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Research Article

Neurophysiological Evaluation of Autonomic Dysfunction in Spinal Muscular Atrophy: A Case-Control Study

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Introduction. Spinal muscular atrophy (SMA) is an autosomal recessive disorder causing lower motor neuron degeneration leading to weakness and muscle atrophy due to reduction of survival motor neuron (SMN) protein. Although SMA was considered an exclusively motor neuron disease, few reports indicate the involvement of nonmotor neurons. The aim of this study is to investigate autonomous nervous system (ANS) involvement in SMA. *Materials and Methods*. We investigated 9 SMA adult patients and 36 age- and sex-matched controls. ANS was evaluated by sympathetic skin response (SSR). *Results*. SSR was not elicited in 28% of measurements in cases and in 0% of measurements in controls ($p < 0.001$). Both palmar ($p < 0.001$) and plantar ($p < 0.001$) SSR latencies were significantly longer in cases than controls. Palmar SSR amplitudes were smaller ($p = 0.036$) in patients compared to controls. *Conclusions*. This study provides new evidence of ANS dysfunction in SMA patients.

1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disorder caused by mutations in *SMN1* gene that encodes survival motor neuron (SMN) protein. SMA disease severity ranges from extremely severe to a relatively mild adult-onset form [1]. SMN immunohistochemistry has shown intense immunoreactivity not only in motor neurons but also in sympathetic preganglionic neurons of the thoracic intermediolateral nucleus, subserving autonomous function [2]. Although SMN protein is ubiquitously but unevenly expressed throughout cerebral and spinal cord areas, its exact role in the survival of neurons is not clarified [1–4].

Although autonomic nervous system (ANS) dysfunction is not considered part of motor neuron disorders, evidence of ANS dysfunction is accumulating [5]. Involvement of the ANS in amyotrophic lateral sclerosis (ALS) has been supported by various studies and mainly attributed to loss of neurons in the intermediolateral nucleus and vagus nerve atrophy [6, 7]. Similarly, in spinobulbar muscular atrophy (SBMA), a predominantly sensorimotor neuronopathy, subclinical autonomic disturbance has been reported [8] and has been attributed to diffuse nuclear accumulations of mutant androgen receptor in the intermediolateral nucleus and sympathetic ganglia and in the nucleus ambiguous [9].

In view of the former considerations, we sought to investigate in the present case-control study the involvement of ANS in SMA adult patients. For the purpose of the study, sympathetic skin response (SSR) was chosen to investigate the sympathetic nervous system (SNS). SSR has been previously used in ALS patients [6, 7] and in children suffering from SMA [10].

2. Methods

2.1. Study Design. A case-control study was carried out at the outpatient clinic of a tertiary-care referral academic hospital in Athens, Greece, between September 2022 and June 2023. Written informed consent was obtained by all participants. The present study was approved by the local Ethics Committee of our Institution (*EBΔ*23/14-01-2022) and followed the principles of the Helsinki Declaration and its later amendments [11].

2.2. Study Population. All adult patients with a genetically confirmed diagnosis of SMA were included in the study. Controls were recruited after open invitation to participate in the research. Exclusion criteria for controls were the presence of diabetes mellitus or history of neuromuscular disorders.

2.3. Demographic and Clinical Data. The following data were collected on patients' demographic data (age and sex) and clinical characteristics (type and treatment received).

2.4. Sympathetic Skin Response (SSR). SSR measurements are described in detail in previously published studies by our group [7, 12].

2.5. Statistical Analysis. Statistical analysis was performed using the Statistical Package for Social Science (SPSS Inc., version 25.0 for Windows; IBM, Armonk, NY, USA). Descriptive statistics are given as the mean and standard deviation (SD), frequency, and percentage. Normality of data distribution was investigated with the Kolmogorov-Smirnov test. Statistical comparisons between different groups were performed using the chi-square test (or exact test) for binary outcomes and Student's t -test or Mann–Whitney U-test for continuous variables as appropriate. A two-tailed p value of less than .05 was considered significant.

3. Results

3.1. Demographic and Clinical Characteristics. A total of 36 healthy subjects (21 women and 15 men) and 9 patients (4 women and 5 men) were included (ratio 1 : 4 between cases and controls). The mean age of controls was 39 years, ranging between 25 and 60 years; the mean age of SMA patients was 41 years, ranging between 22 and 66 years. The two groups did not differ in age ($p = 0.727$) and sex ($p = 0.482$). Clinical characteristics of patients are presented in Table 1.

3.2. SSR Measurements. SSR (palmar and plantar) was not elicited in 5 out of 18 measurements (28%) in SMA patients but was always present in controls ($p < 0.001$ by Fisher's exact test). Plantar SSR was not elicited in one case, while in three cases, both plantar and palmar SSR could not be elicited (Figure 1). SMA patients had longer palmar ($p < 0.001$) and plantar SSR latencies ($p < 0.001$) compared to controls (Table 2). Palmar SSR amplitudes were lower in SMA patients compared to controls ($p = 0.036$; Table 2). This difference was not significant in plantar SSR ($p = 0.069$; Figure 2). In terms of severity, patients with the worst results did not differ from those with better results.

4. Discussion

The aim of this study was to investigate ANS dysfunction in SMA patients. SSR was not elicited in 28% of measurements in cases and in 0% of measurements in controls. Latencies were significantly longer, and amplitudes were significantly smaller in SMA patients compared to controls. The findings of our study support the idea of ANS involvement in SMA patients.

Few studies have studied ANS involvement in SMA. Although patients with SMA type 1 do not live long enough to exhibit nonmotor dysfunction, Hachiya et al. described sympathetic-vagal imbalance on R-R interval and an abnormality in finger cold-induced vasodilatation, in three cases of SMA type 1 with long survival [13] without giving a plausible explanation. Bach et al. described severe symptomatic bradycardia in 15/63 type 1 SMA patients [14]. Similarly, Senel et al. compared 6 SMA patients (types 1 and 2) to age-matched healthy children [15]. Heart rate variability (HRV) differed between groups and improved after obstructive sleep apnea syndrome therapy (noninvasive mechanical ventilation). HRV abnormalities were attributed to cardiac involvement, including the presence of thinner cardiac sympathetic nerves and reduced neuronal branching as shown in microscopic examinations [16]. On the contrary, type 2 and 3 SMA patients do not develop cardiac disease more often than the general population, and heart disease is attributed to hypertension and/or coronary artery disease [1].

SSR was only previously investigated in one study [10]. Arai et al. studied 10 SMA patients (types 1, 2, and 3) and compared them to healthy children using finger cold-induced vasodilatation, sympathetic skin response, and HRV, to investigate ANS dysfunction. Finger cold-induced vasodilatation was abnormal in 60% of SMA patients, and amplitudes of SSR to sound stimulation were absent or low in all six patients. No significant difference was documented in HRV and SSR latency and amplitudes to electric stimulation. Although the authors conclude that the observed ANS dysfunction resembles that in ALS, they do not attribute it directly to the primary effect on the intermediolateral nucleus, since it was thought to remain intact in SMA patients.

In our study, which included type 2 and 3 SMA adult patients, all of them receiving new treatments long after the onset of symptoms, SSR to electric stimulation was significantly abnormal compared to age and sex-matched controls. This finding is compatible to similar findings with other motor neuron diseases, such as ALS [7] and in the juvenile muscular atrophy of the distal upper limb [17]. In both cases, the responsible lesion of these abnormalities

Table 1: Clinical characteristics of SMA patients.

	Age (years)	Gender	SMN2 copies	SMA type	Onset age (mo: months; y: years old)	Age first treatment	Treatment	Walking (6-minute walk test)	Respiratory support	FEV1 (%)	FVC (%)	FEV1/FVC (%)	Scoliosis	Surgical treatment for scoliosis
Patient 1	47	Male	4	III	2 y	46	Nusinersen	0	No	78	88	91	Yes	No
Patient 2	66	Female	3	III	7 y	65	Nusinersen	0	No	105	124	92	Yes	No
Patient 3	22	Male	3	II	16 mo	18	Nusinersen	0	No	51	49	109	Yes	Yes
Patient 4	27	Male	3	II	7 mo	22	Nusinersen	0	No	14	15	99	Yes	Yes
Patient 5	32	Male	3	II	10 mo	32	Risdiplam	0	Yes (BiPap)	NA	NA	NA	Yes	Yes
Patient 6	22	Female	3	II	13 mo	18	Nusinersen	0	No	21	19	116	Yes	Yes
Patient 7	47	Male	3	II	14 mo	43	Nusinersen	0	No	52	49	111	Yes	Yes
Patient 8	48	Female	3	III	18 mo	48	Risdiplam	0	No	51	49	110	Yes	Yes
Patient 9	58	Female	3	III	4 y	58	Risdiplam	0	No	79	77	111	Yes	No

Abbreviations: SMN2: survival motor neuron; SMA: spinal muscular atrophy; FEV1: forced expiratory volume in the first second; FVC: Forced vital capacity; NA: not applicable.

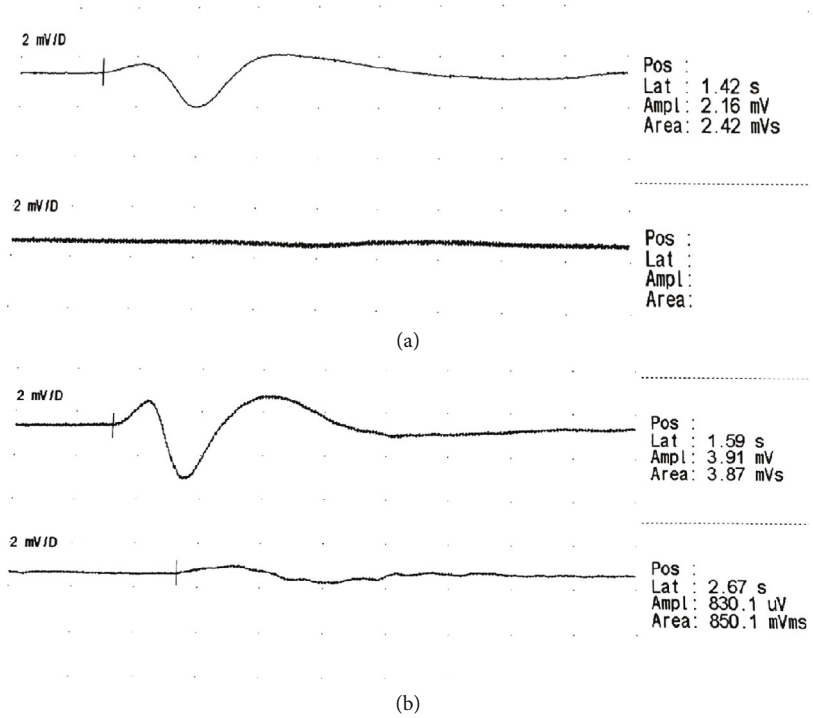

Figure 1: SSR recordings from SMA patients. (a) No response is obtained from plantar, delayed response obtained from the palm. (b) Delayed responses with low amplitudes are obtained from palm and plantar.

Table 2: Comparison of SSR measurements between groups.

Characteristic	SMA ($n = 9$)	Controls ($n = 36$)	p
SSR PALM LAT, mean (SD) (s)	1.52 (0.17)	1.23 (0.21)	**<0.001**
SSR PALM AMP, mean (SD) (mV)	1.71 (1.3)	3.14 (2.04)	**0.036**
SSR PLANT LAT, mean (SD) (s)	2.19 (0.4)	1.69 (0.27)	**<0.001**
SSR PLANT AMP, mean (SD) (mV)	0.8 (0.13)	1.85 (1.6)	0.069

Abbreviations: SSR: sympathetic skin response; PALM: palmar; PLANT: plantar; LAT: latency; AMP: amplitude. Statistically significant p-values are shown in bold.

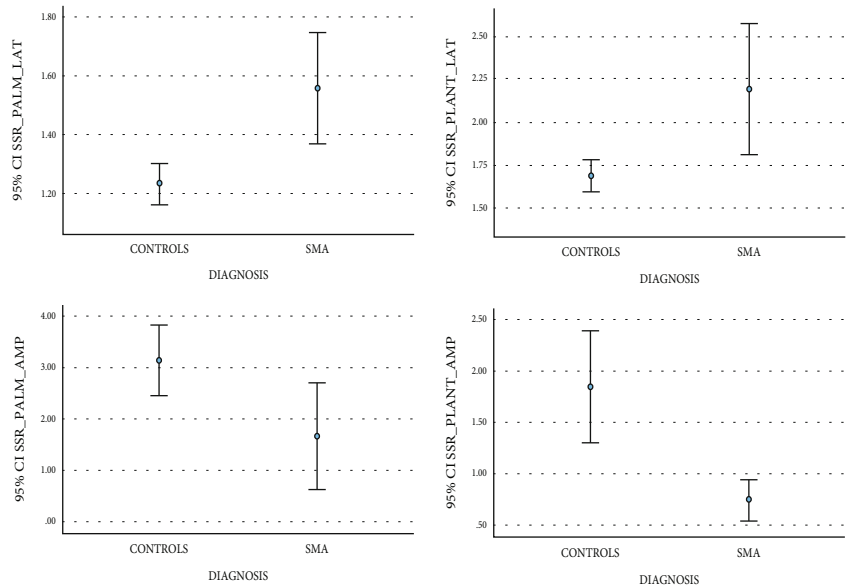

Figure 2: Comparison of SSR latencies and amplitudes between patients and controls. Mean latencies were significantly shorter in controls compared to patients. Mean amplitudes were higher in controls compared to patients.

was hypothesized to be located in the descending sympathetic tract in the cervical spinal cord and the intermediolateral nucleus, known to be immunoreactive to SMN [2], and, therefore, expected to be dysfunctional in SMA patients. A very recent study using confocal corneal microscopy revealed sensory neurodegeneration in SMA, compatible with small nerve fiber damage [18], which could also contribute to autonomic dysfunction.

The discrepancy between our findings and those of Arai et al. might be attributed to the fact that their study included only children, some of them suffering from type 1 SMA, the more severe form, whereas, in our study, only adult patients with milder clinical phenotypes were included. The longer survival of our patient population might have given the opportunity to other nonmotor involvement to emerge, even though in subclinical form.

Certain limitations of the present study should be highlighted, including the small sample size, the case-control design, the lack of standardized clinical assessment of autonomic dysfunction, and the fact that SSR assess solely sympathetic ANS.

Although SMA is considered a motor neuron disease, there is increasing evidence that other parts of the nervous system may be involved, including ANS. In addition, musculoskeletal complications such as scoliosis and contractures and the need for respiratory assistance add pain and distress to an already burdened patient. ANS dysfunction may contribute to the pathophysiology of neuropsychiatric complications, and vice versa, pain and other stressful conditions may contribute to dysautonomia. Similarly, in other nonmotor diseases, such as fibromyalgia, anxiety disorder, chronic fatigue syndrome, and more recently post-COVID syndrome [12, 19], ANS involvement has been suggested to interpret symptoms like pain, fatigue, arthralgia, myalgia, and mood disorders.

This study contributes to the limited relevant literature of the multisystem nature of SMA. More studies, with simultaneous assessment of other parameters such as R-R interval variability, cold-induced vasodilation, and confocal corneal microscopy, in an extended SMA population, including SMA type 4, are needed to further elucidate the etiopathogenic mechanism of ANS dysfunction in SMA.

Data Availability

The datasets used and analysed during the current study are included in this article. More detailed datasets are available from the corresponding author on reasonable request.

Additional Points

Highlights. (i) Although spinal muscle atrophy (SMA) is considered an exclusively motor neuron disease (MND), there is emerging evidence of potential autonomous nervous system (ANS) involvement. (ii) Results from sympathetic skin response (SRR) demonstrated ANS dysfunction in SMA patients compared to matched controls.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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