Clinical and preclinical evidences of somatosensory involvement in amyotrophic lateral sclerosis

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron neurodegenerative disease. Although it has been classically considered as a motor system circumscribed disease, there is an increasing amount of evidence highlighting the involvement of other neural and non-neuronal systems. In this review, we will discuss currently existing literature regarding the involvement of the sensory system in ALS. Human studies have reported intradermic small fibre loss, sensory axonal predominant neuropathy, as well as somatosensory cortex hyperexcitability. In line with this, ALS animal studies have demonstrated the involvement of several sensory components. Specifically, they have highlighted the impairment of sensory-motor networks as a potential mechanism for the disease. The elucidation of these "non-motor" systems involvement, which might also be part of the degeneration process, should prompt the scientific community to consider ALS as a pure motor neuron disease, which may in turn result in more holistic research approaches.

ABBREVIATIONS

ALS: amyotrophic lateral sclerosis

BMP: bone morphogenic protein

DRG: dorsal root ganglia

DTI: diffusor tensor imaging

fALS: familial amyotrophic lateral sclerosis

FTLD: frontotemporal lobal degeneration

GAP-43: growth-associated protein 43

LEPs: laser evoked potentials

MEP: motor evoked potential

MN: motor neuron

MRI: magnetic resonance imaging

MT: magnetization transfer

PMN: progressive motor neuronopathy

rsfMRI: resting state functional MRI

sALS: sporadic amyotrophic lateral sclerosis

SEPs: sensory evoked potentials

SGCs: satellite glial cells

TBCE: tubulin binding cofactor E

TMS: transcranial magnetic stimulation

1. INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is the most common neurodegenerative disease involving motor neurons (MNs) (Riancho et al. 2019). The incidence of ALS ranges between 0.7 and 3 cases per 100,000 habitants, and is more frequent among Caucasians (Chio et al. 2013; Riancho et al. 2016). ALS is characterised by progressive muscular atrophy and weakness, which commonly leads to death within 2-3 years after diagnosis which is usually related to respiratory failure (van Es et al. 2017). Histologically, ALS shows MN loss accompanied by atrophy at both the motor cortex and spinal cord anterior horn as well as corticospinal tract sclerosis (Zufiria et al. 2016). With the exception of cases related to SOD1 and FUS, typically, ALS MNs exhibit TDP43 intracytoplasmic aggregates, which have been considered the hallmarks of ALS (Riancho et al. 2019).

ALS cases can be divided into familial ALS (fALS) and sporadic ALS (sALS) (Zufiria et al. 2016). fALS cases, which represent 5-10% of total cases, are related to mutations in specific causative genes (*C9ORF72, SOD1, TARDBP, FUS etc*.) which directly induce MN degeneration (Al Chalabi and Hardiman 2013). sALS cases are considered to be secondary to the interaction between the individual genetic risk and environmental conditions. Upon this conception, ALS would develop in individuals in whom the sum of genetic risk, ageing, and environmental exposure would reach a particular threshold, upon which, specific disease mechanisms would be triggered and subsequently auto perpetuated (Riancho et al. 2018).

Although fALS represents a small percentage of cases, its study is of great importance because it can help shed light on the pathogenesis of the disease, not only in the familial cases, but also in the sporadic ones. Although the pathogenesis of ALS has not been fully elucidated yet, our knowledge about disease mechanisms has significantly improved during last decade. In this context, several crucial cellular pathways, such as gene processing disorders, energetic metabolism, proteostasis, axonal transport, hyperexcitability, or surrounding glial cell disorders have been associated to degeneration of MNs (Riancho et al. 2019). Regarding hyperexcitability, it was the rationale for the use of riluzole, an anti-glutamate agent approved for the treatment of ALS patients with a modest effect in survival.

In recent years, our paradigm of the disease has also changed, and ALS is now increasingly being considered as a multisystem disease rather than a MN-circumscribed disorder.

From its initial description by Professor Charcot in the 19th century, ALS had been classically considered as a neurodegenerative disease exclusively affecting MNs (van Es et al. 2017). However, during the past few decades, an increasing number of investigations have been published supporting the theory that ALS might not only be a "motor system disease". In this sense, a non-motor constellation of manifestations, including dysautonomic, Parkinsonian, cognitive and sensory problems have been reported in ALS patients (Shimizu et al. 2000; Geser et al. 2009; Ringholz et al. 2005; van del Graaff et al 2009; McCombe et al. 2017). Probably, the most solid evidence for this multisystem involvement came from the identification of the C9orf72 hexanucleotide expansion as a shared pathogenic condition for frontotemporal lobar degeneration (FTLD) and ALS. Currently, we all admit that FTLD and ALS are not two independent disorders but two conditions of the same disease spectrum, which in up to 15% of cases may concur in the same patient (Ringholz et al. 2005). Furthermore, in ALS patients not meeting FTLD criteria, some degree of cognitive impairment has been reported. In different clinical series, cognitive impairment seems to be present in up to 50% of cases and has been characterised as an unfavourable independent prognostic factor (Chio et al. 2019; Phukan et al. 2007). Cognitive disorders and their relationship with ALS have been extensively

studied and reviewed. However, we also consider the sensory manifestations of ALS of great importance (previously reviewed by Tao et al. 2018), because of two reasons. First, awareness of sensory disturbances might help clinicians better manage patient symptomatology in a holistic manner. Second, a better understanding of non-motor symptoms will potentially provide new perspectives for new diagnostic/therapeutic strategies.

In this article, we will review the existing literature, both from clinical and preclinical perspectives, supporting the involvement of the sensory system in ALS patients and trying to incorporate it into the pathogenesis of the disease. For drug/molecular target nomenclature, BJP's Concise Guide to Pharmacology has been followed (Alexander et al. 2015).

2. CLINICAL EVIDENCES SUPPORTING THE COEXISTENCE OF SENSORY DISORDERS IN ALS PATIENTS

2.1. Pain and sensory symptomatology in ALS patients.

Most clinicians agree that a large proportion of ALS patients have pain or minor sensory symptomatology during the disease (Chio et al. 2016; Hammad et al. 2007). This has been reported to be particularly frequent in fALS cases secondary to SOD1 mutations (Abe et al. 1996). The first reports in the literature suggesting some degree of sensory alteration in patients suffering from ALS come from the 1960s, when Fincham et al assessed sensory nerve conduction in patients with MN disease (Fincham and Vanallen 1964).

Globally, up to 20-30% of ALS patients may refer to the occurrence of sensory symptoms, although sensory examination is usually normal in most patients (Hammad et al 2007). Among sensory symptoms, tingling paraesthesia is the most frequently complaint. Occasionally, objective sensory loss may occur as a part of a motor neuron "plus" syndrome (including paraneoplastic and other complex syndromes) and might precede or follow motor symptoms.

Pain was a mainly neglected symptom in ALS until about 15 years ago (Chio et al 2016). However, the importance of identification and assessment of pain in patients with ALS cannot be overlooked due to the fact that it has profound detrimental effects on the quality of life of ALS patients (Wallace

et al. 2014). Indeed, pain management is considered in the main guidelines of ALS treatment (Miller el al. 2009). The epidemiology of pain in the ALS spectrum has not been fully elucidated yet. There are few systematic studies on pain in patients with ALS and a few longitudinal studies have reported the frequency of pain to be between 15-85% (Chio et al 2016). Regarding pain characteristics, there is also a great variability in both clinical manifestations and localisation depending on whether the pain represents primary mechanisms or results from the secondary effects of MN degeneration. Primary causes of pain in ALS include pain with neuropathic features, spasticity, and cramps. Among them, cramps are the major cause of pain in a substantial proportion of patients, particularly in those with spinal onset (Caress et al 2016), while spasticity is typically observed at advanced stages. Secondary causes of ALS develop as the disease progresses and progressive paresis induces immobility, degenerative changes in connective tissue, bones, and joints, leading to musculoskeletal pain. In this regard, joint contractures, periscapular arthritis, and decubitus ulcers are causes of pain, particularly towards the end of the disease (Chio et al. 2016). Non-invasive ventilation may be another cause of pain in ALS patients for two reasons. On the first reason is that some patients present poor adaptation to ventilatory devices, while the second possible reason is the fact that non-invasive ventilation is commonly associated to skin lesions on the nasal bridge. In addition, dyspnoea itself, is known to activate several nociceptive pathways (Bouvier et al 1985). Treatment strategies for pain in ALS should be directed to reduce its intensity and, if possible, prevent it from becoming chronic. Pharmacological treatments, sometimes combined with physiotherapy, constitute the main approach for primary types of pain, whereas non-pharmacological strategies are generally indicated for the secondary sources of pain. (Chio et al. 2016)

2.2. Involvement of sensory components in ALS patients

According to the different components of the sensory pathway, we have divided existing reports into three distinct categories: i) sensory peripheral nervous system ii) sensory ascending spinal tracts and iii) somatosensory cortex. Most relevant studies are summarised in Table 1.

2.2.1. Sensory peripheral nervous system

The peripheral sensory pathway is made up of different components, including posterior spinal roots, plexus, peripheral nerves, and sensory peripheral receptors.

Two main types of studies have focused on this level of the sensory system. First, there are a large number of studies assessing sensory peripheral nerve conduction, some of which included sural nerve biopsy. Complementarily, other researchers have investigated peripheral sensory receptors, as well as intraepidermal nerve fibres at the skin level. Regarding neurophysiological studies assessing sensory involvement in ALS patients, some important issues that might potentially bias the obtained results should be mentioned: first, the vast majority of reported studies included a small number of participants; second, as ALS is typically an adulthood disease, most of the included patients may also exhibit other comorbidities such as diabetes (and consequently diabetic polyneuropathy) or cervical myelopathy that might influence both nerve conduction studies and somatosensorial evoked potential, thus behaving as confounding factors; third, in a big proportion of these studies, ALS patients were not stratified by important parameters such as age, nutritional state or disease severity, conditions that could potentially influence the reported results.

With regard to nerve conduction studies, several investigators reported some degree of sensory nerve conduction impairment in ALS patients. One of the earliest studies, performed by Heads et al (1991), provided evidence of early axonal atrophy, increased remyelination, and a predominance of the small diameter fibres. Importantly, these findings correlated to disease duration (Heads et al. 1991). Not long after, and consistently with these data, another study evaluated sensory nerve conduction in 19 ALS patients, evidencing significant falls in potential amplitudes with preserved nerve conduction velocities, in comparison to healthy controls (Gregory et al. 1993). Of high interest is the study performed by Hammad et al (2007) which included 103 patients with a clinical diagnosis

of ALS. In their investigation, up to 32% and 27% of ALS patients presented with sensory symptoms and abnormalities in sural sensory nerve conduction studies, respectively. In addition, sural nerve biopsy, which was performed in 22 patients, revealed histological abnormalities in 91% of patients. Such abnormalities included loss of predominantly large-calibre myelinated fibres, accompanied by axonal loss and axonal regeneration (Hammad et al. 2007). In this line, other studies reported similar rates of sensory nerve conduction disorders in ALS patients, presenting ALS as a multisystem neurodegenerative disorder that might occasionally include some degree of sensitive neuropathy (Isaacs et al. 2007; Pugdahl et al. 2007). Interestingly, it has been suggested that distal sensory nerve conduction tests evaluating antidromic dorsal sural nerve and orthodromic medial plantar, appear abnormal more often than conventional sensory nerve conduction evaluations (Isak et al. 2016b). More recently, a cohort of 150 oriental ALS patients, with a diagnosis of definite or probable ALS, were retrospectively assessed. Interestingly, the analysis of sensory nerve conduction studies revealed that they exhibited alterations in up to 15% of patients (Liu et al. 2019).

However, published studies evaluating peripheral sensory disturbances are not fully concordant. Opposite results were reported by Matamala et al (2018). In their investigation, they performed a case-control study involving 28 sALS patients and 28 age-matched controls and evaluated sensory nerve action potentials (Matamala et al. 2018). Another prospective study involving 32 sALS patients and 32 controls who were studied for nerve conduction and sural nerve biopsy, did not find specific sensory abnormalities either. However, histological analysis demonstrated abnormal axonal swellings among all ALS patients which were negative for growth-associated protein 43 (GAP-43), thus suggesting an insufficiency of regeneration in small sensory nerve fibres (Isak et al. 2017). In line with this, another retrospective study including 17 ALS patients who had undergone a sural nerve biopsy reported a significant axonal loss in more than two-thirds of the patients (Luigetti et al. 2012).

Regarding peripheral receptors and intraepidermal nerves, due to their important role in the pathogenesis of ALS, Ren et al evaluated the involvement of both sensory and autonomic nervous

systems by investigating the presence of TDP43 deposits in skin nerve fibres in patients and control subjects. Regarding sensory disorders, ALS patients showed a significant reduction in intraepidermal nerve fibre density as well as a significant loss in Meissner´s corpuscles (Ren et al. 2018). In addition, in comparison with controls, a large proportion of ALS patient biopsies demonstrated TDP-43 deposits in nerve fibres, thus emerging as a new potential biomarker (Ren et al. 2018). In our opinion, these intriguing results should be taken cautiously until replicated by other groups. Importantly, as previously discussed, ALS patients with sensory manifestations have characteristically been associated with SOD1 mutations which typically do not exhibit TDP-43 aggregates (Riancho et al. 2019). However, they are concordant with the results recently published by our group in which we reported abnormal TDP43 aggregates in dermic-derived fibroblasts from sALS patients (Riancho et al. 2020).

The loss of both intraepidermal nerve fibres and Meissner´s corpuscles had also been reported in another study enrolling 41 sALS patients and 41 matched controls. Intriguingly, researchers described that these findings were associated to a partial reduction in skin vascular vessels, and that those abnormalities correlated with disease progression (Nolano et al. 2017). In this line, other authors also reported intraepidermal fibre loss in ALS patients, but failed to correlate the severity of these findings with disease onset, clinical phenotype, as well as disease course and severity (Dalla et al. 2016). Another study including both spinal and bulbar onset ALS patients, demonstrated that spinal, but not bulbar onset patients, exhibited distal small fibre neuropathy consisting of abnormal thermal-pain thresholds as well as reduced intraepidermal nerve fibre density (Truini et al. 2015).

In summary, although there is not full concordance among published reports, most of them agreed on the presence of subtle sensory symptoms and signs of axonal predominant sensory neuropathy in nerve conduction studies. These findings correlated with histological findings that frequently evidenced a predominantly large-calibre myelinated fibre loss as well as some degree of axonal degeneration. These histologically subtle alterations did not often manifest clinically or electrophysiologically. Regarding the assessment of peripheral sensory receptors and intraepidermal

nerve fibres at a dermic level, it seems clear that there exists a reduction of both in ALS patients, particularly in the spinal forms of the disease. In favour of its biological plausibility, abnormal TDP-43 deposits have been documented in intraepidermal nerve fibres of ALS patients.

2.2.2. Sensory ascending spinal tracts

Within the spinal cord, sensory tracts ascend through the dorsal (light touch, vibration, proprioception) and anterolateral (pain and temperature) columns. Sensory evoked potentials (SEPs) constitute a widely used neurophysiological technique to evaluate the transmission of sensory impulses at dorsal spinal columns.

The first reported study assessing SEPs in ALS was performed almost 40 years ago and included 45 patients with the disease (Cosi et al. 1984). The authors reported a pathological slowing of conduction along the central sensory pathways, that in some patients was also accompanied by a decreased amplitude response (Cosi et al. 1984). Subsequently, other investigators have reported a similar rate of SEP alterations in ALS patients, ranging from 50-60% of cases (Radtke et al. 1986, Theys et al 1999). Interestingly SEP differences did not significantly progress over the 180 day follow-up period, thus suggesting that although frequent at diagnosis, sensory subclinical abnormalities are usually not as rapidly progressive as motor manifestations (Theys et al. 1999). Apart from the standard SEPs, late SEPs' components (N60, P100), which reflect on cortical pathways involved in cognitive-motor functions, have been reported to be significantly depressed in ALS patients (Sangari et al 2018).

In recent years, laser evoked potentials (LEPs) have emerged as a complementary tool to SEPs to evaluate central conduction of pain stimulus. Several authors have incorporated this technique for sensory assessment of ALS patients. A case-control study including 24 ALS patients and 23 controls concluded that the former exhibited abnormal delayed latencies when compared to healthy subjects, also supporting the presence of degeneration of sensory subcortical structures (Simone et al. 2010). One study combining both SEP and LEPs in 18 ALS patients and 31 controls, obtained concordant findings with previous literature, suggesting an impairment of sensory tracts in more

than half of studied patients. Interestingly, LEPs appeared as a more sensitive tool than SEPs to evaluate sensory disturbances in patients with MN disease (72% and 56%, respectively) (Isak et al. 2016a).

Magnetic resonance imaging (MRI) has also been used to assess spinal sensory tracts in ALS patients. Cohen-Adad et al (2013) performed the first study in which diffusion tensor imaging (DTI) and magnetisation transfer (MT) were measured in the spinal cord of 29 patients and 21 healthy controls, respectively. Interestingly, at both lateral and dorsal segments of the spinal cord, significant differences between ALS patients and control subjects were detected in DTI and MT sequences, suggesting a subjacent degeneration of the two sensory dorsal and anterolateral tracts (Cohen-Adad et al. 2013). In line with these findings, a complementary investigation examined sensory spinal columns combining DTI sequences at dorsal columns and SEPs after median and ulnar nerve stimulation. Taken together, at early stages of the disease, DTI spinal imaging and SEPs were able to identify that up to 85% of ALS patients have subclinical sensory impairment (Iglesias et al. 2015).

In conclusion, SEPs and LEPs appear as useful tools for evaluating ascending sensory tracts at the spinal cord. In comparison to healthy controls, an important proportion of ALS patients show prolonged nerve conduction latencies within these techniques, thus suggesting some degree of impairment at spinal levels. In this regard, LEPs seem to be a bit more sensitive than SEPs in identifying such alterations. Likewise, DTI and MT MRI sequences have demonstrated spinal alterations at both dorsal and anterolateral tracts, reinforcing the concept, that although asymptomatic in most cases, sensory ascending tracts frequently exhibit some degree of alteration in ALS patients.

2.2.3. Somatosensory cortex

The somatosensory cortex constitutes the highest level in the sensory pathway. It comprises the primary somatosensory cortex and the secondary somatosensory cortex. In a simplistic representation, the former would be responsible for processing somatic sensations, while the latter would be responsible for the perception of that sensation. The primary somatosensory

cortex is located in the parietal lobe at the postcentral gyrus. It is situated just posterior to the central sulcus adjacent to the primary motor cortex. Interestingly, somatosensory cortex, particularly its secondary areas, are widely interconnected with other brain areas, including the motor cortex (Brazis P et al. 2011).

Based on their close anatomical and functional relationship, Mochizuki et al evaluated the number of neurons in the primary motor and somatosensory cortex in ALS patients. Interestingly, the authors described a significant decrease of neurons and Betz cells in both locations compared to control subjects. In addition, a positive correlation between the number of neurons at motor and somatosensory cortex was evidenced, thus suggesting that interdependent mechanisms may exist between these areas once neurodegeneration is initiated (Mochizuki et al. 2011). These findings are also supported by isolated clinical cases of ALS patients, in whom "unexplained" parietal lobe atrophy was evidenced by MRI with disease progression (Shimizu et al. 2020).

Recently, the concept of brain connectome modified our conception of brain functions. Upon this conception, the distinct cerebral areas would be very widely interconnected, resulting in different functional networks (Hodge et al. 2016). In this regard, to investigate functional coherence within the sensory-motor network, 12 ALS patients were studied by resting state functional MRI (rsfMRI) analysis. After comparing ALS patients with healthy controls, a decreased functional coherence was evidenced at distinct sensory-motor network areas. Intriguingly, sensory-motor network impairment in specific areas, such as right postcentral gyrus – precentral gyrus – superior frontal gyrus, was associated with lower ALSFRS-r scores, suggesting a more severe disease evolution (Zhou et al. 2014).

Lately, somatosensory cortex hyperexcitability is also being considered as a potential biomarker for short survival in patients with ALS. This relies on the theory that at a particular point of the disease, somatosensorial cortex hyperexcitability might reflect a compensatory mechanism of sensory cortex for motor disturbances (Hamada et al. 2007).

According to this hypothesis, Shimizu et al (2018) studied a cohort of 145 sALS patients and 73 healthy controls and followed them until death or tracheotomy. Intriguingly, median survival was significantly shorter in patients who had larger somatosensory cortical amplitudes in SEPs. Subsequent multivariate analyses identified a more pronounced N20p-P25p amplitude as an independent prognostic factor (Shimizu et al. 2018). In line with this study, a marked disinhibition of somatosensory cortex in ALS patients from the second year of disease evolution has been recently reported (Nardone et al. 2020).

In addition to the sensory-motor integration at a cortical level, there are also relevant connections between sensory and motor systems at the spinal cord.

The dorsal root ganglia contain the cell bodies of neurons of the sensory pathway that transmit the somatosensory information from the periphery to the CNS through the dorsal and anterolateral tracts of the spinal cord (Haberberger et al., 2019). Apart from transmitting sensory information, proprioceptive sensory neurons are key in modulating motor behaviours by integrating the sensory and motor systems into the CNS. Thus, proprioceptive DRG neurons transmit peripheral information about muscle contractions to lower MNs as a feedback system to generate appropriate motor responses (Imai and Yoshida, 2018). Consequently, in addition to inducing somatosensory disorders, damage to proprioceptive neurons may secondarily contribute to the pathogenesis of motor disturbances in ALS. Differently from MNs at the anterior horn, each sensory neuron is wrapped by the cell bodies and laminar processes of several satellite glial cells (SGCs), forming a morphological and functional unit (sensory neuron – SGC units) (Haberberger et al 2019). SGCs play an important regulatory role in sensory neuron function, particularly in controlling the neuronal microenvironment. (Haberberger et al. 2019).

Recently, Sangari el al (2016) reported an impaired spinal integration of these systems in ALS patients. In their study, transcranial magnetic stimulation (TMS) was applied over the motor cortex to induce motor evoked potential (MEP) in contralateral triceps. Then, median and ulnar nerve stimulations at wrist level were combined with TMS to evaluate the resulting changes in MEPs.

Although there were no differences in MEP recruitment curves between ALS and healthy subjects, MEP threshold was significantly higher in the latter. In addition, although nerve stimuli MEPs increased in both groups, but facilitation was stronger in ALS patients. This, led the authors to speculate that spinal network properties likely compensate for depression of afferent inputs, thus leading to MN hyperexcitability which may in turn contribute to excitotoxicity (Sangari et al 2016).

In summary, an important number of studies support the involvement of somatosensory cortex and sensory-motor networks in ALS patients. In this regard, different studies have pointed out to somatosensory hyperexcitability as an independent biomarker of short survival.

3. PRECLINICAL EVIDENCE SUPPORTING THE INVOLVEMENT OF THE SENSORY SYSTEM IN ALS

Complementary to clinical studies, several preclinical studies support some degree of sensory system dysfunction in this disease (Table 2). Most of them used the transgenic SOD1 mouse model. Up to 20% of fALS cases are due to SOD1 mutations. This gene encodes the superoxide dismutase 1 protein, which is involved in several cellular functions, including the oxidative stress response (Riancho et al. 2019). SOD1 mutations are also the basis of a commonly used transgenic mouse model expressing the human *SOD1* gene with the G93A mutation (Gurney et al. 1994). High-copy $SOD1^{G93A}$ transgenic mice have been reported to recapitulate much of the pathophysiology of human ALS, including progressive MN degeneration, progressive neuromuscular function loss and reduced lifespan (Gurney et al. 1994). Despite the fact that this mouse model is based on a SOD1 familial form of ALS, and consequently does not exhibit the cytoplasmic TDP43 aggregates, several authors have highlighted its translational usefulness for the study of sALS (Bosco et al. 2010).

Guo et al (2009) first studied sensory disturbances in the transgenic $SOD1^{G93A}$ murine model. In their study, transgenic mice were used to explore the sensory system at several levels, including dorsal roots, dorsal ganglia, and posterior column tracts. Interestingly, they concluded that, from an histological perspective, transgenic SOD1 mice exhibited significant damage in the sensory system, which basically consisted of Wallerian-like degeneration in axons of both dorsal root and dorsal

funiculus, as well as mitochondrial abnormalities in dorsal root ganglia sensory neurons (Guo et al. 2009). Subsequently, different investigations focused on the distinct sensory pathway levels to assess the presence or absence of pathology. On this basis, published studies might be divided into those evaluating pathology at: i) dorsal root ganglion sensory neurons and large sensory conduction fibres, ii) small intraepidermal sensory fibres, and iii) sensory-motor networks.

3.1. Dorsal root ganglion sensory neurons and large sensory conduction fibres

Several reports have tried to characterise sensory disturbances in sensory neurons at the dorsal root ganglion and large sensory peripheral nerves. First, Vaughan et al (2015) assessed two strains of transgenic mice harbouring mutations in SOD1 (G93A) and TARDBP (A315T), and evaluated retrograde axonal transport. Interestingly, the analysis of proprioceptive nerve endings in muscle revealed early disturbances at Ia/II proprioceptive nerve endings in muscle spindles before the motor symptomatic phase had initiated. Intriguingly, in TDP43 transgenic mice, clear sensory abnormalities were evident even in the absence of MN axon lesions (Vaughan et al. 2015). Also, sensory abnormalities have been evaluated in progressive motor neuronopathy (PMN) transgenic mice, characterised by a missense loss of function mutation in the tubulin binding cofactor E (TBCE). These animals show an aggressive form of motor axon dying back and microtubule loss, similar to that observed in ALS patients associated to TUBA4A mutations. Histological analysis showed evidence of sural sensory neuropathy with axonal discontinuities and bead-like spheroids. In addition, transgenic mice showed a marked impairment of microtubule polymerisation in dorsal root ganglion neurons which would likely result in a compromised microtubule-based transport in those neurons, thus providing a new potential explanation for the axonal pathology in sensory nerves (Schafer et al. 2017).

Coming back to the SOD1 transgenic mice model, it has been demonstrated that dorsal ganglion sensory neurons accumulate misfolded mutant SOD1 protein. However, this protein accumulation was not associated with endoplasmic reticulum stress, nor did it induce unfolded protein responses. If confirmed, these findings might indicate underlying differential vulnerability mechanisms between

anterior horn MNs and sensory neurons in ALS (Taiana et al. 2016). In the same line, Vaughan et al (2018) characterised mutant TDP43 ^{A315T} cultured sensory neurons and compared them with mutant SOD1^{G93A} and control cultured sensory neurons, respectively. Interestingly, both SOD1 and TDP43 mutant neurons were reported to have slower rates of neurite growth and lesser elaboration of neuritic branches. Mutation-bearing sensory neurons were also more sensitive to the microtubule inhibitor vincristine than control neurons. Interestingly, the analysis of several factors involved in stress responses, such as ATF3 or PERK, demonstrated important differences between SOD1 and TDP43 sensory neurons (Vaughan et al. 2018).

3.2. Small intraepidermal sensory fibres

Sensory small nerve fibres have also been studied in SOD1 transgenic mice. It has been noted that these mice displayed small fibre pathology with intraepidermal nerve fibre loss, reduction of Meissner´s corpuscles, and axonal degeneration which characteristically preceded the disease onset and progressed over time (Sassone et al. 2016; Rubio et al. 2016). Complementarily, the culture of small diameter dorsal root ganglion neurons of mutant mice showed stress features and peripherin 56 (a peripherin splice variant) accumulation, which induced axonal damage because its dissembled light and medium neurofilaments subunits. These important findings suggest a new potential mechanism for small fibre pathology in ALS and reinforce the role of peripherin in the pathogenesis of the disease (Sassone et al. 2016).

3.3. Sensory-motor networks

Although motor manifestations are the key feature of ALS, several investigators have studied motor networks to elucidate whether degenerative mechanisms initiated at anterior horn MNs or in other cells of these motor circuits. Within this scenario, Held et al (2019) recently reported a Drosophila SOD1^{G85R} knock-in model. Their results showed that transgenic larvae at early stages exhibited a significant motor function deterioration that was not associated with a clear degeneration of spinal MNs, thus suggesting that other components within the sensory-motor networks might be altered. Interestingly, a defect in the proprioceptor sensory neurons, which are necessary for the relay of the

contractile status of muscles back to the central nerve cord, was identified. Mechanistic approaches suggested that this defect in sensory feedback might be related to bone morphogenic protein (BMP) pathway (Held et al. 2019). Not long after, abnormalities in proprioceptive sensory neurons involved in jaw reflex were reported in SOD1 transgenic mice as another potential target for the disease. These included impaired action potential burst discharge related to sodium channels. Interestingly, other brainstem sensory neurons such as the mechanoreceptive and nociceptive trigeminal ganglion neurons did not exhibit pathological features (Seki et al. 2019).

4. CONCLUDING REMARKS

Although ALS has been classically considered as a motor system circumscribed disease, there is an increasing amount of evidence that other neurological and probably non-neurological systems may also be involved. This also occurs in other neurodegenerative diseases such as Parkinson´s disease in which non-motor symptomatology has been proved to have a great relevance in the pathogenesis of the disease. In this regard, the sensory system has been extensively reported both from preclinical and clinical studies to be affected in ALS patients. Even though they are not usually described by patients, due to the high heterogeneity of the disease, subtle sensory alterations seem to be present in a subgroup of ALS patients.

These evidences will probably have a double positive effect. On the one hand, a better understanding of the clinical spectrum of the disease will translate into better care of ALS patients. In contrast, the identification of new, “non-motor” systems involvement, that might also be part of the degeneration, should prompt the scientific community to consider ALS as a non-cell-autonomous disease. On this basis, more holistic research approaches would hopefully translate into more successful results.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al. 2019).

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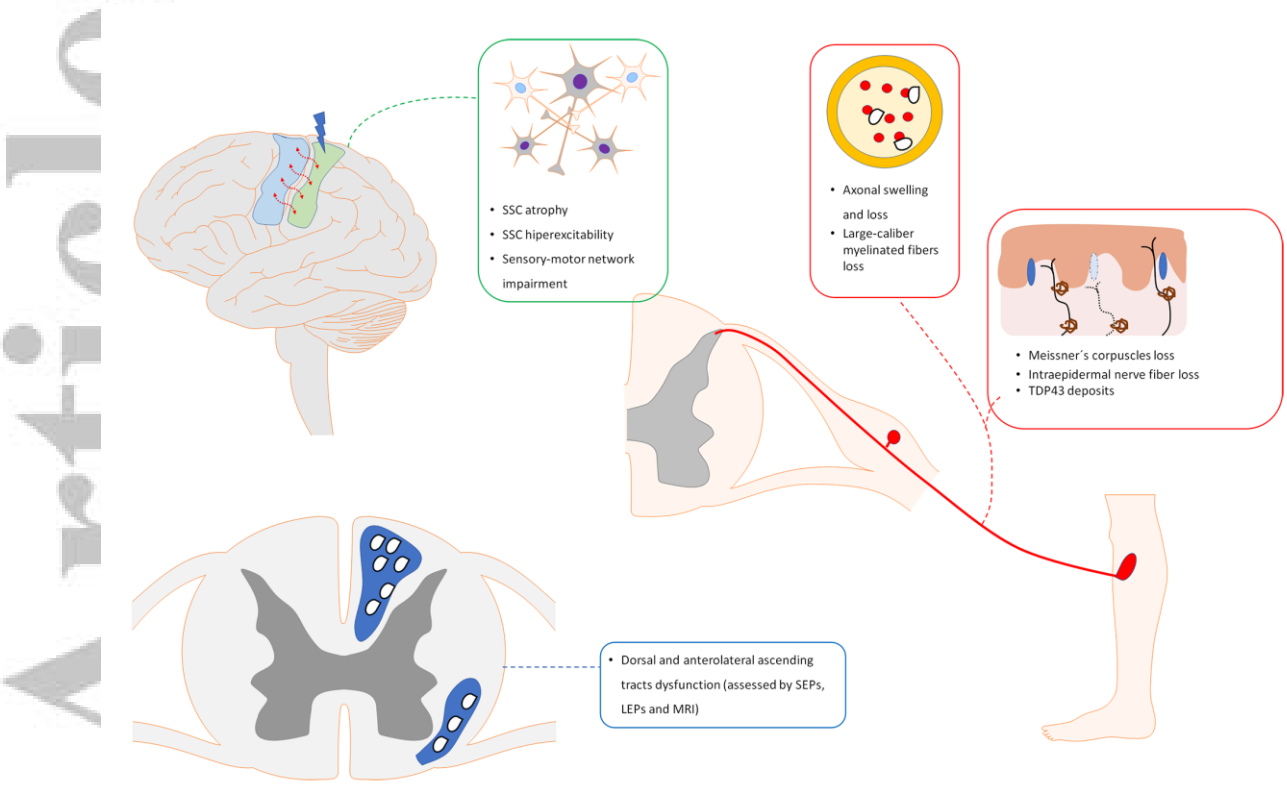

FIGURE 1. Evidences of sensory involvement in ALS from human studies.

Sensory involvement in ALS patients include the peripheral nervous system, the spinal cord sensory ascending tracts, as well as the somatosensory cortex. This figure illustrates the main pathological findings reported at each level.

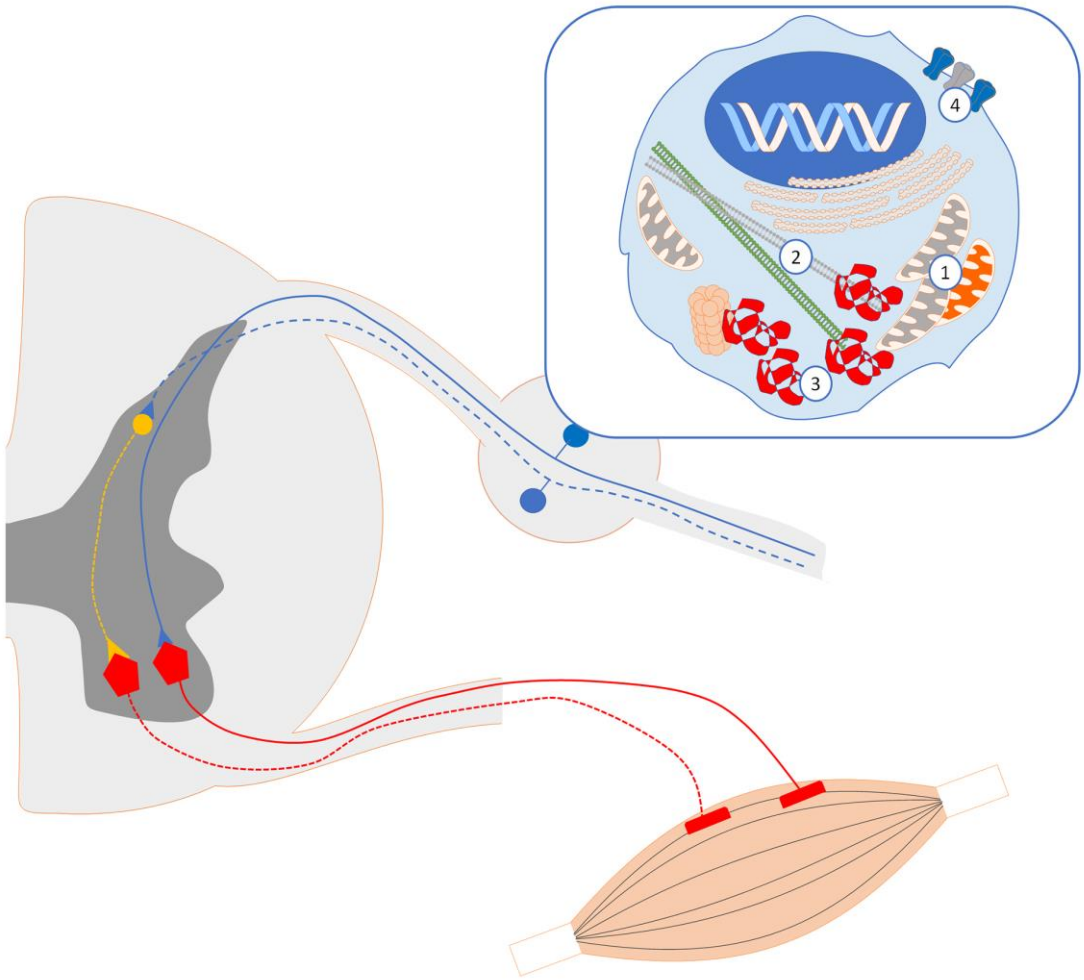

FIGURE 2. Preclinical evidences of sensory involvement in ALS.

A spinal cord segment is represented. Dorsal root ganglion sensory neurons (DRGSN) may be a potential target of the disease. Similar pathogenic mechanisms to that observed in spinal cord anterior horn motor neurons (MNs) have been reported in DRGSN. These include mitochondrial dysfunction (1), cytoskeletal abnormalities (2), SOD1 aggregation (3) as well as pathological hyperexcitability (4). In addition, the sensory-motor networks at spinal cord, in which a direct interaction between DRGSNs and anterior horn MNs occurs, emerge as new potential pathogenic mechanism that might favour the local propagation of the disease.

TABLE 1. MAIN CLINICAL STUDIES SUPPORTING SENSORY INVOLVEMENT IN ALS

Author (year)	Number of patients	Main findings
Peripheral nervous system		
Heads et al 1991	-	Early axonal atrophy, increased remyelination and predominance of smaller fiber diameters.
Gregory et al 1993	19 ALS	Axonal sensory nerve neuropathy.
Hammad et al 2007	103 ALS	Sensory symptoms in 32% of patients. Abnormalities in sural sensory nerve conduction in 27% of patients Histological abnormalities (large-calibre myelinated fibers loss, axonal loss and axonal regeneration) in 91% of patients.
Isaacs et al 2007	5 ALS	Sensory neuropathy. Axonal degeneration in sural biopsy.
Pugdahl et al 2007	88sALS	Sensory neuropathy in 22.7% of patients.
Luigetti et al 2012	17 ALS	Axonal loss in up to a 2/3 of patients.
Truini et al 2015	24 ALS (11 bulbar/13 spinal)	Abnormal thermal-pain thresholds and reduced intraepidermal nerve fibre density in spinal onset forms.
Isak et al 2015	18 ALS/31 control	Distal sensory nerve conduction tests evaluating antidromic dorsal sural nerve exhibit a higher sensitivity.
Dalla Bella et al 2016	57 ALS	Intraepidermal nerve fibers reduction. No correlation between intraepidermal nerve fibers and disease onset/course nor disease severity.
Isak et al 2017	32 ALS/32 contol	No alteration in nerve conduction studies. Histological analysis with abnormal axonal swelling and fibers negative for GAP43 in ALS.
Nolano et al 2017	41 ALS/41 control	Intraepidermal nerve fiber density reduction, loss of Meissner´s corpuscles and loss small vascular vessels in ALS.
Ren et al 2018	18 ALS/ 18 controls	Reduction of the intraepidermal nerve fiber density and loss of Meissner´s corpuscles. TDP43 aggregates in nerve fibers.
Matamala et al 2018	28sALS/28 control	No significant differences in sensory nerve conduction studies.
Liu J et al 2019	150 ALS	Sensory nerve conduction alterations in up to 15% of patients.
Ascending spinal tracts		
Cosi et al 1984	45 ALS	Pathological slowing along central sensory pathways. Altered amplitude of potentials in some ALS patients.
Radtke et al 1986	17 ALS	Altered SEPs in 56% of ALS patients.
Theys et al 1999	50 ALS	SEP abnormalities in up to 60% of ALS patients. No progression of SEPs abnormalities over 6 months.
Simone et al 2010	24 ALS/23 control	Altered LEPs in ALS patients No correlation between LEP abnormalities, pain intensity and clinical features.
Isak 2016	18ALS/31 control	LEP more sensitive to assess sensory disturbances in comparison to SEP (72 and 56 % respectively).
Cohen-Adad et al 2013	29 ALS/21 control	DTI and MT MRI sequences appeared altered in anterolateral and dorsal segments of spinal cord of ALS patients.
Iglesias et al 2015	21 ALS/21 control	Combination of both DTI sequences and SEP identified subclinical sensory defects in up to 85 percent of ALS patients at early stages of the disease.
Somatosensory cortex		
Hamada et al 2007	26 ALS/15 control	Cortical SEPs amplitude are associated to motor disturbances. Early cortical response appears enlarged in ALS patients at a moderate stage and markedly attenuated in patients with more advanced forms.
Mochizuki et al 2011	-	Concomitant neuronal loss at primary motor cortex and somatosensory cortex in ALS patients.
Zhou et al 2014	12ALS/12 control	Sensory-motor network impairment is associated to more severe forms of the disease
Shimizu et al 2018	145ALS/73 control	Larger somatosensory cortical amplitudes in SEPs are an independent factor for poor prognosis in ALS patients.
Nardone et al 2020	-	Marked disinhibition of somatosensory cortex in ALS patients from year 2 of disease evolution onwards

DTI: diffusion tensor imaging; LEPs: laser evoked potentials; MT: magnetization transfer; SEPs: sensory evoked potentials;

TABLE 2. MAIN PRECLINICAL STUDIES SUPPORTING SENSORY INVOLVEMENT IN ALS

Author	Animal model	Main findings
Guo et al. 2009	hSOD1^{G93A} mice	Wallerian-like degeneration in axons of both dorsal root and dorsal funiculus. Mitochondrial abnormalities in dorsal root ganglia sensory neurons.
Vaughan et al. 2015	hSOD1 (G93A) mice TDP43 (A315T) mice	Early disturbances in Ia and II proprioceptive nerve endings in muscle spindles before initiation of the motor symptomatic phase
Rubio et al. 2016	hSOD1-G93A mice	Marked reduction of intraepidermal nerve fibers, Meissner's corpuscles, and subepidermal nerve density at early stages.
Sassone et al. 2016	hSOD1-G93A mice	Small fiber pathology with intraepidermal nerve fiber loss and axonal degeneration, possibly induced by peripherin 56 accumulation.
Taiana et al. 2016	hSOD1-G93A mice	Misfolded SOD1 accumulation in dorsal ganglion sensory neurons. No evidence of ER stress neither UPR activation.
Schafer et al. 2017	PMN mice	Axonal sensory nerve pathology. Disorders in microtubule-based transport in dorsal root ganglion neurons.
Schafer et al. 2017	PMN mice	Axonal sensory nerve pathology. Disorders in microtubule-based transport in dorsal root ganglion neurons.
Vaughan et al. 2018	SOD1(G93A) and TDP43 (A315T) sensory neurons	Slower rates of neurite growth and fewer neuritic elaboration in mutated neurons. Differential response to stress between SOD1 and TDP43 sensory neurons.
Held et al. 2019	Sod1-G85R Drosophila	Defect in the sensory feedback as a potential initiating event for ALS motor dysfunction.
Seki et al. 2019	hSOD1-G93A mice	Early proprioceptive sensory neurons degeneration. Nav1.6 Na+ channel deficiency contributing to arrhythmic burst discharge.

ER: endoplasmic reticulum; PMN: progressive motor neuronopathy; UPR: unfolded protein response