Quantified Corticospinal Tract Diffusion Restriction Predicts Neonatal Stroke Outcome

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Background and Purpose—Neonatal arterial ischemic stroke occurs in ≥1:4000 births. Many children experience motor deficits but acute predictors of outcome are lacking. Diffusion-weighted MRI changes in descending corticospinal tracts remote from arterial ischemic stroke may represent pre-Wallerian degeneration. We verify and quantify this signal and correlate it with motor outcome.

Methods—Fourteen neonates with acute arterial ischemic stroke and ≥12 months follow-up with the Pediatric Stroke Outcome Measure were included. Quantitative measurements of descending corticospinal tracts diffusion-weighted MRI signal were developed using Image J software.

Results—Ipsilesional descending corticospinal tract diffusion-weighted MRI signal was abnormal in 10 neonates with decreased apparent diffusion coefficients (P<0.001). Poor outcome correlated with: (1) percentage of peduncle (P=0.002); (2) length of descending corticospinal tracts P<0.001); and (3) volume of descending corticospinal tracts (P=0.002). None of: (1) any peduncle; (2) any posterior limb of the internal capsule; or (3) infarct volume correlated with outcome. All children without descending corticospinal tracts signal had normal outcome. Chronic Wallerian degeneration was seen in all children with hemiparesis. Software-assisted analysis was superior to visual inspection with excellent reliability (intra-class correlation coefficient ≥0.9).

Conclusion—Descending corticospinal tracts diffusion-weighted MRI signal is predictive of motor outcome from neonatal arterial ischemic stroke. This accurate, reliable, and simple tool will impact decision making in acute neonatal stroke. (Stroke. 2007;38:974-980.)

Key Words: cerebral palsy ■ diffusion-weighted imaging ■ neonate ■ stroke

We developed and validated a simple software-assisted technique to quantify DCST DWI changes in neonatal AIS and correlate them with motor outcome.

Methods

Patient Selection

Patients were identified through the Children’s Stroke Program at the Hospital for Sick Children, Toronto. Inclusion criteria were (1): term neonate (>36 weeks); (2) diagnosed acute AIS (<28 days old); (3) MRI with DWI and apparent diffusion coefficient (ADC) measurements; (4) no clinical or radiographic evidence of other neurological abnormality; and (5) standardized neurological examination at ≥12 months.

A consecutive cohort diagnosed between 1999 (DWI availability) and 2004 was evaluated. All patients were registered in the Canadian Pediatric Ischemic Stroke Registry and followed through the Children’s Stroke Program. Medical records were reviewed including standardized screening for neonatal AIS risk factors. Motor outcomes were classified using the previously validated Pediatric Stroke Outcome Measure and expressed as either good (no hemiparesis or mild with normal function) or poor (moderate to severe hemiparesis).
resis). The study was approved by the institutional Research Ethics Board.

**DWI/ADC Measures and Computer-Assisted Thresholding**

A systematic technique for the quantification of DCST DWI signal change was developed using *Image J* freeware from the National Institutes of Health (http://rsb.info.nih.gov/ij/) (Figure 1). All MR studies were performed with a 1.5-Tesla superconducting system (Signa; GE Medical Systems). Axial DWI was completed with single-shot spin-echo echo-planar sequences (TR/TE=10 000/100; 20 cm field of view; 128×192 matrix; 5 mm thickness, no gap) $b=1000$ s/mm$^2$, and ADC maps generated from DWI datasets.

DCST slices were labeled as medulla, pons, midbrain, or PLIC according to predefined landmarks, and cropped to isolate DCST portions. The thresholding tool of *Image J* scores each pixel as positive or negative on a scale of 1 to 255 degrees of brightness. The lower threshold was adjusted upwards until positive pixels first appeared in DCST regions bilaterally. Assuming one side is normal, the value immediately below this was then used as a cut-off, with any remaining positive pixels considered as abnormal and measured. Slices were analyzed from medulla upwards so stroke side was not appreciated. DWI signal was considered significantly abnormal if 10 or more pixels were positive or if an adjacent slice to this had 5 to 9 pixels positive. Having >5 positive pixels was not considered significant because normal side-to-side variability is 2 to 3 pixels.

Seven measures of DWI signal change were then defined:

1. PLIC: Scored as positive or negative if any PLIC slice met the criteria.
2. Peduncle: Same for midbrain slices.
3. Percentage Peduncle: Total peduncle area was measured using freehand tracing and area calculator tools. The number of positive pixels was divided into this area to determine percentage of peduncle affected.
4. Section of Peduncle: Peduncle slices were divided into medial, middle, and lateral thirds using the drawing tool (Figure 1). A third was scored as positive if abnormal pixels were evident in its territory.
5. Length of DCST: The total number of positive slices was multiplied by the slice thickness (5 mm) to obtain this measurement in millimeters.

6. Relative Volume of DCST Affected: Total volume of patient brain parenchyma was determined using the threshold tool. Total volume of abnormal DCST signal was then summed and divided into this volume.

7. Relative Volume of Infarct: In a similar fashion, total infarct volume was determined with the threshold tool and divided into total brain volume.

ADC values were measured by placing a uniformly sized voxel over symmetrical DCST regions of each slice. The ADC values of the most positive DWI slice were expressed as the percentage of affected (stroke) side to unaffected side.

**WD Measures**

Follow-up T1-weighted brain stem sections were analyzed using a previously described technique. After defining the section midline, volumes of DCST portions were obtained using the freehand tool. An asymmetry index (AI) was calculated as: asymmetry index = $\frac{\text{AU}−\text{AA}}{\text{AU}+\text{AA}}$, where AA and AU refer to the area of the affected (AA) and unaffected sides (AU).

**Validation Measures and Visual Inspection**

All DCST DWI measures were performed on 2 separate occasions by a single investigator neurologist (A.K.). A second blinded investigator (T.V.) with no experience in MR interpretation was trained to follow detailed written instructions to repeat measurements for all patients. All DWI threshold and anatomical measurements were compared for both intra-rater and inter-rater correlations. A blinded neuroradiologist experienced in neonatal DWI imaging (M.S.) reviewed all DCST slices without knowledge of stroke side. A slice was scored as positive if it appeared asymmetrically bright in a region consistent with the DCST. Visual inspection results were then compared with the CAT method.

**Statistical Analysis**

Correlations between motor outcome and dichotomous variables were assessed using Fisher exact test. For continuous variables, the Student $t$ test or Mann-Whitney test were used for variables with and without evidence of normalcy, respectively. Bonferroni, Holm method, and Hochburg variation were applied to correct for multiple comparisons. Reliability was assessed using the intra-class correlation coefficient (2-way mixed for intra-rater, 2-way random for inter-rater). Statistical analyses were performed using SPSS 14.0.
<table>
<thead>
<tr>
<th>Pt</th>
<th>GA</th>
<th>BW</th>
<th>Resus</th>
<th>Possible Risks</th>
<th>Presentation</th>
<th>MR</th>
<th>Location</th>
<th>Outcome</th>
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<td>39</td>
<td>2465</td>
<td>APGAR 8,9</td>
<td>22q11 deletion</td>
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<td>9,9</td>
<td>Low AT (transient)</td>
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<td>8,9</td>
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<td>3975</td>
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<td>4019</td>
<td>6,7</td>
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Stroke locations include frontal (F), parietal (P), temporal (T), occipital (O), and basal ganglia/internal capsule (BG/IC).

AT indicates antithrombin; CHD, congenital heart disease; C/S, cesarean section; FHR, fetal heart rate; IPPV, intermittent positive pressure ventilation; MCA/PCA, middle/posterior cerebral arteries; NE, neonatal encephalopathy; NP, nonprogression; PC, protein C; PDA, patent ductus arteriosus; PPHN, persistent pulmonary hypertension; SVD, spontaneous vaginal delivery; Sz, seizure.
Results

Patient Population

From 89 cases of neonatal AIS, 75 were excluded as follows: no acute DWI, 42; concomitant brain injury, 21; watershed infarction, 7; or inadequate follow-up, 5. Fourteen term neonates (8 male) were analyzed. Clinical characteristics are summarized in Table 1. All presented with seizures and none demonstrated focal neurological deficit. A typical variety of potential risk factors were identified. Events occurred predominantly within the middle cerebral artery territory (13/14), more commonly on the left (9/14). All MR scans were completed between days 2 and 8 of life except for 1 on day 23, 72 hours after a cardiac procedure. At a median follow-up of 19 months (range, 12 to 63), outcomes included normal (9), mild (1), moderate (2), and severe (2) hemiparesis.

Restricted Diffusion of the DCST

DCST DWI signal ipsilateral to AIS was quantifiably different from the contralateral side in 10 of 14 neonates. Results are summarized in Table 2. Affected DCST locations included the PLIC, cerebral peduncle, basis pontis, and medullary pyramids (Figure 2). Corresponding ADC values were

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<th>MiP</th>
<th>LaP</th>
<th>%P</th>
<th>PLIC</th>
<th>mm</th>
<th>VolCST</th>
<th>VolInf</th>
<th>Follow-Up, months</th>
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<td>20%</td>
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<td>100%</td>
<td>100%</td>
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<td>100%</td>
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<td>0.210</td>
<td>11.18</td>
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Significance (P) 0.21 0.3 0.04 0.10 0.002 0.07 0.002 0.002 0.45

DWI signal is Negative (Neg) or Positive (Pos) in the peduncle in general (Ped), the medial (MeP), middle (MiP), or lateral (LaP) segments, or the PLIC. Variables include the percentage of peduncle (%P), vertical length of DCST in millimeters (mm), and relative volumes of DCST affected (VolCST) and infarct (VolInf). Motor outcome is good (normal or mild hemiparesis) or poor (moderate or severe hemiparesis).

Figure 2. Restricted diffusion signal in the DCST. Left middle cerebral artery infarction (A) results in DWI signal changes throughout the DCST. PLIC and cerebral peduncle involvement are evident on coronal (B) and sagittal images (C). Signal in the basis pontis and medullary pyramids can be seen on left (D) but not right (E) parasagittal sections.
decreased (0.904±0.13 versus 1.113±0.098×10³ mm²/sec; P=0.0001) confirming restricted diffusion.

All children without DCST DWI signal had normal outcome (n=4). After correcting for multiple comparisons, poor motor outcome was significantly correlated with three of the seven DCST DWI measures:

**Predictor 1**
The percentage of cerebral peduncle affected was higher in children with poor outcome (37.49±23.0% versus 3.76±5.3%; P=0.002). All children with poor outcome had ≥25% of peduncle affected (range, 25% to 68%). Detection of any positive DWI signal in either the peduncle or PLIC was not significantly correlated with outcome (P=0.21 and 0.07, respectively).

**Predictor 2**
The length of DCST affected correlated with poor motor outcome (Figure 3). Children with good outcome showed a mean length of 8.5±8.8 mm, whereas those with poor outcome measured an average of 35±4.1 mm (P=0.002). All patients with poor outcome had ≥20 mm of DCST affected, although this was never seen with a good outcome.

**Predictor 3**
The relative volume of the DWI DCST lesion correlated with poor motor outcome (0.018±0.02% versus 0.21±0.09% for good and poor outcome respectively, P=0.002). All children with poor outcome had ≥0.09% of brain volume affected whereas none with good outcome achieved this volume. Infarct volume was not significantly correlated (3.52±3.1 versus 11.18±11.1, respectively; P=0.45).

Involvement of the middle third of the peduncle was associated with poor motor outcome (P=0.04) but this level of significance did not satisfy the correction for multiple comparisons. All 5 children with hemiparesis had involvement of the middle third compared with only 1 of 9 children with normal outcome. Involvement of the medial (P=0.30) or lateral (P=0.10) thirds was not correlated (Figure 4).

**Visual Inspection Versus CAT Technique**
Visual inspection was less accurate in identifying DCST DWI signal. Of 130 slices analyzed, 16 (12%) were incorrectly interpreted (10 false-positive, 6 false-negative). Taking the CAT method as the gold standard, visual inspection was 77% sensitive and 93% specific. Visually estimated signal in the peduncle did correlate with outcome but in the PLIC or any DCST did not.

**Wallerian Degeneration**
Follow-up imaging (n=9) demonstrated atrophy of DCST brain stem regions where acute DWI signal was observed (Figure 5). Expressed as the brain stem asymmetry index, the degree of WD correlated with poor motor outcome (3.79±1.3 versus 8.68±3.8; P<0.05). All children with poor motor outcome demonstrated WD of the peduncle, whereas none of those with good outcomes did.

**Technique Validation**
All measures were highly reproducible. For DWI DCST measures, inter-rater and intra-rater reliabilities demonstrated intraclass correlation coefficients of 0.986 (0.981 to 0.990) and 0.995 (0.994 to 0.997), respectively. For cerebral peduncle area measurements, inter-rater and intra-rater values were 0.892 (0.462 to 0.978) and 0.986 (0.930 to 0.997), respectively. No observer disagreement occurred for anatomical assignments or division of the cerebral peduncle into thirds.

**Discussion**
We have developed and validated a simple technique for detecting and quantifying restricted DCST diffusion signal in neonatal AIS that correlates with motor outcome. Our technique is routinely available in the acute time frame as DWI.
imaging is the current standard for neonatal stroke diagnosis. Although DCST DWI signal detected by visual inspection alone appears useful, additional quantification by a simple computer-assisted technique adds predictive power.

Prognosticating outcome in the acute timeframe is of crucial importance to families and essential in selecting patients for treatment interventions. Existing neuroprotective strategies in neonatal stroke are predominantly supportive and selecting high-risk patients will be essential in their validation and randomized trials of evolving neuroprotective interventions. Published guidelines support controversial pharmacological interventions such as anti-coagulation therapy, a problem requiring better tools to weigh relative ratios of risk to benefit. As the evidence base for rehabilitational strategies in perinatal stroke develops, accurate and early predictors of outcome will improve patient selection.

Visual DCST signal detection limited to the peduncle has been suggested to correlate with outcome. However, our results suggest that more detailed quantification throughout the DCST carries more predictive power. Infarct location and volume have some predictive power in neonatal AIS, but this association has been inconsistent with smaller infarcts proving particularly difficult to correlate with outcome. We demonstrated that infarct volume is not well associated with motor outcome but the volume of affected DCST is powerfully correlated. Highlighting this were several patients with small infarct volumes but very abnormal DCST DWI measures who ultimately had poor outcomes. This suggests that more “function-specific” imaging may better predict specific functional outcomes. DCST tractography with diffusion tensor imaging (DTI) may have similar potential, but its utility in stroke is unproven and technological requirements limit availability. The now-routine use of DWI, combined with our system’s ease of use and virtually zero cost, makes it a highly practical tool in neonatal stroke evaluation.

Stroke-induced DCST DWI findings have rarely been reported in adults despite a much greater experience with DWI. This suggests that such changes may be relatively unique to the younger brain, perhaps related to differences in myelination or brain water content, although these suggestions are speculative. Our findings confirm previous suggestions that DCST DWI signal reflects restricted diffusion of water. It will be interesting to apply our methods to other populations of children with DCST injury including neonatal hypoxic-ischemic encephalopathy and older children with stroke.

WD was first described 150 years ago, and chronic changes on neuroimaging in pediatric stroke are well-described. However, little is known regarding how the earliest phases of WD might be represented on neuroimaging. Because of the dependency of the axon on the cell body for survival, degenerative changes occur distal to the location of neuronal injury and the earliest phases (axonolysis, myelinolysis) are similar in the peripheral and central nervous systems. That both the degree of acute DWI signal change and chronic atrophy of DCST correlated with outcome suggests that both reflect different stages of the WD process. In a study of 20 neonates with perinatal hemispheric brain lesions, the degree of WD on follow-up imaging was also highly correlated with severity of spastic hemiparesis. Whereas a smaller study did not show the same correlation, severity of stroke-induced hemiplegia did correlate with DTI abnormalities, further suggesting that function-specific imaging may be most useful. The acute pathological studies of neonatal stroke required to confirm that DCST DWI signal represents early WD will be difficult to complete.

Quantified DWI signal in the DCST correlates with motor outcome from neonatal AIS. Study limitations including a retrospectively and narrowly selected patient population and modest sample size will need to be overcome in future studies. The accuracy and reproducibility of this simple tool, and its ready availability in the acute timeframe, will impact imaging.

**Figure 4.** Involvement of peduncle middle third may correlate with outcome. Involvement of lateral (A) or medial peduncle (B) was not correlated to outcome but involvement of the middle third (C), where DCST are anatomically located, demonstrated an association.
prognostication and approaches to treatment of neonatal stroke.

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Disclosures
None.

References

Figure 5. Wallerian degeneration. Follow-up T1-weighted MRI demonstrates volume loss where DWI signal was present acutely at levels of peduncle (A), basis pontis (B), and medullary pyramid (C). Expressed as an asymmetry index, the degree of WD correlated with poor motor outcome.
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