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## We Need New Tools to Evaluate Neurological Development *in Utero* and after Birth

Fetuses, newborns, and young infants are highly susceptible to neurological injury.[1,2] Damage to primordial structures during early development can result in malformations.[3–5] Later, injuries can disrupt many of these basic structures in the growth phase.[6,7] Many infectious and non-infectious stimuli can trigger inflammation with its changes, including vasomotor dysregulation with edema and temperature instability, and leukocytosis.[8,9] Our ability to restore damaged neurological structures is still limited, and therefore, the emphasis remains on early detection by cranial imaging and supportive measures.[4,10,11]

Similar to diseases affecting other organs, the debate continues about the relative contribution of infectious agents, vasomotor changes, and immaturity of the immune system in the pathogenesis of various neurodevelopmental disorders.[12] Many infectious agents that affect the fetus *in utero* or during early infancy cannot be treated in a timely fashion.[13] Many drugs still need evaluation, and some that are currently in use have limited efficacy.[14] Others have had unacceptable short- and long-term adverse effects.[15] To appropriately tailor these treatments and minimize risk, accurate neuroimaging is important for early detection of pathogen-induced and other inflammatory changes.[16,17] If we can understand the temporal evolution of these changes, we might be able to make a difference. There is a need for monitoring paradigms and new treatments. All treatment modalities are not uniformly available or affordable in different parts of the world, and hence there is a need for computational systems to assess, monitor, and treat these highly susceptible patients.[18] If we know the possibilities, we can educate and motivate our care providers to acquire and learn these tools.[19]

Our journal, the *Newborn* aims to cover fetal/neonatal problems that begin during pregnancy or occur after birth during the first 1000 days after birth. In this 2nd issue of the second volume, we present 8 important articles **(Figure 1)**. In an original study, McLean et al.[20] evaluated a cranial ultrasound scoring system for prediction of abnormal early neurodevelopment in preterm infants. In a retrospective, single-center study, they studied cranial ultrasound scans of 242 preterm infants at a chronological age of 6 weeks to compare this scoring system to conventional sonographic detection of abnormalities such as intracranial hemorrhages, white matter lesions, and cystic periventricular leukomalacia.[21–23] The aim was to determine whether the scoring system could enhance our accuracy in predicting developmental delay or cerebral palsy (CP) in preterm infants.[24,25] They did not find any differences in sensitivity/specificity[26] when the entire cohort was studied. However, in the subset with severe cranial ultrasound abnormalities, the cUS scores showed higher sensitivity (57% vs. 27%, [95% CI: 12 to 49]) but lower specificity (68% vs. 96%, [95% CI: -21 to -34]) for predicting CP. Similarly, there was higher sensitivity (44% vs. 12% [95% CI: 23 to 41]) but lower specificity (74% vs. 98%, [95% CI: -15 to -32]) for developmental delay. These newer methods of clinical screening can help in prioritization, use of specific neuroimaging protocols and laboratory investigations, tailoring of therapeutic methods, and the frequency and goals of follow-up.[27]

There are two important studies in this issue that focused on necrotizing enterocolitis and chorioamnionitis, respectively. In addition to local effects in the damaged organ systems, both these conditions are known to affect neurodevelopmental outcomes.[28–34] In the first, Rothers et al.[35] compared patients with necrotizing enterocolitis (NEC) and controls and evaluated the impact of enteral feeding and antibiotic treatment on stool total bile acid (TBA) content. Accumulation of ileal bile acids is a crucial component of NEC pathophysiology; infants who develop NEC show high coefficients of variation of TBAs (CV-TBAs).[36,37] High values for CV-TBA levels predicted NEC status among infants, but the type of feeds and antibiotic usage did not drive this relationship. In the second study, Buchanan and colleagues[38] examined Th17 and calgranulin responses in maternal-cord blood dyads of preterm gestations with histologic chorioamnionitis.[39] Our understanding of the Th17 responses in chorioamnionitis is relatively limited.[40] The authors have examined Th17 responses[41] in 47 maternal–cord blood dyads of preterm gestations,[42] for Th17-linked cell frequencies and plasma calgranulin (S100A8, S100A12).[43–45] In those with fetal inflammation, there was increased frequency of Th17 cells and plasma levels of calgranulin.[46,47] Cord blood S100A12

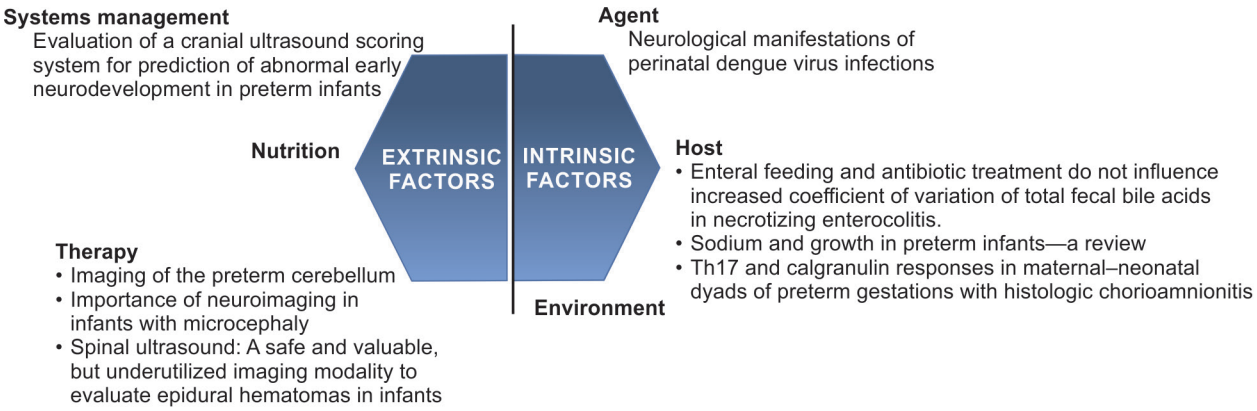


Fig. 1: **Areas of focus in the *Newborn*, volume 2, issue 2.** The *Newborn* has expanded the traditional agent-host-environment trinodal disease model to a hexagonal system. The three additional foci represent extrinsic factors that can affect health; these originate in therapy, nutrition, and systems management. In volume 2, issue 2, we cover 4 of these foci, namely infectious diseases, host factors, therapy, and systems management.

levels correlated with Th17 cell frequencies.[48] These data are interesting and are likely to evoke further examination in larger samples and in appropriate animal models.[49]

This issue carries considerable information on emerging goals and methods of neurological imaging in premature and critically ill infants. Rangwani and her colleagues[50] have provided an overview of the overall evaluation of microcephaly, a head (occipitofrontal) circumference that is 2 standard deviations or lesser than average, accounting for age and gender.[51,52] We can now use neuroimaging to enhance current methods of clinical evaluation. They have described the implications of altered brain volume, the size and shape of the skull, and the timing of onset of these abnormalities.[17] There is a clear need for a multifaceted approach. In another article, Kalamdani and coworkers[53] have focused on the role of medical imaging in the assessment of cerebellar injury in preterm infants. The cerebellum continues to grow during the 3rd trimester and is at a higher risk of structural abnormalities resulting from altered formation or partial destruction.[54] The authors have summarized the advances in posterior fossa imaging and the appearance of various abnormalities on cranial ultrasound and high-resolution anatomical and functional magnetic resonance imaging (MRI). The role of advanced MRI modalities like functional MRI,[55] diffusion tensor imaging,[56] and MR spectroscopy[57] are also discussed in some detail. In another article, Ogu et al.[58] have described a series of cases where they used spinal ultrasound to evaluate epidural hematomas.[59] The accessibility, cost-effectiveness, and accuracy of spinal ultrasound make it an appealing alternative to MRI.[60] They have discussed the advantages of incorporating spinal ultrasound into clinical practice for timely and convenient diagnosis of spinal epidural hematomas in neonates and young infants.

Araya et al.[61] have reviewed sodium homeostasis in neonates. In premature and critically ill term infants, sodium depletion has important implications in extrauterine growth restriction and cardiometabolic and neurodevelopmental disorders.[62] There are compelling data from animal models, which still need to be confirmed in human subjects. The authors aim to increase the awareness of sodium homeostasis in preterm infants and have provided sodium intake recommendations based on currently available literature.

Finally, Singh and coworkers[63] have described neurological manifestations of perinatal dengue. Dengue viruses are single-stranded RNA viruses; these are mosquito-borne human pathogens seen in periequitorial and tropical regions.[64,65] Mother-to-fetus transmission of the virus leads to congenital dengue disease.[66] These should be suspected in endemic regions in infants with fever, a maculopapular rash, and thrombocytopenia. Neurological manifestations include intracerebral hemorrhages, neurological malformations, and acute focal/disseminated encephalitis/encephalomyelitis.[67] We do not have proven specific therapies yet; supportive management is focused on close monitoring and maintenance of intravascular volumes.

## References


1. Baburamani AA, Ek, CJ, Walker DW, Castillo-Melendez M. Vulnerability of the developing brain to hypoxic-ischemic damage: contribution of the cerebral vasculature to injury and repair? Front Physiol 2012;3:424.
2. Vaccarino FM, Ment LR. Injury and repair in developing brain. Arch Dis Child Fetal Neonatal Ed 2004;89:F190–192.
3. Ferrer-Vaquer A, Hadjantonakis AK. Birth defects associated with perturbations in preimplantation, gastrulation, and axis extension: from conjoined twinning to caudal dysgenesis. Wiley Interdiscip Rev Dev Biol 2013;2:427–442.
4. Glenn OA, Barkovich AJ. Magnetic resonance imaging of the fetal brain and spine: an increasingly important tool in prenatal diagnosis, part 1. AJNR Am J Neuroradiol 2006;27:1604–1611.
5. Ismail KM, et al. Fetal magnetic resonance imaging in prenatal diagnosis of central nervous system abnormalities: 3-year experience. J Matern Fetal Neonatal Med 2002;12:185–190.
6. Hennekam RC, et al. Elements of morphology: general terms for congenital anomalies. Am J Med Genet A 2013;161A:2726–2733.
7. Reichel TF, et al. Fetal central nervous system biometry on MR imaging. AJR Am J Roentgenol 2003;180:1155–1158.
8. Morley LC, Debant M, Walker JJ, Beech DJ, Simpson NAB. Placental blood flow sensing and regulation in fetal growth restriction. Placenta 2021;113:23–28.
9. Bartkeviciene D, et al. Leukocytosis as a prognostic marker in the development of fetal inflammatory response syndrome. Libyan J Med 2013;8:21674.
10. Moltoni G, Talenti G, Righini A. Brain fetal neuroradiology: a beginner's guide. Transl Pediatr 2021;10:1065–1077.
11. Glenn OA, Barkovich J. Magnetic resonance imaging of the fetal brain and spine: an increasingly important tool in prenatal diagnosis: part 2. AJNR Am J Neuroradiol 2006;27:1807–1814.
12. Rohrer JE, Grover ML, Moats CC. Utilising the epidemiologic triad in analysing quality improvement data: antibiotic use for respiratory infections as a case example. Qual Prim Care 2013;21:165–170.
13. Arora N, Sadovsky Y, Dermody TS, Coyne CB. Microbial Vertical Transmission during Human Pregnancy. Cell Host Microbe 2017;21:561–567.
14. Turner MA. Clinical trials of medicines in neonates: the influence of ethical and practical issues on design and conduct. Br J Clin Pharmacol 2015;79:370–378.
15. Allegaert K, van den Anker JN. Adverse drug reactions in neonates and infants: a population-tailored approach is needed. Br J Clin Pharmacol 2015;80:788–795.
16. Sorokan ST, Jefferies AL, Miller SP. Imaging the term neonatal brain. Paediatr Child Health 2018;23:322–328.
17. Dubois J, et al. MRI of the neonatal brain: A review of methodological challenges and neuroscientific advances. J Magn Reson Imaging 2021;53: 1318–1343.
18. Coleman JJ, Ferner RE, Evans SJ. Monitoring for adverse drug reactions. Br J Clin Pharmacol 2006;61:371–378.
19. Raschle N, et al. Pediatric neuroimaging in early childhood and infancy: challenges and practical guidelines. Ann N Y Acad Sci 2012;1252:43–50.
20. McLean G, Razak A, Ditchfield M, Lombardo P, Malhotra A. Evaluation of a cranial ultrasound scoring system for prediction of abnormal early neurodevelopment in preterm infants. Newborn 2023;2(2):122–127.
21. Van Camp L, Steyaert L. Cystic periventricular leukomalacia: A condition that became uncommon in the premature neonate, diagnosed on transcranial ultrasound. J Belg Soc Radiol 2016;100:8.

22. Rogers B, et al. Cystic periventricular leukomalacia and type of cerebral palsy in preterm infants. J Pediatr 1994;125:S1–8.
23. Tan AP, Svrckova P, Cowan F, Chong WK, Mankad K. Intracranial hemorrhage in neonates: A review of etiologies, patterns and predicted clinical outcomes. Eur J Paediatr Neurol 2018;22:690–717.
24. Petersen MC, Kube DA, Palmer FB. Classification of developmental delays. Semin Pediatr Neurol 1998;5:2–14.
25. Sun H, et al. Machine Learning-Based Prediction Models for Different Clinical Risks in Different Hospitals: Evaluation of Live Performance. J Med Internet Res 2022;24:e34295.
26. Shreffler J, Huecker MR. Diagnostic testing accuracy: Sensitivity, specificity, predictive values and likelihood ratios. Updated 2023 Mar 6. In *StatPearls [Internet]*. StatPearls Publishing, Treasure Island (FL), 2023.
27. Pacurar EE, et al. Database integration of protocol-specific neurological imaging datasets. Neuroimage 2016;124:1220–1224.
28. Lu J, Martin CR, Claud EC. Neurodevelopmental outcome of infants who develop necrotizing enterocolitis: The gut-brain axis. Semin Perinatol 2023;47:151694.
29. Hickey M, Georgieff M, Ramel S. Neurodevelopmental outcomes following necrotizing enterocolitis. Semin Fetal Neonatal Med 2018;23:426–432.
30. Rees CM, Pierro A, Eaton S. Neurodevelopmental outcomes of neonates with medically and surgically treated necrotizing enterocolitis. Arch Dis Child Fetal Neonatal Ed 2007;92:F193–198.
31. Xiao D, et al. Maternal chorioamnionitis and neurodevelopmental outcomes in preterm and very preterm neonates: A meta-analysis. PLoS One 2018;13(12):e0208302.
32. Tsamantioti E, Lisonkova S, Muraca G, Ortqvist AK, Razaz N. Chorioamnionitis and risk of long-term neurodevelopmental disorders in offspring: a population-based cohort study. Am J Obstet Gynecol 2022;e281–287,e17.
33. Polam S, Koons A, Anwar M, Shen-Schwarz S, Hegyi T. Effect of chorioamnionitis on neurodevelopmental outcome in preterm infants. Arch Pediatr Adolesc Med 2005;159:1032–1035.
34. Soraisham AS, Trevenen C, Wood S, Singhal N, Sauve R. Histological chorioamnionitis and neurodevelopmental outcome in preterm infants. J Perinatol 2013;33:70–75.
35. Rothers JL, Calton CM, Stepp JMB, Halpern MD. Enteral feeding and antibiotic treatment do not influence increased coefficient of variation of total fecal bile acids in necrotizing enterocolitis. Newborn 2023;2(2):128–132.
36. Halpern MD, et al. Bile acids induce ileal damage during experimental necrotizing enterocolitis. Gastroenterology 2006;130:359–372.
37. Knapp S, et al. Elevated coefficient of variation in total fecal bile acids precedes diagnosis of necrotizing enterocolitis. Sci Rep 2020;10:249.
38. Buchanan CQ, et al. Linked Th17 and calgranulin responses in maternal-cord blood dyads of preterm gestations with histologic chorioamnionitis Newborn 2023;2(2):133–141.
39. Conti N, et al. Term histologic chorioamnionitis: a heterogeneous condition. Eur J Obstet Gynecol Reprod Biol 2015;188:34–38.
40. Goldstein JA, Gallagher K, Beck C, Kumar R, Gernand AD. Maternal-fetal inflammation in the placenta and the developmental origins of health and disease. Front Immunol 2020;11:531543.
41. Crome SQ, Wang AY, Levings MK. Translational mini-review series on Th17 cells: function and regulation of human T helper 17 cells in health and disease. Clin Exp Immunol 2010;159:109–119.
42. Black A, Bhaumik S, Kirkman RL, Weaver CT, Randolph DA. Developmental regulation of Th17-cell capacity in human neonates. Eur J Immunol 2012;42:31–319.
43. Longbottom D, Sallenave JM, van Heyningen V. Subunit structure of calgranulins A and B obtained from sputum, plasma, granulocytes and cultured epithelial cells. Biochim Biophys Acta 1992;1120:215–222.
44. Wang S, et al. S100A8/A9 in Inflammation. Front Immunol 2018;9:1298.
45. Meijer B, Gearry RB, Day AS. The role of S100A12 as a systemic marker of inflammation. Int J Inflam 2012;907078.
46. Viemann D. S100-Alarmins are essential pilots of postnatal innate immune adaptation. Front Immunol 2020;11:688.
47. Saito S, Nakashima A, Shima T, Ito M. Th1/Th2/Th17 and regulatory T-cell paradigm in pregnancy. Am J Reprod Immunol 2010;63:601–610.
48. Golubinskaya V, et al. Expression of S100A alarmins in cord blood monocytes is highly associated with chorioamnionitis and fetal inflammation in preterm infants. Front Immunol 2020;11:1194.
49. Swearengen JR. Choosing the right animal model for infectious disease research. Animal Model Exp Med 2018;1:100–108.
50. Rangwani S, Orman G, Mhanna M, Maheshwari A, Huisman TAGM. Importance of neuroimaging in infants with microcephaly. Newborn 2023;2(2): 147–156.
51. Harris SR. Measuring head circumference: Update on infant microcephaly. Can Fam Physician 2015;15:680–684.
52. Hanzlik E, Gigante J. Microcephaly. Children (Basel) 2017;4.
53. Kalamdani P, Athalye-Jape G, Desai S, et al. Imaging of the preterm cerebellum. Newborn 2023;2(2):115–121.
54. Spoto G, et al. Cerebellum and prematurity: A complex interplay between disruptive and dysmaturational events. Front Syst Neurosci 2021;15:655164.
55. Glover GH. Overview of functional magnetic resonance imaging. Neurosurg Clin N Am 2011;22(2):133–139.
56. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. Neurotherapeutics 2007;4:316–329.
57. Kreis R, et al. Terminology and concepts for the characterization of in vivo MR spectroscopy methods and MR spectra: Background and experts' consensus recommendations. NMR Biomed 2020;34:e4347.
58. Ogu JC, Adindu E, Ogu J, Maheshwari A, Huisman TAGM. Spinal ultrasound: A safe and valuable, but underutilized imaging modality to evaluate epidural hematomas in infants. Newborn 2023;2(2):172–177.
59. Aoki N. Epidural haematoma in the newborn infants: therapeutic consequences from the correlation between haematoma content and computed tomography features. A review. Acta Neurochir (Wien) 1990;106:65–67.
60. Nair N, Sreenivas M, Gupta AK, Kandasamy D, Jana M. Neonatal and infantile spinal sonography: A useful investigation often underutilized. Indian J Radiol Imaging 2016;26:493–501.
61. Araya BR, Ziegler AA, Grobe CC, Grobe JL, Segar JL. Sodium and growth in preterm infants: A review. Newborn 2023;2(2):142–146.

62. Greenberg JH, Tufro A, Marsenic O. Approach to the treatment of the infant with hyponatremia. Am J Kidney Dis 2015;65:513–517.
63. Singh S, Allaha JA, Panghal A, Maheshwari A, Boppana S. Neurological manifestations of perinatal dengue. Newborn 2023;2(2):157–171.
64. Clyde K, Kyle JL, Harris E. Recent advances in deciphering viral and host determinants of dengue virus replication and pathogenesis. J Virol 2006;80:11418–11431.
65. Malavige GN, Fernando S, Fernando DJ, Seneviratne SL. Dengue viral infections. Postgrad Med J 2004;80:588–601.
66. Basurko C, et al. Estimating the risk of vertical transmission of dengue: A prospective study. Am J Trop Med Hyg 2018;98:1826–1832.
67. Li GH, Ning ZJ, Liu YM, Li XH. Neurological manifestations of dengue infection. Front Cell Infect Microbiol 2017;7:449.

**Akhil Maheshwari,** MD
**Kei Lui,** MD
**Mario Motta,** MD