OBSTETRICS

Risk factors for periventricular white matter injury in very low birthweight neonates

Michael E. Tsimis, MD; Clark T. Johnson, MD; Radhika S. Raghunathan, BS; Frances J. Northington, MD; Irina Burd, MD, PhD; Ernest M. Graham, MD

BACKGROUND: The development of periventricular white matter injury (PWMI) in the preterm neonate is the most common insult portending neurologic impairment and is linked with the later development of cerebral palsy. The pathogenesis of PWMI targets premyelinating oligodendrocytes of the periventricular region secondary to free radicals, cytokine toxicity, and excitatory neurotransmitters. The primitive nature of the vasculature in the developing fetal cortex lends to its predilection to PWMI and cerebral ischemia with less arterial anastomoses at arterial border zones and failure to compensate for global hypotension, termed the "pressure-passive" circulation.

OBJECTIVE: Our objective is to determine the relative risk (RR) of fetal metabolic acidosis and perinatal infection in the development of PWMI in very low birthweight (VLBW) (<1500 g) neonates.

STUDY DESIGN: This is a cohort study of all VLBW neonates admitted to our neonatal intensive care unit from April 2009 through December 2014, comparing those who developed PWMI on neonatal head ultrasound at 6 weeks of life to those who did not. Neonates with chromosomal or major congenital abnormalities were excluded. Generalized linear modeling, adjusting for variables significantly different on bivariate analysis, was conducted.

RESULTS: During this 5-year and 8-month period there were 374 VLBW neonates admitted; 35 (9.4%) had PWMI. VLBW neonates without PWMI were significantly more likely to have intrauterine growth restriction (2.9% PWMI, 21.5% no PWMI; $P = .006$), while those neonates with PWMI had a significantly lower gestational age (26.3 ± 2.2 vs 28.0 ± 2.5 weeks; $P < .001$) and birthweight (868 ± 237 vs 993 ± 276 g; $P = .009$). There was no significant difference in umbilical arterial pH (7.25 ± 0.15 vs 7.27 ± 0.09; $P = .34$), base deficit (4.6 ± 6.0 vs 3.4 ± 3.3 mmol/L; $P = .11$), or pH <7.0 or base deficit >12 mmol/L at birth (10.7% vs 3.2%; $P = .09$). On bivariate analysis neonates with PWMI had a significant increase in positive cerebrospinal fluid (CSF) cultures (22.9% vs 1.5%; $P < .001$). The initial lumbar puncture was performed at a similar day of life, and neonates with PWMI had significantly elevated CSF white blood cell counts (5%, 50%, and 95%; 16, 175, and 709/mm^3; 1, 3, and 27/mm^3; $P = .008$). Generalized linear modeling, adjusted for gestational age and the presence of intrauterine growth restriction, showed that fetal metabolic acidosis had RR 2.59 (95% confidence interval, 1.14–5.92; $P = .02$) and neonatal CSF infection had RR 4.94 (95% confidence interval, 2.4–10.3; $P < .001$) for association with PWMI.

CONCLUSION: The RR of neonatal CSF infection being associated with PWMI was 2-fold greater than metabolic acidosis at the time of birth. Decreasing the incidence of CSF infections would have a greater impact on preventing PWMI, a precursor of cerebral palsy.

Key words: fetal metabolic acidosis, neonatal infection, very low birthweight neonates

Introduction

Among very low birthweight (VLBW) neonates (<1500 g) 10% will exhibit cerebral palsy and half show cognitive, behavioral, and attention deficiencies.[1-3] The most common lesion predisposing these infants to the later development of neurologic impairment is periventricular white matter injury (PWMI), which, when present, results in cerebral palsy in 60-100% of survivors.[4] PWMI is diagnosed with a higher prevalence at autopsy suggesting the difficulty in making an accurate clinical diagnosis with noninvasive measures. Ultrasound detection of PWMI, albeit of a lesser yield than autopsy diagnosis, occurs in 5-15% of VLBW neonates.[5] PWMI is a specific insult affecting the deep cerebral white matter characterized by 2 elements: periventricular focal necrosis and diffuse white matter reactive gliosis.[6]

The pathogenesis of PWMI is predominantly to premyelinating oligodendrocytes, abundantly found in the periventricular region. The neurologic injury is traced back to free radical generation, cytokine toxicity, and increased presence of excitatory neurotransmitters such as glutamate.[6] The preterm neonatal brain exhibits 2 properties causing a propensity for further damage in the form of PWMI. First, the vascular architecture of the preterm brain predisposes to PWMI in arterial border zones secondary to immature vasculature and fewer arterial anastomoses in these regions.[7] Second, the pressure-passive circulation does not allow the preterm neonate to compensate for systemic hypotension, causing a predisposition to cerebral ischemia.[8] The loss of white matter volume results in the presence of hypertrophic astrocytes in response to diffuse injury.[6,9]

Since PWMI can be diagnosed by a head ultrasound within 6 weeks of birth it has been hypothesized to be linked with both intrapartum hypoxia-ischemia and perinatal infection. A prior case-control study from our institution that matched 150 preterm neonates at <32 weeks with PWMI to 150 controls without PWMI on cranial ultrasound found that culture-positive neonatal infection was associated with a significantly increased risk of cerebral

Cite this article as: Tsimis ME, Johnson CT, Raghunathan RS, et al. Risk factors for periventricular white matter injury in very low birthweight neonates. Am J Obstet Gynecol 2015;volume;x.ex-x.ex.

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2015.09.108

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white matter injury, and that intrapartum hypoxia-ischemia occurred rarely in the PWMI group and was no different than in the controls.[10] Our hypothesis is that perinatal infection has a stronger association with PWMI than fetal metabolic acidosis. Since case-control studies can be biased by control selection and are unable to determine relative risk (RR), our objective in this study was to evaluate a cohort of all VLBW infants admitted to our neonatal intensive care unit (NICU) to determine the RR of fetal metabolic acidosis and perinatal infection associated with PWMI.

Materials and Methods

This is a cohort study of all VLBW neonates admitted to an urban university referral center from April 28, 2009, through Dec. 31, 2014, a period of 5 years and 8 months. This study was approved by our institutional review board. Neonates with major congenital malformations, chromosomal abnormalities, and genetic syndromes were excluded. It is standard practice in our NICU to perform a cranial ultrasound at 6 weeks of life for all VLBW neonates to rule out PWMI. VLBW neonates with PWMI identified on cranial ultrasound were compared to those whose cranial ultrasound at 6 weeks of life was normal. Cranial ultrasounds were all performed in the NICU. Transfontanellar cranial ultrasonography was performed using state-of-the-art ultrasound equipment (Zonare Medical Systems, Mountain View, CA). Standardized optimized sets of coronal and sagittal images were obtained through the anterior fontanel using curved and linear-array transducers (8-17 MHz). Cranial ultrasounds were evaluated by a pediatric neuroradiologist within our institution for overall white matter echointensity, gray-white matter differentiation, echointensity of the central gray matter, ventricular size (based on the largest ventricle size), germinal matrix hemorrhage (based on classification from I-III by Papile et al[11]), periventricular hemorrhagic infarction (previously known as grade IV hemorrhage), and cystic periventricular leukomalacia. Diffuse white matter injury was defined as generalized white matter volume loss, with or without echointensity alterations. Focal white matter injury was defined as focal areas of decreased echointensity representing remote ischemia or hemorrhage.

Infant and maternal medical records were reviewed to identify relevant clinical data. Preeclampsia was defined as proteinuria, edema, and the presence of new-onset hypertension. Intrauterine growth restriction (IUGR) was defined as an estimated fetal weight <10th percentile for gestational age on growth sonography.[12] Oligohydramnios was defined as an amniotic fluid index <5.0 cm at the time of the admission at which delivery occurred with intact membranes. The diagnosis of nonreassuring fetal heart rate tracing was made by the physician attending delivery prior to performing a cesarean. It is the policy within our institution to obtain umbilical arterial cord gases at all deliveries, and we determined the number of neonates with an umbilical arterial pH <7.0 or base deficit >12 mmol/L at birth, a degree of metabolic acidosis that increases the probability that neonatal encephalopathy had an intrapartum hypoxic-ischemic component.[13] The clinical diagnosis of chorioamnionitis was made in the presence of maternal fever, with the presence of at least 1 other finding of fetal tachycardia, uterine tenderness, or purulent vaginal discharge. Patients diagnosed with clinical chorioamnionitis were immediately started on intravenous ampicillin and gentamicin if not allergic. It is the practice within our institution to send the placenta to pathology for all VLBW deliveries; and all the placentas in the study were examined by an attending pathologist at our institution. Histologic chorioamnionitis was diagnosed when any polymorphonuclear leukocytes were seen in either the chorion or amnion, or in significant amounts in the subchorionic space. Histologic funisitis was diagnosed when polymorphonuclear leukocytes were seen in the umbilical cord. Placental infarct was defined as an area of collapsed villi with ghostlike appearance due to loss of nuclear basophilia with the intervillous space obliterated by increased fibrin deposition and villous agglutination.

Software was used for statistical analysis (Stata, Version 13; StataCorp LP, College Station, TX). Bivariate analysis was performed using the Student *t* test to analyze continuous, normally distributed variables, and nonnormally distributed continuous variables were analyzed using a Wilcoxon rank sum test. The χ^2 or Fisher exact test were used to analyze categorical variables. Categorical variables with multiple components such as race were compared using χ^2. Variables with a *P* value of <.10 in bivariate analyses were utilized in a generalized linear model. To estimate the adjusted RR of covariates on outcome a modified Poisson approach with robust estimates of variance was used. Final variable significance in the generalized linear model was determined by statistical significance as defined by a confidence interval (CI) that did not include 1.0 and a *P* value <.05. For each variable in the generalized linear model, RR with 95% CI, receiver operator characteristic (ROC) curves, sensitivity, specificity, positive predictive value, and negative predictive value were determined.

Results

During this 5-year and 8-month period, a total of 374 VLBW infants were admitted to our NICU; 35 (9.4%) were diagnosed with PWMI by cranial ultrasound. Maternal clinical variables did not differ between the groups with the exception that neonates without PWMI were significantly more likely to have IUGR (Table 1). There was no difference in maternal demographics, cesarean delivery, multiple gestations, or nonreassuring fetal heart rate tracing noted prior to delivery. The groups did not differ in the presence of clinical chorioamnionitis or in histologic chorioamnionitis or funisitis (Table 1).

Neonates in this VLBW cohort diagnosed with PWMI were born at a significantly lower gestational age and birthweight, and were more likely to have 1- and 5-minute Apgar scores <7, chronic lung disease, intraventricular hemorrhage, and seizures; they also had a longer length of stay in the NICU

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