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Laser and somatosensory evoked potentials in amyotrophic lateral sclerosis

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HIGHLIGHTS

- Abnormal LEPs, indicating impairment in A-delta fibres, were found in 72.2% of ALS patients.
- Abnormal SSEPs, indicating impairment in A-beta fibres, were found in 55.6% of ALS patients.
- N1 amplitude of UE-LEPs, and N2 and P2 latencies of LE-LEPs, correlated with the severity of ALS.

ABSTRACT

Objective: Mild involvement of sensory nerves has been reported in previous studies in ALS patients. In this study, we assessed sensory pathways in ALS patients using laser evoked potentials (LEPs) and somatosensory evoked potentials (SSEPs).
Methods: We recruited 18 ALS patients and 31 healthy subjects. Neodymium-doped yttrium aluminium perovskite (Nd:YAP)-laser was used to evoke LEPs in upper (UE) and lower (LE) extremities. N1 and N2P2 potentials were obtained from contralateral insular cortex (T3 or T4) and vertex (Cz), respectively. Median SSEPs were recorded from C3′ or C4′ and tibial SSEPs from Cz′.
Results: Compared to controls, ALS patients had longer N2 and P2 latencies, and smaller N2P2 amplitudes in both UE- and LE-LEPs ($p < 0.05$), and longer latencies for median and tibial SSEPs ($p < 0.05$). LEPs and SSEPs were abnormal in 72.2% and 56.6% patients, respectively.
Conclusions: Cortical potentials showed that A-beta or A-delta sensory fibres, or both, were impaired in more than half of the ALS patients.
Significance: The findings support that ALS is a multi-systemic disorder involving, although to a lesser degree, other systems than the motor.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease of mainly upper and lower motor neurons (Duleep and Shefner, 2013). The diagnosis of ALS generally requires normal sensory nerve conduction studies (NCS) (Brooks et al., 2000; de Carvalho et al., 2008), and normal sensory nerve action potentials are reported in several studies (Ertekin, 1967; Fincham and Van Allen, 1964; Stålberg and Sanders, 1992). However, many other studies have shown involvement of large diameter (A-beta) sensory fibres in ALS patients using NCS (e.g., Hammad et al., 2007; Isaacs et al., 2007; Isak et al., 2016; Pugdahl et al., 2007, 2008) and somatosensory evoked potentials (SSEPs) (Cosi et al., 1984; Bosch et al., 1985; Matheson et al., 1986; Ogata et al., 2001; Hamada et al., 2007).

Small calibre sensory fibres (A-delta and C fibres) are not routinely assessed in ALS. Yet, these fibres are the elements of autonomic and nociceptive pathways and their involvement has been demonstrated in ALS, especially in the late stages (Shimizu et al., 1995; Pavlovic et al., 2010). In a recent study, mild autonomic impairment was demonstrated in ALS patients (Piccione et al., 2015), and decreased heart rate variability was shown to be correlated with sudden death (Pinto et al., 2012).

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Pain, a reflection of small calibre sensory fibre involvement, is often considered as a symptom that increases the burden of the ALS patients (Rivera et al., 2013), and is mainly considered to be of musculoskeletal origin (Borasio et al., 2001). Neuropathic pain is usually not considered in ALS, as sensory nerves are accepted to be intact, unless there is an injury due to orthoses or cachexia. However, neuropathic pain could possibly develop if small calibre sensory fibres are affected during the progression of ALS.

As NCS and SSEPs fail to assess thinly myelinated A-delta fibres, specialised neurophysiological tests, such as laser evoked potentials (LEPs) or contact heat evoked potentials (CHEPs), are required to detect loss or dysfunction of these fibres (Chen et al., 2001; Cruccu et al., 2008). LEPs are one of the most reliable and widely accepted laboratory tools to assess nociceptive pathways (Cruccu et al., 2004; Valeriani et al., 2012), and CHEPs are shown to be useful in studying thermal and nociceptive pathways (Chen et al., 2001). In ALS, these techniques have been used in a few studies with conflicting results. One study showed abnormal LEPs in the upper extremities (Simone et al., 2010), while another study showed fully intact CHEPs (Xu et al., 2009).

In this study, we aimed to assess the involvement of A-beta and A-delta sensory fibres in ALS patients using clinical examination, SSEPs, and LEPs.

2. Methods

The study was carried out at the Department of Clinical Neurophysiology, Aarhus University Hospital, Denmark. Approval was given by the local Ethical Committee of the Central Denmark Region and by the Danish Data Protection Agency, and all participants signed an informed consent document at inclusion.

2.1. Patients and controls

Eighteen ALS patients (4 females, 14 males) aged 40–74 years (mean age 59.7 ± 11.7), and 31 age matched controls (22 females, 9 males), aged 40–69 years (mean age 55.9 ± 9.4), participated in the study. The patients were recruited from the Department of Neurology, Aarhus University Hospital and Department of Neurology, Vejle Hospital in Denmark.

The ALS patients were classified as definite (16 patients) and probable (2 patients) based on clinical evidence of upper motor neuron degeneration, and clinical and electromyographic evidence of progressive lower motor degeneration in at least two of four regions (brain stem, cervical, thoracic, or lumbosacral segments) (de Carvalho et al., 2008). The exclusion criteria were: (1) Radiological or clinical evidence of radiculopathy, plexopathy, or entrapment neuropathy. (2) Evidence indicating neurological diseases other than ALS; including ALS-mimic disorders (Traynor et al., 2000), atypical motor neuron syndromes as ALS variants showing sensory involvement (e.g., Kennedy's disease) (Verma and Bradley, 2001), and all conditions affecting peripheral nerves such as diabetes, impaired glucose tolerance, vitamin deficits, kidney failure, thyroid diseases, alcohol abuse, and previous oncologic diseases. (3) Cerebellar or extrapyramidal signs. (4) Patients with pure upper- or lower motor neuron findings. (5) Pacemaker or other implants for safety reasons. (6) Pregnancy. (7) Patients who could not tolerate neurophysiologic procedures due to severe cachexia and respiratory insufficiency. (8) Dementia, as LEPs require full cooperation of the subjects. Cerebral magnetic resonance imaging and cognitive status of the patients were evaluated before recruitment.

Three patients had bulbar onset, while 11 patients had onset in upper extremities (UE) and four in lower extremities (LE). Mean disease duration prior to neurophysiological examination was 33.5 ± 18.4 months, and revised ALS-functional rating scale (ALSFRS-R) (Cedarbaum et al., 1999) ranged from 5 to 47 (Supplementary Table S1). Follow-up within three years confirmed the ALS diagnosis (Supplementary Table S1).

2.2. Neurological examination

Sensory functional status was assessed in proximal (arms and legs) vs. distal (hands and feet) parts of the limbs by standard clinical neurological examination methods for exploring vibration, position, pinprick and cold/heat sensations.

2.3. Pain

Pain in ALS patients was assessed using clinical evaluation and the painDETECT questionnaire containing seven questions addressing symptoms and pattern of neuropathic pain. On a scale from 1 to 38, a score of $\geqslant 19$ indicates that pain is likely to have a neuropathic component, while a score of $\leqslant 12$ renders a neuropathic pain component unlikely (Freynhagen et al., 2006).

2.4. Laser evoked potentials

Neodymium-doped yttrium aluminium perovskite (Nd:YAP) laser beams (Stimul 1340, Electronic Engineering, Florence, Italy) with wavelength of 1.34 μm, pulse duration 11 ms, energy density of 12.38–36.25 J/cm^2, and diameter of irradiated area of 6 mm were used as stimulus to obtain LEPs under fibre-optic guidance.

LEPs were recorded as described by Cruccu et al. (2008). Six mm stainless steel disc electrodes were used for cortical recordings and placed on Cz, T3 or T4, Fp1 or Fp2 (according to right or left sided stimulation), and nasion. The Cz electrode was referred to the nasion electrode to record N2 and P2 potentials (upper trace in Fig. 1), and the contralateral temporal (T3 or T4) electrode was referred to the ipsilateral frontal (FP1 or FP2) electrode to record the N1 potential (lower trace in Fig. 1). An electrode was placed on the left orbicularis oculi muscle and referenced to an electrode on the cheek served as an electro-oculogram to detect ocular artefacts. Recordings were obtained on Keypoint.Net (Dantec, Skovlunde, Denmark). Filter settings were 0.5–100 Hz, sweep speed was 100 ms/division, and sensitivity was 30 μV/division.

The subjects rested on a coach. They wore protective goggles and were instructed to keep their eyes open and gaze slightly downwards during laser irradiations. The laser irradiations on hand and foot were delivered unilaterally on the weakest side. The beams induced a painful pin-prick sensation and the subjects quantified the pain after each stimulation, using a numerical rating scale (NRS) from 0 (no pain) to 10 (worst pain imaginable) (Jensen et al., 1986). A NRS score of 4 as usually sufficient to yield clear LEPs. In order to avoid nociceptor fatigue or sensitisation, we displaced consecutive laser beams slightly for each stimulus and delivered the beams pseudorandomly with interstimulus intervals of 15–20 s. A stimulus intensity of 36.25 J/cm^2 was determined as maximum in order to avoid skin damage and patient intolerance.

Approximately 30 cortical potentials were evoked. After excluding the recordings contaminated with artefacts, 15–20 recordings with clear cortical potentials were averaged and stored for analysis off-line. N1 and N2P2 potentials were determined based on the criteria given by Cruccu et al. (2008). Latencies of N1, N2, and P2 potentials and amplitudes of N1 (baseline to peak), and N2P2 complex (peak to peak) were evaluated.

LEPs were determined to be absent if a N2P2 potential could not be obtained, i.e. a LEP with absent N1 potential but available N2P2 potential was accepted as recordable.