagnosis of chorioamnionitis had histological signs of chorioamnionitis. This discrepancy between the clinical and histological diagnoses of chorioamnionitis in centers performing a clinical trial, and presumably particularly attuned to maternal–fetal health, is reminiscent of the stratification of brain cancers two decades ago prior to molecular classification. It also further confirms the poor alignment between a clinical and a histological diagnosis of chorioamnionitis.

While neonatal encephalopathy is the "classic" clinical scenario in the NICU, the catalysts to the pathophysiology may vary widely. Just as it has been recognized that detecting efficacy in intervention

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trials of severe traumatic brain injury in children and adults requires more mechanism-informed, precise stratification than the Glasgow Coma Score, babies with neonatal encephalopathy need defined and specific diagnoses that incorporate rigorous scientific advances that move beyond clinical presentation, basic neuroimaging, and histopathology. In the context of the data presented here, newborns with placentae demonstrating chronic changes of maternal or fetal malperfusion and villitis did not derive benefit from neonatal EPO. During an intervention trial, if newborns with chronic placental abnormalities had been excluded through explicitly defined criteria in the initial stratification, then the efficacy of EPO for those newborns without chronic placental abnormalities may have been more readily evident. Modifications such as this to trial design would decrease the number of subjects needed to enroll, and thus reduce both the time and expense of the clinical trial. Indeed, incorporation of the wealth of information in the placenta may refine stratification and inform both trial enrollment and outcome analyses. Future studies on the long-term imaging correlations, including diffusion, with placental pathology are also warranted.

Taken together, these data stress the need for precision in diagnostic criteria, terminology, and stratification of placental abnormalities, as well as standardized collection practices. Specifically, this report also reveals the necessity of placental collection and evaluation for all clinical trials on perinatal brain injury. In addition to insights from histopathology, proteomic and epigenetic analyses of placenta may be especially useful for assessing the impact of injury in the developing brain. A shift to retaining the placenta for possible histological, biochemical, and molecular analyses should be considered. If a newborn is discharged after an uneventful neonatal admission, then extensive pathological analyses might not be needed. Conversely, the information gleaned from potential stratification and accelerated advances in treatment would more than offset the extra costs of placenta analyses. However, implementation of new approaches are not without challenges. For placental pathology to truly enter the domain of precision medicine, histological information or molecular surrogate biomarkers will need to be rapidly available, with information gathered in real time to facilitate diagnosis and urgent treatment. Notably, time is a major barrier to implementation of many biomarker approaches using the placenta. Pathological analyses requires expert procedures and interpretation, and emerging proteomic or epigenetic approaches may take even longer time.[8] Importantly, it is likely that acute and chronic in utero central nervous system (CNS) injuries will require different postnatal identification and treatment strategies, with development of separate, specific, rapid molecular biomarker assays. Despite these challenges, more studies have linked perinatal, childhood, and long-term neurodevelopmental outcomes with placental histology and molecular markers across the spectrum of perinatal brain injury, including prenatal opioid and alcohol exposure, CNS injury from preterm birth and intraventricular hemorrhage, and neurotoxin exposure.[9–12] While the final diagnosis may be the same, neonatal encephalopathy at term, just like chorioamnionitis, likely exists as a spectrum of illnesses with unique features that our current classification systems gloss over, relative to the precision offered by molecular characterization. Arguably, repair of the injured developing nervous system, and its lifelong consequences, is one of the greatest remaining challenges faced in clinical practice, and deserving of the most advanced methodologies available.

AUTHOR CONTRIBUTIONS

L.L.J. and S.R. drafted the commentary, and edited and approved the final manuscript.

ADDITIONAL INFORMATION

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