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White Matter Injury in Term Newborns With Neonatal Encephalopathy

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ABSTRACT: White matter injury (WMI) is the characteristic pattern of brain injury detected on magnetic resonance imaging in the premature newborn. Focal noncystic WMI is increasingly recognized in populations of term newborns. The aim of this study was to describe the occurrence of focal noncystic WMI in a cohort of 48 term newborns with encephalopathy studied with magnetic resonance imaging at 72 ± 12 h of life, and to identify clinical risk factors for this pattern of injury. Eleven newborns (23%; 95% CI 11–35) were found to have WMI (four minimal, three moderate, and four severe). In 10 of the 11 newborns, the WMI was associated with restricted diffusion on apparent diffusion coefficient maps. An increasing severity of WMI was associated with lower gestational age at birth ($p = 0.05$), but not lower birth weight. Newborns with WMI had milder encephalopathy and fewer clinical seizures relative to other newborns in the cohort. Other brain injuries were seen in three of the 11 newborns: basal nuclei predominant pattern of injury in one and cortical strokes in two. These findings suggest that WMI in the term newborn is acquired near birth and that the state of brain maturation is an important determinant of this pattern of brain injury. **(*Pediatr Res* 65: 85–89, 2009)**

Cystic periventricular leukomalacia describes white matter injury (WMI) with characteristic topography that is well-recognized by cranial ultrasound in premature newborns (1,2). The increasing use of early-life magnetic resonance imaging (MRI) has revealed a spectrum of WMI that includes focal noncystic WMI (1,3,4). WMI is increasingly recognized as the most prevalent pattern of brain injury in the premature newborn (3,5,6). The severity of WMI in premature newborns is a predictor of adverse neurodevelopmental outcome (3,7). Recent studies suggest that the vulnerability of the premature newborn to WMI relates to the vulnerability of specific developmentally regulated cell populations prevalent in the white matter in the early-mid third trimester of gestation: *e.g.* late oligodendrocyte progenitor cells and subplate neurons (8–11).

However, WMI does not occur exclusively in premature newborns, and is increasingly recognized in some populations of term newborns. Term newborns with congenital heart disease (CHD) seem to be at particularly high risk of WMI, perhaps due to impairments in *in utero* brain development (12–15). Recent *in vivo* data suggest that newborns with CHD have delayed brain development before cardiac surgery, possibly as a result of impaired cerebral oxygen delivery *in utero* (15). WMI is also recognized in the setting of term neonatal encephalopathy (NE). In a series of postmortem examinations of term newborns with NE, three of 21 newborns (14%) had small foci of established gliosis in the periventricular white matter, in addition to evidence of acute hypoxic-ischemic lesions (16). In newborns with basal ganglia injury in the context of NE, white matter damage is seen on MRI in nearly one half of the cases (17,18). However, the timing of injury and risk factors for WMI in term newborns with NE remain largely unknown.

The aim of this study was to describe the occurrence and radiologic appearance of WMI in the term newborn with NE and to identify clinical risk factors for this pattern of injury. Based on the vulnerability of the premature newborn to WMI, we hypothesized that in term infants with NE, earlier gestational age (GA) at birth, but not birth weight, would be associated with an increasing severity of WMI.

METHODS

Study population. The series of newborns with WMI is derived from a cohort of term newborns with NE examined between 2004 and 2007 at the *British Columbia's Children's and Women's Health Centre*, the provincial tertiary-level center for pediatric care. The newborns were scanned with computed tomography (CT) and MRI with diffusion-weighted imaging (DWI) on day 3 (72 ± 12 h) of life for clinical indications; during this time period, the clinical practice was to scan newborns with both CT and MRI/DWI as described below. This cohort was originally reviewed to compare the detection of brain injury with clinical CT, MRI, and DWI on the third day of life (19). In addition to term GA (≥36 wk), inclusion criteria for this retrospective cohort study comprised the presence of clinically recognizable encephalopathy in the first few days of life and at least one of the following: 1) fetal distress at delivery immediately preceding delivery, 2) requirement for resuscitation at birth, 3) Apgar score ≤5 at 5 min, or 4) metabolic acidosis. Newborns with clinical evidence of congenital malformations, genetic abnormalities, and antenatal (congenital) cerebral infection were excluded. The

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Abbreviations: ADC, apparent diffusion coefficient; **CHD,** congenital heart disease; **CT,** computed tomography; **DWI,** diffusion-weighted imaging; **NE,** neonatal encephalopathy; **WMI,** white matter injury

Clinical Research Ethics Board at *University of British Columbia* and *BC Children's Hospital* approved this clinical chart and radiology record review.

Details regarding pregnancy, labor, delivery, and perinatal data were collected from a review of the medical records. An encephalopathy score was calculated (range 0–7) to grade the newborn's neurologic status in the first 3 days of life, assigning 1 point each for abnormalities in feeding, alertness, tone, respiratory status, reflexes, and 2 points for clinical seizures (20,21). Seizures were assessed independently and scored on a scale of 0 to 10 (normal to severe) (22).

Brain imaging studies. MRI scans were performed with sedation according to a standard clinical protocol at 72 ± 12 h of life within the time frame that has previously been suggested to be optimal for detecting neonatal hypoxic-ischemic encephalopathy (23,24). All studies were carried out with a Siemens 1.5 Tesla Avanto using VB 13A software and included the following sequences (TR/TE/AVG/FOV/thickness/gap): axial and coronal T_1-weighted spin echo images (800/20/1/230/4 mm/0.2 mm), axial fast spin echo T_2-weighted images (4000/101/2/230/4 mm/0.5 mm), and isotropic diffusion-weighted images (DWI) b = 700, 1000, with apparent diffusion coefficient (ADC) maps (3300/82/4/210/4 mm/0.2 mm).

All CT studies were performed on a *Philips Brilliance* 16 slice multidetector CT scanner using the same procedure used at our institution since 1986. The scanner was calibrated to a water phantom or an acrylic head phantom embedded with acrylic of 20, 25, 35, and 40 Hounsfield units before every study. All CT studies were performed without sedation at 72 ± 12 h after birth with axial 3 mm slices angled at 20° from the canthomeatal line and using these factors: 120 kV at 300 mA.

CT and MR images were interpreted by an experienced pediatric neuroradiologist (K.J.P.) who was blinded to the newborn's identity and medical history. Brain lesions on MRI scans (T_1, T_2, and DWI) were scored with a validated system for acute and subacute signal abnormalities (25). Newborns were then classified into four patterns of brain injury: 1) normal, 2) watershed predominant, 3) basal nuclei predominant, 4) maximal injury in both the basal nuclei and the cortex (Total) (26). A fifth category was added to account for the cases of focal-multifocal injury, such as WMI and strokes. The presence of WMI was characterized by foci of abnormal T_1 hyperintensity in the absence of marked T_2 hypointensity in the white matter, or by low-intensity foci on T_1-weighted images (cysts) (3). The severity of WMI (Fig. 1) was scored as minimal (≤3 lesions of ≤2 mm), moderate (>3 lesions or lesions >2 mm, but involving no >5% of the hemisphere), or severe (≥5% of hemispheric involvement) (3). Location of white matter lesions were described as anterior (anterior to the frontal horn of the lateral ventricles), posterior (posterior to the occipital horn of the lateral ventricles), or mid-region (between the anterior and posterior white matter regions), as reported in a previous study (5).

Data analysis. Statistical analysis was performed with Stata 9.2 (Stata Corporation LP, College Station, TX). Nonparametric test for trend (Cusick's test) was used to evaluate the effect of GA and birth weight on the severity of WMI. Other clinical characteristics of newborns with WMI and without WMI were compared using Fisher's exact test and Mann-Whitney U test for categorical and continuous data respectively. A p value of <0.05 was considered to be significant.

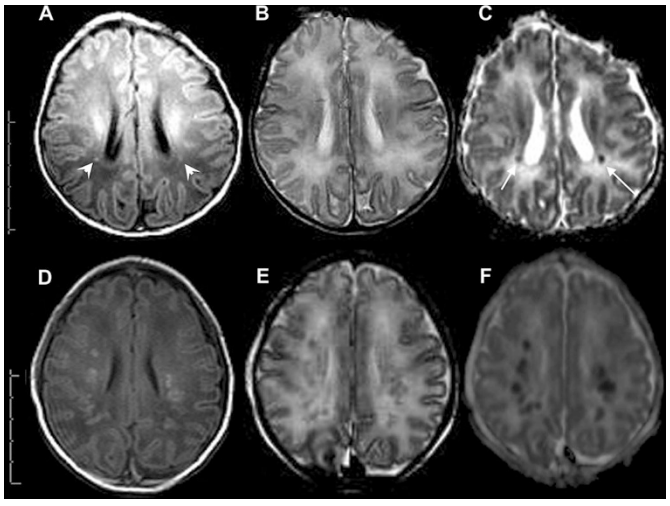

Figure 1. Severity of acute white matter injury. White matter injury (WMI) has a wide range of severity in the term newborn. *A–C*: Mild WMI: Patient 2 shows mild bilateral WMI with hyperintense lesions (arrowheads) on T_1-weighted sequence (*A*) and focal restricted diffusion (arrows) on ADC map (*C*) in the white matter near the trigone of the left and right lateral ventricles. No abnormalities are detected on T_2-weighted sequence (*B*). *D–F*: Severe WMI: Patient 8 shows severe WMI with widespread, bilateral signal abnormalities on both T_1-weighted sequence (*D*) and ADC map (*F*). These lesions are seen on T_2-weighted imaging as abnormal signal hypointensities (E). Each mark on the scale bar represents 1 cm.

RESULTS

White Matter Injury. Of the 48 newborns with NE (29 males) that met the inclusion criteria of the study, 11 (6 males) (23%; 95% CI 11–35) had WMI on MRI. There was an even distribution of the severity of the lesions: minimal (4), moderate (3), and severe (4) (Table 1). Most newborns had multiple focal lesions; only three had two lesions or less. In three infants, the lesions were clustered in a single region (anterior, mid-regions, or posterior), but in the remaining infants, WMI was found in multiple locations. The foci of WMI were most often located posteriorly in the brain of newborns, with more anterior frontal lobe lesions seen in newborns with more severe injury (Table 1). In all but one newborn, multifocal lesions were evident on both standard MRI (areas of T_1 hyperintensity) and DWI (areas of reduced average diffusivity, Fig. 1); in one newborn areas of T_1 hyperintensity were evident without changes on the DWI scan. T_2-weighted imaging only demonstrated WMI in two infants with areas of mild to moderate hypointensity (Table 1). WMI was not detected on CT in any of the 11 newborns. Together, this suggests that most of the WMI lesions are not hemorrhagic. Although the CT scans did not reveal WMI, subdural hemorrhages were observed in six newborns (noted on MRI/DWI in two of these infants), and intraventricular hemorrhages were observed in three (noted on MRI/DWI in two of these infants). Gradient echo images obtained in two of the newborns were both negative for WMI.

Other types of injury. Of the 11 newborns with WMI, three had additional types of brain injury. One newborn had a predominant pattern of injury involving predominantly the

Table 1. *Term newborns with white matter injury: Description of brain injury on MRI*

	WMI score		Location of the lesions				
ID	T_1	T_2	Anterior	Mid-region	Posterior	DWI	Associated lesions
1	1	0			+	Negative	
2	1	0			+	Positive	
3	1	0			+	Positive	
4	1	0		+	+	Positive	
5	2	0	+			Positive	Stroke (36 mm)
6	2	0	+	+	+	Positive	Strokes (7 and 27 mm)
7	2	0		+		Positive	
8	3	3	+	+	+	Positive	
9	3	0	+	+	+	Positive	
10	3	1		+	+	Positive	Basal nuclei injury
11	3	0	+	+	+	Positive	

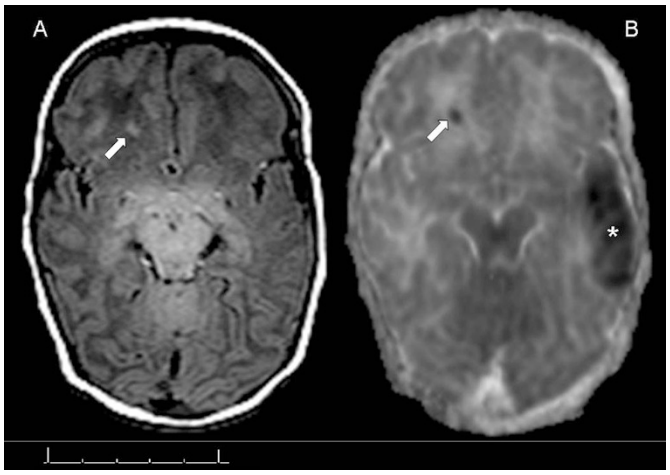

Figure 2. Acute focal white matter injury and acute stroke. T_1-weighted sequence of patient 5 (*A*) shows a focal area of white matter injury (WMI) (arrow) in the right frontal lobe. In addition to the focal WMI, the ADC map (*B*) better demonstrates a large focal stroke (star) in the territory supplied by the left middle cerebral artery. The stroke extends from the inferior temporal lobe to the parietal lobe border. Each mark on the scale bar represents 1 cm.

basal nuclei, as seen on DWI, in addition to the WMI. Two others with WMI had strokes. One infant had an infarct in the territory supplied by the left middle cerebral artery (Fig. 2) and the other infant had two infarcts, one in the left insula and a smaller infarct in the right occipital lobe. In the remaining eight newborns, WMI was an isolated pattern of injury. In comparison, the predominant patterns of injury on DWI in the newborns without WMI were: normal (16), watershed predominant (4), basal nuclei predominant (7), total (7), and focal injury (stroke) (3).

Follow-up scans. Of the 11 newborns with WMI, four had a follow-up MRI scan on day 10. The WMI was similar in severity and extent on both day 3 and day 10 scans.

Clinical features. Lower GA at birth was significantly associated with an increasing severity of WMI ($p = 0.05$) (Table 2). In contrast, lower birth weight was not associated with an increased severity of WMI ($p = 0.6$).

Compared with those without WMI, the newborns with WMI had less severe encephalopathy ($p = 0.02$) and clinical seizures were less frequently recognized ($p = 0.02$). Other clinical characteristics were similar between the two groups (Table 3). In addition, the occurrence of pregnancy-induced hypertension, gestational diabetes mellitus, signs of fetal distress, and meconium aspiration were not significantly different in newborns with and without WMI. None of the newborns with WMI had histopathological chorioamnionitis or postnatal infection. Among the 11 newborns with WMI, clinical features did not distinguish between those with otherwise normal brain and those with additional brain abnormalities (*i.e.* strokes or basal nuclei predominant pattern).

Table 3. *Clinical features of the newborns with and without white matter injury*

Median (IQR)	Newborns with neonatal encephalopathy		*p*
	No WMI	WMI	
n (male)	37 (23)	11 (6)	0.7
Head circumference (cm)	34.0 (33.0–35.0)	34.2 (33.0–36.0)	0.5
Apgar Score at 5 min	5 (3–7)	6 (5–8)	0.3
Cord pH	7.0 (6.9–7.2)	7.0 (6.9–7.1)	0.8
Cord base excess	12.6 (7.0–19.9)	18.5 (12.5–19.0)	0.2
Lactate	7.8 (4.8–14.3)	11.9 (5.7–14.0)	0.8
Resuscitation Score	5 (4–5)	5 (4–5)	0.7
Encephalopathy Score	6 (4–7)	4 (2–4)	0.02
Seizure Score	5 (2–5)	2 (0–4)	0.02

IQR, interquartile range.

DISCUSSION

In a cohort of 48 term newborns with NE uniformly imaged with MRI and MR DWI on the third day of life, WMI was identified in 11 (23%). The imaging characteristics of the WMI were similar to those seen in the premature newborn (1,3,4). In previous neuropathological studies, up to 20% of newborns with periventricular leukomalacia may be full term (27). However, multifocal WMI is recognized commonly on MRI in low birth weight and preterm neonates (1–3,28). Interestingly, preterm infants with WMI have quantifiably less mature white matter than those without WMI (29). In our study cohort, younger GA at birth, but not lower birth weight, was associated with an increasing severity of WMI. This supports the hypothesis that the state of brain maturation is an important risk factor for this pattern of brain injury in the term newborn with encephalopathy.

Recently, the pathogenesis of WMI has been attributed to the vulnerability of two developmentally regulated cell types in the immature brain: *i.e.* late oligodendrocyte progenitor cells and subplate neurons. In an experimental sheep model, Riddle et al. (11) have demonstrated that the topography of WMI relates more closely to the distribution of the vulnerable late oligodendrocyte progenitor cell than to areas of reduced perfusion. Furthermore, the timing of white matter vulnerability in the human newborn overlaps with the proliferative period of late oligodendrocyte progenitor cell populations. The number of oligodendrocyte progenitor cells peaks between the 25th and 34th weeks of gestation, which corre-

Table 2. *Association between the gestational age at birth and birth weight with the severity of white matter injury*

Median (IQR)	Severity of white matter injury			*p**
	None	Mild	Moderate-severe	
n	37	7	4	
Gestational age at birth (wk)	40.0 (39.0–41.0)	38.7 (37.7–41.0)	38.3 (36.3–40.0)	0.05
Birth weight (g)	3115 (2665–3542)	2950 (2695–3300)	3352 (2982–4032)	0.6

* Cusick's non-parametric test for trend.
IQR, interquartile range.

sponds to the period when preterm newborns are at high risk of acquiring WMI (8–10,30,31). This finding of WMI in term NE is also consistent with data from experimental animal models which showed that animals of term-equivalent age may develop WMI after *in utero* hypoxic or inflammatory insults (32,33). A recent study demonstrated that mild hypoxic-ischemic insult in a term-equivalent neonatal rat model of hypoxic-ischemic brain injury was more likely to produce injury in white matter with relative sparing of gray matter than a moderate insult (34). In our cohort of term newborns, those with WMI had less severe encephalopathy and less frequent seizures than those without WMI, consistent with a milder brain insult. However, it is unknown whether the WMI in these term newborns resulted from heterogeneous oligodendrocyte progenitor cell maturation resulting in prolonged white matter vulnerability, a feature of the insult (*e.g.* mild hypoxia-ischemia), or some other unmeasured risk factor related to the care of the "early" term newborn with encephalopathy. Consistent with previous reports, WMI in the term newborn may accompany more commonly recognized patterns of brain injury such as basal nuclei injury (17,18). A recent review suggests that prolonged venous hypertension causing chronic engorgement of the medullary veins can result in injury to white matter without typical signs of hemorrhage, and may be another putative mechanism of WMI in the term newborn (35).

WMI is not the typical predominant pattern of injury in term newborns with hypoxic-ischemic brain injury (26,35–37). However, WMI has been reported to be one of the most commonly acquired injuries in term newborns with CHD, identified before and after cardiac surgery in more than half of newborns with CHD studied with MRI, or at autopsy (12–14). Recently, using MR spectroscopic and diffusion tensor imaging, newborns with CHD were found to have widespread impairment of brain metabolism and microstructural alterations, even in brain regions which seemed to be unaffected (15). These data suggest that the propensity to multifocal WMI in term newborns with CHD is related to delays in brain development. The greater contribution of lower GA at birth, as opposed to lower birth weight, supports the hypothesis that the developmental state of the brain may be the critical risk factor for development of WMI in the term newborn with NE.

Although WMI has been reported previously in term newborns with NE (16,17), to our knowledge, this is the first systematic examination of the occurrence of WMI and its associated risk factors in a cohort of infants studied with MRI at a uniform age in relation to birth. Serial MRI scans in term newborns with WMI have demonstrated that the abnormal multifocal T_1-hyperintensities become less apparent over time, possibly leading to an underestimate of the incidence and severity of these lesions on later scans (6). The failure to detect the WMI on CT, despite observing subdural/intraventricular hemorrhage, and the lack of T_2 change associated with these lesions in most newborns suggest that the WMI in these term newborns with NE were largely not hemorrhagic.

The restricted diffusion associated with most of the lesions identified in this series suggests that the WMI originated within days before the scan. Indeed, the peak change on MR diffusion images of WMI has been shown to occur between days 2 to 4 after insult on MR diffusion images with subsequent pseudonormalization by the seventh day (38). These data suggest that WMI in term newborns may be part of the spectrum of perinatal brain injury, and does not represent injury acquired *in utero* at an earlier GA. However, it is possible that WMI acquired *in utero* may have been more difficult to detect and thus underrepresented in our data. Although none of the newborns had chorioamnionitis or other infections (39,40), the relatively small sample size of this cohort may preclude statistical modeling of all potential risk factor that may be implicated in the pathogenesis of WMI.

In summary, noncystic WMI is a distinct and common pattern of brain injury (23%) in term newborns with NE. It occurs particularly in infants with milder encephalopathy and younger GA at birth. The younger GA of the affected newborns suggests that the maturational state of the cerebral white matter is a contributing factor. The restricted diffusion associated with these lesions, uniformly imaged at 3 days of life, implies that this injury is acquired around birth and is not the late manifestation of remote *in utero* injury sustained during the third trimester of pregnancy. Together, these findings also support MRI with DWI as the primary imaging modality for term newborns with NE. Because WMI in the preterm newborn is associated with subsequent widespread impairments of cerebral development (41,42), future prospective studies are warranted to examine the association between multifocal WMI in the term newborn with encephalopathy and neurodevelopmental outcome.

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