SHORT COMMUNICATION

Voxel-based diffusion tensor imaging detects pyramidal tract degeneration in primary lateral sclerosis

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Objective: Primary lateral sclerosis (PLS) is a progressive degenerative disorder affecting upper motor neurons and requires a clinical diagnosis. Diffusion tensor imaging (DTI) is a quantitative method for assessing white matter fibre integrity. The purpose of the study was to evaluate the involvement of upper motor neurons by using DTI in PLS.
Methods: A patient with PLS was compared with eight age-matched controls. Differences in fractional anisotropy (FA) index were assessed using DTI on a voxel-by-voxel basis.
Results: Decreased FA was observed in the proximal part of the pyramidal tract bilaterally, which indicated degeneration of the pyramidal cells.
Conclusion: Voxel-based DTI could be used as an objective marker for detecting upper motor neuron degeneration in PLS.

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Primary lateral sclerosis (PLS) is an adult onset, non-hereditary degenerative disorder of the upper motor neuron related to a selective loss of precentral pyramidal neurons. It is characterised by progressive spinobulbar spasticity owing to pyramidal tract degeneration, but preservation of the anterior horn motor neurons and no involvement of the lower motor neuron [1–4]. Currently there is no defining test or disease marker; thus, the diagnosis is usually made based on clinical presentation [1, 2].

Diffusion tensor imaging (DTI) is an MRI technique that provides information about white matter fibre orientation and integrity *in vivo* based on the principles of free water molecules movement. Water molecules move in a random manner (isotropic diffusion); however, the presence of obstacles, such as axonal membranes and myelin sheaths, restrict the motion in a particular direction resulting in anisotropic diffusion. The fractional anisotropy (FA) index is a measure of the degree of directionality of diffusion [5, 6]. The assessment of FA has been used as a measure of white matter degeneration in many diseases as it can detect and quantify the degeneration of fibres along white matter tracts [5, 6]. The method that is usually used is the region of interest (ROI) approach [7]. Nowadays, an automated method of analysis is used for a voxel-wise comparison of DTI data throughout the whole brain [8, 9].

In this report a single case of PLS was studied using DTI on a voxel-by-voxel comparison with a control group to detect upper motor neuron involvement.

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Methods and materials

A 52-year-old woman complained of stiffness in the legs and difficulty in walking since 2005. The symptoms gradually worsened over the years and followed an ascending pattern resulting in spastic tetraparesis. She also complained of urgent diuresis. She had been previously healthy. The family history was negative for neurological illness. There was no history of cognitive decline, change in judgement, personality or memory.

General examination was normal. Neurological examination showed asymmetric spasticity in lower and upper limbs, more prominent in the left leg. The jaw-jerk and limb tendon reflexes were increased with ankle clonus, bilateral Babinsky and Hofmann signs. The gait was spastic. There were no sensory abnormalities. Nerve conduction studies and electromyography (EMG) studies were normal. Haematology, serum biochemistry, cerebrospinal fluid (CSF) examination, and autoantibody panel were normal.

MR examination was performed on a 1.5 T MR unit (Gyroscan, ACS NT; Philips Medical Systems, Best, the Netherlands) using a head coil. As a part of a standard brain MR protocol, DTI images were obtained using a single-shot multislice spin-echo planar diffusion tensor pulse sequence (echo time (TE): 131 ms, repetition time (TR): 9807 ms, matrix size: 112 × 128, thickness: 3 mm, field of view (FOV): 230 mm). The maximum *b*-value was 700 s mm^{-2} applied along 16 non-collinear weighting directions.

Data were acquired from eight healthy age-matched volunteers using the same diffusion protocol with the patient. Brain MRIs were normal and there was no history of neurological disease. Local ethics committee approval and written informed consent from all participants were obtained.

The DTIs were analysed using the DTI studio software and FA maps were derived. Image post-processing was performed using MATLAB 7.0 (MathWorks, Natick, MA) and Statistical Parametric Mapping SPM 5 (Welcome Department of Cognitive Neurology, London, UK). The steps to assess differences in FA between the PLS patient and the control group were the following:

a) spatial normalisation of the T_2 weighted images obtained for b_0 of all participants by using the Montreal Neurological Institute (MNI) template. The FA maps were then normalised by using parameters determined from the normalisation step of the b_0 images. Finally, the normalised FA maps were smoothed with a 10 mm isotropic Gaussian Kernel;
b) a new dataset was created by subtracting the patient's FA map from every FA map of all eight control participants;
c) a one-sample Student's *t*-test was applied in the new data set and the results constituted a T map;
d) a threshold of $p<0.05$ corrected for multiple comparison was used to demonstrate areas where there were statistically significant differences in FA.

Voxel-based DTI analysis showed a statistically significant decrease of FA in the PLS patient when compared with the controls. The regions involved the proximal parts of the pyramidal tracts bilaterally in the precentral gyrus (Figure 1 and Table 1).

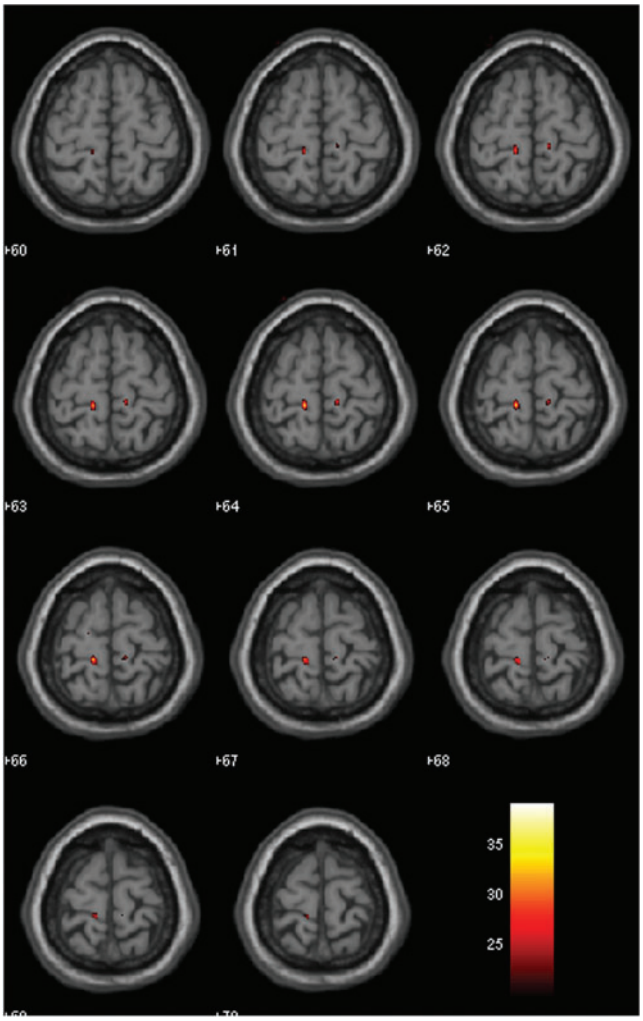

Figure 1. Brain regions with decreased fractional anisotropy (FA). Results from the comparison between the primary lateral sclerosis (PLS) patient and the control group are overlaid on axial T_1 weighted images. Colour represents areas with a statistically significant decrease in FA in the patient compared with the controls ($p<0.05$ corrected for multiple comparison). Statistical significance increases from red to yellow in the colour scale. Decreased FA index was observed bilaterally in the precentral gyrus indicating degeneration of the pyramidal cells. All scans which show differences are included.

Discussion

In this report the degree of upper motor neuron involvement was assessed using the FA on a voxel-by-voxel basis throughout the whole brain in a patient with PLS. Decreased FA values were observed in the patient along the proximal corticospinal track bilaterally when compared with the control group.

It is now considered that PLS is part of the range of motor neuron diseases consisting of PLS, amyotrophic lateral sclerosis and progressive spinal muscular atrophy [1, 3, 4]. It is characterised by upper motor neuron degeneration without lower motor neuron involvement. Commonly used criteria are adult onset, negative family history, progression, spasticity with paresis of the legs for more than 3 years and dysfunction limited to the corticospinal tract [1, 3, 4]. Symptoms typically begin when patients are in their 50s and 60s, and PLS is equally distributed in both sexes. PLS is still a clinical diagnosis as there is no disease marker [1, 2, 10]. A variety of investigations are usually carried out to exclude other causes. The differential diagnosis includes amyotrophic lateral sclerosis, hereditary spastic paraparesis, multiple sclerosis, B12 deficiency, compressive lesions at the foramen magnum or cervical spinal cord and infection with HIV or HTLV-1.

Our patient presented with typical signs and symptoms for PLS. The sites of onset were the lower limbs followed by an ascending pattern of slowly progressive course of symptoms. The main findings were severe spasticity with accompanying corticospinal tract signs, such as hyperreflexia, Babinski's sign and pseudobulbar reflexes. No clinical or laboratory findings of lower motor neuron involvement were observed.

According to previous reports on patients with PLS, MRI shows atrophy of the frontoparietal part of the brain, which is most prominent in the pre-central area, with concomitant degeneration of the underlying white matter [2, 6]. To our knowledge, there is only one previous study that evaluated FA in patients with PLS by means of ROI approach focusing on the posterior limb of the internal capsule; in this study, patients with PLS showed decreased FA when compared with controls [7]. Limitations of the ROI-based approach include that it is restricted to predefined regions, it is subject to operator bias, the ability to accurately determine the boundaries of the corticospinal tract and to avoid partial volume contamination from non-corticospinal tract fibres.

Table 1. Voxel-based diffusion tensor imaging results

Region volume (mm^3)	Z-score	Tailarch co-ordinates (x, y, z)	Location of local maxima
552	5.86	−12, −30, 64	Left precentral gyrus
232	5.60	12, −28, 64	Right precentral gyrus
216	5.53	34, −12, 42	Right precentral gyrus
48	5.34	34, −44, 32	Right precentral gyrus
48	5.31	−26, −36, 26	Left precentral gyrus

Summary of the size, Z-score, co-ordinates (corresponding to Tailarch space) and the location of brain regions in which the patient demonstrated decreased FA when compared with controls.

Voxel-based DTI is an objective, automated and unbiased technique that assesses changes in diffusion orientation and magnitude throughout the whole brain without prior assumption of brain areas of potential interest [8, 9]. The patient in our case demonstrated decreased FA along the proximal part of the descending corticospinal tract before it reached the posterior limb of the internal capsule. Without a voxel-by-voxel analysis it would be difficult to precisely determine the margins of the pyramidal tract in that region and to evaluate differences with controls. Decreased values of FA indicate a breakdown of the barriers that restrict free water movements, thus reflecting axonal degeneration [5]. The bilateral decrease of FA is consistent with the symmetric course of the disease [1].

No significant difference in FA was observed in the internal capsule despite the fact that FA is high in that area as it contains very coherent and tightly packed fibres of the corticospinal tract. The disease duration in our patient was 3 years [1]. In a previous study that evaluated FA in PLS patients the mean disease duration was 5 years [7]. Furthermore, the course of the disease tends to be prolonged [1]. Pathological studies have shown that upper motor neuron pathology starts in the primary motor and premotor cortex with degeneration and complete absence of Betz cells [2, 3, 11]. Degeneration of motor fibres and gliosis along the corticospinal tract is secondary to the upper motor neuron loss [12]. We can assume that as the disease progresses, degeneration of the pyramidal tract follows a descending pattern to the spinal cord.

Conclusion

This report supports the potential role for voxel-based DTI as an objective and quantitative marker for detecting and monitoring upper motor neuron's involvement in PLS. Markers for upper motor neuron's involvement are needed because clinical evaluation alone is insufficient in distinguishing entities with similar presentation. Such markers may improve diagnostic accuracy and enable patients with suspected PLS to access treatment sooner. Finally they would also improve the understanding of the disease process and the prognosis.

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