Cerebellar Atrophy in Childhood Arterial Ischemic Stroke
Acute Diffusion MRI Biomarkers

Sarah Mah, BHSc; Gabrielle deVeber, MD; Xing-Chang Wei, MD; Natalia Liapounova, MD; Adam Kirton, MD

Background and Purpose—Crossed cerebellar atrophy is uncommon in childhood arterial ischemic stroke. Acute corticospinal tract diffusion-weighted imaging (CST-DWI) changes occur in stroke of all ages. Contralateral CST-DWI is unexplained but approximates corticopontocerebellar pathways. We hypothesized that cerebellar atrophy can be quantified on clinical neuroimaging in childhood arterial ischemic stroke and is predicted by contralateral CST-DWI.

Methods—Consecutive children (>28 days–18 years) were included with the following features: (1) acute, unilateral, middle cerebral artery arterial ischemic stroke, (2) DWI <14 days from stroke onset, (3) anatomic T1 MRI >6 months, and (4) Pediatric Stroke Outcome Measure >12 months. Blinded scorers measured cerebellar volumes (left/right/hemisphere/vermis/total) using Osirix software. Cerebellar volumes ratios (nonstroke/stroke) were expressed as asymmetry indices (AI), with chronic/acute ratio <1.0 suggesting crossed atrophy. Acute brain stem and cerebellum (peduncle, hemisphere) DWI ratios were scored. Software measures were compared with visual inspection. Associations between AI, motor outcome (good/poor), and contralateral CST-DWI were sought. Rater reliabilities were assessed.

Results—Twenty-three children were studied (median age, 6.3±4.4 years; 62% male). Baseline cerebellar volumes were comparable (right=56.9 cm³, left=57.1 cm³). Cerebellar atrophy was suggested across the sample with overall AI <1.0 (0.973±0.05; P=0.009). Visual atrophy detection was specific (>100%) but insensitive (54%). Children with poor motor outcome did not have lower AI (0.983±0.027 versus 0.965±0.068; P=0.40); however, children with acute contralateral CST-DWI did (0.928±0.078 versus 986±0.040; P=0.03). Acute cerebellar DWI did not predict atrophy. Rater reliabilities were excellent (>0.92).

Conclusions—Cerebellar atrophy can be demonstrated on MRI in childhood arterial ischemic stroke. Association with acute contralateral pontine DWI signal suggests early degeneration of corticopontocerebellar connections. The clinical significance of cerebellar atrophy in childhood stroke remains to be determined. (Stroke. 2013;44:2468-2474.)

Key Words: cerebellum ■ diffusion magnetic resonance imaging ■ pediatrics ■ stroke

Arterial ischemic stroke (AIS) causes neurological morbidity in children. Most childhood AIS involves the middle cerebral artery distribution, resulting in supratentorial lesions of motor systems. Many children with AIS have lifelong hemiparesis and physical disability. Improved understanding of poststroke motor neurophysiology is identifying new therapeutic targets in adults and possibly children.

Described by von Monakow in 1914, diaschisis is a focal depression of neurological function at a distance from the original site of injury but anatomically connected to it by fiber tracts. An established example is crossed cerebellar diaschisis where functional changes in the cerebellum contralateral to supratentorial lesions are thought to reflect disrupted corticopontocerebellar connections. Crossed cerebellar diaschisis is well described in adult stroke where it may associate with neurological outcome. Only 1 single-photon emission computed tomography study of children with congenital hemiplegia has examined cerebellar diaschisis in children.

A related concept to diaschisis is that of crossed cerebellar atrophy (CCA), postulated to represent chronic anatomic changes secondary to the metabolic depression of acute diaschisis. Although evaluation of diaschisis requires functional imaging, CCA is measured with either neuroimaging volumetrics or neuropathologically. A retrospective computed tomography imaging cohort study of 103 adults with supratentorial stroke found CCA in 8.7%. There have been no quantitative neuroimaging studies of CCA in childhood stroke.

Clinically relevant, early imaging biomarkers remote from stroke lesions are also emerging. Acute diffusion MRI signal in the descending corticospinal tracts has been associated with motor outcome in neonatal, childhood, and adult stroke. Such early outcome predictors may inform stroke recovery.
mechanisms and aid in patient selection for clinical trials. Our study of brain stem diffusion changes in childhood AIS discovered unexpected acute diffusion lesions in the contralateral pons in some patients. The pathophysiology of these lesions is unknown.

We hypothesized that CCA can be quantified on clinical neuroimaging in children with AIS and is associated with acute contralateral pontine diffusion lesions and poor motor outcome.

Methods

Population

This was a retrospective, observational study using data obtained prospectively from an established cohort of childhood AIS (SickKids Children’s Stroke Program). Research Ethics Board approval from both study sites and informed consent were obtained. Inclusion criteria were the following: (1) age ≥28 days to <18 years at time of stroke; (2) clinical and radiographically confirmed unilateral AIS in the middle cerebral artery territory; (3) diffusion-weighted MRI within 14 days of clinical onset; (4) T1 anatomic MRI 6 months from stroke; (5) no additional neurological disorders; (6) Pediatric Stroke Outcome Measure (PSOM) at >12 months.

Long-term motor outcomes were classified using the PSOM—the validated, standardized neurological clinical outcome measure for childhood stroke. The PSOM is an objective, disease-specific measure containing 115 clinical test items suitable for infant to adult ages (including adjusted scoring for children <2 years of age). The PSOM measures neurological deficits and function across 5 subscales: right/left sensorimotor, language production and comprehension, and cognitive/behavior. Summary scores for each domain are scaled: 0 (no deficit), 0.5 (mild, no functional impact), 1 (moderate), or 2 (severe). Motor scores were dichotomized into good (0/0.5) versus poor (1/2).

Neuroimaging

MRI were obtained at the Hospital for Sick Children using a 1.5-Tesla system (Signa, GE Medical Systems, Milwaukee, WI). Diffusion images were obtained using single-shot spin-echo echo-planar sequences (repetition time/echo time 10000/100, 20-cm field of view, 128×192 matrix, 5-mm thickness, no gap; b1000 sec/mm²). Original DICOM images were securely transferred to the Seaman’s MRI Center (Calgary) for offline analysis. Any compromise in image quality on visual or software analysis resulted in exclusion.

Cerebellar Volumetrics

Methodology for cerebellar volume measurements is summarized in Figure 1. Axial T1-weighted images were used. The firstfield of interest drawing tool in OsiriX facilitated detailed tracing of cerebellar anatomy. Four regions of interest were drawn on any axial slice containing cerebellum using predefined anatomic landmarks. Areas of cerebellar hemisphere and vermis were measured to generate 4 areas: right hemisphere, right vermis, left hemisphere, and left vermis. The OsiriX volumetric tool then automatically calculated total volumes (cm³) for each section and side (right and left cerebella). Raters were blinded to all clinical information and began with most inferior slice, working in a caudal-cranial direction to maintain blinding to side of stroke. The same procedure was performed at 2 time points: acute T1 images defined baseline volumes and chronic (>12 months) T1 images re-evaluated volume changes over time. All measurements were relabeled as ipsilesional or contralesional once stroke side was revealed. Chronic T1 scans were visually inspected by a single investigator (A.K.) blinded to outcome and volumetric results and scored as having crossed cerebellar volume loss or not.

To control for natural asymmetry in cerebellar volumes within patients, individualized ratios were calculated (contralesional/ipsilesional) for both the acute and chronic images. The chronic ratio was then divided by the acute ratio for each patient to yield an asymmetry index (AI). Therefore, AI<1 would suggest chronic atrophy of the contralesional cerebellum consistent with cerebellar atrophy. The primary imaging outcome was total cerebellar volume AI. Additional anatomic imaging outcomes of interest included comparisons of hemispheric versus vermian volumes and the ability to detect chronic cerebellar atrophy by visual inspection alone.

Figure 1. Volumetrics methods. A, Using T1 images, freehand region of interest (ROIs) were drawn around each hemisphere and vermis with area measurements (cm²) generated by the software. ROIs were drawn on all axial slices from the most inferior slice at which cerebellum was visible to most superior (B). The software then aggregated these measurements to generate total volumes of each section (cm³) and 3-dimensional renderings as shown for right (top) and left (bottom) cerebellar hemispheres (C). The child shown had both visually detectable and volumetrically confirmed crossed cerebellar diaschisis.
Acute Diffusion-Weighted Imaging for Measurement of Diffusion Signal Intensity

The acute axial diffusion images (b=1000) were used for all analyses. Apparent diffusion coefficient maps were also examined. Despite potential advantages of the more quantifiable apparent diffusion coefficient values, anatomic resolution was poor with a high risk of contamination from neighboring cerebrospinal fluid spaces given the areas of interest. Three specific targets were evaluated on the acute diffusion-weighted images:

1. Cerebellar parenchyma. The freehand region of interest drawing tool in Osirix traced left and right cerebellar hemispheres and vermis using predefined landmarks on all cerebellar slices. Mean signal intensity (arbitrary units) was calculated for each measurement, and individualized ratios were calculated (contralesional/ipsilesional signal intensity).

2. Middle Cerebellar peduncles. Left and right middle cerebellar peduncle region of interests were also defined. Only tissue connecting the cerebellum to the pons on axial images was measured. Given the resolution limitations of diffusion images, contamination by small components of the superior or inferior peduncle could not be entirely excluded. As above, diffusion was blindly measured for each side and region, relabeled as ipsilesional or contralesional, and converted to ratios.

3. Brain stem. Methodology for quantification of acute brain stem diffusion changes in this population is previously reported. Briefly, a thresholding method (Image J software) quantified diffusion-weighted imaging (DWI) asymmetry within the corticospinal tracts, including the basis pontis. As this level also includes corticopontocerebellar fibers, it was exclusively examined for contralesional signal and scored as present or absent.

Analysis

Frequency distributions assessed normality. Dichotomous group comparisons of continuous data used independent, 2-tailed t tests. Because of a limited number of predefined, hypothesis-driven comparisons, no corrections for multiple comparisons were applied. Associations between visually and software-scored atrophy were calculated with sensitivity/specificity and predictive values calculated. Interclass correlation coefficients assessed intrarater and inter-rater reliabilities. Statistical analysis used SPSS version 19.0.

Results

Population

The sample of 23 children is summarized in Table 1. From the potentially eligible population of 96, exclusions included inadequate acute imaging (43), poor quality imaging (21), incomplete anatomic imaging (6) and no PSOM >12 months (3). Median age at stroke was 6.3±4.4 years (range, 0.19–16), and 62% were male. Seventeen (74%) children had left-sided strokes. Median time to diffusion MRI was 3.0±2.7 days (range, 0–10). Follow-up imaging time was a median of 2.5±2.0 years (range, 0.5–7.6). Median clinical follow-up interval (most recent PSOM) was 3.2±1.1 years. Motor outcome was poor in 13/23 (57%), and follow-up interval did not differ between good and poor groups (P=0.41).

Table 1. Patient Characteristics

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ACA indicates anterior cerebral artery; BG, basal ganglia; CATH, catheterization procedure; CHD, congenital heart disease; DIS, dissection; DWI, diffusion-weighted imaging; ENC, encephalitis; FEAN, iron deficiency anemia; F/O/P/T, frontal, occipital, parietal, or temporal lobes; HMAL, hematologic malignancy; ICA, internal carotid artery; IDIO, idiopathic; MCA, middle cerebral artery; MMD, moyamoya disease; PLIC, posterior limb internal capsule; PVAR, postvaricella angiopathy; and VAS, vasculitis.
Chronic CCA
Evidence of CCA could be detected visually (Figure 2). Our volumetric method demonstrated high reliabilities in both intra- and inter-rater analyses (intraclass correlation coefficients 0.98, 0.94). At baseline, mean cerebellar volumes were comparable between sides (60.6±14.6 cm$^3$ and 61.0±14.5 cm$^3$; $P=0.72$). Mean baseline asymmetry ratio was 0.999±0.026 (range, 0.963–1.06) and not different from 1.0 ($P=0.877$).

The mean AI, representative of chronic asymmetry, for the entire population was 0.973±0.054 (range, 0.808–1.08) and was significantly <1.0 ($P=0.009$). Sixteen patients (70%) had AI<1, suggesting crossed cerebellar atrophy. Within this group, the mean AI was 0.95±0.046 cm$^3$ (range, 0.808–0.997). Of these 16 patients, 9 (56%) were visually identified as having cerebellar volume loss, whereas none of the group with AI≥1 were visually scored as demonstrating atrophy. Those with visually detectable atrophy had significantly lower AI than those who did not (0.86±0.052 versus 0.960±0.044; $P=0.01$). Visual detection was highly correlated with software-quantified crossed cerebellar volume loss ($P=0.002$). Estimates of the diagnostic abilities of visual inspection are summarized in Table 2 and suggest high specificity and positive predictive value but limited sensitivity (56%) and negative predictive value (44%).

No difference was found in mean AI values between good and poor motor outcomes (0.983±0.027 versus 0.965±0.068; $P=0.40$). Results are summarized in Figure 3A. Independent analysis of hemispheric and vermian AI measures also did not associate with motor outcome (0.972±0.042, $P=0.393$; 0.999±0.076, $P=0.876$).

Acute Diffusion Imaging Markers
Cerebellar and peduncular diffusion measurements were completed in 23 and 22 children, respectively (single case had peduncle artifact). No side-to-side differences in diffusion signal were detected for the cerebellar hemispheres or peduncles (all $P>0.34$). Diffusion ratios for hemispheres and peduncles were 0.992±0.041 and 0.981±0.087 and neither differed from 1.0. No correlation was found between acute hemispheric or peduncle DWI and chronic atrophy ($P=0.33$ and 0.24, respectively).

A significant association was observed between the presence of contralesional acute DWI signal in the basis pontis and chronic cerebellar volume loss on the same side (Figure 3B). Those with contralesional pontine DWI signal demonstrated lower AI values (0.928±0.078) compared with those without (0.986±0.040; $P=0.03$). When the association of contralesional pontine DWI signal with AI of the hemisphere or vermis were analyzed independently, only hemispheric changes were significant (0.972±0.042; $P=0.02$).

Discussion
We provide objective evidence of CCA after childhood AIS. Our results suggest this process is common and detectable on visual inspection, although using simple software analysis is more sensitive. An association with acute contralesional pontine diffusion signal may provide an early imaging biomarker to predict CCA in children as well as an explanation for this previously unexplained phenomenon.

Seventy percent of our cohort had cerebellar AI<1, suggestive of possible atrophy. This prevalence seems comparable with studies of crossed cerebellar diaschisis after middle cerebral artery stroke in adults. However, such a rate of CCA seems significantly higher than in adult stroke, where estimates are <10%.9,13,20–22 Although speculative, one possible explanation could be greater plasticity and apoptotic vulnerability in pediatric brains.11,23 In addition, our imaging inclusion criteria may have created a selection bias for more severe or recurrent cases (ie, more likely to receive serial imaging), potentially resulting in an overestimation of CCA prevalence.

Although our anatomic methods carried limitations, our results suggested that volume loss was selective for the
cerebellar hemisphere rather than vermis. Normative values for cerebellar asymmetry in children are also not established. We deliberately did not include a control population because our measurements were internally controlled, both within individuals (AIx) and over time (change from baseline asymmetry). That baseline AI centered around 1.0 with small SDs supports both our measurement methods and the presumption that cerebellar volumes are normally symmetrical in children.

We add novel pediatric data to what was very limited literature on cerebellar atrophy in childhood. A single study by Hamano et al.12 explored cerebellar diaschisis using single-photon emission computed tomography in childhood hemiplegia. Using qualitative assessments of asymmetries in cerebellar blood flow, their results suggested crossed cerebellar diaschisis in 6 of 55 patients (11%). Comparable features of this study with ours include symmetry comparisons with the normal, nonlesioned cerebellar hemisphere, and a high proportion of cases with probable AIS because this is the leading cause of unilateral hemiplegic cerebral palsy.24 However, lesion timing was clearly earlier in development than in our series because most presumably occurred in the perinatal period. Also the presence of other nonvascular causes of hemiplegic cerebral palsy makes their study population more heterogeneous. We suggest that future studies of crossed cerebellar diaschisis should aim to combine acute functional imaging with acute and chronic anatomic imaging and focus on more specific disease states rather than heterogeneous lesions underlying clinical syndromes.

We found no correlation between CCA and long-term neurological outcomes according to the PSOM. Specific outcomes of interest included motor function, evidence of cerebellar dysfunction such as ataxia, and overall neurological outcome. Few adult stroke studies of crossed cerebellar diaschisis have correlated imaging findings with specific deficits attributable to cerebellar dysfunction such as ataxia. Furthermore, those reporting ataxia often include original supratentorial lesions of the thalamus or parietal lobes, which may independently cause contralesional ataxia and limb uncoordination.25,26 Another study by Kim et al.23 did not find clinical signs of cerebellar dysfunction despite the presence of diaschisis after supratentorial stroke. Clinical detection of cerebellar dysfunction may be further complicated by signs attributable to stroke-induced dysfunction of pyramidal or other motor systems. Other studies in adult stroke suggest that an absence of crossed cerebellar diaschisis is correlated with favorable outcome, whereas its presence associates with poor neurological outcome; however, infarct volume may be responsible for both, and diaschisis may persist in the absence of neurological deficits or cerebellar dysfunction.23,27,28 Further studies of the relationship between crossed cerebellar diaschisis or atrophy and outcome should include measurement of, and correction for, other variables associated with the outcomes of interest such as lesion volume.

Although interesting, chronic imaging markers of any neurophysiological process generally carry less clinical use. In contrast, acute imaging markers might allow earlier identification of pathological processes, more accurate prediction of long-term outcomes, and patient selection for clinical trials, including novel rehabilitation interventions. Our results suggest routine acute diffusion imaging may provide such a marker. We demonstrated a positive association between acute diffusion changes in the contralesional basis pontis and CCA. Why the same acute diffusion imaging changes could not be tracked beyond the basis pontis into the middle cerebellar peduncle or cerebellar hemisphere is unknown. However, the dense convergence of corticopontocerebellar fibers in the basis pontis could account for why this region seems most likely to demonstrate such signal. Regardless, our results seem

Table 2. Diagnostic Use of Visual Inspection for Crossed Cerebellar Atrophy in Childhood AIS

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<tr>
<td>Cerebellar volume loss</td>
<td>− 7 7</td>
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</table>

Sensitivity = 9/(9+7) = 56%.
Specificity = 100%.*
Positive predictive value = 100%.*
Negative predictive value = 7/(9+7) = 44%.

Software-quantified asymmetry ratios (AI) < 1.0 were considered the gold standard for evidence of contralesional cerebellar volume loss.

*Values are only estimates with accurate calculation limited by low numbers and zero values.

Figure 3. Imaging markers and outcomes of cerebellar diaschisis. Mean asymmetry index (AI) did not differ between good and poor motor outcome groups (A) but was significantly lower in children whose acute diffusion MR demonstrated contralesional pontine diffusion signal (B; P = 0.03).
to provide a logical explanation for the previously described appearance of contralesional basis pontis diffusion signal in some children with AIS. Why the same signal was not observed in a similar study of brain stem acute diffusion changes in adult stroke is unclear but may relate to factors affecting expression of diffusion changes in younger brains, such as brain water content or myelination.

Our study was limited in its ability to detect complex or subtle correlations between cerebellar atrophy and neurological outcomes. Our sample size was modest as were potential effect sizes based on adult evidence. Another limitation was the use of neuroimaging studies that were obtained by clinical protocol and did not include volumetric acquisitions. Additional limitations were incurred by the PSOM being the primary clinical outcome measure. Although it is reasonably comprehensive, well validated, and clearly the established measure in childhood stroke, its resolution carries limits. The PSOM does include test items for cerebellar-specific findings, including ataxia, nystagmus, and others. Many adult cerebellar diaschisis studies have used potentially more robust and validated numeric stroke scale scores. The dichotomization of motor outcomes into good versus poor was required for this study to evaluate for possible large effects on general motor outcome. Those children with larger or specifically located strokes would be expected to have more CCA, but also more severe contralateral sensorimotor deficits, potentially clouding the ability to clinically detect cerebellar dysfunction. Our ability to measure subtle differences in cerebellar function in hemiparetic children across many ages and multiple raters using the PSOM was, therefore, likely limited. An alternative interpretation is that there are no clinical functional consequences of cerebellar atrophy.

Different mechanisms have been proposed for crossed cerebellar diaschisis. The widely held view is that acute contralateral cerebellar changes represent a loss of excitatory cortical efferents after injuries such as stroke. Collaterals of lateral corticospinal fibers to the pons generate pontine projections to the contralateral cerebellum. Primary, stroke-induced disruption occurring at cortical or subcortical supratentorial levels could, therefore, damage such crossing corticopontocerebellar tracts to affect projections to contralateral cerebellar Purkinje cells, either directly or via cerebellar relay neurons. Persistent disruption of this pathway may result in irreversible functional deactivation, transneuronal degeneration, and atrophy of the cerebellar hemisphere after acute reductions in blood flow and metabolism. Our current and previous findings of contral senatoral diffusion MRI changes in the basis pontis in acute childhood AIS and their association with CCA further support this model of disrupted corticopontocerebellar pathways in childhood stroke. In summary, our findings provide quantitative evidence for CCA in childhood AIS. Acute diffusion imaging changes in the contralatal basis pontis represent an early imaging biomarker of CCA. Improved recognition and larger studies are required to determine clinical significance.

Disclosures

Dr. Kirton received support from the Heart and Stroke Foundation of Canada.

References

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