

Corticospinal Tract Degeneration in Amyotrophic Lateral Sclerosis: A Diffusion Tensor Imaging and Fibre Tractography Study

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Abstract

Introduction: Motor neuron damage and cortical spinal tract (CST) degeneration in amyotrophic lateral sclerosis (ALS) are difficult to visualise and quantify on conventional magnetic resonance imaging (MRI). **Clinical Picture:** We studied 8 ALS patients and 12 normal volunteers using diffusion tensor imaging (DTI) and fibre tractography using fibre assignment by continuous tracking (FACT) to study the fibres of the CST and the posterior thalamic radiation (PTR), a non-motor tract. **Outcome:** Fibre tractography was successfully performed in all normal volunteers and all patients except 1. The fibre bundles of the CST, but not the PTR, were significantly reduced ($P < 0.05$) in patients compared to normal volunteers. **Conclusion:** Fibre tractography can visualise axonal degeneration in the CST and may provide supplementary information about upper motor neuron disease in ALS patients.

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Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterised by spinal and cortical motor neuron degeneration.¹ Although electromyography, muscle biopsy and motor unit number estimation are useful for the evaluation of lower motor neuron (LMN) damage, there is at present no objective and quantitative technique to detect upper motor neuron (UMN) damage.² Prolonged central motor conduction time using transcranial magnetic stimulation has been reported in patients with ALS, but the method suffers from poor sensitivity and inconsistent results.^{2,3} A method that directly correlates with the underlying pathological changes would be desirable to measure disease progression in ALS, especially for future clinical trials.

Recently, magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) have been used to study the UMN in ALS.⁴⁻⁶ DTI uses magnetic resonance imaging (MRI) in multiple diffusion sensitising gradient directions to measure the preferential movement of water along fibre

bundles to study the function and microstructural integrity of white matter.⁴ By solving the diffusion tensor equation, DTI indices such as mean diffusivity (MD, a measure of the magnitude of water diffusion) and fractional anisotropy (FA, a measure of the strength of directionality of water diffusion) may be calculated.⁷ In addition to these quantitative diffusion metrics, the DTI directional information may be used for fibre tractography, which creates 3-dimensional reconstructions of white matter axonal bundles. Several authors have reported using fibre tractography to visualise the white matter fibre bundles such as the commissural and association fibres, and the corticospinal tract (CST), in normal subjects.⁸⁻¹³ We have previously demonstrated that combined whole-brain MRS and DTI metrics can detect axonal degeneration in the CST in patients with ALS. FA and the ratio of N-acetyl-aspartate to creatine at various locations in the CST were significantly lower in ALS patients than in normal volunteers.⁶ In this report, we use DTI fibre tractography to measure the white matter fibre bundles in

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the ALS patients studied previously. Our hypothesis is that the CST fibre bundles, but not the non-motor tracts, are reduced in ALS patients compared to normal individuals.

Clinical Picture

Subjects

The patient and volunteer MRI data used were the same as in our previous report.⁶ Eight right-handed patients (4 men, 4 women; mean age, 45.75 years) with clinically definite ALS based on El Escorial^{14,15} criteria (6 with limb-onset and 2 with bulbar onset disease) and 12 healthy age-matched normal volunteers (8 men, 4 women; mean age, 45.08 years) were included after informed consent was obtained.

MRI and Post-processing

All patients and volunteers underwent diffusion-weighted single-shot echo-planar imaging (TR 8000 ms, TE 70 ms; 6 mm section thickness with 0.5 mm gap, acquisition matrix 128 x 128; FOV 24 cm; b values 0 and 1000 s/mm², applied along 25 non-collinear directions) on a 1.5 T clinical MRI system (General Electric, Milwaukee, USA). Twenty-eight axial sections were acquired with voxel size 1.875 mm in 5 to 8 minutes. Two observers (SHTC, CCTL) who were blinded to the clinical details analysed the DTI studies by consensus reading using DTI Studio. To validate the diffusion metrics against our prior study, 20 to 28 mm² elliptical regions of interest (ROIs) were placed to measure FA and MD at the posterior limb of the internal capsule. Fibre assignment by continuous assignment (FACT) was performed similar to methods described previously.⁹⁻¹¹ Briefly, the principal eigenvector (associated with the highest eigenvalue) was calculated from the diffusion tensor on a pixel-by-pixel basis. The principal eigenvector, measuring the main direction of water diffusion, was assumed to represent the local fibre direction. The fibre trajectory was initiated by a seed pixel which was propagated in both directions based on the principal eigenvector, and limited by a preset FA (>0.10) and turning angle (<40 degrees) thresholds.⁹⁻¹¹ In order to obtain the 3-dimensional reconstruction of selected fibre bundles, ROIs, based on

prior knowledge of anatomical landmarks, were placed in the white matter through which the fibre tract passes.¹¹

We performed fibre tractography on the CST as well as the posterior thalamic radiation (PTR), a non-motor tract, and visually compared these fibre bundles between the normal volunteers and ALS patients. For CST, 2 ROIs were placed based on the FA maps at the cerebral peduncle and the subcortical white matter based on prior anatomical knowledge,⁶ taking care to exclude non-CST crossing fibres. To track the PTR, ROIs were placed at the posterior portion of the thalamus and occipital lobe.¹⁰

The number of pixels that the white matter fibres pass through was automatically recorded by the software. This quantity of total pixels was taken as a measurement of the volume of fibres tracked in its entire path. The means of FA and MD measurements at the posterior limb of the internal capsule and the number of pixels that the CST and PTR pass through were compared between volunteer and patient groups using the Mann-Whitney test for independent samples, with statistical significance established at $P < 0.05$.

Outcome

The results of DTI measurements are shown in Table 1. ALS patients had significantly lower FA (0.53 ± 0.03) than normal volunteers (0.58 ± 0.03 , $P = 0.001$). MD values were also higher in patients ($7.49 \pm 0.29 \times 10^{-4}$ mm²/sec) than in normal volunteers ($7.28 \pm 0.22 \times 10^{-4}$ mm²/sec), although this difference did not reach statistical significance ($P = 0.088$).

Using fibre tractography, the CST and PTR could be visualised in all volunteers and 7 of 8 ALS patients. In the last patient, the CST and PTR could not be demonstrated and the patient was excluded from further analysis. Three out of 7 ALS patients showed visibly decreased volume of CST fibre bundles compared with normal volunteers (Fig. 1), but there was no discernible difference in the PTR fibres (Fig. 2). The total number of pixels through which the CST passes in ALS patients was significantly decreased (603.44 ± 253.62) compared to normal volunteers (826.00 ± 148.30 , $P = 0.028$), but the pixels occupied by the PTR in patients

Table 1. DTI Measurements and Fibre Tractography in ALS Patients

| | Measurement | Normal volunteers | ±SD | ALS patients | ±SD | P |
|------------|-------------------|-------------------|--------|--------------|--------|--------|
| ROI at PIC | Mean FA | 0.58 | 0.03 | 0.53 | 0.03 | 0.001* |
| | Mean MD | 7.28 | 0.22 | 7.49 | 0.29 | 0.088 |
| CST | Mean pixel number | 826.00 | 148.30 | 603.44 | 253.62 | 0.028* |
| PTR | Mean pixel number | 1068.41 | 132.23 | 1203.06 | 340.23 | 0.317 |

ALS: amyotrophic lateral sclerosis; CST: corticospinal tract; DTI: diffusion tensor imaging; FA: fractional anisotropy and pixel number have no units; MD: Mean diffusivity is expressed in units of $\times 10^{-4}$ mm²/s; PIC: posterior limb of internal capsule; PTR: posterior thalamic radiation; ROI: region of interest

*Significantly different at $P < 0.05$

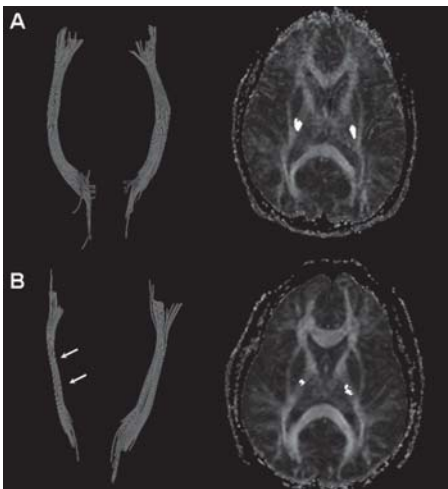


Fig. 1. CST in normal volunteers and ALS patients. CST analysed by fibre tractography displayed as 3-dimensional fibre bundles (left) and overlaid on conventional axial colour maps (right) from a normal volunteer (A) and an ALS patient (B). The right CST in the ALS patient shows decreased fibre bundles (arrows) compared to the normal volunteers.



Fig. 2. Posterior thalamic tracts (PTR) in normal volunteers and ALS patients. PTR displayed as 3-dimensional fibre bundles (left) and overlaid on conventional colour maps (right) from a normal volunteer (A) and an ALS patient (B). There is no visible difference in the volume of reconstructed fibre bundles.

(1203.06 ± 340.23) was not significantly different compared to normal volunteers (1068.41 ± 132.23 , $P = 0.317$).

Discussion

Conventional brain MR imaging methods have limited application in the study of ALS; findings of atrophy, hyperintensity of the CST on T2-weighted images, hypointensity of the motor cortex are not sensitive or specific for UMN involvement.^{6,16,17} Several studies using DTI have described reduced FA and elevated MD in selected regions of the CST.⁴⁻⁶ In our previous report, we found lower FA values at multiple levels of the CST including the subcortical white matter, centrum semiovale, periventricular white matter and the posterior limb of the internal capsule.⁶ In this study, we first validated our previous FA and MD results at the level of the posterior limb of the internal capsule using a different post-processing software program in order to assess the reproducibility of our previous study, and were able to replicate significantly lower FA and (non-significantly) elevated MD values.

Using the fibre-tracking programme, we were also able to visualise the 3-dimensional reconstruction of the CST, PTR and obtain information on the volume, structure and organisation of these white matter fibre bundles. Previous pathological reports have described axonal loss and volume reduction in the CST in ALS,² and our finding of decreased pixel number may represent CST degeneration. Fibre tractography is a method that has the potential to non-invasively visualise and identify entire axonal fibre bundles, and may be helpful to extend the information provided by DTI beyond the isolated region of interest measurements of FA and MD. Studies in normal individuals have shown

reproducible fibre tract reconstructions that were in good qualitative agreement with existing anatomical knowledge.⁸⁻¹¹ This information has the potential to assist in understanding the normal and pathological processes that affect the entire neural network, and have been applied to conditions such as epilepsy¹⁸ and neoplasms^{19,20} (Lim, unpublished data). Although preliminary, our findings in ALS patients suggest that fibre tractography can also be used to study the CST. The visualisation of an entire white matter fibre bundle rather than merely isolated ROIs within a neural network may be useful in degenerative diseases that do not affect all anatomical sites uniformly. In ALS, CST degeneration in a caudo-cranial direction also affects the cortical gray matter, and progressive abnormal changes in FA with time might be expected, at least in some patients.²¹ Therefore, combined imaging of the cortex and CST, perhaps using voxel-based morphometry, FA, MD measurements, fibre tractography and MRS, should be explored for their potential to study the health of the CST as a whole neural bundle in complex diseases such as ALS.

Although there was visible reduction in the fibre bundle and decrease in the pixel number in CST suggestive of fibre degeneration in ALS patients, there was no significant difference in the PTR between ALS patients and normal volunteers. The PTR contains primarily the optic radiation, the sensory visual pathway that terminates in the occipital lobe,¹⁰ and even if affected by widespread white matter disease would not be expected to degenerate as much as the CST in ALS. Our study findings are therefore consistent with a motor neuron disease that preferentially affects the motor pathways rather than the sensory fibre tracts, and we believe that this is the first report that uses DTI fibre

tractography to measure the difference in affected and unaffected white matter fibre bundles between ALS patients and normal volunteers. Using a similar FACT fibre tractography method, some authors have found asymmetry in the arcuate fibres (which are involved in language processing) but not in the CST (which are not) in normal individuals, suggesting that tractography can be used to provide information about different neural systems and models for language lateralisation.²²

The fibre-tracking programme was successful in all but 1 patient, and appears to be fairly robust and applicable in DTI studies of ALS patients. There are, however, mathematical limitations to the FACT method of fibre tractography, especially for crossing and merging fibres,²³ and it is also operator dependent, with user-defined FA and turning angle thresholds. Nevertheless, some authors have found that consistent quantitative physical and geometric properties of neuronal fibre pathways can be obtained by using this method,²³ and early reports suggest that fibre tractography methods can be fairly robust and reproducible.^{9-12,22,23} Other groups have used similar DTI fibre reconstruction methods and described the qualitative decreased volume of fibre bundles in the white matter tracts in patients with cerebellar atrophy and focal cortical dysplasia.^{24,25}

In addition to producing a visual and qualitative 3-dimensional reconstruction of the fibre bundles, the software can also provide a relative measurement of the fibre tracts by quantifying the number of pixels that they pass through. By applying consistent thresholds in a blinded fashion to both normal volunteers and patients, we were able to show that the difference between groups was unlikely to be due to chance. Although this pixel number measurement has no real meaning in terms of absolute fibre number or density, and is only a crude and arbitrary count of fibre volume, there is potential to use it for comparative studies if carried out in a consistent (by standardising the acquisition parameters such as matrix size and slice thickness that affect pixel size) and unbiased manner. However, fibre tractography is currently still an experimental method for studying ALS, and further work needs to be done to assess the effects of asymmetry and regional differences in the CST.^{26,27} It is unclear from our study whether the results may be dependent on the choice of thresholds selected. Other limitations of our study include the small sample size and consequent lack of correlation with clinical severity, single time point study and patient selection bias in using a patient population which had previously been shown to have abnormal CST detected by DTI and MRS. Hence, little or no information about disease progression can be derived, and any conclusion should be made with caution. Larger, better statistically powered longitudinal studies

combining measurements of FA, MD and fibre tractography in ALS patients, preferably with clinical stratification and controlling for variability of brain volume, might be helpful in the future.

Conclusion

We found that the FA values and fibre bundles were significantly reduced in the CST but not the non-motor tracts in patients with ALS. DTI can visualise axonal degeneration and may provide useful and quantitative supplementary information on UMN disease in the study of ALS patients, potentially to measure disease progression and treatment effect in future studies.

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