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Electroencephalography May Provide Insight Into Timing of Premature Brain Injury

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The report by Kidokoro et al¹ in this issue of *Pediatrics* addresses the potential roles of electroencephalography in (1) diagnosis of periventricular leukomalacia (PVL) and (2) determination of its severity in premature infants (gestational age < 33 weeks). The authors concluded that to accomplish these goals, at least 2 electroencephalograms are needed, 1 within 48 hours of birth to detect “acute-stage abnormalities” (ASAs) and another in the second week of life to detect “chronic-stage abnormalities” (CSAs). The severity of both ASAs and CSAs correlated with the severity of PVL. The findings have implications for 2 major issues: (1) the diagnosis of PVL and (2) the timing of the insult(s) that led to the white-matter lesion.

Before addressing the 2 major issues just noted, it must be emphasized that the infants with PVL as defined in this study likely represent only the minority of premature infants with subsequent neurodevelopmental disability. Thus, the “final diagnosis of PVL” in the study by Kidokoro et al was made for only 7.6% of the study population ($n = 723$) at 24 months of age by the demonstration of both white-matter volume loss by MRI and spastic diplegia or quadriplegia (ie, cerebral palsy) by neurologic assessment. The majority of the infants had had “cystic” lesions (echolucencies) according to neonatal cranial ultrasound scans. The important point is that the infants in this study represent the severe end of the spectrum of brain injury in premature infants. Fully 25% to 50% of infants of <1500 g birth weight exhibit cognitive/attentional/behavioral/socialization defects, predominately without cerebral palsy and with less severe MRI-demonstrable white-matter abnormality.² Thus, the infants reported by Kidokoro et al represent a severely affected subset of the premature population.

Concerning the role of electroencephalography in the diagnosis of PVL, earlier work by Watanabe et al and others^{3–7} has shown that the finding of positive rolandic sharp waves was specific but not very sensitive for identification of overt cystic PVL. The demonstration of occipital sharp waves (negative polarity) and frontal sharp waves (positive polarity) increased sensitivity for cystic PVL. Most commonly, these abnormal sharp waves appeared in the second week of life, and the cystic abnormalities appeared on cranial ultrasound scans in the third week. However, for detection of less severe white-matter disease, this outstanding Japanese group turned to serial electroencephalographic studies, with an emphasis on ASAs, characterized by increasing degrees of discontinuity, slow frequencies, and attenuated voltage, and CSAs, characterized by “deformed” slow activity and abnormal sharp waves, including those noted above.^{1,8–10} In the current report, the most common

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sequence of findings was ASA in the first 4 days of life and CSA in the next 10 days. The severity of the early ASA and the later CSA correlated with the severity of PVL, with the most severe electroencephalographic abnormalities observed in infants who evolved to show “extensive cystic PVL.”

The electroencephalogram was not a perfect diagnostic tool; thus, ~10% of the infants with PVL (all noncystic) had normal electroencephalogram results at all 3 time periods of the study (1–4, 5–14, and 15–28 days). However, cranial ultrasonography has similar deficiencies in diagnosis; for example, in a recent large study, 43% (51 of 120) of premature infants with later cerebral palsy had normal neonatal cranial ultrasound study results.¹¹ In another report, ~10% of premature infants with later cerebral palsy had normal ultrasonographic study results.¹² Moreover, concerning cystic PVL, De Vries et al¹² have shown that late ultrasound studies are important for detection; of 35 cases of cystic PVL, cysts were apparent at ≤ 14 days in only 10%, and of the 90% in which cysts were detected after 14 days, ~50% did not exhibit cysts until >28 days.¹² Neonatal MRI is superior to ultrasonography for detection of less severe PVL¹³ and for prediction at term of later cerebral palsy.^{14,15} For prediction of neurodevelopmental disability without cerebral palsy, the most common clinical constellation in premature survivors, the value of MRI for detection of white-matter abnormalities by either conventional methods (eg, diffuse high signal intensity) or advanced methods (eg, altered measures of overall diffusion or of anisotropic diffusion) was strongly supported by recent work.^{2,15–19}

These observations indicate that MRI in the neonatal period, perhaps near term-equivalent age, is the most effective tool for identification of a broad spectrum of white-matter injury in premature infants. The screening role for ultrasonography in detection of relatively severe injury is supported, especially when high-resolution transducers are used and studies are conducted beyond 28 days of age.¹² An additional value for serial electroencephalography in detection of relatively severe disease is suggested by the work of Kidokoro et al,¹ but the particular skill of this group in interpretation of electroencephalograms of premature infants may be difficult to replicate in many medical centers.

Concerning the value of electroencephalography in identification of the timing of the insult that leads to PVL, the data of Kidokoro et al¹ are of particular interest. Thus, ASAs were apparent in the first 2 weeks in 62% of the infants, usually between days 1 and 4. CSAs generally appeared later, most often between days 5 and 14. Notably, in a previous study this group showed that ASAs, especially severe ASAs, were present most often on days 1 and 2 and not on the day of birth.⁸ These findings are consistent with available ultrasonographic findings. In the study by Kidokoro et al,¹ no infants showed ultrasound abnormalities at birth, echogenicities appeared first between the second and fourth days of life, and the mean interval between echogenicities and echolucencies (“cysts”) was 16 to 18 days, consistent with timing of tissue dissolution after focal necrosis in the newborn.² Similarly, in the study by De Vries et al,¹² cysts appeared after 15 days of age in 90% and after 28 days in 50% of the subjects. Taken together, the data suggest that, at least in these relatively severe forms of PVL with later cerebral palsy, the most common timing of the responsible insult(s) was near the time of birth or very early after birth. The likely nature of the insult(s) has been discussed in detail elsewhere,² but various combinations of infection/systemic inflammation and hypoxia-ischemia seem most plausible.

This timing of the responsible insult(s) has important implications for the formulation of potentially protective interventions such as antioxidants, glutamate receptor antagonists, etc^{2,20} and raises the possibility that, in some cases, such interventions may be needed for only a relatively brief period. However, this conclusion may not be correct for less severe PVL and its associated neuronal deficits, not studied by Kidokoro et al in this study, in

which there may be more protracted action of pathogenetic factors and, thus, a need for longer periods of protective intervention.

ABBREVIATIONS

PVL	periventricular leukomalacia
ASA	acute-stage abnormality
CSA	chronic-stage abnormality

References

1. Kidokoro H, Okumura A, Hayakawa F, et al. Chronological changes in neonatal electroencephalographic findings in periventricular leukomalacia. *Pediatrics* 2009;124(3):e477–e484.
2. Volpe, JJ. *Neurology of the Newborn*. 5. Philadelphia, PA: Elsevier; 2008.
3. Baud O, D'Allest AM, Lacaze-Masmonteil T, et al. The early diagnosis of periventricular leukomalacia in premature infants with positive rolandic sharp waves on serial electroencephalography. *J Pediatr* 1998;132(5):813–817. [PubMed: 9602191]
4. Watanabe K, Hayakawa F, Okumura A. Neonatal EEG: a powerful tool in the assessment of brain damage in preterm infants. *Brain Dev* 1999;21(6):361–372. [PubMed: 10487468]
5. Vermeulen EJ, Sie LTL, Jonkman EJ, et al. Predictive value of EEG in neonates with periventricular leukomalacia. *Dev Med Child Neurol* 2003;45(9):586–590. [PubMed: 12948325]
6. Sofue A, Okumura A, Hayakawa F, Watanabe K. Sharp waves in preterm infants with periventricular leukomalacia. *Pediatr Neurol* 2003;29(3):214–217. [PubMed: 14629903]
7. Okumura A, Hayakawa F, Kato T, et al. Abnormal sharp transients on electroencephalograms in preterm infants with periventricular leukomalacia. *J Pediatr* 2003;143(1):26–30. [PubMed: 12915820]
8. Maruyama K, Okumura A, Hayakawa F, Kato T, Kuno K, Watanabe K. Prognostic value of EEG depression in preterm infants for later development of cerebral palsy. *Neuropediatrics* 2002;33(3):133–137. [PubMed: 12200742]
9. Kubota T, Okumura A, Hayakawa F, et al. Combination of neonatal electroencephalography and ultrasonography: sensitive means of early diagnosis of periventricular leukomalacia. *Brain Dev* 2002;24(7):698–702. [PubMed: 12427517]
10. Kidokoro H, Okumura A, Kato T, et al. Electroencephalogram and flash visual evoked potentials for detecting periventricular leukomalacia. *Neuropediatrics* 2008;39(4):226–232. [PubMed: 19165711]
11. Kuban KC, Allred EN, O'Shea TM, et al. Cranial ultrasound lesions in the NICU predict cerebral palsy at age 2 years in children born at extremely low gestational age. *J Child Neurol* 2009;24(1):63–72. [PubMed: 19168819]
12. De Vries LS, Van Haastert IL, Rademaker KJ, Koopman C, Groenendaal F. Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. *J Pediatr* 2004;144(6):815–820. [PubMed: 15192633]
13. Inder TE, Anderson NJ, Spencer C, Wells SJ, Volpe J. White matter injury in the premature infant: a comparison between serial cranial ultrasound and MRI at term. *AJNR Am J Neuroradiol* 2003;24(5):805–809. [PubMed: 12748075]
14. Nanba, Y.; Matsui, K.; Aida, N., et al. Magnetic resonance imaging regional T1 abnormalities at term accurately predict motor outcome in preterm infants. *Pediatrics*. 2007. Available at: www.pediatrics.org/cgi/content/full/120/1/e10
15. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *N Engl J Med* 2006;355(7):685–694. [PubMed: 16914704]

16. Spittle AJ, Boyd RN, Inder TE, Doyle LW. Predicting motor development in very preterm infants at 12 months' corrected age: the role of qualitative magnetic resonance imaging and general movements assessments. *Pediatrics* 2009;123(2):512–517. [PubMed: 19171616]
17. Dyet LE, Kennea NL, Counsell SJ, et al. Natural history of brain lesions in extremely preterm infants studied with serial magnetic resonance imaging from birth and neurodevelopmental assessment. *Pediatrics* 2006;118(2):536–548. [PubMed: 16882805]
18. Krishnan, ML.; Dyet, LE.; Boardman, JP., et al. Relationship between white matter apparent diffusion coefficients in preterm infants at term-equivalent age and developmental outcome at 2 years. *Pediatrics*. 2007. Available at: www.pediatrics.org/cgi/content/full/120/3/e604
19. Counsell SJ, Edwards AD, Chew AT, et al. Specific relations between neurodevelopmental abilities and white matter microstructure in children born preterm. *Brain* 2008;131(pt 12):3201–3208. [PubMed: 18952670]
20. Khwaja O, Volpe JJ. Pathogenesis of cerebral white matter injury of prematurity. *Arch Dis Child Fetal Neonatal Ed* 2008;93(2):F153–F161. [PubMed: 18296574]