Sensory changes in pediatric patients with spinal muscular atrophy: an electrophysiologic study

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Context
Spinal muscular atrophy (SMA) is well known to be a pure motor neuron disease. However, it was reported that sensory neuron degeneration can also occur in pediatric SMA.

Aim of the work
The aim of the present study was to assess peripheral and central sensory abnormalities in pediatric SMA patients.

Materials and methods
The present study included 29 type I and 11 type II SMA patients diagnosed on the basis of clinical history and typical electromyographic patterns, and 25 age-matched and sex-matched healthy pediatric participants, who comprised the control group. Sensory and motor conduction studies were carried out for both groups. Sensory conduction studies of sural and median nerves assessed peak latency, sensory nerve action potential (SNAP) amplitude, and sensory nerve conduction velocity. Mixed posterior tibial somatosensory evoked potential latency and amplitude were also assessed for both groups.

Results
SMA I patients had lower sural and median SNAP amplitudes, as well as lower peroneal and femoral compound muscle action potential amplitudes, slower tibial motor conduction velocity (MCV), and prolonged femoral and peroneal distal latency compared with the control group. SMA II patients had lower sural SNAP amplitude, slower sural sensory nerve conduction velocity, lower tibial somatosensory evoked potential amplitude, and lower tibial peroneal and femoral compound muscle action potential amplitudes, as well as slower tibial motor conduction velocity and prolonged peroneal distal latency, compared with the control group.

Conclusion
Sensory neuron and/or axonal affection have been demonstrated in the studied series of pediatric SMA patients suggesting that the pathological changes in SMA may also involve the sensory system.

Keywords:
electrophysiology, pediatric spinal muscular atrophy, sensory changes, spinal muscular atrophy

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Introduction

Spinal muscular atrophy (SMA) is a hereditary disease characterized by the degeneration and loss of motor neurons in the spinal cord and the brain stem [1,2]. It is caused by a genetic deficiency of a protein called survival motor neuron (SMN) protein. Reduced level of SMN protein leads to a catastrophic loss of motor neurons [3]. SPA type I patients exhibit weakness before 6 months of age and are unable to sit without support, whereas SMA II patients, between 6 and 18 months of age, are able to sit unsupported at some point in their clinical course [4–6]. Patients with evident peripheral sensory changes were not diagnosed as SMA based on the diagnostic criteria for infantile SMA [5]. Recently, experimental studies [7] revealed that SMA mice not only lost motor neurons over time but also lost the sensory neuron endings, which connect to motor neurons. In addition, several histological studies demonstrated axonal degeneration in sensory as well as motor nerves of SMA I patients [8–11]. Several studies have analyzed nerve conduction in SMA. Two studies [12,13] found no reduction in sensory nerve conduction velocity (SNCV) in any type of SMA, although one [12] reported that sural nerve responses were below detection in all SMA I patients. Others [9] reported axonal degeneration of the sural nerve as a part of the disease. Pathological changes in the somatosensory responses were also reported in pediatric SMA patients [14].

In light of these contradictory findings, the aim of the present study was to assess peripheral and central sensory abnormalities in pediatric SMA patients in a narrow age range.

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Aim of the work

The aim of the present study was to assess peripheral and central sensory abnormalities in pediatric SMA patients.

Materials and methods

The study included 40 pediatric SMA patients diagnosed on the basis of clinical history and typical electromyographic patterns. A total of 29 type I and 11 type II SMA patients were recruited from those attending the outpatient clinic of the Physical Medicine and Rehabilitation Department in El-Shatby Hospital, Faculty of Medicine, Alexandria University, Egypt. Patients were diagnosed as SMA I or SMA II according to the criteria established by the International SMA Collaboration Workshop of 1990 [15]. In addition, the study included 25 age-matched and sex-matched healthy pediatric participants, without any evidence of neuromuscular disorder, as controls. Before their inclusion in the study, the participants' parents signed informed consent. The study was approved by the local ethics committee.

Sensory, somatosensory, and motor electrophysiological studies were carried out for both groups. Electrophysiological study was carried out using Neuropack 2 electromyography apparatus from Nihon Kohden (Japan). Temperature of the room was adjusted for standardized results.

Sensory conduction study

Sensory nerve conduction study of the sural and median nerves was carried out and assessed peak latency (PL), sensory nerve action potential (SNAP) amplitude, and SNCV. All the procedures were carried out using pediatric surface electrodes and pediatric bipolar electrodes for stimulation.

SNAPs were evoked by the antidromic stimulation at the middle of the wrist and recorded using a ring electrode placed on the second finger for the median nerve. The SNAPs of the sural nerve were recorded by a stimulator positioned at a variable surface position, depending on the length of the leg, and from two electrodes placed below the lateral malleolus. All the SNAPs analyzed were the average of approximately 30 responses evoked by the supramaximal stimulation of the sensory nerve. The latency of sensory conduction was measured from the stimulus artifact to the positive peak of the SNAP, and the SNAP amplitude was measured from the positive to the negative peak.

Mixed posterior tibial somatosensory evoked potential

Mixed posterior tibial somatosensory evoked potential (SSEP) was carried out by stimulating the posterior tibial nerve and cortical recording. The cathode of the stimulating electrode was directed proximally. The recording was according to the international 10–20 system for international electromyographic electrode placement. The active electrode was placed on areas corresponding to the lower limbs, 2 cm behind Cz, namely Cz', and reference electrode was placed midway between Fpz and Fz, namely Fpz'. The stimulation site for the posterior tibial nerve was above and behind the medial malleolus. The ground electrode was placed between the stimulating and recording electrodes.

Using this montage, a signal-averaged polyphasic cortical potential was recorded from each site. The PL of P37 for lower limbs was measured in ms and the peak amplitude of the descending limb of the wave was measured in μV.

Motor conduction study

Motor conduction studies (MCS) of posterior tibial, deep peroneal, and femoral nerves were carried out for both groups. To evoke compound muscle action potentials (CMAPs), supramaximal electrical stimuli (0.2–0.3 ms) were delivered through a stimulator placed either over the posterior tibial nerve at the ankle and popliteal fossa or over the deep peroneal nerve at anterior ankle and below fibular neck. Femoral nerve motor study was carried out recording rectus femoris and stimulating femoral nerve below the inguinal ligament. Surface-recording electrodes were placed over the main bulk of the abductor hallucis muscles for recording CMAPs from the posterior tibial nerves and over the main bulk of the extensor digitorum brevis muscles for recording CMAPs from the deep peroneal nerves. Distal latency (DL) and CMAP amplitude of the studied motor nerves were also recorded. DLs were measured from the stimulus artifact to the initial negative deflection from baseline. The CMAP amplitudes were measured from the negative to the positive peak. In addition, motor conduction velocity (MCV) of tibial and deep peroneal nerves were assessed.

Needle electromyography

Needle electromyography of the tibialis anterior and gluteus medius muscles of both sides was carried out for the pediatric SMA patient group to confirm the diagnosis of SMA.

The nerve conduction parameters from SMA I patients (PL, SNAP, SNCV, DL, CMAP, and MCV)

were compared with those recorded from non-SMA participants less than or equal to 6 months of age, whereas nerve conduction parameters from SMA II patients were compared with controls between 7 months and 1 year of age.

Statistical analyses

Statistical analysis were carried out using IBM SPSS statistics for windows (version 20.0, Armonk, NY: IBM Corp.). The statistical significance level was set at *P* value less than 0.05. Descriptive statistics, including means, SDs, and median were calculated for each of the studied parameters. The raw data for each parameter were compared between the patient and control groups using Student's *t*-test for normally distributed variables, and the Mann–Whitney test for abnormally distributed variables. The Mann–Whitney *U*-test was used to compare the medians of all electrophysiological variables of SMA I patients and controls except sural PL and SNCV, median SNCV, tibial MCV, and CMAP amplitudes of peroneal and femoral nerves. Sural PL and SNCV, median SNCV, tibial MCV, and CMAP amplitudes of peroneal and femoral nerves of SMA I patients and controls were compared using *t*-test. The Mann–Whitney *U*-test was used to compare the medians of all electrophysiological variables of SMA II patients and controls except tibial MCV, which was compared between the two groups using the *t*-test. Differences were considered statistically significant at *P* value less than 0.05.

Results

SMA I patients had statistically significant lower sural ($P = 0.00$) and median nerve SNAP amplitudes ($P = 0.02$), with otherwise no statistical difference between the two groups regarding the mixed SSEP responses (Table 1). Regarding MCS parameters, SMA I patients had significantly lower peroneal and femoral CMAP amplitudes, slower tibial MCV ($P = 0.04$), and prolonged femoral and peroneal DL ($P = 0.03$). There was no difference between the two groups regarding other MCS parameters (Table 2).

On the other hand, SMA II pediatric patients had statistically significant lower sural SNAP amplitudes ($P = 0.02$), slower sural SNCV ($P = 0.02$), and lower mixed SSEP response amplitudes ($P = 0.03$) compared with controls (Table 3). Regarding MCS parameters, SMA II patients had significantly lower tibial ($P = 0.00$), peroneal ($P = 0.01$), and femoral CMAP amplitude ($P = 0.00$), as well as slower tibial MCV ($P = 0.001$), and prolonged peroneal DL ($P = 0.05$) compared with controls. There was no difference between the two groups regarding other electrophysiological parameters (Table 4).

Table 1 Comparison between spinal muscular atrophy I patients and control group regarding sensory conduction studies and somatosensory evoked potential variables

Parameters	SMA I (n = 29)	Control (n = 15)	Statistical test (P value)
Sural PL (ms)[a]			
Mean (SD)	2.24 (0.37)	2.3 (0.12)	−0.31
Median	2.22	2.3	0.76
Sural SNAP (μV)			
Mean (SD)	9.87 (4.96)	42 (16.16)	0.00
Median	11.00	42	0.00*
Sural SNCV (m/s)[a]			
Mean (SD)	33.55 (6.60)	34.40 (0.69)	−0.25
Median	32.60	34.40	0.80
Median PL (ms)			
Mean (SD)	2.20 (0.54)	2.36 (1.25)	69
Median	2.15	2.27	0.60
Median SNAP (μV)			
Mean (SD)	17.80 (11.74)	33.59 (18.99)	27
Median	14.80	34.30	0.02*
Median SNCV (m/s)[a]			
Mean (SD)	34.18 (6.48)	29.97 (9.49)	1.31
Median	33.15	32.10	0.20
Tibial SSEP latency (ms)			
Mean (SD)	29.31 (5.04)	32.14 (32.14)	51
Median	30.05	32.20	0.31
Tibial SSEP amplitude (μV)			
Mean (SD)	3.69 (1.44)	3.50 (0.82)	82
Median	4.20	3.50	0.53

PL, peak latency; SMA, spinal muscular atrophy; SNAP, sensory nerve action potential; SNCV, sensory nerve conduction velocity; SSEP, somatosensory evoked potential; [a]*t*-Test used for comparison; *Statistical significance level at $P \leq 0.05$.

Needle electromyography of tibialis anterior and gluteus muscles of both sides in SMA I patients showed profuse denervation potentials (positive sharp waves and fibrillation potentials) with drop out of motor units and polyphasic units on volition. SMA II patients showed profuse denervation potentials at rest with giant motor units and drop out on volition.

Discussion

Until recently, SMA was considered to be exclusively a disease of motor neurons. Sensory neuron involvement or axonal loss were not observed in most patients with SMA.

The present study assessed peripheral and central sensory conduction changes in pediatric patients with SMA type I and II. The studied SMA I patients had statistically significant lower sural and median nerve SNAP amplitudes, whereas SMA II patients had lower sural SNAP amplitudes and slower sural

Table 2 Comparison between spinal muscular atrophy I patients and control group regarding motor conduction studies variables

Parameters	SMA I (n = 29)	Control (n = 15)	Statistical test (P value)
Tibial DL (ms)			
Mean (SD)	3.09 (0.76)	2.61 (0.25)	149
Median	3.10	2.55	0.11
Tibial CMAP (mV)			
Mean (SD)	7.71 (7.97)	9.08 (3.52)	117
Median	7.05	8.83	0.46
Tibial MCV (m/s)[a]			
Mean (SD)	28.22 (3.17)	34.70 (9.39)	2.11
Median	28.20	33.00	0.04*
Peroneal DL (ms)			
Mean (SD)	3.75 (1.24)	2.62 (0.40)	18.5
Median	3.20	2.70	0.03*
Peroneal CMAP (mV)[a]			
Mean (SD)	0.38 (0.50)	2.39 (2.43)	2.438
Median	0.00	1.17	0.03*
Peroneal MCV (m/s)			
Mean (SD)	28.82 (3.03)	35.08 (10.416)	5
Median	27.65	33.30	0.28
Femoral DL (ms)			
Mean (SD)	3.18 (1.31)	2.14 (0.40)	70.5
Median	2.60	2.40	0.03*
Femoral CMAP (mV)[a]			
Mean (SD)	3.71 (3.47)	6.61 (1.90)	2.519
Median	3.17	6.33	0.03*

CMAP, compound muscle action potential; DL, distal latency; MCV, motor conduction velocity; SMA, spinal muscular atrophy; [a]*t*-Test used for comparison; *Statistical significance level at $P \leq 0.05$.

Table 3 Comparison between spinal muscular atrophy II patients and control group regarding sensory conduction studies and somatosensory evoked potential variables

Parameters	SMA II (n = 11)	Control (n = 10)	Statistical test (P value)
Sural PL (ms)			
Mean (SD)	2.63 (0.67)	2.52 (0.38)	58
Median	2.48	2.40	0.92
Sural SNAP (μV)			
Mean (SD)	8.67 (4.25)	15.81 (7.64)	22.5
Median	10.30	15.30	0.02*
Sural SNCV (m/s)			
Mean (SD)	34.49 (7.40)	43.21 (9.027)	22
Median	33.00	42.25	0.02*
Median PL (ms)			
Mean (SD)	2.04 (0.33)	2.76 (0.78)	4
Median	1.80	2.92	0.09
Median SNAP (μV)			
Mean (SD)	18.50 (26.33)	25.98 (4.92)	5
Median	8.00	26.80	0.15
Median SNCV (m/s)			
Mean (SD)	38.80 (10.38)	49.46 (10.95)	5
Median	37.00	52.60	0.15
Tibial SSEP latency (ms)			
Mean (SD)	33.66 (8.11)	32.14 (3.14)	27
Median	31.00	32.20	0.81
Tibial SSEP amplitude (μV)			
Mean (SD)	4.35 (0.55)	5.3 (0.4)	45.5
Median	4.00	5.3	0.03*

PL, peak latency; SMA, spinal muscular atrophy; SNAP, sensory nerve action potential; SNCV, sensory nerve conduction velocity; SSEP, somatosensory evoked potential; *Statistical significance level at $P \leq 0.05$.

SNCV compared with controls. This could possibly be due to axonal degeneration with the loss of fast conduction axons leading to low SNAP amplitude and slowing of SNCV. Previous reports have shown axonal degeneration of both large and small myelinated fibers of the sural nerve along with signs of Wallerian degeneration [11]. In agreement with our results, a study by Yonekawa *et al.* in 2013 [1] found reduced SNAP amplitude of the sural nerve in three of the five SMA I patients studied; however, no apparent reduction in SNAP amplitudes of median nerves was detected. In addition, they found that SNCVs were slower in the median and sural nerves of three SMA I patients compared with controls. Similarly, a study conducted by Schwartz and Moosa [12] in 1977 did not find measurable sural nerve responses in any of their SMA I patients, but the underlying mechanisms were not discussed. In contrast to our results, a study by Yonekawa *et al.* [1] in 2013 reported no sensory changes in SMA II patients, which could be attributed to the age of the studied SMA II patients – they studied SMA II patients aged more than 1 year, whereas the present work studied SMA II patients aged between 7 months and 1 year who might had more severe pathology. Meanwhile, a study by Yonekawa *et al.* [1] in 2013 reported only a single case of SMA II with axonal degeneration of the sural nerve (unpublished case). A study by Rudnik-Schöneborn *et al.* in 2003 [9] also reported clear evidence for a marked axonal loss of the sural nerve in patients with severe and classic SMA I, whereas patients with SMA II or III did not show peripheral nerve pathology. It was suggested that this might be related to the amount of SMN protein that seems to be sufficient to maintain sural nerve function in milder forms of SMA [9]. Similarly, a study by Ling *et al.* [16] in 2010 reported that sensory neurons and their afferents are affected by a deficiency in SMN protein leading to the degeneration of sensory axons in SMA patient.

The current study also demonstrated lower mixed SSEP response amplitudes of SMA II patients, suggesting the possibility of central sensory pathways affection or sensory neuron degeneration. Similarly, a study by Cheliout-Heraut *et al.* [14] in 2003 observed alterations of the somatosensory thalamocortical responses, as well as a delay in the central conduction time in pediatric SMA patients.

Many neurodegenerative diseases are thought to involve abnormalities of the sensory-motor synaptic

Table 4 Comparison between spinal muscular atrophy II patients and control group regarding motor conduction studies variables

Parameters	SMA II (n = 11)	Control (n = 10)	Statistical test (P value)
Tibial DL (ms)			
Mean (SD)	3.39 (0.76)	2.90 (0.81)	81.5
Median	3.50	2.80	0.17
Tibial CMAP (mV)			
Mean (SD)	3.48 (4.37)	16.33 (5.62)	4
Median	1.40	15.30	0.00*
Tibial MCV (m/s)[a]			
Mean (SD)	32.85 (6.29)	45.35 (8.12)	−3.778
Median	30.40	46.00	0.001*
Peroneal DL (ms)			
Mean (SD)	3.20 (0.70)	2.10 (0.52)	22
Median	2.90	2.05	0.05*
Peroneal CMAP (mV)			
Mean (SD)	0.61 (0.26)	4.22 (1.98)	6
Median	0.53	4.00	0.01*
Peroneal MCV (m/s)			
Mean (SD)	32.67 (1.53)	35.15 (13.65)	6
Median	33.00	37.50	0.21
Femoral DL (ms)			
Mean (SD)	2.46 (0.91)	2.93 (1.01)	41
Median	2.80	2.40	0.84
Femoral CMAP (mV)			
Mean (SD)	0.46 (0.33)	7.43 (1.22)	0.00
Median	0.37	7.33	0.00*

CMAP, compound muscle action potential; DL, distal latency; MCV, motor conduction velocity; SMA, spinal muscular atrophy; [a]*t*-Test used for comparison; *Statistical significance level at $P \leq 0.05$.

connections [17–19]. Several studies have demonstrated that sensory synaptic abnormalities can be detected in amyotrophic lateral sclerosis [20–23], and in a mouse model of amyotrophic lateral sclerosis [20,24]. In the studies of autopsied spinal cord tissues from the SMA type I patients, a reduction in synaptophysin-immunoreactivity has also been reported in the ventral horn of the spinal cord [16,25]. It was reported that SMA mice had weaker sensory-motor neuron synapse connections than do control mice, and that the pattern of weakness matched the developmental pattern of muscle weakness associated with the disease [7]. Accordingly, it could be suggested that SMA may also affect sensory neurons. Other studies demonstrated that sensory motor synapse loss occurs in SMA but as a consequence, not a cause, of motor neuron dysfunction [26].

In the current study, SMA I and II pediatric patients exhibited low CMAP amplitudes of motor nerves compared with controls. This reduced CMAP amplitude is the main electrophysiological finding in patients with motor neuron degeneration, but usually with a normal or only minimally reduced MCV [27,28]. It suggests diffuse loss of ventral horn motor neurons in SMA I and SMA II patients. Slowing of the MCV with prolonged DL was also found in both SMA I and II patients in the present study. These slower MCVs could be due to the demyelination or loss of fast-conducting myelinated axons, because loss of myelinated peripheral axons can reduce conduction velocity by up to 40% [29]. These results run in accordance with those of several previous studies [13,30]. Chien and Nonakal [8] in 1989 reported that the number of large myelinated axons was markedly decreased in almost all intramuscular nerve bundles in the biopsies of SMA I patients. This reduced MCV in the studied SMA I and II patients may reflect loss of spinal motor neurons followed by Wallerian degeneration of axons. In contrast to the results of the present study, a study by Yonekawa *et al.* [1] in 2013 found normal MCVs in SMA II and suggested that the loss of large diameter myelinated fibers is more severe in SMA I patients. Again, this contradictory result could be attributed to young age of SMA II patients in the current study, and to the possibility that SMA II in our patients might be of more severe form than those studied by Yonekawa and his colleagues.

Much information about histopathologic changes of the central and peripheral nervous system in SMA has been retrieved from post-mortem studies, and has often been limited to patients with severe SMA I. Most studies reported on axonal degeneration affecting large and small myelinated fibers of the sural nerve along with scattered ovoids as signs of Wallerian degeneration [11,31,32]. It was reported that peripheral motor nerves degenerate as a result of anterior horn cell loss. However, as neuronal chromatolysis was not limited to the spinal cord but also evident in Clarke's column and the thalamus at least in some patients, Werdnig–Hoffmann disease was regarded as a multisystemic disease involving both motor and sensory systems [33].

Conclusion

Sensory changes have been detected in the studied series of pediatric SMA (type I and II) patients. Reduced SNAP amplitudes, slower SNCV, and low SSEP amplitude suggest that sensory neuron degeneration, sensory-motor synapses loss, and/or axonal degeneration of sensory nerves, especially large myelinated fibers, can occur in pediatric SMA patients. This process probably develops as a part of the pathogenesis of SMA but might be slower than motor neuron degeneration.

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Conflicts of interest

There are no conflicts of interest.

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