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Diffusion tensor imaging of peripheral nerve in patients with chronic inflammatory demyelinating polyradiculoneuropathy: a feasibility study

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Abstract

Introduction The purpose of this study was to assess the clinical feasibility of diffusion tensor imaging (DTI) for the evaluation of peripheral nerves in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). *Methods* Using a 3-T magnetic resonance imaging scanner, we obtained DTI scans of the tibial nerves of 10 CIDP patients and 10 sex- and age-matched healthy volunteers. We prepared fractional anisotropy (FA) maps, measured the FA values of tibial nerves, and compared these values in the two study groups. In nine patients, we also performed tibial nerve conduction studies and analyzed the correlation between the FA values and parameters of the nerve conduction study.

Results The tibial nerve FA values in CIDP patients (median 0.401, range 0.312–0.510) were significantly lower than those in healthy volunteers (median 0.530, range 0.469–0.647) (Mann–Whitney test, $p<0.01$). They were significantly correlated with the amplitude of action potential (Spearman correlation coefficient, $p=0.04$, $r=0.86$) but not with nerve conduction velocity ($p=0.79$, $r=0.11$).
Conclusion Our preliminary data suggest that the noninvasive DTI assessment of peripheral nerves may provide useful information in patients with CIDP.

Keywords Magnetic resonance imaging · Diffusion tensor imaging · Peripheral nerve · Chronic inflammatory demyelinating polyradiculoneuropathy

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Introduction

Diffusion tensor imaging (DTI) is a noninvasive technique to evaluate the neuronal tract structure in vivo [1, 2]. In addition to conventional magnetic resonance imaging (MRI), assessment by DTI provides new information about the effects of the disease processes on tissue microstructure. In particular, assessment of the anisotropy index facilitates evaluation of the structural integrity and directional coherence of the nerve fibers. Although DTI has been widely used in central nervous system studies, its application in the assessment of peripheral nerves, especially in the clinical setting, has been limited [3–11].

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic neuropathy thought to be of immune origin. Its classic presentation includes sensory and motor symptoms in the distal and proximal segments of all

limbs, which evolve in the course of more than 8 weeks. Increased protein concentrations in cerebrospinal fluid and heterogeneous slowing of nerve conduction are typical of the condition. The pathologic hallmark of CIDP is loss of the myelin sheath of the peripheral nerves [12]. The diagnosis of CIDP can be difficult and may require nerve biopsy. Earlier MRI studies of peripheral nerves in CIDP patients revealed hypertrophy and increased T2 signal intensity of spinal nerve roots and the brachial plexus, sometimes accompanied by abnormal contrast enhancement [13–16]. In a few cases, MRI demonstrated enlargement of the intercostal nerves and nerve trunks of the extremities [14, 17, 18]. In recent reports, diffusion neurography was used to demonstrate enlarged nerve roots [19], and elevated apparent diffusion coefficient (ADC) values were observed in brachial and lumbar plexuses of CIDP patients [20]; however, these studies did not evaluate the anisotropy index. To the best of our knowledge, ours is the first study to evaluate the anisotropy index of peripheral nerves in CIDP patients.

The purpose of this study was to investigate clinical feasibility of DTI for the evaluation of peripheral nerve in CIDP patients.

Materials and methods

Study population

Our study received institutional review board approval, and informed consent was obtained from all participants before entry into the study. We persuaded 10 consecutive CIDP patients (seven men and three women ranging in age from 30 to 69 years, mean 57.4±13.6 years) who were admitted to our hospital from August 2008 to January 2010 to join this study. All 10 patients agreed to participate in the study. Their diagnosis was based on published clinical criteria (2006 European Federation of Neurological Societies/

Peripheral Nerve Society criteria) [21]. One patient in our study population had diabetes mellitus. None of the patients had a history of exposure to neurotoxic agents. The disease duration at the time of MRI study ranged from 3 months to 20 years (mean 8.2±6.6 years). Five patients had received no treatment before the MRI examination. Five patients had undergone therapy with immunoglobulin, and two had also received treatment with corticosteroid before the MRI examination. We also recruited 10 sex- and age-matched healthy volunteers (seven men and three women ranging in age from 34 to 69 years, mean 55.6±13.8 years); all were asymptomatic, had no neurological diseases, and did not take drugs with possible effects on peripheral nerves.

MRI examination

All images were obtained on a 3-T MRI unit (Signa Excite HD 3.0; General Electric Medical Systems, Milwaukee, WI, USA). The participants were imaged in the supine position, and a quadrature lower-extremity coil was used. We scanned the symptomatic side of the distal crus of each patient and the bilateral distal crura of each volunteer. The examined crus was immobilized with cushions.

We obtained DTI- and T2-weighted MRI scans in the axial plane. The diffusion tensor images were acquired using a single-shot spin echo diffusion-weighted echo planar imaging sequence with the following parameters: repetition time (TR) 3,500 ms, echo time (TE) 93 ms, number of acquisition 9, field of view (FOV) 20×20 cm, image matrix 192×192 (in-plane resolution 1.04× 1.04 mm), slice thickness/gap 5:5 mm. A b value of 1,000 s/mm^2 was applied in 15 directions. A total of seven axial slices were acquired from 4 to 10 cm proximal to the upper margin of the talus. The total DTI acquisition time was 8 min 31 s. The T2-weighted images, obtained for anatomical reference, were acquired using a fast-spin-echo sequence at TR 4,500 ms, TE 102 ms, echo train length 20,

Fig. 1 a Anatomical T2-weighted image. *Arrow* indicates the tibial nerve. b ROI on FA map. ROI is placed including entire tibial nerve to measure maximum FA value of the nerve
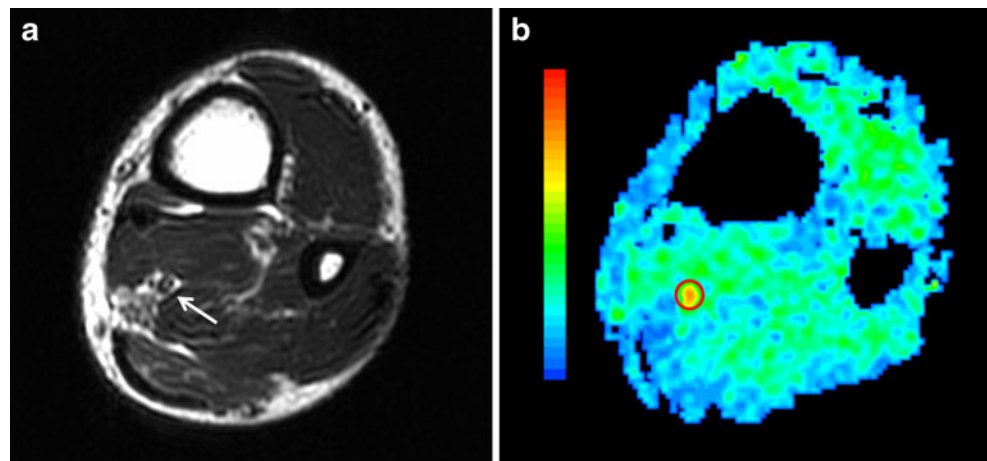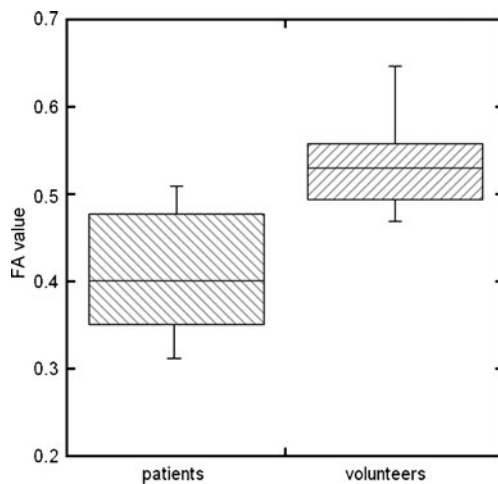
Fig. 2 Box plots showing FA values of tibial nerve in CIDP patients and healthy volunteers. In a box plot, the box is divided at the median, and the *top* and *bottom* of box represent the upper and lower quartiles. The *error bars* extend to the largest and smallest observed data points. The FA values in CIDP patients are significantly lower than those in healthy volunteers ($p < 0.01$)

number of acquisition 2, and image matrix 320×224. FOV and slice thickness/gap were the same as for DTI.

The raw diffusion tensor data were transferred to an independent workstation (Advantage Windows 4.2; General Electric Medical Systems) and processed with a computer software program (FUNCTOOL; General Electric Medical Systems). The fractional anisotropy (FA) values were calculated on a pixel-by-pixel basis, and FA maps were generated. We did not apply distortion correction because this method frequently causes severe misregistration artifacts at crural DTI. Circular or ovoid regions of interest (ROI) were placed manually to surround the anatomic location of the tibial nerve on the FA maps with reference to T2-weighted images, carefully not including neighboring muscle which had relatively high FA value (Fig. 1). The ROI was 20–26 mm^2 in size and covered the entire tibial

nerve. The maximum FA value was measured from the ROI in each slice, and the mean value of seven slices was calculated. The average of the bilateral FA values was recorded in the volunteers and used for analysis.

Nerve conduction study

In nine of the 10 patients, we performed tibial nerve conduction studies between 20 days before and 4 days after MRI study. Nerve conduction studies were performed on the same side as the MRI studies. Tibial nerve conduction velocities and the amplitude of action potentials were recorded.

Statistical analysis

As our sample size was small, we performed statistical analyses with nonparametric tests. To compare the FA values between the patients and volunteers, we used the Mann–Whitney test. To assess the correlation between the FA values and the parameters of nerve conduction study in the patients, we used the Spearman correlation coefficient. A value of $p < 0.05$ was considered statistically significant. We employed commercially available statistical software (Statcel ver. 2, OMS, Japan) for analyses.

Results

Figure 2 presents the median and the range of the tibial nerve FA values in our study population. The median FA value was 0.401 (range 0.312–0.510) in the CIDP patients and 0.530 (range 0.469–0.647) in the volunteers; the difference was statistically significant ($p < 0.01$). Representative cases are shown in Figs. 3 and 4.

In the nerve conduction study on nine patients, no action potential was evoked in two patients whose tibial nerve FA

Fig. 3 Anatomical T2-weighted image (**a**) and FA map (**b**) in a 67-year-old male healthy volunteer. Tibial nerve (*arrow*) is shown in red on FA map, which indicates apparently higher FA value than surrounding tissue. The maximum FA value of tibial nerve is 0.55. Some distortion occurs in FA map
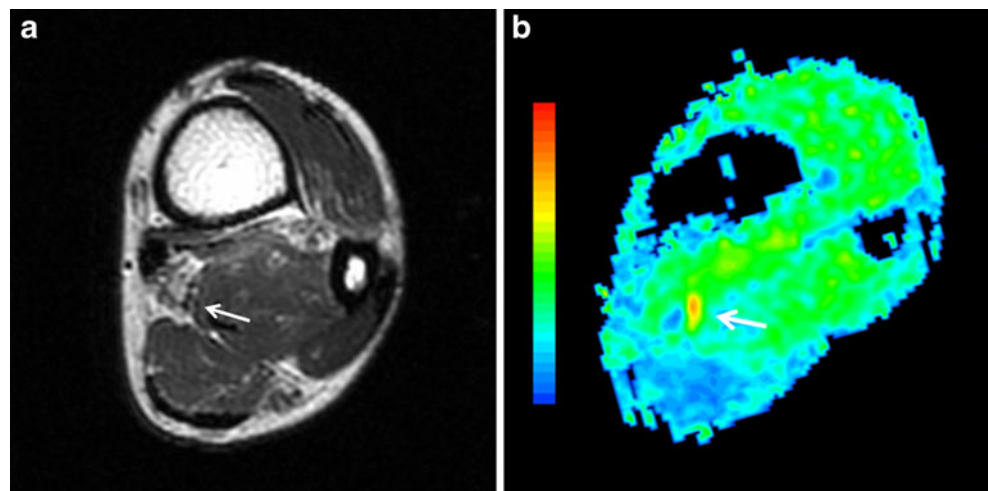
Fig. 4 Anatomical T2-weighted image (**a**) and FA map (**b**) in a 66-year-old male patient with CIDP. Tibial nerve (*arrow*) is shown in yellow-green on FA map, which indicates slightly higher FA value than surrounding tissue. The maximum FA value of tibial nerve is 0.42. No notable tibial nerve abnormality is found on T2-weighted image
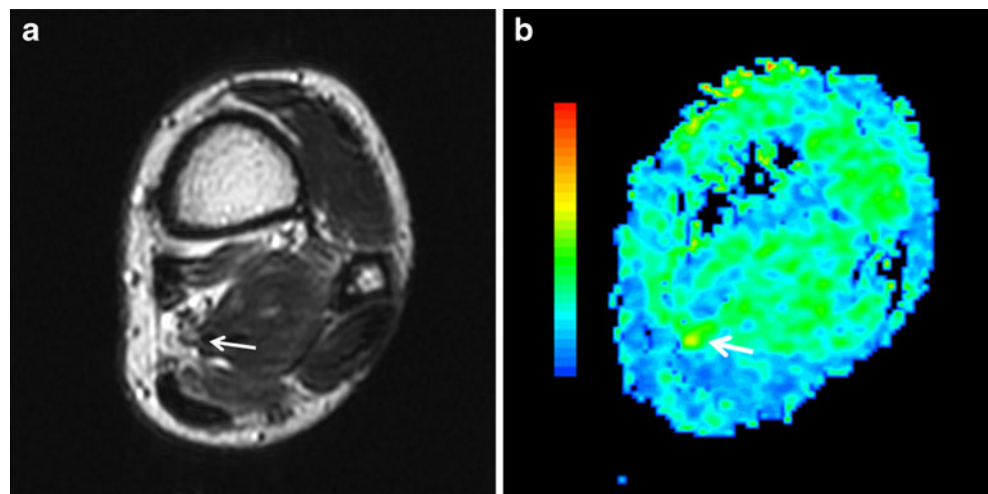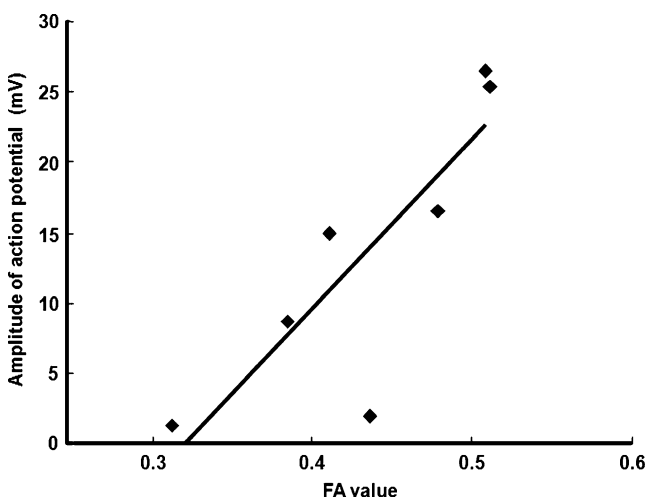
values were very low (0.312 and 0.351, respectively). In the other seven patients, we observed a significant correlation between the FA value and the amplitude of action potential (p=0.04, r=0.86, Fig. 5) but not the nerve conduction velocity (p=0.79, r=0.11, Fig. 6).

Discussion

Our study demonstrates the ability of DTI to detect distal peripheral nerve abnormalities in CIDP patients that tend not to be demonstrated on conventional MRI scans. DTI is considered to be sensitive in the detection of nerve pathology and may represent an additional method for the diagnosis and management of CIDP.
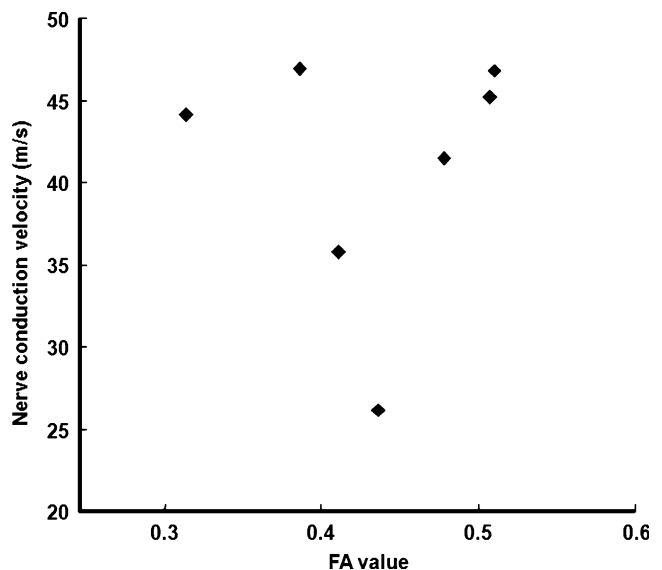
FA is considered to reflect altered peripheral nerve conditions more sensitively than the ADC [7, 11]. In other studies [6–8], the measurement of peripheral nerve FA values was combined with tractography. Tractographic

assessment was difficult in our CIDP patients because their tibial nerve FA value was low. It was difficult to place ROI accurately along the margin of the tibial nerve on the FA map. Therefore, we used ROI larger than the nerve diameter and recorded maximum FA in the ROI rather than mean FA of the tibial nerve. Hiltunen et al. [5] also measured maximum FA in their DTI study of distal peripheral nerves.

Our finding that FA was decreased in the tibial nerves of CIDP patients is compatible with previously reported pathological changes. Multifocal inflammatory and demyelinating processes involving the peripheral nerve in a diffuse manner are causative factors in the development of CIDP, and demyelination and remyelination are pathological hallmarks of CIDP [12]. In addition, chronic demyelinating

Fig. 5 Correlation plots showing the amplitude of action potential (*y-axis*) versus the FA values (*x-axis*) in CIDP patients. The FA values are significantly correlated with the amplitude (p=0.04, r=0.86)

Fig. 6 Correlation plots showing the nerve conduction velocity (*y-axis*) versus the FA values (*x-axis*) in CIDP patients. The FA values are not significantly correlated with the nerve conduction velocity (p=0.79, r=0.11)

lesions frequently induce axonal degeneration, and mononuclear cell infiltrates have been observed in the endoneurium, perineurium, and the epineurium [12]. These pathological changes are thought to degrade the structural integrity and directional coherence of the nerve fibers, resulting in a reduction of anisotropy.

In our study, the FA values were significantly correlated with the amplitude of the action potentials, but not with nerve conduction velocity. The action potential amplitude is thought to correlate with axonal damage and nerve conduction velocity with the degree of demyelination [22]. Our results imply that the FA values of the peripheral nerves were correlated with the axonal condition rather than the myelin condition. According to Takagi et al. who performed histopathological and DTI analyses of regenerating peripheral nerves, the FA value correlated more strongly with axonal density and axonal diameter than with myelin density and myelin thickness [9]. Our findings are consistent with theirs and support the hypothesis that axonal membranes play a major role in anisotropic water diffusion in neural fibers [23, 24].

Hiltunen et al. [5], who used a 3-T MRI unit, reported maximum FA values of tibial nerves at ankle level as 0.73–0.79 in three healthy volunteers. Maximum FA values of tibial nerves in healthy volunteers in our study were lower than those reported by them. We posit that this difference is at least partly attributable to the different MRI instruments and the different scan parameters for DTI used in their and our study. Hiltunen et al. used a slice thickness of 3.5 mm for DTI. On the contrary, we used a larger slice thickness of 5 mm which might increase partial volume effects, resulting in reductions of measured maximum FA values of the nerves. Also, the volunteers in their study were younger than ours (age range 22–36 vs. 34–69 years); this may partly explain the difference in the FA values of the tibial nerves. Additional factors contributing to the difference between their and our findings may be related to racial differences; our study subjects were Japanese while theirs were of Nordic ancestry.

Our study has some limitations. First, our study population was relatively small, and the disabilities ascribable to the crura were mild. Consequently, we could not analyze the relationship between diffusion tensor abnormalities and disability. Second, as we could not directly correlate DTI results with nerve histology, we can only speculate but not definitely state the cause of reduction of FA in CIDP patients. Third, as the spatial resolution of DTI is low, we were only able to evaluate relatively thick peripheral nerves such as the tibial nerve. The application of parallel imaging techniques using a dedicated multichannel coil will improve image quality, and the availability of higher-field-strength magnets will result in DTI scans with higher spatial resolution and a better signal-to-noise ratio.

DTI as a quantitative assessment method, in combination with electrophysiological measurements, may be useful for the diagnosis and monitoring of peripheral nerve diseases other than CIDP. For example, longitudinal DTI studies may help in the evaluation of therapies in patients with Guillain-Barré syndrome. The assessment of peripheral nerves by DTI may also be useful in the differentiation between neurogenic and myogenic muscle atrophies. Furthermore, DTI may become important in the assessment of proximal nerve trunks that cannot be evaluated with standard electrophysiological methods.

In conclusion, our preliminary study suggests that the noninvasive assessment of peripheral nerves by DTI may provide useful information in patients with CIDP. Further studies are underway to confirm the clinical significance of this technique in CIDP and other peripheral nerve diseases.

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