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What is This?
Case Series: Fractional Anisotropy Along the Trajectory of Selected White Matter Tracts in Adolescents Born Preterm With Ventricular Dilation

Nathaniel J. Myall, MS¹, Kristen W. Yeom, MD², Jason D. Yeatman, BA³, Shayna Gaman-Bean, MD⁴, and Heidi M. Feldman, MD, PhD⁴

Abstract
This case series assesses white matter microstructure in 3 adolescents born preterm with nonshunted ventricular dilation secondary to intraventricular hemorrhage. Subjects (ages 12-17 years, gestational age 26-29 weeks, birth weight 825-1624 g) were compared to 3 full-term controls (13-17 years, 39-40 weeks, 3147-3345 g) and 3 adolescents born preterm without ventricular dilatation (10-13 years, 26-29 weeks, 630-1673 g). Tractography using a 2 region of interest method reconstructed the following white matter tracts: superior longitudinal/arcuate fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinate fasciculus, and corticospinal tract. Subjects showed increased fractional anisotropy and changes in the pattern of fractional anisotropy along the trajectory of tracts adjacent to the lateral ventricles. Tensor shape at areas of increased fractional anisotropy demonstrated increased linear anisotropy at the expense of planar and spherical anisotropy. These findings suggest increased axonal packing density and straightening of fibers secondary to ventricular enlargement.

Keywords
prematurity, ventricular dilation, diffusion tensor imaging, tractography, fractional anisotropy, intraventricular hemorrhage, preterm

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Comparisons of white matter tracts between preterm subjects and full-term controls have generally demonstrated a decrease in fractional anisotropy with prematurity. The purpose of this case series was to assess the effect of ventricular dilatation on microstructural properties of white matter tracts in 3 adolescents born preterm with nonshunted ventricular dilatation secondary to intraventricular hemorrhage. The authors hypothesized that fractional anisotropy would be decreased relative to full-term controls and preterm comparisons without ventricular dilatation. Because of the distortion caused by ventricular enlargement, the authors chose to examine the tracts in the native space of each subject using tractography.

**Case Series**

All participants were recruited as part of a larger cohort of preterms and controls. Written consent was obtained from parents and verbal assent from participants. Three preterm subjects were asymptomatic at the time of this study and scored based on cranial ultrasound findings. Ventricular dilation had grade III or III-IV intraventricular hemorrhage in all subjects were incidentally found on imaging to have enlargement of the lateral ventricles. Review of neonatal records revealed a history of grade III or III-IV intraventricular hemorrhage in all subjects based on cranial ultrasound findings. Ventricular dilation had arrested spontaneously without shunting in each subject. All subjects were asymptomatic at the time of this study and scored within the normal range in intelligence quotient when assessed. The authors then compared the same anatomical regions of the tracts, the tracts were clipped to include only those streamlines between the 2 defining regions of interest. The remaining fiber group was divided into 30 equidistant segments, and the weighted mean of fractional anisotropy at each segment was calculated.

The authors then compared patterns of fractional anisotropy along the trajectory of each tract between groups. To assure that they compared the same anatomical regions of the tracts, the tracts were clipped to include only those streamlines between the 2 defining regions of interest. The remaining fiber group was divided into 30 equidistant segments, and the weighted mean of fractional anisotropy at each segment was calculated. The authors then compared patterns of fractional anisotropy along the trajectory of each tract between groups. To assure that they compared the same anatomical regions of the tracts, the tracts were clipped to include only those streamlines between the 2 defining regions of interest. The remaining fiber group was divided into 30 equidistant segments, and the weighted mean of fractional anisotropy at each segment was calculated. The authors then compared patterns of fractional anisotropy along the trajectory of each tract between groups. To assure that they compared the same anatomical regions of the tracts, the tracts were clipped to include only those streamlines between the 2 defining regions of interest. The remaining fiber group was divided into 30 equidistant segments, and the weighted mean of fractional anisotropy at each segment was calculated.
<table>
<thead>
<tr>
<th></th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
<th>Full-Term Control 1</th>
<th>Full-Term Control 2</th>
<th>Full-Term Control 3</th>
<th>Preterm Comparison 1</th>
<th>Preterm Comparison 2</th>
<th>Preterm Comparison 3</th>
</tr>
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<tr>
<td>Gender</td>
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<tr>
<td>Age at diffusion tensor imaging scan (years)</td>
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<td>17</td>
<td>17</td>
<td>15</td>
<td>13</td>
<td>17</td>
<td>13</td>
<td>12</td>
<td>10</td>
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<tr>
<td>Birth weight (g)</td>
<td>1624</td>
<td>997</td>
<td>825</td>
<td>3317</td>
<td>3345</td>
<td>3147</td>
<td>630</td>
<td>1192</td>
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<td>26.0</td>
<td>40.0</td>
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<tr>
<td>Total IQ</td>
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<td>87</td>
<td>116</td>
<td>118</td>
<td>111</td>
<td>107</td>
<td>77</td>
<td>95</td>
<td>109</td>
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<tr>
<td>Papile classification(^a)</td>
<td>Grade III, bilateral</td>
<td>Grade III-IV, bilateral</td>
<td>Grade III</td>
<td>113</td>
<td>87</td>
<td>116</td>
<td>118</td>
<td>111</td>
<td>107</td>
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<tr>
<td>Ventricle dilation(^b)</td>
<td>Mild</td>
<td>Mild-moderate</td>
<td>Moderate</td>
<td>Slight prominence</td>
<td>Symmetric</td>
<td>Symmetric</td>
<td>Symmetric</td>
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<td>Ventricle symmetry</td>
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<td>Asymmetric (left &gt; right)</td>
<td>Asymmetric (right &gt; left)</td>
<td>Symmetric</td>
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<td>Symmetric</td>
</tr>
</tbody>
</table>

\(^a\) Based on cranial ultrasound findings during the neonatal period. Severity of intraventricular hemorrhage graded according to the Papile classification system.

\(^b\) Based on clinical assessment of T1 scans taken at the time of the study.
The authors found increased fractional anisotropy in adolescents born preterm with ventricular dilation secondary to corticospinal tract (Figure S5) compared to controls and preterms.

**Discussion**

The authors found increased fractional anisotropy in adolescents born preterm with ventricular dilation secondary to corticospinal tract (Figure S5) compared to controls and preterms.
intraventricular hemorrhage. Diffusion tensor imaging studies of prematurity have generally demonstrated decreased fractional anisotropy in white matter that can persist into adolescence. Other studies in this population have also reported positive correlations between fractional anisotropy and cognitive outcomes in various domains. It is generally inferred from these results that higher fractional anisotropy is a marker of intact white matter unaffected by injury. These findings suggest that high fractional anisotropy in prematurity has different implications in the case of children born preterm with ventricular dilation.

The most likely explanation for these results is that ventricular enlargement caused changes in the organization and density of axons. Diffusion tensor imaging studies of space-occupying tumors in the brain have demonstrated increased fractional anisotropy, increased axial diffusivity, and decreased radial diffusivity in the surrounding nonedematous white matter. The authors of these studies speculate that fiber displacement by tumor increases the alignment of surrounding axons, resulting in a greater density of fibers within a given area of white matter. In their model, the increased packing of axons limits diffusion in the perpendicular direction, producing a decrease in radial diffusivity. The pressing of the tumor mass against white matter also stretches and straightens axons, leading to increased diffusion in the parallel direction and increased axial diffusivity. Consistent with this model, the authors found changes in the tensor shape in voxels with increased fractional anisotropy in subjects with ventricular dilation. The decrease in planar and spherical anisotropy in these subjects could be suggestive of axonal straightening and increased axonal density, respectively.

This study also highlights the importance of examining fractional anisotropy along the trajectory of fiber tracts. The authors found elevations in fractional anisotropy in regions along the tracts adjacent to the lateral ventricles in subjects with ventricular dilation. Measuring the mean alone potentially misses important information about the behavior of a tract along its entire length. The method presented here has the advantage of identifying areas along tracts that are important in driving the changes in mean values.

In conclusion, the authors report an increase in fractional anisotropy in multiple white matter tracts in adolescents born preterm with ventricular dilation secondary to intraventricular hemorrhage. These results suggest that the overall effect of prematurity on white matter microstructure varies with multiple factors including enlargement of the ventricles.

Acknowledgments
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Figure 2. Axial (a) and radial diffusivity (b) along the trajectory of the right superior longitudinal/arcuate fasciculus. Areas of increased fractional anisotropy along the tract seen in Figure 1c are associated with both increased axial diffusivity and decreased radial diffusivity compared to full-term controls and preterm comparisons.

Author Contributions
NJM was responsible for data collection, data analysis, and writing the first draft of the manuscript. KWY clinically reviewed image scans, verified placement of regions of interest in each subject, and reviewed the manuscript. JDY collected and processed all image scans and provided theoretical and methodological expertise. SGB assisted with data collection by drawing regions of interest for the corticospinal tract. HMF conceived of the study, interpreted results, provided theoretical expertise, and revised earlier drafts of the manuscript.

Declaration of Conflicting Interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The protocol was approved by the Institutional Review Board of Stanford University School of Medicine and performed in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

References


