Diminished White Matter Injury over Time in a Cohort of Premature Newborns

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Objectives To determine the rate of magnetic resonance imaging (MRI)-detected noncystic white matter injury (WMI) in a prospective cohort of premature newborns, and to evaluate its associations with changes in clinical predictors of WMI over the study period.

Study design A prospective cohort of premature newborns (<33 weeks gestational age) was studied with MRI within 4 weeks of birth and near term-equivalent age. A pediatric neuroradiologist scored the severity of WMI on T_1-weighted MRI according to published criteria. WMI was classified as none/mild or moderate/severe. Subjects with severe cystic WMI, periventricular hemorrhagic infarction, or motion artifact on MRI were excluded. Changes in clinical characteristics and predictors of WMI over the study period (1998-2011) were evaluated. Predictors of moderate/severe WMI, including birth year, were evaluated using multivariate logistic regression.

Results Among 267 newborns, 45 (17%) had moderate/severe WMI. The rate of moderate/severe WMI decreased over the study period ($P = .002$, χ^2 test for trends). On multivariate logistic regression, the odds of moderate/severe WMI decreased by 11% for each birth year of the cohort (OR, 0.89; 95% CI, 0.81-0.98; $P = .02$). Prolonged exposure to indomethacin also was independently associated with reduced odds of moderate/severe WMI.

Conclusion The decreasing burden of MRI-detected moderate/severe noncystic WMI in our cohort of premature newborns is independent over time of changes in the known clinical predictors of WMI. Prolonged exposure to indomethacin is associated with reduced WMI. *(J Pediatr 2015;166:39-43)*.

Newborns born premature (<37 weeks gestational age) are highly susceptible to white matter injury (WMI) owing to developmental vulnerability of the immature white matter to such conditions as hypoxia, ischemia, and inflammation.[1-4] WMI is associated with later development of motor, cognitive, and language deficits, as well as with cerebral visual impairment.[4,5]

WMI encompasses a spectrum of cystic and noncystic injury, of which cystic WMI is the most severe.[3,4] Cranial ultrasound has a high sensitivity for detecting cystic WMI; however, magnetic resonance imaging (MRI) is superior for identifying noncystic lesions[6-8] and prognosticating neurodevelopment.[9] We have previously shown that the prevalence of ultrasound-detected cystic WMI decreased over the 10-year period from 1992 to 2002 among newborns at our institution, and that the decreased duration of mechanical ventilation over the same period accounted for a portion of the decline in cystic WMI.[10]

Whether the rate of MRI-detected noncystic WMI has also diminished over time is not known. Characterizing the temporal trend in MRI-detected WMI may explain the mechanism underlying the incidence of neurodevelopmental disabilities in preterm populations over time.[11] We analyzed the rate of moderate/severe noncystic WMI in a cohort of premature newborns imaged with MRI soon after birth and near term-equivalent age, and evaluated its association with changes in clinical predictors of WMI over time, including infection,[12] prolonged ventilation,[10,13] and prolonged indomethacin exposure.[14]

Methods

The present study is a cross-sectional analysis of baseline data for subjects enrolled in a prospective cohort study. The cohort comprised 315 newborns at <33 weeks gestational age evaluated with MRI during early infancy at the University of California San Francisco (UCSF) between January 1998 and August 2011. Exclusion

MRI	Magnetic resonance imaging
NEC	Necrotizing enterocolitis
PDA	Patent ductus arteriosus
RR	Risk ratio
UCSF	University of California San Francisco
WMI	White matter injury

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criteria for the cohort include clinical evidence of a congenital malformation or syndrome, congenital infection, and clinical status too unstable for transport for MRI. All parents of eligible newborns in the intensive care nursery at UCSF were approached for study participation, and 342 declined to participate. Further information about study subjects whose parents' declined enrollment is not available.

For the present study, we excluded newborns with severe motion artifact on MRI (n = 17) and those with severe WMI on ultrasound due to periventricular hemorrhagic infarction (n = 22) or cystic WMI (n = 9), leaving 267 newborns available for analysis. We excluded newborns with severe cystic WMI to focus the analysis on noncavitary white matter lesions that are best detected by MRI. Newborns enrolled before January 2003 (n = 90) were included in the study of Hamrick et al,[10] which reported cystic WMI in all newborns admitted to the UCSF intensive care nursery between 1992 and 2002. Parental consent was obtained following a protocol approved by the UCSF Committee on Human Research.

MRI

MRI scans were obtained after birth as soon as the newborns were clinically stable. A custom MRI-compatible incubator with a specialized neonatal head coil was used to provide a quiet, well-monitored environment for the newborns, minimizing patient movement and improving the signal-to-noise ratio.[15] MRI scans were acquired using a 1.5-T scanner (General Electric Sigma; GE Medical Systems, Milwaukee, Wisconsin or Siemens Avanto; Siemens Medical Solutions, Malvern, Pennsylvania) and a specialized, high-sensitivity, neonatal head coil built into the MRI-compatible incubator (custom-built or from Lammers Medical Technologies, Luebeck, Germany). MRI scans included axial spin-echo T_2-weighted images (repetition time, 3000 ms; echo time, 60 120 ms; field of view, 240 mm with a 256 × 256 matrix; slice thickness, 4 mm; gap, 2 mm) and sagittal volumetric 3-dimensional spoiled gradient echo T_1-weighted images (repetition time, 36 ms; echo time, min; field of view, 180 mm; 1.0 mm isotropic).

A single pediatric neuroradiologist (A.B.) blinded to the clinical history (other than premature birth) evaluated all MRI scans. The severity of WMI on T_1-weighted MRI was scored according to our published criteria as none, mild (≤3 areas of signal abnormality each <2 mm in diameter), moderate (>3 areas of signal abnormality or areas of signal abnormality >2 mm but <5% of the hemisphere involved), or severe (>5% of hemisphere involved).[6] WMI was further classified as absent/mild or moderate/severe.

Medical records were reviewed and clinical data extracted by a single investigator (S.A.), who was blinded to the severity of WMI. Antenatal variables included exposure to prenatal steroids and magnesium sulfate using pharmacy records. Perinatal variables included neonatal resuscitation score (0-6),[16] gestational age, and birth weight. Neonatal variables included prolonged mechanical ventilation, severe infection, hypotension requiring pressor support, patent ductus arteriosus (PDA), number of indomethacin doses for treatment of PDA, PDA ligation, and necrotizing enterocolitis (NEC). Newborns with culture-positive sepsis, clinical signs of sepsis with negative blood culture, or meningitis were classified as having severe infection. Prolonged mechanical ventilation was defined as ≥7 days of endotracheal intubation and mechanical ventilation. Indomethacin exposure was categorized as absent, brief (1-3 doses), or prolonged (≥4 doses).[14] Newborns at <28 weeks gestational age were routinely treated with a brief course of indomethacin for prophylaxis of PDA until April 2011. Otherwise, indomethacin was administered to newborns with hemodynamically significant PDA at the discretion of the treating neonatologist. Newborns with clinical signs and symptoms of NEC and radiographic evidence of pneumatosis intestinalis were classified as having NEC. Of the 35 newborns with NEC, 20 (57.1%) required surgical intervention.

Statistical Analyses

Only exposures and predictors that occurred before MRI were included in the analysis. Clinical characteristics were compared between newborns with none/mild WMI and moderate/severe WMI using the χ^2 or Fisher exact test for categorical variables and Kruskal-Wallis test for continuous variables. Newborns were divided into epochs of birth year: 1998-2001 (n = 63), 2002-2004 (n = 74), 2005-2008 (n = 72), and 2009-2011 (n = 58). The proportion of newborns with noncystic WMI per epoch was evaluated using a χ^2 test for trends. Demographics and clinical predictors were evaluated across epochs of birth year using a χ^2 test for trends for categorical variables and variance-weighted least squares regression for continuous variables. Variables with significant association ($P \leq .10$) were evaluated as predictors of moderate/severe WMI using multivariate logistic regression. Birth year was evaluated as a continuous predictor in the multivariate model. Effect modification of the association between prolonged indomethacin exposure and moderate/severe WMI by gestational age was evaluated in a multivariate regression model, adjusting for gestational age, postnatal age at MRI, PDA ligation, hypotension, infection, duration of mechanical ventilation, and birth year.

Results

The mean gestational age of the cohort was 28.3 ± 2.3 weeks (IQR, 26.4-30 weeks), and the newborns were imaged with MRI at a mean of 31.8 ± 2 weeks (IQR, 30.6-33 weeks) postmenstrual age. Among the 267 newborns, 222 (83.1%) had absent/mild WMI and 45 (16.9%) had moderate/severe noncystic WMI as detected on MRI within 4 weeks of birth (**Table I**). Nine newborns had evidence of severe cystic WMI on early MRI throughout the study period and were excluded from the analysis.

Follow-up MRI was obtained at a mean postmenstrual age of 36.3 ± 2.2 weeks (IQR, 34.9-37.3 weeks) in 182 study subjects (68.2%). Newborns who did not undergo follow-up MRI were more likely to have had moderate/severe WMI