Reduced Ipsilesional Cortical Volumes in Fetal Periventricular Venous Infarction

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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
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

![Figure. Periventricular venous infarction volumetric methods. Volumes rostral to superior thalamus (A and B) were measured within bilateral anterior, middle, and posterior segments (C), using OsiriX software (D).](image-url)

| Table 1. Volumetric Analysis in Children With Periventricular Venous Infarction |
|---------------------------------|---------------------------------|---------------------------------|--------|-----------------|
|                                 | Ipsilesional                     |                                 | Contralesional                   |
|                                 | Mean ± SD | Range                     | Mean ± SD | Range                     |
| Gray matter                     | 108.39±14.94 | 82.73–148.69 | 112.46±12.99 | 85.92–148.41 |
| Middle                          | 26.51±3.34  | 19.71–34.02             | 26.69±5.53  | 13.97–38.11 |
| Anterior                        | 49.19±5.58  | 34.36–57.33             | 50.87±5.92  | 38.61–60.79 |
| Posterior                       | 49.19±5.58  | 34.36–57.33             | 50.87±5.92  | 38.61–60.79 |
| Total                           | 184.09±19.76 | 147.25–235.40           | 190.03±21.83 | 143.63–246.29 |
| White matter                    | 44.05±14.87 | 22.87–79.28             | 50.32±13.04 | 27.90–83.54 |
| Middle                          | 7.81±2.38   | 3.94–12.70              | 7.78±2.90   | 1.95–13.05  |
| Total                           | 65.14±19.20 | 38.09–108.35            | 72.01±16.82 | 40.64–117.28 |

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


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*Stroke*. 2012;43:1404-1407; originally published online January 26, 2012;
doi: 10.1161/STROKEAHA.111.645077
*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

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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