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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

Table I. Clinical characteristics by severity of WMI

Characteristics	Degree of WMI: None/mild (n = 222)	Degree of WMI: Moderate/severe (n = 45)	*P* value*
Gestational age, wk, mean ± SD	28.1 ± 2.3	28.9 ± 2.5	.06
Postmenstrual age at MRI, wk, mean ± SD	31.7 ± 2	32.3 ± 2	.03
Birth weight, g, mean ± SD	1072 ± 342	1182 ± 412	.14
Neonatal resuscitation score, median (IQR)	5 (4-5)	5 (4-5)	.36
Prenatal steroids, n (%)	189 (85.1)	39 (86.7)	.68
Prenatal magnesium sulfate, n (%)	119 (53.6)	24 (53.3)	.99
Hypotension, n (%)	116 (52.3)	24 (53.3)	1.0
Infection, n (%)	107 (48.2)	27 (60)	.10
Ventilation ≥7 days, n (%)	91 (41)	20 (44.4)	.67
NEC, n (%)	32 (14.4)	3 (6.7)	.16
PDA, n (%)	90 (40.5)	15 (33.3)	.23
Indomethacin therapy, n (%)			.04
None	108 (48.7)	28 (62.2)	
Brief (1-3 doses)	52 (23.4)	12 (26.7)	
Prolonged (≥4 doses)	62 (27.9)	5 (11.1)	

*P values from the χ^2 test or Fisher exact test for categorical variables or the Kruskal-Wallis test for continuous variables.

detected on early MRI (risk ratio [RR], 1.46; 95% CI, 0.98-2.18; P = .08) and NEC requiring surgical intervention (RR, 1.69; 95% CI, 1.05-2.73; P = .06).

Clinical Characteristics and WMI over Time

Demographics, clinical predictors of WMI, and rates of moderate/severe WMI were evaluated across epochs of birth year (Table II). The rate of moderate/severe WMI decreased significantly over time on early MRI (P = .002; Figure), as well as on MRI near term-equivalent age (P = .01). Other trends noted over the study period included increased exposure to prenatal steroids (P = .09) and magnesium sulfate (P = .06), decreased postmenstrual age at the time of MRI (P = .005), and a reduced proportion of newborns requiring prolonged mechanical ventilation (P = .001).

Clinical Predictors Associated with Moderate/Severe WMI on Early MRI

We evaluated clinical predictors associated with moderate/severe WMI on early MRI using univariate and multivariate logistic regression (Table III). Adjusting for the effects of gestational age, postmenstrual age at MRI, prenatal steroids, magnesium sulfate, infection, duration of indomethacin therapy, and prolonged ventilation, birth year remained strongly associated with reduced odds of moderate/severe WMI detected on MRI within 4 weeks of birth (OR, 0.89; 95% CI, 0.81-0.98; P = .02). The magnitude of the effect of birth year on the odds of moderate/severe WMI remained similar when hypotension was also evaluated in the model.

Findings on Follow-Up MRI

Moderate/severe WMI was present in 28 newborns (15.4%) who underwent MRI near term-equivalent age. Six newborns with absent/mild WMI on early MRI developed moderate/severe WMI on follow-up imaging, and 8 newborns with moderate/severe WMI on early MRI had absent/mild WMI on MRI near term-equivalent age. A history of ≥2 severe infections was associated with an increased risk of worsening WMI on follow-up MRI (RR, 5.07; 95% CI, 1.32-19.51; P = .01). Adjusting for the effects of gestational age, postnatal age at MRI, prenatal steroids, magnesium sulfate, duration of indomethacin therapy, infection, and prolonged ventilation, birth year was independently associated with reduced odds of moderate/severe WMI on follow-up MRI (OR, 0.86; 95% CI, 0.75-0.99; P = .06). Prolonged mechanical ventilation was associated with significantly increased odds of moderate/severe WMI on follow-up MRI (OR, 3.79; 95% CI, 1.15-12.55; P = .03).

Prolonged Indomethacin Exposure Is Associated with Reduced WMI

The association between indomethacin exposure and moderate/severe WMI was also evaluated in a second regression

Table II. WMI and clinical predictors of WMI across epochs of birth year

Characteristics	Birth year epoch: 1998-2001 (n = 63)	2002-2004 (n = 74)	2005-2008 (n = 72)	2009-2011 (n = 58)	*P* value*
Gestational age, wk, mean ± SD	28.4 ± 2.4	28 ± 2.5	28.3 ± 2.5	28.4 ± 1.8	.75
Birth weight, g, mean ± SD	1148 ± 398	1036 ± 352	1082 ± 379	1106 ± 271	.20
Prenatal steroids, n (%)	56 (89)	58 (78)	58 (81)	56 (97)	.09
Prenatal magnesium sulfate, n (%)	33 (52)	40 (54)	28 (39)	42 (72)	.06
Hypotension, n (%)	41 (65)	30 (41)	31 (43)	38 (66)	.92
Infection, n (%)	32 (51)	40 (54)	35 (49)	27 (47)	.84
Ventilation for ≥7 days, n (%)	38 (60)	30 (41)	24 (33)	19 (33)	.001
PDA, n (%)	24 (38)	25 (34)	28 (39)	28 (48)	.24
Prolonged indomethacin (≥4 doses), n (%)	19 (30)	12 (16)	21 (29)	16 (28)	.60
NEC, n (%)	10 (16)	6 (8)	14 (19)	5 (9)	.69
Postmenstrual age at MRI wk, mean ± SD					
Scan 1	32.6 ± 2.3	31.7 ± 1.8	31.8 ± 1.8	31.2 ± 1.9	.005
Scan 2	37.7 ± 2.6	36.4 ± 2.2	35.7 ± 2	35.9 ± 2	.004
Moderate/severe WMI, n (%)					
Scan 1	16 (25)	15 (20)	11 (15)	3 (5)	.002
Scan 2	8 (29)	12 (19)	4 (8)	4 (9)	.01

*P values from the χ^2 test of trends for categorical variables or variance-weighted least squares regression for continuous variables.

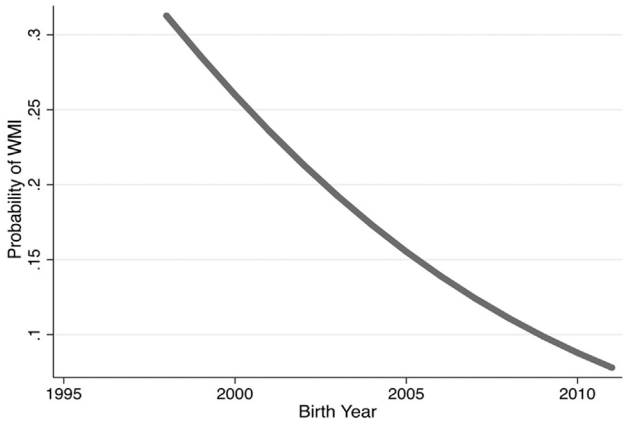

Figure. Probability of moderate/severe WMI on early MRI per birth year derived from univariate logistic regression.

model (data not shown), in which indomethacin exposure was characterized as absent, brief (1-3 doses), or prolonged (≥4 doses). There was no interaction between gestational age and the association of prolonged indomethacin exposure with diminished moderate/severe WMI ($P = .22$ for interaction). Adjusting for the effects of gestational age, postmenstrual age at MRI, hypotension, PDA ligation, prolonged ventilation, infection, and birth year, newborns treated with a prolonged course of indomethacin had significantly reduced odds of moderate/severe WMI on early MRI compared with unexposed newborns (OR 0.22; 95% CI, 0.060-0.79; P = .02).

Prolonged indomethacin was not significantly associated with moderate/severe WMI on MRI performed near term-equivalent age (OR, 0.53; 95% CI, 0.20-1.43; $P = .20$). In a sensitivity analysis assuming that the severity of WMI remained unchanged in the 85 newborns who did not have a follow-up MRI, newborns with prolonged exposure to indomethacin had significantly reduced odds of moderate/severe WMI compared with unexposed newborns (OR, 0.43; 95% CI, 0.19-0.98; $P = .045$).

Table III. Clinical predictors associated with moderate/severe WMI

Characteristics*	OR (95% CI)	*P* value	aOR (95% CI)†	*P* value
Gestational age, wk	1.15 (1.0-1.32)	.05	1.21 (0.96-1.52)	.10
Postmenstrual age at MRI, wk	0.98 (0.85-1.12)	.70	1.06 (0.88-1.28)	.55
Prenatal steroids	1.24 (0.45-3.39)	.68	1.06 (0.36-3.09)	.92
Prenatal magnesium sulfate	1.0 (0.52-1.93)	1.0	1.37 (0.68-2.78)	.38
Infection	1.54 (0.83-2.84)	.15	1.82 (0.83-3.96)	.13
Ventilation ≥7 days	1.0 (0.98-1.01)	.64	1.79 (0.67-4.78)	.24
Indomethacin therapy				
None	Ref		Ref	
Brief (1-3 doses)	0.82 (0.40-1.68)	.60	1.02 (0.42-2.45)	.97
Prolonged (≥4 doses)	0.26 (0.10-0.71)	.008	0.29 (0.09-0.9)	.03
Birth year	0.88 (0.8-0.97)	.007	0.89 (0.81-0.98)	.02

*Predictors evaluated on univariate logistic regression if $P \leq .10$ on comparison of newborns with absent/mild WMI and moderate/severe WMI, or $P \leq .10$ on test of trend across birth year epochs.
†Multivariate logistic regression model adjusting for all variables in the Table.

Discussion

In this cohort of premature newborns born at <33 weeks gestational age and imaged with MRI as part of a research protocol, the prevalence of moderate/severe focal noncystic WMI decreased significantly from 1998 to 2011. Changes that occurred throughout the study period included imaging newborns at a younger postmenstrual age, increased administration of antenatal steroids and magnesium sulfate, and reduced duration of mechanical ventilation. Even accounting for differences in clinical predictors over the study period, the odds of moderate/severe WMI decreased in each birth year of the cohort.

Our results indicate ongoing reduction in WMI over a 20-year period.[10] A cohort study from our institution demonstrated a decreased prevalence of ultrasound-detected severe cystic WMI from 1992 to 2002 among premature newborns, and this was partially explained by a reduced duration of mechanical ventilation over the same period.[10] The current study shows reduction in noncavitary WMI during the end of the previous period and the subsequent 10 years. There was no association between the trend in noncystic WMI on early MRI over time and the duration of mechanical ventilation; however, prolonged mechanical ventilation was a strong risk factor for moderate/severe WMI on follow-up MRI. These findings support the previous observation that respiratory disease in newborns is associated with cerebral white matter abnormalities at term-equivalent age.[13] In addition, recurrent infection was associated with worsening severity of WMI at term-equivalent age, which we have reported previously.[12]

We found that prolonged exposure to indomethacin was independently associated with reduced WMI detected on MRI within 4 weeks of birth, which is consistent with a previous study by Miller et al[14] that found decreased WMI among newborns 24-28 weeks gestation at birth treated with prolonged indomethacin. Our results extend this finding, and suggest that the beneficial effects of indomethacin may extend across a wider range of gestational age, up to 33 weeks. Prolonged indomethacin was not associated with reduced moderate/severe WMI on follow-up MRI in the subset of newborns imaged near term-equivalent age. However, in a sensitivity analysis assuming the severity of WMI was unchanged in newborns who did not have a follow-up MRI, the association of prolonged indomethacin with reduced moderate/severe WMI was sustained at term-equivalent age.

There are 2 potential mechanisms by which indomethacin may reduce WMI. As a prostaglandin synthesis inhibitor, the anti-inflammatory effects of indomethacin could mitigate the upstream mechanism by which inflammation leads to WMI or death of oligodendrocyte precursor cells.[2,3,17,18] Indomethacin also widens the range of cerebral vascular autoregulation and decreases cerebral blood flow.[19,20] Previous

clinical trials have shown that a short course of prophylactic indomethacin decreases the incidence and severity of intraventricular hemorrhage and reduces the occurrence of symptomatic PDA.[19,21] Individual trials have not demonstrated an associated reduction in WMI among indomethacin-treated newborns[19]; however, in those trials, ultrasound was the main imaging modality used to evaluate WMI. We were unable to evaluate whether the duration of symptomatic PDA was associated with WMI. Because newborns were not randomized to prolonged indomethacin in our cohort, we cannot exclude the possibility of unmeasured variables confounding the association between prolonged indomethacin and reduced WMI.

Unmeasured changes in clinical care that occurred over the study period may account for the observed independent association between birth year and diminished odds of moderate/severe WMI. Care practices that were not measured include noninvasive ventilatory support, orogastric tube insertions for feeding, and handling practices, among others. Changes in such factors over time might have led to a decreased cumulative incidence of small, recurrent hypoxic-ischemic insults, which in turn may have translated into the decreased rate of noncystic WMI.

All MRI scans were obtained using the same imaging protocol, and the same pediatric neuroradiologist scored the severity of WMI; thus, differences in imaging technique and interpretation do not explain the decreased noncystic WMI in our cohort. A single study investigator systematically reviewed all medical records to characterize the clinical predictors. Although we did not specifically adjust the model with a standardized illness severity score, the model was adjusted for component variables that contribute to illness severity, such as prolonged ventilation, hypotension, and infection. Several markers of illness severity did not change over time in our cohort; thus, we do not believe that enrollment of less systemically ill newborns over the study period accounts for our findings.

In summary, in a prospective cohort of premature newborns born between 1998 and 2011 and evaluated with MRI soon after birth we found a decreased rate of moderate/severe noncystic WMI that was independent of changes in clinical predictors of WMI over time. Further study is underway to evaluate whether the reduced burden of WMI and birth year are associated with improved neurodevelopmental outcomes in this cohort. Prolonged treatment with indomethacin was associated with reduced WMI, and a randomized controlled trial is needed to determine whether this is an effective therapy for alleviating WMI in premature newborns. ■

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