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;43:1404-1407.)*

**Key Words:** perinatal stroke ■ fetal stroke ■ cerebral palsy ■ hemiplegia

Perinatal stroke is the leading cause of hemiplegic cerebral palsy (CP) in term-born children.1 Periventricular venous infarction (PVI) is a distinct and common variety.2 PVI is the in utero version of germinal matrix hemorrhage, which is well described in delivered preterm infants.3 Hemorrhage causes obstruction of medullary veins, leading to impaired drainage and venous infarction of the periventricular white matter (WM). Hemiplegic CP results when this infarct damages the corticospinal tracts.

The isolated, subcortical nature of PVI suggests that children might only have motor deficits. Preliminary studies suggest that PVI children tend to avoid the more complex, “cortical” morbidities of arterial perinatal strokes including epilepsy and cognitive, language, or behavioral deficits.4 Emerging evidence, however, suggests that PVI children may incur such problems. Volumetric analysis has demonstrated cortical gray matter (GM) abnormalities associated with neurological outcome in other premature WM injuries (eg, periventricular leukomalacia).5 Cortical volumes have not been explored in PVI.

We hypothesized that ipsilesional cortical GM volumes are reduced in PVI and correlate with weakness severity and nonmotor deficits.

**Methods**

In this retrospective case series, subjects were identified through the population-based Alberta Perinatal Stroke Project (APSP). PVI diagnosis required previously validated imaging criteria.6 Additional inclusion criteria included (1) anatomic axial T1 MRI (for volumetric analysis), (2) age at imaging, 12 months (adequate myelination) to 18 years, and (3) no additional neurological disorder.

Images were obtained on a Siemens Avanto 1.5-T MRI scanner (Siemens, Erlangen, Germany). Axial spin-echo T1-weighted images were acquired (TR=580 ms; TE=15 ms; field of view, 24 cm; slice thickness/gap, 5/1 mm; acquisition matrix, 256×256; number of excitations=1). A technique quantifying GM and WM volumes, using OsiriX software (Version 3.8, Antoine Rosset, UCLA, Los Angeles), was validated. Cortical GM and WM volumes were measured rostrally from the superior thalamus (Figure, A and B). Six regions were defined on the lowest slice to segment those cortical sections potentially affected by the PVI lesion (middle region; Figure, C) from anterior and posterior control regions bilaterally. 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 115-point examination as 0 (no deficit), 0.5 (mild deficit, minimal functional impact), 1 (moderate deficit), or 2 (severe deficit) across 5 categories: right and left sensorimotor, language production and

Table 1. Volumetric Analysis in Children With Periventricular Venous Infarction

<table>
<thead>
<tr>
<th></th>
<th>Ipsilesional</th>
<th>Contralateral</th>
<th>t Test</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<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>112.46±12.99</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>26.51±3.34</td>
<td>26.69±5.53</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Posterior</td>
<td>49.19±5.58</td>
<td>50.87±5.92</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>184.09±19.76</td>
<td>190.03±21.83</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td><strong>White matter</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>44.05±14.87</td>
<td>50.32±13.04</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>7.81±2.38</td>
<td>7.78±2.90</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Posterior</td>
<td>13.29±3.13</td>
<td>13.91±3.71</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>65.14±19.20</td>
<td>72.01±16.82</td>
<td>&lt;0.001</td>
<td></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.
comprehension, and cognitive/behavioral. PSOM scores were assigned prospectively within the clinical research program. Weakness was dichotomized into mild/moderate (0.5 or 1) or severe (2). An outcome of “cortical dysfunction” was defined as any abnormal language or cognitive/behavioral PSOM score.

Our primary hypothesis of decreased ipsilesional GM (effect size, 5%; power, 90%; type 1 error, 0.05) required 22 subjects. Paired t tests compared ipsilesional to contralesional volumes within subjects. Independent t tests assessed differences in GM volumes between those with and those without severe weakness and cortical deficits. With a limited number of predefined, hypothesis-driven comparisons made, multiple comparisons were not corrected for. Rater correlations used Spearman ρ. Analyses used SPSS 17.0 (SPSS Inc, Chicago, IL).

Results

Twenty-two children were included. Median age at imaging was 8±5.3 years (range, 1–18 years). Methodology demonstrated high inter-rater (ρ=0.943) and intrarater (ρ=0.988) reliabilities and minimal observer bias (ρ=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 cm³, P=0.007). Ipsilesional posterior GM volumes were also lower (49.19±5.58 versus 50.87±5.92 cm³, P=0.03). Anterior GM volumes were comparable (26.51±3.34 versus 26.69±5.53 cm³, P=0.42). Total ipsilesional cortical GM volumes were lower (184.09±19.76 versus 190.03±21.83 cm³, P=0.007). Mean ipsilesional WM volumes were reduced in the middle region only (44.05±14.87 versus 50.32±13.04 cm³, P<0.001), and total ipsilesional WM volume was reduced (65.14±19.20 versus 72.01±18.82 cm³).

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,7 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


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 Value</th>
<th>Mild/Moderate (n=14)</th>
<th>Severe (n=6)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray matter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</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±8.83</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>5.23±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>
</tr>
<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 cm³.


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