ΑΙΣΘΗΤΙΚΕΣ ΔΙΑΤΑΡΑΧΕΣ ΣΤΗΝ ΠΛΑΓΙΑ ΜΥΑΤΡΟΦΙΚΗ ΣΚΛΗΡΥΝΣΗ: ΝΕΥΡΟΦΥΣΙΟΛΟΓΙΚΗ ΔΙΕΡΕΥΝΗΣΗ

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ΠΕΡΙΛΗΨΗ

Η Πλαγία Μυατροφική Σκλήρυνση (ΠΜΣ) είναι μια προοδευτική νευροεκφυλιστική νόσος και θεωρείτο ως «αμιγώς» κινητική νόσος, επηρεάζοντας τον ανώτερο και κατώτερο κινητικό νευρώνα. Κατά τη διάρκεια της νόσου όμως, ορισμένοι ασθενείς εμφανίζουν συνοδά μη κινητικά συμπτώματα, και έτσι η ΠΜΣ θεωρείται πλέον πολυσυστηματική διαταραχή. Οι γνωστικές διαταραχές και η εξωπυραμιδική σημειολογία είναι συχνά ευρήματα. Η διαταραχή αισθητικότητας στην ΠΜΣ έχει συζητηθεί αρκετά και αμφισβητηθεί. Ο στόχος αυτής της ανασκόπησης είναι να παρουσιάσει τη νευροφυσιολογική αξιολόγηση (Σωματοαισθητικά Προκλητά Δυναμικά, Αισθητικές Ταχύτητες Αγωγής και Συμπαθητικό Δερματικό Αντανακλαστικό) της αισθητικότητας στην ΠΜΣ και να συζητήσει τους πιθανούς παθογενετικούς μηχανισμούς που μπορεί να την επηρεάζουν.

Λέξεις κλειδιά Πλαγία Μυατροφική Σκλήρυνση, Αισθητικές διαταραχές, Σωματοαισθητικά Προκλητά Δυναμικά, Αισθητικές Ταχύτητες Αγωγής, Συμπαθητικό Δερματικό Αντανακλαστικό

SENSORY INVOLVEMENT IN AMYOTROPHIC LATERAL SCLEROSIS: NEUROPHYSIOLOGICAL EVALUATION

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Abstract

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder considered as a "pure" motor disease affecting upper and lower motor neurons. In the course of the disease, some patients exhibit concomitant nonmotor signs, and thus ALS is now considered a multisystem disorder. Cognitive or behavioral impairment and extrapyramidal symptoms are common findings. Sensory impairment in ALS has long been debated and disputed. The aim of this review is to present the neurophysiological assessment (Somatosensory Evoked Potentials, Sensory Conduction Studies and Sympathetic Skin Response) of sensory involvement in ALS and to discuss potential pathogenic mechanisms underlying it.

Key words Amyotrophic Lateral Sclerosis, Sensory Impairment, Somatosensory Evoked Potentials, Sensory Conduction Studies, Sympathetic Skin Response

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease affecting upper and lower motor neurons, leading to weakness and eventually death from neuromuscular respiratory failure. Until recently, ALS was considered a pure motor disease, but involvement of non-motor areas of the brain is recognized and ALS is now considered a multisystem disorder.[1] Many of these non-motor symptoms are under-diagnosed and left unreported during illness, probably overwhelmed by the fulminant course of the disease. Most of these non-motor symptoms are poorly understood and underlying mechanisms remain undefined.

The most common non-motor symptoms reported across systematic reviews and cohort studies are cognitive-behavioral impairment, neuropsychiatric disorders, such as depression and anxiety, fatigue, sleep disorders and parkinsonism. Besides those relatively commonly occurring non-motor symptoms there is a list of others, occurring with variable prevalence.[1-6] Most of these are investigated through questionnaires, and subsequently, their report lack objectivity. Moreover, in most cases these are not ALS-specific questionnaires for investigating various symptoms, and thus, the ones used are non-disease specific. As a consequence, symptoms might be missed or overestimated.

Among non-motor symptoms, a special interest involves sensory impairment, since until lately, sensory symptoms were considered among exclusion criteria for the diagnosis of ALS,[7] and only in the revised El Escorial criteria,[8] deficits in sensory system are considered a feature in ALS.

Evidence for the involvement of sensory system has been derived from patients' subjective descriptions, quantitative sensory studies, neurophysiologic and imaging studies, as well as from pathologic studies.

Evidence of large myelinated fiber involvement has been proposed for ALS patients who showed raised vibration thresholds but normal thresholds for touch-pressure or for thermal cooling.[9] In a recent study by Chowdhury et al.,[2] 30% of ALS patients complained of unexplained sensory symptoms either tingling or paresthesia, that did not follow any definite distribution. In this paper, sensory conduction studies (SCS) were normal. In a large cohort study by Hammad et al,[10] including 103 ALS patients, numbness, tingling, and pain were reported in 23 of 103 (22%) patients. Abnormalities on sensory examination were found in significant proportion, in 21 of 103 (20%) patients, while diminished vibration sense was the most frequent finding (12/103), followed by diminished pinprick sensation (10/103), impaired thermal sensation (9/103), and reduced joint position sense (1/103). Sensory symptoms, signs, or both were present in 33 subjects (32%), either in stocking and glove pattern or as focal symptoms in a single limb. In this cohort study, SCS showed abnormalities, mostly low sensory nerve action potentials (SNAP) amplitudes in a similar proportion (36%). Similarly, in Martinez et al retrospective study,[6] paraesthesias occurred in 13% of patients.

In an older study by Cho et al.,[11] a similar percentage of ALS patients reported sensory symptoms (25/77, 32.5%) but only 4 (5.2%) had objective sensory change such as hypesthesia and decreased vibration sense and only 1 had neurophysiological evidence of polyneuropathy. On the other hand, very old studies questioned sensory involvement in ALS patients.[12-14] Finally, there are systematic reviews [1,3,5,15] of non-motor symptoms in ALS, where there is no special reference to sensory involvement, while an extensive list of other symptoms appears.

The aim of this study is to review the neurophysiological assessment of sensory involvement in ALS and to discuss potential pathogenic mechanisms underlying it.

Somatosensory Evoked Potentials (SEP)

Measurement of somatosensory evoked potentials (SEPs) from the electric stimulation of peripheral nerves, mainly the median or tibial nerve, has been part of the clinical workup of patients with ALS to investigate for concomitant sensory pathology.[16] The earliest was published in 1984,[17] but new reports are published, showing continued interest in this topic.

The results show great heterogeneity, mainly due to the heterogeneity of the examined population, e.g. diseases stage (early stage vs locked-in stage), type of clinical subgroup (primary lateral sclerosis vs progressive muscular atrophy), or the presence of concomitant cognitive impairment, that might affect late cortical responses.

The main findings and their interpretations from the relevant publications are presented in Table 1. Most studies show prolonged Central Conduction Time (CCT).[11,17-26] others demonstrate increased amplitudes of cortical responses,[21,27-31] while other studies found reduced amplitudes.[17,23,32,34] In some studies, amplitudes were found larger in early stages, that progressively decreased or lost.[21,29] In other studies, SEPs were absent, either at onset or during disease progression.[29,35] Several other abnormalities are reported, especially when paired stimuli are used, such as increased S2/S1 ratio (paired pulse stimulation/single pulse stimulation) [36] and lesser suppression at short Interstimulus Intervals (ISI),[37] as described in Table 1.[36-49] There is only one study that reports no SEP abnormalities in ALS patients.[50] Regarding the interpretation of the findings, they mainly focus on two axes; either in the primary involvement of the somatosensory cortex in terms of

hyperexcitability, analogous to that of pyramidal neurons,[18,27,28,30,36] or in the secondary involvement, due to disturbed cortical inhibition by inhibitory interneurons.[37,38]

TABLE 1. Somatosensory Evoked Potentials in ALS patients.

STUDY	ALS/CNTR	SEP	RESULT	CONCLUSION
Shimizu et al., 2023[18]	17 CLIS	Median	N20, N13 abolished, prolonged latencies CCT (N13-N20) prolonged	Central somatosensory pathway is severely involved
Shimizu et al., 2023[27]	14/13	Median	High amplitudes N20, P25, N30	Excitability of the primary sensory cortex and secondary motor cortex is enhanced in ALS
Cengiz et al., 2023[36]		paired pulse SEP	increased S2/S1 ratio	increased somatosensory cortical excitability
Norioka et al., 2021[28]	145/57	Median	Large N20 and P25	Hyperexcitability of the sensory cortex pyramidal neurons.
Harada et al., 2021[32]	23/14	Pain SEPs intra-epidermal needle electrode	Lower amplitudes	Correlated with cognitive dysfunction
Khalili-Ardali et al., 2021[35]	4 CLIS	Median	Absent SEPs	Heterogeneity of the results
Nardone et al., 2020[33]		High-frequency SEP	Amplitude reduction of post-synaptic HF-SEP burst	Reflects the activity of cortical inhibitory interneurons, disinhibition, involves the somatosensory cortex.
Shimizu et al., 2020[29]	1	Median	Enlarged N20 initially, progressive deterioration, finally loss	Multisystem neurodegeneration involving the central sensory pathway
Höffken et al., 2019[38]	15/15	Paired SEPs median	Reduced inhibition	Disinhibition of the somatosensory cortex in ALS. Primary characteristic or compensatory up-regulation due to functional motoric impairment
Shimizu et al., 2018[30]	145/ 73	Median	Larger amplitude of N20p-P25p	Sensory cortex hyperexcitability predicts short survival in patients with ALS
Sangari et al., 2017[34]	21/21	Median Ulnar	Late SEP (N60, P100) depression	Abnormal cortical excitability in areas involved in cognitive-motor functions
Isak et al., 2016[19]	18/31	Median Tibial LEPs	Longer latencies	Beta or a-delta sensory fibres, or both impaired
Iglesias et al., 2015[20]	21/21	Median Ulnar	Slow CCT	Identify 85% of patients with subclinical sensory defect
Hamada et al., 2007[21]	26/15	Median	Early cortical response enlarged, attenuated in the severe form, CCT prolonged	Compensatory function of the sensory cortex for motor disturbances
Sonoo et al., 2004[31]	5/-	Median	N10 far-field potential larger	Lack of cancellation by slower motor axons.
Restuccia et al., 2003[39]	6/14	Upper limb	Decrease of the N13 cervical	
Machii et al., 2003[37]	10/7	Median paired pulse stimuli	Less suppression at short ISI	Sensory cortex is disinhibited or hyperexcitable
Ogata et al., 2001[40]	12/-	Median Tibial	Abnormal	Clinical subtype of ALS

Ahlskog et al., 1999[48]	16 / (Guam)	Tibial	Mildly abnormal	
Theys et al., 1999[22]	50/		Slowing in the peripheral and central sensory pathways	Subclinical abnormalities of the sensory system in ALS
Matsumoto et al., 1999[41]	14/	Simultaneous stimulation of bilateral posterior tibial nerves C2, T12	Abnormalities	Spinal cord conduction velocities of ascending fibers are disturbed
Georgesco et al., 1997[51]	24/17	Tibial, sural, plantar, saphenous	Marked alterations	Impairment of pyramidal control of the sensory system and Clark's column
Zanette et al., 1996[42]	39/	Tibial	Altered early (P40) Spared late (N60)	Neuronal loss in the somatosensory cortex
Cho et al., 1996[11]	77		Abnormal CCT 4/37	Degeneration on central sensory pathways
De Carvalho et al., 1995[43]	33/		Abnormal in 3 ALS 7/8 SCC	Useful in the differential diagnosis between ALS and SCC
Kang and Fan, 1995[50]	12/		Normal	Differential aids between ALS and CSM
Gregory et al., 1995[49]	19/12	Median	N19 increased latency	Neuronal degeneration in ALS is not restricted to motor neurons.
Georgesco et al., 1994[26]	28/		Lack or delay of some components	Widespread sensory disturbance
Constantinovici, 1993[44]	10/	Median Tibial	Abnormal	Reflect physiological dysfunction in the sensory system
Palma et al., 1993[23]		Median	Reduction of N13 amplitude, prolonged P22	Do not implicate the involvement of somatosensory pathway
Constantinovici, 1989[45]	10	LL	Abnormal	
Ghezzi et al., 1989[24]	27		Abnormally delayed	
Facco et al., 1989[25]	19	Median	N9-N13 was significantly delayed, but the N13-N20 was normal	
Radtke et al., 1986[46]	17	UL LL	Abnormal	Sensory system involvement in ALS
Dasheiff et al., 1985[47]	1		Abnormal	Abnormal SEPs need not exclude a diagnosis of ALS
Cosi et al., 1984[17]	45	Median Tibial	Increased latency N13 and cortical potentials. Decreased amplitude	Pathological slowing of conduction along the central sensory pathways

ALS: Amyotrophic Lateral Sclerosis, CCT: Central Conduction Time, CLIS: Completely Locked-In State, CNTR: Controls, CSM: Cervical Spondylotic Myelopathy, HF: High Frequency, ISI: Interstimulus Interval, LEP: Laser Evoked Potentials, LL: Lower Limb, S2/S1 (paired pulse stimulation / single pulse stimulation), SCC: Spinal Cord Compression, SEP: Somatosensory Evoked Potentials, UL: Upper Limb.

The hypothesis of somatosensory cortical hyperexcitability is based on the findings of large amplitude of N20-P25 cortical potentials. One possible pathogenetic mechanism leading to increased amplitudes, is a compensatory change of somatosensory cortex to the excitability and/or degeneration of motor cortex, as if the hyperexcitable motor cortex has induced the sensory cortex hyperexcitability.[30] Another view is that somatosensory cortex is primary hyperexcitable, due to ALS-pathology spreading from motor cortex to neighbor cortices through corticofugal transsynaptic connections.[52]

The hypothesis of disinhibition is supported by the two studies using paired stimuli.[37,38] The phenomenon of paired-stimulation suppression is assumed to be the result of strong c-aminobutyric acid (GABA)-dependent inhibitory and weaker NMDA-dependent excitatory interneuronal circuits. Therefore, reduced paired-pulse inhibition might reflect diminished GABAergic effects or in the contrary, upregulated glutaminergic effects that suppress inhibition.

Another proposed interpretation involves cognitive dysfunction,[32-34] especially when late responses are altered. As late SEPs are considered N60, generated by somatosensory area 2 (S2) and P100, generated in temporal cortex. The finding of larger depression of late, compared to early, cortical potentials in ALS cannot be attributed solely to the impaired sensory afferent inputs. Late SEPs are involved in higher-order sensorimotor and cognitive functions through insula, and in limbic function through amygdala and hippocampus. It is now generally accepted that cognitive impairment occurs in up to 50% of ALS patients,[1,3,4,15] thus S2 area involvement is expected and account for late SEPs abnormalities.

In addition to sensory cortex involvement, abnormal SEPs have been attributed to A-Beta or A-delta sensory fiber damage,[19] spinal cord involvement,[26,41] or reflect a nonspecific broad involvement of the sensory system.

In conclusion, SEPs are used relatively often in ALS, considering the fact that ALS is a motor neuron disease. Although results vary between studies, the vast majority show abnormalities. No finding can be considered pathognomonic in ALS nor can be used to distinguish it from other diseases on those grounds.

Sensory Conduction Studies (SCS)

SCSs, unlike SEPs, are routinely performed in all neurophysiological laboratories. Surprisingly, studies systematically reporting SCS in ALS patients are not as numerous as those using SEP and are presented in Table 2. The oldest one found, dates back to 1967 [12] and makes references to even older studies.[13,14] These pioneering studies failed to demonstrate any abnormality in the SCS, and concluded that sensory involvement in ALS, either clinical or neurophysiological, is extremely rare. Most of the following studies, with only rare exceptions[53–55] resulted in abnormal SCS. Most common finding was the low amplitude of SNAP and, less often, slow conduction velocity. When the distal nerves, dorsal and plantar, were examined, the pathological results were even more revealing. [56] In some cases a diagnosis of polyneuropathy was established [57,58] or entrapment neuropathy was suggested.[59]. In some studies, neurophysiological findings did not correlate with disease progression[22,59] while other reports correlation with disease stages.[60]

TABLE 2. Sensory Conduction Nerve Studies in ALS patients

STUDY	ALS/CNTR	SENSORY SYMPTOMS	NCS RESULTS	COMMENTS
Nolano et al, 2023[60]	149/41	32.2%	24% low AMPL reduction (ulnar)	NCV abnormalities increased across clinical stages significant loss of IENF
Sista et al, 2022[61]	99 C9ALS / 99 non-C9ALS		C9ALS higher AMPL (median)	NCV was not sufficient to discriminate between groups
Van Nguyen et al, 2022[53]	48/		SCV normal	
Imai et al, 2020[62]	190/		Low AMPL (median) has a relatively good prognosis	Decreased sensory input is likely protective for motor neurons in ALS
Sang et al, 2019[63]	4 FAS		Low AMPL (median) 2/4	
Liu et al, 2019[64]	150		22/150 14.7% abnormal (median, ulnar, sural)	
Pegat et al, 2019[58]	31 C9-ALS / 22 nonC9-ALS		C9-ALS 31% nonC9-ALS 21% sensory neuropathy	No significant difference between groups
Isak et al, 2016[56]	18/31		Conventional NCS 44.4% Distal sensory NCS 66.7%*****	Distal sensory NCS were more often abnormal than conventional sensory NCS
Ren et al, 2016[65]	154		Sural: 2.73% Median: 1.82% Ulnar: 1.22%	Abnormal sensory nerve conduction is only found in a few of ALS patients
Dalla Bella et al, 2016[66]	57		Sural normal 55/57 (96%)	IENF density reduced in 75.4% ALS, 50% of FOSMN
Truini et al, 2015[67]	24		SCV 23/24 (95%) normal	IENF density was reduced in spinal-onset ALS, not in bulbar-onset
Pugdahl et al, 2008[68]	35/35		Reduced AMPL-CV 6/35 (17%) Sural	Minor abnormalities are not uncommon
Hammad et al, 2007[10]	103	32%	Low AMPL 27% sural	Pathologic abnormalities 91% large fiber 73%, small fiber 23% Axonal degeneration and regeneration
Pugdahl et al, 2007[69]	88		20/88 (22.7%) abnormalities	Degeneration of motor neurons and dorsal root ganglion cells
Koszewicz et al, 2005[55]	19/20		ulnar, sural nerve did not differ	
de Carvalho et al, 2000[54]	70/35		SCV normal (ulnar)	Low SSR AMPL Longer SSR latencies
Theys et al, 1999[22]	50		Low AMPL (sural)	Subclinical abnormalities of the sensory system, but nonprogressive
Schulte-Mattler et al, 1999[59]	23/23		Low AMPL (median)	Sensory nerve conduction data did not correlate with clinical findings MCV data did not correlate with SCV data Nerve entrapment may contribute
Emeryk-Szajewska et al, 1998[70]	105		Slow CV, low AMPL Median 25%, Sural 11%	
Kothari et al, 1996[57]	126	7/54 clinical symptoms	54/126 Neuropathy Polyneuropathy 9/54 (7%)	

Matsumoto et al, 1995[71]	16		median CNAP by MNG Low AMPL, slow CV	
Gregory et al, 1993[49]	19/12	2/19 symptoms	Low AMPL (median, radial, sural)	
Mondelli et al, 1993[72]	64		Low AMPL (median 17%, ulnar 11%, sural 22%)	Progressive neuronopathy of peripheral sensory fibers
Shefner et al, 1991[73]	18		near nerve electrodes 9/18 slow CV 3/18 low AMPL	
Ertekin, 1967[12]	15		Normal	In agreement with the clinical experience that sensory involvement is rare

AMPL: Amplitude, CNAP: Compound Nerve Action Potentials, CV: Conduction Velocity, FAS: Flail Arm Syndrome, FOSMN: Facial Onset Sensory and Motor Neuronopathy, IENF: Intraepidermal Nerve Fibre Density, MCV: Motor Conduction Velocity, MNG: Intraneural Microneurography, NCV: Nerve Conduction Velocity, SCV: Sensory Conduction Velocity

*** Distal sensory NCS: antidromic dorsal sural and orthodromic medial plantar**
Conventional sensory NCS: unilateral median sensory and bilateral sural nerves

Clinical neurophysiologic techniques are able to study only the large myelinated fibers, A-alpha, A-Beta (diameter >7μm). Therefore, any neurophysiological abnormality observed, refers only to motor fibers and sensory fibers mediating touch, vibration, and position senses. Those that mediate cold temperature and pain sensations are small myelinated (A-delta), and those that mediate warm, itch, and pain sensations are unmyelinated C fibers, not detectable by common electrodiagnostic technics. Moreover, efferent postganglionic sympathetic autonomic fibers are also unmyelinated C fibers. For the SNAP, the peak-to-peak amplitude and the area under the waveform of the compound potential reflects the number of nerve fibers activated, whereas conduction velocity depends mainly on the diameter of the fiber and the thickness of the myelin sheath.

Bearing this in mind, the results of SCS in ALS point to a loss of cells in the dorsal root ganglion (DRG) and/or axons of large myelinated fibers. By means of NCV, sensory axonal neuropathy cannot be distinguished from ganglionopathy.[69] Kawamura et al[74] in 1981, provided autopsy evidence of a reduction of large L5 spinal ganglion neurons in ALS. This finding lead to the assumption that the primary pathology rests in DRG, which in turns leads to secondary axonal loss in peripheral nerves, followed by demyelination. New insights into sensory nerve pathology were provided by studies of sural nerve biopsies. In 1991, Heads et al,[75] reported early axonal atrophy, increased remyelination and a shift in the diameter distributions curve towards smaller fiber diameters. Furthermore, the severity of sensory nerve pathology correlated with disease duration. They hypothesized that DRG neuronopathy is the primary pathology, affecting preferentially large fibers and resulting in axonal degeneration with secondary demyelination. Later studies reported sural pathology in ALS. Hammad et al[10] reported that sural nerve biopsies were abnormal in 20 of 22 (91%) patients, large fibers were predominantly affected and the involvement was that of axonal degeneration and regeneration. Inflammatory infiltrates were not seen in any of the patients with ALS or controls. Luigetti et al, in 2012, [76] reviewed 17 sural nerve biopsies of ALS patients, and confirmed the involvement of sensory fibers in 70% of cases. All the above pathological studies, confirm the notion that ALS in not confined to motor neurons, but also affect sensory neurons in DRGs and their axonal projections.

Besides loss of cells in DRG, Rubio et al[77] offered another plausible interpretation. They performed immunohistochemical analysis of fibers in epidermis, as well as sympathetic sudomotor fibers in the footpads of $SOD1^{G93A}$ mice and wild type littermates. The number of DRG neurons from different sensory populations remained unchanged during all stages, while cutaneous sensory axons are affected in the $SOD1^{G93A}$ mouse. Thereby they concluded that loss or lack of growth of the distal portion of sensory axons with preservation of the corresponding neuronal bodies suggest a distal axonopathy rather that a dying forward pathology. This is in line with the general concept that besides the established hypothesis that ALS is restricted to corticofugal projecting neurons ("dying forward"), an alternative hypothesis might include the dying back independent degeneration for motor fibers, and respectively of sensory terminals.[78] This hypothesis is further supported by the finding that more abnormalities in distal NCS than conventional NCS could be a consequence of size dependent "under-nourishment" of the most distal

axonal region, that is, distal axonopathy due to dying back.[56]

Sympathetic Skin Response (SSR)

As expected, SSR has been used in ALS cohort studies even less frequently than the previously described methods. The SSR is a somato-sympathetic reflex with a spinal, a bulbar, and a suprabulbar component, the precise pathways in humans being not yet precisely defined. SSR is easy to apply, non-invasive and readily obtainable on most electrophysiological equipment. The efferent arc of the reflex is subserved by unmyelinated postganglionic sympathetic class C fibers that arise from the sympathetic ganglia and join the major peripheral nerves to reach the sweat glands, providing them with cholinergic innervation.[79] SSR is commonly used to assess sympathetic nervous system function, but equally is useful to asses C fibers, that are inaccessible by standard NCS. As such, SSR has been a tool in assessing small fiber neuropathy in cases where small fibers are predominantly or concomitantly affected, as in cases of Diabetes Mellitus[80,81] and Amyloidosis.[82,83] Because of the long path of the reflex, an abnormal SSR result alone cannot distinguish between different sites of lesions, even more so since its exact path remains unclear.

We have identified 11 studies of SSR in ALS patients and the results are presented in Table 3. All studies yielded abnormal results, ranging from prolonged latencies and low amplitudes to complete absence of the response. Most commonly, abnormal results were found in lower limbs. When it was described, SSR results, did not correlate with disease duration, with one exception,[84] and thus the process of degeneration is supposed to be rather slow, compared with that of motor neurons.

Table 3. Sympathetic Skin Response results in ALS patients

STUDY	ALS/CNTR	RESULT	COMMENT
Chen et al, 2024[85]	1 (FUS)	Prolonged LAT LL	
Pazian Martins et al., 2023[86]	11 sALS,14 fALS/26	Absence LL	
Ozturk et al, 2022[87]	29/29	Low AMPL UL-LL	Remained stable after1 year Slow degeneration process
Papadopoulou et al., 2022[88]	21/28	Low AMPL Prolonged LAT 3/21 Absent	No correlation to disease duration
Hu et al., 2016[89]	120/130	Low AMPL Prolonged LAT	No correlation to disease duration Damage to the unmyelinated postganglionic fibers
Koszewicz et al., 2005[55]	19/20	Low AMPL Prolonged LAT	Sudomotor fibers lesion
Oey et al., 2002[90]	16/12	Prolonged LAT UL, LL 3/16 Absent	
Miscio and Pisano, 1998[84]	31/48	UL Normal LL 7/31 Absent	Correlation to functional disability and duration of the disease.
Masur et al., 1995[91]	15/20	Low AMPL Prolonged LAT	No correlation to the stage or the duration of disease
Dettmers et al., 1993[92]	25/22	Prolonged LAT LL 10/25 Absent	
Barron et al., 1987[93]	1	Abnormal	

ALS: Amyotrophic Lateral Sclerosis, S: Sporadic, F: Familial, AMPL: Amplitude, CNTR: Controls, FUS: fused in sarcoma gene mutation, LAT: Latency, LL: Lower Limb, UL: Upper Limb

In the majority of cases, SSR was performed to evaluate autonomic dysfunction in ALS. Dysautonomia has been widely investigated in ALS patients, primarily through the measurement of heart rate variability (HRV). All studies reported similar findings, that is, decreased HRV, indicative of sympathovagal imbalance, that could explain cases of circulatory collapse or sudden death among ALS patients.[94–98] As described, due to the long path of the reflex arc, including CNS parts, it is difficult to localize the origin of degeneration. There has been a lot of speculation. SSR abnormalities have been attributed to loss of neurons in the intermediolateral nucleus between the dorsal and ventral horns of the spinal cord, and this notion is further supported by histological findings.[88,90] Other researches have proposed that abnormal

results are caused by damage to the unmyelinated postganglionic fibers.[55,89] In the second case, this damage to unmyelinated small fibers, could account for impairment in pain and thermal sensation in ALS patients.

ALS patients experience pain in a significant proportion. In several studies, the prevalence of pain ranges from 46% to 85%.[99–103] Pain in most studies is characterized as non-neuropathic, not involving the pain pathways, and is attributed mainly to musculoskeletal problems. Prolonged immobility and postural changes are the main causes of pain in ALS. However, pain may be reported by ALS patients early in the course of the disease, even before severe immobility is noted. Inflammatory injury may cause sensitization not only to nociceptive pathways but to neuropathic ones as well, through damage to peripheral nerves or to the central nervous system. As mentioned in the previous section, histopathological evidence from sural biopsies, shows a predominant involvement of large myelinated fibers, which do not conduct pain. Thus, if neuropathic pain is to be considered, the pathogenesis should be sought in small unmyelinated fibers.

Besides SSR, other methods have also confirmed small fiber involvement in ALS. A significant loss of Intraepidermal Nerve Fibre Density (IENF) has been constantly reported,[60,66,67] but also, other studies report normal IENF.[104] Corneal confocal microscopy (CCM) is a non-invasively method to quantify the corneal small fiber neuropathy. In several studies CCM quantified significant corneal neuropathy in ALS[104–106] while other failed to do so, since no significant differences were found between ALS and control groups for all corneal parameters.[107] Thus, based on the above, the involvement of small fibers in ALS is still debatable and needs further evidence to support it.

Conclusions

It is widely accepted that ALS is not a pure motor neuron disorder, but also affects non-motor areas, causing a variety of non-motor symptoms. Sensory impairments are recorded when sought after. They are often mild and there is no significant progression nor correlation with disease stage. Neurophysiology has contributed substantially to the thorough investigation of the presence of sensory involvement and its pathogenic mechanisms. Although the results can be confusing and sometimes contradictory, they shed light in our understanding of this polymorphous disease, whose nature is still enigmatic.

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