Maternal Race, Demography, and Health Care Disparities Impact Risk for Intraventricular Hemorrhage in Preterm Neonates

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Objective To determine whether risk factors associated with grade 2-4 intraventricular hemorrhage (IVH) differs between infants of African ancestry and white infants.

Study design Inborn, appropriate for gestational age infants with birth weight 500-1250 g and exposure to at least 1 dose of antenatal steroids were enrolled in 24 neonatal intensive care units. Cases had grade 2-4 IVH and controls matched for site, race, and birth weight range had 2 normal ultrasounds read centrally. Multivariate logistic regression modeling identified factors associated with IVH across African ancestry and white race.

Results Subjects included 579 African ancestry or white race infants with grade 2-4 IVH and 532 controls. Mothers of African ancestry children were less educated, and white case mothers were more likely to have more than 1 prenatal visit and multiple gestation ($P \leq .01$ for all). Increasing gestational age ($P = .01$), preeclampsia ($P < .001$), complete antenatal steroid exposure ($P = .02$), cesarean delivery ($P < .001$), and white race ($P = .01$) were associated with decreased risk for IVH. Chorioamnionitis ($P = .01$), 5-minute Apgar score <3 ($P < .004$), surfactant use ($P < .001$), and high-frequency ventilation ($P < .001$) were associated with increased risk for IVH. Among African ancestry infants, having more than 1 prenatal visit was associated with decreased risk ($P = .02$). Among white infants, multiple gestation was associated with increased risk ($P < .001$), and higher maternal education was associated with decreased risk ($P < .05$).

Conclusion The risk for IVH differs between infants of African ancestry and white infants, possibly attributable to both race and health care disparities. *(J Pediatr 2014;164:1005-11)*.

Intraventricular hemorrhage (IVH) is a developmental disorder with significant neurodevelopmental morbidity.[1-7] Often attributed to alterations in cerebral blood flow to the immature germinal matrix microvasculature, IVH occurs against the backdrop of preterm birth in which risks and protective environmental factors are well known.[8-12]

Women of African ancestry are at greater risk for preterm labor and delivery compared with white women,[13-16] and, even in the era of sophisticated perinatal intensive care strategies, a disproportionate number of very low birth weight (BW) infants are born to mothers of African ancestry.[14,15] Compared with white women, more women of African ancestry who deliver prematurely receive inadequate prenatal care and less education, and their neonates are less likely to receive surfactant or assisted ventilation.[17] The rate of IVH-related mortality in neonates of African ancestry is twice that in white neonates,[18] suggesting that both preterm birth and its sequelae reflect the interaction of race and health care disparities.

Lower gestational age (GA) and BW, male sex, white race, neonatal transport, chorioamnionitis, illness severity, delivery room resuscitation, assisted ventilation, and respiratory distress syndrome and its complications are associated with an increased risk for IVH, whereas antenatal corticosteroid exposure, cesarean delivery, and preeclampsia are associated with a decreased risk for IVH.[19-24] Advances in neonatal and perinatal care and the increased survival of extremely low BW infants may be altering these associations, however.[25] The contributions of race and health care disparity to the incidence of IVH remain largely unexplored. In the present study, we aimed to evaluate whether risk factors associated with IVH differ in a recent prospective cohort of appropriate for GA inborn infants of African ancestry and white infants exposed to a partial or complete course of antenatal steroids and with centrally read cranial ultrasounds.[26,27]

BW	Birth weight
GA	Gestational age
GMH	Germinal matrix hemorrhage
HFV	High-frequency ventilation
IVF	In vitro fertilization
IVH	Intraventricular hemorrhage
PND	Postnatal day

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Methods

Infants born between June 1, 2007, and October 31, 2012, with BW 500-1250 g and grade 2-4 IVH and matched infants of the same BW range with normal cranial ultrasound findings were enrolled into a prospective study of the environmental and genetic risk factors for IVH at 24 university-affiliated hospitals in the US and Sweden. The study procedures and protocols were reviewed and approved by the Institutional Review Board of each participating institution. Written informed consent was obtained from a parent/guardian of each case and control subject.

Case infants were eligible who had grade 2-4 IVH based on a masked review of cranial ultrasound by a sonographer and met the following criteria: inborn, exposure to at least 1 dose of antenatal steroid, BW 500-1250 g, appropriate size for GA,[28] no evidence of congenital or chromosomal disorders or infections, no family history of coagulopathy, and not a sibling of an enrolled subject. Control infants met these criteria, had 2 normal cranial ultrasounds within the required time interval (described below), and were matched with cases based on the following criteria: site, sex, and BW range (ie, 500-749 g, 750-999 g, and 1000-1250 g). In addition, every effort was made to match controls based on self-reported maternal race and ethnicity. Enrollment was limited to 1 sibling of a multiple birth set; if more than 1 sibling of a multiple birth set had IVH, then the sibling to be included as a case was selected at random. If both multiples had the same grade of IVH, then the enrolled sibling was selected from a random table; if not similar, then the sibling with the higher grade of IVH was enrolled.

Eligibility and study group were based on clinical cranial ultrasound findings. Cases had grade 2-4 IVH within the first 28 postnatal days (PNDs); controls had 2 normal cranial ultrasounds, the first within PND 5-10 and the second within PND 21-35, both without IVH, germinal matrix hemorrhage (GMH), periventricular leukomalacia, ventriculomegaly, or central nervous system malformations. The grading system for grade 2-4 IVH follows that of Papile et al[29]: grade 2, GMH with blood within the ventricular system; grade 3, GMH with blood filling at least 50% of the ventricular system and ventricles measuring at least 1.1 cm at the midbody of the lateral ventricle on a sagittal scan; grade 4, GMH with IVH and intraparenchymal hemorrhage.

Although the initial screening was based on imaging reports from patient records, eligibility was confirmed by at least 1 site sonographer who had successfully completed standardized online study training showing images of GMH, grade 2-4 IVH, and ventriculomegaly. All site sonographers were required to pass an online quiz composed of 10 different sets of ultrasound images before being "certified" to read the site ultrasounds for study enrollment.

After subject enrollment, cranial ultrasounds were submitted for central review by at least 1 of 4 study sonographers who were blinded to the subjects' case-control status. Eligibility and group assignment were based on the following criteria: GMH, ventriculomegaly, and grade 2-4 IVH. When the site and central readings were not in agreement, images were sent to a second blinded sonographer for review. When both central reviewers concurred that the images did not support eligibility, the subject was excluded. If the reviewers disagreed, then the images were sent to the study's head sonographer for final review.

Data were collected from medical records and entered into a secure online database housed at Yale University. Maternal data included age, highest educational level, prenatal care, primary medical insurance, maternal magnesium sulfate within 72 hours before delivery, preeclampsia, clinical chorioamnionitis, and antenatal steroid exposure within 7 days before delivery.

Delivery room variables included Apgar scores and the need for resuscitation. Neonatal data included receipt of indomethacin within 6-12 hours of birth, caffeine within the first 2 PNDs, high-frequency ventilation (HFV) within the first 7 PNDs, GA, BW, sex, multiple birth, and reported race and ethnicity. In addition, data for surfactant use, pneumothorax, and seizures were collected for the first 28 PNDs. Data definitions are provided in **Table I** (available at www.jpeds.com).

The neonates in our cohort are part of an ongoing study investigating the genetic and environmental contributions to IVH, and 1100 of the 1111 infants (99%) had a genetic assessment of race.[30,31]

Statistical Analyses

The primary study outcome was grade 2-4 IVH. Continuous variables were analyzed using the Student *t* test or Wilcoxon rank-sum test, and categorical variables were analyzed using the Fisher exact test, comparing African ancestry cases with African ancestry controls, white cases with white controls, all cases with all controls, and African ancestry cases with white cases. Stratified categorical data were analyzed using the Mantel-Haenzel test. To identify risk factors independently and significantly associated with grade 2-4 IVH, a multivariate logistic regression model was built based on stepwise variable selection, using site, significant variables in the univariate analyses (all cases vs all controls), and their interactions with race. Post hoc univariate analyses were performed with selected data for African ancestry vs white cases and for those variables with significant race-interaction terms in the logistic regression model. SAS version 9.3 (SAS Institute, Cary, North Carolina) was used for all analyses, and $P < .05$ was considered to indicate statistical significance.

Results

During the study period, at total of 12 022 infants were screened for study eligibility at the participating sites (**Figure**; available at www.jepds.com). There were 981 infants with grade 2-4 IVH who met the eligibility criteria as cases; of these, 146 infants died in the neonatal intensive care unit. Infants who died before enrollment had a lower