Diffusion tensor imaging characterization of occult brain damage in relapsing neuromyelitis optica using 3.0T magnetic resonance imaging techniques

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ABSTRACT

Studies of relapsing neuromyelitis optica (RNMO) using advanced MRI techniques are limited compared with those done on multiple sclerosis (MS). The present study used diffusion tensor imaging (DTI) to investigate whether occult brain damage exists in RNMO patients. DTI scans using a 3.0T MRI scanner were performed in 24 clinically confirmed RNMO patients whose conventional brain MRI results were normal, and also in 24 age- and sex-matched healthy control subjects. DTI data were processed to generate fractional anisotropy (FA) and mean diffusivity (MD) maps, and region of interest (ROI) analyses were performed to obtain these parameters in white matter (including medulla oblongata, cerebral peduncle, optic radiation, genu of corpus callosum, splenium of corpus callosum, and internal capsule) and gray matter (including thalamus and putamen). Regional measures from patients at stable and acute phases were compared with healthy controls. Both acute and stable NMO patients had a higher average FA in ROIs of the thalamus and putamen. Acute NMO patients had significantly higher average MDs than controls in the genu of corpus callosum and optic radiation, and significantly lower average MDs in the medulla oblongata. Stable NMO patients had increased MDs in the genu of corpus callosum and optic radiation, but lower MDs in the medulla oblongata, internal capsule and thalamus. The DTI findings confirm the presence of occult tissue damage in normal-appearance white and gray matter, especially deep gray matter, in RNMO patients. This study adds further to the evidence that DTI is suitable as a tool for characterizing subtle brain tissue damage.

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Introduction

Neuromyelitis optica (NMO) is a severe form of demyelinating autoimmune disease characterized by the selective involvement of the optic nerves and spinal cord in a mono- or multi-phasic manner (Devic, 1984; Ghezzi et al., 2004; Wingerchuk et al., 1999). The incidence rate of NMO is about 1 in 100,000 in Western countries (Marignier et al., 2010), however, there are no precise statistics for China. The disease is also known as Devic’s disease or Devic’s syndrome to commemorate the author of the initial report (Devic, 1984). Age at onset follows a unimodal distribution with a peak between 21-and 41-years-of-age. The distinctive clinical manifestation is the co-occurrence of optic neuritis with myelitis (Yamakawa et al., 2000). Viral infection may have an important relationship with the disease, although whether NMO is evoked directly by viral infection, as suggested by Merle et al. (1998), is unclear. It remains contentious whether NMO is a form of multiple sclerosis or a separate neurological entity, although more recent evidence favors the latter view. The evidence includes epidemiology, course of disease, clinical manifestation, pathology, CSF analyses, and especially, the discovery of serum autoantibody IgG, which may be a sensitive and specific marker for NMO (de Seze et al., 2002, 2003; Lucchinetti et al., 2002). Despite the apparent differences between multiple sclerosis and NMO, it remains difficult to distinguish the two conditions, both clinically and in lab analyses. MRI is an important tool in diagnosing NMO. As a consequence, new diagnostic criteria was proposed for NMO, with a supportive criteria being a contiguous spinal cord MRI lesion extending three or more segments (Wingerchuk et al., 1999). A more recent revision of the criteria considered a brain MRI not meeting the diagnostic criteria.
criteria for MS as a supportive criterion for NMO (Wingerchuk et al., 2006).

Recently, along with the development of MRI and increased recognition of NMO, quantitative MRI techniques including DTI, MTI and fMRI have been used to study NMO. These techniques may provide more detail than is possible using MRI, and may be useful in the diagnostic work-up of patients and increasing the understanding of NMO pathobiology. However, there has been no study involving a large number of patients concerning the possible presence of abnormalities in normal-appearance brain tissue. The present study investigated whether and where occult brain damage exists in RNMO patients using DTI.

Materials and methods

Subjects

Thirty patients were recruited from inpatient or outpatient departments with a relapsing course, in acute or stable stages, satisfying the proposed diagnostic criteria of NMO—which included optic neuritis (acute myelitis) and at least two supportive criteria (contiguous spinal cord MRI lesion extending three or more segments, brain MRI not meeting diagnostic criteria for multiple sclerosis, and NMO-IgG seropositive status) (Wingerchuk et al., 2006). Of the thirty patients, six were excluded due to multiple lesions in the white matter of the brain (n=3), poor quality DTI image (n=2), and presence of dysmyotonia (n=1). The final group of 24 patients (three male, 21 female) all displayed normal brain MRIs and were free of other disease. Eighteen patients underwent DTI during acute relapse prior to receiving corticosteroids or other immunosuppressive agents. Thirteen patients underwent DTI during stable stage disease and after treatment with corticosteroids or other immunosuppressive treatments within the previous 2 months. The study was approved by the local ethical committee, and written informed consent was obtained from all participants before the MRI examinations.

MRI acquisition

Brain imaging was performed in all participants using an EXCITE 3.0T MRI system (GE, Milwaukee, WI, USA) at the Department of Radiology in the West China Hospital, Sichuan University. The apparatus was equipped with an eight-channel phased-array head coil. DTI-MRI was performed using a SE-EPI sequence in 50 axial planes with 15 non-collinear diffusion sensitization gradients (b=1000 s/mm²) to generate the tensor. A reference image with no diffusion weighting (b₀ image) was also obtained. The imaging parameters were TR=12000 ms, TE=70.8 ms, NEX=2, FOV=240×240 mm², acquisition matrix=128×128, and the section thickness was 3 mm without intersection gaps.

Imaging procession and statistical analysis

DTI-Studio free software (version 2.40, Radiology Department, Johns Hopkins University, Baltimore, MD; available at http://cmrm.med.jhmi.edu/) was used to compute all diffusion-weighted images to generate FA maps and MD maps from the DTI data. The average FA and MD values in brain ROIs were measured with ROIEditor software (version 1.0.1, available at www.mristudio.org). The regions included white matter (medulla oblongata, cerebral peduncle, optic radiation, genu of the corpus callosum, splenium of the corpus callosum, and internal capsule) and gray matter (thalamus and putamen) (Fig. 1). All types of ROIs were first defined on the FA images, and then transferred onto the MD images. The boundary of each ROI was carefully defined within the target structure to reduce the partial volume effect. All ROIs were manually outlined and measured by two personnel blinded to the group status, with the average values presented. This can increase the relative accuracy. In addition, we analyzed the intraclass correlation coefficient between the two data groups measured by two personnel (Tables 1 and 2). All statistical evaluations were performed with SPSS17.0 software (SPSS, Cary, NC, USA). The regional measures from patients in the stable and acute phases were compared with healthy controls respectively using Student’s t-tests for independent samples. P<0.05 was considered statistically significant.

Results

Our study cohort includes 24 clinically confirmed cases of NMO. Their mean age was 37.3 ± 11.1 years (range 22–62 years), the mean course of disease was 30.4 ± 27.9 months (range 5–120 months), the mean age of onset was 34.5 ± 10.8 years (range 20–61 years), and the mean Kurtzke EDSS score was 3.63 ± 1.76 (range 1.0–6.0). Twenty-four age- and sex-matched healthy volunteers (three male, 21 female) with normal brain MRIs served as control subjects. Among all the participating patients, seven received DTI scans during both the acute and stable stage; thus, 31 DTI scans were presented in total.

Average FA and MD values of ROIs from patients with RNMO in both the acute and stable stages, and the control subjects, are presented in Tables 3 and 4. For bilateral structures, e.g., the thalamus, we conducted group comparisons for the left and right side separately and found the results were less significant for all structures than comparisons done on the L-R combined ROI. Thus, we only present results derived from the unified ROIs for bilateral structures. Patients at the acute stage of RNMO had a higher FA (P<0.05) in the thalamus and putamen than did control subjects. These patients also had a higher MD (P<0.05) in the genu of corpus callosum and optic radiation and a lower average MD (P<0.05) in the medulla oblongata than did control subjects (Table 3). Compared with control subjects, patients in stable stage RNMO had a higher FA (P<0.05) in the thalamus and putamen and a higher MD (P<0.05) in the genu of corpus callosum and optic radiation but had a lower MD (P<0.05) in the medulla oblongata, internal capsule and thalamus (Table 4). In addition, in order to avoid measurement bias, we outlined the ROIs on the T2W image and transferred them onto the FA maps. We then calculated the intraclass correlation coefficient between DTI- and T2-derived ROIs (Table 5).

Discussion

Conventional MRI of the spinal cord, brain and optic nerve has been extensively used in the examination of NMO patients for a long time. During the acute phase, the affected regions of the cord are usually swollen, presenting as hyperintensity on T2-weighted images and hypointensity on T1-weighted images, and may enhance after Gd administration. The cord lesions usually extend over three or more vertebral segments (Filippi and Rocca, 2004; Filippi et al., 1999). It was believed that brain MRI was negative at the onset of the disease (Wingerchuk et al., 1999), but with the development of MRI and the further recognition of the disease, early pathological changes in the brains of those with NMO have been revealed. Changes may be sporadic demyelinating lesions, possibly related to age or other pathological changes (de Seze et al., 2002; Fazekas et al., 1994; Filippi and Rocca, 2004; O’Riordan et al., 1996; Wingerchuk et al., 1999). More recently, the refinement of MRI and its application has revealed that damage exists in brain tissue that is judged to be normal in conventional MRIs of MS patients (Bozzali et al., 2002; Cercignani et al., 2001; Rashid et al., 2004; Rovaris et al., 2005). Whether occipital brain damage exists in NMO patients remains unclear (Filippi et al., 1999; Rocca et al., 2004a, 2004b; Yu et al., 2006, 2008). The use of MRI to investigate the occult damage of normal-appearance brain matter in eight patients with RNMO found no difference between patients and control subjects (Filippi et al., 1999). Another study, which used both DTI and MTI to investigate the abnormal changes in the normal-appearance white matter and normal-
appearance gray matter in patients with NMO, reported a reduced magnetization transfer ratio and increased apparent diffusion coefficient in the normal-appearance gray matter of patients (Rocca et al., 2004a). Another study utilizing fMRI described an abnormal pattern of movement-associated cortical activations in patients with NMO (Rocca et al., 2004b). DTI has been used to investigate diffusion abnormalities both in normal-appearance white matter and normal-appearance gray matter (Yu et al., 2006) Diffusion abnormalities were also described in the corticospinal tract and optic radiation (Yu et al., 2008). The latter two studies indicate that secondary

![Fig. 1. FA images showing ROIs of the thalamus (A), putamen (B), genu of the corpus callosum (C), splenium of the corpus callosum (D), optic radiation (E), cerebral peduncle (F), medulla oblongata (G) and internal capsule (H).](image)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Intraclass correlation coefficient (between acute patients).</th>
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<tr>
<td></td>
<td>Acute (Examiner 1) Acute (Examiner 2)</td>
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<tr>
<td>FA1</td>
<td>FA2</td>
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<tr>
<td>0.762</td>
<td>0.852</td>
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<th>Table 2</th>
<th>Intraclass correlation coefficient (between stable patients).</th>
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<td></td>
<td>Stable (Examiner 1) Stable (Examiner 2)</td>
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<tr>
<td>FA1</td>
<td>FA2</td>
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<tr>
<td>0.898</td>
<td>0.850</td>
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</table>
Degeneration can be caused by lesions in the spinal cord and optic nerve. The present study mainly performed ROI analysis, which revealed that both acute and stable NMO patients had a higher FA in ROIs of the thalamus and putamen, and an increased MD in ROIs of the genu of corpus callosum and optic radiation. Reduced MD was evident in the medulla oblongata, cerebral peduncle, and thalamus, and an increased FA in ROIs of the thalamus and putamen. The present study has also further added evidence to the use of DTI as a tool for characterizing subtle brain tissue damage. The MD value is more sensitive than the FA value in diffusion imaging, and the simultaneous use of both can easily detect abnormalities. The present use of 3.0T MRI likely yielded more precise results. And lastly, some of these ROIs may have some WM fibers passing though, but there is little interaction between them.

However, the possibility of measurement errors cannot be excluded, and the recruited number of patients in the present study was still limited, although it is more than in previous studies.

Conclusions

DTI revealed for the first time the presence of occult tissue damage both in normal-appearance white matter and normal-appearance gray matter in NMO patients; especially in the deep gray matter including the thalamus and putamen. The present study has also further added evidence to the use of DTI as a tool for characterizing subtle brain tissue damage. The MD value is more sensitive than the FA value in diffusion index, and the simultaneous use of both can easily detect abnormalities.

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