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Case Series: Fractional anisotropy profiles of the cerebellar peduncles in adolescents born preterm with ventricular dilation

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Abstract

This case series assesses white matter microstructure of the cerebellar peduncles in 4 adolescents born preterm with enlarged ventricles and reduced white matter volume in the cerebrum but no apparent injury to the cerebellum. Subjects (ages 12–17 years, gestational age 26–32 weeks, birth weight 825–2211g) were compared to a normative sample of 19 full-term controls (9–17 years, mean gestational age 39 weeks, mean birth weight 3154g). Tract profiles for each of the cerebellar peduncles were generated by calculating fractional anisotropy (FA) at 30 points along the central portion of each tract. One or more case subjects exhibited higher FA beyond the 90th percentile in the inferior, middle and superior cerebellar peduncles. Findings demonstrate that differences in cerebellar white matter microstructure can be detected in the absence of macrostructural cerebellar abnormalities.

Keywords

Cerebellum; White Matter; Tractography; Diffusion MRI; Preterm

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Author Contributions

Conceived and designed experiments: KET, YL, MBS, HMF. Performed experiments: KET, YL. Analyzed the data: KET. Neuroradiological Review: KWY. Manuscript Preparation: KET, HMF.

Declaration of Conflicting Interests

The authors declare no conflicts of interest.

Ethical Approval

The Stanford University Institutional Review Board (IRB) approved this study and consent procedures, IRB-6985. A parent or legal guardian provided informed written consent and children provided written assent.

Introduction

Preterm birth is associated with adverse neurodevelopmental outcomes in multiple domains¹. Delays and disorders have been attributed to injury and dysmaturity of cerebral white matter and related disturbances in deep cortical and deep gray matter structures^{2,3}. Increasing evidence points to injury and impaired development of the cerebellum as another contributor to poor outcomes⁴. Cerebellar hemorrhage occurs in 15% of infants weighing less than 750 grams at birth⁵, in children with additional cerebral injuries, especially leukomalacia⁶, and may result in volume reduction by term-equivalent age⁶. Most neuroimaging studies of the cerebellum in children born preterm evaluate total volume⁶, volume of particular structures⁷ or lobules⁸. Using these methods it was shown that cerebellar white matter volume is reduced in preterm born children, suggesting that preterm-related white matter differences are not limited to the cerebrum.

White matter structures can be interrogated *in vivo* using diffusion magnetic resonance imaging (dMRI), which measures the rate and direction of water diffusion to infer tissue organization in the brain⁹. The predominant measure generated using this method is fractional anisotropy (FA), a scalar value from 0 to 1 that represents the level of directional preference in water diffusion at any voxel⁹. After preterm birth, dMRI can detect changes in cerebral white matter microstructure that are not apparent on conventional clinical scans¹⁰. Only a handful of dMRI studies have interrogated diffusion properties of cerebellar white matter in children born preterm^{11–13}. We used dMRI to evaluate FA of the inferior, middle, and superior cerebellar peduncles, the major white matter tracts of the cerebellum, in a case series of adolescents born preterm with clear injury to the cerebrum but no apparent injury to the cerebellum. We sought to determine if dMRI would reveal microscopic differences in tissue structure not apparent on conventional scans.

Case Series

All participants were recruited to a larger study of white matter differences in children and adolescents born preterm. Nineteen participants born full term served as the normative group. Four adolescents born preterm had enlargement of the lateral ventricles and cerebral white matter volume loss but no visible cerebellar abnormalities on conventional MRI scans. The cortical white matter tracts of three of these participants (subjects 1–3) were examined in a previous case report¹⁴. Table 1 includes demographic, cognitive testing, and clinical characteristics of the normative group and the four Cases. Neonatal records for Case subjects revealed a history of grade III or III–IV intraventricular hemorrhage on perinatal cranial ultrasound; however, for all Cases, ventricular dilation had arrested spontaneously without requiring a shunt procedure. One case subject had mild right-hemiplegic cerebral palsy and one subject showed motor discoordination. All subjects scored within the normal range in intelligence quotient.

MRI data were acquired on a 3T Signa Excite (GE Medical Systems, Milwaukee, WI). All subjects were scanned for research purposes and without the use of sedation. Imaging parameters, data preprocessing steps, and analysis of motion in the control group and Cases are described in the supplemental materials. dMRI fiber tractography and tract quantification

were performed using mrDiffusion (<http://white.stanford.edu/software/>). Methods for fiber tract identification, segmentation, and quantification of the inferior cerebellar peduncles (ICP), the middle cerebellar peduncle (MCP), and superior cerebellar peduncles (SCP) have previously been described in detail¹⁵. In brief, for each cerebellar peduncle, fiber tracking was initiated within the child's native space by seeding a manually placed region of interest (ROI) on the principal diffusion direction (red-green-blue) map. Fibers were tracked using a deterministic streamlines tracking algorithm^{16–18}. Tracking proceeded in all directions and stopped when FA dropped below a minimum threshold of .15 or when the angle between two adjacent steps was greater than 30°. Each fiber group was then restricted by a second manually placed ROI. We analyzed the portion of the tract between the two waypoint ROIs. FA tract profiles were generated using the open source package AFQ (<https://github.com/jyeatman/AFQ.git>) based upon the DTI processing and analysis package mrDiffusion (white.stanford.edu/software/). Both packages are implemented Matlab (Mathworks, Natick, MA). Diffusion properties were quantified by resampling each fiber to 30 equidistant nodes. For each tract in each individual, FA was summarized at each node by taking a weighted average of all streamlines at that node¹⁹.

We created mean FA tract profiles for each of the peduncles by calculating the mean and standard deviation of FA at each node (30 total) from individual participants of the normative group. We compared the individual FA tract profiles of the Cases to the corresponding mean FA tract profiles of the normative group. The magnitude of individual Case variation was assessed by computing Z-scores for the mean FA in 3 locations along each tract, corresponding to the average FA for nodes 1–10, 11–20 and 21–30 for each tract. We considered Z-scores ≥ 1.5 , corresponding roughly to the 10th or 90th percentile, to be of potential clinical relevance. We take this approach in order to be more sensitive to potential individual differences that might otherwise be obscured by comparison of mean tract measures.

Results

DTI tractography identified the bilateral ICP, the MCP, and the bilateral SCP in all four Cases (Figure 1a). Figure 1b–f demonstrates the FA tract profiles obtained in these Cases overlaid on the FA tract profiles of the normative group. Individual differences in FA levels were apparent for one or more of the Cases within specific segments of the left ICP, MCP and left and right SCP (Figure 1b, d, e, f). FA along the trajectory of the right ICP in each Case closely resembled the mean FA of the normative group (Figure 1c).

Figure 2 shows the standardized mean FA (Z-score) for each of the 4 Cases in relation to the normative group mean FA in 3 locations along each of the 5 tracts. At least one Case subject had a mean value of ≥ 1.5 Z-score in each of the cerebellar tracts (Table 2), except the right ICP. In the left ICP, Subject 4 exhibited higher FA than the normative group in two locations (Figure 1b; Figure 2a; Table 2). All four Cases exhibited higher mean FA than the normative group in the left lateral third of the MCP (Figure 1d; Figure 2c; Table 2). Three of the 4 Cases had higher mean FA in the right lateral third of the MCP (Figure 1d; Figure 2c; Table 2) and in the anterior third of the right SCP (Figure 1f; Figure 2e; Table 2). One or

two Cases showed higher mean FA in the posterior and medial third of the left and right SCP (Figure 1e,f; Figure 2d,e; Table 2).

Discussion

dMRI revealed differences in FA along the trajectory of the cerebellar peduncles in adolescents born preterm whose conventional MRI scans showed only cerebral and no cerebellar abnormalities. The Cases demonstrated increased FA relative to the normative group within distinct segments of left ICP, the MCP the right and left SCP. These findings suggest that dMRI methods have greater sensitivity than conventional MRI for detecting differences in cerebellar white matter structures following preterm birth and can be used to examine individual clinical cases as well as group samples.

FA differences were most apparent within the MCP. These microscopic differences could reflect changes in white matter tissue structure as a result of direct injury or dysmaturation of the cerebellum. Alternatively, FA differences in these Case subjects could reflect changes in tissue structure resulting from remote cerebral events related to ventricular enlargement and intraventricular hemorrhage⁶. Such cerebellar changes could occur via trophic trans-synaptic interactions with the cerebrum²⁰ conveyed by afferent axonal projections contained within MCP²¹. The MCP has been implicated in motor and non-motor functions. Studies involving larger samples will be important for establishing how specific cerebral pathologies associated with prematurity may impact cerebellar white matter development and how these changes relate to functional outcomes in the population.

Three of the four Cases exhibited higher FA than the normative group within segments of the right SCP. FA differences in the right SCP may have important implications for understanding functional outcomes in children born preterm. The right SCP conveys efferent information to higher-order cortices, including left prefrontal areas²². These regions have been implicated in supporting cognitive abilities affected after prematurity, including attention, executive functioning, speech and language skills¹. Further studies linking dMRI of the cerebellar peduncles to behavior¹¹ will likely be important for understanding functional outcomes in children born preterm.

The clinical Cases demonstrated elevated FA relative to the normative control group in the cerebellar peduncles. Subjects 1–3 were previously observed to have higher FA within the superior longitudinal/arcuate fasciculus¹⁴. In other studies, preterm children have been observed to demonstrate lower or higher FA within the cerebrum^{14, 23–25}. Increased FA within the SCP has been reported for children who underwent cerebellar tumor resection and had residual neurological findings attributable to an injured cerebellum²⁶. While higher levels of FA have been observed in association with favorable neurobiological factors such as increased myelination and increased axonal density²⁷, such findings have also been shown to occur in regions where the proportion of crossing-fibers is low²⁸. A limitation of diffusion tensor imaging is that it assigns one principle direction to each voxel. New methods of dMRI can show more than one principle direction per voxel. Distinguishing amongst possible interpretations for FA will require combining neuroimaging techniques for estimating the amount of crossing fibers^{29, 30} and tissue myelination³¹.

A possible confound of the present study is the wide age-range of the normative sample. While the authors cannot completely rule out the possibility that higher levels of FA observed within the preterm participants may be accounted for by their age, this possibility is unlikely given that FA within the current normative sample did not differ between younger (9–12 years) and older (13–17 years) subgroups, did not correlate with age, and demonstrated low degrees of individual variation for all tract profiles¹⁵. It is also possible that higher FA observed within the case subjects may reflect motion-related artifacts that have been reported in previous voxel-based dMRI studies^{32–34}. However, this possibility is expected to be minimal given that case subjects demonstrated similar degrees of motion relative to the control group, and that tractography was performed within native space, thus minimizing susceptibility to partial voluming from artifacts due to subject motion or cardiac pulsation.

In summary, the present findings suggest that there may be microscopic changes in the cerebellar peduncles in children born preterm, even in absence of focal cerebellar injury, evidence of prior hemorrhage, or obvious volume reduction. Larger studies and application of the most sensitive methods of dMRI of cerebellar and cerebral white matter may increase our understanding of outcomes of children born preterm.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

All elements of the study were performed at Stanford University. The results have not been previously published elsewhere. The authors thank the children and families who participated in the study; Jason D. Yeatman, Robert Dougherty, and Brian Wandell for helpful suggestions regarding the analyses; and the developmental-behavioral pediatrics research group for discussions of the results.

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Figure 1.

Tractography of cerebellar peduncles and cerebellar FA tract profiles for Clinical Case Subjects 1–4. (a) Tract renderings for the 3 cerebellar peduncles are shown on sagittal T1 images for each clinical Case Subject 1–4. Only tract renderings for the left hemisphere are shown. (b–f) FA tract profiles of individual Case subjects 1–4 (dashed colored lines) relative to the mean FA tract profile of the normative group (thick solid colored lines) at 30 equidistant locations along each of 5 cerebellar tracts. Tract profiles of the normative group are color-coded to match tract renderings. 25th and 75th percentiles are indicated by dark gray shading. 10th and 90th percentiles are indicated by light gray shading. (ICP = inferior cerebellar peduncle; MCP = middle cerebellar peduncle; SCP = superior cerebellar peduncle; L = left; R = right).

Figure 2.

Group and individual variance in FA tract profiles. (a–e) Mean FA of the normative group is plotted for each tract in 3 locations corresponding to the average FA from nodes 1–10, 11–20, and 21–30 respectively. Symbols represent individual Clinical Case subjects. Error bars represent ± 1 standard deviation of the normative group. Symbols placed above error bars represent the clinical subjects observed to have FA values greater than ± 1.5 standard deviations from the normative group mean. (ICP = inferior cerebellar peduncle; MCP = middle cerebellar peduncle; SCP = superior cerebellar peduncle; L = left; R = right).

Demographic and clinical characteristics of the normative control group and four adolescents born preterm with ventricular enlargement and reduced white matter volume in the cerebrum.

Table 1

	Normative Group (n=19)	Clinical Cases			
		Subject 1 Adolescent born preterm	Subject 2 Adolescent born preterm	Subject 3 Adolescent born preterm	Subject 4 Adolescent born preterm
Demographics					
Age	Mean = 13 (2.3)	17	17	12	16
Males	9	Male	Female	Male	Male
Perinatal data					
GA (weeks)	Mean = 39 (1.1)	27	26	29	32
Birth weight	Mean = 3154 (407)	997	825	1624	2211
Motor functioning	Normal	Poor coordination	None	None	Mild CP
Cognitive Testing					
Total IQ	111(15.7)	87	116	113	121
Clinical T1 MRI Results					
Ventricular dilatation	1/19 mild	Mild-moderate	Moderate	Mild	Mild
Ventricular Asymmetry	2/19 mild	Asymmetric	Asymmetric	Symmetric	Asymmetric
White matter Volume loss	None	Severe	Severe	Severe	Moderate
Cerebellar Abnormalities	None	None	None	None	None

GA = Gestational Age; values in () = standard deviation; CP = cerebral palsy

Degree of Variation from the normative group mean (Z-Score) for Tract Locations where Clinical Case Subjects 1–4 demonstrate Z-score 1.5 standard deviations above the mean of the control group

Table 2

Tract	Location 1 (nodes 1–10)				Location 2 (nodes 11–20)				Location 3 (nodes 21–30)			
	S1	S2	S3	S4	S1	S2	S3	S4	S1	S2	S3	S4
ICP-L (Z-score)	–	–	–	1.5	–	–	–	–	–	–	–	–
MCP (Z-score)	2.7	2.4	2.2	2.8	–	–	–	–	1.6	–	1.9	2.9
SCP-L (Z-score)	1.9	–	–	1.6	–	–	–	–	–	–	–	–
SCP-R (Z-score)	1.9	–	–	–	2.1	–	–	–	2.8	2.0	1.8	–

S = Subject; ICP = Inferior Cerebellar Peduncle, MCP = Middle Cerebellar Peduncle, SCP = Superior Cerebellar Peduncle; L = Left; R = Right.