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Patterns of structural reorganization of the corticospinal tract in children with Sturge-Weber syndrome

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Abstract

Background—Reorganization of the corticospinal tract (CST) after early damage can limit motor deficit. In this study, we explored patterns of structural CST reorganization in children with Sturge-Weber syndrome.

Methods—Five children (age 1.5–7 years) with motor deficit due to unilateral Sturge-Weber syndrome were studied prospectively and longitudinally (1–2 years follow-up). CST segments belonging to hand and leg movements were separated, and their volume was measured by diffusion tensor imaging (DTI) tractography using a recently validated method. CST segmental volumes were normalized and compared between the SWS children and age-matched healthy controls. Volume changes during follow-up were also compared to clinical motor symptoms.

Results—In the SWS children, hand-related (but not leg-related) CST volumes were consistently decreased in the affected cerebral hemisphere at baseline. At follow-up, two distinct patterns of hand CST volume changes emerged: (i) Two children with extensive frontal lobe damage showed a CST volume decrease in the lesional hemisphere and a concomitant increase in the non-lesional (contralateral) hemisphere. These children developed good hand grasp but no fine motor skills. (ii) The three other children, with relative sparing of the frontal lobe, showed an interval increase of the normalized hand CST volume in the affected hemisphere; these children showed no gross motor deficit at follow-up.

Conclusions—DTI tractography can detect differential abnormalities in the hand CST segment both ipsi- and contralateral to the lesion. Interval increase in the CST hand segment suggests

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structural reorganization, whose pattern may determine clinical motor outcome and could guide strategies for early motor intervention.

Keywords

Sturge-Weber syndrome; corticospinal tract; motor deficit; reorganization; diffusion tensor imaging; tractography; longitudinal study

INTRODUCTION

The corticospinal tract (CST) is one of the most important pathways of the brain, connecting the motor cortex to the spinal cord, enabling voluntary motor control of the limbs. About 80-90% of CST fibers cross to the contralateral side in the medulla and exert motor control of the contralateral limbs, while some fibers, especially those related to the trunk and proximal upper extremity motor functions, remain uncrossed.^{1,2} Although the normal anatomy of the CST is well studied, we have less knowledge about its structural development and reorganization following brain injury. According to data obtained using transcranial magnetic stimulation (TMS) in patients with unilateral CST injury, the brain can utilize several different compensatory strategies to restore motor functions.³ One of these mechanisms involves the ipsilateral CST projections that can take over control of the paretic limbs to a certain extent.^{4,5} If a unilateral CST injury occurs during early life, the ipsilateral projections may remain permanent instead of being eliminated.^{4,5} If CST injury is inflicted at an older age, e.g., in adult stroke patients, the compensatory recruitment of remaining (although limited) ipsilateral CST projections can occur.⁵ Occasional recovery of the affected CST has also been well documented.³

Our knowledge about the CST has been expanded by radiographic information provided by diffusion tensor imaging (DTI). DTI enables the *in vivo* study of neural tracts based on water diffusion along the axons.⁶⁻⁸ While DTI has been widely used to study the anatomy and reorganization of the CST after injury, the current techniques mainly investigate the CST as a whole, disregarding possible differences in the segments related to the upper vs. lower limb motor control. Our group has recently developed and validated a novel DTI approach to separate and quantify function-specific segments, associated with hand vs. leg vs. face movements, of the CST.⁹⁻¹² In the present longitudinal study, we utilized this approach in a small pediatric population with early unilateral brain injury and motor deficit due to Sturge-Weber syndrome (SWS). SWS is characterized by facial port-wine birthmarks and leptomeningeal vascular malformation.¹³ Clinical symptoms, including motor deficit, cognitive decline and seizures, commonly manifest in the first year of life.¹⁴ As the leptomeningeal involvement and underlying brain damage is limited to one hemisphere in 85% of the cases, SWS is an excellent clinical model for studying reorganization of the brain, including the CST, after an early (often ongoing) postnatal unilateral brain injury.^{15,16} In this study, we hypothesized differential changes in the CST segments associated with hand vs. leg motor control, and also looked for patterns of structural reorganization and their relation to clinical symptoms.

MATERIALS AND METHODS

Study subjects

Five children (3 boys, 2 girls) with unilateral SWS and some degree of motor dysfunction, and 24 control children were selected for the study. All SWS children participated in a prospective, longitudinal clinical and neuroimaging study of children with SWS approved by the Wayne State University Human Investigations Committee (WSU HIC). Parents signed the Informed Consent Form. For each patient, MR scans were acquired at two time points, at least 1 year apart (see clinical data in **Table 1**). Evaluation of motor functions was performed on the day of the MR scans. Clinical assessment of gross motor functions was performed by a pediatric neurologist (HTC), and presence and severity of hand weakness (with or without grasp) was noted. Gross motor functions were also assessed via standardized semi-structured interview (Vineland Adaptive Behavior Scales- 2nd Edition), and, in children with no gross motor abnormalities, fine motor dexterity was also assessed by Purdue Pegboard task (30 months to 5 years of age) or the Grooved Pegboard task (above 5 years of age) by a certified pediatric neuropsychologist (MEB).¹⁷⁻¹⁹ MR DTI data in the SWS patients were compared to age-matched control groups of 4-4 normal subjects, with a total of 24 control children (3 normal groups at baseline and 3 at follow-up; due to similar age, patients 1-3 shared the same control groups for both the first and the second time point, see **Table 1**). These children were selected from a clinical DTI database of children who underwent MRI at our hospital due to history of seizures. None of the control children had structural lesions on MRI, and none of them had motor impairment or significant developmental delay based on their clinical reports. We had permission from the WSU HIC to use the clinically acquired MRI scans from these children after de-identification.

MRI acquisitions

For children with SWS, a Siemens MAGNETOM Trio 3T scanner (Siemens Medical Solutions, Erlangen) with a standard head array coil was used to acquire diffusion weighted images at TR = 6,600 ms, TE = 97 ms, FOV = 256 mm, matrix size = 128×128, slice thickness = 2 mm, and zero gap covering the whole brain using 64 isotropic gradient directions with $b = 1000 \text{ s/mm}^2$, one $b = 0$ acquisition, and NEX=2. All children had additional native and post-contrast MRI sequences to establish the diagnosis of SWS and the extent of brain involvement. For the controls, clinical MR scans were performed on a 3T GE-Signa scanner (GE Healthcare, Milwaukee, WI) equipped with an 8-channel head coil and ASSET. DWI was acquired with a multi-slice single shot diffusion weighted echo-planar-imaging (EPI) sequence at repetition time (TR) = 12,500 ms, echo time (TE) = 88.7 ms, field of view (FOV) = 240 mm, 128×128 acquisition matrix (nominal resolution = 1.89mm), contiguous 3mm thickness in order to cover entire axial slices of whole brain using 55 isotropic gradient directions with $b = 1000 \text{ s/mm}^2$, one $b = 0$ acquisition, and number of excitations (NEX)=1.¹² Approximate scanning time for the acquisition was about 12 minutes using double refocusing pulse sequence to reduce eddy current artifacts. Sedation during the scanning was performed with pentobarbital (3 mg/kg) followed by fentanyl (1µg/kg).

DTI analysis of the cortico-spinal tract segments (hand and leg)

Whole brain ICA+BSM (independent component analysis combined with a ball-stick model) tractography was performed to reconstruct streamlines of white matter fibers, as described previously.^{9,10} To identify two segments of streamlines associated with primary motor pathways of hand and leg, maximum *a posteriori* probability classifier was applied, which can automatically classify individual streamlines into one of three segments, hand, leg, and face, based on their stereotactic atlases constructed from healthy children.¹¹ For each segment, a streamline visitation map was created by the number of streamlines passing through each voxel. Voxels having more than 5 visits were assumed to belong to each motor pathway. Streamline volume was measured by calculating the total volume of all voxels belonging to the pathway. Finally, *relative* (i.e., normalized) streamline volume of the CST segments (hand and leg) was obtained by normalizing the streamline volume to the white matter volume of the non-lesional hemisphere in SWS and to the corresponding hemisphere in controls.

RESULTS

Relative streamline volumes in the hand and leg CST segments

In the normal control groups, relative CST streamline volumes were relatively stable across age groups, i.e., they showed no clear age-related changes in the hand or leg CST segments. Relative streamline volumes in the leg segment were consistently lower on the right as compared to the left side (**Figure 1**). In the SWS patients, the relative streamline volumes showed different distributions in the hand and leg CST segments (**Figure 1**). The hand-related CST volumes in the lesional hemispheres were lower than those of the non-lesional hemispheres in every patient ($p = .005$; Wilcoxon's test) and also lower than the values of the age-matched control groups in all cases, except the oldest SWS patient with minimal motor dysfunction ($p < .001$; Mann-Whitney's test). The distributions of leg-related relative streamline volumes were more variable, but they were within or even above the normal range in 70% (7/10) of the cases (counting the 5 baseline and 5 follow-up measurements) in the affected hemisphere.

Interval changes in CST streamline volume and hand motor functions: two distinct patterns

Based on the CST streamline volume and corresponding motor status changes between the first and second time points in the SWS children, two distinct patterns were observed: (1) patients #1 and 2, with extensive hemispheric damage on MRI, including the frontal lobe, showed an interval decrease in relative streamline volume of the hand-related CST segment in the lesional hemisphere, and a concomitant increase in the volume in the non-lesional (contralateral) hemisphere at follow-up (**Figure 1A**; **Figure 2**). Although their weakness persisted, both of them developed a good grasp in the affected hand by this time. (2) Patients # 3-5 (all with partial or complete sparing of the frontal lobe on MRI) showed an interval increase in the hand-related relative streamline volume in the lesional hemisphere, although the volumes were still below the normal range at follow-up in patients #3 and 4. Contralateral streamline volumes were within the normal range (mean $\pm$ 2SD) in all but one

case (**Figure 1 B**). None of these patients had gross motor weakness at follow-up, although two of them showed mild fine motor impairment (**Table 1**).

DISCUSSION

The two main findings of this study include: (i) consistently lower CST streamline volume in the hand segment (but not in the leg segment) in the affected hemisphere, and (ii) the presence of two patterns of longitudinal changes in hand-related relative CST volumes, suggesting two distinct forms of structural reorganization associated with different functional outcomes. The interval decrease of the relative volume of the hand segment of the affected CST, observed in two young children (#1 and 2), is consistent with the notion that SWS is often a progressive disorder. The concomitant increase of *contralateral* (non-lesional) CST streamline volumes in these two children likely represents an adaptive mechanism through the ipsilateral (uncrossed) motor pathway. This was particularly striking in the youngest child (patient #1), where the affected CST hand segment volume dropped to a very low value at follow-up, while the contralateral volume was high at baseline and increased further, extending above the normal range at follow-up. Both of these children (#1 and 2) had extensive hemispheric damage, involving the frontal lobe, and they achieved a good hand grasp but no fine motor skills at follow-up. These features are consistent with previous studies using fMRI and TMS documenting that extensive early-onset lesions were associated with ipsilateral motor recovery mechanisms.²⁰ The efficacy of ipsilateral CST reorganization is strong in infancy although starts to decline as early as in the prenatal period.⁴ Still, there is ample evidence that ipsilateral CST projections remain functional during the first several years of postnatal life, and they retain plasticity, which can be induced by a damage of contralateral CST projections.²¹⁻²³ Our findings strongly suggest that such plasticity can result in an enlarged CST volume detectable by DTI. Although our CST tracking did not separate fibers that eventually cross at the level of the medulla from those which remain ipsilateral, it is likely that the increase in volume involved ipsilateral fibers, which contributed to the hand grasp observed in these children. Since the CST in the affected hemisphere was severely damaged but not completely destroyed in either patient, the role of partial reorganization in the affected hemisphere (e.g., in CST segments that normally do not serve hand motor functions) could not be excluded. Future studies separating fibers that cross vs. those which do not cross in the medulla can further address this issue; feasibility of such separation by DTI tractography has been demonstrated recently.²⁴

The remaining three children (#3-5), with complete or partial sparing of the frontal lobe in the affected hemisphere, showed an interval increase of the relative CST volume *ipsilateral* to the angioma, suggesting a partial recovery in the hand segment. This was most striking in patient #3, where the CST hand segment was barely detectable at baseline but was close to the normal range at 1-year follow-up. All these three children obtained or retained good gross hand motor functions during follow-up, consistent with a limited CST injury, which apparently did not prompt structural reorganization in the contralateral CST segments. Microstructural recovery of the damaged CST has been demonstrated in previous studies involving adult stroke patients, both in cross-sectional and longitudinal settings.²⁵⁻²⁹ The ultimate clinical outcome after CST injury is likely the net effect of CST damage and

compensatory remodeling affecting both the ipsi- and contralateral tracts.²⁹ Detection and quantitative analysis of various CST segments, linked to hand vs. leg motor functions, allows a more detailed analysis of imaging correlates of clinical motor deficits.

Limited hand motor functions in children can be a source of considerable impairment of quality of life. The findings of this pilot study indicate that the applied DTI tractography method, which can separate CST segments associated with hand and leg function, is able to detect subtle, microstructural hand CST alterations in children, including those with mild motor deficit.¹² This can be particularly important in young children, where objective, accurate assessment of clinical motor deficit is difficult. Detection of CST damage may guide early motor intervention, such as constraint-induced movement therapy, which can induce changes in motor activation measured by fMRI in chronic stroke patients.³⁰ Longitudinal changes in DTI parameters of the CST (e.g., increasing fractional anisotropy) can occur during spontaneous motor recovery after stroke.²⁵ Increase in fiber volume was also reported in the arcuate fasciculus after intense speech therapy in aphasic patients,³¹ and also in the right arcuate fasciculus after surgical resection of the left arcuate fasciculus in children who underwent epilepsy surgery.³² The activity of the motor cortex, ipsi- or contralateral to the lesion, can be altered by repetitive TMS.^{23,33-35} Our results suggest that DTI has the capacity to evaluate the early structural reorganization pattern after CST injury and may also assess effects of interventions aiming to improve motor functions.

This pilot study has several limitations. The number of patients was small, and the observed patterns of CST changes need to be confirmed in larger groups and after longer follow-up, where additional patterns may also emerge. We did not have a well-defined clinical measure for leg motor functions, although the streamline volume changes did not suggest any obvious imaging pattern of reorganization for the leg-related CST segments. A potential pitfall is the use of different MR scanners for data acquisition in SWS children vs. normal controls, although analysis was done with the same software. However, our main findings of interval changes in relative streamline volumes did not require the control group, which was used to assess if these volumes in the SWS children were in the normal range. We believe that the use of relative (rather than absolute) streamline volumes diminished interscanner variability as well as age-dependence of the measured values, and the use of age-matched controls groups made these comparisons even more reliable. Interscanner variability is an increasing problem in longitudinal MRI studies and multicenter collaborations due to frequent scanner upgrades and developing technology.³⁶ Therefore, future larger-scale studies will likely encounter this issue. Our pilot study suggests that despite these limitations, DTI is sensitive to detect CST injury related to hand motor deficit and to study different patterns of structural reorganization. This approach could enhance the assessment of the severity of early CST damage, predict prognosis, advise targeted interventions and give feedback for rehabilitative methods in children with early motor injury.

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Figure 1.

Normalized hand- and leg-related CST streamline volumes of the non-lesional (blue) and lesional (red) hemispheres of patients with Sturge-Weber syndrome, and of the left (light gray) and right (dark gray) hemispheres of the age-matched control groups. The 2 standard deviation range of CST streamline volume of the control groups are shown (black error bars). The CST streamline volumes have been normalized to the white matter volume of the nonlesional hemisphere in the Sturge-Weber group, and to the ipsilateral white matter volume in the controls. The left and right diagrams represent two patterns of longitudinal changes in hand-related relative streamline volumes. Group 1 had interval decrease of hand-related streamline volume ipsilateral to the lesion, but an increase in contralateral CST volume; this was associated with persistent weakness but good hand grasp. Group 2 showed interval increase of hand-related relative streamline volume in the lesional hemisphere associated with gaining or retaining good hand motor functions on follow-up.

Figure 2.

Representative examples of CST reorganization patterns in children with unilateral SWS. Patient 1 (upper panel; see also Table 1) with left hemispheric SWS involvement showed abnormally low streamline volume on the affected side at both time points, but an interval increase of the contralateral hand CST segment was observed during the 1-year follow-up. Patient 4 (lower images) with right hemispheric (parietal angioma) involvement showed an

interval increase of the hand segment ipsilateral to the lesion. White arrows denote streamlines increased on the follow-up scan, as compared to the baseline.

Table 1

Clinical data of the study subjects

Patient	Sex	Age at 1 st neuro symptoms	Age		SWS angiona location	Additional MRI findings	Hand motor functions		Control groups	
			Baseline	Follow-up			Baseline	Follow-up	mean age±SD	
1	M	0.3y	1.5y	2.5y	L-FTPO	L-FTPO atrophy	R paresis	same, but grasp improved		
2	F	0.4y	1.8y	3.1y	R-TPO	R-F atrophy	L paresis	same, but grasp improved	1.5±0.6y	2.8±0.3y
3	F	0.1y	1.7y	2.7y	R-TPOF	limited R-F atrophy	L paresis	improved; fine motor		
4	M	0.9y	4.4y	5.4y	R-P	R-P atrophy	mild L fine motor	normal	4.3±0.3y	5.5±0.6y
5	M	7.0y	10.0y	12.0y	R-TPO	R-TPO atrophy, small subcortical infarct	L fine motor	L fine motor	9.4±0.5y	12.7±1.6y

Abbreviations: M=male; F=female; y=year(s); L=left; R=right; F=frontal; P=parietal; O=occipital; T=temporal; SWS=Sturge-Weber syndrome; SD=standard deviation