Tractography-Based Quantitation of Corticospinal Tract Development in Premature Newborns

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Abstract

Objective—To evaluate the impact of early brain injury and neonatal illness on corticospinal tract (CST) development in premature newborns serially studied with diffusion tensor tractography (DTT).

Study design—Fifty-five premature newborns (median 27.6 weeks PMA) were scanned with MRI early in life and at term-equivalent age. Moderate-severe brain abnormalities (abnormal-MRI) were characterized by moderate-severe white matter injury or ventriculomegaly. DTT was used to measure CST diffusion parameters which reflect microstructural development: fractional anisotropy (FA) and average diffusivity (D_{av}). The effect of abnormal-MRI and neonatal illness on FA and D_{av} were assessed using multivariate regression for repeated measures adjusting for age at scan.

Results—Twenty-one newborns (38%) had abnormal-MRI on either scan. FA increased with age significantly slower in newborns with abnormal-MRI (0.008/week) relative to newborns without these MRI abnormalities (0.011/week) (*interaction* term $P=0.05$). D_{av} was higher in newborns with abnormal-MRI (1.5×10^{-5} mm²/sec; $P<0.001$) for any given age at scan. In the 23 newborns (42%) with postnatal infection, FA increased more slowly (*interaction* term $P=0.04$), even when adjusting for the presence of abnormal-MRI.

Conclusions—CST microstructural development is significantly impaired in premature newborns with abnormal-MRI or postnatal infection, with a pattern of diffusion changes suggesting impaired glial cell development.

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Keywords

White matter injury; Corticospinal tract; Diffusion tensor magnetic resonance imaging; Diffusion tensor tractography; Premature newborns; Postnatal infection

Early brain abnormalities such as white matter injury (WMI), intraventricular hemorrhage (IVH) and ventriculomegaly are associated with impairments in early motor and cognitive function (1). How these brain injuries impact the motor pathways in the developing brain, however, is largely unknown.

Diffusion tensor imaging (DTI) enables *in vivo* quantification of microstructural development of these white matter pathways by measuring the overall extent (average diffusivity; D_{av}) and directionality (fractional anisotropy; FA) of water diffusion (2, 3). Previous DTI studies suggest that early brain injury impairs white matter development, even in brain regions that are normal on conventional MRI (4). However, the region of interest (ROI)-based approach used in these studies may not be optimally sensitive to changes in an individual white matter functional pathway. Diffusion tensor tractography (DTT) is a more sophisticated DTI technique for the 3D reconstruction of specific white matter tracts (5), such as the corticospinal tract (CST). DTT has been used to quantify CST tract-specific diffusion measurements in premature newborns with normal MRIs (2, 3). Focal brain injuries in term newborns with congenital heart disease have been linked to impaired CST development (6). The impact of early brain injury in the premature newborn on DTT measures of CST development has not yet been addressed.

The objective of this study was to evaluate the impact of early brain injury and neonatal illness on CST development in premature newborns serially studied with DTT. We hypothesized that brain abnormalities in the premature newborn are associated with impaired CST development as newborns develop from early-life to term-equivalent age (TEA).

METHODS

This prospective study was approved by the University of British Columbia Clinical Research Ethics Board. Premature newborns (24–32 weeks postmenstrual age; PMA) were recruited at the Children's & Women's Health Centre of British Columbia from April 2006 to April 2008. Age at birth was calculated based on the last menstrual period or early ultrasound (<24 weeks); if the difference in age was greater than seven days, the ultrasound date was used. Exclusion criteria included: (1) congenital malformation or syndrome, (2) antenatal infection, or (3) large parenchymal hemorrhagic infarction (>2 cm) on head ultrasound. Of eligible newborns, 80 provided informed consent for the study (59%) with serial DTT obtained in 55 (20 not scanned serially, 5 inadequate quality DTT due to patient motion).

Data regarding pre- and postnatal factors possibly associated with brain abnormalities were obtained by detailed chart review. Prolonged premature rupture of membrane was defined as rupture of membrane >18 hours. Chronic lung disease was diagnosed if the infant required

oxygen after 36 weeks PMA. In the absence of a universally accepted definition, hypotension was diagnosed if newborns were treated with saline boluses or vasopressors for low blood pressure (7). Postnatal infection was defined according to Stoll's criteria, but given the sample size, a summary variable of "any clinical infection", including clinical and culture-positive infections, was analyzed (8).

Magnetic resonance imaging studies

Newborns were imaged within the first weeks of life when they were clinically stable and again at TEA, as previously described (9).

An experienced pediatric neuroradiologist blinded to the clinical history reviewed the MRIs. WMI was scored from minimal to severe, using a validated system (1). IVH was graded according to Papile et al (10). To account for the frequent overlap in brain abnormalities in this population, moderate to severe MRI abnormalities (abnormal-MRI) on either scan were defined as 1 of: moderate or severe WMI, severe IVH (grade 3 or small parenchymal hemorrhagic infarction (<2cm)), or any degree of ventriculomegaly (1). Severe IVH was not observed in this cohort. Twenty random scans were rescored; intra-rater reliability of WMI, IVH and ventriculomegaly scores were high (Kappa 0.94–0.97).

Diffusion tensor tractography (DTT)

The diffusion tensor describes an ellipsoid in space characterized by the diffusion eigenvalues (λ_1 , λ_2 , λ_3) in the three orthogonal directions and their corresponding eigenvectors. In brain white matter, axial diffusivity (λ_1) is oriented along the direction of the main tracts and radial diffusivity (λ_2 and λ_3) is oriented perpendicular to these tracts. Average diffusivity (D_{av}) reflects the mean of these eigenvalues. Fractional anisotropy (FA) reflects the variance of the eigenvalues, ranging from 0 (isotropic diffusion) to 1 (anisotropic). As brain white matter matures, D_{av} decreases and FA increases. DTT of the CST was performed offline using DTIStudio, based on the Fiber Assignment by Continuous Tracking (FACT) method (5, 11). CST fiber tracking was initiated with a seeding region of interest (ROI) in the posterior limb of the internal capsule at the level of the Foramen of Monro, with an FA threshold of 0.15 (Figure 1, A). Tracks were terminated if FA dropped below 0.03 or the angle between the primary eigenvectors of consecutive voxels exceeded 50° (3, 6), or they did not pass through two limiting ROIs at the precentral gyrus and cerebral peduncle (Figure 1, B). Tract-based diffusion statistics including FA, D_{av} , axial (λ_1) and radial diffusivity [$(\lambda_2 + \lambda_3)/2$] were calculated (12). As left and right CST FA did not differ ($P=0.3$), and given our sample size, values were averaged bilaterally. To compare DTT with ROI-based DTI, CST diffusion parameters at the level of the PLIC were obtained by placing a rectangular ROI on the axial colour FA maps at the level of the Foramen of Monro.

Data Analysis

Statistical analyses were performed using Stata 9.2 (Stata Corporation, College Station, TX). Intra-rater reliability of DTT and ROI analyses were assessed in 30 random scans using intraclass correlation coefficient (ICC) and Bland-Altman limits of agreement (13). Clinical risk factors in newborns with and without abnormal-MRI were compared using Fisher exact

tests (categorical variables) or Mann-Whitney U tests (continuous/ordinal). The effects of abnormal-MRI on DTT parameters were analyzed using multivariate regression for repeated measures (generalized estimating equation) to account for serial scans. PMA at scan was included in each regression model to statistically adjust for the effect of age at scan. An interaction term was added to determine whether abnormal-MRI modified the change in DTT parameters over time. The effects of clinical variables on CST development were explored in similar models, always adjusting for PMA at scan.

RESULTS

Fifty-five premature newborns delivered at a median PMA of 27.6 weeks (range: 24–32; interquartile range (IQR) 26.4–30) participated. Twelve newborns (22%) were delivered before 26 weeks PMA. The newborns were serially imaged at median PMA 32 weeks (range: 27.4–40.4; IQR: 30–34) and again at median 40.3 weeks (range: 34.3–46.4; IQR: 39–43). Of the 55 newborns, 21 (38%) exhibited moderate to severe MRI abnormalities (abnormal-MRI) on either the first or second scan: 15 (27%) on the first scan and 15 (27%) on the second (Table I). In 9 newborns, the severity of WMI (n=5) or ventriculomegaly (n=4) was less apparent on the second scan; in 6 newborns moderate WMI (n=1), or ventriculomegaly (n=5) was only apparent on the second scan. One newborn with severe WMI on MRI had PVL identified on clinical head ultrasound. Newborns with abnormal-MRI were more likely to be exposed to prolonged ruptured membranes, with a trend to greater exposure to postnatal infections (Table II).

Quantitation of normal CST development using DTT

With increasing PMA in premature newborns without abnormal-MRI, there was a significant increase in FA [0.011 per week (95% confidence interval (CI): 0.009–0.014; $P<0.001$] and a decrease in D_{av} [1.9×10^{-5} mm²/sec/week (95% CI: 1.4×10^{-5} – 2.4×10^{-5} ; $P<0.001$)] (Figure 2, A and B). The increase in FA resulted because the decrease in axial diffusivity (λ_1) (0.8×10^{-5} mm²/sec/week (95% CI: 0.27×10^{-5} – 3×10^{-5} ; $P=0.003$) was of lesser magnitude than the decrease in radial diffusivity (λ_2 and λ_3) [2.5×10^{-5} mm²/sec/week (95% CI: 1.9×10^{-5} – 3.1×10^{-5} ; $P<0.001$)] (Figure 2, C and D).

Effect of moderate to severe MRI abnormalities on CST development

The rate of increase of CST FA was significantly slower in newborns with abnormal-MRI (0.008 per week; 95% CI: 0.005–0.010), relative to those without these changes (interaction term $P=0.05$) (Figure 2, A). The lower rate of change of FA in newborns with abnormal-MRI over time is due to the significantly higher radial diffusivity (λ_2 and λ_3) [1.9×10^{-5} mm²/sec/week (95% CI: 1.3×10^{-5} – 2.5×10^{-5} ; $P<0.001$)] in newborns with abnormal-MRI, in the context of axial diffusivity (λ_1) that is not significantly different [0.6×10^{-5} mm²/sec/week (95% CI: 0.08×10^{-5} – 1.3×10^{-5} ; $P=0.09$)] (Figure 2, C and D). In contrast, the *rate of change* of D_{av} values over time did not significantly differ in newborns with abnormal-MRI (interaction term $P=0.2$). However, for any given PMA, D_{av} is 1.5×10^{-5} mm²/sec/week higher on average (95% CI: 0.8×10^{-5} – 2.0×10^{-5} ; $P<0.001$) in newborns with abnormal-MRI (Figure 2, B).

Effect of WMI and IVH on CST development

Severe WMI alone was significantly associated with lower FA (0.1; 95% CI: 0.08–0.12, $P < 0.001$). Additionally, severe WMI was associated with higher values of radial diffusion (λ_2 and λ_3) ($P = 0.007$), but was not associated with a difference in axial diffusion (λ_1) ($P > 0.05$). IVH did not significantly affect FA or D_{av} ($P > 0.05$).

Effect of clinical risk factors on CST development

In multivariate models adjusting for PMA at scan and for serial studies, neither prolonged rupture of membranes nor gestational age at birth were significantly associated with the DTI measures of CST development ($P > 0.05$ for FA and D_{av}). In contrast, postnatal infection significantly modified the effect of PMA at scan on the DTI parameters. In newborns with infection, FA increased more slowly (0.007 per week; 95% CI: 0.005–0.01) than in newborns without infection (0.011 per week; 95% CI: 0.008–0.014) (interaction term $P = 0.04$) (Figure 2, E). D_{av} decreased at a borderline slower rate in newborns with postnatal infection (1.3×10^{-5} mm²/sec/week; 95% CI: 0.8×10^{-5} – 1.8×10^{-5}) relative to those without infection (1.9×10^{-5} mm²/sec/week; 95% CI: 1.4×10^{-5} – 2.5×10^{-5}) (interaction term $P = 0.08$) (Figure 2, F). When abnormal-MRI was added to these models, the presence of infection remained associated with a slower increase in CST FA over time ($P = 0.03$) and a borderline less rapid decline in D_{av} ($P = 0.08$).

ROI-based quantitation of CST development

Similar to DTT findings in newborns without abnormal-MRI, FA increased with increasing PMA [0.01 per week (95% CI: 0.007–0.012; $P < 0.001$)]. In contrast with the DTT findings, the rate of change of FA was not significantly different in newborns with and without abnormal-MRI (interaction term $P = 0.22$). However, for any given PMA, FA was significantly lower (0.007 per week; 95% CI: 0.005–0.01) in newborns with abnormal-MRI ($P = 0.004$). D_{av} , axial and radial diffusivity were not significantly different in premature newborns with abnormal-MRI compared to those without ($P = 0.1$ – 0.9).

Comparison of Reliability of CST Diffusion Parameters on DTT and ROI

Intra-rater reliability was higher with DTT measures than ROI-based measures obtained from the PLIC (Table III; available at www.jpeds.com).

DISCUSSION

In this study, premature newborns with moderate to severe MRI abnormalities were found to have impaired development of the CST as they developed to TEA, characterized by higher overall diffusion and a slower increase in diffusion directionality. The impact of early injury on brain development, however, is not immediate; these differences in CST development in newborns with and without MRI abnormalities become more apparent over time. Consistent with previous studies, premature newborns without moderate to severe MRI abnormalities had robust CST development characterized by decreasing overall diffusion (D_{av}), increasing directionality of water diffusion (FA) and radial diffusion decreasing more rapidly than axial diffusion (2, 3, 12). These results of CST development in premature neonates with normal MRIs are also seen in neonatal animal models of white matter development, demonstrating

an increase in diffusion anisotropy which coincides with the maturation of the oligodendrocyte lineage (14). Thus, changes in water diffusion with increasing age are associated with very early myelination events which can be measured by FA and D_{av} .

The novel use of DTT to assess CST maturation in premature newborns with brain injuries highlights the importance of serial imaging to assess altered brain development. Consistent with previous findings, focal or multifocal brain injuries were most readily detected on the first scan (1). However, the abnormalities of microstructural brain development were most apparent on the second scan. WMI has been previously shown to attenuate white matter maturation in premature newborns studied with ROI-based DTI measures (4). In addition to affecting microstructural development, early brain injuries in premature newborns also impair macroscopic structural development of the cerebral cortex, basal ganglia and myelinated white matter (15, 16). These early brain abnormalities and structural changes may contribute to adverse neurodevelopmental outcome at later ages (1). Together, these data indicate that early brain injury is associated with more widespread impairments of brain development beyond that visualized with conventional MRI.

The normal increase in white matter FA and decrease in D_{av} during development from early in premature life to TEA has been attributed to the development of microstructural components of white matter (e.g. microtubules, neurofilaments) and the maturation of oligodendroglia (OL) progenitors to mature OLs (14, 17). The measurement of axial and radial diffusivity provides important insight into the impact of early brain injury at this microstructural level. The pathogenesis of WMI is linked to a particular vulnerability of late-OL progenitors (18). Recently, hypoxia-ischemia was shown to arrest the development of OL progenitors (19). Elevated radial diffusivity and unchanged axial diffusivity values are seen with increasing white matter maturation in premature newborns with MRI abnormalities compared to those with normal MRI (12). Our findings in premature newborns are also consistent with the lower FA and higher radial diffusivity of the CST observed in children with congenital hemiparesis (20) and in infants with motor dysfunction (21). Changes in radial diffusivity are thought to reflect myelination and pre-myelination events, whereas changes in axial diffusivity are thought to reflect the integrity of the axon and its internal components (22). Our results suggest that the elevated radial diffusivity levels in premature newborns with MRI abnormalities reflects the impairment of the oligodendrocytes surrounding the axon, as opposed to intra-axonal processes, reducing the barriers to free water diffusion in the orientation perpendicular to the CST. The slower rate of CST maturation in newborns with moderate to severe MRI abnormalities, particularly the higher radial diffusivity (perpendicular to the axons), may in fact reflect impaired maturation of the OL lineage. However, the imaging resolution of DTT precludes a distinction at the cellular level of a loss of glial elements or their developmental arrest.

Recent studies have recognized that premature newborns with postnatal infections are more likely to acquire WMI (23, 24). Progressive WMI is now recognized in some premature newborns, particularly those exposed to postnatal infections (23). Our findings suggest that postnatal infections are associated with a delayed development of the CST: less rapid increase in FA and less rapid decline in D_{av} . The results of Segovia et al further suggest a potential for ongoing white matter susceptibility in regions of arrested OL development (19).

Together with our findings, this raises the hypothesis that postnatal infections in premature newborns increase the susceptibility to acquiring new white matter lesions by impairing white matter maturation, leaving an increased pool of vulnerable oligodendrocyte progenitor cells. The delayed CST development observed in newborns with infection is consistent with the increased risk of adverse outcomes in premature newborns exposed to postnatal infections (8).

The importance of postnatal infection contrasts with the role of chorioamnionitis (i.e. antenatal infection). In two recent MRI studies, chorioamnionitis was not a significant risk factor for abnormal brain development (9, 25). This difference may relate to the timing of the infection, the germs involved or the environment in which the infection occurs.

Consistent with the findings of Partridge et al (6), our observations show FA values from the PLIC to be systematically higher than those obtained from DTT; D_{av} values were lower. This highlights the variability of diffusion along the tract, where diffusion at one level is not representative of diffusion over the entire tract. Furthermore, ROI analysis may miss changes in white matter tracts as it represents a region that might contain more than one tract, whereas DTT is limited to a single tract. Our study demonstrates a high degree of reliability between repeated DTT measures of the CST, and ROI-based measures were slightly less reproducible with greater potential for inconsistent ROI placement (2, 3). Recent advances in DTI analysis tools, such as tract-based spatial statistics, have enabled group comparisons without the need for manual ROI placement (26, 27). However, these techniques have not yet been validated across the age range from early premature life to TEA with the dramatic changes observed in brain size and shape. Despite the increased technical requirements relative to ROI analyses, DTT provides a robust and reliable method of assessing abnormalities in brain maturation in preterm infants.

Although this is the largest group of premature newborns studied serially with DTT of the CST, the sample size limits our ability to detect the effects of individual types of brain injury. Given the frequent co-occurrence of these injuries, the primary analyses focused on composite of moderate to severe abnormalities, previously found to be predictive of adverse outcome (1). Additionally, the widespread nature of most brain injuries precludes the examination of the specific effect of lesion location on CST development. An association between the severity of motor impairment and microstructural changes in the CST have been previously demonstrated in children with congenital hemiparesis (20) and in infants with motor dysfunction (21). Careful follow-up of our cohort, therefore, is required to confirm a similar association between microstructural CST development and motor outcome, and to determine whether systemic illness such as infection leads to subsequent motor deficits through impaired corticospinal tract development, or other motor or sensory pathways (28).

The current study demonstrates that corticospinal tract maturation is impaired in premature newborns with moderate to severe MRI abnormalities. The change in radial, as opposed to axial diffusivity, suggests a loss of glial cells around axons or a failure of early myelination events, consistent with experimental observations of an arrest in the developmental progression of the oligodendrocyte lineage with brain injury. Our findings also suggest that

the vulnerability to acquiring new white matter injuries in newborns with postnatal infection may be related to delayed white matter development.

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Figure 1. Diffusion tensor tractography of the corticospinal tract in a premature newborn studied serially

Representative images from a premature newborn delivered at 27 weeks gestational age and studied with MRI at: (A) 29 weeks of postmenstrual age (B) and 45 weeks postmenstrual age. (Top) Axial diffusion tensor imaging encoded anisotropy color map illustrating the region of interest in the posterior limb of the internal capsule (in white). The color convention used to display the predominant diffusion direction has red representing right-left, green representing anterior-posterior, and blue representing superior-inferior anatomical directions (2). (Bottom) 3D renderings of the DTT delineated corticospinal tract (CST) in red. A seeding ROI was first placed at the posterior limb of the internal capsule (Top, in white) and then limiting ROIs were placed at the precentral gyrus and cerebral peduncle to define the tract. Diffusion parameters were averaged over the entire length of the tract.

Effect of Abnormal-MRI on CST Development

Effect of Postnatal Infection on CST Development

Figure 2. Developmental trajectory of CST diffusion parameters obtained from serial DTT scans in premature newborns with and without moderate to severe MRI abnormalities (abnormal-MRI) and in those with or without postnatal infections

A. The rate of change of fractional anisotropy is significantly different in infants with and without abnormal-MRI (significant interaction). Fractional Anisotropy increases less rapidly in newborns with abnormal-MRI (*interaction term* $P=0.05$).

B. Average Diffusivity is higher in newborns with abnormal-MRI ($P=0.2$). The rate of change of average diffusivity is not significantly different.

C. Axial diffusivity is not significantly different in newborns with abnormal MRI ($P=0.7$).

D. Radial diffusivity is higher in newborns with abnormal MRI ($P=0.1$).

E. Fractional Anisotropy increases less rapidly in newborns with infection (*interaction term* $P=0.04$).

F. Average Diffusivity decreases less rapidly in newborns with infection (*interaction term* $P=0.07$).

Table 1

Distribution of brain abnormality findings on MRI

	White Matter Injury			
Number (%)	Normal	Mild	Moderate to severe	P-value
<i>First Scan</i>				
IVH (Grades 1–2)				0.20
Absent	27 (66%)	4 (80%)	4 (44%)	
Present	14 (34%)	1 (20%)	5 (56%)	
Ventriculomegaly				0.01
Absent	36 (85%)	3 (60%)	4 (44%)	
Present	5 (12%)	2 (40%)	5 (56%)	
<i>Second Scan</i>				
IVH (Grades 1–2)				0.41
Absent	36 (77%)	1 (33%)	4 (80%)	
Present	11 (23%)	2 (67%)	1 (20%)	
Ventriculomegaly				0.13
Absent	37 (79%)	3 (100%)	2 (40%)	
Present	10 (21%)	0	3 (60%)	

Table 2

Clinical features of the premature newborns with and without moderate to severe MRI abnormalities on first scan

	Moderate to Severe MRI Abnormalities		
Number (%) or Median (IQR)	No	Yes	P-value
Number	34	21	
Male Sex	15 (44%)	10 (48%)	
Prenatal			
Preeclampsia	9 (26%)	2 (10%)	0.17
Prolonged Ruptured Membrane	4 (12%)	8 (38%)	0.04
Histological Chorioamnionitis	11 (33%)	9 (45%)	0.56
Postnatal			
C-section Delivery	17 (50%)	13 (62%)	0.42
Gestational Age at Birth	27.9 (26.7 – 30)	26.9 (25.9 – 29.6)	0.16
Patent Ductus Arteriosus	12 (35%)	11(52%)	0.27
Days Intubated	2 (1 – 9)	12 (0 – 54)	0.20
Chronic Lung Disease	13 (38%)	10 (48%)	0.58
Hypotension	7 (21%)	8 (38 %)	0.22
Postnatal Infection	11 (32%)	12 (57%)	0.09

Table 3

Intra-rater reliability measurements for the repeated quantification of corticospinal tract (CST) fractional anisotropy (FA) and average diffusivity (D_{av}) using the diffusion tensor tractography and region of interest (measured at the posterior limb of the internal capsule) methods

Method	ICC	95% CI	Mean Difference	Bland Altman Limits of Agreement
DTT				
FA	0.99	0.98 – 0.99	–0.005	–0.02 – 0.01
D_{av}	0.97	0.95 – 0.99	-0.3×10^{-5}	$-9.4 \times 10^{-5} - 8.8 \times 10^{-5}$
ROI				
FA	0.91	0.84 – 0.97	0	–0.06 – 0.06
D_{av}	0.88	0.80 – 0.96	-1.5×10^{-5}	$-13.1 \times 10^{-5} - 10.2 \times 10^{-5}$