WHITE MATTER VARIATIONS ASSOCIATED WITH SEVERITY OF PUNCTATE WHITE MATTER LESIONS: ASSESSMENT BY DIFFUSION TENSOR IMAGING BASED ON TRACT-BASED SPATIAL STATISTICS (TBSS)

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Target audience Pediatric radiologist and pediatrician

Introduction Punctate white matter lesions (PWML) are common brain injuries at any gestational age. It has been reported that isolated PWML often had a normal outcome, while widespread PWML may give rise to delays in language development, spastic diplegia, or visual impairment[1]. These findings indicated that neurodevelopmental outcomes ought to be associated with the severity of PWML. However, it is unclear whether the impaired WM structures due to PWML in different degrees are different and what the relationship between the severity of PWML and outcomes is. Previous DTI studies have demonstrated the robustness of tract-based spatial statistics (TBSS) in detecting multiple WM damages in PWML neonates[2]. This study aimed to use TBSS to detect and document the WM variations among neonates with PWML of different degrees.

Table 1 MR imaging grading of PWML

	Grade I	Grade II	Grade III
Number of lesions	1 or 2	≥3	≥3
Size of lesion	≤3mm diameter	1 lesion >5 mm diameter	Multiple lesions >5 mm diameter
Distribution	≤2 areas affected	≤2 areas affected	extensively affected

Table 2 Clinical characteristics of all subjects

Demographics	Normal group (21 cases)	PWML group (36 cases)		
		Grade I (18 cases)	Grade II (7 cases)	Grade III (11 cases)
Gestational age, wks	33^{+6} (30^{+1}~35^{+3})	34^{+3} (32^{+0}~35^{+6})	33^{+4} (30^{+5}~34^{+5})	33^{+5} (32^{+3}~35^{+3})
Ages at MR scan, wks	35^{+2} (32^{+1}~36^{+5})	35^{+4} (33^{+2}~37^{+2})	35^{+0} (32^{+1}~36^{+3})	34^{+6} (33^{+1}~36^{+4})
Birth weight, g	1827 (1420~2570)	2180 (1590~3570)	1888 (1480~2700)	2070 (1640~3150)

Methods *Subjects:* 36 preterm neonates with PWML and 21 normal controls underwent MRI within 14 days after birth were enrolled. According to Miller's MR grading standard for PWML[3] (showed in **Table 1**), 18, 7, 11 neonates were included as grade I, II, III, respectively. Clinical details of all neonates were given in **Table 2**. The gestational age, ages at MR scan and birth weights were similarly distributed between normal group and PWML group, and among PWML neonates in different grade. *MRI acquisition:* All neonates were all sedated (oral chloral hydrate, 25-50 mg/kg) before MRI scanning. Conventional MRI and DTI were performed on a 3T scanner (GE, Signa HDxt). DTI protocols were: 35 directions, b value=1000s/mm^2, TR/TE=5500/95ms, slice thickness= 4 mm without gap, field of view = 180mm×180mm, matrix = 256×256, voxel size= 0.70×0.70×4mm^3. *Image analysis:* The DTI images were processed with FMRIB Software Library (FSL, Oxford, United Kingdom). After extracting brain images and eddy current correction, FA, MD and three eigen-value maps (λ1, λ2 and λ3) were generated. Then axial diffusivity (AD=λ1) and radial diffusivity (RD= [λ2+λ3]/2) were obtained. TBSS was used to align FA images of all subjects to the target image (a representative FA image) and affine the aligned images into 1×1×1 mm^3 standard spaces for preterm neonates we previously established (replaced original MNI152 standard space for adult). Then the mean FA image and its skeleton were created. The aligned FA image of each subject was projected onto the mean FA skeleton (threshold = 0.15). The resulting FA skeleton images were fed into voxel-wise cross-subject statistics to identify differences on major WM tracts between normal group and PWML group in three grades. The results were corrected for multiple comparisons by controlling family-wise error rate after threshold-free cluster enhancement (TFCE). All tests were taken to be significant at p<0.05.

Results The result of TBSS showed no significant increased or decreased DTI metrics in major WM tracts of neonates with grade I PWML. For grade II, there was decreased FA in optic radiation (OR), cerebral peduncle (CP), posterior limb of internal capsule (PLIC), splenium of corpus callosum (SCC) and body of corpus callosum (BCC) (the left part of **Fig.1**). For grade III, there were decreased FA, increased RD and MD in OR, PLIC, SCC, BCC, genu of corpus callosum (GCC), external capsule (EC) and corona radiate (CR) (the right part of **Fig.1**) The *P* values of voxel-wise statistical analysis on FA between normal and grade III PWML group (presented as light blue) were greater than those in analysis between normal and grade II PWML group (presented as blue).

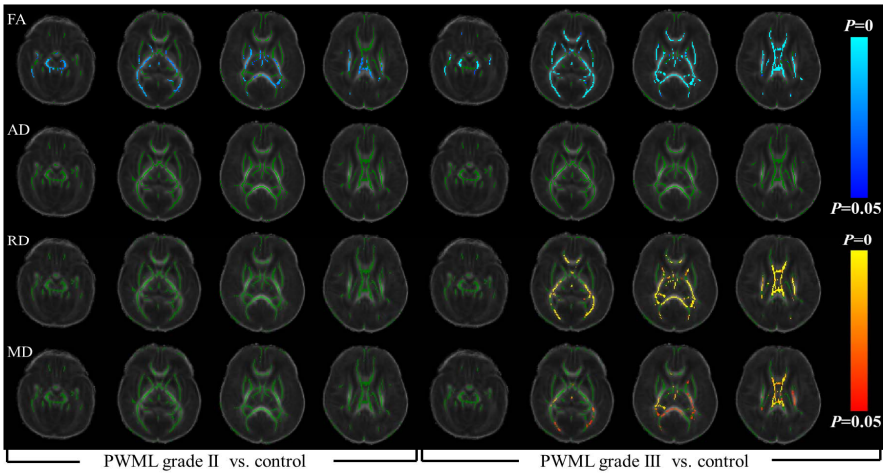

Fig.1 DTI metrics (FA, AD, RD, MD) changes along major white matter tracts in PWML neonates of grade II and III revealed by TBSS. Regions in light blue-blue represented where DTI metrics significantly decreased in PWML neonates with *P* value 0-0.05 (TFCE-corrected), while regions in yellow-red represented where DTI metrics significantly increased in PWML neonates with *P* value 0-0.05 (TFCE-corrected). Green regions represented mean FA skeleton.

Discussion Firstly, this study demonstrated that PWML of grade I may not impair WM integrity, while PWML of grade II or III could affect WM integrity in different degrees. There was only decreased FA in neonates with PWML of grade II, which might be due to mild alterations in WMs. In more severe patients (grade III), decreased FA changing with increased RD, which reflected increased diffusion perpendicular to WM fibers, indicated deficits or delays in myelination. In addition, damaged WM tracts in PWML neonates of grade III were more widespread than them in PWML neonates of grade II, and the *P* values of voxel-wise statistics on FA between normal group and grade III PWML group were also greater. These findings suggested that, relative to PWML of grade II, PWML of grade III can bring more severe destructions to WMs and may indicate a worse outcome. Both in grade II and III PWML, the damaged WM tracts in OP and corticospinal tract (from PLIC to CR) might lead to impairment to motorial and visual performance. In grade III PWML, additional damaged WM tracts in GCC and EC can also be observed, suggesting impairments in coordination and integration during later period.

Conclusions This was the first study that demonstrated different variations of WM tracts due to PWML in different grades. PWML in grade I may not impair WM integrity and indicate a normal outcome, while PWML in grade II and III can lead to multiple WM damages and may be associated with adverse outcome to different degrees. Further study will be carried out to follow up these neonates longitudinally.

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