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RESEARCH ARTICLE

Autonomic impairment in primary lateral sclerosis

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Abstract

Purpose Prior studies reported evidence of autonomic involvement in motor neuron disease and suggested more severe dysfunction in upper motor neuron predominant syndromes. Hence, we sought to characterize autonomic impairment in primary lateral sclerosis.

Methods Neurological evaluations, thermoregulatory sweat tests, and autonomic reflex screens were analyzed retrospectively in 34 primary lateral sclerosis patients (28 definite and 6 probable). Patients with other potential causes of autonomic failure and patients with autonomic testing results compromised by artifact were excluded.

Results A total of 17 patients reported autonomic symptoms. Orthostatic lightheadedness was most frequent (8 patients), followed by bladder (7), bowel (5), and erectile dysfunction (3). The autonomic reflex screens of 33 patients were reviewed; 20 patients had abnormal studies. The thermoregulatory sweat tests of 19 patients were reviewed; 11 patients had abnormal studies. Composite Autonomic Severity Score was calculated for 33 patients and found abnormal in 20/33 patients (60.6%): 15/20 patients (75%) had mild impairment, and 5/20 patients (25%) had moderate impairment. The frequencies of testing abnormalities were: sudomotor 18/20 (90%), cardiovagal 9/20 (45%), and adrenergic 6/20 (30%). Sweat loss pattern analysis showed global, regional, and mixed patterns to be more common than length-dependent and distal patterns.

Conclusion We found evidence of frequent autonomic dysfunction in primary lateral sclerosis, which is generally of modest severity akin to prior reports for amyotrophic lateral sclerosis, but more commonly in a pattern consistent with preganglionic/ganglionic localization. This suggests that primary lateral sclerosis, as with amyotrophic lateral sclerosis, is a multisystem disease that affects the autonomic nervous system.

Keywords PLS · Autonomic · TST · ARS · Anhidrosis

Introduction

There is growing evidence that motor neuron disease (MND) is a multisystem disease with a wide range of involvement beyond the anterior horn cells and corticospinal tracts. Evidence for involvement of the autonomic nervous system (ANS) in MND, such as amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA), has accumulated. [1, 6] Previous studies have shown that in MND there is neuronal loss in the thoracic intermediolateral (IML) nucleus of the spinal cord containing sympathetic preganglionic neurons, [9, 21] and sacral IML nucleus of the spinal cord containing parasympathetic preganglionic neurons. [11] Itoh and colleagues reported increased perikaryal Ta-51 [monoclonal antibody that specifically binds phosphorylated high molecular weight neurofilament proteins (pNFH)] immunoreactivity in ventral horn cells as well as IML column neurons in ALS patients compared with controls. [8] Prior clinical studies suggested more significant autonomic impairment in upper motor neuron syndromes compared with classic ALS and lower motor neuron predominant disease, but small numbers of patients were included. [19] The degree and pattern of autonomic impairment in those patients remains unclear. Hence, we sought to characterize autonomic impairment in primary lateral sclerosis (PLS).

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Methods

Study design

After institutional review board (IRB) approval, we conducted a search in the autonomic database of Mayo Clinic-Rochester for the diagnosis of primary lateral sclerosis (PLS) and upper motor neuron disease. Medical records of patients seen between 1990 and 2022 were retrieved. Only patients with final diagnosis of definite or probable PLS, according to the PLS consensus diagnostic criteria, who had undergone autonomic testing were included. [23] Disease severity was assessed by the PLS Functional Rating Scale, which consists of 12 subscales evaluating bulbar, motor, and respiratory functions; it has a total score of 68, and the higher the score, the better the function. [16] Autonomic tests were performed to patients who complained of autonomic symptoms or patients with initial suspicion of other neurodegenerative disease (e.g., an alpha synucleinopathy). We excluded patients with other causes of autonomic failure (e.g., diabetes) and those with autonomic test results compromised by artifact, including cardiac arrythmia and medications effects. On the basis of these criteria, 34 PLS patients were included: 28 with definite PLS and 6 with probable PLS. Neurological and autonomic evaluations (performed at Mayo Clinic by neuromuscular and autonomic specialists), thermoregulatory sweat tests (TST), and autonomic reflex screens (ARS) were analyzed retrospectively in all patients. ARS and TST were done in standardized fashion using normative data for age and gender. The results of TST and ARS were reviewed by autonomic specialists.

Autonomic reflex screening (ARS)

ARS testing consisted of sympathetic sudomotor [quantitative sudomotor axon reflex test (QSART) or QSWEAT at forearm, proximal leg, distal leg, and foot] [14], cardiovagal (heart rate variability in response to deep breathing and Valsalva maneuver), and cardiovascular adrenergic testing (blood pressure profile during Valsalva maneuver and tilt table test). [12] QSART at proximal and distal standard sites was used to assess the integrity of the sympathetic postganglionic sudomotor axon and the pattern of involvement using iontophoresis of acetylcholine [15]. Sweat volume was considered abnormal if it was less than 5% of controls or if there was a relative decrease at the foot site less than one-third of the adjacent proximal values [2]. Patterns of abnormal sweating on QSART were (1) length-dependent, isolated to foot site, or a gradient involving foot and leg sites; (2) non-length-dependent; (3) focal, isolated to a single site; and (4) global, with all sites affected.

Thermoregulatory sweat test (TST)

TST was performed as a modification of Guttmann's quinizarin sweat test [5]. It assesses the integrity of central and peripheral sudomotor pathways [3]. Sweating is demonstrated by a change in color of the indicator powder applied on the anterior body surface of a patient lying supine inside a sweat cabinet. Results were expressed as percent of anterior body surface anhidrosis, calculated from digital photographs [3]. Patterns of anhidrosis were (1) length-dependent, affecting fingers, legs below the knees, and/or lower abdomen (anhidrosis < 25%); (2) focal, isolated to a dermatome or peripheral nerve territory; (3) segmental, involvement of a few adjacent roots or plexus; (4) regional: large areas but < 80% (may or may not be contiguous); (5) global, ≥ 80% of body surface affected; and (6) mixed.

Localization of sweat abnormality

Lesions sites were classified as preganglionic (central), post-ganglionic (peripheral), or mixed based on TST and QSART. QSART evaluates only the postganglionic sympathetic sudomotor, and a reduced or absent sweating on QSART indicates a postganglionic (peripheral) lesion, while TST evaluates the pattern of abnormality and quantify sweat response (the percentage of the anhidrosis) of the whole body; therefore, absent sweating in an area on TST with normal QSART indicates a preganglionic (central) lesion [2, 14]. Hence, combining TST and QSART is useful for localizing the lesion in the autonomic nervous system [14]. Moreover, certain patterns of anhidrosis on TST are more compatible with peripheral (e.g., distal) or mixed/central (e.g., global) localization.

Severity

The composite autonomic severity score (CASS) was calculated. The CASS was subdivided into three subscores: CASS sudomotor (range 0–3), CASS cardiovagal (range 0–3), and CASS adrenergic (range 0–4). The total CASS score ranged from 0 to 10 points. Based on CASS score, autonomic failure was graded as absent (0), mild (1–3), moderate (4–6), and severe (7–10) failure [4, 13].

Statistical analysis

The IBM statistical package for the social science (SPSS) statistics was used for statistical analysis. Descriptive statistics were used to express continuous results. Continuous variables were presented as mean or median ± standard deviation. The Spearman rho tested correlations among

Table 1 Demographic and clinical features

Category	PLS ($n=35$)
Males	15 (42.9%)
Age of onset (years)	62.7 ± 10.6 (33–84)
Definite PLS	29 (82.9%)
Probable PLS	6 (17.1%)
Autonomic symptoms	18 (51.4%)
Orthostatic lightheadedness	9 (50%)
Bladder symptoms	7 (38.8%)
Bowel symptoms	5 (27.8%)
Erectile dysfunction	4 (22%)
Decreased sweating	1 (5.6%)

Values are *n* (%) or mean ± SD (range)

continuous variables. Statistical significance was defined as $p \leq 0.05$.

Results

Demographic and clinical features are summarized in Table 1. A total of 18 patients (51.4%), 7 males and 11 females, had documented symptoms suggestive of autonomic dysfunction; among those, orthostatic lightheadedness was the most frequent symptom, and decreased sweating was the least reported symptom. Bowel and bladder symptoms were more common among females, and they included urgency, incontinence, constipation, and diarrhea.

ARS studies of 33 patients were reviewed (1 patient had a TST but not an ARS); 18/33 (54.5%) had abnormal ARS. TST studies of 19 patients were reviewed; 11/19 (57.9%) had abnormal TST. The mean percentage of anhidrosis was 15.9% ± 27.4 (range 0–92%). Six patients had normal QSART with abnormal TST, while four patients had normal ARS and normal TST.

CASS score was calculated for 33 patients, with a mean score of 1.6 ± 1.7. The score was abnormal in 20/33 (60.6%). Autonomic impairment was mild (CASS 1–3) in 15/20 patients (75%) and moderate (CASS 4–7) in 5/20 patients (25%). In the studied PLS group of patients, no one had severe autonomic impairment. Among those with abnormal testing, the frequencies of abnormalities were: sudomotor 18/20 (90%), cardiovagal 9/20 (45%), and adrenergic 6/20 (30%). Six patients were found to have adrenergic impairment on autonomic reflex screen with median cardiovascular adrenergic CASS subscore of 2 (range 2–3) and median blood pressure recovery time (PRT) of 5.4 s (range 2.7–9.1 s; mild prolongation); PRT was calculable for five patients and incalculable in one due to partial blood pressure flat top response to Valsalva maneuver. Four of the six patients with adrenergic impairment developed orthostatic hypotension on tilt-table study, three of whom were symptomatic with lightheadedness. One of the patients without adrenergic impairment on Valsalva maneuver reported subjective lightheadedness not associated with hemodynamic change on tilt. No other patients reported symptoms on tilt-table. Interestingly, all of the four patients with adrenergic impairment and orthostatic hypotension on tilt had additional non-neurogenic components to the orthostatic hypotension [including orthostatic hypotension (OH) beyond what is expected for the degree of adrenergic impairment, delayed OH, and early and recovered OH], which may indicate a degree of deconditioning and/or hypovolemia in some of these the patients. There was a negative correlation between CASS score and the duration of symptoms ($r=-0.13$), but that was not statistically significant, ($p=0.5$). However, there was a weak negative correlation between CASS score and the PLS functional severity scale score ($r=-0.4$) that was statistically significant ($p=0.01$).

Based on ARS and TST findings, sweat loss pattern analysis showed length-dependent and distal distribution in 8 patients and regional, mixed, and global distribution in 10 patients. The latter was more consistent with preganglionic/ganglionic autonomic lesion (Fig. 1).

Discussion

MND are neurodegenerative disorders that were thought to be limited to motor neurons. Recently, this concept has been revisited, and growing evidence has shown that these

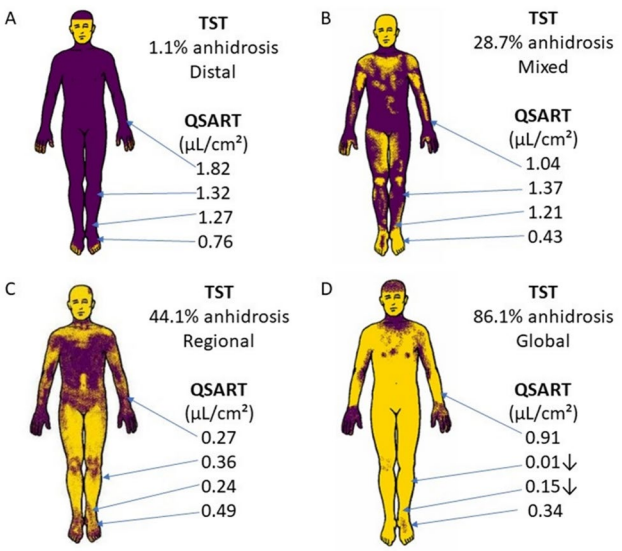

Fig. 1 Anhidrosis patterns with the TST. (**A**) Distal TST anhidrosis and normal QSART. (**B**) Mixed TST anhidrosis and normal QSART. (**C**) Regional TST anhidrosis and normal QSART. (**D**) Global TST anhidrosis and abnormal QSART (non-length-dependent pattern)

disorders may involve the autonomic nervous system as well. [1, 6, 20] Previous clinical, neurophysiological, and histopathological studies have suggested possible involvement of autonomic nervous system in MND. This might be attributed to degeneration of the IML nucleus or central pathways, as shown in previous studies [9, 21]. However, the degree and pattern of autonomic impairment in PLS remains poorly understood.

In the current study, we performed a retrospective comprehensive analysis of autonomic symptoms and standardized autonomic tests in a cohort of PLS patients evaluated at Mayo Clinic. The main finding of this study is that autonomic impairment is frequent in PLS, albeit generally mild. Autonomic symptoms are common in our cohort, being reported by more than 50% of the patients; orthostatic intolerance was the most frequent symptom, followed by bowel, bladder, and erectile dysfunction. There was no report of sexual dysfunction among females. Bladder and bowel symptoms have been reported by ALS patients in previous studies [17, 22]. Bladder symptoms were reported frequently by 60% of PLS patients in a previous study conducted by a Mayo Clinic team [7], and urinary urgency was reported by 25% of PLS patients included in the NEALS primary lateral sclerosis registry [18]. Bladder symptoms may be explained not solely by autonomic involvement but also as a result of Onuf nucleus involvement, as was previously reported in ALS [10]. Autonomic function testing was abnormal in more than 50% of the patients; autonomic impairment was mild in most patients (75%) and moderate in 25%. None of our patients had severe autonomic impairment. The study also showed that there was a statistically significant negative correlation between the disease severity and autonomic impairment, but this finding should be interpreted with caution. The negative correlation between the duration of symptoms and autonomic impairment was not significant.

The most frequent abnormality was in the sudomotor domain (90%), although sweat abnormality was not a frequent symptom, followed by cardiovagal (45%) and adrenergic impairment (30%). Previous studies in ALS showed less common sudomotor and adrenergic abnormalities, but the overall degree of autonomic dysfunction found was similarly modest [19]. Further detailed analysis of the sweat loss pattern based on QSART and TST showed that central or mixed patterns were more common than length-dependent or distal distribution. Such findings differ from the sweat patterns in ALS and may suggest central autonomic involvement [19]. Anhidrosis is usually underreported unless severe. When severe, it is usually reported as heat intolerance with activity and increased ambient heat. We postulate that symptoms of anhidrosis may have been underreported due to several factors, including mild sweat impairment, incomplete autonomic review of systems, and motor impairment limiting the patient's ability to exercise to their potential and appreciate inability to sweat.

Our findings suggest that PLS is associated with a generally modest degree of autonomic dysfunction in addition to upper motor neuron involvement, which contributes to the overall phenotype of this MND. Orthostatic lightheadedness, which was the most frequent autonomic symptom in this study, cannot be readily explained on the baasis of the generally modest autonomic (including adrenergic) impairment. The severity of autonomic dysfunction is similar to what has been reported in ALS, and it correlates with the disease severity. The main limitation of our study is the selection bias since we only selected patients who had autonomic tests, the retrospective design of the study, and the lack of pathologic correlation.

Conclusion

In the current study, we found evidence of frequent autonomic dysfunction in PLS, which is generally of modest severity akin to prior reports in ALS, but more commonly in a pattern consistent with central localization. As with ALS, this suggests that PLS is a multisystem disease that affects the autonomic nervous system. Larger, prospective studies may be useful to confirm and expand on our findings.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the IRB of Mayo Clinic, which determined that our study did not need ethical approval. An IRB official waiver of ethical approval was granted from the IRB of Mayo Clinic.

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