Life Sciences 203 (2018) 242–245

Contents lists available at ScienceDirect

Life Sciences

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

Review article

Sensory nerve disturbance in amyotrophic lateral sclerosis

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ARTICLE INFO

Keywords:
Amyotrophic lateral sclerosis
Sensory abnormalities
Electromyography
Neuropathy

ABSTRACT

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disorder, characterized by the selective degeneration of upper and lower motor neurons. The common clinical symptoms of ALS are caused by the degeneration and dysfunction of motor neurons. With the progression of our understanding of the pathogenesis of the disease, an increasing number of extramotor phenotypes have been linked to ALS. It has long been believed that sensory neurons localized in the dorsal root ganglia are not involved in ALS. In addition, sensory nerve injury can clearly be considered as an important basis that does not support the diagnosis of ALS. However, accumulating evidence has revealed abnormalities in sensory neurons in both ALS patients and mouse models. This review summarizes the discoveries related to sensory nerve disturbance in ALS, which may provide insightful information that will help us better diagnose and understand the disease.

1. Introduction

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a lethal neurodegenerative disease characterized by the selective death of motor neurons in the cerebral cortex, brainstem, and spinal cord. The common clinical symptoms of ALS are caused by the degeneration and dysfunction of motor neurons and include weakness in the limbs and difficulties with speech, swallowing and breathing [1]. Most cases are classified as sporadic ALS (SALS), and approximately 10% of cases are classified as familial ALS (FALS) [2].

Accompanied by the advances in the field of genetics related to ALS, an increasing number of extramotor phenotypes have been linked to ALS, such as cognitive impairment and psychiatric symptoms [3]. It has long been believed that sensory neurons localized in the dorsal root ganglia are not affected in ALS, and sensory neuropathy has not been widely recognized as part of the ALS syndrome [4]. However, accumulating evidence has revealed abnormalities in sensory neurons in both ALS patients and mouse models. Here, we summarized the discoveries related to sensory nerve impairment in ALS.

2. Sensory nerve disturbance in ALS patients

The prevalence of sensory disturbance in ALS patients has been reported in a series of clinical cohorts. In 1985, a study detecting thermal thresholds in 40 patients with motor neuron disease and 40 controls found that abnormalities in the thermal thresholds were seen in 80% of the patients, indicating that small fibers were involved in motor neuron disease [5]. Another study that was performed in the early 1990s determined sensory nerve function in 19 ALS patients and 12 controls by using numerous clinical and neurophysiological tests [6]. The results revealed a significant decline in the amplitudes of sensory nerve action potentials (SNAP) and a highly significant increase in median nerve somatosensory-evoked potential N19 latencies in ALS patients compared with controls. Recently and more frequently, evidence of sensory nerve dysfunction in ALS has been found by using various techniques. Approximately 2–20% of ALS patients have complaints of sensory symptoms and signs [7–10]. Among these symptoms, numbness is the most frequent symptom, followed by neuropathic pain, tingling and diminished temperature sensation. Sensory disturbance in ALS may differ among patients with different phenotypes. FALS cases have been found to have more frequent abnormal sensory features than SALS cases [11]. In bulbar-onset ALS patients, thermal-pain perceptive thresholds were found to be normal, and skin biopsies also disclosed normal intraepidermal nerve fiber density (IENFD). However, in patients with spinal-onset ALS, the thermal-pain thresholds were abnormal, and distal IENFD was reduced [12]. Electromyographic and pathological studies are the most used techniques for identifying the sensory disturbance in ALS patients.

3. Electromyography (EMG) and nerve conduction studies

Sensory nerve fibers are usually classified as either small fibers or large fibers. Small sensory fibers include thinly myelinated A δ fibers and unmyelinated C fibers, terminating in muscle, skin, and viscera.

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https://doi.org/10.1016/j.lfs.2018.04.052
Received 31 January 2018; Received in revised form 16 April 2018; Accepted 26 April 2018
Available online 27 April 2018
0024-3205/

Large myelinated fibers have peripheral branches encapsulated by accessory structures that can modify sensory transduction.

In a study containing 103 ALS patients, it was reported that SNAP were reduced in 27% of patients with ALS, with a mean reduction in the response amplitude of 54% [7]. These results were confirmed by a multicenter study performed in the European population. Reductions in both SNAP and conduction velocity (CV) were found in 17% of patients [13]. Another European multicenter study, including 88 patients with ALS, revealed that 20 (22.7%) of the patients had abnormalities in sensory nerve conduction studies (NCS) in at least one nerve, and 11 (12.5%) of the patients had been diagnosed with electrophysiological polyneuropathy [14]. Similar results were also found in a recent case-control study. Abnormal sensory NCS were found in 8 ALS patients (44.4%) and in one control (3.2%). Furthermore, abnormal distal sensory NCS were found in 12 ALS patients (66.7%) and 3 controls (9.6%) [15].

Abnormal sensory evoked potentials (SEPs) have also been found in patients with ALS. A study performed in the United States evaluated SEPs in 16 ALS patients and found that 7 of the patients showed abnormal SEPs after lower-extremity stimulation, while 2 of the patients showed abnormal SEPs after upper-extremity stimulation. A total of 47% of all ALS patients studied demonstrated at least one EP abnormality [16]. Another study revealed that raw SEPs were smaller in over 40% of patients, although the difference compared to healthy subjects did not reach significance. The peripheral conduction time was normal in ALS patients according to the N9 latency, while the central conduction time was found to be slower based on the N20 latency [17]. These studies underscored the notion that minor sensory abnormalities in ALS patients are not uncommon.

4. Sensory nerve pathologic findings

Skin and nerve biopsies are commonly used in sensory pathologic studies. It has been reported that pathologic abnormalities are present in 91% of ALS patients who have undergone sural nerve biopsy [7]. A case-control study that included 28 patients with ALS and 17 age-matched controls revealed a significant reduction in epidermal nerve fiber density in the distal calf of ALS patients compared with controls using skin biopsy. In addition, the proportion of subjects with small-fiber neuropathy was significantly higher in the ALS group than in the controls (79% vs 12%, respectively) [18]. Another study that performed skin biopsies in the distal legs of ALS and facial-onset sensory and motor neuronopathy (FOSMN) patients found that the IENFD was reduced in 75.4% of pure ALS and 50% of FOSMN patients. All of the ALS patients, including those with bulbar-, flail limb-, pyramidal-, and spinal-type onsets, demonstrated similar IENFD value reductions [19]. Similarly, ALS patients were found to have a loss of both IENFD and Meissner corpuscles (MCs) and reduced densities of pilomotor nerves and vascular beds compared with healthy controls in a study including 41 ALS patients and 41 healthy controls [20]. Recently, a study that performed skin and sural nerve biopsies in 31 ALS patients showed increased axonal swelling ratios in ALS patients, and GAP-43 antibody staining was negative in all the patients [21].

5. Other evidence for sensory abnormalities in ALS

Approximately 60% of ALS patients have been found to demonstrate abnormal spinal diffusion tensor imaging (DTI) metrics, indicating anatomical damage to sensory fibers in ALS patients [17]. Corneal confocal microscopy (CCM), an imaging technique allowing in vivo evaluation of corneal small sensory fibers, was used to examine a group of sporadic ALS patients in a recent study, revealing that both small fiber sensory nerve numbers and branching were significantly reduced in ALS patients. Furthermore, bulbar function disability scores were found to be significantly associated with corneal nerve fiber damage [22].

The use of laser-evoked potentials (LEPs) is an extensively validated method for assessing nociceptive pathway function. In a study containing 24 patients and 23 healthy subjects, LEPs were recorded when the dorsum of both hands was stimulated by a laser, with a stimulus intensity of 7.5 W, an interstimulus interval of 10 s and a duration of 25 ms. The results demonstrated that the latencies of the N2, P2 and N1 waves were higher in ALS patients, and the N1 amplitude was increased in ALS patients. The authors attributed these abnormalities to degeneration of subcortical structures and increased pain processing at the cortical level in ALS patients [23]. More recently, another study detected sensory pathways in 18 ALS patients and 31 healthy subjects using LEPs and SEPs. The results showed that 72.2% and 56.6% of ALS patients had abnormal LEPs and SSEPs, respectively, suggesting that ALS is a multisystemic disorder [24]. In addition, Dettmers et al. (1993) evaluated skin sympathetic skin responses (SSRs) in 25 amyotrophic lateral sclerosis patients and found the absence of SSRs in 10/25 patients. More often, these absences were found in spinal-onset patients than in bulbar-onset patients. The authors proposed that central processing or efferent pathways were responsible for these phenomena [25]. Similarly, Hu et al. (2016) reported prolonged mean SSR latencies and reduced mean SSR amplitudes in ALS patients in a recent study that included 120 ALS patients and 130 healthy controls. In addition, it was found that SSR impairments occur mainly in the lower extremities [26]. In another study, Shindo et al. (2011) used SSRs, skin blood flow, and skin sympathetic nerve activity (SSNA) to evaluate the sudomotor and vasomotor functional impairments in 20 ALS patients and 20 controls. The resting frequency of SSNA was significantly higher and the increased SSNA associated with mental arithmetic was smaller in ALS patients than in controls, indicating that sympathetic hyperactivity was related to sudomotor and vasoconstrictive skin responses [27].

Several ALS causative genes have been linked to sensory abnormalities. Three mutations, namely, V31A [28], D90A [29] and G93S [30], in SOD1 have been reported to be associated with sensory abnormalities at the early stage of the disease. A patient carrying a mutation of TARDBP demonstrated severe damage in sensory neurons during the early course of the disease [31]. The studies that have demonstrated sensory disturbance in ALS in clinical cohorts are summarized in Table 1.

6. Sensory nerve impairment in ALS animal models

It has been reported that the ALS mouse model SOD1G93A demonstrates small fiber pathology, with IENFD loss. Small-diameter dorsal root ganglion (DRG) neurons from ALS transgenic mice showed axonal stress features and accumulation of a peripherin splice variant [32]. In addition, large DRG proprioceptive neurons from SOD1 mutant ALS transgenic mice have been shown to undergo a degenerative process involving the inflammatory recruitment of macrophagic cells. A similar phenomenon was also detected in the spinal cord dorsal horn [33]. Another study revealed that Ia/II proprioceptive sensory neurons were injured by ALS disease-causing mutations, including SOD1G93A and TDP43A315T, in the presymptomatic stage of the disease. The pathological changes began in peripheral nerve endings [34]. Skin biopsies performed in the SOD1G93A mouse model found significant reductions in the IENFD, Meissner's corpuscles, and the subepidermal nerve density at 4 weeks. The biopsies also demonstrated more severe axonal loss in the epidermis than in deeper structures, indicating that distal axonal neuropathy was one of the mechanisms of degeneration [35]. Transgenic mice that express a human SOD1 mutant (hSOD1-G93A) have both motor and sensory neuropathies, exhibiting not only typical dysfunction of motor neurons and axons but also significant damage to the sensory system, with Wallerian-like degeneration in axons of the dorsal roots and dorsal funiculi, as well as mitochondrial damage to sensory neurons localized in dorsal root ganglia [36].