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White Matter Volume and Anisotropy in Preterm Children: A Pilot Study of Neurocognitive Correlates

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ABSTRACT: The objectives of this study were to evaluate the differences in whole brain white matter (WM) volume and anisotropy between preterm and term children and to determine the relationships with cognitive outcome. Twenty-five low birth weight (BW), preterm, neurologically normal children between 8.8 and 11.5 y of age were recruited for volumetric and diffusion-tensor magnetic resonance imaging (DTI), together with 13 age-matched term control subjects. Subsequent intelligence quotient (IQ) testing was performed for 21 preterm children within 6 mo of imaging studies. We computed the mean volume and fractional anisotropy (FA) of the whole brain WM and compared the differences between the two groups. Mean WM volume and FA were significantly lower in the preterm group ($p = 0.014$ and $p < 0.001$, respectively). Multiple regression analysis found both WM volume and FA to be independent variables significantly affecting full scale IQ (FSIQ) ($r^2 = 0.407$, $p = 0.021$ and $r^2 = 0.496$, $p = 0.005$, respectively) after adjusting for BW, gestational age (GA), and gender. In the evaluation of the whole brain WM of preterm children, we found that both volume and FA remain reduced at late childhood with both parameters significantly affecting long-term cognitive outcome. **(*Pediatr Res* 61: 732–736, 2007)**

Nearly 90% of very low BW (VLBW) premature infants now survive the neonatal period due to major advances in neonatal intensive care (1). However, approximately 10% of VLBW preterm infants later exhibit cerebral palsy, 30%–50% later manifest neurodevelopmental handicap during their preschool years, and 50% require special help in grade school. Even in the absence of global intellectual deficits, premature infants are at increased risk of learning disabilities, academic difficulties (2,3), and behavioral problems (4,5). Nearly 20% repeat a grade in school by age 8 y (6).

With recent advances in magnetic resonance imaging (MRI), subtle brain anomalies are now described in preterm children using qualitative and quantitative MR methods, such as decrease in cortical complexity (7) and decreases in total cortical gray matter (GM) (8–10) and WM volume (11–13), as well as regional reduced tissue volume (14–16). Furthermore, an association has been found between some of these abnormalities, such as delay in gyral development being highly related to the presence and severity of WM abnormalities (17). To date, WM volumetric studies in preterm infants and children have demonstrated total WM volume reduction to be significantly correlated with BW (11) and GA (12,18), and some studies further show the adverse effect of regional WM changes on neurocognitive function (19–21).

DTI is a relatively new quantitative MRI technique advantageous for the evaluation of the WM fibers in the brain because it is able to evaluate the directional variability of water diffusion. In WM tracts, the movement of water molecules is relatively free in the direction parallel to its length but restricted in the perpendicular directions by barriers such as axonal membrane and myelin sheaths surrounding it (22). This property, termed diffusion anisotropy, can be quantified by the index derived from DTI, FA. Although axonal membrane is implicated to be the primary source of anisotropy, the degree of anisotropy can be modulated by myelination (22). DTI can therefore be used to study the macro- and microstructure of WM and also estimate myelination and WM maturation *in vivo*. This technique is therefore potentially more sensitive for the detection of WM diseases than conventional MRI.

Developmental changes in the preterm brain have been demonstrated using DTI (23,24). With increasing GA, WM becomes increasingly anisotropic (25). DTI has also been used to elucidate differences in the development of WM in preterm infants compared with term infants. Premature newborns with evidence of early WM injury (WMI) on conventional imaging are found to have lower FA in the central WM and internal capsule when reassessed at term (26). Another study showed that premature newborns with WMI on conventional MRI do not have the expected increase in FA at multiple WM sites at term (27). These effects on WM FA have been found to persist into the teenage years (28,29). Thus, these studies indicate that injury related to premature birth has deleterious effects on the development of WM.

In a cohort of VLBW preterm children, we studied the quantitative imaging parameters of cerebral WM by volumetric studies and DTI, comparing with term normal age-matched

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Abbreviations: BW, birth weight; **DTI,** diffusion-tensor magnetic resonance imaging; **FA,** fractional anisotropy; **FSIQ,** full scale IQ; **GM,** gray matter; **M-U,** Mann-Whitney *U* test; **VLBW,** very low birth weight; **WM,** white matter; **WMI,** white matter injury; **3D SPGR,** three-dimensional spoiled gradient recalled

controls. We hypothesized that mean WM volume and anisotropy are reduced in children who are born preterm with VLBW compared with controls. We also evaluated whether these parameters of WM damage correlate with cognitive outcome.

METHODS

The study was approved by the hospital institutional review board and informed written consent was obtained from the controls, patients, and parents.

Subjects. We randomly recruited 25 subjects born prematurely from the VLBW registry that was set up in Hong Kong between January 1993 and December 1995. All infants with BW <1500 g who were discharged from public hospitals were enrolled in the registry. A total of 210 infants were enrolled.

Inclusion criteria for premature subjects was GA <37 wk, BW <1500 g, good past health apart from prematurity, and neurologically normal with the ability to cooperate during the MRI scan by keeping still for 20 min. The last inclusion criterion was included because we believed that it was ethically not justifiable to sedate children for this study. Therefore, this limited the study subjects to those with no major cognitive or behavioral deficits.

Children with congenital brain malformations or syndromes or congenital brain infection were excluded.

Thirteen age-matched term control subjects selected from a preexisting database were recruited for comparison. All control subjects were neurologically normal with GA >37 wk and BW >2500 g. The control subjects were also matched for socioeconomic status and educational level.

Neurodevelopmental and cognitive assessments. The preterm cohort was invited to return for cognitive function assessment by a clinical psychologist using the Hong Kong Wechsler Intelligence Scale for Children (HKWISC) and a full neurologic examination by a pediatric neurologist within 6 mo after MRI study. The HKWISC is a norm-referenced instrument for assessing the intellectual function of children aged 5 y 0 mo through 15 y 11 mo. It provides a full-scale intelligence quotient (FSIQ) with a mean of 100 and a SD of 15. A FSIQ of 90–109 is considered as average intelligence, whereas an FSIQ of 70–79 is considered limited intelligence and an FSIQ of 80–89 as low average intelligence (30).

Perinatal risk factors, including BW and GA, were recorded from the case notes.

MRI studies. MRI was performed using a Signa 1.5-Tesla imager (General Electric Medical Systems, Milwaukee, WI) with a standard head coil. The following sequences were performed in all patients: axial spin-echo T1-weighted, fast spin-echo proton density, and T2-weighted images, coronal fluid-attenuated inversion recovery sequences, three-dimensional spoiled gradient recalled (3DSPGR) images (slice thickness = 3 mm with no gap of the whole brain, TR/TE/TI = 11.3/4.2/600 ms, acquisition matrix = 256 × 256, flip angle = 15 degrees, field of view = 23 cm), DTI (echo planar imaging, TR/TE = 10,000/84 ms, b factor = 1200 s/mm (2), diffusion-weighted images in 25 noncollinear directions with one nondiffusion-weighted (b0) image, acquisition matrix = 128 × 128, field of view = 28 cm, slice thickness = 5 mm with 1.5-mm gap, imaging time approximately 5 min). The diffusion-weighted MR images were transferred to a workstation (Advantage Workstation, GE Medical Systems) for data processing using a commercial software program (FUNCTOOL; GE Medical Systems) and FA maps were generated accordingly.

Image analysis. All image manipulations were performed using SPM2 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, UK) and MATLAB 6.5 (The MathWorks, Inc., Natick, MA). In SPM2, segmentation of image not normalized to standard space involves three steps: (1) the image is normalized to standard space using an appropriate template, (2) the normalized image is segmented in standard space, and (3) the output of the second step is transformed back to the space of the original image. In our analysis, we performed the image processing in two phases. In the first phase, we created customized 3DSPGR and b0 templates because the use of customized templates would improve the accuracy of the normalization process. We performed this by linearly normalizing our subject's 3DSPGR and b0 images to the pediatric T1-weighted template CCHMC2_fp (Cincinnati Children's Hospital Medical Center, Cincinnati, OH) (31). In the second phase, the original 3D SPGR and b0 images were segmented using the respective customized templates created in phase 1 to parcel images into GM, WM, and cerebrospinal fluid (CSF). WM volume was calculated by adding up the probability values of all voxels of a 3DSPGR WM segment and multiplying the total by the volume of one voxel. Inherently registered with FA image, segmentation outputs from the b0 image were used to create a WM mask by evaluating the following formula (I_WM>I_GM)&(I_WM>I_CSF)&[I_WM>(1-I_GM-I_WM-I_CSF)] using ImCalc function in SPM2, and the resulting mask was subsequently used to calculate the mean FA value of the WM. Figure 1*A* shows a 3DSPGR image superimposed with the contour of its WM segmentation output. Figure 1*B* shows the WM mask derived from segmentation output of the b0 image used to map out the WM region in the FA map. For more details on the image processing, please refer to our previous publication (32).

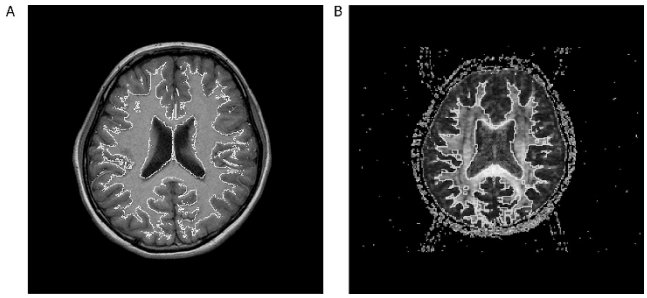

Figure 1. (*A*) 3DSPGR image superimposed with the contour of its WM segmentation output. (*B*) WM mask derived from segmentation output of the b0 image used to map out the WM region in the FA map.

Statistical analysis. We computed the mean WM volume and FA and compared the differences between the two groups using a *t* test. We further evaluated the gender effect on WM volume and FA using a *t* test. Spearman's correlation, followed by multiple regression analyses, was performed to determine the association between WM volume, FA, gender, BW, GA, and FSIQ in the preterm group.

RESULTS

Preterm patients. Twenty-five preterm children (14 males, 11 females) aged 8.8 to 11.5 y (mean age, 10.14 y, SD = 0.76 y) were included. BW and GA were 1141.6 ± 213.9 g (mean ± SD) and 29.4 ± 3.1 wk (mean ± SD), respectively. Except for three subjects who had mild increased signal in the periventricular WM on T2-weighted images, conventional MRI was normal. All children were attending normal mainstream schools. None had neurologic deficits or cerebral palsy on clinical examination.

Control subjects. Thirteen control subjects (nine males, four females) aged 8.5–12.5 y (mean age, 10.11 y, SD = 1.18 y) were included for comparison with the preterm group.

There were no significant differences in gender ($p = 0.501$, Fisher's exact test), age [$p = 0.605$, Mann-Whitney *U* (M-U) test] and parental socioeconomic status ($p = 0.079$, M-U test) between the preterm group and the control group. Educational level was significantly lower in the preterm group compared with the control group ($p = 0.045$, M-U test).

MRI findings. Mean WM volume and mean WM FA of the preterm group and the controls are summarized in Table 1, with stratification into male and female gender in Table 2. WM volume and FA was significantly lower in the preterm group compared with the control group ($p = 0.014$ and $p <$

Table 1. *Mean WM volume and mean WM FA in the preterm and term groups*

	Preterm ($n = 25$), Mean (SD)	Term controls ($n = 13$), Mean (SD)	% Reduction	*p*
Mean WM volume (mL)	341.8 (32.9)	368.9 (25.8)	7.35	0.014
Mean WM FA	0.346 (0.014)	0.364 (0.012)	4.95	<0.001

Table 2. *Mean WM volume and mean FA in the preterm as compared to term males and females*

	Male	Female	*p* value of gender difference
Mean WM volume (SD)/mL			
Control (N =13)	372.2 (27.9) (n = 9)	361.7 (22.2) (n = 4)	0.523
Premature (N = 25)	341.0 (34.4) (n = 14)	348.7 (27.7) (n = 11)	0.563
Mean FA (SD)			
Control (N = 13)	0.362 (0.013) (n = 9)	0.369 (0.008) (n = 4)	0.341
Premature (N = 25)	0.339 (0.014) (n = 14)	0.355 (0.009) (n = 11)	0.005

0.001, respectively). Mean WM volume reduction was 7.35% and mean FA reduction was 4.95%. Males were found to have significantly lower FA compared with females in the premature group (p = 0.005). However, when the interaction of prematurity and gender on FA was tested using two-way analysis of variance, this was found to be not significant (p = 0.284). There was no significant difference in WM volume between males and females in the premature group.

IQ tests. Of the 25 preterm children, 21 returned for IQ tests. The FSIQ was 106 ± 12.8 (mean ± SD). Verbal IQ and performance IQ were 109 ± 12.1 and 101 ± 13.9, respectively (mean ± SD).

Factors affecting cognitive function. Using Spearman's univariate analysis, significant correlations were found between FSIQ and WM volume (r = 0.584, p = 0.005), FSIQ and BW (r = 0.485, p = 0.026), and FSIQ and GA (r = 0.474, p = 0.030). FA was not found to significantly affect FSIQ. On inspection of the scatterplot, we detected an outlier, but the correlation remained not significant even after removal of the outlier (p = 0.072). Subsequently, we performed multiple regression analysis after removal of the outlier.

Significant correlations were also found between GA and BW (r = 0.757, $p < 0.001$) and gender and FA (r = 0.592, p = 0.002). Gender difference was not shown to affect WM volume.

Multiple regression analysis found both WM volume and FA to be independent variables significantly affecting FSIQ after adjusting for GA, BW, and gender (r^2 = 0.407, p = 0.021 and r^2 = 0.496, p = 0.005, respectively) (Fig. 2*A* and *B*).

DISCUSSION

We studied quantitative parameters of WM damage by MRI using volumetry and DTI. In this cohort of neurologically normal low BW preterm children with minimal changes on conventional MRI findings, we found both mean WM volume and anisotropy to be reduced compared with term matched control subjects. In addition, both parameters significantly correlated with FSIQ, with WM FA having a stronger association than WM volume.

The mechanisms of perinatal brain injury in the preterm newborn are not fully understood. Although hypoxia-ischemia insults are a well-established cause of WMI, particularly in the preterm infant, recent studies demonstrate the role of inflammatory processes in perinatal preterm brain injury and the susceptibility of the developing oligodendrocytes toward ischemic inflammatory insults (33) and glutamate toxicity (34,35).

In a primate model of prematurity using baboons born prematurely, a marked predominance of cerebral WMI was observed in 50% of the prematurely born animals. The injury ranged from small patches of reactive astrocytosis to more extensive damage with activated microglia, small cystic lesions, and endothelial hypertrophy. The extent of WMI ranged from approximately 0.5% to 2.5% of total WM and occurred most frequently in the parietal and occipital lobes (36).

Our findings of reduced WM volume are in agreement with most studies of preterm children. These studies have found between 2.5% and 11% of total WM reduction in the preterm group (11–13). Up to 15% total WM reduction has been found in preterm infants with preexisting periventricular leukomalacia (37). Evaluation of the regional WM changes has shown diffuse alteration with areas of both deficit and excesses. Allin *et al.* (38) evaluated VLBW adults and found symmetrical WM excesses in the anterior part of the internal capsule, the insular cortex, and the arcuate fasciculus. WM deficits were seen symmetrically in the posterior part of the internal capsule and the superior, middle frontal, pre- and post-central gyri, and the optic radiation and unilaterally involving the left uncinate fasciculus. A recent preterm birth cohort of 50 adolescents showed diffuse regional WM volume decreases (18). Bilateral involvement of the superior and inferior longitudinal fasciculus was present. Other studies found a decrease in the corpus callosum (20,39) and the temporal lobe WM volume (40). Furthermore, regional WM volumes have been associated with neurodevelopmental outcome. Peterson *et al.*

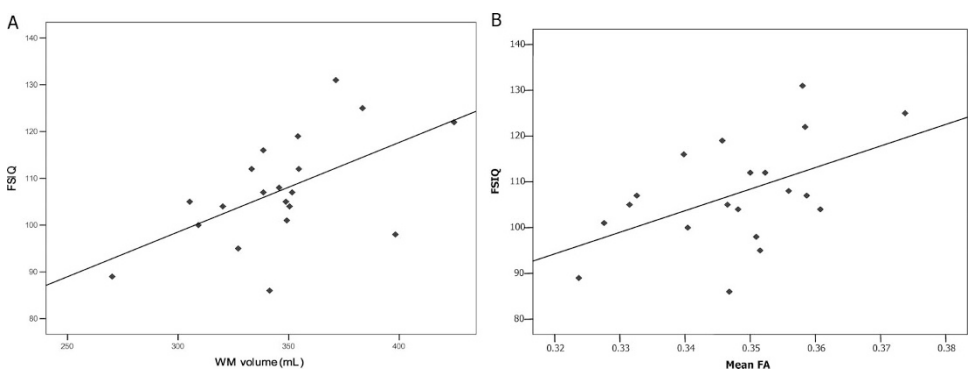

Figure 2. (*A*) Scatterplot of FSIQ *versus* mean WM volume of preterm children (n = 20) (r^2 = 0.407, p = 0.021). (*B*) Scatterplot of FSIQ *versus* mean FA of preterm children (n = 20) (r^2 = 0.496, p = 0.005).

(21) showed that WM volumes of preterm infants in the sensorimotor and midtemporal regions, when assessed near term, correlated strongly with neurodevelopmental outcome at 18–20 mo of corrected age (Spearman's $\rho > 0.9$ for right sensorimotor and right midtemporal region, $\rho = 0.83$ for left sensorimotor region, $\rho = 0.77$ for left midtemporal region). Voxel-based morphometry analyses of the WM in a group of preterm, neurologically normal children at the age of 7.5–8 y revealed that regional WM volume in the parietal lobe was related to absolute IQ scores, whereas IQ decline over time was associated with regional WM volume in the frontal, temporal, and occipital regions (19).

In our cohort, we found a moderate but significant positive correlation of whole brain WM volume and FSIQ ($r^2 = 0.407$, $p = 0.021$).

To date, only a few studies have evaluated the diffusion characteristics in WMI of prematurity at long-term follow up (28,29,41). It has been proposed that decreased WM anisotropy is related to poor myelination and axonal injury secondary to damage to the axonal-oligodendroglial unit (26). None have studied the relationship of the quantitative index, FA, with neurocognition in these cohorts. Significant correlations have been found between WM FA and IQ in both normal and diseased populations. Nagy *et al.* (42) found that the development of cognitive abilities in childhood is correlated with maturation of WM; specifically, working memory and reading abilities were found to correlate with increased FA in the superior and inferior left frontal lobe and the left temporal lobe respectively. Similar correlations have been found between cognitive function and chronic malignant phenylketonuria (43), Alzheimer's disease (44), ischemic leukoaraiosis (45), relapsing-remitting multiple sclerosis (46), and treatment-induced WMI in childhood cancer survivors (32). Recently, WM FA was found to correlate with FSIQ in the WM association areas of bilateral frontal and occipitoparietal regions in a cohort of normal children (47).

We found a trend of a more severe reduction in FA in premature males compared with females. Gender effect on FA in the premature cohort has not been described in the literature. However, preterm males appear to be particularly vulnerable to neurodevelopmental deficits compared with preterm females, with greater impairment in speech (48), learning, and academic achievement (49–51). Significant reduction in the total WM volume was found in preterm males compared with term males (11). Also, preterm adolescent boys were found to have a smaller mid-posterior callosal area compared with girls, and their verbal IQ and verbal fluency scores were positively associated with total mid-sagittal corpus callosum size and mid-posterior surface area (20). Thus, there is evidence that the male gender may be more susceptible to WMI than females.

Our cohort is limited by a relatively small sample size, and the study population was skewed toward children who all attend normal mainstream schools with the mildest form of learning problems.

With the decline in the incidence of overt pathologies such as periventricular leukomalacia and intraventricular hemorrhage, more sensitive MRI techniques with the use of quantitative indices may be required to detect and evaluate the subtle WM changes in the preterm brain.

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