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Corticospinal Dysgenesis and Upper-Limb Deficits in Congenital Hemiplegia: A Diffusion Tensor Imaging Study

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ABSTRACT

OBJECTIVES. Precision grasping critically relies on the integrity of the corticospinal tract as evidenced in congenital hemiplegia by the correlation found between corticospinal dysgenesis and hand-movement deficits. Therefore, corticospinal dysgenesis could be used to anticipate upper-limb deficits in young infants with congenital hemiplegia. However, most studies have quantified corticospinal dysgenesis by measuring the cross-sectional area of cerebral peduncles on T1 MRI, a measure biased by other structures present in the peduncles. The purpose of this study was to evaluate the extent to which this may have hampered the conclusions of previous studies. We also aimed to investigate the relationship between upper-limb deficits and a more accurate measure of corticospinal dysgenesis to provide a tool for anticipating upper-limb deficits in infants with congenital hemiplegia.

METHODS. To address this issue, we measured corticospinal tract areas in 12 patients with congenital hemiplegia and 12 matched control subjects by using the diffusion tensor imaging technique. Corticospinal dysgenesis was quantified by computing a symmetry index between the area of the contralateral and ipsilateral corticospinal tracts. This value was then compared with that resulting from the conventional MRI method.

RESULTS. The symmetry indexes gathered with these 2 methods were highly correlated, although the diffusion tensor imaging symmetry indexes were significantly smaller. This indicates that, in patients with congenital hemiplegia, the conventional MRI measurement has led to a systematic underestimate of corticospinal dysgenesis. These 2 estimates of corticospinal dysgenesis were also correlated with upper-limb impairments and disabilities. Although the symmetry index computed from peduncle measurements was correlated solely with deficits in stereognosis, the diffusion tensor imaging index correlated with stereognosis, digital and manual dexterities, and ABILHAND-Kids, a measure of manual ability in daily life activities.

CONCLUSIONS. The diffusion tensor imaging symmetry index provides a useful prognostic tool for anticipating upper-limb deficits and their consequences in daily life activities.

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Key Words

corticospinal tract dysgenesis, functional assessment of children, diffusion tensor imaging, DTI, cerebral palsy

Abbreviations

CH—congenital hemiplegia
DTI—diffusion tensor imaging
ANOVA_{RM}—analysis of variance for repeated measures

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THE CORTICOSPINAL SYSTEM is known to play a critical role in controlling fine finger movements. In monkeys, after an early corticospinal tract lesion, whereas the power grip is preserved, the precision grip between the thumb and index finger remains permanently impaired.^{1,2} Along the same lines, in humans, a correlation has been found between corticospinal tract degeneration and the severity of motor deficits in both adult stroke^{3–5} and congenital hemiplegia (CH).^{6,7} In most studies, corticospinal tract degeneration has classically been quantified by measuring the cross-sectional area of the cerebral peduncles in the mesencephalon on T1-weighted MRI.^{6–8} However, such an estimate of the corticospinal area is unavoidably biased, because it includes the substantia nigra and other corticofugal descending pathways.^{9,10} A more specific measure of corticospinal tract cross-sectional area can be performed using diffusion tensor imaging (DTI). This technique is based on the quantification of the Brownian motion of water molecules. In cerebral white matter, water diffuses preferentially along the direction of axons and is restricted perpendicular to axons. This directional dependence of diffusion, called anisotropy, provides a unique tool to identify white matter tracts and to study their microstructural organization and integrity *in vivo*.^{11–13} So far, the white matter tracts, and particularly the corticospinal tract, have been widely studied with DTI in normal adults,¹⁴ infants,¹⁵ stroke patients,^{16–19} and children with cerebral palsy.^{20–22} These studies have evidenced the accuracy of DTI to visualize and describe the corticospinal tract. In adult patients with stroke, a few studies have used diffusion imaging to investigate the correlation between corticospinal tract injury and functional deficits.^{16,18,19} These studies have demonstrated that an early measure of corticospinal tract degeneration could provide the functional outcome of these patients.

In children with CH, the correlation between corticospinal tract degeneration measured with diffusion imaging and upper-limb functional abilities has never been investigated in detail. It has been shown that DTI was able to assess Wallerian degeneration by measuring a decrease in anisotropy as early as a few days after the initial insult, which is a significant amount of time before the occurrence of visible signs of corticospinal tract atrophy.²³ This decrease in anisotropy can even be observed in neonates,^{21,24–26} giving an early estimate of corticospinal tract degeneration, whereas fine finger movements are not yet mature^{27,28} and, thus, cannot be appraised. In this way, dysgenesis could be detected during or even before the crucial period during which a microstructural reorganization of the corticospinal tract and corticospinal projections takes place. Indeed, in cats, it has been suggested recently that treatments during this period could partly reverse the consequences of lesions on developing corticospinal projections²⁹ and the consequences of the lack of motor experience of a par-

alyzed forelimb on both function and the development of corticospinal axons.³⁰

The aim of the present study was to investigate the strength of the relationship between corticospinal tract dysgenesis and upper-limb deficits by using DTI for a more precise measure of the corticospinal tract as compared with conventional MRI and by correlating this measure with a detailed assessment of the upper-limb function. Our work was performed on children with chronic-stage CH where the Wallerian degeneration has led to atrophy, but we hypothesize that an early measurement of corticospinal tract dysgenesis with DTI (decreased anisotropy) might be used in young infants to anticipate motor deficits and their consequences in everyday life activities. This could allow children with CH to receive suitable treatments during this crucial period, presumably during the first months of life.^{31,32}

METHODS

Subjects

Twelve children with CH (10 boys and 2 girls) and 12 age- and gender-matched control subjects participated in the present study. The children were between 10 and 16 years old (mean age: CH, 12.5 ± 2.1 years; control subjects, 12.6 ± 2.0 years). This study was authorized by the ethical committee of the Université Catholique de Louvain School of Medicine (2003/24SEPT/163). Subjects and parents gave their written informed consent.

Normal school level, implying no cognitive deficits, was a selection criterion to participate in this study. The severity of the hemiplegia was categorized according to the Gross Motor Function Classification as level 1 or 2. A brief description of each patient is provided in Table 1.

Upper-Limb Assessment

Upper-limb function was assessed on both hands by using different tests and functional scales, starting with the affected hand. A version of the manual form perception test³³ was used to evaluate stereognosis. In this test, when children were unable to explore objects, the examiner helped them to close their hands around the object. A clinical test based on the position of the metacarpophalangeal joints was used for testing proprioception.⁷ The tactile pressure-detection threshold was measured on the index finger with a Semmes-Weinstein aesthesiometer by using a modified version of Bell-Krotoski's procedure.³⁴ The grating orientation task (JVP domes) was used to assess tactile spatial resolution with a procedure adapted to children.³⁵ The grip strength was measured with a Jamar dynamometer.³⁶ Manual dexterity was evaluated with the box and blocks test,³⁷ and digital dexterity was measured by means of the Purdue pegboard test.³⁸ Manual ability was assessed by the ABILHAND-Kids questionnaire.³⁹ For a thorough de-

TABLE 1 Clinical Description, Scores on the Gross Motor Function Classification, Lesion Description, and Corticospinal Asymmetry

Patient No. (Gender)	Age, y	Clinical Description	GMFC Level	Lesion Description (MRI)	CTsym, %
1 (M)	10.1	L hemiparesis	1	R widespread cortico-subcortical macrocystic encephalomalacia (insula, frontal, and temporal lobes), R ventricular widening	36
2 (M)	10.5	L hemiparesis	2	R widespread micropolygyria (frontal lobe, insula, and part of temporal lobe)	27
3 (M)	10.9	R hemiparesis	1	L subcortical encephalomalacia (ovale centrum, periventricular white matter, and caudate nucleus), L ventricular widening	60
4 (M)	11.1	R hemiparesis	1	L periventricular leukomalacia, L caudate nucleus lesion	71
5 (M)	11.6	L hemiparesis	1	L moderate ventricular widening	53
6 (F)	11.9	L hemiparesis	2	R widespread cortico-subcortical macrocystic encephalomalacia (parietal and frontal lobes), L discrete parietal lesion, R ventricular widening	61
7 (F)	12.6	L hemiparesis	1	R microcystic and macrocystic gliosis in the ovale centrum, R caudate nucleus lesion, R ventricular widening	88
8 (M)	13.3	R hemiparesis	1	Very discrete periventricular leukomalacia (bilateral parietal, R frontal)	69
9 (M)	13.9	R hemiparesis	1	Bilateral (with L predominance) periventricular leukomalacia and ventricular widening	21
10 (M)	15.1	L hemiparesis	2	L widespread cortico-subcortical macrocystic encephalomalacia (temporal, frontal, and parietal lobes; insula; part of occipital lobe; caudate and lenticular nuclei; and thalamus), L ventricular widening	67
11 (M)	15.6	L hemiparesis	2	Bilateral periventricular leukomalacia mainly in posterior regions, important white matter atrophy with R predominance, drained hydrocephaly	26
12 (M)	15.9	L hemiparesis	1	R widespread cortico-subcortical macrocystic encephalomalacia (insula, frontal, and parietal lobes; caudate and lenticular nuclei), R ventricular widening	33
				R large macrocystic gliosis in ovale centrum; L closed schizencephaly in the antero-medial frontal area	

M indicates male; F, female; R, right; L, left; CTsym, corticospinal tract symmetry index measured with DTI; GMFC, gross motor function classification.

scription of these tests and functional scales, see the Appendix.

Grip strength, manual dexterity, and digital dexterity scores were *z*-transformed with respect to normative data (C. Arnould, PhD, B. Ga dit Gentil, PT, Y.B., and J.L.T., unpublished data, 2006). This procedure accounts for gender, age, and handedness and allows the results of all of the tests, on either limb, to be expressed on a common scale. A *z* score range between -2.5 and 2.5 was considered not significantly different from normal (99% of normal population).

MRI

Morphologic MRI and DTI were performed for all of the patients and control subjects by using a 6-channels head coil on a 1.5-T whole-body magnetic resonance scanner (Intera, Philips Medical Systems, Best, Netherlands) equipped with explorer gradients (40 mT/m). All of the images were acquired in the axial plane, parallel to the

anterior commissure-posterior commissure.⁴⁰ A three-dimensional gradient echo T1-weighted sequence was used for anatomic images. For DTI acquisitions, a single shot spin-echo echoplanar sequence was used, with diffusion gradients applied in 16 noncollinear directions ($b = 800$ seconds/mm²). Sixty contiguous slices were acquired with a field of view of 246×246 , a matrix of 128×128 , and a slice thickness of 2.2 mm. Other imaging parameters were: repetition time, 7859 milliseconds; echo time, 80 milliseconds; sensitivity encoding (parallel imaging scheme) reduction factor, 2.5; and number of signal averages, 2.

Indexes of Corticospinal Symmetry

Two measures were performed in a blinded manner to estimate corticospinal tract symmetry in patients and control subjects. In a conventional approach, the area of the cerebral peduncles was measured in an axial plane, 5 or 6 sections below the anterior commissure-posterior

commissure plane, passing through the mammillary bodies. The impaired and nonimpaired areas were then compared, giving the conventional MRI symmetry index⁷ according to the following formula: (contralateral area/ipsilateral area) $\times$ 100. The terms “contralateral” and “ipsilateral” were defined toward the paretic hand. In control children, the symmetry index was calculated as (nondominant side area/dominant side area) $\times$ 100.

The second approach used the DTI data that were processed offline by using the Pride software (Philips Medical System). In each voxel, the tensor data set was calculated including the 3 eigenvalues (quantification of the diffusion) associated with the 3 eigenvectors (direction of the diffusion), which characterize the ellipsoid representing diffusion in the three-dimensional space. A color-coded DTI map was then generated according to the scheme proposed by Pajevic and Pierpaoli,⁴¹ where the fiber direction was indicated by the direction tensor's main eigenvector (the preferred direction of diffusion), coded as blue for craniocaudal, green for anteroposterior, and red for left-right direction. The brightness of each voxel was weighted by the fractional anisotropy, which quantifies the degree of preferred directionality and is calculated from the 3 eigenvalues. On this color-coded DTI map, the corticofugal projection fibers are displayed in blue, and the corticospinal tract is particularly well delineated at the level of the lower pons (level of the middle cerebellar peduncles), because all of the fibers run coherently in the craniocaudal direction. This level was chosen to manually delineate the left and right corticospinal tracts,¹⁴ and the corticospinal tract area calculated in pixels was converted to millimeters squared. A DTI symmetry index was then calculated for children with CH and control subjects in the same manner as that for the conventional MRI index.

Statistics

A 1-way analysis of variance for repeated measures (ANOVA_{RM}) or a Friedman test in nonparametric conditions was performed on measurements of upper-limb impairments, peduncular area, and corticospinal tract area to compare the 4 groups of data, namely, the paretic and nonparetic sides of patients with CH and the dominant and nondominant sides of control subjects. A Tukey pairwise multiple-comparison procedure was used to determine which treatments were significantly different. This posthoc analysis automatically corrects the effects of multiple comparisons. In children with CH, a 1-way ANOVA_{RM} was also used to compare the symmetry indexes gathered with conventional MRI and with DTI.

Spearman correlations (rank analysis) were conducted to investigate the relationship between hand function and MRI measures and the correlation between both symmetry indexes. The use of rank analysis correlations allowed the study and modeling of nonlinear

associations between 2 variables by using a regression technique to find the best predictor of y in a family of x functions. In our results, nonlinear associations between 2 variables have been modeled by sigmoid curves, because this function was the most adapted to the group of data points. The equation of these sigmoid curves is as follows:

$$y = y_0 + \frac{y_1 - y_0}{1 + e^{-\left(\frac{x - x_0}{b}\right)}}$$

where y_1 and y_0 represent the 2 plateaus of the sigmoid, and x_0 is the projection on the x -axis of half the y value composed between the 2 plateaus ($x_0 = y_1 - y_0/2$). x_0 also represents the change of convexity of the sigmoid. The b term is a slope indicator.

RESULTS

Corticospinal Tract Dysgenesis

Figure 1 shows the cross-sectional area of the cerebral peduncles and corticospinal tracts as measured, respectively, with conventional MRI and DTI in a control subject and a patient with CH. This figure shows that the patient with CH demonstrated a significant asymmetry of the corticospinal tracts when compared with the control subject. This asymmetry was observed in all of the children with CH, whatever the technique used to quantify the corticospinal tract dysgenesis.

Table 2 gives the cross-sectional areas of the cerebral peduncles measured with the conventional MRI method and those of the corticospinal tracts measured with the DTI technique in both patients with CH and control subjects. In control subjects, no difference was found between the areas of both cerebral peduncles and between the areas of both corticospinal tracts. In children with CH, the ipsilateral peduncle and corticospinal tract were normal when compared with control values. The areas of the contralateral peduncle and corticospinal tract of children with CH were significantly smaller than the ipsilateral ones. As a result, the indexes of symmetry of children with CH calculated with conventional MRI and with DTI were significantly smaller than those of control subjects (Fig 2A). Figure 2B illustrates the correlation between corticospinal tract dysgenesis measured with DTI and that estimated with conventional MRI in children with CH. The symmetry indexes calculated with both methods were highly correlated ($r = 0.860$; $P < .001$) but significantly different (ANOVA_{RM}, $F = 53.145$; $P < .001$). The DTI index ($51\% \pm 21.7\%$ [mean $\pm$ SD]) was systematically lower than the conventional MRI index ($73\% \pm 20.6\%$ [mean $\pm$ SD]; Fig 2B).

Upper-Limb Deficits and Correlation With Corticospinal Tract Dysgenesis

ANOVA_{RM} was used to compare upper-limb functions of both hands within and between patients with CH and

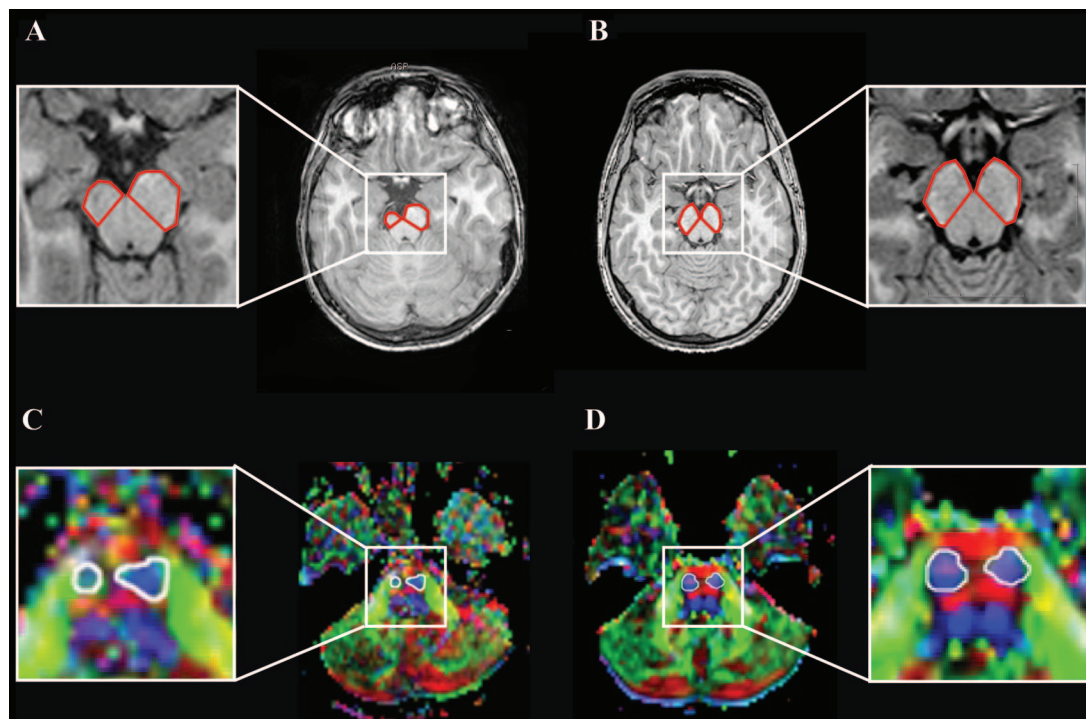


FIGURE 1

Cross-sectional area of corticospinal tract estimated with MRI and DTI. A and B, T1-weighted MRI in a transverse plane at the level of the mammillary bodies. Highlighted in red, the cerebral peduncles of A, a child with CH (patient 11; MRI index: 63%), and of B, an unimpaired child (control 5; MRI index: 101%). C and D, DTI in an axial plane through middle cerebellar peduncle. The axon direction is coded in color: red, left-right direction; green, anteroposterior; blue, craniocaudal. The perimeter of corticospinal tract fibers is highlighted in white. The DTI index reached 26% for patient 11 and 96% for control subject 5.

control subjects (see "Methods"). The results showed significant differences for stereognosis, proprioception, tactile spatial resolution, force, and manual and digital dexterity ($ANOVA_{RM}$, all $P < .003$). Posthoc analysis showed major impairments in the paretic hand of children with CH when compared with their nonparetic hand and with the nondominant hand of control subjects (Tukey test, all $P < .001$). The nonparetic hand of children with CH was not significantly different from the dominant hand of control subjects (all $P > .839$). The tactile pressure-detection thresholds of children with CH were not different when compared with control values ($P = .568$). The ABILHAND-Kids scores of children with CH were significantly lower than the scores of control subjects ($P < .001$).

In children with CH, the conventional MRI index was only correlated with deficits in stereognosis in the paretic hand (Table 3). The DTI index was highly correlated

with stereognosis, manual dexterity, digital dexterity, and manual ability as estimated by the ABILHAND-Kids questionnaire (Table 3). No correlation was found between the 2 symmetry indexes and the proprioception, tactile pressure detection, and tactile spatial resolution (Table 3).

Figure 3 illustrates the relationship among manual dexterity, digital dexterity, manual ability, and the DTI index. For these 3 variables, the nonlinear relation between hand deficits and DTI index was better fitted by a sigmoid function (see "Methods"). The 3 curves had a parallel evolution with a simultaneous change of convexity ($67.07 < x_0 < 68.54$). For major corticospinal tract dysgenesis, during the first plateau of the sigmoids, functional deficits were not correlated with DTI index. During the sharp increase of the sigmoids, the scores obtained in functional tests increased rapidly with the increasing corticospinal tract symmetry index. In pa-

TABLE 2 Comparison Between Cerebral Peduncles and Between Corticospinal Tracts

Variable	CH _{contra} Mean (SD)	CH _{ipsi} Mean (SD)	CTRL _{Ndom} Mean (SD)	CTRL _{Dom} Mean (SD)	ANOVA _{RM} <i>P</i>	Posthoc			
						<i>P</i> , CH _{ipsi} / CH _{contra}	<i>P</i> , CH _{contra} / CTRL _{Ndom}	<i>P</i> , CH _{ipsi} / CTRL _{Dom}	<i>P</i> , CTRL _{Ndom} / CTRL _{Dom}
Peduncle area, mm ²	121 (31.3)	172 (34.5)	172 (22.0)	176 (22.3)	<.001	<.001	<.001	.992	.986
CS tract area, mm ²	48 (21.1)	97 (23.3)	92 (17.8)	97 (19.2)	<.001	<.001	<.001	.911	.877

CH indicates patients with CH; ipsi, ipsilateral to the paretic hand; contra, contralateral to the paretic hand; CTRL, controls; Dom, dominant side; Ndom, nondominant side; CS, corticospinal.

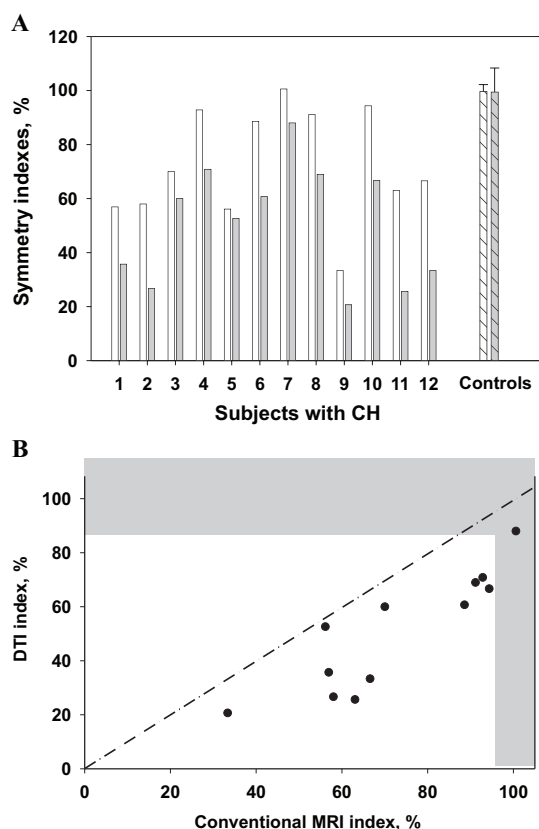


FIGURE 2

Symmetry indexes measured with DTI and MRI. A, Symmetry indexes calculated for the 12 children with CH with MRI (white bars) and DTI (gray bars). The values for control subjects (mean $\pm$ SD) are represented by the 2 bars on the right. B, Correlation between corticospinal dysgenesis in patients with CH as estimated with the conventional MRI index and the DTI index. The dashed line represents a perfect correspondence between both indexes. The shaded areas display the values for control subjects (mean $\pm$ 2 SD).

tients with an index of symmetry $>72\%$ to 80% , the motor performance was indistinguishable from that of control subjects.

Figure 4 illustrates the nonlinear relationship between stereognosis and indexes of symmetry estimated with DTI. Stereognosis of children with CH reached normal values with a DTI index of 77% . For patients show-

TABLE 3 Correlation Between Hand Deficits and Symmetry Indexes in Patients With CH

Variable	Conventional MRI Index		DTI Index	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Stereognosis	0.828	$<.001$	0.959	$<.001$
Proprioception	0.439	.143	0.47	.117
Touch detection	−0.448	.136	−0.513	.084
Tactile spatial resolution	−0.557	.055	−0.553	.058
Force ^a	0.284	.352	0.543	.062
Manual dexterity ^a	0.427	.157	0.699	.010
Digital dexterity ^a	0.442	.143	0.709	.009
ABILHAND-Kids	0.327	.284	0.676	.014

^aTests in which age has an influence between 10 and 16 years were converted in z score (relative to a normal reference population) before statistics were performed.

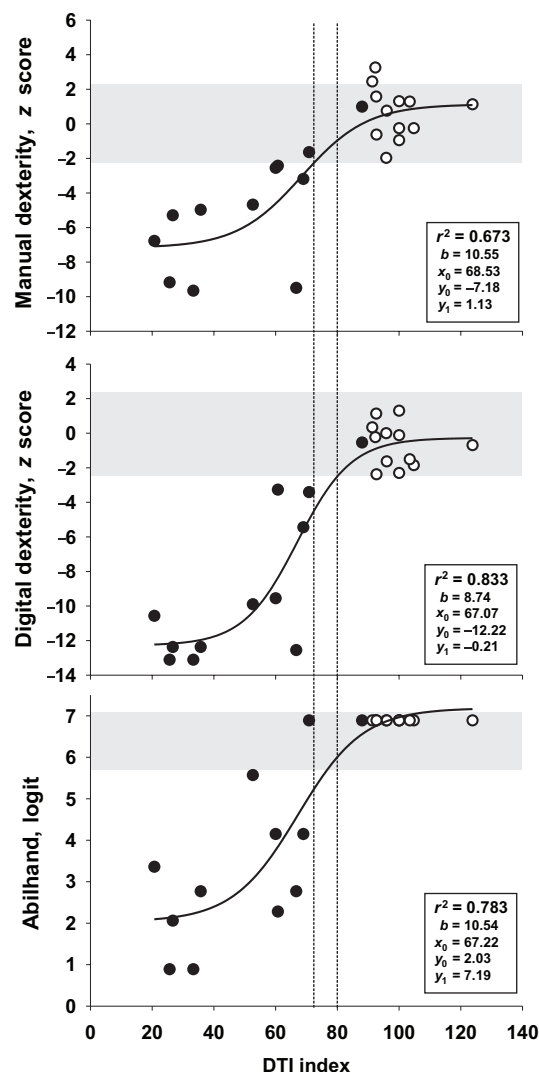


FIGURE 3

Correlations between functional deficits and DTI symmetry indexes in children with CH (filled circles) and controls (open circles). Sigmoid curves are fitted in the graphs ($y = y_0 + [(y_1 - y_0)/(1 + e^{-(x-x_0)/b})]$). Shaded areas represent ± 2.5 SD of normal children. Two vertical dotted lines define an interval ($72\% - 80\%$) during which all sigmoids join normal values.

ing a lower symmetry index, the scores increased gradually with the value of the DTI index.

DISCUSSION

Corticospinal Tract Dysgenesis

In our study, the DTI symmetry index ($51\% \pm 21.7\%$ [mean $\pm$ SD]) of children with CH was systematically smaller than the MRI index ($73\% \pm 20.6\%$ [mean $\pm$ SD]). The conventional MRI measure is unavoidably biased because, at the level of the mesencephalon, the corticospinal tract fibers represent $<10\%$ of the fibers traveling through the cerebral peduncle; 90% of the cerebral peduncle thus consists of other corticofugal descending pathways, such as the corticopontine, corticobulbar, and corticoreticular tracts arising from temporal,

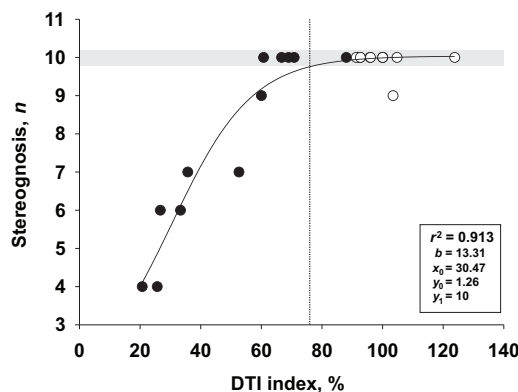


FIGURE 4

Correlations between stereognosis and corticospinal symmetry indexes measured with DTI. Children with CH are represented by the filled circles, and control subjects are indicated by open circles. Children with CH reach normal values in stereognosis from 77% of corticospinal tract symmetry. Before 77%, results from children with CH progressively worsened, whereas the index of symmetry decreased.

frontal, and parietal lobes.^{10,22} Even at a lower level, that is, in the pons or medulla oblongata, the measure remains biased by other structures, and it is even more difficult to detect the asymmetry on anatomic images.⁸ The DTI technique allows us to delineate the corticospinal tract among other structures, and its measurement at the level of the lower pons is particularly easy, because it appears as a well-defined blue area on color-coded DTI maps.¹⁴ At this level, most of the corticopontine fibers stop traveling in a craniocaudal orientation; these fibers are, therefore, excluded from the measure, and a more valid and precise assessment of the corticospinal tract can be obtained, even if the area delineated on color-coded DTI maps remains contaminated by the corticobulbar fibers.^{10,22} Consequently, the smaller symmetry indexes provided by DTI suggest that measurements with conventional MRI systematically underestimate the extent of corticospinal tract dysgenesis in CH.

Our results showed that the cross-sectional area of the unaffected corticospinal tracts of children with CH was not significantly different from that of the dominant side of control subjects. Although previous transcortical magnetic stimulation studies suggest an overgrowing of the unaffected corticospinal tract of children with CH,³² no major changes could be detected on imaging. Even using fiber tracking, allowing one to count the fiber bundles pertaining exclusively to the corticospinal tract, Thomas et al²² showed that the slight increase in fiber count in the unaffected corticospinal tract of subjects with CH was insignificant when compared with control subjects. Our results are also consistent with previous findings in monkeys in which no structural reorganization of ipsilateral corticospinal fibers could be evidenced after early unilateral corticospinal damage.⁴² Altogether, these results suggest that, whereas a slight increase in fiber count could be noticed, indicating some microstructural reorganization,^{21,22} no major overgrowth of

the ipsilateral corticospinal tract takes place to compensate for motor deficits resulting from the lesion. As a result of this absence of ipsilateral overgrowing, the lower value of the conventional MRI and DTI indexes in CH reflects only the Wallerian degeneration consequent to the lesion.

The lesions of our patients were predominantly destructive (see Table 1). However, their heterogeneity in both etiology and timing of the original insult could have an effect on the corticospinal tracts, because their reorganization after a lesion could be related to the gestational age at which the lesion occurred.^{43,44} We made an attempt to correlate the functional assessment with the timing of the insult based on MRI indication⁴⁴ but were unable to provide differences in the functional data between earlier and later insults during pregnancy. This observation supports the use of indexes based on the corticospinal tract dysgenesis. Indeed, both the extent of central structures lesions⁴⁵ and, in this study, the timing of insult remained uncertain as to provide tools to anticipate motor deficits. On the other hand, the estimate of the Wallerian dysgenesis, consequent to the initial lesion but crucial to the motor performance, should be a reliable index, whatever the extent and etiology of the insult.

Correlation Between Corticospinal Tract Dysgenesis and Upper-Limb Deficits

A large number of studies have provided evidence that the performance of fine finger movements depends on the integrity of the corticospinal tract.⁴⁶ In our study, the conventional MRI index correlated only with stereognosis, whereas the DTI measures correlated with stereognosis, digital dexterity, manual dexterity, and ABILHAND-Kids. Because the measurement of symmetry index with DTI is more focused on corticospinal tract fibers (see above), it is not surprising to observe more relevant correlations with hand deficits than with a conventional MRI measure. The correlation between corticospinal tract dysgenesis measured with DTI and ABILHAND-Kids underlies the capability of this index to predict a child's difficulty in performing manual activities in everyday life. Furthermore, the correlation of manual dexterity, digital dexterity, and stereognosis with the DTI index is consistent with the relationship established between these hand impairments (stereognosis and manual and digital dexterity) and manual ability measured with ABILHAND-Kids.⁴⁷

The relationship between symmetry indexes measured with DTI and manual dexterity, digital dexterity, and ABILHAND-Kids was modeled by a sigmoid function. The first plateau of the sigmoid suggested that, for very large corticospinal dysgenesis, whatever the value of the corticospinal tract dysgenesis, children showed dramatic impairments. During the sharp increase, the scores obtained in functional tests increased rapidly with

the increasing corticospinal tract symmetry index. Finally, during the interval between 72% and 80% of the symmetry index, children with CH reached the values of control subjects for all of the tests. This evolution of hand performance relative to the DTI symmetry index could be of major interest in the development of an early predictive tool.

Recent studies in cats have pointed out the importance of crucial periods in the developing corticospinal tract.^{30,48} Crucial periods are defined as windows during which the development of central structures depends on the match between the environment and the brain's expectation.⁴⁹ During this crucial period in corticospinal tract development, after a competition principle, inhibition of primary sensorimotor areas induces permanent changes in projection topography.⁴⁸ Furthermore, it has been suggested that these changes could be partially rebalanced during the weeks after this crucial period but not later.²⁹ Still, in cats, the role of the motor experience has been demonstrated in the postnatal development and function of corticospinal axons.³⁰ In humans, both transcortical magnetic stimulation³¹ and DTI studies in neonates⁴⁹ have suggested the existence of such crucial periods in the development of the immature central nervous system, most likely in the first months of life.^{30,31,44,50} Therefore, treatments that could have an effect on the remodeling of corticospinal tracts after central lesions should be applied very early.⁵¹ Hence, this explains the interest in a prognostic tool using DTI to anticipate motor deficits. Indeed, whereas DTI first encountered problems in the detection of disease in the immature brain because of the high water content of the tissues,⁵² it is now considered to be particularly adapted for investigating fiber tracts in neonates and preterm children even before myelination occurs.^{24,26,53} Furthermore, it has been regarded as the best technique to detect white matter injury in neonates as compared with conventional MRI or ultrasound.^{26,54} This early detection of corticospinal tract degeneration relies on the measurement of the relative or fractional anisotropy, which is reduced by the early breakdown of myelin and axons, mainly by increasing the transversal component of the diffusion (perpendicular to the axons) in the injured white matter tract.

Additional longitudinal studies should be performed to correlate the corticospinal tract dysgenesis assessed with DTI at an early stage by measuring the fractional anisotropy and the area measurement performed on color-coded DTI maps at a chronic stage. Awaiting the availability of such studies, we hypothesize that an early measure of corticospinal tract dysgenesis (decreased anisotropy) may allow us to anticipate the motor deficits in neonates and to define more accurately early therapeutic strategies.

CONCLUSIONS, PERSPECTIVES, AND LIMITATIONS OF THE STUDY

In this study, we have shown the superiority of DTI over conventional MRI for assessing corticospinal tract dysgenesis. The correlation between corticospinal tract dysgenesis and upper-limb deficits in children with chronic-stage CH is of major interest for the design of a tool to precisely predict the upper-limb functional outcome in young infants. Such an early prognostic tool could allow children with CH to receive suitable treatments during the first months of life. For this purpose, the next step will be to carry out longitudinal investigations to correlate our observations relying on the atrophy of the corticospinal tract with the early evaluation of corticospinal tract degeneration by using anisotropy measurements.

Our measure of corticospinal dysgenesis was based on area measurement on color-coded DTI maps. This approach was chosen because of its easy application in clinical routine, but improvements of the signal/noise ratio on DTI maps and the availability of semiautomatic programs should provide even more precise tools in the future, such as fiber tracking. However, even our simple analysis-based color-coded maps are not without potential pitfalls. DTI is particularly sensitive to artifacts generated by eddy currents, motion, and susceptibility that create ghosting and geometric distortions.⁵⁵ Our system equipped with powerful gradients and parallel imaging allowed us to record good-quality DTI maps, but some degree of shape distortion cannot be excluded, especially at the level of the brainstem. The clinical use of more sophisticated DTI analysis, such as quantitative fiber tracking, still requires improvements of the signal/noise ratio, better artifacts correction schemes, and the availability of semiautomatic programs, including a solution for the intravoxel crossing problem.

APPENDIX

Stereognosis

Blindfolded subjects were presented with 5 three-dimensional geometric forms (circle, triangle, square, lozenge, and octagon) and 5 everyday life objects (toothbrush, tennis ball, sweet, comb, and cup). The children had to recognize the object placed into their hand. The score (on 10 points) was equal to the number of objects correctly recognized.³³

Proprioception

The subjects were blindfolded before starting the test. The metacarpophalangeal articulation of the thumb and index finger was passively mobilized (maximum, 30°). The child was asked to identify the direction of the movements. Five trials were performed with each finger. The score (on 10 points) was the number of correct responses.⁷

Pressure-Detection Threshold

The tactile pressure detection was measured at the tip of the index finger with a Semmes-Weinstein aesthesiometer, which consists of a set of 20 gradually smaller monofilaments calibrated to apply a decreasing force (448–45 mg) when pressed and bent against the skin. Blindfolded children had to report when they felt the filament applied perpendicularly to the finger pulp according to the methods of the limits. The tactile pressure-detection threshold was the force (milligrams) required to bend the smallest filament the child felt.³⁴

Tactile Spatial Resolution

The tactile spatial resolution was measured with the grating orientation task by using the JVP domes on the index finger of blindfolded children. This test consists of a set of 8 different plastic domes having equidistant bar and groove widths. Each dome was manually applied to the skin for 1 to 2 seconds starting with the largest grating (3 mm), applied for 10 consecutive trials using a randomized orientation of the bars (ie, the bars parallel or transverse to the long axis of the finger). The next smaller grating (2 mm) was applied following the same procedure and so forth. The test was stopped when the probability of correct answers for the grating reached 50%. The tactile spatial resolution performance was determined by the tactile acuity grating score (Med-Core, St Louis, MO, 2004), which is a simple linear interpolation estimate of the 75% correct grating width.³⁵

Grip Strength

The patient was sitting with the arm along the body, at 90° of elbow flexion, with the forearm in pronosupination, the wrist between 0° and 30° of dorsiflexion, and 0° to 15° of cubital deviation. One training trial was performed before starting the test. The child was asked to grasp the Jamar dynamometer as strong as possible. Three consecutive measures were registered, respecting a 1-minute rest between them. The score was the average of the 3 trials.³⁶

Manual Dexterity

The manual dexterity was evaluated with the box and blocks test, which consists of moving, 1 by 1, the maximum number of blocks (side: 2.5 cm) from 1 compartment of a box to the opposite within 60 seconds. A 15-second period for practice was allowed before starting the test. The score, for each hand, was the number of blocks transported.³⁷

Digital Dexterity

The digital dexterity was measured by using the Purdue pegboard test, which is composed of a board containing 2 rows of holes and 2 cups containing pins. Within 30 seconds, the subjects had to pick up, 1 at a time, as many pins as possible and place them into the holes in the

board. They were allowed to practice with 3 or 4 pins before starting. The test was performed 3 times with each hand, alternating the dominant hand and the non-dominant hand. The score, for each hand, was the mean number of pins placed during the 3 trials.³⁸

ABILHAND-Kids

The ABILHAND-Kids questionnaire measures a child's ability to manage daily activities requiring the use of the upper limbs. Parents are asked to estimate their child's difficulty in performing each activity when done without help, irrespective of the limb(s) used and whatever the strategies used to do the activity. The manual ability is rated on a 3-level response scale. The score, given in logit, is the conversion of the ordinal score into a linear measure of ability located on a unidimensional scale.³⁹

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