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Diminished white matter injury over time in a cohort of premature newborns

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Abstract

Objectives—To determine the rate of magnetic resonance imaging (MRI) detected non-cystic 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—Prospective cohort of premature newborns (<33 weeks' gestation) 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. We excluded subjects with severe cystic WMI, periventricular hemorrhagic infarction, or motion artifact on MRI. 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=0.002, chi-squared test of trends). On multivariate logistic regression, the odds of moderate/severe WMI decreased 11% for each birth year of the cohort (odds ratio 0.89, 95% confidence interval 0.81–0.98, P=0.04). Prolonged exposure to indomethacin was also independently associated with reduced odds of moderate/severe WMI.

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Conclusions—The decreasing burden of MRI-detected moderate/severe non-cystic 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.

Keywords

preterm; magnetic resonance imaging; brain injury; indomethacin

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

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

It is not known whether the rate of MRI-detected non-cystic WMI has also diminished over time. Characterizing the temporal trend of 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 non-cystic WMI in a cohort of premature newborns imaged with MRI soon after birth and near term-equivalent age (1998–2011), and evaluated its association to changes in clinical predictors of WMI over time, including infection (12), prolonged ventilation (10,13), and prolonged indomethacin exposure (14).

Methods

This is a cross-sectional analysis of baseline data for subjects enrolled in a prospective cohort study. The cohort is comprised of 315 newborns <33 weeks' gestation evaluated with MRI during early infancy at the University of California, San Francisco (UCSF) from January 1998 to August 2011. Exclusion criteria for the cohort include clinical evidence of a congenital malformation or syndrome, congenital infection, or clinical status too unstable for transport to the MRI. All parents of eligible newborns in the intensive care nursery at UCSF were approached for study participation, among whom 342 declined participation. Further information about study subjects whose parents' declined enrollment is not available. For the current 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 white matter injury (n=9), leaving 267 newborns available for analysis. We excluded newborns with severe cystic WMI in order to focus the analysis on non-cavitary white matter lesions that are best detected by MRI. Newborns enrolled prior to January 2003

(n=90) were included in the study by Hamrick et al (10), which reported cystic WMI in all newborns admitted to the UCSF intensive care nursery from 1992 to 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 newborns were clinically stable. A custom MR-compatible incubator with a specialized neonatal head coil was used to provide a quiet, well-monitored environment for newborns, minimizing patient movement and improving the signal-to-noise ratio (15). MRI scans were acquired using a 1.5-tesla scanner (General Electric Sigma; GE Medical Systems, Milwaukee, WI or Siemens Avanto; Siemens Medical Solutions USA Inc, Malvern, PA) and a specialized, high-sensitivity, neonatal head coil built into the MRI-compatible incubator (custom-built or Lammers Medical Technologies; LMT Lammers Medical Technology, Luebeck, Germany). MRI scans included axial spin-echo T_2-weighted images (repetition time (TR), 3000ms; echo time (TE), 60,120ms; field of view [FOV], 240mm with 256×256 matrix; slice thickness, 4mm; gap, 2 mm) and sagittal volumetric 3-dimensional spoiled gradient echo T_1-weighted images (TR, 36ms; TE, min; FOV, 180mm; 1.0mm isotropic).

A single pediatric neuroradiologist (AJB) evaluated all MRI scans blinded to the clinical history (other than premature birth). The severity of WMI on T_1-weighted MRI was scored according to our published criteria: 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), severe (>5% of hemisphere involved) (6). WMI was further classified as absent/mild or moderate/severe.

Medical records were reviewed and clinical data were extracted by a single investigator (SA) 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 to 6), 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 <28 weeks' gestation 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 evidence of pneumatosis intestinalis on X-ray were classified as having NEC. Of 35 newborns with NEC, 20 (57.1%) required surgical intervention.

Statistical Analyses—Only exposures and predictors that occurred prior to MR imaging were included in the analysis. Clinical characteristics were compared between newborns with none/mild WMI and moderate/severe WMI using chi-squared 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 non-cystic WMI per epoch was evaluated using chi-squared test for trends. Demographics and clinical predictors were evaluated across epochs of birth year using chi-squared test of trends for categorical variables and variance-weighted least squares regression for continuous variables. Variables with significant association (P≤0.1) 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 (interquartile range 26.4 to 30 weeks) and newborns were imaged with MRI at 31.8 ± 2 weeks (interquartile range 30.6 to 33 weeks) postmenstrual age. Among the 267 newborns, 222 (83.1%) had absent/mild WMI and 45 (16.9%) had moderate/severe non-cystic WMI on MRI within 4 weeks of birth (Table I). There were 9 newborns with evidence of severe cystic WMI on early MRI throughout the study period that were excluded from the analysis.

A follow-up MRI was obtained at a mean postmenstrual age of 36.3 ± 2.2 weeks (interquartile range 34.9 to 37.3 weeks) in 182 study subjects (68.2%). Newborns that did not have follow-up imaging were more likely to have had moderate/severe WMI on early MRI (risk ratio 1.46, 95% confidence interval 0.98 – 2.18, P=0.08), and NEC requiring surgical intervention (risk ratio 1.69, 95% confidence interval 1.05 – 2.73, P=0.06).

Clinical characteristics and white matter injury over time

Demographics, clinical predictors of WMI, and the rate 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=0.002; Figure), as well as MRI near term-equivalent age (P=0.01). Other trends over the study period included increased exposure to prenatal steroids (P=0.09) and magnesium sulfate (P=0.06), decreased postmenstrual age at the time of MRI (P=0.005), and a reduction in the proportion of newborns that required prolonged mechanical ventilation (P=0.001).

Clinical predictors associated with moderate/severe white matter injury 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 course, and prolonged ventilation, birth year remained strongly associated with reduced odds of moderate/severe WMI on MRI within 4 weeks of birth (odds ratio 0.89, 95% confidence interval 0.81 – 0.98, P=0.02). 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.

MRI findings on follow-up MRI

Moderate/severe WMI was present in 28 newborns (15.4%) imaged near term-equivalent age. There were 6 newborns with absent/mild WMI on early MRI who developed moderate/severe WMI on follow-up imaging, and 8 newborns with moderate/severe WMI on early MRI that had absent/mild WMI near term-equivalent age. Two or more severe infections was associated with an increased risk of worsening WMI on follow-up MRI (risk ratio 5.07, 95% confidence interval 1.32 – 19.51, P=0.01). Adjusting for the effects of gestational age, postnatal age at MRI, prenatal steroids, magnesium sulfate, duration of indomethacin course, infection, and prolonged ventilation, birth year was independently associated with reduced odds of moderate/severe WMI on follow-up MRI (odds ratio 0.86, 95% confidence interval 0.75 – 0.99, P=0.06). Prolonged mechanical ventilation was associated with significantly increased odds of moderate/severe WMI on follow-up imaging (odds ratio 3.79, 95% confidence interval 1.15 – 12.55, P=0.03).

Prolonged indomethacin exposure is associated with reduced white matter injury

The association between indomethacin exposure and moderate/severe WMI was also evaluated in a second 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 (interaction P=0.2). Adjusting for the effects of gestational age, postmenstrual age at MRI, hypotension, PDA ligation, prolonged ventilation, infection, and birth year, newborns treated with prolonged indomethacin had significantly reduced odds of moderate/severe WMI on early MRI compared with unexposed newborns (odds ratio 0.29, 95% confidence interval 0.087–0.97, P=0.04).

Prolonged indomethacin was not significantly associated with moderate/severe WMI on MRI near term-equivalent age (odds ratio 0.53, 95% confidence interval 0.20–1.43, P=0.2). In a sensitivity analysis assuming the severity of WMI was unchanged in the 85 newborns that did not have a follow-up MRI, newborns with prolonged exposure to indomethacin had significantly reduced moderate/severe WMI compared with unexposed newborns (odds ratio 0.43, 95% confidence interval 0.19–0.98, P=0.045).

Discussion

In this cohort of premature newborns born <33 weeks' gestational age and imaged with MRI as part of a research protocol, moderate/severe focal non-cystic 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, as well as 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 white matter injury 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 non-cavitary WMI during the end of the previous period and the following ten years. There was no association between the trend of non-cystic 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 previously reported (12).

We found prolonged exposure to indomethacin was independently associated with reduced WMI on MRI within 4 weeks of birth, which is consistent with a prior study by Miller et al (14) that demonstrated 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 ages 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 that 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 two 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 (2,3,16,17). Indomethacin also widens the range of cerebral vascular autoregulation and decreases cerebral blood flow (18,19). Prior 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 (18,20). Individual trials have not demonstrated an associated reduction in WMI among indomethacin-treated newborns (18); however, 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. As newborns were not randomized to prolonged indomethacin in our cohort, we cannot exclude unmeasured variables confounding the association between prolonged indomethacin and reduced WMI.

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

All MRI scans were obtained using the same imaging protocol and the same pediatric neuroradiologist scored the severity of WMI, and therefore, differences in imaging technique and interpretation do not explain the decreased non-cystic 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 comprise 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 think enrollment of less systemically ill newborns over the study period accounts for our findings.

In summary, we observed a decreased rate of moderate/severe non-cystic WMI in a prospective cohort of premature newborns evaluated with MRI soon after birth from 1998 to 2011, and this 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 to alleviate WMI in premature newborns.

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Abbreviations

MRI	Magnetic resonance imaging
PDA	Patent ductus arteriosus
WMI	White matter injury

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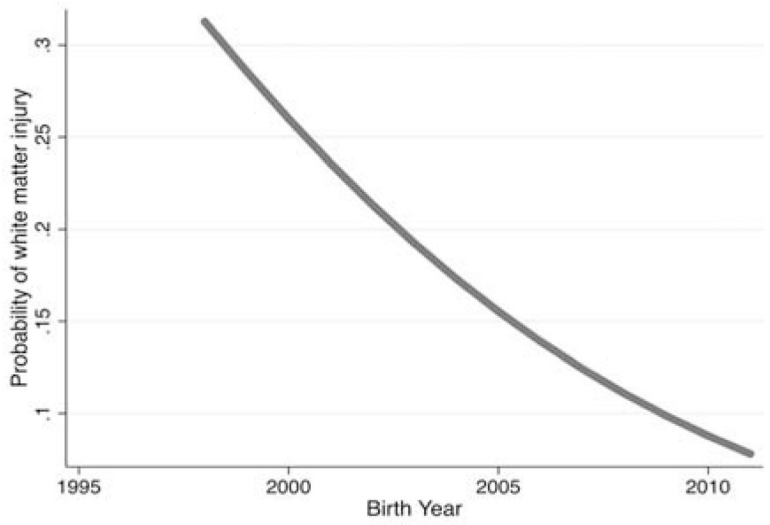

Figure.

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

Table 1

Comparison of clinical characteristics by moderate/severe white matter injury

Characteristic*	White matter injury		P-value**
	None/Mild N=222	Moderate/Severe N=45	
Gestational age (wks)	28.1 ± 2.3	28.9 ± 2.5	0.06
Postmenstrual age at MRI (wks)	31.7 ± 2	32.3 ± 2	0.03
Birth weight (grams)	1072 ± 342	1182 ± 412	0.1
Neonatal resuscitation score	5 (4 – 5)	5 (4 – 5)	0.4
Prenatal steroids	189 (86)	39 (89)	0.7
Prenatal magnesium sulfate	119 (56)	24 (56)	1
Hypotension	116 (54)	24 (53)	0.5
Infection	107 (48.2)	27 (60)	0.1
Ventilation ≥7 days	91 (41)	20 (44)	0.7
Necrotizing enterocolitis	32 (14)	3 (7)	0.2
Patent ductus arteriosus	90 (40)	15 (33)	0.2
Indomethacin			0.04
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)	

* Data presented as mean ± standard deviation (range), number (%) or median (interquartile range)

** P-value refers to chi-squared test or Fisher's exact test for categorical variables, or Kruskal-Wallis test for continuous variables

Table 2

White matter injury and clinical predictors of white matter injury across epochs of birth year

Characteristic*	Birth year epoch				P-value**
	1998–2001 N=63	2002–2004 N=74	2005–2008 N=72	2009–2011 N=58	
Gestational age (wks)	28.4 ± 2.4	28 ± 2.5	28.3 ± 2.5	28.4 ± 1.8	0.8
Birth weight (grams)	1148 ± 398	1036 ± 352	1082 ± 379	1106 ± 271	0.2
Prenatal steroids	56 (89)	58 (78)	58 (84)	56 (98)	0.09
Prenatal magnesium sulfate	33 (52)	40 (54)	28 (44)	42 (75)	0.06
Hypotension	41 (65)	30 (43)	31 (44)	38 (67)	0.9
Infection	32 (51)	40 (54)	35 (49)	27 (47)	0.8
Ventilation ≥7 days	38 (60)	30 (43)	24 (33)	19 (33)	0.001
Patent ductus arteriosus	24 (38)	25 (34)	28 (39)	28 (48)	0.2
Prolonged indomethacin (≥4 doses)	19 (29)	12 (16)	21 (29)	16 (28)	0.6
Necrotizing enterocolitis	10 (16)	6 (8)	14 (19)	5 (9)	0.7
Postmenstrual age at MRI (wks)					
Scan 1	32.6 ± 2.3	31.7 ± 1.8	31.8 ± 1.8	31.2 ± 1.9	0.005
Scan 2	37.7 ± 2.6	36.4 ± 2.2	35.7 ± 2	35.9 ± 2	0.004
Moderate/severe WMI					
Scan 1	16 (25)	15 (20)	11 (15)	3 (5)	0.002
Scan 2	8 (29)	12 (19)	4 (8)	4 (9)	0.01

* Data presented as mean ± standard deviation or number (%)

** P-value refers to chi-squared test of trends for categorical variables, or variance-weighted least squares regression for continuous variables

Table 3

Clinical predictors associated with moderate/severe white matter injury

Characteristic*	Odds ratio (95% CI)	P-value	Adjusted odds ratio (95% CI)**	P-value
Gestational age (wks)	1.15 (1.0 – 1.32)	0.05	1.21 (0.96 – 1.52)	0.1
Corrected age at MRI (wks)	0.98 (0.85 – 1.12)	0.7	1.06 (0.88 – 1.28)	0.6
Prenatal steroids	1.24 (0.45 – 3.39)	0.7	1.06 (0.36 – 3.09)	0.9
Prenatal magnesium sulfate	1.0 (0.52 – 1.93)	1.0	1.37 (0.68 – 2.78)	0.4
Infection	1.54 (0.83 – 2.84)	0.2	1.82 (0.83 – 3.96)	0.1
Ventilation ≥7 days	1.0 (0.98 – 1.01)	0.6	1.79 (0.67 – 4.78)	0.2
Indomethacin				
None	Ref		Ref	
Brief (1–3 doses)	0.82 (0.40 – 1.68)	0.6	1.02 (0.42 – 2.45)	1.0
Prolonged (≥4 doses)	0.26 (0.10 – 0.71)	0.008	0.29 (0.09 – 0.9)	0.03
Birth year	0.88 (0.8 – 0.97)	0.007	0.89 (0.81 – 0.98)	0.02

* Predictors evaluated on univariate logistic regression if P≤0.1 on comparison between newborns with absent/mild WMI and moderate/severe WMI, or P≤0.1 on test of trend across birth year epochs.

** Multivariate logistic regression model adjusting for all variables in table.