Antecedents and Outcomes of Abnormal Cranial Imaging in Moderately Preterm Infants

Girija Natarajan, MD[1], Seetha Shankaran, MD[1], Shampa Saha, PhD[2], Abbot Laptook, MD[3], Abhik Das, PhD[2], Rosemary Higgins, MD[4], Barbara J. Stoll, MD[5], Edward F. Bell, MD[6], Waldemar A. Carlo, MD[7], Carl D'Angio, MD[8], Sara B. DeMauro, MD, MSCE[9], Pablo Sanchez, MD[10], Krisa Van Meurs, MD[11], Betty Vohr, MD[3], Nancy Newman, RN[12], Ellen Hale, BS, RN, CCRC[13], and Michele Walsh, MD[12], on behalf of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network*

Objectives To describe the frequency and findings of cranial imaging in moderately preterm infants (born at $29^{0/7}$-$33^{6/7}$ weeks of gestation) across centers, and to examine the association between abnormal imaging and clinical characteristics.

Study design We used data from the Neonatal Research Network Moderately Preterm Registry, including the most severe early (≤28 days) and late (>28 days) cranial imaging. Stepwise logistic regression and CART analysis were performed after adjustment for gestational age, antenatal steroid use, and center.

Results Among 7021 infants, 4184 (60%) underwent cranial imaging. These infants had lower gestational ages and birth weights and higher rates of small for gestational age, outborn birth, cesarean delivery, neonatal resuscitation, and treatment with surfactant, compared with those without imaging ($P < .0001$). Imaging abnormalities noted in 15% of the infants included any intracranial hemorrhage (13.2%), grades 3-4 intracranial hemorrhage (1.7%), cystic periventricular leukomalacia (2.6%), and ventriculomegaly (6.6%). Histologic chorioamnionitis (OR, 1.47; 95% CI, 1.19-1.83), gestational age (0.95; 95% CI, 0.94-0.97), antenatal steroids (OR, 0.55; 95% CI, 0.41-0.74), and cesarean delivery (OR, 0.66; 95% CI, 0.53-0.81) were associated with abnormal imaging. The center with the highest rate of cranial imaging, compared with the lowest, had a higher risk of abnormal imaging (OR, 2.08; 95% CI, 1.10-3.92). On the classification and regression-tree model, cesarean delivery, center, antenatal steroids, and chorioamnionitis, in that order, predicted abnormal imaging.

Conclusion Among the 60% of moderately preterm infants with cranial imaging, 15% had intracranial hemorrhage, cystic periventricular leukomalacia or late ventriculomegaly. Further correlation of imaging and long-term neurodevelopmental outcomes in moderately preterm infants is needed. *(J Pediatr 2017;■■:■■-■■).*

In 2014, 9.6% of US births were preterm (<37 weeks of gestation), including 1.2% at 32-33 weeks and 0.9% at 28-31 weeks.[1,2] Despite their substantial numbers, these moderately preterm (MPT) infants, born at 29-33 weeks of gestation, are a largely unstudied population.[3,4] MPT infants have significant neonatal morbidities and frequently require respiratory support and intravenous nutrition. Up to 19% of MPT infants are discharged home with continuing medical needs.[5,6] Compared with full-term children, MPT children have increased risks of cerebral palsy (8- to 14-fold increase), intellectual disability or developmental delays (2-fold), seizures (4-fold), and other neurodevelopmental disabilities (2-fold).[7,8] Despite the increased risk of long-term neurodevelopmental problems in MPT infants, there is relatively little information about early neurologic injury in this group of patients. This finding may be related to the lack of consistent cranial imaging practices. The American Academy of Neurology guidelines recommend routine head

ANS	Antenatal steroids
CART	Classification and regression-tree
GA	Gestational age
ICH	Intracranial hemorrhage
MPR	Moderate Preterm Registry
MPT	Moderately preterm
MRI	Magnetic resonance imaging
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NRN	Neonatal Research Network
PDA	Patent ductus arteriosus
PVL	Periventricular leukomalacia

From the [1]Wayne State University, Detroit, MI; [2]RTI International, Research Triangle Park, NC; [3]Women and Infants Hospital of Rhode Island, Providence, RI; [4]*Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD; [5]Department of Pediatrics, UT Health McGovern Medical School, Houston, TX; [6]Department of Pediatrics, University of Iowa, Iowa City, IA; [7]Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL; [8]University of Rochester Medical Center, Rochester, NY; [9]Department of Pediatrics, University of Pennsylvania, PA; [10]Department of Pediatrics, Nationwide Children's Hospital, Ohio State University, Columbus, OH; [11]Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA; [12]Department of Pediatrics, Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland, OH; and [13]Emory University, Atlanta, GA

*List of additional members of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network is available at www.jpeds.com (**Appendix**).

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ultrasound screening in preterm infants born at less than 30 weeks of gestation.[9] Whether and how often MPT infants are evaluated is unclear.

The purpose of this study was to describe the rates of cranial imaging in MPT infants and the frequency of abnormal findings across centers in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) MPT Registry.[10] We also examined the association between abnormal findings on cranial imaging and baseline characteristics as well as neonatal morbidities before the initial hospital discharge. We hypothesized that abnormal cranial imaging in MPT infants would be uncommon and would vary with center, as well as antepartum and birth characteristics, similar to extremely preterm infants.[11] We hypothesized further that death and morbidities among survivors would be more common in MPT infants with abnormal cranial imaging compared with infants with normal imaging.

Methods

This was a secondary analysis of prospectively collected data from the NICHD NRN MPT Registry.[10] The MPT Registry included all live born infants from $29^{0/7}$-$33^{6/7}$ weeks of gestation cared for at an NRN site between March 1, 2012, and October 21, 2013. Infants were excluded if there was a prenatal diagnosis that influenced the decision to withdraw or limit intensive care. All participating NRN sites obtained institutional review board approval for the study and either parental consent or approval for waiver of parental consent.

The MPT Registry included data on (a) maternal characteristics, such as age, marital status, highest level of education, insurance, ethnicity and race; (b) pregnancy complications, such as multiple birth, prenatal care, hypertension, clinical and histologic chorioamnionitis; (c) labor and delivery characteristics, including antenatal steroids (ANS) and mode of delivery; and (d) neonatal information, such as birth location (outborn or inborn), sex, gestational age (GA), small for GA status, Apgar scores, birth resuscitation and stabilization, and birth weight.

The MPT Registry included information on whether or not cranial imaging was performed on or before 28 days of age, defined as early imaging, or after 28 days of age and closest to 36 weeks of postmenstrual age, defined as late imaging. Results of imaging as reported by the local reader were recorded and included the presence and severity of intracranial hemorrhage (ICH), the presence and location of periventricular leukomalacia (PVL), ventricular dilation, and porencephalic cysts. Results of late imaging included cranial ultrasound imaging, computed tomography, or magnetic resonance imaging (MRI). Cystic PVL was defined as presence of cysts (echolucencies) in the periventricular white matter, whether single or multiple, bilateral or unilateral, diffuse or focal, and irrespective of size. A porencephalic cyst was defined as a single cyst within the cerebral hemisphere, whether congenital or evolving over time at the site of a previous parenchymal hemorrhage. Choroid plexus cysts were not recorded. For the current study, abnormal cranial imaging was defined as any ICH, cystic PVL, ventricular dilation, or porencephalic cyst, according to the interpretation of the local reader.

Data were abstracted for death, type of feeding, and respiratory support at 36 weeks postmenstrual age, morbidities, and duration of stay. Age at which full oral feedings were attained was recorded (defined as oral intake of 120 mL/kg/day). Respiratory support was defined as assisted ventilation (high frequency or conventional), nasal intermittent mandatory ventilation, continuous positive airway pressure, nasal cannula or supplemental oxygen by any delivery system. Patent ductus arteriosus (PDA) was defined as clinical evidence of left-to-right ductal shunt or echocardiographic evidence of PDA with documentation of left-to-right ductal shunting. Medical or surgical treatment for PDA was noted. Other morbidities included early-onset and late-onset sepsis and necrotizing enterocolitis, defined as modified Bell staging 2 or 3 and therapies such as surfactant and the type of respiratory support at 28 days. Infants who were transferred to another hospital before discharge home had cranial imaging data available, if performed clinically, but did not have available outcomes at discharge.

Statistical Analyses

Descriptive data were presented as means and SD or medians and IQR for continuous measures and numbers and proportions for categorical data. Comparisons between groups were conducted using *t*-tests and χ^2 tests, as appropriate. Stepwise logistic regression analysis and classification and regression-tree (CART) analysis were used to evaluate the adjusted association between clinical characteristics and abnormal cranial imaging. Factors previously associated with ICH or cystic PVL in extremely preterm infants including GA, small-for-GA, sex, race, center, ANS, mode of delivery, birth resuscitation, and histologic chorioamnionitis were adjusted for in the regression and CART analyses. Variables were allowed to enter the model at $P < .1$ and allowed to stay at $P < .05$. ORs and 95% CIs were generated for each included factor. The CART analysis was performed using Salford Predictive Modeler software V7.0 (Salford Systems, San Diego, California) to determine risk factors for abnormal cranial imaging and important patterns and relationships in data. The development of a classification tree with a series of binary splits was done by recursive partitioning and automatic selection of optimal cutpoints of variables. The decision tree was pruned to achieve best fit. Each binary split in a classification tree yielded 2 subgroups, one with a higher proportion of cases (abnormal cranial imaging) and the other with a higher proportion of controls. The optimal cutpoint for each variable was determined by the software using the available data. Also, the more closely associated a variable was in relation to outcome, the higher it was on the decision tree. CART models are designed to handle a large number of predictor variables without making assumptions about their relative importance, does not assume that data are linearly related, and the results are resistant to the influence of outlier data. Assuming a range of prevalence rates between 10% and 20% of neonatal morbidities (any of the following: respira-

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