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Editorial

Placental assessment provides insight into mechanisms and timing of neonatal hypoxic-ischemic encephalopathy

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1. Introduction

A recent, case-control study of the placenta in 73 cases of neonatal encephalopathy (NE) by Vik et al. [1] provides insight into mechanisms and timing of neonatal hypoxic-ischemic encephalopathy (HIE). The study included approximately 50% in which "birth asphyxia" was considered the most likely cause of the NE. The analyses of the placenta were primarily prospective and utilized a careful, newly formulated, systematic approach to histological analysis. The histological parameters assessed were grouped into three categories: inflammatory (e.g., chorioamnionitis), or maternal or fetal vascular malperfusion. The principal, distinguishing finding between cases and controls was the occurrence of placental histology consistent with *fetal* vascular malperfusion (FVM), which was observed in 24% of the placentas in the total group with NE [1]. No differences in *maternal* vascular malperfusion or inflammation were observed between NE cases and controls. The findings re: FVM are similar to those from recent studies of the placenta in infants with presumed HIE which identified lesions consistent with FVM in approximately 20–30% of cases [2, 3]. In the study of Mir et al. [3], findings consistent with FVM constituted the only individual predictor of abnormal neurodevelopmental outcome, and in the report of Harteman et al. [2], similar findings were highly predictive of MRI-demonstrated injury to basal ganglia/thalamus, the structures most sensitive to neonatal hypoxic-ischemic injury. Moreover, a recent careful study of 46 infants with neonatal arterial stroke identified FVM in 50% of cases (versus 17% of controls) [4].

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2. Placental findings/FVM

The placental findings of FVM include extensive avascular villi, vascular obstructive lesions, necrotic fragments in villous stroma and vascular thrombi [1, 5], often accompanied by abnormalities of the umbilical cord. Severe forms of FVM have been termed previously as "fetal thrombotic vasculopathy". The disturbances of the umbilical cord may include intrinsic anatomic lesions (e.g., knots, coils, strictures), potentially obstructing anatomic lesions (e.g., placental insertion abnormalities), or potentially obstructing clinical conditions (e.g., prolapse, entanglements, oligohydramnios). The placental findings of FVM are considered to be secondary to chronic, partial or recurrent intermittent obstruction of umbilical blood flow, thereby leading to umbilical venous obstruction, and, as a consequence, venous congestion, stasis, thrombosis (in severe cases) and focal ischemia involving the distal portions of the villous tree [5]. The consequences for the fetus would be expected to include impaired fetal blood flow and oxygenation, and ultimately, cardiac insufficiency and compromised cerebral blood flow and oxygenation. Based on histological features, FVM is considered to evolve in most cases over *a subacute to chronic period prior to delivery* and not closer to delivery than approximately 48 hours prior [5].

3. Implications of FVM for HIE

The findings of FVM thus suggest that a state of impaired fetal blood flow and oxygenation exists for many days to weeks prior to delivery. *What are the implications of these data re: the mechanisms and timing of brain injury in neonatal HIE?* Re: *mechanisms* of HIE, available data indicate that neonatal HIE in fact is related to hypoxia-ischemia [6]. This conclusion is based on data derived from (1) human neuropathology, (2) MRI studies of living infants, and (3) experimental models. Neuropathological studies of asphyxiated term infants show injury to regions vulnerable to hypoxia-ischemia, e.g., parasagittal cerebral cortex, hippocampus, basal ganglia, thalamus and brain stem [7, 8]. The vulnerability relates to intrinsic vascular and metabolic factors (see ref. 6 for review). MRI studies of infants with presumed HIE show a similar topography [9–13]. Moreover, and critically, excellent small and large animal models of neonatal hypoxia-ischemia exhibit similar areas of injury [14–16].

Re: *timing* of the hypoxic-ischemic insults(s) in neonatal HIE, MRI studies suggest that the large majority of cases with NE characterized as HIE sustain the brain injury during a relatively acute, peripartum period [6, 9]. This timing is based on assessment of diffusion-based and conventional MRI and is relatively accurate for timing measured in days [6, 17]. The nature of the acute hypoxic-ischemic insults in most cases is often difficult to ascertain definitively, although sentinel events are relatively clear examples. The latter were present in 20% of the total group of NE in the study of Vik et al. [1], or presumably 40% of the cases with HIE (recall that one-half of the cases of NE were thought to be related to causes other than hypoxia-ischemia). In a recent well-characterized series of HIE, 36% exhibited a sentinel event [18].

4. FVM may prime the brain for acute hypoxic-ischemic injury

The study of Vik et al. [1] raises the possibility that a substantial proportion of infants with apparent *acute* hypoxic-ischemic injury presumed to be peripartum in origin have a *subacute, chronic* abnormality of the placenta, i.e., FVM, that *primes* the infants to sustain *acute* brain injury in the peripartum period *under conditions that might not lead to HIE in the absence of FVM*. Impaired fetal blood flow and oxygenation with FVM over the last days or week(s) of pregnancy can be postulated to lead to sufficient cerebral hypoxia-ischemia to reduce cerebral glycogen and energy reserves and to impair cerebrovascular autoregulation, thereby priming the brain for injury with subsequent acute insult(s) [19]. An additional important factor in priming could involve microglia. Because hypoxemia-ischemia is a potent activator of cerebral neuroinflammation, mediated especially by activated microglia, a subsequent acute insult in a fetus with FVM could lead to enhanced activation. Activated microglia lead to brain injury by release of reactive oxygen and nitrogen species and pro-inflammatory cytokines and by enhancement of glutamate excitotoxicity [19, 20]. The specific biochemical, cellular and cerebrovascular changes associated with subsequent acute cerebral hypoxemic-ischemic insults have been reviewed elsewhere [19]. Thus, the fetus with FVM might sustain hypoxic-ischemic injury during the acute peripartum period under conditions that would not harm a fetus without the pre-existing placental lesion. Indeed,

studies in small and large animal models have shown with "normal" vaginal delivery transient but significant disturbances in cerebral carbohydrate and energy metabolism [19].

A potentially important, additional potentiating factor for the occurrence of acute peripartum hypoxic-ischemic injury in the infant with FVM involves systemic infection/inflammation. Although in the study of Vik et al. [1] there was no significant difference in inflammatory lesions of the placenta in NE cases (12%) vs. controls (18%), other studies of presumed HIE have shown considerably higher incidences of inflammation [2, 3, 21, 22]. In a large meta-analysis of infants with cerebral palsy, a statistically significant increase in cerebral palsy in term infants was associated with histological evidence for chorioamnionitis [23]. Potentiation of hypoxic-ischemic injury by concomitant systemic inflammation has been shown in numerous animal models [19]. The central cellular mediators of the deleterious effect are brain microglia, as discussed earlier.

5. Does FVM lead to subacute/chronic brain injury and NE but without acute peripartum injury?

The study of Vik et al. [1] raises an important question concerning the possibility that FVM may cause a subacute/chronic hypoxic insult sufficient to lead to NE but not the acute peripartum injury of neonatal HIE. This question arises because approximately 50% of cases of NE in the study of Vik et al. [1] apparently did not have overt signs of neonatal HIE, i.e., acidemia, etc., but did have increased likelihood of FVM. More data will be needed in subsequent work that prospectively delineates placental, neonatal, MRI and followup findings in infants with NE.

6. Implications for prevention of brain injury

The finding that FVM is associated with NE and particularly neonatal HIE raises the question of whether detection of FVM in utero could lead to institution of preventative measures prior to labor. Recent advances in study of placental structure *and* physiology in human pregnancy by sophisticated MRI methods suggest that such detection may be possible in the near future [24]. The findings could lead to altered management of labor and delivery, peripartum use of neuroprotective agents, etc., to prevent fetal/neonatal brain injury. Insight into placental malfunction and its detection *in vivo* could represent a critical new avenue of preventative research.

7. Conclusions

This commentary, initiated by a recent report of placental findings in NE [1], outlines the key placental disturbance, i.e., FVM, and its implications re: the mechanisms and timing of brain injury in neonatal HIE. The findings suggest that FVM, a subacute/chronic lesion, could prime the infant's brain for acute peripartum hypoxic-ischemic injury. Additionally, the data raise the question of whether FVM can cause prepartum brain injury. The findings provide a fertile foundation for crucial subsequent studies.

References

[1] Vik T, Redline R, Nelson KB, Bjellmo S, Vogt C, Ng P, et al. The placenta in neonatal encephalopathy: A case-control study. J Pediatr. 2018;202:77-85.

[2] Harteman JC, Nikkels PG, Benders MJ, Kwee A, Groenendaal F, de Vries LS. Placental pathology in full-term infants with hypoxic-ischemic neonatal encephalopathy and association with magnetic resonance imaging pattern of brain injury. J Pediatr. 2013;163(4):968-75.

[3] Mir IN, Johnson-Welch SF, Nelson DB, Brown LS, Rosenfeld CR, Chalak LF. Placental pathology is associated with severity of neonatal encephalopathy and adverse developmental outcomes following hypothermia. Am J Obstet Gynecol. 2015;213:849 e1-7.

[4] Bernson-Leung ME, Boyd TK, Meserve EE, Danehy AR, Kapur K, Trenor CC, et al. Placental pathology in neonatal stroke: A retrospective case - control study. J Pediatr. 2018;195:39-47.

[5] Redline RW, Ravishankar S. Fetal vascular malperfusion, an update. APMIS. 2018;126(7):561-9.

[6] Volpe JJ. Neonatal encephalopathy: An inadequate term for hypoxic-ischemic encephalopathy. Ann Neurol. 2012;72(2):156-66.

[7] Alderliesten T, Nikkels PG, Benders MJ, de Vries LS, Groenendaal F. Antemortem cranial MRI compared with postmortem histopathologic examination of the brain in term infants with neonatal encephalopathy following perinatal asphyxia. Arch Dis Child Fetal Neonatal Ed. 2013;98(4):F304-9.

[8] Volpe JJ. Hypoxic-ischemic injury in the term infant: Pathophysiology. In: Volpe JJ, Inder TE, Darras BT, deVries LS, duPlessis AJ, Neil JJ, et al., editors. Volpe's Neurology of the Newborn. 6th ed. Philadelphia, PA: Elsevier; 2018. pp. 500-9.

[9] Cowan F, Rutherford M, Groenendaal F, Eken P, Mercuri E, Bydder GM, et al. Origin and timing of brain lesions in term infants with neonatal encephalopathy. Lancet. 2003;361(9359):736-42.

[10] Miller SP, Ramaswamy V, Michelson D, Barkovich AJ, Holshouser B, Wycliffe N, et al. Patterns of brain injury in term neonatal encephalopathy. J Pediatr. 2005;146:453-60.
[11] Martinez-Biarge M, Diez-Sebastian J, Rutherford MA, Cowan FM. Outcomes after central grey matter injury in term perinatal hypoxic-ischaemic encephalopathy. Early Hum Dev. 2010;86(11):675-82.
[12] Martinez-Biarge M, Diez-Sebastian J, Kapellou O, Gindner D, Allsop JM, Rutherford MA, et al. Predicting motor outcome and death in term hypoxic-ischemic encephalopathy. Neurology. 2011;76(24):2055-61.
[13] Kinney HC, Volpe JJ. Hypoxic-ischemic injury in the term infant: Neuropathology. In: Volpe JJ, Inder TE, Darras BT, deVries LS, duPlessis AJ, Neil JJ, et al., editors. Volpe's Neurology of the Newborn. 6th ed. Philadelphia, PA: Elsevier; 2018. pp. 484-99.
[14] Williams CE, Gunn AJ, Mallard C, Gluckman PD. Outcome after ischemia in the developing sheep brain: An electroencephalographic and histological study. Ann Neurol. 1992;31(1):14-21.
[15] Gunn AJ, Parer JT, Mallard EC, Williams CE, Gluckman PD. Cerebral histologic and electrocorticographic changes after asphyxia in fetal sheep. Pediatr Res. 1992;31(5):486-91.
[16] Yager JY, Ashwal S. Animal models of perinatal hypoxic-ischemic brain damage. Pediatr Neurol. 2009;40(3):156-67.
[17] Inder TE, Volpe JJ. Hypoxic-ischemic injury in the term infant: Clinical-neurological features, diagnosis, imaging, prognosis, therapy. In: Volpe JJ, Inder TE, Darras BT, deVries LS, du Plessis AJ, Neil JJ, et al., editors. Volpe's Neurology of the Newborn. 6th ed. Philadelphia, PA: Elsevier; 2018. pp. 510-63.
[18] Parker SJ, Kuzniewicz M, Niki H, Wu YW. Antenatal and intrapartum risk factors for hypoxic-ischemic encephalopathy in a US birth cohort. J Pediatr. 2018;203:163-9.
[19] Inder TE, Volpe JJ. Pathophysiology: General Principles. In: Volpe JJ, Inder TE, Darras BT, deVries LS, du Plessis AJ, Neil JJ, et al., editors. Volpe's Neurology of the Newborn. Chapter 13, 6th ed. Philadelphia, PA: Elsevier; 2018. pp. 325-88.
[20] Mallard EC, Williams CE, Gunn AJ, Gunning MI, Gluckman PD. Frequent episodes of brief ischemia sensitize the fetal sheep brain to neuronal loss and induce striatal injury. Pediatr Res. 1993;33:61-5.
[21] Wintermark P, Boyd T, Gregas MC, Labrecque M, Hansen A. Placental pathology in asphyxiated newborns meeting the criteria for therapeutic hypothermia. Am J Obstet Gynecol. 2010;203:e1-9.
[22] Hayes BC, Cooley S, Donnelly J, Doherty E, Grehan A, Madigan C, et al. The placenta in infants>36 weeks gestation with neonatal encephalopathy: A case control study. Arch Dis Child Fetal Neonatal Ed. 2013;98(3):F233-9.
[23] Shi Z, Ma L, Luo K, Bajaj M, Chawla S, Natarajan, et al. Chorioamnionitis in the development of cerebral palsy: A meta-analysis and systematic review. Pediatrics. 2017;139:e20163781.
[24] Hutter J, Slator PJ, Jackson L, Gomes ADS, Ho A, Story L, et al. Multi-modal functional MRI to explore placental function over gestation. Magn Reson Med. 2019;81(2):1191-204.