Bangladesh Journal of Neuroscience 2021; Vol. 37 (1): 37-43

Sympathetic Skin Response in Young Patients with ALS

HASAN M[1*], ALAM SM[2], RAHMAN HZ[3],MUZAHID MAA[4], JANNAT M[5], SAHA S[6],ISLAM MS[7], CHOWDHURY A[8]

Abstract

Background: *Motor neuron disease (MND) is now considered as the third most common neurodegenerative disorder. Among several types of MND, amyotrophic lateral sclerosis (ALS) is the most common and relentlessly progressive incurable disorder. Many hypotheses have been put forward to see autonomic involvement in ALS. Previous studies have found an association between sympathetic skin response (SSR) and ALS as a part of autonomic involvement. SSR may be absent or increased in latency or decreased in amplitude in ALS which are associated with severity of illness.* ***Objective:*** *The objective of this study was to see the association of SSR in young patients with ALS.* ***Materials and Methods:*** *This case control study was carried out in the Department of neurology, BSMMU, Dhaka, from April 2018 to September 2019. Total 38 subjects of less than 40-years-age were enrolled as study population after satisfying inclusion and exclusion criteria. Among them, 19 were grouped as case and rest 19 were control. All patients with ALS were diagnosed according to The Revised El Escorial diagnostic criteria fulfilling definite, probable, probable lab-supported and possible cases of ALS with no family history of ALS. The SSR was recorded on NIHON KOHDEN Neuropack MEB-9400 S1 Series EMG/NCV/EP Measuring System in the department of Neurology, BSMMU.* ***Results:*** *The mean age of the cases was 25.68 ± 7.71 years all of whom were male. The mean disease duration was 17.9±7.8 months at the time of examination; and 15(78.9%) had mild disease and 4(21.1%) had moderate severity of disease. We observed mean onset latency in cases to be 1521.2±230.2ms in upper limb and 2551.0±404.0ms in lower limb; which were significantly longer than control group (p value <0.001). We also noticed mean SSR amplitude to be 1.01±0.88mV in upper limbs and 0.59±0.53mV in lower limbs which were significantly lower than control group (p value <0.001). In upper limb, among 19 cases, SSR was absent in 2 (10.5%) and increased latency in 6(31.6%) which was significantly different than control (p=0.006). In lower limbs, SSR was absent in 9 (47.4%) cases and increased latency in 9(47.4%) cases which also was significantly (<0.001) different than control group.* ***Conclusion:*** *The present study revealed significant association of sympathetic skin response abnormality in young patients with ALS.*

Key Words*: Amyotrophic Lateral Sclerosis, Sympathetic Skin Response, Nerve Conduction Study, Motor Neuron Disease.*

Background

Motor neuron disease (MND) is a rare progressive degenerative disease of the motor neurons of motor cortex, brainstem, and spinal cord[1]. It is the third most common neurodegenerative disorder after Alzheimer's and Parkinson's disease[2]. The prevalence of MND is 4-6 per 100,000 in most parts of the world[3], with a mean age of onset is 63 years[4].

1. Dr. Mehedi Hasan, Medical Officer, Dept of Neurology, BSMMU
2. Dr. SK. Mahbub Alam, Associate Professor, Dept of Neurology, BSMMU
3. Prof. Hasan Zahidur Rahman, Professor, Dept of Neurology, BSMMU
4. Dr. Md. Abdullah Al Muzahid, Consultant, Department of Neurology, Proactive Medical College &Hospital
5. Dr. Maftahul Jannat, Medical Officer, Dept of Neurology, BSMMU
6. Dr. Sujan Saha, Assistant Registrar, Dept of Neurology, NINS
7. Dr. Md. Shofikul Islam, Assistant Registrar, Dept. of Neurology, M Abdur Rahim Medical College & Hospital
8. Dr. Ashish Chowdhury, Registrar, Dept of Internal Medicine, North Bengal Medical College & Hospital

MND is subdivided into several subtypes on the basis of symptoms and signs including Amyotrophic lateral sclerosis (ALS), Progressive bulbar palsy (PBP), Progressive muscular atrophy (PMA), Primary lateral sclerosis (PLS), Flail arm syndrome, Flail leg syndrome and ALS with multi-system involvement[4]. Lord Russell Brain proposed the term Motor neuron disease (MND) to incorporate these conditions into a single spectrum of disorder[4].

Amyotrophic lateral sclerosis (ALS) is the most common form of adult onset MND[5].ALS is a relentlessly progressive, presently incurable disorder with an incidence of about 1/100000[6]. Fifty percent of ALS patients die within 30 months of symptom onset, 20% survive between 5 years and 10 years and only10% of patients with ALS survive for more than 10 years[2]. The full pathogenesis of ALS is not well understood but several important factors can be noted including: genetics, excitotoxicity, oxidative stress, mitochondrial dysfunction, impaired axonal transport, neurofilament aggregation, inflammatory dysfunction, deficits of neurotrophic factors, dysfunction of signaling pathways and apoptosis[4].

Though ALS has traditionally been considered to be a pure motor disease, non-motor manifestations may also occur. Evidence for subclinical involvement of both sympathetic and parasympathetic nervous systems in ALS has also accumulated[7]. Studies of sudomotor function have provided evidence of sympathetic postganglionic cholinergic denervation in ALS[7]. Decreased heart rate variation, alterations of the excretory function of the salivary glands, and disturbance of the gastrointestinal tract suggest parasympathetic abnormalities, while SPECT studies have shown disordered cardiac sympathetic innervation[8]. Electrophysiological study showing alterations of the SSR in ALS, indicates degeneration of sympathetic nerve fibers, possibly involving sudomotor function[8].Postmortem histology shows neuronal degeneration in Onuf's nucleus in the ventral horns of the spinal cord, indicating alterations in bowel and bladder innervation. Although autonomic symptoms in ALS are usually subclinical, these findings suggest that ALS may be a multisystem degenerative disorder[7].

Cutaneous vasomotor and sudomotor dysfunction of varying severity have been reported in patients with ALS. Sudomotor function can be assessed bySSRstudies, which frequently show abnormal latencies in patients with ALS[9]. In previous studies of sudomotor or sweat gland function, SSR latency measured at the palms or soles showed gradual prolongation in patients with a longer disease duration. Patients with early ALS showed a higher sweating rate, which gradually decreased as the disease advanced[9]. A previous study demonstrated that absent SSR was related to severity of the disease and itsimpairment may be a subclinical manifestation of ALS[10]. It wasalso shown that, there was impairment of SSR in ALS, which may be present when there wassub-clinical involvement of autonomic nervous system[10].

Methods:

This case control study was performed in BSMMU from April 2018 to September 2019. Nineteen patients with ALS according to revised El Escorial diagnostic criteria, who were less than 40 years old with no family history, nor any other neurodegenerative disorders, cranio-cervical trauma, DM, CKD, GBS or any drugs causing autonomic dysfunction; were enrolled as case. Similar number of age and sex matched healthy volunteers were enrolled as control.

After ethical clearance from Institutional Review Board (IRB), informed written consent was taken from each patient or his/her attendant. The data was collected through face-to-face interview with the patient and attendant and thorough physical examination was done. The ALS Functional Rating Scale-Revised (ALSFRS-R) was used to assess the patients' functional status. SSR assessment was done by using *NIHON KOHDEN Neuropack MEB-9400 S1 Series EMG/NCV/EP Measuring System*in the department of neurology, BSMMU, Shahbag, Dhaka. Other necessary investigations were also done and prescribed data collection form was filled up.

Data were analyzed using SPSS 22.0 for windows software. Continuous parameters were expressed as mean±SD and categorical parameters as percentage. Comparisons between groups (continuous parameters) were done by unpaired *t* test. Categorical parameters were compared by Chi-Square test.A p-value of d"0.05 was considered significant.

Results:

Table-I

Distribution of the study subjects by age (n=38)

		Case (n=19)	Control (n=19)	p-value
Age group (years)	<20	7(36.8%)	2(10.5%)	0.146^{ns}
	20-29	6(31.6%)	7(36.8%)	
	30-39	6(31.6%)	10(52.6)	
	Mean±SD	25.68±7.71	27.32±5.32	
Sex group	Male	19(100.0%)	17(89.5%)	0.486^{ns}
	Female	0(0.0%)	2(10.5%)	
	Total	19(100.0%)	19(100.0%)	

Chi-square test was done, ns= not significant

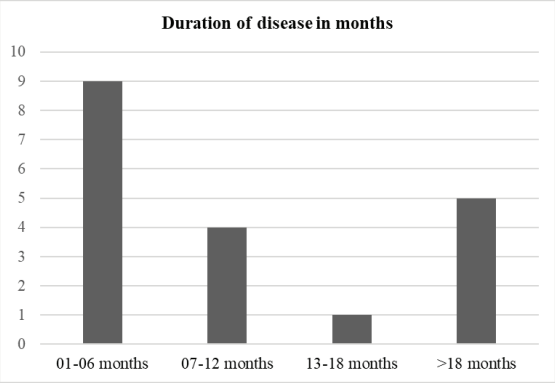

Fig.-1: *Bar diagram showing duration of disease in months*

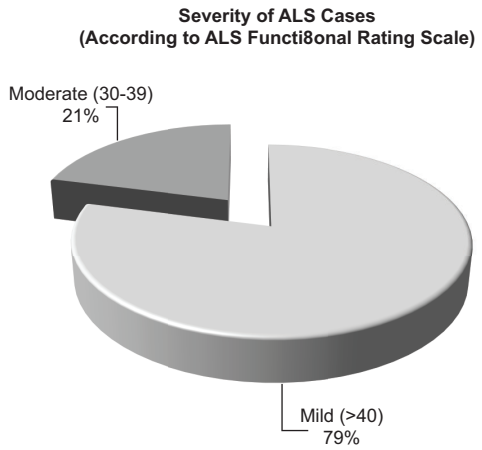

Fig.-2: *Pie Chart showing severity of ALS cases*

Table-II

Distribution of the study subjects by SSRof upper limbs between case and control group (n=38)

SSR of upper limbs	Case(n=19)	Control(n=19)	p-value
Normal	11(57.9%)	19(100.0%)	0.006*
Delayed	6(31.6%)	0(0.0%)	
Absent	2(10.5%)	0(0.0%)	
Total	19(100.0%)	19(100.0%)	

Table-III

Distribution of the study subjects by SSR of lower limbs between case and control group (n=38)

SSR of lower limbs	Case(n=19)	Control(n=19)	p-value
Normal	1(5.3%)	19(100.0%)	<0.001*
Delayed	9(47.4%)	0(0.0%)	
Absent	9(47.4%)	0(0.0%)	
Total	19(100.0%)	19(100.0%)	

Chi-square test was done, *significant

Table-IV

Comparison of SSR latency between two groups (n=38)

SSR Latency	ALS Mean±SD (ms)	Control Mean±SD (ms)	p-value
Upper limbs	1521.2±230.2	1209.2±195.4	<0.001*
Lower limbs	2551.0±404.0	1490.2±225.7	<0.001*

Unpaired t-test was done, *significant

Table-V

Comparison of SSR Amplitude between two groups (n=38)

SSR Amplitude	ALS Mean±SD (mv)	Control Mean±SD (mv)	p-value
Upper limbs	1.01±0.88	3.49±0.45	<0.001*
Lower limbs	0.59±0.53	1.63±0.21	<0.001*

Unpaired t-test was done, *significant

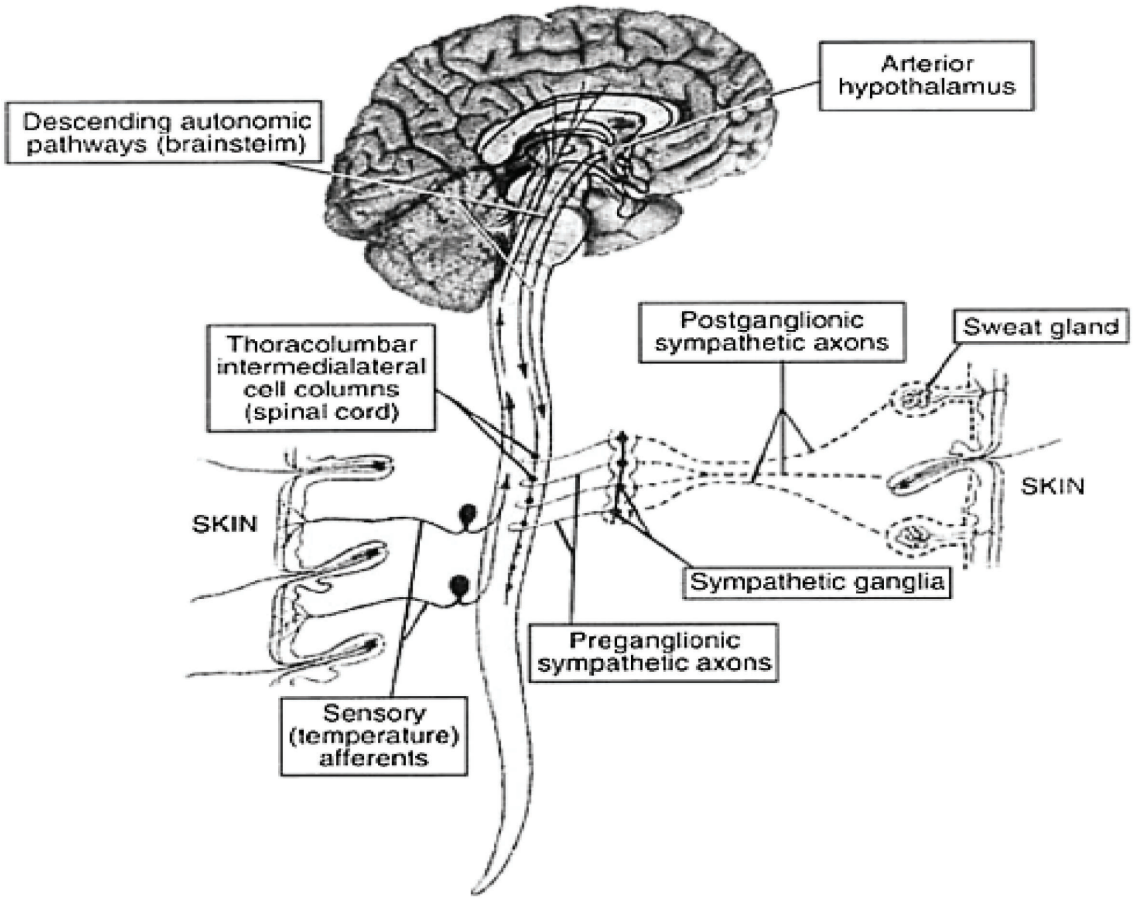

Fig.-3: *The pathway of sympathetic skin response*[10].

Sympathetic skin response: wave forms

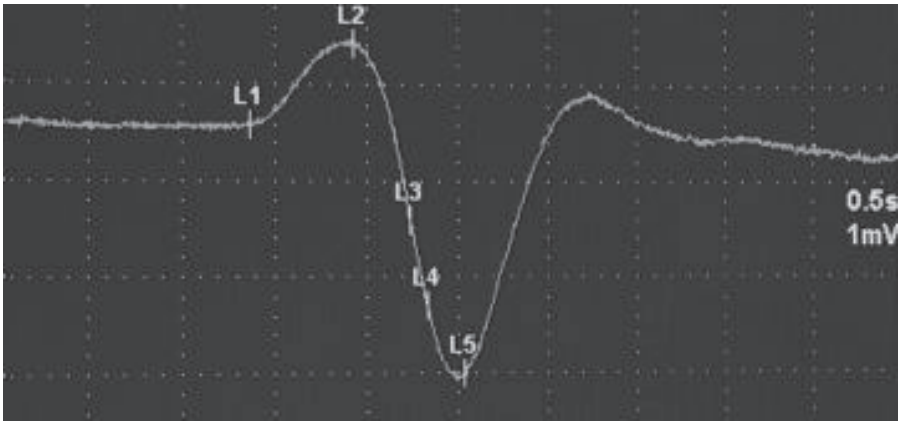

Fig.-4: *Normal SSR in upper limb*

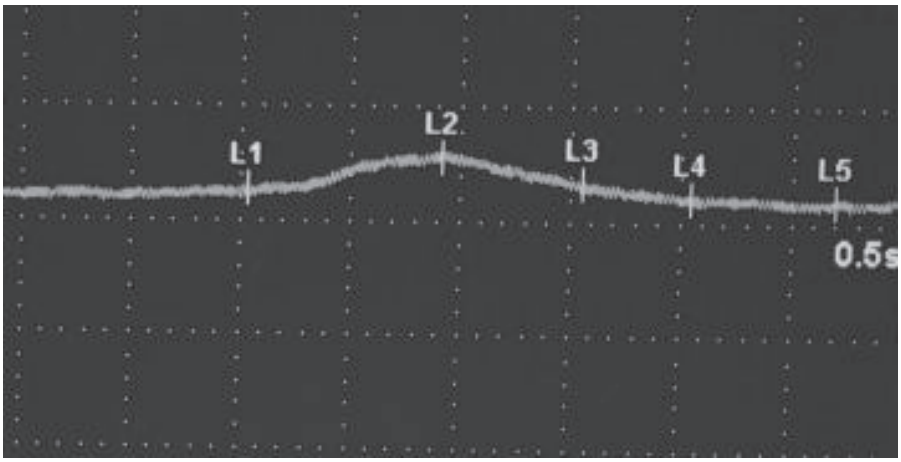

Fig.-5: *Normal SSR in lower limb*

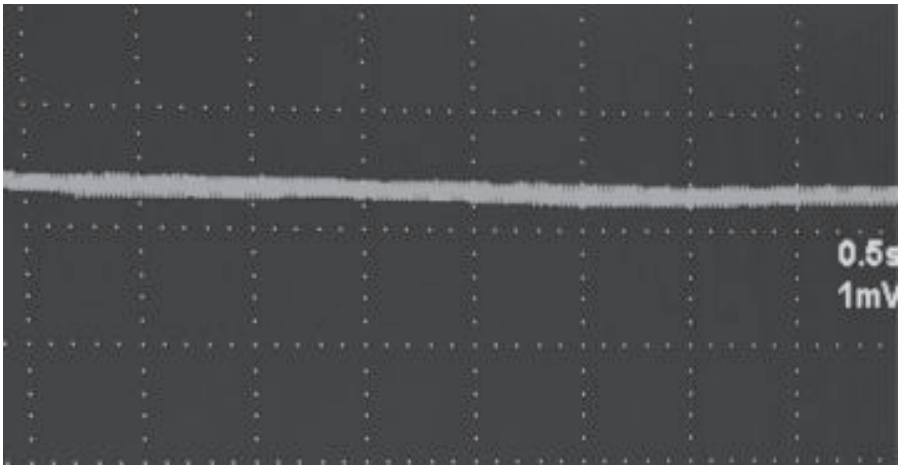

Fig.-6: *Absent SSR in lower limb*

Source: BSMMU Electrophysiology Lab.

Discussion:

This study was intended to find out the association of sympathetic skin response in early amyotrophic lateral sclerosis.Nineteen cases and 19 controls were selected after fulfilling inclusion and exclusion criteria. The mean age of the cases was 25.68±7.71years and mean age of the controls was27.32±5.32years. All of the cases were male, and among control 2 were female. There was no significant difference between case and control regarding age and sex.

In this study we found that mean disease duration was 17.9±7.8months at the time of examination. Minimum duration was 3 months and maximum duration was 10 years. Disease duration of majority of patients [9(47.4%)] were within 1 to 6 months. A previous study showed 17±11 months of mean duration of symptoms[11]. Following the ALS functional rating scale score[12]; we categorized mild (>40), moderate (39-30), severe (<30) and advanced (<20). In this study, 15(78.9%) had mild disease and 4(21.1%) had moderate severity of disease.

SSR is normally present in both hands and feet under the age of 60 years, but in subjects older than 60 years it is decreased[13]. SSR response is considered abnormal when increased in latency or decreased in amplitude or remained absent. Some study considered increased latency and decreased amplitude as abnormal[10]. Another research group states that, absent response is considered to be abnormal[14].

For SSR; mean onset latency and amplitude of 1500 ± 0.1ms and 3.1 ± 1.8 mV for the hands, and 2050 ± 0.10 ms and 1.4 ± 0.8 mV for the feet were considered normal for our study[15].We observed mean onset latency in cases to be 1521.2±230.2ms in upper limb and 2551.0±404.0ms in lower limb; which were significantly longer than control group (p value <0.001). We also noticed mean SSR amplitude to be 1.01±0.88mV in upper limbs and 0.59±0.53mV in lower limbs which were significantly lower than control group (p value <0.001).A previous study also found similar type of result[10].

In upper limb, among 19 cases, SSR was absent in 2 (10.5%), increased latency in 6(31.6%) and normal response in 11(57.9%) cases. Among the control population all 19 (100%) had normal SSR, which was statistically significant (p=0.006). In lower limbs, SSR was absent in 9 (47.4%) cases, increased latency in 9(47.4%) cases and normal response in 1(5.3%) cases. Among the control population all 19 (100%) had normal SSR, which was statistically significant (<0.001). A previous study showed 10 (40%) out of 25 cases, had absent SSR in lower limb[11].

Sympathetic skin response(SSR) is a momentary change of the electrical potential of the skin generated by sweat gland[14].It originates by activation of reflex arc with different kinds of internal or externally applied arousal stimuli[14].Reflex arc includesafferent pathway consisting of myelinated somatosensory fibers,central processing involving the mesencephalic reticular formation, the posterior thalamus, and cortical structures andthe efferent pathway consisting of the preganglionic myelinated and postganglionic nonmyelinated axons and the neuroglandular junction[11].

SSR shape is most often either biphasic or triphasic in the hands, and biphasic in the feet; it is seldom monophasic[13]. The amplitude of hand waveform larger and shorter latencies than feet. The amplitude of the SSR is age dependent. SSR is normally present in both hands and feet under the age of 60 years,but in subjects older than 60 years it is found in only 50% of feet and in 73% of hands[13].

SSR abnormalities have been reported in diabetic neuropathy[16], Parkinson's disease,multiple system atrophy, multiple sclerosis, other neurodegenerative disorders, chronic kidney disease, Hereditary Motor and Sensory neuropathy,Hereditary Sensory Autonomic Neuropathy, distal small fiber peripheral neuropathy, alcoholic subjects, scleroderma, Sjogren's disease etc[14].

Conclusion:

The present study revealed significant association of sympathetic skin response abnormality in young patients with ALS. The onset latency was prolonged and amplitude was decreased in young ALS patients than control group, which was statistically significant.

Ethical issues:
All patients gave informed written consents and the study was approved by Institutional Review Board of Bangabandhu Sheikh Mujib Medical University.

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

References

1. Imam I, Ball S, Wright D, Hanemann CO, Zajicek J. The epidemiology of motor neurone disease in two counties in the southwest of England. Journal of neurology. 2010 Jun;257(6):977-81.
2. Talbot K. Motor neurone disease. Postgraduate medical journal. 2002 Sep 1;78(923):513-9.
3. Ringel SP, Murphy JR, Alderson MK, Bryan W, England JD, Miller RG, Petajan JH, Smith SA, Roelofs RI, Ziter F and Lee MY. The natural history of amyotrophic lateral sclerosis. Neurology. 1993 Jul; 43(7):1316-1316.
4. Wijesekera LC, Leigh PN. Amyotrophic lateral sclerosis. Orphanet journal of rare diseases. 2009 Dec;4(1):1-22.
5. Gordon PH. Amyotrophic lateral sclerosis: an update for 2013 clinical features, pathophysiology, management and therapeutic trials. Aging and disease. 2013 Oct;4(5):295.
6. Zarei S, Carr K, Reiley L, Diaz K, Guerra O, Altamirano PF, Pagani W, Lodin D, Orozco G, Chinea A. A comprehensive review of amyotrophic lateral sclerosis. Surgical neurology international. 2015;6.
7. Baltadzhieva R, Gurevich T and Korczyn AD. Autonomic impairment in amyotrophic lateral sclerosis. Current opinion in neurology.2005 May;18(5):487-493.
8. Beck M, Giess R, Magnus T, Puls I, Reiners K, Toyka KV, Naumann M. Progressive sudomotor dysfunction in amyotrophic lateral sclerosis. Journal of Neurology, Neurosurgery & Psychiatry. 2002 Jul 1;73(1):68-70.
9. Shindo K, Watanabe H, Ohta E, Nagasaka T, Shiozawa Z, Takiyama Y. Sympathetic sudomotor neural function in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis. 2011 Jan 1;12(1):39-44.
10. Hu F, Jin J, Qu Q, Dang J. Sympathetic skin response in amyotrophic lateral sclerosis. Journal of Clinical Neurophysiology. 2016 Feb 1;33(1):60-5.
11. Dettmers C, Fatepour D, Faust H, Jerusalem F. Sympathetic skin response abnormalities in amyotrophic lateral sclerosis. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine. 1993 Sep;16(9):930-4.
12. Armon C. Ethics of clinical research in patients with ALS: is there a risk of exploitation?. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2018 Apr 3;19(3-4):161-6.
13. Drory VE, Korczyn AD. Sympathetic skin response: age effect. Neurology. 1993 Sep 1;43(9):1818-.
14. Vetrugno R, Liguori R, Cortelli P, Montagna P. Sympathetic skin response. Clinical autonomic research. 2003 Aug;13(4):256-70.
15. Elie B, Guiheneuc P. Sympathetic skin response: normal results in different experimental conditions. Electroencephalography and clinical neurophysiology. 1990 Sep 1;76(3):258-67.
16. Niakan E, Harati Y. Sympathetic skin response in diabetic peripheral neuropathy. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine. 1988 Mar;11(3):261-4.