Outcome of Preterm Infants with Transient Cystic Periventricular Leukomalacia on Serial Cranial Imaging Up to Term Equivalent Age

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Objective To determine the outcome of preterm infants whose cystic periventricular leukomalacia "disappeared" on serial screening cranial imaging studies.

Study design Infants ≤26 weeks of gestation born between 2002 and 2012 who had cranial imaging studies at least twice, the most abnormal study at <28 days of age and another closest to 36 weeks, were reviewed. The outcome of late death (after 36 weeks postmenstrual age) or neurodevelopmental impairment (NDI) in surviving infants at 18-26 months corrected age was compared between the infants with no cystic periventricular leukomalacia on both studies and cystic periventricular leukomalacia that disappeared (cystic periventricular leukomalacia at <28 days but not at 36 weeks), persisted (cystic periventricular leukomalacia on both studies), or appeared late (cystic periventricular leukomalacia only at 36 weeks). Predictors of NDI were evaluated by logistic regression.

Results Of 7063 eligible infants, 433 (6.1%) had cystic periventricular leukomalacia. Among the 433 infants with cystic periventricular leukomalacia, cystic periventricular leukomalacia disappeared in 76 (18%), persisted in 87 (20%), and 270 (62%) had late cystic periventricular leukomalacia. Loss to follow-up ranged between 3% and 13%. Death or NDI was more common in infants with disappeared cystic periventricular leukomalacia compared with those with no cystic periventricular leukomalacia (38 of 72 [53%] vs 1776 of 6376 [28%]; OR [95% CI] 2.8 [1.8-4.6]). Disappeared, persistent, and late cystic periventricular leukomalacia were all also independently associated with NDI (OR 1.17, 1.21, and 1.16, respectively).

Conclusions Infants with "disappeared" cystic periventricular leukomalacia are at increased risk of adverse outcome similar to infants with persistent or late cystic periventricular leukomalacia. *(J Pediatr 2017;■■:■■-■■).*

Detection of cystic periventricular leukomalacia by cranial ultrasonography screening for high-risk preterm neonates provides important information related to prognosis that can influence strategies for long-term follow-up and care.[1] Cystic periventricular leukomalacia on routine screening cranial ultrasonography is typically first seen about 3 weeks after injury.[2] However, cystic periventricular leukomalacia may remain apparent for only a few weeks in the periventricular region before the cystic areas coalesce, collapse, and then disappear, often resulting in ventriculomegaly being the visible sequel on cranial ultrasonography.[3-5]

We previously analyzed dataset from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) Generic Data Base Registry (GDB) and reported that in approximately 1 of 7 (14.3%) preterm infants for whom cystic periventricular leukomalacia was noted on any cranial ultrasound <28 days chronological age (CA), cystic

BPD	Bronchopulmonary dysplasia
CA	Chronological age
CT	Computed tomography
GA	Gestational age
GDB	Generic Data Base Registry
MRI	Magnetic resonance imaging
NDI	Neurodevelopmental impairment
NEC	Necrotizing enterocolitis
NICHD	National Institute of Child Health and Human Development
NRN	Neonatal Research Network
PMA	Postmenstrual age

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The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Center for Research Resources, and the National Center for Advancing Translational Sciences provided grant support for the Neonatal Research Network's Generic Database and Follow-up Studies through cooperative agreements. The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2017.12.010

periventricular leukomalacia was not apparent, ie, had disappeared, on the follow up cranial imaging obtained at 36 weeks postmenstrual age (PMA).[6] Although detection of cystic periventricular leukomalacia is strongly associated with subsequent neurodevelopmental outcome,[1] little is known about the outcome of preterm infants in whom cystic periventricular leukomalacia disappears compared with that of infants with persistent cystic periventricular leukomalacia.[5] This prompted us to use our follow-up data registry to determine the outcome for infants who never had cystic periventricular leukomalacia and infants whose cystic periventricular leukomalacia disappeared, persisted, or appeared late.

Our primary hypothesis was that the outcome for preterm infants whose cystic periventricular leukomalacia disappeared would differ from that of infants who never had cystic periventricular leukomalacia, and that the outcome in those whose cystic periventricular leukomalacia disappeared would not differ compared with those in whom it persisted, and those in whom cystic periventricular leukomalacia appeared late on screening imaging. We also hypothesized that cystic periventricular leukomalacia related variables, such as disappeared, persistent, and late cystic periventricular leukomalacia, along with clinical risk factors, could be used in multivariable regression analysis to predict neurodevelopmental impairment (NDI) in preterm infants. Accordingly, the objective was to compare the primary outcome of late death (after 36 weeks PMA) or NDI in infancy for preterm infants who never had cystic periventricular leukomalacia compared with infants whose cystic periventricular leukomalacia disappeared, persisted, or appeared late.

Methods

Prospectively collected data on all infants cared for and/or born at centers of the *Eunice Kennedy Shriver* NICHD Neonatal Research Network between January 2002 and December 2012 and entered in the NRN's GDB registry were reviewed retrospectively. The registry contains records of maternal antepartum and intrapartum data, which were collected soon after infant's birth and, in the case of the infant, collected prospectively from day one until death, or discharge from hospital or 120 days, whichever occurred first. The GDB includes information on NDI in surviving preterm infants who received follow-up assessments at 18-26 months corrected age (infants were seen at 18-22 months corrected age before July 1, 2012, and at 22-26 months corrected age after that). The follow-up evaluations performed also changed over time with the Bayley II examination used before mid-2007 and subsequently the Bayley III examination. Trained research coordinators collected the data using prespecified definitions. Data collection was approved by the local institutional review boards of the NRN centers participating in the GDB registry.

All infants born at $22^{0/7}$ through $26^{6/7}$ weeks PMA, who were entered in the GDB registry during the study period, survived beyond 36 weeks PMA, and had screening cranial imaging done at both of the 2 time points (ie, within 28 days CA and closest to 36 weeks PMA) were included for this analysis.

We compared the composite outcome of late death (death after 36 weeks PMA) or NDI (in surviving infants) among infants with (1) "no cystic periventricular leukomalacia"—no cystic periventricular leukomalacia on cranial imaging at both 28 days CA and close to 36 weeks PMA; (2) "disappeared" cystic periventricular leukomalacia—cystic periventricular leukomalacia observed only on cranial ultrasonography within the first 28 days CA but not apparent on the cranial imaging close to 36 weeks PMA; (3) "persistent" cystic periventricular leukomalacia- cystic periventricular leukomalacia present on cranial ultrasonography within the first 28 day CA and also on the cranial imaging close to 36 weeks PMA; and (4) "late" cystic periventricular leukomalacia—those infants who had cystic periventricular leukomalacia detected only on the cranial imaging closest to 36 weeks PMA.

Study Definitions

The GDB collects information regarding the presence of parenchymal cystic area(s) including the cystic periventricular leukomalacia and porencephalic cysts, if present on any cranial ultrasonography performed during first 28 days of birth. If more than 1 cranial ultrasonography is done in the first 28 days, results from the cranial ultrasonography with the most severe findings are recorded. Data regarding cystic periventricular leukomalacia and porencephalic cyst are collected and documented separately from imaging studies (ultrasonography, computed tomography [CT] scan, or magnetic resonance imaging [MRI]) done closest to 36 weeks PMA. In infants with more than 1 imaging modality close to 36 weeks PMA, the results to be recorded were MRI, sonogram, and then CT scan. The nature of screening cranial imaging studies (ultrasonography, CT scan, or MRI) performed close to 36 weeks PMA was center dependent. The radiologists at each participating center read the scans, and the findings recorded were based on the radiologists' reports. Cystic periventricular leukomalacia on cranial ultrasonography was defined as "characteristic lucencies in the periventricular area (most commonly dorsal and lateral to the external angle of the lateral ventricle and may be diffuse or focal in distribution along the front to back axis of the head)."[6] "Hyperechogenicity in the periventricular area" or ventriculomegaly was not considered to be cystic periventricular leukomalacia.[6] Cystic periventricular leukomalacia diagnosed by MRI on late imaging (closest to 36 weeks PMA) is based on a similar definition as for cranial ultrasonography (ie, presence of cysts). Porencephalic cyst was used to describe all other forms of cystic disease than periventricular leukomalacia.

Gestational age (GA) was based on the obstetrician's best estimate. Birth weight <10th percentile for GA and sex was small for GA. Antenatal steroids included any corticosteroid given to the mother for fetal indications. Postnatal steroid treatment included use of any corticosteroid for bronchopulmonary dysplasia (BPD). Blood culture positivity after 72 hours of age and antimicrobial therapy for ≥5 days defined late-onset sepsis. Intracranial hemorrhage included blood in the ventricles or in parenchyma. The date of the image with most severe grade of intracranial hemorrhage prior to 28 days, the presence of

FLA 5.5.0 DTD ■ YMPD9643_proof ■ February 2, 2018