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Visualization of maturation of the corpus callosum during childhood and adolescence using T2 relaxometry

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Abstract

Previous studies have shown that maturation of the white matter in terms of its relative signal intensity changes on MRI is almost complete at 2–3 years of age. We hypothesized that quantitative analysis may show maturation of the white matter during childhood and adolescence. In the present study we performed multi-echo T2 relaxometry in 33 healthy subjects (girls, 15; boys, 18) aged 3–15 years. T2 relaxation times of the genu and splenium were measured. In healthy subjects, the T2 relaxation times were significantly correlated with age in both girls ($r = 0.611$, $p = .016$) and boys ($r = 0.721$, $p = .001$) in the splenium, but not in the genu ($p > .05$). To further confirm genu-to-splenium signal intensity ratio changes, a total of 389 brain MRIs were retrospectively selected from the patients who had normal results (189 girls/women, 200 boys/men; age range, 3–20 years). The genu-to-splenium signal intensity ratio was obtained from the T2-weighted images. In patients with normal MRI, the genu-to-splenium signal intensity ratio was significantly decreased with age ($p < .001$) by 16 years. The T2 relaxation times gradually increase in the splenium during childhood and adolescence, suggestive of maturation.

Keywords: Human development; Corpus callosum; Magnetic resonance imaging

1. Introduction

It has been suggested that the splenium and genu mature on T2-weighted images of magnetic resonance imaging (MRI) at 6 months and 8 months, respectively (Barkovich et al., 1988). The authors also suggested that the whole white matter except the peripheral arborization reaches an adult appearance at approximately 18 months. A study using relaxometry suggested that both T1 and T2 relaxation times of gray and white matter of the human brain show rapid decrease during infancy, and decrease slowly during adolescence (Holland et al., 1986). In this study, the corpus callosum matures at 1 year, and that the internal capsule is the last to develop, with maturation occurring at 10 years. Myelination of the white matter was considered responsible for this signal intensity change, which was not observed after 2–3 years of age except at the internal capsule (Barkovich et al., 1988; Holland et al., 1986).

The water molecules in the white matter are located within myelin sheath, axon, and interstitial tissue. A large proportion of water molecules within the axon and interstitial tissue are likely unbound to macromolecules, and thus have longer T2 relaxation times (Whittall et al., 1997). Therefore, thicker axons and/or larger interstitial space may give rise to longer T2 relaxation times. The axonal diameter increase with decrease of density gradually occurs in the splenium of rhesus monkey (LaMantia and Rakic, 1990a,b), which may be true in human. Accordingly, it can be assumed that the gradual increase of

Abbreviations: MRI, magnetic resonance imaging; CST, corticospinal tract; SENSE, sensitivity-encoding; ROI, region of interest; G–S ratio, genu-to-splenium signal intensity ratio; DTI, diffusion-tensor imaging; FA, fractional anisotropy.

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axonal diameter in the splenium, which is part of the maturation, may parallel an increase of interstitial space, i.e. decrease of axonal density, thus giving rise to gradual increase of T2 relaxation times.

During childhood and adolescence, previous studies using T2 relaxometry showed gradual, but insignificant decrease of T2 relaxation times in the splenium with age (Hassink et al., 1992; Holland et al., 1986). However, they used dual-echo T2 relaxometry, which may not measure T2 relaxation times accurately (Graham et al., 1996; Whittall et al., 1997). Therefore, multi-echo T2 relaxometry may demonstrate different results as compared with the previous studies. The purpose of this study was to investigate whether the T2 relaxation times change in the splenium of the corpus callosum on multi-echo T2 relaxometry during childhood and adolescence.

2. Materials and methods

We obtained T2 relaxometry in healthy volunteers at 3.0 T first due to its higher signal-to-noise ratio. Thereafter, we retrospectively validated our results by using the data from patients with normal T2-weighted MRI. It is desirable to evaluate the T2-weighted MRI obtained at the same 3.0 T scanner. However, the patients with normal brain MRI obtained at 3.0 T were limited in number. Therefore, we analyzed patients with normal T2-weighted MRI obtained at 1.5 T.

2.1. T2 Relaxometry in healthy normal volunteers

Thirty-three healthy subjects (girls, 15; boys, 18) aged 3–15 years (mean, 10.9 years) were enrolled in this study as volunteers. The parents of all healthy subjects gave consent for MRI. No sedation was required. The institutional review board of our hospital approved this study. Subjects having abnormalities discovered while obtaining the MRI were excluded in imaging analysis.

2.1.1. T2 relaxometry

All healthy subjects were examined on a 3.0 T scanner (Intera Achieva, Philips Medical Systems, Best, Netherlands) with an eight-channel sensitivity-encoding (SENSE) head coil. A multi-echo 3-D Carr-Purcell-Meiboom-Gill sequence (Georgiades et al., 2001) was used for transverse T2 relaxometry with the following parameters: 256 × 128 matrix (256 × 256 after reconstruction); repetition time, 4294 ms; 8 echoes (20–160 ms) with an increment of 20; echo train length, 8; field of view, 220 mm; SENSE factor 2. The thickness was 3 mm without gap.

2.2. MR imaging in patients

To further validate our study using T2 relaxometry, we selected normal brain MRIs to validate whether signal intensity of the splenium on T2-weighted imaging gradually increase with age. From the records of our institute between January 2002 and October 2006, a total of 389 normal brain MRIs were selected from patients who underwent MRI for minor neurologic symptoms and signs (headache, 198; fever, 125; dizziness, 34; eye diseases, 18; syncope, 10; facial palsy, 4). The patients were 189 girls/women and 200 boys/men aged 3–20 years (mean, 11.8 years ± 5.2 [S.D.]). Two neuroradiologists verified the normality of all MRIs in consensus. The number of patients at any given age was greater than 20.

2.2.1. Conventional imaging

All patients were examined with 1.5 T scanners (Signa Horizon, G.E. Medical Systems, Milwaukee, Wis [$n = 226$]; Intera, Philips Medical Systems, Best, Netherlands [$n = 172$]) equipped with a manufacturer-supplied quadrature head coil (G.E.) and a six-channel SENSE head coil (Philips). The following conventional sequences were performed: sagittal T1-weighted (333 (G.E.) or 400 (Philips)/11 [repetition time ms/echo time ms], one signal acquired), transverse fast spin-echo T2-weighted (4000–4058/80–114, one signal acquired), and transverse T1-weighted (311 (G.E.) or 420 (Philips)/11, one signal acquired) MR imaging. The thickness and slice gap were 5 mm and 2–2.5 mm, respectively. The field of view was 220 or 240 mm. The matrix of T2-weighted imaging was 256 × 256 (G.E.) or 512 × 267 (512 × 352 after reconstruction, Philips).

2.3. Data analyses

2.3.1. T2 relaxometry maps in healthy volunteers

To avoid cerebrospinal fluid contamination, the regions of interest (ROIs) in each subject were carefully drawn on the transverse images with echo time of 100 ms in each center of the genu and splenium by a neuroradiologist who was blind to the subject's age. The areas of the ROIs ranged from 15 to 50.0 mm^2 according to the size of the genu or splenium. These ROIs were transferred onto the T2 relaxometry maps, and T2 relaxation times were recorded in each center of the genu and splenium. The absolute signal intensity on T2-weighted imaging may be different between 3.0 and 1.5 T. Therefore, we additionally measured genu-to-splenium signal intensity ratios (G–S ratios) on the images obtained with echo time of 100 ms. The same ROIs for T2 relaxation time measurement were used. The G–S ratios were recorded in all subjects.

2.3.2. Conventional T2-weighted images in patients with normal MRI

A neuroradiologist who did not involve in measurement of T2 relaxation times drew ROIs in the center of the genu and splenium of all patients on the transverse T2-weighted images without information regarding the age of patients. The areas of the ROIs ranged 15 mm^2 to 60 mm^2 according to the size of the genu or splenium. The G–S ratios were recorded in all patients.

2.4. Statistical analyses

The Spearman rank correlation test was performed to assess whether T2 relaxation times of the genu and splenium or G–S ratios may correlate with age in healthy subjects. To test whether the G–S ratios change with age (3 to 20 years of age) in patients, a linear regression analysis was performed. The variable of gender was included in the analysis to test its difference in the G–S ratio change pattern. The Kruskal–Wallis test was performed to test differences in the G–S ratio among older adolescents. The Mann–Whitney test was performed to test differences in the G–S ratio between the two age groups identified with the Kruskal–Wallis test. The age range of the older adolescents was determined by a box plot. A p-value less than .05 was considered to indicate statistical significance. All the statistical analyses were performed with statistical software (SPSS, version 12; Chicago, IL).

3. Results

3.1. T2 Relaxometry in healthy subjects

The T2 relaxation times of the genu and splenium of all subjects ranged from 64.09 to 73.06 (mean, 68.74; S.D., 2.59) and from 69.56 to 83.93 (mean, 77.50; S.D., 3.77), respectively. The T2 relaxation times were significantly correlated with age in both girls ($r = 0.611$, $p = .016$) and boys ($r = 0.721$, $p = .001$) in the splenium, but not in the genu ($p > .05$) (Fig. 1). The G–S ratios on the images with echo time of 100 ms were also significantly correlated with age in both girls ($r = -0.873$, $p < .001$) and boys ($r = -0.806$, $p < .001$). The signal intensity on T2 relaxation maps was gradually increased in the splenium (Fig. 2).