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COMMENT

Prematurity and perinatal inflammation is associated with a complex electroencephalographic phenotype

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Pediatric Research (2022) 92:20–21; https://doi.org/10.1038/s41390-022-02100-0

A meta-analysis was performed by the authors in this issue regarding perinatal inflammation in preterm infants who were assessed by electroencephalography (EEG).[1] Their selected methodology resulted in only 2 studies from 41 eligible articles that met their chosen criteria. These authors' critique based on these two studies concluded that a meta-analysis could not be performed given the small number of subjects with heterogeneity in study design. Both studies statistically compared selected prenatal and neonatal variables with amplitude-integrated EEG (aEEG) findings. Only one study assessed correlations with specific reference to placental findings concerning clinical and histologically confirmed chorioamnionitis and lesions of malperfusion. Preclinical and clinical research articles were discussed that support an association of perinatal inflammation with altered EEG maturation. These authors advocated for the use of conventional EEG to assess preterm children associated with inflammatory etiologies, stressing peripartum timing of diseases that promote brain injury.

Prematurity is a complex phenotype as assessed by postnatal EEG monitoring. EEG-state analyses offer a comprehensive interpretation of inter-related cerebral and noncerebral behaviors representing neuronal activities.[2] This neurophysiologic monitoring tool reflects complicated interdependences among brain circuitries throughout the neuroaxis. EEG-state studies provide a continuous record of EEG patterns that represent cerebral activities in relation to subcortical input from autonomic, rapid eye movement, and motility parameters. Caudal to cephalad expressions of these physiologic behaviors change across developmental time with brain maturation.

Each physiologic biomarker in an EEG-state study serves as one complex phenotype within a specific brain region, subserved by interconnected neuronal activities to other complex phenotypes. Each behavior depicts the flow of information from genomic, molecular, cellular, tissue into organism networks explained by a systems biology perspective. Serial EEG-states also express postnatal continuity of trimester-specific brain function influenced by the interactions among multisystemic components of the maternal, placental, fetal (MPF) triad, and neonate. These neurophysiologic activities provide a proxy for gene–environment interactions (G × E) influencing the MPF triad with origins before conception. Interpretations of these studies offer a comprehensive functional neurologic profile over the first 1000 days to be applied for clinical and research use.[3]

Trimester-specific G × E interactions influence the MPF triad and neonate with favorable or adverse outcomes. Visual and computer-analyzed neonatal EEG-sleep states provide diagnostic and prognostic insights regarding time-dependent inter-relationships among multiple organ systems. Neurophysiologic recordings can be applied to comparisons of functional brain organization and maturation between preterm and full-term infants who are healthy or express disease. Bedside aEEG analyses extend the neurophysiologic interpretations of conventional EEG-state studies for medically fragile infants who better tolerate one or two electrodes while clinically unstable.

The child born prematurely is more likely than the term infant to experience brain maldevelopment or injury as part of a MPF triad. These adverse neurologic outcomes result from both diseases and environmental stressors. Healthy conditions are required beginning with a woman's reproductive health prior to conception. Placental implantation and development following conception depend upon immunological tolerance between mother and embryo–fetus to maintain viability and health for more optimal MPF triad development as pregnancy progresses. Disease pathways such as maternal immune activation[4] begin during the first trimester that alter gas exchange, nutrients, and growth factor delivery. Ischemic placental syndrome[5] follows as a second and third trimester disease of angiogenesis that further compromises fetal health and viability. These antepartum conditions then contribute to abnormal neonatal outcomes after perinatal stresses closer to delivery such as those associated with multiple forms of the inflammatory state. Successful transition from fetal to neonatal life requires a healthy triad prior to and during the perinatal period. Combined etiopathogenetic mechanisms during the prenatal period contribute to suboptimal outcomes for the MPF triad and neonate when further stressors or disease occur closer to, during, and after parturition.

Infectious and noninfectious inflammatory processes during pregnancy potentially alter embryonic–fetal brain precursor neuronal populations, beginning before appearance of the neural plate at 17–19 days after conception. Diverse maternal diseases include infectious, hypertensive, metabolic, autoimmune, and mental health disorders. Different combinations of conditions contribute to altered brain development or injury mediated through abnormal neuronal pathways. These mechanisms for placental disease are mediated by abnormal trophoblastic cellular development even prior to the placenta assuming primary

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Received: 30 March 2022 Accepted: 10 April 2022
Published online: 25 May 2022

responsibility to sustain the fetus after 8 weeks gestational age. Inflammatory conditions as delivery approaches contribute to abnormal maternal and fetal outcomes, including prematurity, premature rupture of membranes, fetal demise, and preeclampsia, often superimposed on earlier disease states. Neonatal depression with or without ongoing encephalopathic signs collectively represent antepartum and peripartum adverse conditions that reflect brain structure and function. Neonatal medical complications potentially worsen brain injuries that had prenatal origins.

One classification scheme suggested 12 distinct phenotypic categories of prematurity, although 30% of this cohort could not be identified by the etiologies identified using selected demographic, clinical, and sonographic data.[6] Prematurity represents a complex condition resulting from G × E interactions affecting the MPF triad and neonate.[7] Trimester-specific maladaptive responses can consequently alter the brain. Genetic resilience or vulnerability based on inherited, de novo, and epigenetic modifications reflect mitotic and postmitotic aberrations that adversely influence the MPF triad over time. Impaired neuronal pathways alter neuroplasticity within interconnected structures as the developing nervous system matures.

Encephalopathy of prematurity (EP) more recently redefined a historically older concept in evolutionary biology, combining diagnostic consideration of developmental and destructive processes.[8] EP can be assessed by EEG-state analyses when considering the influences of prenatal and postnatal conditions. The choice of any one diagnostic study following delivery for a preterm child must consider how to evaluate brain structure and function most accurately. The clinician needs to consider the developmental niche when a disease state initially began in relation to when clinical expression documented abnormalities. There may be a considerable time lag between disease onset and phenotypic presentation.

There is an important role for 1–2 channel quantified aEEG signals for critically ill preterm infants who require close supportive medical supervision without excessive physical manipulation. This technology can best be applied by comparing results with serial conventional EEG sleep studies. Multiple cerebral and non-cerebral channels better depict brain health or disease by considering the nervous system responses to primary brain disorders or systemic diseases that secondarily impair the brain. Neurophysiologic technologies can be optimally applied to clinical situations by first integrating knowledge of MPF triad factors that preceded and/or occurred concurrent with perinatal conditions that include but are not limited to inflammatory states. Neurophysiologic monitoring combined with clinical signs, metabolic–genetic studies, and neuroimaging provides a more comprehensive assessment from acute through convalescent phases of neonatal care. Neurologic sequelae expressed during childhood and adulthood have developmental origins during the first 1000 days, as represented by structural and functional studies.

Placental cord analyses are an important post hoc verification of acute and chronic disease processes that precede and/or occur contemporaneously with perinatal conditions, such as inflammatory states. As with any diagnostic test, pathological analyses have limitations in sensitivity and specificity of MPF triad diseases. Recent international consensus guidelines presented four categories of pathological lesions with clinical relevance, including chorioamnionitis/funisitis, villitis, villous dysmaturity, and maternal–fetal malperfusion.[9] These guidelines require revisions, as developmental neuroscience and placental research advances reveal new relationships. Adverse influences of neuroinflammation by microglial activation, for example, adversely affect diverse neuronal populations through trimester-specific G × E effects on MPF triad and neonatal health.[3]

Single institution or multi-institutional studies need to examine larger and more homogenous cohorts, applying more accurate cluster analyses of factors applicable to population-based and patient-specific situations to best assign diagnostic and therapeutic protocols. Innovative prenatal genetic and brain–placental magnetic resonance imaging studies will better predict adverse outcomes starting during prenatal life when more effective neurotherapeutics can be offered. More effective neurocritical care interventions can then more selectively offer appropriate options to prevent, rescue, or repair brain injuries.[10]

Fetal neurologists should offer consultations early during fetal brain maturation to initiate this trimester-specific diagnostic process. Modifications as the pregnancy continues can be planned through interdisciplinary collaboration, dependent on maternal levels of medical care. Neonatal neurology consultations then can include EEG-state and aEEG studies to diagnose and monitor brain disorders. Neurophysiological studies offer a functional measure of preserved or abnormal brain activities that complement other diagnostic tools, such as neuroimaging and neurogenetic analyses. Integration of all testing results can be effectively applied to a diagnostic process that more accurately predicts neurologic sequelae and provides effective interventions to lower neurologic burden of disease.

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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