Correlation of Corpus Callosal Morphometry with Cognitive and Motor Function in Periventricular Leukomalacia

Abstract

Purpose: We aim to correlate size and shape of corpus callosum with severity of motor and cognitive impairments in children with periventricular leukomalacia (PVL).

Methods: Children with PVL were stratified based on the severity of their motor and cognitive impairments. An age-matched control group was established. The corpus callosum was identified on mid-sagittal $T_1$-weighted spin-echo (TR/TE: 550/15) MR images. The shape characteristics of the corpus callosum were measured with respect to a template via a shape transformation. The degree of callosal-shape transformation was quantified by a deformation function, which in turn was compared, using point-wise t-tests, for controls versus patients, diplegic versus quadriplegic patients, and patients with mild versus severe cognitive impairment.

Results: 29 children with spastic cerebral palsy and PVL and 32 age-matched controls were identified. In the PVL group, the entire corpus callosum was significantly smaller than in the control group ($p = 0.001$). Significant differences existed in the shape of the corpus callosum between patients with diplegic versus quadriplegic and between patients with severe versus mild cognitive impairment.

Conclusion: Global and regional corpus callosal morphology can be quantified using deformation functions.

Key words
Corpus callosum - morphometry - cognitive function - motor function - periventricular leukomalacia - cerebral palsy

Introduction

Cerebral palsy is a term that describes a group of non-progressive motor impairment syndromes caused by abnormal early brain development [14,16,21,23]. Based on the predominant clinical features, cerebral palsy is classified into spastic, extrapyramidal, and mixed types [5,14].

Cerebral palsy is the most prevalent form of chronic motor disability in children, and its incidence has not diminished in the modern era of sophisticated obstetrical and neonatal care. In the preterm infant, periventricular leukomalacia (PVL) is the dominant pattern of brain injury that later manifests as spastic cerebral palsy with variable degrees of cognitive impairment [2]. Selective vulnerability of the immature cerebral blood vessels and oligodendroglia in the periventricular white matter to fluctuations in cerebral perfusion and to oxygen free radicals is thought to be responsible for this specific pattern of brain injury in the preterm infant [17,22,30].

MR imaging features of PVL are strongly related to spastic cerebral palsy (spastic diplegia or quadriplegia) [10,29]. These features are due to injury to developing periventricular white matter during the late second, early third trimester of pregnancy with resultant $T_1$ and/or $T_2$ prolongation, thinning of the corpus callosum due to destruction of white matter fibers contributing to this commissural tract (Fig. 1) and enlargement of the lateral ventricles and irregularities of the lateral ventricular walls [3,10,11,28].

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Correlation between late MR imaging findings of PVL with severity of motor deficit and cognitive impairment can be used to predict the level of neuropsychological dysfunction before formal testing is feasible, and to institute early rehabilitative programs [12,13,15,18,31]. The severity of periventricular white matter injury as demonstrated by MR imaging, has correlated with degree of motor impairment [12,13,15,18,31]. However, inconsistent results have been published with regards to correlation with degree of cognitive impairment. These inconsistencies have been attributed to methodological differences in quantifying MR findings and to variability in neuropsychological testing [12,13,15,18,31].

The corpus callosum contains topographically organized white matter fibers that provide the main connection between corresponding regions in the two cerebral cortices and the primary route for integration of motor, sensory and cognitive functions [24,25]. Several studies have shown strong correlation between impaired cognition and specific abnormalities of the corpus callosum [6,26,27]. The corpus callosum is more easily and, perhaps, reliably quantifiable than periventricular white matter, and might therefore serve as a more useful index of white matter injury and predictor of severity of impairments.

In this study, we intend to mathematically quantify global and regional corpus callosal morphometric changes in patients with PVL and correlate these changes with motor and cognitive function. In our analysis, we use methodology based on shape transformations [7,8]. This methodology can capture subtle and local characteristics of the corpus callosal morphology, and it can examine group differences as well as correlations between morphology and motor or cognitive function via point-wise statistical maps.

Our null hypotheses are: 1) No difference in the global and regional size or shape of the corpus callosum between controls and children with spastic cerebral palsy secondary to PVL. 2) No change in the global and regional size or shape of the corpus callosum with severity of motor deficit and cognitive impairment.

Materials and Methods

Subjects

The charts of 65 children currently followed at the Center for Cerebral Palsy and Motor Disorders were reviewed for gender, gestational age, availability of MR imaging exam, severity and type of motor and cognitive impairments.

Clinical inclusion criteria were: the presence of spastic diplegia/quadruplegia, and the availability of a brain MR imaging study performed at our institution. Children with mixed (pyramidal and extra-pyramidal) cerebral palsy and spastic hemiparesis were excluded.

The children were stratified into: 1) Two groups based on the severity of motor impairment; mild (diplegia), and severe (quadriplegia); 2) Two groups of different cognitive impairment levels, mild (LCI) and severe (SCI), based on established composite score ranges for Bayley Scales of Infant Development and the Stanford-Binet Intelligence Scale.

The control group consisted of healthy siblings of patients with Rett’s syndrome and Turner’s syndrome who were imaged as part of an ongoing study and children who had brain MR imaging for symptoms referable to the orbits, base of skull or posterior fossa.

All children included in the study had a standard pediatric brain MR imaging study performed on a 1.5-T magnet (Signa; GE Medical Systems: Milwaukee, WI): 2-dimensional sagittal and axial T₁-weighted spin-echo (SE) (TR/TE: 550/15), axial double echo SE (TR/TE1/TE2: 3000/20/80). Complete corpus callosal coverage with the sagittal T₁-weighted SE sequence was obtained using fifteen 5-mm-thick slices (in-plane resolution of 0.94 mm²). All MR exams were reviewed by a neuroradiologist.

For the children with spastic cerebral palsy, MR imaging findings limited to PVL (T₁ and/or T₂ prolongation in the periventricular white matter, reduction in the periventricular white matter especially in the regions of the atria, and irregularities of the lateral ventricular walls) were used for inclusion in the study. The presence of other MR imaging findings associated with congenital or other perinatal brain damage (i.e., schizencephaly, deep gray matter abnormalities, hemispheric gray matter damage, germi-

Fig. 1a and b  (a) Mild and (b) severe thinning of the corpus callosum demonstrated on mid-sagittal T₁-weighted SE (TR/TE: 550/15) MR images in two children with spastic diplegia and quadriplegia, respectively.
PVL group: Twenty-nine children (male/female: 20/9, age range at the time of the MR imaging exam: 1.0 to 13.5 years, gestational age range: 29 – 40 weeks) with spastic cerebral palsy and MR imaging findings limited to PVL fulfilled the above clinical and MR imaging inclusion criteria.

Control group: Thirty-two children (male/female: 25/7, age range at the time of the MR imaging exam: 1.1 to 17 years) were included in the control group so that their age composition was not significantly different than the four subject groups at the 0.05 level.

In the motor impairment subgroups there were 11 patients with diplegia and 15 patients with quadriplegia. Three patients were excluded because the severity of their motor impairment was not clear on chart review.

In the cognitive impairment subgroups there were 16 patients with mild (LCI) and 11 patients with severe (SCI) impairment. Two patients were excluded because the severity of their cognitive impairment was not clear on chart review.

Image processing
The analysis was performed on mid-sagittal T1-weighted SE MR sections. The corpus callosum was arbitrarily divided into five segments because the borders of the rostrum, genu, body, and splenium were not clearly defined on sagittal MR imaging. To divide the corpus callosum, a line was drawn tangential to inferior border of the rostrum and splenium. From this line, perpendicular lines were drawn at the anterior and posterior edge of the genu and splenium, and at regular distances dividing the corpus callosum into five segments of equal length. The most anterior segment contained the rostrum and genu, the second segment contained the anterior body of the corpus callosum, the third segment contained the mid body of the corpus callosum, the fourth segment contained the posterior body of the corpus callosum, and the fifth segment contained the splenium. Regional shape analysis of the corpus callosum was based on previously published methodology [7,8]. Briefly, a reference template of the corpus callosum, established in a previous study, was used as a measurement unit [6]. Shape characteristics of each subject were measured with respect to the template via a shape transformation, which elastically adapts the template to an individual’s corpus callosum. Embedded in this shape transformation were all the shape characteristics of the individual corpus callosum, with the template used as a measurement unit. Inter-individual differences were then examined via analysis of the corresponding shape transformations. As shown previously, shape analysis and size measurements were independent of the particular choice in of the template used in the analysis [7].

In this study, we calculated a particular quantity that reflects local size properties of the corpus callosum, referred to as the deformation function (the determinant of the Jacobian of the shape transformation). Fig. 2 demonstrates the properties of the deformation function. In particular, Fig. 2 shows a reference template, and two synthesized corpus callosal shapes along with the corresponding deformation functions that were calculated via our method. Visual or quantitative comparison of these deformation functions demonstrated the differences between the two callosa in Figs. 2 b and c. Note that since the deformation functions were defined based on the same template, they can be directly compared using point-wise statistics, in order to measure local size differences. Area measurements of the corpus callosum or any region of interest within the corpus callosum were readily obtained by integrating the deformation function within the region of interest.

Statistical analysis
Multiple range test (modified least significant difference, Bonferroni) was used to compare the age composition of the control group and four subject groups.

The deformation functions were analyzed statistically using point-wise t-tests. In particular, we performed the following group comparisons: controls versus patients, diplegic versus quadriplegic patients, and patients with relatively severe (SCI) versus relatively mild (LCI) cognitive impairment. One of the confounding factors in our analysis was variability in the overall size of the corpus callosum, which confounds regional measurements. Therefore, we also examined the deformation functions
Results

There was no statistical difference in age among the control group and the four subject groups (p > 0.1).

Controls versus patients: The comparison of the normalized deformation functions (Figs. 3c and 3d) showed a relative preservation of the first (genu and rostrum) and fifth segment (splenium), compared to the rest of the corpus callosum in the subject group. We stress that no corpus callosal region was larger in absolute value in the patients. The results of Fig. 3 suggest that the occipital and anterior most prefrontal fibers were relatively less affected by the disease.

Diplegic versus quadsplegic patients: The normalized deformation functions demonstrated a thicker corpus callosal body in diplegics, which reached significance in the superior aspect of the third segment (mid body) of the corpus callosum (Fig. 4).

Severe versus mild cognitive impairment: The normalized deformation functions of the SCI group were significantly greater than those of the LCI group in the fourth (posterior body) and fifth segments (splenium) of the corpus callosum and (Fig. 5). The normalized deformation functions of the LCI group were significantly greater than those of the SCI group in the second segment (anterior body) of the corpus callosum, suggesting relative preservation of anterior most prefrontal fibers in the former group (Fig. 5).

Discussion

Topographical organization of fibers coursing through the human corpus callosum has been the subject of several investigations both in the adult and pediatric brain. Conclusions regarding cerebral interhemispheric connections through the corpus callosum have been based on the anatomical location of cortical and subcortical lesions and on transcranial magnetic cortical stimulation [4,9,19,20]. Specifically, based on neuropathological findings, De Lacoste et al [9] correlated location of cerebral cortical lesions with the site of Wallerian degeneration in the corpus callosum. They found that: a) fibers from the inferior frontal and anterior inferior parietal regions cross through the first segment (rostrum and genu) of the corpus callosum, b) fibers from the superior parietal, temporoparieto-occipital junction, and occipital regions cross through the fifth segment (splenium) of the corpus callosum, and c) fibers from the posterior superior frontal region cross through the second and third segments (anterior and mid body) of the corpus callosum. Interestingly, the same investigators found two “acallosal” cortical regions, anterior superior frontal and mid temporal, in which no corresponding callosal Wallerian degeneration was found. In another study, using MR imaging and segmental cross-sectional area measurements of the corpus callosum, Moses et al [20] found a similar cortico-callosal topography in children with pre- and perinatal brain injury.
They also were unable to demonstrate, on MR imaging, compensatory axonal retention manifest as regional hypotrophic growth of the corpus callosum following early brain injury. Two recent studies [4,19], looking at the functional topography of the corpus callosum found that fibers crossing through the fifth segment (splenium) were important in mediating reading in patients with dominant hemispheric posterior communicating in-farcts and that fibers crossing through the third and fourth segments (mid and posterior body) were responsible for mediating interhemispheric inhibition between the motor cortices.

In this study, we use the shape and size of the corpus callosum to evaluate for differences between patients with PVL and controls, and between different subgroups of patients categorized based on severity of motor and cognitive impairment. The corpus callosum is chosen because a) it is invariably affected in PVL as a result of periventricular white matter injury; b) it connects association areas of the two cerebral hemispheres, hence, influencing cognition; c) it is easily demonstrable, in its entirety, with sagittal MR imaging; d) it is reliably quantifiable using computer-based semi-automated algorithms that require little manual editing. The latter is due to large differences in signal intensity ranges and well-defined boundaries between the corpus callosum and adjacent structures on sagittal T1-weighted MR imaging.

The comparison between patients and controls (Fig. 3) provides a reasonable explanation for the reported relative sparing of verbal abilities in patients with PVL [12,15,31]. The relative preservation of the regions associated with verbal fluency (splenium of the corpus callosum) on the normalized deformation functions adds support to the proposed topographic functional specialization of the corpus callosum. Also, the global reduction in size of the corpus callosum in patients with PVL compared to controls further supports lack of neuroplastic axonal retention and calloidal hypertrophy following early injury observed by Moses et al [20], and underscores the utility of the corpus callosum as an indirect measure of periventricular white matter loss.

The presence of a thicker corpus callosal body in diplegics is in agreement with evidence that the premotor and motor cortical areas connect through the central portion of the corpus callosum (third segment) [12,13,18].

Potential limitations of this study are in part related to its retrospective nature. We are unable to directly quantify periventricular white matter volumes because of the unavailability of MR images with high gray-white matter contrast. Also, we are limited to clinical information available in the patients' charts; for example, categorization of the severity of cognitive impairment is based on available composite scores without discrimination between language and visual-motor abilities. The influence of reported gender differences in sub-regions of the corpus callosum on the comparisons made in this study was not assessed due to the limited number of patients. Finally, this study was probably influenced by sampling bias in that children with spastic cerebral palsy who undergo brain MR imaging are usually more severely affected and may not constitute a representative sample.

In conclusion, global and regional corpus callosal morphometry can be quantified using deformation functions, which describe the shape transformation of a template to an individual’s corpus callosum and allow point-wise statistical comparisons.

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