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Altered microstructural connectivity of the superior and middle cerebellar peduncles are related to motor dysfunction in children with diffuse periventricular leucomalacia born preterm: A DTI tractography study

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ABSTRACT

Purpose: To investigate the microstructural integrity of superior cerebellar peduncles (SCP) and middle cerebellar peduncles (MCP) by using DTI tractography method, and further to detect whether the microstructural integrity of these major cerebellar pathways is related to motor function in children with diffuse periventricular leucomalacia (PVL) born preterm.

Materials and methods: 46 children with diffuse PVL (30 males and 16 females; age range 3–48 months; mean age 22.4 ± 6.7 months; mean gestational age 30.5 ± 2.2 weeks) and 40 healthy controls (27 males and 13 females; age range 3.5–48 months; mean age 22.1 ± 5.8 months) were enrolled in this study. DTI outcome measurements, fractional anisotropy (FA), for the SCP, MCP and cortical spinal tract (CST) were calculated. The gross motor function classification system (GMFCS) was used for assessing motor functions.

Results: Compared to the controls, patients with diffuse PVL had a significantly lower FA in bilateral SCP, MCP and CST. There was a significant negative correlation between GMFCS levels and FA in bilateral SCP, MCP and CST in the patients group. In addition, significant inverse correlation of FA value was found between not only the contralateral but also the ipsilateral CST and SCP/MCP.

Conclusions: These findings suggest that the injury of SCP and MCP may contribute to the motor dysfunction of diffuse PVL. Moreover, the correlations we found between supratentorial and subtentorial injured white matter extend our knowledge about the cerebro-cerebellar white matter interaction in children with diffuse PVL.

1. Introduction

Periventricular leucomalacia (PVL) has long been investigated as a leading cause of motor and cognitive impairment in subjects who were born prematurely. It was accompanied by neuronal/axonal deficits that involve the cerebral white matter (WM), thalamus, basal ganglia, cerebral cortex, brainstem, and cerebellum. The diffuse PVL, which is more diffusely apparent in cerebral white matter, accounts for the vast majority of PVL cases, and it is known to be a high risk factor of spastic diplegic or quadriplegia cerebral palsy (CP) [1].

The cerebellum is an important key in many functions, including cognitive function, fine motor skills, coordination and motor sequencing. The constantly development of the neuroimaging has allowed us to diagnose cerebellum injury in preterm infants, as well as the structural and functional outcomes in survivors [2–4]. In 2005, Johnson et al. described cerebellar injury as a complication of extremely low birthweight, suggesting that injury to the cerebellum in the extremely premature survivor who has cerebral palsy is common and associated with a more adverse clinical picture [2]. Limperopoulos et al. performed volumetric MRI at term equivalent in 74 infants <32 weeks gestation. Cerebellar volumes were decreased in all infants with abnormal supratentorial findings.

Abbreviations: SCP, superior cerebellar peduncles; MCP, middle cerebellar peduncles; DTI, diffusion tensor imaging; PVL, periventricular leucomalacia; CP, cerebral palsy; FA, fractional anisotropy; GMFCS, gross motor function classification system; CST, cortical spinal tract; WM, white matter; ROI, region of interest; SD, standard deviation.

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Infants with periventricular hemorrhagic infarction had reduced brain volumes in the contralateral cerebellar hemisphere. These findings suggested a trophic relationship between developing cerebral and cerebellar tissues [4].

Cerebellar influences are mediated by extensive connections with the cerebral cortex, the limbic system and the thalamus. The middle cerebellar peduncle (MCP) is the largest cerebellar peduncle and it is the major input pathway to the cerebellum. The dentate nucleus sends fibers through the superior cerebellar peduncles (SCP) which is the major output pathway of the cerebellum to the contralateral motor areas of the cerebral cortex. Thus, MCP and SCP complete a circuit between the cerebral and cerebellar cortices whose main function was suggested to coordinate the motor output of the cerebral cortex [5]. Quantitative MRI studies reported decreased size of SCP and MCP in patients with neurodegenerative disorders such as progressive supranuclear palsy, multiple system atrophy and Parkinson's disease [6,7]. Atrophy of SCP and MCP on these patients was associated with variety of motor, sensory and cognitive dysfunctions. Therefore, identifying damage to these pathways and how it may interfere with motor function is an important step in discovering the neurobiological mechanisms which may result in motor outcomes. However, to the best of our knowledge the cerebellum white matter injury has been little studied in diffuse PVL children.

DTI is a powerful technique which is excellent for studying white matter microstructure. DTI noninvasively examines the molecular diffusion of water in vivo and yields a quantitative diffusion parameter, fractional anisotropy (FA), which is related to axonal packing and myelination [8]. Since these structural elements are responsible for neural connectivity, DTI measurements are expected to contribute greatly to the understanding of pathways between brain regions. Therefore, in the present study, we examined the microstructural integrity of the SCP and MCP through the measurement of FA value using the DTI tractography approach. The main aim of this study was to investigate whether the diffuse PVL patients show evidence of structural injury in WM of the cerebellum and whether the cerebellum WM injury contributes to the motor dysfunction observed in patients with diffuse PVL. In addition, we assessed the correlation of microstructural integrity between WM of the cerebellum and the supratentorial motor white matter, cortical spinal tract (CST), to investigate the cerebro-cerebellar white matter interaction in children with diffuse PVL.

2. Method

2.1. Patients and controls

The study sample consisted of preterm-born children (gestational age <37 weeks) born in the First Hospital of China Medical University. Inclusion criteria for this study were: (1) children with spastic diplegia or tetraplegia CP symptoms, (2) diffuse PVL diagnosed by neuroradiological evaluation on conventional MRI. Exclusion criteria were: subjects with structural abnormalities such as a cortical infarction ($n = 10$), malformation ($n = 12$) or any other type of congenital anomalies in the cerebrum or cerebellum regions on MRI ($n = 11$). The final study population consisted of 46 children (30 males and 16 females; age range 3–48 months; mean age 22.4 ± 6.7 months; mean gestational age 30.5 ± 2.2 weeks). Of all the patients, 35 children had spastic diplegia, 11 had spastic tetraplegia CP. Each patient was submitted to a standardized evaluation protocol that included neurological evaluation and MRI study including DTI. Meanwhile, 40 age-matched normal controls (27 males and 13 females; age range 3.5–48 months; mean age 22.1 ± 5.8 months) with normal MRI findings and no neurological abnormalities were recruited for comparison. The study was approved by the hospital's research ethics board and written informed consent was provided by all the participants' parents or legal guardians. Characteristics of study participants are summarized in Table 1.

Table 1
Characteristics of study participants.

Characteristic	Controls ($N = 40$)	Diffuse PVL ($N = 46$)
Gestational age, week, mean ± SD	38.2 ± 1.2	30.5 ± 2.2
Birth weight, g, mean ± SD	3637 ± 315.8	2137 ± 336.7
Gender (male:female)	27:13	30:16
Age at MRI, mh, mean ± SD	22.1 ± 5.8	22.4 ± 6.7

2.2. Motor function assessment

The motor dysfunction scale was evaluated using the gross motor function classification system (GMFCS) [9]. This is a functional, five-level classification system for CP that is based on self-initiated movement with particular emphasis on sitting and walking. Patients were graded according to GMFCS scale. Out of 46 patients, 15 patients had a mild degree of motor dysfunction (4 subjects with grade I and 11 subjects with grade II), and 31 patients had moderate-to-severe dysfunction (grade III in 9, grade IV in 16 and grade V in 6 subjects).

2.3. MR data acquisition

We acquired the MRI and DTI data on the 1–3 days after motor function assessment. MRI was performed using a 3.0 T scanner (Signa HDx, GE Healthcare, Milwaukee, USA) with an eight channel phased-array head coil. All the children were sedated during MRI examinations using chloral hydrate by enteroclysis under standard protocol use. Initially, all individuals underwent routine clinical pulse sequences, including sagittal and axial fast inversion recovery (IR) T1-weighted sequences (5 mm slice thickness, no interslice gap, repetition time 297–599 ms, echo time 10.5–13 ms) and axial fat-suppressed fast spin-echo (FSE) T2-weighted sequences (repetition time 3992–4525 ms, echo time 110 ms).

DTI was acquired after all of the routine clinical sequences and consisted of a single-shot spin-echo planar sequences in axial sections, with repetition time ranging from 6.2 to 9.4 s and echo time of 80 ms. The slice thickness was 3 mm without a gap. 40–60 axial slices parallel to the anterior–posterior commissure (AC-PC) line were acquired, covering the entire brain. The maximum b value was 800 s/mm^2, used in a scheme of 15 different gradient directions. Total acquisition time was 6 min and 57 s.

2.4. DTI data processing and statistical analysis

All DTI acquisition data were transferred offline and processed using DTI Studio (Johns Hopkins University and Kennedy Krieger Institute, Baltimore, MD, USA; http://www.mri.kennedykrieger.org). To correct for image distortions produced by Eddy currents and head movement, the Automatic Image Registration (AIR) program was used. Fiber tractography (FT) was performed on the basis of the fiber assignment by continuous tracking (FACT) method [10]. A multiple-ROI approach was used to reconstruct all tracts of interest. For the SCP (Fig. 1a), ROI 1 was placed in the coronal plane passing through the tip of the central lobule of the cerebellum with its superior–inferior oriented fibers coded with light blue color (Fig. 1b). ROI 2 was placed posterior to the medial longitudinal fasciculus in the axial plane (Fig. 1c). The MCP is generated from single ROIs on the coronal view with green color (Fig. 2a and b). These fiber tracts form a midline crossing transverse pontine fibers (thick arrow), and some extend to cortical