Histological Characteristics of the Fetal Inflammatory Response Associated with Neurodevelopmental Impairment and Death in Extremely Preterm Infants

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Objective To test the hypothesis that increasing severity of the fetal inflammatory response (FIR) would have a dose-dependent relationship with severe neurodevelopmental impairment or death in extremely preterm infants.

Study design We report 347 infants of 23-28 weeks gestational age admitted to a tertiary neonatal intensive care unit between 2006 and 2008. The primary outcome was death or neurodevelopmental impairment at the 18- to 22-month follow-up. Exposure status was defined by increasing stage of funisitis (stage 1, phlebitis; stage 2, arteritis with or without phlebitis; stage 3, subacute necrotizing funisitis) and severity of chorionic plate vasculitis (inflammation with or without thrombosis).

Results A FIR was detected in 110 placentas (32%). The rate of severe neurodevelopmental impairment/death was higher in infants with subacute necrotizing funisitis compared with infants without placental/umbilical cord inflammation (60% vs 35%; $P < .05$). Among infants with stage 1 or 2 funisitis, the presence of any chorionic vasculitis was associated with a higher rate of severe neurodevelopmental impairment/death (47% vs 23%; $P < .05$). After adjustment for confounding factors, only subacute necrotizing funisitis (risk ratio, 1.87; 95% CI, 1.04-3.35; $P = .04$) and chorionic plate vasculitis with thrombosis (risk ratio, 2.21; 95% CI, 1.10-4.46; $P = .03$) were associated with severe neurodevelopmental impairment/death.

Conclusion Severe FIR, characterized by subacute necrotizing funisitis and severe chorionic plate vasculitis with thrombosis, is associated with severe neurodevelopmental impairment/death in preterm infants. *(J Pediatr 2013;163:652-7)*.

Although advances in neonatal care have reduced mortality in extremely preterm infants,[1] the risk of adverse neurodevelopmental outcomes remains high. Neurodevelopmental impairment at 18-22 months corrected age occurs in nearly 40% of extremely low birth weight (birth weight ≤1.0 kg) infants.[2-4] The incidence of histologically identified chorioamnionitis (termed histological chorioamnionitis [HCA]) in preterm births is approximately 50% and is inversely related to gestational age.[1,5,6] Chorioamnionitis may induce preterm delivery via a maternal inflammatory response. Exposure to inflammation also may injure the immature brain, particularly when chorioamnionitis is associated with a fetal inflammatory response (FIR).[7-11] The association between HCA and neurodevelopmental impairment is inconsistent, perhaps because of varying definitions of intrauterine inflammation.[3,9,12-18] It is possible that the maternal inflammatory response and the FIR are associated with different risks for neurodevelopmental impairment and mortality.[3]

Any evidence of mural inflammation in the umbilical vessels and the chorionic plate vessels indicates FIR,[19-22] because these vessels are continuous with the fetal cardiovascular system and are considered of fetal origin.[6,7] Among preterm placentas with HCA, 50%-70% demonstrate funisitis,[6,15] and approximately 30% have chorionic plate vasculitis.[23,24] It has been estimated that FIR occurs in approximately 25%-40% of all preterm births[5,6,9,24,25]; however, the severity of the FIR has not been consistently reported.[3,5,22,23] Evidence suggesting an association between FIR and neurodevelopmental impairment in preterm infants[7,8,10,15,19,20] is difficult to interpret, owing to limited information regarding the severity of inflammation[3] and imprecise measurement of effect, related mainly to sample size limitations.[19]

We hypothesized that an increasing duration and/or severity of placental histopathology compatible with FIR would have a dose-dependent relationship with the rate of neurodevelopmental impairment/death in preterm infants.

aRR	Adjusted risk ratio
BSID III	*Bayley Scales of Infant and Toddler Development, Third Edition*
FIR	Fetal inflammatory response
HCA	Histological chorioamnionitis
IVH	Intraventricular hemorrhage
RR	Risk ratio

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Methods

This was a retrospective cohort study using prospectively collected data on inborn infants at $23^{0/7}$ to $28^{6/7}$ weeks gestational age admitted to the tertiary neonatal intensive care unit at the University of Alabama at Birmingham between 2006 and 2008. The primary composite outcome was severe neurodevelopmental impairment by 18-22 months corrected age or death at any time before follow-up. Composite scores for cognitive, language, and motor domains at 18-22 months corrected age were determined by trained and certified examiners using the *Bayley Scales of Infant and Toddler Development, Third Edition* (BSID III).[26] Neurologic examination and vision and hearing assessments were performed as well. Severe neurodevelopmental impairment was defined as the presence of 1 or more of the following: moderate or severe cerebral palsy, BSID III cognitive score <70, Gross Motor Function Classification System level ≥2, blindness, and/or hearing loss despite amplification.[26,27]

Demographic, clinical, and outcome data were collected prospectively from the infants' medical charts by trained research nurses. Waiver of authorization and informed consent were obtained from the University of Alabama at Birmingham's Institutional Review Board. Infants with major congenital anomalies, those without placental evaluation, and those lost to follow-up were excluded.

At our center, placental pathology is routinely analyzed in cases of preterm delivery. Each placenta and umbilical cord is assessed individually regardless of singleton or multiple gestation. For the present study, placentas of extremely preterm infants were evaluated by 2 pathologists (O.F.-P. and S.R.) using prospectively defined standards within the first 48 hours after delivery.[13,21] The presence of any vasculitis in the umbilical cord (funisitis) or vasculitis in the placental chorionic plate was considered to indicate FIR. For analyses of dose dependence, infants were categorized into 5 groups by increasing stage and severity of FIR based on placental and umbilical cord histopathology (**Table I**). Subacute necrotizing funisitis is a robust indicator of duration and intensity of fetal inflammation,[20,21] and chorionic plate vasculitis is an important gauge of both magnitude and ability of neutrophils to mount an FIR.[6,20,21] The severity of maternal response was analyzed as well. Severe HCA was defined as intense inflammation (polymorphonuclear aggregates of ≥10-20 cells) with or without microabscesses.[20,21] Mild to moderate HCA was defined as HCA without signs of severe inflammation.[21]

Potential covariates included maternal age, gestational age, race/ethnicity, twin and other multiple gestations, clinical chorioamnionitis identified by obstetrical assessment, premature rupture of membranes more than 18 hours before delivery, maternal preeclampsia, use of antenatal steroids, use of antepartum antibiotics, 5-minute Apgar score <3, and birth weight. Secondary outcomes included early-onset sepsis, defined as a positive blood culture at age ≤72 hours; late-onset sepsis, defined as a positive blood culture at age ≥72 hours and treatment for more than 5 days; severe intraventricular hemorrhage (IVH), defined as grade 3 or 4 IVH[28]; and periventricular leukomalacia, defined as at least 1 cystic area in the brain parenchyma identified by neuroimaging at 28 days after birth.

Previous data indicated that the proportion of extremely preterm infants with severe neurodevelopmental impairment or death was approximately 38%.[2] Assuming a hypothetical risk ratio (RR) for severe neurodevelopmental impairment/death in exposed infants relative to unexposed infants of 1.5 (least extreme RR detected), we planned a study with a minimum of 89 exposed infants and at least 177 unexposed infants (a 1:2 of exposed to unexposed infants), for a power of 80% and an α value of 0.05 using the χ^2 test. Unadjusted comparisons of baseline characteristics were performed using the Student *t*-test and one-way ANOVA (Tukey method) for continuous variables and the χ^2 test and Fisher exact test for categorical variables. Poisson regression was used to estimate RRs and 95% CIs for the association between severe neurodevelopmental impairment/death and the severity of placental histopathology with and without adjustment for birth weight, multiple gestation, and preeclampsia. A similar approach was used for secondary outcomes including death, severe neurodevelopmental impairment, individual components of neurodevelopmental impairment, and short-term neurologic morbidity (IVH and periventricular leukomalacia).

Effect-measure modification between FIR and antenatal steroids for the outcome of neurodevelopmental impairment/death was assessed by joint exposure in additive and multiplicative scales. For this analysis, FIR and antenatal steroids were analyzed as risk factors. Exposure to FIR and no steroids/incomplete course of antenatal steroids was considered the high-risk category. The reference group (exposure to neither) was used to establish the baseline risk for neurodevelopmental impairment/death, combining all other potential causes of neurodevelopmental impairment/death, and to illustrate the effect of adding the other 3 categories (exposure to FIR and antenatal steroids (high-risk); exposure to FIR, not antenatal steroids; exposure to antenatal steroids, not FIR) to the baseline risk (departure from additivity). Under the assumption of a possible biologic interaction, the magnitude of risk observed in the high-risk category was expected to be greater than the relative risks observed in the other 2 nonreference categories after addition and/or multiplication of the obtained values.

All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, North Carolina).

Results

Of a total of 399 eligible preterm infants, 347 had outcome data at 18-22 months corrected age (87%). Of these 347 infants, 110 (32%) had placental/umbilical cord features indicative of FIR. Baseline characteristics of infants by exposure to FIR are presented in **Table II**. The mean birth weight was 830 g, and the median gestational age was 26 weeks. The

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