Acute Corticospinal Tract Wallerian Degeneration Is Associated With Stroke Outcome

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Background and Purpose—In children with stroke, poor motor outcome is associated with early Wallerian degeneration of the corticospinal tract that is seen on diffusion-weighted MRI. In this study we test the hypothesis that early diffusion changes also occur in the corticospinal tract (CST) of adults after stroke and that these lesions are associated with poor outcome.

Methods—In this retrospective study, we assessed images from a serial MRI study of adults with acute middle cerebral/internal carotid artery stroke. MRI-negative TIA patients served as controls. Custom software measured signal along the CST on different sequences, including the apparent diffusion coefficient (ADC). Visual detection of abnormal signal by blinded neuroradiologists was also evaluated. We then determined associations between CST signal changes and 3-month motor outcome (NIHSS score).

Results—Thirty-eight patients (20 stroke/18 control) were included. ADC measures were much more accurate than other MRI sequences for detection of degeneration in the CST. The ADC decreased in a time-dependent fashion in the CST of patients with poor motor outcome but not in those with good outcome. Changes in ADC were maximal at 7 days. Neuroradiologists could visually detect these changes with accuracy comparable to the software method.

Conclusion—CST ADC decreases after acute stroke in patients with poor motor outcome and may represent early Wallerian degeneration. Recognition of this imaging marker may improve early outcome prediction and patient selection for rehabilitation and neuroprotection trials. (Stroke. 2010;41:751-756.)

Key Words: cerebral infarct ■ magnetic resonance ■ prognosis ■ pyramidal tracts ■ Wallerian degeneration

Stroke remains the leading cause of acquired motor disability. Ischemic stroke often damages supratentorial motor systems with resulting hemiparesis. Affected upper motor neurons converge into the descending corticospinal tract (DCST), definable on imaging at the internal capsule, cerebral peduncle, basis pontis, and medullary pyramids. Stroke-induced chronic DCST atrophy on MRI is consistent with Wallerian degeneration, which is antegrade axonal degeneration after proximal neuronal injury. Both pediatric and adult stroke studies have associated DCST atrophy with poor motor outcome, although such clinical findings have limited clinical relevance.

Recent acute stroke studies have described abnormal DCST diffusion-weighted imaging (DWI) signal in neonates and children. Signal appears within hours and is predictive of poor motor outcome. Acute DCST diffusion patterns may also reflect early plastic organization in childhood stroke. Isolated cases of DCST diffusion changes in adult stroke are reported, although diffusion tensor imaging studies suggest similar changes and correlations to outcome. Acute stroke imaging factors such as infarct volume and location have limited prognostic ability. Acute DCST diffusion changes may represent early Wallerian degeneration but pathological studies are yet to confirm this.

DCST diffusion could improve early outcome prediction, facilitating family counseling and patient selection for rehabilitation or neuroprotective trials. Imaging a common “downstream” pathophysiological mechanism like Wallerian degeneration in vivo could represent a novel therapeutic target. We used a homogeneous cohort of acute stroke patients with serial imaging to test the hypotheses that early DCST diffusion is associated with motor outcome.

Materials and Methods

Patient Selection
This was a retrospective, observational study utilizing prospective obtained data from stroke and control populations. Methods were approved by institutional research ethics board. Stroke patients from the MONITOR study (December 2002–August 2003) satisfied these inclusion criteria: (1) ischemic stroke secondary to middle...
cerebral or internal carotid artery occlusion; (2) MRI ≤6 hours from symptom onset; (3) acute DWI lesion; (4) serial imaging (12 hours/24 hours/7 days/30 days); and (5) 3-month neurological outcome including NIHSS. Controls from the VISION study[^19] satisfied these criteria: (1) TIA completely resolved in ≤24 hours; (2) DWI-negative; (3) no white matter disease; and (4) MRI ≤6 hours from symptom onset. The study databases were harvested for original images, demographics, risk factors, clinical presentations, and outcomes.

**MRI**

Stroke patient images were obtained at 5 time points: (1) baseline (≤6 hours); (2) 12±6 hours; (3) 24±6 hours; (4) 7±2 days; and (5) 30±10 days. Controls had 1 baseline MRI, DWI, apparent diffusion coefficient maps (ADC), and fluid-attenuated inversion recovery (FLAIR) images were analyzed. Images were from the same 3-T scanner (Signa; GE Medical Systems) with high performance gradients (40 mT/m; 184-μs rise time) using a standard quadrature head coil and established stroke imaging protocols[^20]. Single-shot echoplanar imaging was used for DWI images (isotropic b=0, 1000 sec/mm²; repetition time=7000 ms; echo time=96.5 ms; 320 mm field of view; 5.0-mm slice thickness; 2.0-mm gap). ADC were derived from b=0 and b=1000 DWI (Stejskal–Tanner equation).

**Quantification of DCST Signal**

Techniques were modified from previously validated methods.[^7] Computer software was designed to quantify multimodal DCST signal in a consistent and blinded fashion. Original DCST images (from cervicomedullary junction to upper midbrain) of all modalities for all patients at all time points were examined directly from the imaging database. Identifiers were removed from images, and control and stroke patients were randomized together. The posterior limb of the internal capsule was not examined because of frequent overlap with the stroke lesion. Image analysis was performed from caudal-to-cranial sections stopping at the midbrain to blind the reader to stroke side. Reviewers were also blinded to all patient data including outcome.

For each patient at each DCST level, a series of all modalities was displayed simultaneously (Figure 1). Regions of interest were drawn by the same individual according to predefined anatomic landmarks at 3 DCST levels: medullary pyramids, basis pontis, and cerebral peduncle (middle third). After the primary scorer measured 10 random patients, they and the second scorer repeated the analysis to ensure high inter-rater and intrarater reliabilities (>0.90). Bilateral regions of interest were drawn individually for DWI/ADC (automatically coregistered) and FLAIR and labeled as left or right. The program then analyzed each region of interest with outputs of area, mean signal intensity (FLAIR and DWI relative units), and mean ADC value (×10^-6 mm²/sec). Therefore, 3 values per side per slice (9–10 slices to span entire DCST) were generated and transferred to a secure database. Side of stroke was then revealed with conversion of previously labeled left or right measures to either ipsilesional or contralesional in stroke patients.

**Visual Inspection**

Two radiologists experienced in stroke imaging (M.G., M.E.) performed randomized visual inspection of all images knowing only the primary hypothesis and that some patients had stroke; they were blinded to all other factors. The radiologists scored as positive any “significantly abnormal signal in a region consistent with the DCST.” Each side of each slice was scored “yes” or “no” for increased DWI/FLAIR or decreased ADC signal. Inter-radiologist reliability was compared. Patients with ≥1 positive ipsilesional slice were considered visually positive.

**Clinical Outcome**

The primary outcome was motor function at 3 months represented by NIHSS motor subscales for upper and lower extremity (ordinal from 0–4). Motor outcomes were dichotomized: scores of 0 to 2 on both motor arm and motor leg were considered good outcome, and scores of 3 or 4 on either motor arm or leg, both motor arm and leg, or death were considered poor outcome.

**Analysis**

Four imaging variables were considered: modality (FLAIR/DWI/ADC); scan time (baseline/12 hours/24 hours/7 days/30 days); brain stem level (medulla/pons/midbrain); and lesion side (ipsilesional/contralesional). Because the number of slices per brain stem level would vary among patients (typically 2 to 3), the mean value per level was used. Our primary analysis addressed DCST signal at the cerebral peduncle because of the large convergence of descending motor fibers, proximity to the stroke, and previous DCST studies.[^7][^9][^21] ADC values were the primary measure attributable to early changes in acute stroke, quantifiable values, and evidence from previous DCST studies.[^7][^9] Because only 1 study has described contralesional DCST signal abnormalities,[^9] the ipsilesional peduncle was the primary focus. Therefore, the primary independent variable was ipsilesional mean midbrain ADC.

Box plots of all raw data were created to explore distribution, homogeneity, and screen for outliers (extreme outliers were removed). ANOVA was then performed on ipsilesional mean midbrain ADC for the good and poor outcome groups to explore differences over time. Repeated-measures ANOVA was performed to evaluate

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**Figure 1.** Computer software measurement of DCST signal. The 3 MRI modalities (FLAIR, DWI, and ADC) are displayed randomly per patient per time interval with coregistration of DWI and ADC images (A). Regions of interest (ROI) are placed over DCST regions based on predefined anatomic landmarks (B). Absolute (ADC) and relative (DWI, FLAIR) signal values are automatically generated and displayed in a labeled database, including anatomic assignment, ROI area, and mean±SD signal intensity or ADC value (not shown).
group and time interactions. Group comparisons (stroke/control and good/poor outcome) for demographics and stroke risk factors used Student t test/Mann-Whitney or \( \chi^2 \)/Fisher exact tests. Control data were used to generate normative ranges (5th–95th percentile) for ADC, DWI, and FLAIR values. Values above (FLAIR and DWI) or below (ADC) these references were considered abnormal. Subsequent \( \chi^2 \) analysis was performed to determine the sensitivity, specificity, and positive and negative predictive values of these cut-offs to predict poor outcome. The same approach examined the ability of radiologists to visually detect abnormal DCST signal and predict outcome. Pearson product–moment correlation coefficient was used for intrarater and inter-rater reliabilities. Statistical analysis used SPSS 15.0.

### Results

#### Patient Population

Twenty stroke patients (11 female) were included. Median age was 74.8 years (range, 36–93 years). Three-month NIHSS was completed in 18 surviving patients. Fifteen had good outcome, whereas 5 (including 2 deaths attributable to stroke) outcomes were poor. Controls included 18 patients (6 female) with a median age of 63.4 years (range, 40–85 years). Demographics and historical stroke variables were comparable between groups aside from older age (\( P=0.04 \)) and higher initial systolic blood pressure (164 vs 138 mm Hg; \( P=0.007 \)) in stroke cases (Table). Within the stroke group, good and poor outcome subgroups were also comparable aside from an increased history of previous TIA/stroke or cardiovascular disease (40% vs 7%; \( P=0.03 \)) in the poor outcome group.

A total of 294 complete (DWI/ADC/FLAIR) images were available, representing 83% of the 354 possible. Thirty-five images were missing: 5 (9%) control and 30 (10%) stroke patients. Another 25 images were of inadequate quality (92% FLAIR). For our primary independent variable (mean peduncle ADC), 95% of scans were available.

#### DCST Signal

Abnormal ipsilesional DCST signal was frequently detected (Figure 2). The software method demonstrated high intrarater (\( r=0.991 \)) and inter-rater reliabilities (\( r=0.990 \)). Variance in ADC peduncle measurements was far less than both DWI and FLAIR in stroke and control patients (mean ipsilesional peduncle in stroke cases at 7 days: FLAIR, 342.89±102.68; DWI, 1007.80±380.25; ADC, 691.34±63.59 mm²/sec). Because pontine (crossing cerebellar fibers) and medullary (small tissue volumes) measures could potentially confound the analysis, we focused on ipsilesional peduncle ADC values.

Time-dependent changes in mean peduncle ADC were observed in the poor outcome group, with decreased values at all time points to 7 days and a return toward baseline at 30 days (Figure 3). ANOVA demonstrated no difference in mean peduncle ADC across time points in the good outcome group (\( F=0.39; \( P=0.81 \)), but there was significant change in the poor outcome group (\( F=3.36; \( P=0.04 \)). On post hoc analysis, decreases in peduncle ADC in the poor outcome group were significant at 7 days (−139.41 mm²/sec; \( P=0.009 \)) but not at the earlier time points of 12 hours (−96.12 mm²/sec; \( P=0.07 \)) and 24 hours (−93.91 mm²/sec; \( P=0.08 \)). Repeated-measures ANOVA of patients with complete serial data (good outcome, n=8; poor outcome, n=2) demonstrated an interaction between outcome and time (\( F=5.13; \( P=0.003 \)).

Control bilateral peduncle ADC values at baseline were normally distributed. Control peduncle ADC range (5th–95th percentile) was 668 to 845×10⁻⁶ mm²/sec (mean 754±53×10⁻⁶ mm²/sec) and comparable to ipsilesional baseline in stroke patients (732±73×10⁻⁶ mm²/sec; \( P=0.15 \)). Mean peduncle ADC values in the poor outcome group were less than in controls at 12 hours (681±68; \( P=0.02 \)), 24 hours (683±111; \( P=0.03 \)), and 7 days (638±73; \( P<0.001 \)) but were not different at baseline and 30 days (\( P>0.15 \)). Because the maximal decrease in poor outcome ADC was seen at day 7 (638±73 vs 712±48×10⁻⁶ mm²/sec; \( P=0.02 \)), this time point was utilized for further 2×2 analysis. At day 7, 4 of 5 patients with poor outcome and only 1 of 13 with good outcome had peduncle ADC values

### Table. Demographic and Baseline Data for Cases and Controls

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Cases</th>
<th>( P )</th>
<th>Stroke Patients</th>
<th>Good Outcome</th>
<th>Poor Outcome</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of patients</td>
<td>18</td>
<td>20</td>
<td></td>
<td></td>
<td>15</td>
<td>5</td>
<td></td>
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<tr>
<td>Age, yr</td>
<td>63 (41–85)</td>
<td>75 (37–94)</td>
<td>0.038</td>
<td>72 (36.6–93.9)</td>
<td>82.1 (70.1–85)</td>
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<tr>
<td>Gender</td>
<td>6 female</td>
<td>11 female</td>
<td>0.522</td>
<td>8 female</td>
<td>3 female</td>
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<tr>
<td>NIHSS baseline</td>
<td>10.6±7.2</td>
<td>8.8±5.6</td>
<td>0.126</td>
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<td></td>
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<tr>
<td>NIHSS 3 mo</td>
<td>2.7±3.3</td>
<td>1.5±1.9</td>
<td>0.006</td>
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<td></td>
<td></td>
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<tr>
<td>Initial systole, mm Hg</td>
<td>137.7 (96–220)</td>
<td>163.7 (121–227)</td>
<td>0.007</td>
<td>164.6 (121–227)</td>
<td>155.6 (130–180)</td>
<td>0.996</td>
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<tr>
<td>Initial diastole, mm Hg</td>
<td>75.9 (50–100)</td>
<td>87.3 (30–114)</td>
<td>0.410</td>
<td>87.1 (30–114)</td>
<td>88 (72–110)</td>
<td>0.442</td>
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<td>Previous TIA or stroke</td>
<td>4 (22%)</td>
<td>3 (15%)</td>
<td>0.687</td>
<td>1 (7%)</td>
<td>2 (40%)</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (33%)</td>
<td>11 (55%)</td>
<td>0.210</td>
<td>8 (53%)</td>
<td>3 (60%)</td>
<td>1.000</td>
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<tr>
<td>Cardiovascular disease</td>
<td>4 (22%)</td>
<td>3 (15%)</td>
<td>0.687</td>
<td>1 (7%)</td>
<td>2 (40%)</td>
<td>0.032</td>
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<tr>
<td>Diabetes</td>
<td>0</td>
<td>3 (15%)</td>
<td>0.232</td>
<td>2 (13%)</td>
<td>1 (20%)</td>
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<tr>
<td>Smoking</td>
<td>3 (17%)</td>
<td>4 (20%)</td>
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<td>3 (20%)</td>
<td>1 (20%)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>5 (28%)</td>
<td>5 (25%)</td>
<td>1.000</td>
<td>3 (20%)</td>
<td>2 (40%)</td>
<td>0.560</td>
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</tr>
</tbody>
</table>

NIHSS (total±SD). Age and blood pressures are mean (range).
below the 5th percentile. The \( \chi^2 \) analysis supported the association between day 7 peduncle ADC and poor outcome \((P=0.008)\). Decreased day 7 peduncle ADC was 80% sensitive and 92% specific (positive predictive value, 0.80; negative predictive value, 0.92) to predict poor motor outcome.

Visual Inspection of DCST Signal

Inter-radiologist agreement for visual DCST scoring of all modalities, brain stem levels, and patient groups was excellent, with >94% of images scored the same \((P<0.001)\). For ipsilesional cerebral peduncle DWI or ADC, 69 of 78 scans (88%) were scored the same \((P<0.001)\). Ipsilesional day 7 peduncle DWI and ADC were used to compare the software method to visual inspection. Radiologists detected decreased ADC or increased DWI in the peduncle of 4 of 5 patients with poor outcome and only 1 of 13 with good outcome. Therefore, the accuracy of visual inspection was comparable to the software method, with suggested sensitivity of 80%, specificity of 92% (predictive value, 0.80; negative predictive value, 0.92), and a significant association with poor outcome \((P=0.008)\).

Contrallesional DCST Diffusion Signal

Examples of late diffusion changes in the contrallesional DCST were discovered. The patient in Figure 2 had contrallesional peduncle diffusion signal develop at day 30 (Figure 2D) and had poor motor outcome. Both radiologists visually detected this contrallesional signal plus single examples in 2 other patients. No overall differences were observed in contrallesional peduncle ADC, DWI, or FLAIR across time or between outcome groups (data not shown).

Discussion

This study contributes adult data to multiple pediatric studies,\(^7\text{-}9,11,13,21,22\) adult case reports,\(^11,12,22\) and diffusion tensor imaging studies,\(^14\) suggesting an association between DCST diffusion and motor outcome. An improved ability to acutely predict stroke outcomes can assist physicians and families in early treatment decisions. Improved early prognostication could also facilitate patient selection for clinical trials and rehabilitation programs. That DCST signal is readily observed on routine stroke imaging suggests these advantages could be realized in routine stroke management.

Our results provide the first direct comparison of DWI, ADC, and FLAIR DCST changes over time. Variability was substantially less for ADC. Pediatric studies suggest DWI changes may be more apparent visually,\(^7\) but our visual analysis suggests comparable accuracy of ADC. DWI measures may also be contaminated by “T2 shine-through,”\(^23\) which was expected to be more prominent in adults because of brain stem small-vessel disease. Combined with quantifiable units of measurement and routine availability, we suggest that ADC is the modality of choice for DCST analysis. Potential limitations of ADC include artifact from neighboring cerebrospinal fluid. Diffusion tensor imaging is less clinically available and our findings appear complimentary to previous studies.\(^14,24\)

Previous studies suggest visual detection of DCST signal is feasible\(^7\text{-}9,11,13,21,22\) but is only 61% to 77% sensitive compared to software methods.\(^7,9\) That our results demonstrate comparable predictive abilities suggests several possibilities. Our new software method could be inferior, although this seems unlikely because it is based on the same principles with several improvements, including coregistration of images and independent analysis of ipsilesional and contrallesional DCST. It also seems improbable that our radiologists were more skilled, although previous studies used pediatric neuroradiologists with less stroke experience. That visual detection appears accurate suggests the DCST should be routinely evaluated in acute stroke.
It is surprising that DCST abnormalities are well-described in neonatal and childhood stroke but there are only anecdotal adult reports. Pediatric studies suggested differences in young brains (myelination, relative water content) as an explanation. However, our results suggest DCST signal may be equally informative in adults, consistent with results in older adolescents. Differences in MRI field strength or the adult DCST may account for the lack of previous observations, including the presence of brain stem small-vessel disease.

Serial imaging permitted examination of the evolution of DCST changes over time. Decreases in ADC were evident within 12 hours in poor outcome patients. Earlier detection would have even greater clinical utility and might be feasible with methodological refinements. Pediatric studies support this evolution over time but suffer from random imaging intervals. Taken together, these studies suggest that DCST diffusion changes evolve in a similar but delayed fashion compared to the infarct itself. That DCST ADC values were maximally decreased at 7 days and returned toward baseline by 30 days is consistent with the well-described evolution of diffusion signal in hemispheric infarcts. Interestingly, MR signal evolution in brain stem infarcts has been described as delayed. The protracted time course of DCST diffusion changes is consistent with an evolving pathological process, such as Wallerian degeneration.

Wallerian degeneration is a pathological series of events common to brain injury processes, including stroke. Pathophysiological complexity in the central nervous system is increasingly understood. Our results support previous suggestions that acute DCST signal represents early Wallerian degeneration.
degeneration, although acute pathological studies confirming this are required. Therefore, early DCST signal may represent a quantifiable, in vivo marker of evolving stroke-induced corticospinal damage. An ability to image a “downstream” pathological process evolving days after stroke could represent a novel therapeutic target. Changes in metabolic parameters on MR spectroscopy have been suggested as similar ongoing poststroke pathological processes. An ability to directly image such processes in stroke could serve future neuroprotective strategies.

Conclusion
We provide the first (to our knowledge) systematic evaluation of acute adult stroke DCST imaging. Our results confirm the existence of DCST diffusion abnormalities and correlation with motor outcome. We validate a simple software method for DCST diffusion quantification while providing evidence that visual inspection is also accurate.

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Disclosures
None.

References
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