Reduced Ipsilesional Cortical Volumes in Fetal Periventricular Venous Infarction

Damon Li, BHSc; Jacquie Hodge, BSc; Xing-Chang Wei, MD; Adam Kirton, MD

Background and Purpose—Perinatal stroke causes most term-born hemiplegic cerebral palsy. Many suffer additional sequelae. Periventricular venous infarction (PVI) is a common fetal stroke in which isolated subcortical injury may cause only motor deficits. However, cognitive, language, and behavioral deficits also occur. We hypothesized that ipsilesional cortical gray matter volumes are reduced in PVI.

Methods—Children (12 months to 18 years) with MRI-confirmed PVI were identified through the Alberta Perinatal Stroke Project. We developed an MRI method to quantify sectional gray (GM) and white matter (WM) volumes from lesioned and unlesioned (control) hemispheres (OsiriX software). Differences in cortical GM and WM volumes were compared between hemispheres in preselected regions “above” the lesion (middle) and anterior and posterior to this. Outcomes dichotomized for “cortical dysfunction” (cognitive, behavioral, language) and motor deficit severity (Pediatric Stroke Outcome Measure) were compared with GM volumes.

Results—Twenty-two children (81% boys; median age, 8 years) were included. Methods demonstrated high intrarater and inter-rater reliabilities ($\rho=0.988$, $\rho=0.943$) and minimal observer bias. Ipsilesional GM volume was significantly reduced in the middle ($P=0.007$) and posterior ($P=0.03$) regions. Middle ipsilesional WM volumes were reduced ($P<0.001$). The degree of GM reduction was not associated with cortical dysfunction or severity of motor deficit.

Conclusions—Ipsilesional GM volume is diminished in PVI. Speculative mechanisms include retrograde neuronal degeneration and disrupted migration. Neuropsychological testing of larger samples is required to determine clinical significance. (Stroke. 2012;43:00-00.)

Key Words: perinatal stroke • fetal stroke • cerebral palsy • hemiplegia
Regional and total hemispheric volumes were manually traced using the ROI draw tool and expressed in cubic centimeters. As a novel methodology requiring manual, subjective tracing, inter-rater and intrarater reliability testing was performed. Observer bias was evaluated by rescoring only the most superior slices, removing possible knowledge of stroke side and character.

Outcomes were assessed using the Pediatric Stroke Outcome Measure (PSOM), in which a pediatric stroke neurologist scores a Table 1. Volumetric Analysis in Children With Periventricular Venous Infarction

<table>
<thead>
<tr>
<th></th>
<th>Ipsilesional</th>
<th></th>
<th>Contralateral</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
<td>Mean ± SD</td>
<td>Range</td>
</tr>
<tr>
<td><strong>Gray matter</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>108.39 ± 14.94</td>
<td>82.73–148.69</td>
<td>112.46 ± 12.99</td>
<td>85.92–148.41</td>
</tr>
<tr>
<td>Anterior</td>
<td>26.51 ± 3.34</td>
<td>19.71–34.02</td>
<td>26.69 ± 5.53</td>
<td>13.97–38.11</td>
</tr>
<tr>
<td>Posterior</td>
<td>49.19 ± 5.58</td>
<td>34.36–57.33</td>
<td>50.87 ± 5.92</td>
<td>38.61–60.79</td>
</tr>
<tr>
<td>Total</td>
<td>184.09 ± 19.76</td>
<td>147.25–235.40</td>
<td>190.03 ± 21.83</td>
<td>143.63–246.29</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>65.14 ± 19.20</td>
<td>38.09–108.35</td>
<td>72.01 ± 18.82</td>
<td>40.64–117.28</td>
</tr>
</tbody>
</table>

Paired t-tests (1-tailed) compare sides at each location. Ipsilesional gray matter volumes were reduced, predominantly in the middle section.
Table 2. Regional Volumes Comparing Cortical Dysfunction and Weakness Severity

<table>
<thead>
<tr>
<th></th>
<th>Cortically Dysfunctional (n=4)</th>
<th>Cortically Functional (n=16)</th>
<th>P</th>
<th>Mild/Moderate (n=14)</th>
<th>Severe (n=6)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray matter</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Middle</td>
<td>3.19±4.14</td>
<td>3.95±8.21</td>
<td>0.86</td>
<td>3.30±8.48</td>
<td>4.96±4.83</td>
<td>0.66</td>
</tr>
<tr>
<td>Anterior</td>
<td>−0.61±1.05</td>
<td>1.29±3.25</td>
<td>0.27</td>
<td>0.60±2.79</td>
<td>1.63±3.68</td>
<td>0.50</td>
</tr>
<tr>
<td>Posterior</td>
<td>0.09±3.73</td>
<td>2.53±4.18</td>
<td>0.30</td>
<td>2.07±4.29</td>
<td>1.97±4.09</td>
<td>0.96</td>
</tr>
<tr>
<td>Total</td>
<td>2.67±5.32</td>
<td>7.77±11.43</td>
<td>0.40</td>
<td>5.9±11.56</td>
<td>8.56±8.52</td>
<td>0.63</td>
</tr>
<tr>
<td>White matter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>5.25±6.92</td>
<td>5.85±8.57</td>
<td>0.89</td>
<td>4.57±5.57</td>
<td>8.42±12.50</td>
<td>0.34</td>
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<tr>
<td>Anterior</td>
<td>0.07±0.64</td>
<td>0.31±1.12</td>
<td>0.69</td>
<td>0.14±1.01</td>
<td>0.55±1.12</td>
<td>0.42</td>
</tr>
<tr>
<td>Posterior</td>
<td>−0.63±1.48</td>
<td>1.30±1.67</td>
<td>0.05</td>
<td>0.90±1.84</td>
<td>0.97±1.82</td>
<td>0.93</td>
</tr>
<tr>
<td>Total</td>
<td>4.66±6.91</td>
<td>7.46±9.11</td>
<td>0.57</td>
<td>5.60±5.43</td>
<td>9.94±13.78</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Independent t tests found no differences between groups. Volumes are mean ± SD cm$^3$.

Results

Twenty-two children were included. Median age at imaging was 8±5.3 years (range, 1–18 years). Methodology demonstrated high inter-rater ($\rho=0.943$) and intrarater ($\rho=0.988$) reliabilities and minimal observer bias ($\rho=0.992$). Volumetric analysis is summarized in Table 1. Mean ipsilesional GM volumes were reduced in the middle region (108.39±14.94 versus 112.46±12.99 cm$^3$, $P=0.007$). Ipsilesional posterior GM volumes were also lower (49.19±5.58 versus 50.87±5.92 cm$^3$, $P=0.03$). Anterior GM volumes were comparable (26.51±3.34 versus 26.69±5.53 cm$^3$, $P=0.42$). Total ipsilesional cortical GM volumes were lower (184.09±19.76 versus 190.03±21.83 cm$^3$, $P=0.007$). Mean ipsilesional WM volumes were reduced in the middle region only (44.05±14.87 versus 50.32±13.04 cm$^3$, $P<0.001$), and total ipsilesional WM volume was reduced (65.14±19.20 versus 72.01±18.82 cm$^3$).

Correlations with outcome are summarized in Table 2. Of the 20 subjects with PSOM scores, 4 (20%) had cortical dysfunction. Mean GM and WM volumes did not differ in any region in this group, though variance was high. Six children (30%) with severe motor dysfunction had GM and WM volumes comparable to those without.

Discussion

We provide evidence of diminished ipsilesional cortical GM volumes in PVI. Speculative mechanisms include injury to progenitor cell populations and/or retrograde degeneration. Although subventricular zone neuronal proliferation peaks between 15–24 weeks’ gestation,9 glial cells essential for cortical development migrate beyond this.8 Pathological evidence suggests reduced cell proliferation in preterm infants with germinal matrix hemorrhage.9 The precise timing of PVI cannot be determined but may overlap with these periods of vulnerability. Alternatively, retrograde degeneration of injured neurons may explain cortical volume loss. Diffusion imaging supports such corticospinal Wallerian degeneration in both adult10 and perinatal11–13 stroke.

Our study was underpowered to demonstrate associations between cortical volumes and nonmotor deficits. In a comparable “white matter” injury of prematurity, periventricular leukomalacia children may have reduced GM volumes attributed to the mechanisms postulated above that correlate with neuropsychological deficits.14,15 The PSOM is a crude measure, and future studies will need comprehensive neuropsychological testing of larger, prospective samples to define the relationship between cortical volumes and cortical deficits in PVI. Improved appreciation of PVI pathophysiology may advance rehabilitation treatments.

Sources of Funding

This work was supported by the Heart and Stroke Foundations of Alberta and Canada, Alberta Children’s Hospital Research Institute, and Canadian Stroke Network.

Disclosures

None.

References

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Stroke. published online January 26, 2012;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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