Clinical Neurology and Neurosurgery 181 (2019) 73–75

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Deterministic-tractography-based approach for diagnosis and disease monitoring of amyotrophic lateral sclerosis

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ARTICLE INFO

Keywords:
Amyotrophic lateral sclerosis
Corticospinal tract
Upper motor neuron signs
Diffusion tensor imaging
Tractography

ABSTRACT

Objectives: Upper and lower motor neuron signs are required for the diagnosis of amyotrophic lateral sclerosis. The detection of upper motor neuron signs is key for the diagnosis, as quite a few patients with amyotrophic lateral sclerosis lack upper motor neuron signs during the course of disease. This study sought to investigate whether deterministic tractography of the corticospinal tract, reflecting upper motor neuron signs, could be a surrogate biomarker for amyotrophic lateral sclerosis.

Patients and methods: Fifteen patients with amyotrophic lateral sclerosis and ten controls underwent imaging on a 3.0 T MRI. The corticospinal tract was reconstructed using deterministic tractography, and the track number was calculated. We analyzed the differences between the groups and the relationship between the track number and disease severity, disease duration, progression rate or upper motor neuron signs.

Results: A reduction in the track number of the corticospinal tract was found in amyotrophic lateral sclerosis compared with controls (Student's t test, $P = 0.008$). The sensitivity and specificity were 0.67 and 0.9, respectively. The track number correlated with disease severity alone ($r = 0.71$, $P = 0.003$), and significantly associated with upper motor neuron signs ($P = 0.004$).

Conclusions: These findings suggest that the deterministic-tractography-based approach is a potential biomarker for the diagnosis and disease monitoring of amyotrophic lateral sclerosis.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder that is characterized by upper and lower motor neuron signs. The accepted diagnostic criteria for ALS requires both upper and lower motor neuron signs. However, quite a few patients with ALS clinically manifest with only lower motor neuron signs, and thus, do not fulfil the diagnostic criteria. Pathological analyses have demonstrated degeneration of the upper motor neurons even in patients diagnosed as having primary muscular atrophy [1,2].

Thus, there is a need for a novel approach to detect degeneration of upper motor neurons instead of upper motor neuron signs. In terms of magnetic resonance (MR), candidate biomarkers for ALS include MR spectroscopy, volumetry, resting state functional MR imaging (MRI) and diffusion tensor imaging (DTI) [3]. DTI allows for the direct assessment of white matter, including the corticospinal tract, which is affected by degeneration of motor neurons. Therefore, many researchers have used DTI to detect the abnormalities of the upper motor neurons in native and standard space. Fractional anisotropy (FA) is a representative value of DTI, but provides limited power for diagnosis [4]. Recently, track number, another potential value derived from DTI, has been applied to the identification of abnormalities in the middle cerebellar peduncle in dystonia and in the nigrostriatal pathway in Parkinson's disease [5,6]. The latter study showed the advantage of track number over FA. This research set out to investigate the usefulness of track number as a disease biomarker for ALS.

2. Materials and methods

2.1. Subjects

Twenty-five consecutive subjects were recruited prospectively from the Department of Neurology of the Tokushima University Hospital between September 2014 and December 2016. Fifteen patients with ALS (13 men and 2 women; age 67 ± 2.9 (mean ± standard error)) were diagnosed according to the revised El Escorial criteria for clinically possible, probable-laboratory-supported, probable or definite ALS [7]. Five of 15 patients were diagnosed pathologically as having ALS (1

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https://doi.org/10.1016/j.clineuro.2019.04.015
Received 30 July 2018; Received in revised form 11 January 2019; Accepted 14 April 2019
Available online 15 April 2019
0303-8467/

Table 1
Characteristics of included subjects (mean ± standard error).

Group	Male (Female)	Age – yr	Disease duration – years	ALSFRS-R	Progression rate	Diagnosis
Control	5 (5)	68 ± 4.0	NA	NA	NA	NA
ALS	13 (2)	67 ± 2.9	1.49 ± 0.302	37.8 ± 1.32	11.2 ± 2.99	2 DEF; 8 PRO; 2 PLS; 3 POS

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, amyotrophic lateral sclerosis functional rating scale revised; DEF, definite; NA, not available; PLS, probable-laboratory-supported; POS, possible; PRO, probable.

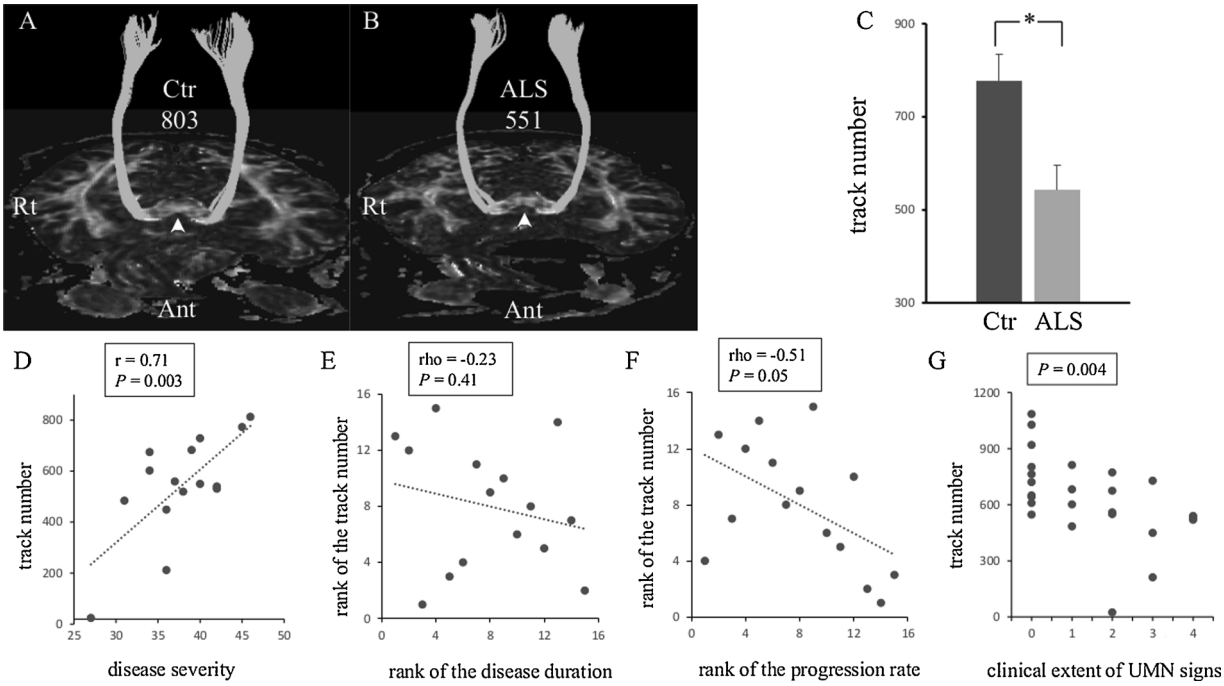

Fig. 1. Reduction in the track number of the corticospinal tract in amyotrophic lateral sclerosis.
(A–C) Tractography of the corticospinal tract (CST) showed a reduced track number in control (Ctr) relative to amyotrophic lateral sclerosis (ALS) (*, $P = 0.008$; Student's t test). Arrowheads indicate the midbrain. (D) The track number in the CST correlated with disease severity (r = 0.71, $P = 0.003$). (E, F) There was no significant correlation between the track number and disease duration or between the track number and progression rate. (G) Track number was significantly associated with the clinical extent of UMN signs ($P = 0.004$; Jonckheere-Terpstra test).
Abbreviations: Ant, anterior; Rt, right; UMN, upper motor neuron.

probable-laboratory-supported, 3 probable, 1 definite). Disease severity was assessed using the ALS functional rating scale revised (ALSFRS-R) [8]. The progression rate was calculated according to the following formula: (48-ALSFRS-R)/disease duration from onset of symptoms [9]. The clinical extent of upper motor neuron signs was scored as previously proposed [10]. Subjects without upper motor neuron signs, normal controls, represent 0, and this score increases along with a greater extent of upper motor neuron signs (maximum score: 5, bulbar, cervical and lumbar lesions). We defined subjects with normal brain MRI and without neurological deficits as normal controls (5 men and 5 women, age 68 ± 4.0). All diagnoses were made at least after 1 year from disease onset. The characteristics of the included subjects are summarized in Table 1.

2.2. Image acquisition

Images were acquired using a 3.0 T Discovery 750 scanner (GE, Milwaukee, WI) with a standard head coil. Scan parameters were as follows: diffusion gradient directions, 33; *b* value, 800 s/mm^2; the field of view (FOV), 240 mm; matrix, 128 × 128; TR, 15,000 ms; TE, 84.9 ms; flip angle, 90; slice thickness, 2.5 mm.

2.3. Fiber tracking

The detailed methods of preprocessing and track reconstruction have been described elsewhere [5]. After preprocessing including correction of Eddy current-induced distortion and head motion by the use of FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL) [11], white matter tracts were reconstructed using TrackVis software (www.trackvis.org) according to fiber assignment by continuous tracking with thresholds of fractional anisotropy value > 0.08 and an angle < 35° in native space [12]. Corticospinal tract was identified using the volume of interest (VOI) of the cerebral peduncle and the VOI of the precentral gyrus as the seed and target, respectively. Furthermore, additional fibers that projected to cerebellum were excluded, and the number of corticospinal tracts was calculated using the option of TrackVis software. The averaged count of the right and left corticospinal tract was used for further analyses.

2.4. Statistics

Shapiro-Wilk test was performed to investigate distribution of continuous variables. Significant differences between groups were determined with two-sided unpaired Student's t test. Pearson product moment correlation coefficient was used to assess the correlations between two factors. Man-Whitney test and Spearman rank correlation coefficient were used if normal distribution was not assumed. For categorical variables, Jonckheere-Terpstra test was performed to assess trends of increasing track number with a lesser extent of upper motor neuron signs. P values of less than 0.05 were considered to indicate

statistical significance. Each area under curve (AUC) was computed for each receiver operating characteristic (ROC) curve. All statistical analyses were performed using the Statistical Package for the Social Sciences version 21 (IBM, Armonk, NY) and R (www.r-project.org).

3. Results

Track number (Ctr, $P = 0.45$; ALS, $P = 0.07$) and disease severity ($P = 0.97$) were assumed to be normally distributed while others were not ($P < 0.05$). Visual assessment revealed that the number of tracks in ALS was reduced compared with Controls (Ctr, Fig. 1A; ALS, Fig. 1B). It was apparent from Fig. 1C that there was a significant difference in track number between groups in the CST (Ctr, 777 ± 57.5; ALS, 543 ± 53.1; Student's t test, $P = 0.008$; Fig. 1C). The AUC of the track number was 0.81 ($P = 0.011$, supplementary Fig. 1), and the cut off, sensitivity and specificity were 606, 0.67 and 0.9, respectively. In contrast, there was no significant difference in the FA value between groups; although the FA value in ALS tended to be decreased compared with Ctr (Ctr, 0.574 ± 0.007; ALS, 0.566 ± 0.007; Student's t test, $P = 0.43$).

Track number correlated positively with disease severity (r = 0.71, $P = 0.003$, Fig. 1D). No correlation was observed between the track number and disease duration (rho = -0.23, $P = 0.41$, Fig. 1E) or between the track number and progression rate (rho = -0.51, $P = 0.05$, Fig. 1F). Track number was significantly associated with the clinical extent of upper motor neuron signs ($P = 0.004$, Fig. 1G). However, this significant trend disappeared without normal controls probably due to small number of subjects ($P = 0.16$).

4. Discussion

The current study demonstrates the potential usefulness of the track number derived from deterministic tractography as a tool for the diagnosis and disease monitoring of ALS. Track number was a sensitive method for detecting the middle cerebellar peduncle abnormality in dystonia; which has been considered a functional disorder without pathological abnormalities [5]. Furthermore, this method was reported to have an advantage over the FA value in detecting degeneration of the nigrostriatal pathway in Parkinson's disease [6]. Several studies have found a partial decrease of the FA value even in the CST in ALS [13–15]. Therefore, the averaged FA value over whole CST provided limited power to detect any difference between ALS and Ctr compared with the track number. A meta-analysis reported that the FA value in the CST was a suboptimal tool for differential diagnosis [4]. In contrast, the track number of CST showed an AUC of 0.8 and specificity of 90%, but the sensitivity was only 67%. Given this result, the track number appeared to be more suitable for a definitive diagnosis than screening. Trend analysis suggested that a reduced number of the CST could be associated with upper motor neuron signs. The track number could help for early diagnosis and future clinical trials of disease modifying drugs, if the reduced number of the CST was accepted as a tool in identifying upper motor neuron signs in patients diagnosed as having primary muscular atrophy due to masking by lower motor neuron signs. In this case, masking of the upper motor neuron signs might be able to be overcome by the track number of the CST. It remains controversial whether local FA value within the CST correlates with disease severity [10,16,17]. However, an excellent correlation was observed between the disease severity and track number, which suggested that the track number could be a potential biomarker for disease monitoring. Further studies are needed to validate the method using the same subjects across two different time points. It is not likely that track number could be a prognostic biomarker as there was no correlation between the track number and progression rate. The main weakness of this study was the relatively small sample size.

This study has shown that the track number of the CST derived from deterministic tractography could be a new candidate biomarker for ALS. Further work is needed to validate these findings.

Conflict of interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Acknowledgements

This work was supported in part by Japan Intractable Disease (Nanbyo) Research Foundation. We would like to thank all subjects for participating in the present study.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2019.04.015.

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