Corticospinal Tract Pre-Wallerian Degeneration
A Novel Outcome Predictor for Pediatric Stroke on Acute MRI
Trish Domi, MA; Gabrielle deVeber, MD; Manohar Shroff, MD; Elizabeth Kouzmitcheva, BSc; Daune L. MacGregor, MD; Adam Kirton, MD

Background and Purpose—In neonatal arterial ischemic stroke, pre-Wallerian degeneration in descending corticospinal tracts (DCST) on diffusion MRI (DWI) predicts poor outcome. This signal has not been studied in older children.

Methods—A consecutive arterial ischemic stroke cohort (1 month to 18 years) with acute DWI and >12 months of follow-up were enrolled (SickKids Children’s Stroke Program). DCST-DWI variables were quantified with a validated software technique and correlations to the Pediatric Stroke Outcome Measure were sought.

Results—Abnormal DCST-DWI signal was detected in 20 of 29 children (69%), with 85% having motor deficits on Pediatric Stroke Outcome Measure. DCST variables correlated with hemiparesis included: (1) any abnormal signal within the course of the DCST; (2) midbrain location; (3) percentage of peduncle; (4) vertical length; and (5) relative volume affected (all $P<0.003$). Unexpectedly, abnormal DWI signal was detected in the contralesional DCST in 7 children, all with severe hemiparesis. DCST signal abnormality increased over time, outlasted infarct DWI changes, and was difficult to appreciate on visual inspection.

Conclusions—DCST-DWI signal is an acute predictor of motor outcome in childhood stroke and can help guide management. Previously unrecognized contralesional DCST signal predicts severe hemiparesis. (Stroke. 2009;40:780-787.)

Key Words: childhood ▪ diffusion weighted imaging ▪ outcome ▪ stroke

Arterial ischemic stroke (AIS) is an important cause of acquired neurological morbidity in children, with motor deficits being most common.1–3 Most events involve the middle cerebral artery territory, often resulting in injury to supratentorial motor systems. The caudally directed motor fiber pathways of the descending corticospinal tracts (DCST) are well-defined on MRI at the posterior limb of the internal capsule, cerebral peduncle, basis pontis, and medullary pyramid.

Prediction of neurological outcome during the acute phase of stroke would improve prognostication for families and facilitate selection of patients for therapeutic interventions and trials. Stroke volume and location have limited ability to predict long-term motor outcome.4,5 Acute diffusion-weighted MRI (DWI) change in the DCST (DCST-DWI), termed pre-Wallerian degeneration (WD), has been recognized and correlated with outcome in acute neonatal AIS.6–8

We recently reported and validated a novel method of DCST-DWI signal measurement in acute neonatal stroke.8 Isolated cases of abnormal DCST-DWI signal have been reported in non-neonatal AIS,9,10,22 but comparison to those without using a standardized outcome measure has not been described.

We used a validated software-assisted technique8 to quantify DCST-DWI changes in consecutive children with acute AIS and hypothesized that the extent of such changes would predict poor motor outcome.

Patients and Methods

Patient Selection
Patients were identified through the Children’s Stroke Program at the Hospital for Sick Children, Toronto. Inclusion criteria were: (1) age >28 days to 18 years; (2) acute unilateral AIS involving the middle cerebral artery territory; (3) DWI within 14 days of clinical event; (4) no evidence of additional neurological abnormality; and (5) neurological follow-up with the Pediatric Stroke Outcome Measure11 at >12 months.

A consecutive cohort with diagnoses between 1999 (DWI available) and 2005 was screened for inclusion. Data on demographics, clinical presentations, investigations for risk factors, and treatments were obtained from health records and structured stroke clinic interviews. Motor outcomes were classified using the validated Pediatric Stroke Outcome Measure2,11 and expressed as either good (mild or no hemiparesis with normal function) or poor (moderate to severe hemiparesis). The study was approved by the institutional Research Ethics Boards.
A previously described and validated technique 8 using Image J freeware from the NIH (http://rsb.info.nih.gov/ij/) was used to quantify abnormal DCST-DWI signal (Figure 1). Briefly, a thresholding tool that assigns each pixel a value of 1 to 255 degrees of brightness was applied to each DCST-containing slice. Abnormal DCST-DWI signal was present when ≥10 pixels within the DCST were brighter compared to the contralateral side. The same blinded investigator (E.K.) scored all images. MR studies were performed with a 1.5-Tesla system (Signa; GE Medical Systems). Axial DWI included single-shot spin-echo echo-planar sequences, (repetition time/echo time [TR/TE] = 10 000/100, 20 cm field of view, 128 × 192 matrix, 5-mm thickness, no gap; b = 1000 sec/mm²).

Anatomically defined DCST locations evaluated included the posterior limb of the internal capsule, midbrain, pons, and medulla. Measures of abnormal DCST-DWI signal were defined as: (1) any positive slice within the DCST at the posterior limb of the internal capsule, midbrain, pons, or medulla; (2) percentage peduncle (%): number of abnormal DCST pixels divided into total peduncle area as measured by freehand and area calculator tools; (3) peduncle sector: abnormal DCST pixels falling within medial, middle, or lateral thirds (sectors) as defined by Image J drawing tool; (4) vertical length of DCST (mm): number of positive slices multiplied by the slice thickness (5 mm); (5) relative volume of DCST affected (%): total volume of abnormal DCST signal divided by total brain volume as determined by threshold and area calculator tools; and (6) relative volume of infarct (%): relative infarct volume was calculated using the threshold tool by dividing the total infarct areas on each affected slice into the total brain volume.

WD Measures
Follow-up (>6 months) T2-weighted brain stem sections were analyzed using a previously described technique. 12 Areas of each DCST portion were measured and an asymmetry index (AI) to quantify chronic DCST WD was calculated: AI = AU−AA/ AU+ AA, where AA and AU are the area of affected and unaffected sides, respectively.

Visual Inspection
An experienced neuroradiologist (M.S.) blinded to stroke side and outcome visually scored each side of all DCST DWI slices as positive if hyperintense signal was seen. Sensitivity, specificity, and positive and negative predictive values for visual inspection were determined taking the computer-assisted method as the gold standard.

Statistical Analysis
For descriptive purposes, nonparametric tests for dichotomous and continuous variables without normal distributions were compared between outcome groups using the Fisher exact and Mann–Whitney tests, respectively. The association between DCST-DWI measures and motor outcome was sought using the Phi coefficient (φ) and Spearman r. Simple logistic regression was performed to determine the independent association of DCST signal (presence/absence) with motor outcome as well as WD (defined as AI >5% between peduncles). A Bonferroni correction for multiple comparisons was applied. Analyses were performed using SAS 9.0.

Results

Patient Population
From January 1, 1999 to September 1, 2005, 96 children beyond 1 month of age with acute, unilateral, middle cerebral artery AIS were identified. Patients were excluded because of no acute DWI (n=43) available, other incomplete imaging (n=21), or inadequate follow-up (n=3). The final cohort included 29 patients (18 male, 11 female) with a median age 6±4.5 years with presentations and risk factors typical for childhood AIS (Table 1).

Most patients presented with focal neurological deficits or seizures. Risk factors included arteriopathy 45% (13/29) (postvaricella angiopathy, vasculitis, and dissection) and congenital heart disease 28% (8/29). AIS was isolated to the middle cerebral artery territory 79% (23/29), left-sided 69% (20/29), and involved cortex (7), subcortical structures (13), or both (9). No non-middle cerebral artery infarcts potentially affecting the DCST at the level of cerebral peduncles were included. Initial MR was completed within 24 hours in 7 of 29 (24%), and between days 2 to 10 in the remainder. Children with good (13) and poor (16) outcome were assessed at similar age (P=0.63) and duration of follow-up (3.12 vs 2.78 years; P=0.62) (Table 2).

Ipsilateral (Ipsilesional) DCST-DWI Signal Abnormalities
Abnormal DCST-DWI signal was detected in 20 of 29 (69%) children. Fifteen (75%) of these had poor motor outcome (moderate to severe hemiparesis) and 5 had good motor outcome, including 3 with mild hemiparesis. In the 9 patients with no DCST signal abnormalities, all but 1 had good motor outcome (Table 2). Abnormal DCST signal was consistently...
detected in the DCST ipsilateral to the stroke (19/20, 95%; Figure 1).

Several DCST-DWI measures were strongly associated with motor outcome and are listed here.

1. Any DCST signal. The presence of any abnormal DCST-DWI signal was highly correlated with motor outcome ($r=0.594; P<0.001$) and found in 94% with poor outcome compared to 38% with good outcome ($P<0.003$).

2. Any midbrain. Abnormal signal in the midbrain correlated highly with poor outcome ($r=0.791; P<0.001$) and was detected more often in children with moderate to severe hemiparesis (94% vs 15%; $P<0.001$). Abnormal pons signal also correlated with poor outcome ($r=0.56; P<0.003$). Associations were not seen at other levels of the DCST.

3. Percentage peduncle. The percentage of cerebral peduncle affected was increased in children with poor outcome (median 13±2.2% vs 0.0±5.4%; $P=0.001$) and correlated with outcome (Spearman $r=0.603; P<0.001$).

4. Vertical length of DCST. Total length of DCST affected was increased in children with poor outcome (median 22.5 mm vs 0.00 mm; $P<0.001$) and highly correlated with outcome (Spearman $r=0.645; P<0.001$).

5. Relative volume of DCST. Volume of affected DCST differed significantly between children with good and poor outcome (0.01% vs 0.06%; $P=0.003$). The relative volume of infarction was minimally associated with outcome (2.21%±2.8 vs 6.62%±6.1; $P<0.02$). No difference between involvements of the medial, middle, or lateral thirds of the peduncle was detected.

Ipsilateral DCST-DWI Signal Abnormality Changes Over Time
Nine patients had multiple DWI scans within 14 days. Ipsilateral DCST signal increased over time in 6 patients, 3 of

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<th>Table 1. Patient Characteristics</th>
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BG/PLIC indicates basal ganglia/Posterior limb internal capsule; CATH, catheterization (<72 hours); CHD, congenital heart disease; DIS, dissection; ENC, encephalitis; F, frontal; FEAN, iron deficiency anemia; HMAL, hematologic malignancy; IDIO, idiopathic; LOC, loss of consciousness; LVFD, left visual field deficit; m, months; MEN, meningitis; MMD, moyamoya disease; O, occipital; P, parietal; PVAR, Postvaricella angiopathy; SDU, speech deficit unspecified; T, temporal; TH, thalamus; VAS, vasculitis; y, years.
whom demonstrated mildly increased infarct volume (Figure 2). One patient demonstrated strong DCST-DWI signal abnormality on follow-up DWI after the infarct diffusion signal had normalized (Figure 3).

Follow-up imaging (3 months to 6.5 years) was available in 28 of 29 patients who were assessed for degree of WD (expressed as brain stem AI). Patients with good outcome had an average AI of 1.38 ± 1.7 vs 9.55 ± 6.1% for those with poor outcome (P = 0.05). The AI was strongly associated with motor outcome (r = 0.747; P = 0.001). Furthermore, the presence DCST signal was predictive of the eventual presence of WD (AI >5%). Thirteen patients (65%) with DCST signal abnormalities went on to have measurable WD (P = 0.02), 12 of whom had abnormal outcome.

**Visual Inspection vs Computer-Assisted Thresholding**
A total of 572 DWI slices were scored by both the computer-assisted thresholding method and blinded visual inspection, 109 (19%) of which demonstrated abnormal DCST signal. Using the computer-assisted thresholding scoring as the gold standard.

### Table 2. DCST-DWI Characteristics and Motor Outcome in Childhood AIS

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<tr>
<th>Group</th>
<th>Patient</th>
<th>Any DCST Signal: Ipsi/Contra/Both PLIC</th>
<th>%Ped Pons</th>
<th>Medulla</th>
<th>Length, mm</th>
<th>Volume DCST</th>
<th>Volume Infarct</th>
<th>Follow-Up, y</th>
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<th>Motor Outcome</th>
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<td>Pos Ipsi Pos 15.54 Neg Neg 20.00 0.05 3.94 4.61 5.92 NORM</td>
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<td>Neg NA Neg 0.00 Neg Neg 0.00 0.00 5.47 1.48 0.67 NORM</td>
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<td>Neg NA Neg 0.00 Neg Neg 0.00 0.00 9.78 1.62 1.57 NORM</td>
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<td>Pos Ipsi Pos 0.00 Neg Neg 5.00 0.01 3.19 1.48 0.4 NORM</td>
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<td>Pos Ipsi Pos 0.00 Neg Neg 5.00 0.01 0.96 6.22 2.36 MILD</td>
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<td>Pos Ipsi Pos 0.00 Neg Neg 5.00 0.01 1.12 4.79 6.17 MILD</td>
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<td>9</td>
<td>Pos Ipsi Pos 0.00 Neg Pos 15.00 0.05 5.60 4.93 0.26 MILD</td>
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<td>10</td>
<td>Neg NA Neg 0.00 Neg Neg 0.00 0.00 2.67 5.03 0.51 MILD</td>
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<td>11</td>
<td>Neg NA Neg 0.00 Neg Neg 0.00 0.00 0.42 1.27 3.63 MILD</td>
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<td>12</td>
<td>Neg NA Neg 0.00 Neg Neg 0.00 0.00 0.11 3.28 0.43 MILD</td>
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<td>13</td>
<td>Pos Ipsi Neg 13.09 Neg Neg 5.00 0.01 0.23 1.51 0.16 MILD</td>
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**Prop/ Mean** 38% 31% 2.20 0% 8% 3.85 0.01 2.22 3.12 8% 1.38

**Significance** 0.003 0.264 0.001 0.003 0.672 <0.001 0.008 0.017 0.621 0.001

NA indicates not applicable; Prop, proportion.
standard, visual inspection of DCST-DWI signal changes had a sensitivity of only 61% and positive predictive value of 58%. Visual inspection demonstrated good specificity (91%) and a negative predictive value of 90%.

Contralesional DCST-DWI Signal Abnormalities

Unexpectedly, abnormalities of the contralesional DCST were detected in 7 children (Figure 4). Six of these (86%) also demonstrated ipsilesional DCST-DWI signal abnormality. All patients with contralesional DCST-DWI signal had severe motor deficits at follow-up ($P=0.008$). Contralesional DCST signal abnormalities continued to evolve over time in 2 patients with serial MRI. One patient with no DCST-DWI signal abnormality at 3 days had contralesional DCST-DWI abnormalities on day 14 with increased infarct size (supplemental Figure I, available online at http://stroke.ahajournals.org).

Discussion

We demonstrate the ability of acute DWI changes within the DCST to predict poor motor outcome in childhood AIS. Prognosticating outcome in acute childhood stroke is of crucial importance to families and essential in selecting patients requiring therapeutic interventions. With advances in our understanding of plastic reorganization mechanisms and the first randomized trials of rehabilitation therapies emerging, prediction of outcome will enhance program selection of patients for early referral for rehabilitation and potentially reduce morbidity. Hemiparesis is the most common deficit after stroke in childhood and its severity correlates with functional disability and reduced quality of life. With 85% of affected patients in our cohort having abnormal outcomes, DCST signal abnormalities appears to be a powerful predictor of persisting hemiparesis in pediatric stroke. These results contribute data from older children to recent studies reporting the value of abnormal DCST-DWI signal in predicting outcome in neonatal AIS.

Detection of DWI signal in the contralesional DCST and its significant correlation with severe hemiparesis was an unanticipated finding. Our comparative measurement technique assumes the nonstroke side of the DCST is normal. Therefore, the detection of contralesional signal was actually inherently minimized, strengthening the assertion that the signal is real. Contralesional increased DCST-DWI abnormalities has likely been previously missed or underestimated by visual inspection alone, and may be more accurately quantified with refined measurement techniques. Current technical limitations of our DWI and ADC approaches...
prevent accurate measurement of diffusion signal in each individual DCST, though we are exploring modifications to facilitate this.

The origin of the contralesional signal is unknown. One hypothesis is that it represents acute metabolic changes in the axons of upper motor neurons from the unlesioned hemisphere newly “recruited into service” to provide motor input to the affected hand. This theory is supported by transcranial magnetic stimulation studies of congenital hemiplegies showing chronic T2 MR DCST signal associated with ipsilateral projections from the contralesional hemisphere. Functional MRI studies showing acute contralesional motor cortex activation in stroke, and the strong correlation with motor outcome. Supratentorial influence on ipsilateral hand motor function may involve uncrossed corticospinal tract neurons or other pathways such as corticoreticulospinal or corticopropriospinal systems. In children with congenital hemiplegia, ipsilateral connections are enhanced. In adults with chronic stroke, their relative role is unclear although they have been associated with worse motor outcome. Detection of ipsilateral pathways using functional MRI or transcranial magnetic stimulation could validate this hypothesis.

Despite a much greater experience with DWI in acute stroke, only isolated adult cases of DCST-DWI signal abnormalities have been described. In contrast, DCST-DWI signal increase is relatively common following acute injury to the neonatal brain. It has been suggested that this difference may relate to age-dependent differences in brain maturation such as increased water content or reduced myelination. However, the current study is the first to complete the age range from early infancy to early adulthood in assessing DCST-DWI signal and shows frequent occurrence that appears independent of age. This suggests that careful evaluation of the DCST in adult stroke, perhaps using a software-assisted system, may uncover previously unrecognized and valuable DCST-DWI changes.

WD is the term used to describe secondary degeneration of axons and their myelin sheaths from numerous causes, including stroke. As the axon is dependent on the cell body for survival, WD changes occur distal to the neuronal injury. In chronic pediatric stroke, WD manifesting as focal DCST atrophy is well-described and correlates with hemiparesis severity. However, little is known regarding how the earliest phases of WD might be represented on neuroimaging. The histopathologic changes of WD within the first 4 weeks (stage 1) are characterized by physical changes of axonal degeneration without substantial biochemical changes in the myelin. Our results suggest that DWI may demonstrate these early changes in the white matter that are not otherwise detectable on conventional MR imaging. In our series, all but 1 of the 15 of 16 patients with abnormal outcome and DCST signal abnormalities had follow-up imaging. That all patients had some degree of chronic asymmetry of the peduncles, combined with the strong correlation of both with poor motor outcome, suggests that acute DCST-DWI signal and chronic atrophy are different stages of the same WD process. Acute pathological studies of the DCST in fatal strokes could corroborate this theory.

Our objective in breaking-down the DCST DWI signal into different components was to appreciate which imaging features might be most important in predicting motor outcome. We believe it is important to consider each of these aspects (length, volume, and amount of peduncle) because they may all be particularly important when evaluating stroke scans by visual inspection alone. Our findings suggest that the signal abnormalities found at the level of the midbrain in the DCST correlate best with poor motor outcome. This finding may reflect the proximity of the midbrain to the infarct or the dense convergence of DCST fibers here. The peduncle may also be the most clinically relevant location for assessment because chronic WD is most evident here, visual detection of signal alone in this area can predict outcome, and all previous studies have focused on this location. We previously showed that DWI signal in the middle third of the peduncle was most highly correlated with hemiparesis in neonates, consistent with the anatomic location of the DCST. However, we also found that DWI signal often extends beyond the expected borders of the DCST into adjacent brain stem. In the current study, dividing the peduncle into thirds failed to increase the predictive ability, suggesting that the same “dispersement” of DWI-DCST signal into neighboring brain stem may limit any finer spatial resolution of our technique.

Previous studies have used apparent diffusion coefficient (ADC) maps to quantify DCST diffusion. However, results have been inconsistent and correlation of ADC with outcome was not as strong as with DWI signal. Difficulties in measuring very small areas of the brain stem, artificial distortion of ADC maps by adjacent cerebrospinal fluid, or other factors may underlie these inconsistencies. Given that the restriction of diffusion has been confirmed by previous studies, the ease of recognizing DWI signal on visual inspection, and the strong associations demonstrated in the current study, DWI appears to be advantageous over ADC for the detection of acute DCST changes in stroke. However, further refinement of ADC measures may be useful in combination with DWI to better understand DCST signal evolution over time in the same manner as they are currently applied in combination to age infarcts.

Emergence of DCST-DWI signal from the time of clinical event can be documented, but descriptions of evolution over time have been limited. We observed examples of increased ipsilesional and contralesional DCST-DWI signal over time, often without concurrent increase in infarct diffusion signal. This suggests that the cellular processes affecting the diffusion of water in the DCST (ie, pre-WD) are different from those within the infarct itself. Because this signal can become more evident over the subacute timeframe, it may be missed with conventional stroke neuroimaging protocols when re-imaging with DWI is not routinely performed after the acute period.

In the current study, visual inspection was less sensitive than the automated method, particularly for contralesional DCST signal. Nearly all previous studies of DCST-DWI have relied on visual inspection alone. In our studies, visual inspection had high specificity in both neonates (93%) and
children (91%) but was insensitive (77% and 61%, respectively), suggesting potential clinical utility of the software system.8

Infarct location and volume have some ability to predict outcome in childhood stroke.2-26,28 However, the prediction of outcome from smaller infarcts has been challenging.8 As in neonatal stroke,8 we demonstrate here that DWI infarct volume is less predictive than the volume of affected DCST. This suggests that such “function-specific” imaging may provide the most accurate prediction of particular outcomes. DCST tractography with diffusion tensor imaging may share a similar potential but technological requirements limit its availability, and diffusion tensor imaging utility in acute stroke remains to be established.27

There are several potential limitations to our study. We included a wide range of age at stroke from early infancy to adolescence during which stroke outcomes may vary. However, we found a positive effect despite this. The long duration of follow-up (median, 2.85; range, 1.01–6.53 years) likely factors in differences in plasticity, which is generally believed to take place maximally in the initial year after stroke. Finally, the most striking divergence in plasticity is likely neonates vs older infants and children. For this reason we excluded neonates from this series.

The presence of DCST-DWI signal was observed in 5 children with good outcome. This is not surprising because factors including good bilateral representation of motor function or other factors may have enabled an improved recovery. However, only 1 child with severe outcome had no DCST signal (patient 17). The absence of signal may be explained by our observation that the signal appears to evolve over time. This patient was imaged relatively early (day 2) and had a very small infarct, which may have been factors. These findings do not diminish the important association of signal presence with poor outcome and WD. Although other factors could explain variability in motor outcomes and in signal, the finding of this association has valuable clinical relevance.

Finally, an important limitation of our study is the issue of small sample size. A larger sample may have increased the power of our findings and enabled testing of a greater number of predictors while controlling other variables (etiologicology of stroke, age, location).

Equipoise in the acute treatment of pediatric stroke is highlighted by consensus guidelines that disagree on pharmacological interventions,28 whereas neuroprotective strategies are only supportive and the use of thrombolytic therapies are unstudied.29 Selecting patients at high risk will be essential in upcoming randomized trials of pediatric stroke therapies and early and accurate outcome predictors including DCST-DWI signal will be critical in weighing the relative risks and benefits of candidate therapies.

DCST-DWI signal abnormalities predicts hemiparesis in childhood AIS. Signal detected by visual inspection alone is useful and should be sought in acute stroke patients. Additional quantification by a simple, computer-assisted technique applicable to standard acute imaging adds predictive power. The presence of contralateral abnormal DCST-DWI signal is a novel and unexplained finding that appears to portend the worst motor outcome. Recognition of DCST-DWI signal abnormalities facilitates acute prognostication and can help guide the management of stroke in children.

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Disclosures
None.

References


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