Correlation of emotional-behavioral outcomes and white matter alterations in VLBW adolescents without overt disability

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Introduction

In humans, birth weight generally correlates to gestational age and is easy to determine. It is estimated that one-third of low birth weight (< 2,500 grams) deliveries are preterm. Weight-based classification of newborns further recognizes Very Low Birth Weight (VLBW) which is less than 1500 grams. Almost all neonates in this VLBW category are born preterm. Preterm infants are vulnerable to brain injuries, and brain injury due to prematurity and impaired brain development are inextricably intertwined[1]. A diverse spectrum of neuronal/axonal disturbances involving thalamus, basal ganglia, cerebellum and cerebral cortex has been shown to be frequent in premature infants. As neuropsychiatric deficits of prematurity are related to brain injury, either gross or subtle, magnetic resonance imaging (MRI) can be an excellent assessment tool. Diffusion tensor imaging (DTI)[2] is powerful to visualize and quantify abnormalities in human brain white matter (WM) connection in vivo. Nevertheless, there are few long-term brain MRI reports of adolescence born VLBW without overt neurological or mental disability. In this study, we attempted to explore the findings of WM abnormalities in this specified group and to evaluate the relationship between WM findings and emotional-behavioral outcomes.

Materials and Methods

Subjects: The subjects were recruited from a data bank of the Kaohsiung Medical University Hospital-Premature Baby Registry. In 1996-1999, a total of 148 children were admitted. The range of this cohort was chosen so that subjects consenting to join this survey would be adolescents from 12 to 15 years old by 2011. At follow–up, 111 adolescents were alive. Of the 41 subjects who were ascertained to be without overt physical or mental disability, 18 adolescents were willing to undergo brain MRI examination. Control adolescents were recruited through advertisement in the neighborhood. Final study subjects consisted of 24 adolescents: 12 adolescents born VLBW without overt neurological or mental disability (M:F=7:5,age=13.1$\pm$1.5ys) and 12 control adolescents born full term (M:F=6:6,age=13.7$\pm$1.6ys). ***Emotional-behavioral Assessments:*** (1) Child Behavior Checklist (CBCL)[3] and (2) Chinese version of the Swanson, Nolan and Pelham IV scales (SNAP-IV)[4] were carried out by obtaining the questionnaires from their parents. ***Data Acquisitions:*** MRI scanning was performed on a 3.0T MRI scanner (Skyra, Siemens, Erlangen, Germany) using a 20-channel phase-array head-neck coil. Head movements were minimized by tightly fixating the head with cushions during the scanning procedure. After tri-planar scans for slice localization, a high-resolution whole brain 3D T1-weighted MPRAGE data and fast spin-echo T2WI were acquired. For those adolescents who had no noticeable findings on conventional T1 and T2 images, three-repeated DTI data were further acquired using a spin-echo diffusion-weighted echo-planar pulse sequence with the following parameters: TR = 4200 sec, TE = 72 msec, matrix = 96×96, FOV = 240 mm x 240 mm, number of averages = 1, slice thickness = 3 mm, and 40 axial slices for whole-brain coverage, number of non-collinear diffusion direction = 30, number of $b0$ = 1, and b-value = 1000 s/mm^2. ***Voxel-based analysis:*** Individual fractional anisotropy (FA) maps were spatially normalized to an international consortium for brain mapping (ICBM) FA template by using linear affine and non-linear demon registrations to respectively minimize global and local differences between the individual and template images. The displacement maps generated from the registration steps were utilized to spatially normalize the corresponding axial (AD), radial (RD), and mean diffusivity (MD) maps. The voxelwise comparisons were performed by using SPM8 on a MATLAB platform. Two-sample t-test was performed to reveal the differences of DTI indices between VLBW subjects and normal controls. Pearson's correlation analysis was further performed on those significant regions in VLBW subjects between FA and emotional-behavioral measures. For voxel-based analysis, significant difference was reported if uncorrected $p < 0.001$ and cluster > 100 voxels. For Pearson's correlation coefficient, significant difference was reported if $p < 0.05$.

Results and Discussion

The results of emotional-behavioral assessments showed significantly higher scores in the social, attention, total problems, SNAP-IV inattentive, and hyperactive-impulsivity in the VLBW adolescents (p<0.05). In voxelwise analysis, the VLBW adolescents had significantly higher AD values, located mostly in bilateral corona radiata, as shown in Figs. 1a – 1c, significantly higher RD values in bilateral corona radiata, bilateral posterior cingulum bundles, bilateral thalamus, and bilateral sagittal stratum, as shown in Figs. 1d – 1f, and significantly higher MD values than the control subjects in bilateral anterior and bilateral superior corona radiata, and bilateral sagittal stratum, as shown in Figs. 1g – 1i. The FA results further showed significantly decreased FA values in the VLBW adolescents, including right superior corona radiata, bilateral posterior cingulum bundles, and bilateral sagittal stratum, as shown in Fig. 1j – 1l. No regions indicating higher FA in the adolescent born VLBW were observed. Table 1 summaries the findings obtained using Pearson's correlation analysis in regions with significant FA difference for the whole subjects. The results suggested that adolescents born VLBW exhibited subtle WM alterations in multiple brain regions even without overt disability. The correlation analysis between FA and emotional-behavioral outcomes indicated that the WM alterations were significantly associated with those emotional-behavioral outcomes.

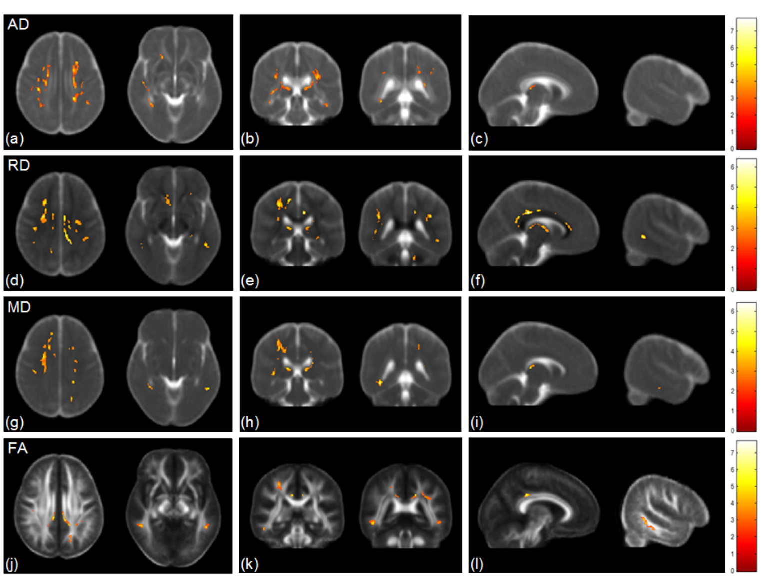

Figure 1

Table 1

Area		Social/ CBCL	Attention/ CBCL	Total problem/ CBCL	SNAP-I	SNAP-HI
SCR	Right	-0.510*	-0.468*	-0.511*	-0.692**	-0.483*
Cg	Left	-0.454*	-0.499*	-0.439	-0.631**	-0.605**
Cg	Right	-0.476*	-0.535*	-0.495*	-0.696**	-0.620**
SLF	Left	-0.536*	-0.537*	-0.568**	-0.750**	-0.627**
ILF	Left	-0.571**	-0.616**	-0.557*	-0.639**	-0.660**
ILF	Right	-0.630**-	-0.615**	-0.651**	-0.728**	-0.660**

SCR: Superior corona radiate; SLF: superior longitudinal fasciculus; ILF: inferior longitudinal fasciculus; Cg: Cingulum. CBCL: Child Behavioral Checklist; SNAP-I: Swanson, Nolan and Pelham scales- Inattention subscale; SNAP-HI: Swanson, Nolan and Pelham scales – hyperactivity impulsivity subscale. (*p<0.05; **p<0.01)

Conclusion

Adolescents born with VLBW and were currently mentally and physically without disability still manifested brain white matter microstructural abnormalities and more emotional-behavioral problems than normal controls. In addition, the DTI indices showed meaningful correlations with behavioral measures. These results indicate that perinatal brain injury persists in adolescence even when clinically the child is without overt disability.

References

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