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Microstructure assessment of the thalamus in Wilson's disease using diffusion tensor imaging

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AIM: To assess diffusion changes of the thalamus in Wilson's disease using diffusion tensor imaging (DTI).

MATERIALS AND METHODS: Fifteen patients with Wilson's disease and an abnormal signal in the thalamus (designated as group 1) and 18 patients with Wilson's disease with a normal-appearing thalamus (designated as group 2) at conventional magnetic resonance imaging (MRI) were recruited. Fifteen age-matched and sex-matched healthy volunteers were also enrolled as the control group (designated as group 3). The fractional anisotropy (FA), primary eigenvalue (λ1), second eigenvalue (λ2), and third eigenvalue (λ3) of the thalamus were measured and the differences were compared.

RESULTS: The FA values of the thalamus were different in the three groups (group 1: 0.36 ± 0.02; group 2: 0.38 ± 0.02; group 3: 0.43 ± 0.02; $F = 54.51$, $p < 0.001$). A statistically significant difference was observed between group 1 and group 2 ($p = 0.003$), group 1 and group 3 ($p = 0.001$), and group 2 and group 3 ($p < 0.001$). The λ1, λ2, and λ3 values of the thalamus were different in the three groups (1.11 ± 0.06 mm^2/s, 1.11 ± 0.06 mm^2/s, and 1.10 ± 0.04 mm^2/s of λ1 in group 1, group 2, and group 3, respectively; 0.82 ± 0.08 mm^2/s, 0.78 ± 0.05 mm^2/s, and 0.72 ± 0.02 mm^2/s of λ2 in group 1, group 2, and group 3, respectively; 0.52 ± 0.05 mm^2/s, 0.49 ± 0.06 mm^2/s, and 0.42 ± 0.06 mm^2/s of λ3 in group 1, group 2, and group 3, respectively; $F = 1.65$, $p = 0.203$ of λ1; $F = 10.55$, $p < 0.001$ of λ2; $F = 4.21$, $p = 0.021$ of λ3; respectively). A statistically significant difference in the λ2 value was observed between group 1 and group 3 ($p < 0.001$) and group 2 and group 3 ($p = 0.005$). A statistically significant difference in the λ3 value was also observed between group 1 and group 3 ($p = 0.007$). No significant difference in the λ1 value was noted between each of the two groups.

CONCLUSIONS: Damage of the thalamus in Wilson's disease patients can be detected using DTI. DTI may provide information regarding thalamus damage in patients with Wilson's disease before abnormal signals on conventional MRI.

Introduction

Wilson's disease (WD), also known as hepatolenticular degeneration, is a progressive disorder of copper metabolism.[1] Conventional magnetic resonance imaging (MRI) is the most commonly used radiological technique, in addition to clinical and laboratory data, for diagnosis and

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monitoring of WD, and it has emerged as a key surrogate measure for treatment outcomes in clinical trials.[2,3] Conventional MRI manifestations have been well described in cases of WD. The basal ganglia are the most affected structures, followed by the thalamus and brain stem.[4,5] The thalamus is a commonly involved region in WD patients; it was reported previously that abnormal signal in the thalamus at conventional MRI was noted in approximately half of patients with WD.[1,6] It is unclear whether an abnormal-appearing thalamus at conventional MRI has pathological changes to the diffusion of the thalamus. Also these data indicate that perhaps 50% of patients with WD do not have an abnormal signal in the thalamus at conventional MRI; however, does this normal-appearing thalamus at conventional MRI have pathological changes?

Diffusion tensor imaging (DTI) is a relatively new technique useful for assessing changes in diffusion. Analysis of additional DTI metrics, such as fractional anisotropy (FA) and eigenvalues, may be useful for identifying microstructural abnormalities.[7–10] It is unclear at present whether DTI can provide information regarding thalamus damage in patients with WD before abnormal signal is detected at conventional MRI. The aim of the present study was to assess diffusion changes of the thalamus in patients with WD using DTI. To the authors' knowledge, this is the first report on the estimation of diffusion in the thalamus using DTI in patients with WD.

Materials and methods

Study population

The local ethics committee approved this retrospective study, and informed consent was obtained from all patients and volunteers. Forty-eight participants, including 33 patients with WD and 15 healthy volunteers, were examined over a 5-year period (from 2008 to 2012) as part of a research study, and all participants were evaluated at East Hospital,The First Affiliated Hospital,Sun-Yat Sen University. Fifteen patients (eight male, seven female, age range 11–25 years, mean age 18.3 ± 3.2 years) with WD with abnormal signal in the thalamus (designated as group 1) and 18 patients (nine male, nine female, age range 10–27 years, mean age 19.5 ± 3.5 years) with WD with a normal-appearing thalamus (designated as group 2) at conventional MRI were enrolled. The percentage of abnormal signal in the basal ganglia in group 1 was 93.3% (14/15) and that in group 2 was 88.9% (16/18). The diagnosis of WD was based on clinical manifestations, low serum copper and ceruloplasmin level, increased 24 h urinary excretion of copper, and the presence of a Kayser–Fleischer (KF) ring. Fifteen age-matched and sex-matched healthy volunteers (eight male, seven female, age range 11–27 years, mean age 18.1 ± 3.3 years) were also included as a control group (designated as group 3).

MRI protocol

All examinations were performed using a 1.5 T MRI machine (Achieva Nova Dual; Philips Healthcare, Best, The Netherlands) equipped with an eight-channel SENSE head coil. Conventional MRI sequences used for the evaluation included spin-echo (SE) T1-weighted images [488 ms repetition time (TR), 15 ms echo time (TE)] obtained in the axial and sagittal planes, with an acquisition time of 2 min, matrix of 256 × 256, and a 250 mm field of view (FOV). Axial T2-weighted images were acquired (3600 ms TR, 100 ms TE). Fluid attenuation and inversion recovery (FLAIR) sequences were obtained in the coronal plane (6000 ms TR, 250 ms TE). The section thickness was 5 mm. DTI was performed by using SE echo-planar imaging (EPI) (9500 ms TR, 70 ms TE, 256 × 256 matrix size, 250 mm field of view, 2 mm section thickness with no gap). Images were obtained with both 32-direction diffusion-encoding ($b = 1000$ s/mm^2 for each direction) and no diffusion encoding ($b = 0$ s/mm^2).

Data analysis

All DTI acquisition data were transferred to a workstation (Philips extended MR workspace 2.6.3.2, Philips Medical Systems) and processed using DTI fibre-tracking software for DTI quantitative analysis. The FA map was reconstructed automatically and the FA, the primary eigenvalue (λ1), the second eigenvalue (λ2), and third eigenvalue (λ3) of the thalamus were measured. The appearance of the thalamus on conventional images and the group to which the patients should be allocated were reviewed by two radiologists (X.P. and P.X.M.) and any discrepancy was resolved in consensus. Regions of interest (ROIs) with an area of approximately 20 mm^2 were placed on the thalamus. Because most of the damage to the thalamus in WD was bilaterally symmetrical, the average value of the bilateral thalamus was adopted. ROI placement is depicted in Fig 1. The DTI measurements were reviewed by a radiologist (L.G.D.). To reduce random variability in the measurements, each value was an average of three different measurements. The mean and standard deviation of the values were calculated for each individual.

Statistical analysis

The statistical analysis was undertaken using SPSS base 17.0 for Windows. A p-value <0.05 was considered statistically significant. The normality of distribution of the parameters was assessed using the Kolmogorov–Smirnov test. One-way analysis of variance (ANOVA) and least significance difference (LSD) tests were used to compare the FA, λ1, λ2, and λ3 values of each group.

Results

The FA, λ1, λ2, and λ3 values of each group varied. The mean and standard deviation of FA, λ1, λ2, and λ3 of each group are listed in Table 1. The FA value of the thalamus in group 2 (Fig 2) was lower than group 3, but higher than group 1 (Fig 3). A statistically significant difference was observed between group 1 and group 2 ($p = 0.003$), group 1 and group 3 ($p = 0.001$), and group 2 and group 3 ($p < 0.001$). The λ1, λ2, and λ3 values of the thalamus in group 2 were higher than group 3, but lower than group 1.