Original Scientific Article
Acta Medica Academica 2024;53(1):24-34
DOI: 10.5644/ama2006-124.440

Autonomic Dysfunction in Amyotrophic Lateral Sclerosis – A Case-Control Study

Mehedi Hasan[1], SK Mahbub Alam[1], Hasan Zahidur Rahman[1], Md. Abdullah Saeed Khan[2], Muhammad Rezeul Huq[3, a]

[1]Department of Neurology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, [2]National Institute of Preventive and Social Medicine, Dhaka, Bangladesh, [3]Department of Neurology, Combined Military Hospital, Dhaka, Bangladesh.

Correspondence: *rhriaz29@gmail.com;* Tel.: + 880 17 12802497

Received: 1 December 2023; **Accepted:** 26 April 2024

Funding: This work was supported by the Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Abstract

Introduction. This study aimed to explore autonomic nervous system involvement in amyotrophic lateral sclerosis (ALS) patients by evaluating sympathetic skin response (SSR). **Materials and Methods.** The study included 35 sporadic (ALS) patients (cases), and 35 healthy age and sex-matched participants (controls) aged <60 years. SSR was recorded in the electrophysiology lab of the Neurology Department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Patients with diseases associated with peripheral or autonomic neuropathy were excluded. Prolonged latency (delayed SSR) or an absent response was considered abnormal SSR. **Results.** SSR was found to be abnormal in 17 (48.6 %) ALS cases, with an absent response in the upper limbs of six cases (17.1%). Abnormal SSR was more prevalent in the lower limbs, with 33 (94.3%) and 20 (57.1%) cases having a delayed or absent response, respectively. In comparison, SSR was normal in all control participants (P-value <0.05). Abnormal SSR was significantly more common in the lower limbs of ALS cases with bulbar palsy than those without bulbar palsy (P-value=0.04). There was no association of SSR with disease severity and duration. **Conclusion.** ALS is significantly associated with abnormal SSR, indicating autonomic nervous system involvement. There could also be an association between bulbar palsy and abnormal SSR among ALS patients. Further studies should be carried out to determine the association of abnormal SSR with disease severity, duration, and type.

Key Words: Amyotrophic Lateral Sclerosis ▪ Sympathetic Skin Response ▪ Autonomic Nervous System ▪ Motor Neuron Disease.

Introduction

Motor neuron disease (MND) is a group of neurodegenerative diseases primarily affecting the motor nervous system (1). Amyotrophic lateral sclerosis (ALS) is the most common form of MNDs, which involves both upper and lower motor neurons (2). The incidence and prevalence of ALS differ from country to country. The incidence may range from as low as 0.26 per 100,000 person-years in Ecuador, to as high as 23.46 per 100,000 person-years in Japan. The point prevalence may vary from 1.57 per 100,000 in Iran to 11.80 per 100,000 in the United States (3). The mean and median age of ALS onset is between 51 and 66 years (4). However, 5-10 % of ALS could be inherited, and genetic mutation is responsible for nearly 60% of inherited cases (5). The putative mechanisms are the death of motor neurons owing to protein aggregation, glutamate excitotoxicity, mitochondrial dysfunction, impaired axonal transport, growth factor deficiency, inflammation, and apoptosis (6).

Once considered a pure motor disease, non-motor manifestations, including autonomic dysfunction, may also occur in ALS. Recent studies have suggested that subclinical impairment of

[a]https://orcid.org/0000-0003-4162-9545

cardiovascular, sudomotor, gastrointestinal, salivary, and lacrimal regulation may occur in ALS even in the early stages (7–9). Besides, ALS patients may die suddenly due to circulatory collapse (7). Among the numerous autonomic manifestations, sudomotor impairments can be assessed simply by clinical and investigation methods. Sympathetic skin response (SSR) is a test of sympathetic autonomic function that records the transient change of the electrical potential of the skin generated by activated sweat glands. The reflex arc of SSR is formed by the somatic sensory afferent limb, the central pathway, and the autonomic sympathetic efferent limb. This response is activated with different internal or externally applied arousal stimuli (10). SSR can be quickly recorded in an electrophysiology lab by most electromyography (EMG) equipment using the surface electrodes. The latency and amplitude of the SSR are recorded in both upper and lower limbs. SSR is a nonspecific test, and abnormalities can be found in autonomic or somatic neuropathy (10). However, this test can be helpful in ALS, which was previously mainly considered to be a disease involving only the motor nervous system, but some recent studies have reported cutaneous vasomotor and sudomotor dysfunction of varying severity in ALS patients (11, 12). In these studies, ALS patients were found to have abnormal latency, amplitude, or absent SSR. Others found an association between disease severity and SSR (13). Autonomic failure might lead respirator dependent patients to circulatory collapse or sudden death. Hence, assessment of autonomic failure is important from a management perspective. Moreover, very few studies have explored the association between autonomic dysfunction and ALS in low resource settings such as Bangladesh. Bangladesh is a densely populated South Asian country that harbors an ethnically diverse group of mostly brown people. Studies have shown that there are racial differences in sympathetic nervous system indicators (14).

Hence, exploring autonomic dysfunction in ALS patients in Bangladesh could also generate information from the perspective of South Asian ethnicity. Therefore, we aimed to study the association between autonomic dysfunction measured by SSR, and ALS, in a tertiary care hospital in Bangladesh.

Methods

Study Participants and Settings

This case-control study was carried out between 2018 to 2019 in the Department of Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Thirty-five ALS patients with no family history of ALS were enrolled as cases according to the revised El Escorial diagnostic criteria (15). The sample size was determined using the following formula:

$$N = \left[\frac{Z\alpha\sqrt{2p(100-p2)} + Z\beta\sqrt{p1(100-p1)+p2(100-p2)}}{(p1-p2)}\right]^2$$

Here: N=Sample size of each group; Zα=1.96 (Z value of standard normal distribution at 95% confidence level); Zβ=1.28 (Z value of standard normal distribution at 90% power); p1= Anticipated probability of exposer among case = 40% (13); p2= Anticipated probability of exposer among control = 0% (13); P=(p1- p2)/2. With this formula, sample size, N=22.

A total of 35 patients with ALS fulfilled the inclusion criteria during our study period and were included as cases. Among these cases, 11 were definite ALS, 10 clinically probable and 14 laboratory supported ALS cases. Patients with ALS who had any of the following characteristics or comorbidities were excluded: age >60 years, multiple system atrophy, Parkinson's disease or other neurodegenerative disorders, pure autonomic failure, multiple sclerosis, history of neck or spinal trauma, critical illness (acute MI, stroke, respiratory failure & heart failure), systemic conditions causing autonomic disturbance (DM, CKD), scleroderma, Sjógren disease, any form of neuropathy (diabetic neuropathy, Guillain-Barré Syndrome, hereditary motor and sensory neuropathy, chronic inflammatory demyelinating polyneuropathy), those taking medications causing autonomic disturbances or that could influence the SSR, patients with an

abnormal sensory response in a nerve conduction study, and patients unwilling to participate in the study. SSR is ordinarily present in both hands and feet under the age of 60 years, but it usually decreases in subjects older than 60 years (16). A detailed clinical history was taken, and relevant bedside examinations were performed to exclude autonomic involvement. None of the patients had complaints suggesting autonomic disturbances such as palpitation, postural dizziness, bowel or bladder disturbances, sexual dysfunction, dryness of mouth or skin, and hyperhidrosis. However, patients with bulbar palsy had hypersalivation. On clinical examinations, none of our cases had tachycardia, postural hypotension, or pupillary abnormalities. An equal number of age- and sex-matched (via frequency-matching) healthy volunteers were registered as the control. All participants underwent an assessment of SSR in the electrophysiology lab of the Department of Neurology, BSMMU.

Study Procedure

Data Collection Instrument

Data were collected using a preformed structured questionnaire through face-to-face interviews with the patient and/or their attendant, and through careful physical examination. The questionnaire included demographic variables, including age and sex, the presenting complaints of the patient and details of neurological examination findings, relevant data to exclude other differentials, types of ALS according to El Escorial diagnostic criteria, duration of ALS, severity of the disease, findings of the nerve conduction study, and SSR. All patients who met the inclusion criteria were enrolled, regardless of the duration of their disease. Patients with ALS were divided into different groups on the basis of the duration of their disease, ranging from 1 to 6 months, 7 to 12 months, 13 to 18 months, and over 18 months. Some newly diagnosed patients with a disease duration of less than 6 months underwent diagnostic EMG and SSR in the same settings. Other diagnosed patients with a disease duration of several months or years who came for follow-up underwent SSR for the study purpose.

Functional Assessment of Patients

The involved anatomical sites and clinical manifestations of autonomic dysfunction were identified by interviewing the cases and the ALS Functional Rating Scale-Revised (ALSFRS-R) was used to assess the patients' functional status (17). On the basis of this scale, the functional severity of the disease was categorized as follows: mild (>40), moderate (39–30), severe (<30), and advanced (<20). We utilized King's ALS clinical staging system to determine the clinical severity of the disease: Stage 1 indicates the involvement of a single region, Stage 2 when two regions are involved, Stage 3 when three regions are involved, and Stage 4 when the patients have bulbar or respiratory involvement (18).

Assessment of Sympathetic Skin Response

SSR assessment was done using the NIHON KOHDEN Neuropack MEB-9400 S1 Series EMG/NCV/EP Measuring System. A conventional nerve conduction study of the median, ulnar, common peroneal, tibial, and sural nerves was done initially. The ambient room temperature was maintained between 22–24°C. We measured SSR in the supine position. Before recording SSR, the limbs were warmed to prevent hypothermia. The electrical stimulus was applied as a single square pulse, 0.1–0.2 MSec in duration, delivered randomly and with a minimal interstimulus interval >30 seconds. The stimulus intensity was between 10 and 30 mA. We measured the latency and amplitude of SSR in all four limbs by placing surface electrodes on the palm and sole, and administering electrical stimuli along the median nerve in the upper limbs and the tibial nerve in the lower limbs (10). The SSR was recorded from both sides if both sides were equally affected, and the best response was considered for analysis. If only one side was affected, the response was recorded from that side. In the case

of asymmetrical involvement, the SSR was recorded from the more affected limb. We measured the latency from the onset of the stimulus artifact to the first deflection from baseline. The height of the wave from baseline to the peak of the first positive or negative deflection was recorded as the amplitude (Figure 1, 2, 3). The normal mean onset latency and amplitude of SSR are 1480±80 millisecond (MSec) and 444±167 microvolt (μV) for the hands; 2060±93 MSec and 203±87.4 μV for the feet (19). An absent response was recorded if no reproducible deflection was found after at least three stimulations. Prolonged latency (delayed SSR) or an absent response was considered abnormal SSR.

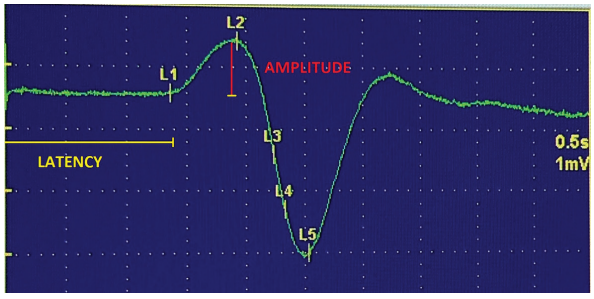

Figure 1. Normal SSR in the upper limb (Sensitivity 1 mV on the vertical axis and 0.5 seconds on the horizontal axis). The horizontal yellow line indicates the latency and the red vertical line indicates the amplitude.

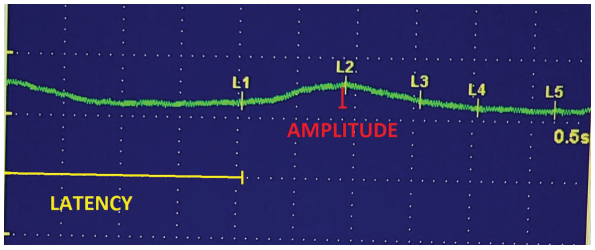

Figure 2. Normal SSR in the lower limb (Sensitivity 1 mV on the vertical axis and 0.5 seconds on the horizontal axis). The horizontal yellow line indicates the latency and the red vertical line indicates the amplitude.

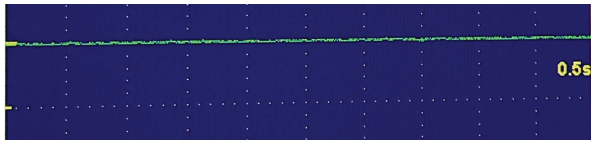

Figure 3. Absent SSR in the lower limb of an ALS patient (Sensitivity 1 mV on the vertical axis and 0.5 seconds on the horizontal axis).

Ethical Considerations

Ethical clearance for the study was given by the Institutional Review Board (IRB), Bangabandhu Sheikh Mujib Medical University (BSMMU) (IRB Number: BSMMU/2018/6176). All the procedures were conducted according to the Declaration of Helsinki. Informed written consent was taken from each patient or their attendant before inclusion.

Statistical Analysis

Both descriptive and analytic statistics were carried out. Data were presented as frequency (percentage) and mean ± standard deviation (SD) for categorical and continuous variables, respectively. Distribution of the quantitative variables were checked using a histogram and the Shapiro-Wilk test. For analytic statistics, the Chi-square test, Fisher's exact test, the independent samples t-test, and the Mann-Whitney U test were used where appropriate. SSR latency and amplitude were compared between ALS patients and control subjects using the Mann-Whitney U test as the data were not normally distributed. Among the ALS patients, the relationship between SSR and the predominantly involved site (limb or bulbar), disease severity, and disease duration were analyzed using the Chi-square test or Fisher's exact test. The Statistical Package for the Social Sciences (SPSS) version 24 (IBM Corp., Armonk, NY, USA) was used for data analysis. A P-value of ≤ 0.05 was considered significant.

Results

Thirty-five patients with ALS aged 16–60 years, and thirty-five age- and sex-matched healthy controls were included. The mean age of the cases and controls was 37.71±15.02 and 38.43±11.22 years, respectively. The majority of cases were aged below 30 years (37.1%), and the majority of controls belonged to the 31–50 year age group (51.4%), however, the difference was not statistically significant (P=0.341). Out of thirty-five cases, 28 (80%) were

male, and seven (20%) were female, whereas in the control group, 30 (85.7%) were male, and five (14.3%) were female (P=0.526) (Figure 4). The male-female ratios of the cases and the control group were 4:1 and 6:1, respectively.

Table 1 describes the clinical characteristics of ALS patients included in the study. The majority of the patients had developed ALS over a period of 1-6 months (42.9%). All four limbs were affected by wasting and weakness in 60% of patients. None of the patients had any features of autonomic nervous system involvement except hypersalivation (31.4%). The majority of the patients had a mild disease (57.1%), followed by 37.1% and 5.8% having a moderate and severe disease, respectively. None of the patients had the advanced stage of the disease.

Out of 35 cases, SSR was abnormal in the upper limbs of 17 (48.6 %) persons. Among them SSR was absent in six (17.1%) cases, and latency was prolonged or SSR was delayed in 11 (31.4%) cases. Eighteen (51.4%) cases had normal SSR. Among the control population, all had a normal SSR. The difference between cases and controls was statistically significant (P-value <0.001). In the lower limbs, SSR was abnormal in 33 (94.3%) persons. It was absent in 20 (57.1%) and delayed in 13 (37.1%) cases. A normal response was found in only two (5.7%) cases. All of the control samples (N=35; 100%) had normal SSR. The difference between cases and controls was statistically significant (P-value <0.001). The median latency (IQR) was statistically significantly higher and the median amplitude (IQR) was statistically significantly lower in both limbs of the cases compared to the controls (P<0.001 for all). See Table 2 for details.

The SSR was delayed or absent in the upper limbs of 27.3% of cases (each) with bulbar palsy and 33.3% and 12.5% of cases without bulbar palsy, respectively. However, the difference was not statistically significant (P=0.625). On the other hand, a significantly higher proportion of cases

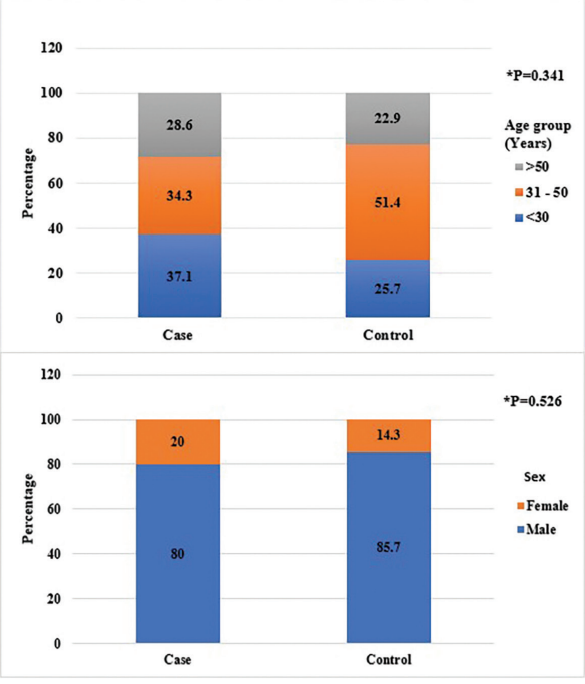

Figure 4. Distribution of case and control by age and sex; *P-value was determined by Chi-square test.

Table 1. Clinical Characteristics of the ALS Patients (N=35)

Clinical characteristics	N (%)
Disease Duration (Months)	
1-6	15 (42.9)
7-12	12 (34.3)
13-18	2 (5.7)
>18	6 (17.1)
Limb wasting and weakness	
All four limbs	21 (60.0)
Both upper limbs	8 (22.8)
Both lower limbs	3 (8.6)
Single upper limb (right)	3 (8.6)
Bulbar palsy (present)	11 (31.4)
Features of ANS involvement	
Hypersalivation	11 (31.4)
Others*	0 (0)
Functional Severity of ALS†	
Mild (>40)	20 (57.1)
Moderate (30-39)	13 (37.1)
Severe (<30)	2 (5.7)
Clinical Severity of ALS‡	
Stage 2	19 (54.3)
Stage 3	4 (11.4)
Stage 4	12 (34.3)

ALS=Amyotrophic Lateral Sclerosis; ANS=Autonomic Nervous System; *Other features of ANS involvement including dry mouth, postural hypotension, and sweating abnormality; †As determined by ALS Functional Rating Scale-Revised (ALFRS-R) (17); ‡As determined by KING's ALS clinical staging (18).

with bulbar palsy had abnormal SSR (9.1% absent, and 81.8% delayed) in the lower limbs compared to cases without bulbar palsy (50% delayed and 45.8% absent, P=0.042) (Table 3).

The distribution of SSR responses was statistically similar across the severity categories of ALS and disease duration for both limbs (P>0.05) (Table 4, 5, 6).

Table 2. Comparison of Sympathetic Skin Response, Its Latency, and Amplitude between Cases and Controls

Sympathetic skin response	Categories	Case (N=35)	Control (N=35)	P-value
Upper limbs; N (%)	Normal	18 (51.4)	35 (100.0)	<0.001*
	Delayed	11 (31.4)	0 (0.0)	
	Absent	6 (17.1)	0 (0.0)	
Lower limbs; N (%)	Normal	2 (5.7)	35 (100.0)	<0.001*
	Delayed	13 (37.1)	0 (0.0)	
	Absent	20 (57.1)	0 (0.0)	
Latency (MSec); Median (IQR)	Upper limbs	1490 (1345–1692)	1175 (1060 –1330)	<0.001†
	Lower limbs	2330 (2195–2880)	1520 (1380–1570)	<0.001†
Amplitude (mV); Median (IQR)	Upper limbs	0.66 (0.24–1.37)	3.63 (3.25–3.80)	<0.001†
	Lower limbs	0.47 (0.18–0.79)	1.54 (1.45–1.76)	<0.001†

IQR=Interquartile range; MSec=Milliseconds; mV=Millivolts; *Chi-square test; †Mann-Whitney U test.

Table 3. Association of SSR with Bulbar Palsy Among Cases (N=35)

SSR	Bulbar palsy		P-value*
	Present (N=11; (N %)	Absent (N=24; (N %)	
Upper limbs			
Normal	5 (45.5)	13 (54.2)	0.625
Delayed	3 (27.3)	8 (33.3)	
Absent	3 (27.3)	3 (12.5)	
Lower limbs			
Normal	1 (9.1)	1 (4.2)	0.042
Delayed	1 (9.1)	12 (50.0)	
Absent	9 (81.8)	11 (45.8)	

SSR=Sympathetic skin response; *Fisher's exact test.

Table 4. Association of SSR with the Severity of ALS (N=35)

SSR	Severity of ALS			P-value*
	Mild (>40) (N=20)	Moderate (30-39) (N=13)	Severe (<30) (N=2)	
	(N (%)	(N (%)	(N (%)	
Upper limbs				
Normal	11 (55.0)	7 (53.8)	0 (0.0)	0.129
Delayed	6 (30.0)	5 (38.5)	0 (0.0)	
Absent	3 (15.0)	1 (7.7)	2 (100.0)	
Lower limbs				
Normal	1 (5.0)	1 (7.7)	0 (0.0)	0.682
Delayed	9 (45.0)	4 (30.8)	0 (0.0)	
Absent	10 (50.0)	8 (61.5)	2 (100.0)	

SSR=Sympathetic skin response; ALS=Amyotrophic lateral sclerosis; *Fisher's exact test.

Table 5. Association of SSR with the KING's ALS Clinical Staging (N=35)

SSR	Severity of ALS			P-value*
	Stage 2 (N=19)	Stage 3 (N=4)	Stage 4 (N=12)	
	N (%)	N (%)	N (%)	
Upper limbs				
Normal	9 (47.4)	3 (75.0)	6 (50.0)	0.843
Delayed	7 (36.8)	1 (25.0)	3 (25.0)	
Absent	3 (15.8)	0 (0.0)	3 (25.0)	
Lower limbs				
Normal	1 (5.3)	0 (0.0)	1 (8.3)	0.051
Delayed	9 (47.4)	3 (75.0)	1 (8.3)	
Absent	9 (47.4)	1 (25.0)	10 (83.3)	

SSR=Sympathetic skin response; ALS=Amyotrophic lateral sclerosis; *Fisher's exact test.

Table 6. Association of SSR with Disease Duration of ALS (N=35)

SSR	Disease duration (months)				P-value*
	(N=15)	7–12 (N=12)	13–18 (N=2)	>18 (N=6)	
	N (%)	N (%)	N (%)	N (%)	
Upper limb					
Normal	7 (46.7)	7 (58.3)	1 (50.0)	3 (50.0)	0.891
Delayed	5 (33.3)	4 (33.3)	0 (0.0)	2 (33.3)	
Absent	3 (20.0)	1 (8.3)	1 (50.0)	1 (16.7)	
Lower limb					
Normal	1 (6.7)	1 (8.3)	0 (0.0)	0 (0.0)	0.945
Delayed	6 (40.0)	3 (25.0)	1 (50.0)	3 (50.0)	
Absent	8 (53.3)	8 (66.7)	1 (50.0)	3 (50.0)	

SSR=Sympathetic skin response; ALS=Amyotrophic lateral sclerosis; *Fisher's exact test.

Discussion

This study aimed to assess autonomic dysfunction in amyotrophic lateral sclerosis patients by testing sympathetic skin response (SSR). SSR is one of the electrophysiological autonomic function tests used to examine autonomic involvement. We found that a large proportion of patients had autonomic nervous system involvement despite the absence of significant clinical features suggestive of autonomic dysfunction.

In our study, the mean age of ALS was found to be lower than in other studies because patients aged 60 years and older were excluded from the study (11, 12). A large-scale population-based study on the epidemiology of ALS patients in Bangladesh is yet to be done. However, in a study of 42 ALS patients, the mean age was reported to be 44.64±16.4 years, which is lower than that of western population-based studies (20), whereas, an Indian study of 1153 ALS patients reported a similar mean age of 46.2±14.1 years (21). To rule out age-related effects on SSR *a priori*, we included only cases and controls less than 60 years of age. So, the mean age of our patients was even less than in previous studies in Bangladesh and India. However, the proportion of male patients was high, reflecting the higher prevalence of ALS among males than females worldwide (22).

The median SSR latency was found to be significantly longer in both limbs of ALS patients compared to the controls. Additionally, SSR amplitude was significantly reduced (or absent responses) in cases compared to the healthy controls. This finding is similar to that of studies conducted by Dettmers et al. (13), Hu et al. (12), and Masur et al. (23), but dissimilar to that of Miscio et al. (24). There are conflicting opinions on whether SSR is a good assessor of autonomic dysfunction in ALS patients. However, the investigation by Oey et al. showed that when several aspects of autonomic dysfunction are considered, the subtle involvement of the autonomic nervous system can be found (25). Therefore, our findings endorse the assertions of autonomic involvement in ALS.

Similar to previous studies, we also noted that delayed or absent SSR was more marked in the lower limbs (12, 13). SSR is length dependent. Hence, a higher frequency of abnormality in the lower limbs is not unusual. Some authors prefer not to consider low amplitude SSR an abnormal response. Vertrugno et al. considered only an absent response as abnormal (10). The reason some authors differ in considering low amplitude abnormal is habituation. With repeated stimuli, the SSR amplitude gradually diminishes (26). However, like Hu et al. (12), we considered increased latency and reduced amplitude of SSR to be abnormal findings. We ensured adequate intervals between stimulations to avoid habituation and to ensure the accuracy of measurements. Moreover, we excluded cases with sensory abnormalities to avoid confusing somatic sensory nerve abnormalities with abnormal sympathetic skin response. As the pathway of SSR involves somatic sensory nerve as the afferent, sensory abnormalities may lead to prolonged latency in SSR. Therefore, it can be argued that the abnormal SSR in our patients was due to autonomic involvement.

We divided our cases according to the anatomical location of the predominant clinical involvement: ALS with bulbar palsy and ALS without bulbar palsy. Interestingly, we found significantly more abnormal SSR in the lower limbs of patients with bulbar palsy compared to patients with predominantly limb involvement. This is opposite to the report by Dettmers et al. (13). More studies are required to draw any conclusions on these associations.

Dettmers et al. demonstrated that SSR was more often absent in the advanced stage of the disease (13). We did not find any statistically significant association between abnormal SSR and the functional or clinical severity of ALS. However, we had only two patients with severe ALS according to the functional severity scale, and four patients with Stage 3 disease according to clinical staging. It would be premature to conclude any association between SSR abnormalities and the severity of the disease. We also did not find any correlation between absent SSR and disease duration. Our finding is supported by the observations by Hu et al. (12) and Masur et al. (23). Nevertheless, more data are needed to rule out or establish any association of SSR with the disease severity or the duration of ALS.

As the afferent pathway in our cases was normal, SSR abnormality in ALS was most likely due to central pathway or sympathetic dysfunction. In most of the previous relevant studies, they found the postganglionic sympathetic pathway was the abnormal linkage in the SSR pathway (12, 13), while others suggested central pathway involvement in addition to the postganglionic sympathetic route (11). In ALS patients with bulbar palsy, the central pathway may play a major role. The specific localization of the involved pathway was beyond the scope of this research. Hence, further studies are recommended.

None of our cases had any clinical feature of autonomic dysfunction except hypersalivation. All our ALS patients with bulbar palsy (N=11) complained of hypersalivation. This prevented us from considering hypersalivation as a symptom of autonomic failure. Previous studies also suggest that abnormal SSR in ALS occurs without clinical expression of autonomic dysfunction (12, 13). Hence, the abnormal SSR among our patients could be an indicator of subclinical autonomic dysfunction.

There are several possible mechanisms behind the autonomic involvement in ALS patients, and

the anterior horn cells, the autonomic nuclei of the spinal cords (intermediolateral column) can be affected by similar mechanisms (27–29). Neuronal loss was found in the spinal cord involving these nuclei. An intracytoplasmic inclusion body was also found inside Onuf's nucleus (30). As contiguous anatomic regions are involved in ALS, neural degeneration may progress to involve the parasympathetic nuclei of the brainstem in patients with bulbar involvement (31). Ultrasonography of the vagus nerve at the level of the thyroid gland revealed atrophy in ALS patients (32). The mechanisms behind autonomic nerve degeneration may be similar to the process causing the death of motor neurons in ALS (6).

Electrochemical skin conductance (33), Quantitative Sudomotor Axon Reflex Test (QSART) (34), ultrasonography of the vagus nerve (8, 9, 32), and skin biopsy (35) are other tests which can be combined with SSR to further confirm autonomic dysfunction in ALS patients. Apart from skin biopsy, the other tests are simple and noninvasive methods. We recommend further study using all these modalities in the same ALS cohort to assess which test is superior in assessing autonomic dysfunction.

Limitations of the Study

Our study had several limitations. The sample size was small. Representation of female participants was low. We evaluated our patients clinically for autonomic dysfunctions by using a questionnaire focusing on symptoms and bedside signs such as postural hypotension. Other evaluations of autonomic dysfunction, such as recording changes in heart rate and blood pressure during the Valsalva maneuver, could not be done. We also could not include other electrophysiological tests such as QSART or ultrasonography of the vagus nerve. However, our results add to the evidence that ALS patients might have subclinical autonomic involvement.

Conclusions

Given our study findings, ALS could be considered a multisystem disease. In addition to motor system involvement, ALS patients might have subclinical autonomic involvement. However, more studies are required to establish any association of the frequency of abnormal SSR with disease severity and duration. Abnormal SSR may have a prognostic value in ALS patients, as we had more abnormal findings in patients with bulbar involvement.

What Is Already Known on This Topic:
Previously ALS and other MNDs were considered to be diseases involving only the motor system. Later, some studies suggested they also involve the autonomic nervous system. Autonomic dysfunction in ALS patients can be assessed by both clinical findings and investigations. One of these assessment tools is SSR. Abnormal SSR in ALS patients is suggestive of autonomic dysfunction. In some studies, there was also an association between abnormal SSR and disease severity and duration.

What This Study Adds:
We found abnormal SSR in ALS patients without any clinical features of autonomic dysfunction. Abnormal SSR in ALS patients may suggest subclinical autonomic dysfunction in South Asian people. There is also a possible association between bulbar palsy and abnormal SSR, which may indicate the prognostic significance of abnormal SSR in ALS patients.

Authors' Contributions: Conception and design: MH, SMA and HZR; Acquisition, analysis and interpretation of data: MH, SMA, HZR, MASK and MRH; Drafting the article: MH, MASK and MRH; Revising it critically for important intellectual content: MASK and MRH; Approved final version of the manuscript: MH, MASK and MRH.

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

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