CORTEX XXX (2018) 1–9

Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Behavioural neurology

Cognitive phenotypes of sequential staging in amyotrophic lateral sclerosis

Dorothée Lulé [a,*], Sarah Böhm [a], Hans-Peter Müller [a], Helena Aho-Özhan [a], Jürgen Keller [a], Martin Gorges [a], Markus Loose [a], Jochen Weishaupt [a], Ingo Uttner [a], Elmar Pinkhardt [a], Jan Kassubek [a], Kelly Del Tredici [a], Heiko Braak [a], Sharon Abrahams [b] and Albert C. Ludolph [a]

[a] University of Ulm, Department of Neurology, Germany
[b] Human Cognitive Neuroscience Unit, Euan MacDonald Centre for Motor Neuron Disease Research & Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, UK

ARTICLE INFO

Article history:
Received 1 August 2017
Reviewed 12 October 2017
Revised 12 December 2017
Accepted 15 January 2018
Action editor Stefano Cappa
Published online xxx

Keywords:
Amyotrophic lateral sclerosis
Diffusion tensor imaging (DTI)
Cognition
Staging
TDP43

ABSTRACT

Sequential spread of TDP43 load in the brain may be a pathological characteristic of amyotrophic lateral sclerosis (ALS). Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) based marker of this pathological feature. Cognitive deficits known to be present in a subset of ALS patients might act as an additional in vivo clinical marker of disease spread.

N = 139 patients with ALS were tested with the Edinburgh Cognitive and Behavioural ALS screen (ECAS) in addition to DTI brain measures of pathological spread. Executive function, memory and disinhibited behaviour were selected for Cognitive-Staging criteria, as these cognitive functions are attributed to cerebral areas analogous to the pattern of MRI markers of TDP43 pathology. ROC curve analyses were performed to define cut-off scores for cognitive stages 2 (executive function), stage 3 (disinhibited behaviour) and stage 4 (memory), and staging was performed according to the cognitive profile subsequently. Associations of Cognitive-Staging (stage 2–4) and MRI-Staging measures were determined.

In total, 77 patients (55%) performed below ROC cut-off scores in either executive function or memory or both and/or were reported to have disinhibited behaviour which permitted Cognitive-Staging. The cognitive profile of patients with discrete MRI stages 2–4 correlated significantly with DTI parameters. For those patients with cognitive impairment, there was a high congruency between MRI and Cognitive-Staging with high specificity and sensitivity of executive functions for MRI stage 2, disinhibited behaviour for MRI stage 3 and moderate of memory for MRI stage 4.

Cognitive impairment follows specific patterns in ALS and these patterns can be used for Cognitive-Staging with a high specificity compared to MRI-Staging. For the individual, cognitive screening is a fast and easy to apply measurement of cerebral function giving valuable information in a clinical context.

© 2018 Elsevier Ltd. All rights reserved.

Abbreviations: ALS, amyotrophic lateral sclerosis; ALS-FRS-R, ALS functional rating scale-revised; DTI, diffusion tensor imaging; FA, fractional anisotropy; FTD, fronto-temporal dementia.

* *Corresponding author*. Oberer Eselsberg 45, 89081 Ulm, Germany.
E-mail address: dorothee.lule@uni-ulm.de (D. Lulé).

https://doi.org/10.1016/j.cortex.2018.01.004
0010-9452/© 2018 Elsevier Ltd. All rights reserved.

Please cite this article in press as: Lulé, D., et al., Cognitive phenotypes of sequential staging in amyotrophic lateral sclerosis, Cortex (2018), https://doi.org/10.1016/j.cortex.2018.01.004

UNCORRECTED PROOF

1. Introduction

There is clear evidence in anatomical post-mortem analyses that intraneuronal inclusions show a distinct pattern throughout the brains of patients with amyotrophic lateral sclerosis (ALS). These phosphorylated 43 kDa TAR DNA-binding protein (pTDP-43) inclusions seem to follow a sequential pattern of cortical spread in at least four stages (Braak et al., 2013; Brettschneider et al., 2013). This spread is closely linked to sequential propagation of oligodendroglia pathology (Fatima, Tan, Halliday, & Kril, 2015) and changes in the white matter connectome (Schmidt, de Reus, Scholtens van den Berg, & van den Heuvel , 2015). Using fractional anisotropy (FA) mapping by diffusion tensor imaging (DTI), evidence for an in vivo marker of these pathological stages has been provided (Kassubek et al., 2014). About one fourth of ALS cases do not consecutively fulfill the DTI criteria of staging and therefore do not allow for conclusive in vivo MRI-Staging (Kassubek et al., 2014). Furthermore, given that MRI is not available in every clinic for every patient and can be difficult for ALS patients with respiratory insufficiency, there is a need to provide additional in vivo measures of spreading patterns. There is a missing link between microstructural changes and functional loss in ALS. Recently, evidence was provided that oculomotor dysfunction is a functional marker of ALS pathology (Gorges et al., 2015). An additional functional parameter might be cognitive and behavioural changes which are the most common non-motor symptoms in ALS and occur in 30–50% of patients (Beeldman et al., 2015; Goldstein & Abrahams, 2013). Behavioural abnormalities are present in up to 30% of patients and underlie the diagnosis of fronto-temporal dementia (FTD) in 5–10% of ALS patients (Strong et al., 2009). According to Bak and Chandran's (2012) hypothesis, the decline in cognitive domains in ALS should be closely associated with disease spread in the motor system (Eisen, Turner, & Lemon, 2014). In fact, executive control, language (Taylor et al., 2013) and verbal fluency are reported to be the most common domains affected in ALS (Goldstein & Abrahams, 2013). Dysfunction of the memory domain is less frequently described (Abrahams et al., 2000; Abrahams, Newton, Niven, Foley, & Bak, 2014; Lulé et al., 2015; Raaphorst, de Visser, Linssen, de Haan, & Schmand, 2010; Wei et al., 2015). Since spread of TDP-43 pathology is associated with neuronal loss, it may be expected to change the profile of cognitive performance mirroring functions of the affected brain areas. Therefore, we hypothesized that cognitive impairments in ALS show a distinct pattern and may serve as a clinical in vivo staging correlate for sequential spreading of DTI measures indicative TDP43 pathology (Kassubek et al., 2014). This study will determine 1.) whether there is a distinct pattern of cognitive and behaviour impairment which is directly associated with MRI staging, 2) whether this pattern may be useful for functional in vivo staging whether Cognitive-Staging is an accurate predictor of MRI-Staging. Cognitive-Staging is fast and easy to obtain, therefore, it may provide valuable information in clinical routine.

2. Methods

2.1. Participants

In total, N = 139 patients (55 female) with probable or definite diagnosis of amyotrophic lateral sclerosis (ALS) were included in the study. Patients underwent standardized clinical-neurological and routine laboratory examinations. They were all diagnosed with sporadic ALS by a board-certified neurologist according to the Airlie House criteria (Miller, Munsat, Swash, & Brooks, 1999) and revised El Escorial criteria (Ludolph et al., 2015). N = 100 had a predominant spinal onset, N = 34 a predominantly bulbar onset and N = 5 had a mixed onset. Severity of physical symptoms were mild to moderate as measured with the revised ALS functional rating scale (ALS-FRS-R) (Cedarbaum et al., 1999) (for detailed sample characteristics see Table 1).

None of the participants had signs of any neurological or psychiatric illness (other than ALS) or overt dementia as these were exclusion criteria for the study. They were all native German speakers. All patients eligible for MRI were consecutively recruited from the out- and inpatient clinics of the Department of Neurology at the Universitätsklinikum Ulm, Germany.

The study was approved by the Ethics Committee of the University of Ulm (No. 19/12) and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants gave written informed consent to the study according to institutional guidelines.

2.2. Study design

Patients were screened for cognitive dysfunction as a functional measure of ALS pathology by a board certified neuropsychologist within 3 days after MRI scanning. All patients received MRI scanning according to a standardized protocol (Kassubek et al., 2014). Staging (1–4) was then determined separately for each individual by a) cognitive and behaviour impairment (Cognitive-Staging) and b) MRI-DTI (MRI-Staging).

Table 1 – Sample characteristics and performance in the Edinburgh Cognitive and Behavioral ALS Screen (ECAS) of N = 139 ALS patients.

	mean	SD	range
Age	60.9	12.2	19–83
Education [years]	13.0	3.0	4–23
Duration since onset [months]	20.4	24.1	2–168
ALS-FRS-R	39.2	6.4	16–48
Progression [48-ALS-FRS/duration in months]	0.8	1.0	.1–6.5
Fluency	13.3	5.9	0–22
Language	24.6	3.6	12–28
Executive function	35.5	6.8	8–45
Memory	15.2	4.3	0–23
Visuospatial function	11.4	1.3	7–19
ALS specific score	73.7	13.3	32–95
ALS non-specific score	26.6	4.8	8–35
Total score	100.3	16.5	41–125

UNCORRECTED PROOF

Please cite this article in press as: Lulé, D., et al., Cognitive phenotypes of sequential staging in amyotrophic lateral sclerosis, Cortex (2018), https://doi.org/10.1016/j.cortex.2018.01.004

دریافت فوری ← متن کامل مقاله

ISIArticles
مرجع مقالات تخصصی ایران

✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
✓ امکان دانلود نسخه ترجمه شده مقالات
✓ پذیرش سفارش ترجمه تخصصی
✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
✓ دانلود فوری مقاله پس از پرداخت آنلاین
✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات