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FOR PEOPLE LIVING WITH **POMPE DISEASE,**

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MOBILITY CAN'T TAKE A DAY OFF

People living with late-onset Pompe disease (LOPD) face obstacles that may challenge their well-being and livelihood. A 2011 Dutch survey of LOPD patients showed[1,2]:

40% (n=32/80) stopped working due to their disease

85% required support from more than 1 caregiver to help with household tasks such as cleaning and grocery shopping

As Pompe disease progresses, it can lead to irreversible loss of mobility, respiratory function, and ability to perform daily activities, as well as premature death.[3,4] In a 2007 international study[5]*:

42% of patients with LOPD depended on a wheelchair

46% required respiratory support

Regular evaluation is recommended in patients with Pompe disease to assess for disease progression and to understand the impact on daily activities and lifestyles.[3]

Explore Pompe disease and its impact on patients at

MORETOPOMPE.COM

*Mean disease duration of patients studied was 11 years.

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Age-related sensory neuropathy in patients with Spinal Muscular Atrophy type 1

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Age-related sensory neuropathy in patients with Spinal Muscular Atrophy type 1

Abstract

Introduction: Spinal muscular atrophy type 1 (SMA 1) is a devastating motor neuron disorder that leads to progressive muscle weakness, respiratory failure and premature death. Although sensory electrophysiological changes have been anecdotally found in pediatric SMA 1 patients, the age of onset of sensory neuropathy remains unknown. *Methods:* Sensory nerve conduction studies (SNCS) of the median and sural nerves were performed in 28 consecutive SMA 1 patients of different ages. Sensory nerve conduction velocities (SNCV) and sensory nerve action potential (SNAP) amplitudes recorded in these patients were compared with those obtained from 93 healthy subjects stratified by age. *Results:* SNAP amplitudes decreased with increasing age in the sural and median nerves, without any significant difference between upper and lower limbs. *Discussion:* Our data suggest that sural and median nerve SNAP amplitudes are normal in younger patients, while an axonal neuropathy appears in older ones.

Key Words:

SMA 1

SNAP

Median Nerve

Sural Nerve

Sensory Neuropathy

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INTRODUCTION

Spinal muscular atrophy (SMA) is a progressive neuromuscular disorder characterized by degeneration of spinal cord alpha motor neurons with progressive muscle atrophy and weakness[1].

Advances in the treatment of SMA, have resulted in longer life expectancy, new therapeutic and neurophysiological research, and a better clinical and neurophysiological understanding of this disease. Although SMA has been classified as a lower motor neuron disease, there are other neurological cells and other tissue types that are selectively vulnerable to reduced levels of SMN protein. This explains why SMA, especially in the more severe forms, may show multi-organ involvement[2-4].

Experimental animal studies suggest that early dysfunction of sensory neurons and disruption of sensorimotor circuits could be involved in the pathophysiological mechanism of SMA 1[5-12]. Axonal degeneration in sensory nerves of SMA 1 patients was demonstrated by both histological[13-16] and electrophysiological studies[17-21]. However, it is still not clear whether sensory neuropathy in SMA 1 is an age and/or length-dependent process.

The aim of this study is to evaluate the sensory nerve conduction velocities (SNCVs) and sensory nerve action potential (SNAP) amplitudes of nerves of different lengths in patients with SMA 1 aged 0 to 16 years, and to compare the results with those from healthy subjects stratified by age.

METHODS

All patients enrolled in this prospective study had a homozygous deletion of exon 7. IRB/local ethics committee approval was obtained, and the parents of all enrolled study subjects provided informed consent. At the time of our examination none of the recruited patients was included in an experimental treatment trial and no targeted genetic therapies

for SMA were available. Other possible etiologies of sensory neuropathy were excluded. A medication history was obtained from all study participants. All secondary neuropathies were ruled out through a nutritional evaluation with the support of specific laboratory studies that excluded any metabolic abnormalities. Glucosec values were always normal and vitamin deficiencies were excluded in all subjects. Patients with feeding and swallowing dysfunction were supported with percutaneous gastrostomy tubes.

Sensory nerve conduction studies were performed in all our patients and in healthy subjects. Age groups were chosen to make the statistical analysis more homogeneous. Inclusion criteria for healthy subjects were no abnormal neurological signs or symptoms and normal laboratory tests.

Sensory nerve conduction studies

SNAPs were recorded from the right sural and median nerves. All procedures were carried out using pediatric surface recording electrodes and pediatric bipolar stimulating electrodes. Skin temperature was $\geq$ 34°C. For the median nerve, the SNAP was recorded by a ring electrode on the second phalanx of the third finger performing antidromic stimulation of the nerve at the wrist. Sural SNAP was recorded by two electrodes placed below the lateral malleolus, stimulating antidromically over the calf, immediately lateral to the midline. The active recording electrode and the reference electrode were placed 2 cm apart, with the first placed just behind the superior edge of the lateral malleolus. Each SNAP analyzed was obtained by the average of approximately 30 responses evoked by a supramaximal stimulation of the sensory nerve. SNCV was measured using the SNAP onset latency. SNAP amplitude was measured from baseline to negative peak.

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Statistical analysis

SNAP amplitudes and SNCV values were described as median and interquartile range. Patients with SMA 1 were compared with healthy subjects by age group. Nonparametric Mann-Whitney U-Test for independent samples was used for the comparisons. Statistical significance was set at $p<0.05$.

RESULTS

Twenty-eight SMA 1 patients with 2 copies of the *SMN2 gene* were enrolled (mean age 6.73±4.3 yrs, 20 females and 8 males), consisting of 3 with SMA 1 subtype 1a, 16 with 1b, and 9 with 1c. No recordable SNAPs were obtained from the sural nerves in 2 patients (both age 12 years) and from both the median and sural nerves in 2 patients (ages 14 and 16 years).Healthy subjects had a mean age 7.03±4.9 yrs (58 females and 35 males). See Table.1 for neurophysiological data.

While in the 2 lower age subgroups (6-24 months and 3-6 years) no statistically significant differences were found between SMA 1 patients and healthy controls, in the third group (7-16 years) the amplitude of the SNAP was significantly lower in SMA 1 patients than in healthy controls for both the median and sural nerves. In this subgroup, we also found a lower SNCV in the sural nerve in patients than in healthy controls (Figure.1).

At the time of the SNCS, 17 patients required invasive respiratory care with tracheostomy, 8 patients required nocturnal ventilation with bilevel positive airway pressure, and 3 patients required no respiratory support.

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DISCUSSION

Our study reveals a connection between the development of an axonal sensory neuropathy and increasing of age in SMA 1 patients.

The data obtained from our study were compared with an external reference that reports the nerve conduction values in normal individuals (data not shown).[22] This comparison suggests that nerve amplitude remains above minimum normal values until 6 years of age and declines in older children, while nerve velocity decreases beginning at 3 years of age.

Although there is some evidence of sensory involvement in SMA 1, published data are scarce and often highly variable. In a sural nerve conduction study in seven unrelated children with SMA 1 the data obtained appeared to be more consistent with an axonal neuropathy. [16] Five out of seven patients showed also an abnormal sensory conduction velocity. Different degrees of axonal loss involving the sural nerves were observed which was particularly severe in four patients. Our results, showing an axonal sensory neuropathy in SMA 1 patients, also agree with what has been found in mouse models of this disease. Sensory neurons cultured from a mouse model of SMA showed defects in neurite outgrowth and growth cone morphology, together with a reduction of beta-actin protein and mRNA in growth cones.[8] Moreover, in mouse models of SMA, sensory neurons were smaller than in control mice, consistent with a reduced overall size of the dorsal root ganglia (DRG).[23] SMA mice also showed a reduction of myelinated dorsal root axons[9] and sensory fibers passing into the ventral horn.[7] Structural defects of sensory neurons have been found to be associated with defects at the level of sensory-motor synapses.[24] Overall reduction of sensory synapses was mostly due to a reduction of vGlut1-positive synapses which primarily originate from proprioceptive neurons. This central feature of sensory-motor involvement appears to be a conserved feature of the disease, since it was observed in different SMA mouse models, including the commonly

used Taiwanese and delta7 models.[9,23] All these data suggest that sensory-motor connectivity defects reported in SMA mice may correspond to the sensory-motor pathology observed in patients.

The small sample of older subjects included in this study represent a limitation of this paper. In addition, particularly in the group of patients with tracheostomy, is not clear whether the sensory nerve abnormalities are primarily due to the SMN protein deficiency or to a secondary neuropathy due to ICU complications. Further studies may clarify the trend of sensory neuropathy in SMA 1 patients during age development by studying the trends of SNAPs in the same patients over time.

A clinical trial of intrathecal AAV9 in patients with spinal muscular atrophy type 2 was recently placed on hold because of DRG toxicity in nonhuman primates. [25] The clinical significance of the DRG inflammation observed in this pre-clinical animal study was not clear and was not seen in prior animal studies with AVXS-101. DRG inflammation may be associated with sensory symptoms. [25]

CONCLUSIONS

Our study shows that sural and median nerve SNAP amplitudes are normal in younger SMA 1 patients, while an axonal neuropathy appears later. Since sensory nerves in both upper and lower limbs are involved, our data do not statistically support a possible length-dependent process. However, the link between axonal damage and increasing age was supported by the absence of sural SNAPs in two older patients and of the median and sural SNAPs in two others. Monitoring SNAP amplitudes could therefore provide further information on the evolution of the disease.

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The neurophysiological assessment of the peripheral somatosensory system should be included in the evaluation of patients with SMA 1. This could aid the development of new therapeutic strategies that will benefit and support all SMA patients.

List of acronyms or abbreviations:

SMA 1 (Spinal muscular atrophy type 1)

Sensory Nerve Conduction Study (SNCS)

Sensory Nerve Action Potential (SNAP)

Sensory nerve conduction velocity (SNCV)

Dorsal root ganglia (DRG)

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Figure.1 SNAP amplitudes and SNCV values by age. Linear trends for normal and SMA-1 patients are displayed with dotted lines.

Table.1 Median and IQ range of Sural and Medial nerve data.

		Sural Nerve		***Median Nerve***	
	Number	*Amplitude (μV)*	*SNCV (m/s)*	*Amplitude (μV)*	*SNCV (m/s)*
		mean±SD	*mean±SD*	*mean±SD*	*mean±SD*
		Median (IQ range)	*Median (IQ range)*	*Median (IQ range)*	*Median (IQ range)*
6-24 months					
SMA 1	9	16.9 (14.3-20.1)	48.7 (47.5-53.3)	45.1 (41.5-46.8)	46.7 (44.1-46.9)
Normative Data	23	15.0 (12.9-17.8)	46.4 (42.2-30.0)	29.7 (22.5-42.7)	47.1 (39.4-50.0)
p		0.133	0.409	0.034	0.742
3-6 years					
SMA 1	10	17.7 (15.0-23.8)	50.0 (49.6-51.4)	48.9 (44.5-56.9)	51.4 (49.8-54.8)
Normative Data	26	18.1 (14.8-23.8)	52.5 (46.7-59.3)	49.1 (31.7-61.9)	50.0 (44.8-54.1)
p		0.715	0.214	0.958	0.117
7-16 years					
SMA 1	9	3.9 (0-8.5)	44.4 (0-47.0)	17.0 (7.3-21.0)	63.8 (25.0-57.0)
Normative Data	44	22.6 (17.3-26.3)	52.4 (49.1-55.6)	43.8 (34.0-55.6)	51.1 (47.2-55.4)
p		**<0.01**	**<0.01**	**<0.01**	0.666

Abbreviations: SMA 1 (Spinal Muscular Atrophy type 1); SNCV (Sensory Nerve Conduction Velocity). Bold font indicates p<0.05

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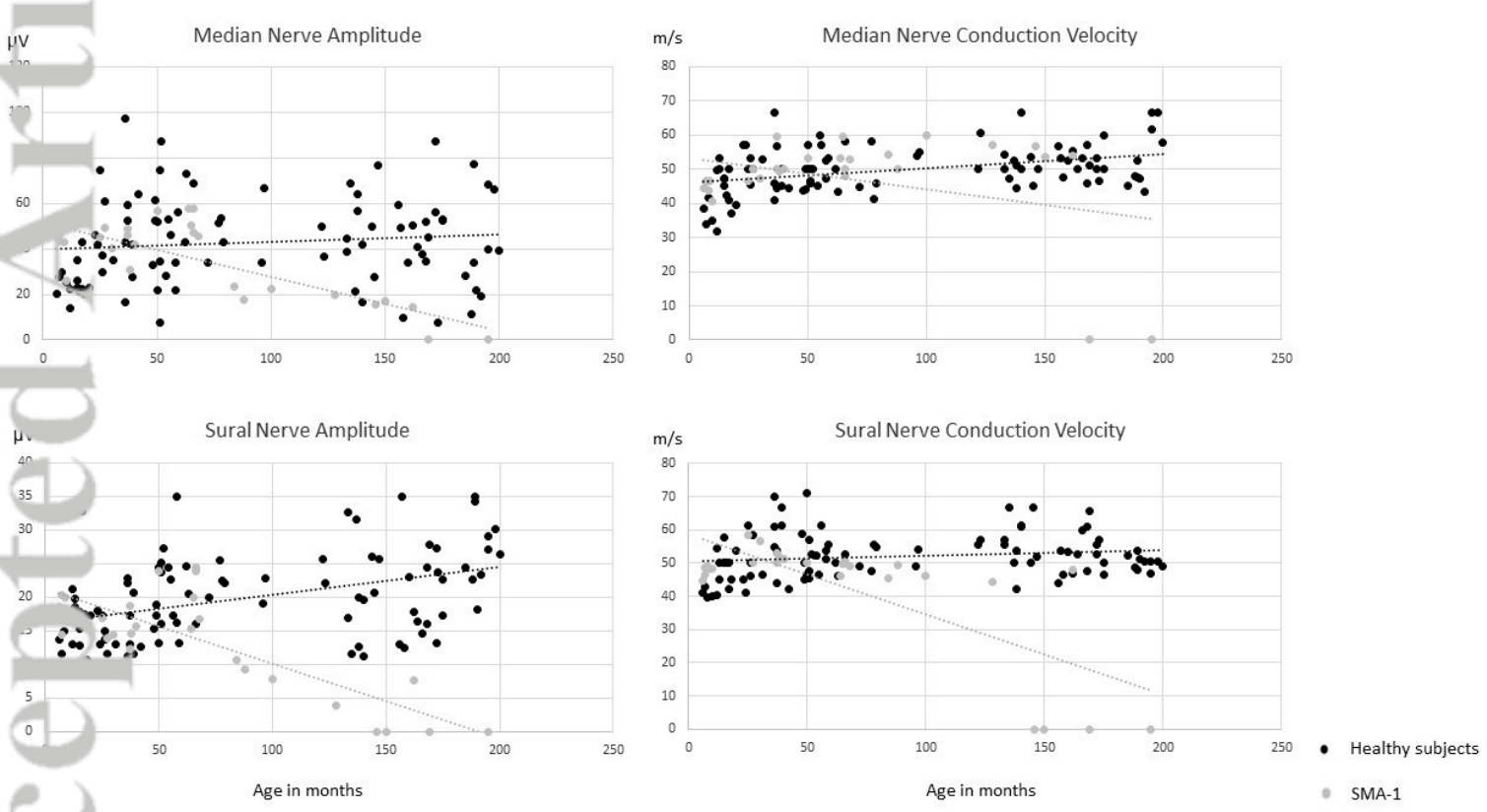

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