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■ Case report ■

Two cases of spinal muscular atrophy type 1 with extensive involvement of sensory nerves

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= Abstract =

Spinal muscular atrophy (SMA) is an autosomal recessive disease characterized by diffuse proximal and distal weakness due to deletion of the survival motor neuron (SMN) gene localized on chromosome 5 (5q11.2-13.3). SMA has been considered as a pure lower motor neuron disorder, and a definitive diagnosis can be established by molecular genetic testing. Here, we describe two patients with severe hypotonia and frequent aspirations at early infancy. Nerve conduction studies showed more extensive sensory involvement in these patients diagnosed to have SMA by genetic study than in classical cases of SMA. To the best of our knowledge, this is the first report of SMA Type 1 with sensory nerve involvement in Korea. **(Korean J Pediatr 2008;51:1350-1354)**

Key Words : Spinal muscular atrophy, Sensory nerve

Introduction

Spinal muscular atrophy (SMA) is due to abnormal continuation of fetal apoptosis of spinal anterior horn cells. A defect of SMN (survivor motor neuron) gene, which is located at chromosome 5 (5q11.2-13.3), causes the disease. Symmetric proximal muscle weakness begins during the fetal period and progresses through infancy and childhood[1)]

Most people with SMA present with motor symptoms such as muscle atrophy and respiratory distress due to the SMN gene defect. Clinically, the examination of children with SMA has revealed no obvious clinical sensory involvement in several studies, and the early pathologic studies done on SMA did not show any evidence of involvement of the sensory system[2)]. However, a few patients with sensory nerve involvement have been reported[3)]. We observed 2 patients with type 1 SMA with extensive sensory nerve involvement and, to the best of our knowledge, this is the first report of a case in Korean children.

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Case report

Patient 1

A 4-month-old girl was transferred to Konkuk University hospital because of severe hypotonia. She was born with a birth weight 2,100 g at 38 weeks and 5 days of gestational age. Her Apgar score was 7 at 1 minute and 9 at 5 minutes. She was a child of nonconsanguineous parents. After birth, she was admitted for a workup examination of intrauterine growth retardation, but discharged because no specific abnormality was observed. There was no history of early death or neurological disease in either parents family.

At the age of 4 months, she visited a local pediatric clinic because she could not control her head. She looked alert, showed social smiling and babbling, and could contact her eyes with her mothers eyes, but her posture was severely hypotonic. There was no sign of ophthalmoplegia or of equinovarus. Deep tendon reflexes were absent. Upper extremity power was grade 3 and lower extremity power was grade 2. Tongue fasciculation was observed. Her serum creatinine kinase level was 195 U/L (reference value: 5-130 U/L). Nerve concuction study showed decreased lower extremity

motor nerve compound muscle action potential and delayed conduction velocity. Abnormal spontaneous potentials, polyphasic motor unit action potentials, and reduced recruitment patterns were noted in needle electromyography of her upper and lower extremities. On the electrodiagnostic study(Medelc Synergy, Oxford Ltd., UK), sustained denervation potential suggested an anterior horn cell disease, including SMA. However, because of sensory nerve conduction abnormality, there was some possibility of sensory motor neuropathy (Table 1-1, 1-2). Genetic diagnosis revealed a deletion of the exon 7 and 8 of SMN-T (telomeric copy of survival motor neuron) and NAIP-T (telomeric copy of neuronal apoptosis inhibitory protein) of the DNA from her peripheral blood. Her respiration had been progressively distressed. Sucking power had become weaker.

This infant underwent a gastrostomy and was supported by noninvasive pressure ventilation as needed. With satisfactory gastrostomy feeding, her weight increased considerably. However, she suddenly vomited and became feverish. She died from aspiration pneumonia at the age of 13 months. Consent for an autopsy was not obtained.

Patient 2

A 49-day-old boy visited our outpatient clinic because of inactivity and poor sucking. He was born without any perinatal problems with a birth weight of 3.01 kg at 40 weeks of gestational age. He was the first child of nonconsanguineous parents. His family history was negative for neuromuscular disorders. Since the age of 1 month, his motor activity and sucking power had decreased. He looked alert and had a normal cranial nerve function. He showed hypotonic posture. Upper extremity power was grade 3 and lower

Table 1-1. Electrophysiologic Study of Patient 1 at Her Age of 4 Months

	Stimulation site	Lat. (ms)	Amp. (mv)	NCV (m/s)
Motor Nerve				
R Median (APB)	Wrist/Elbow	3.4/6.95	0.5/0.4	21.1
		(1.6-2.2)*	(37-47.7)*	(3.5-6.9)*
R Ulnar (ADM)	Wrist/Elbow	no response/no response		
		(1.1-3.2)*	(2.5-7.4)*	(3.5-50)*
R Peroneal (EDB)	Ankle/FH	2.5/5.2	0.3/0.3	34.1
		(1.7-2.4)*	(1.6-8)*	(32.4-47.7)*
R Tibial (AH)	Ankle/Knee	3.6/6.3	0.3/0.1	38.9
		(2.46±0.34)†		(39.9±3.89)†
R Tibial (AH)	Ankle/Knee	3.65/7.3	0.2/0.1	26
Sensory Nerve				
R Median	Wrist	1.45	3.4	34.5
		(1.5-2.3)*	(13-52)*	(36.3-41.9)*
R Superficial peroneal	Lateral leg	no Response		
		(1,7-2.3)*	(9-10)*	
R Sural	Calf	no Response		
		(1,7-2.3)*	(9-10)*	

Abbreviations : Lat, latency; Amp, amplitude; NCV, nerve conduction velocity; F, F wave; L, left; R, right; B, both; APB, abductor pollicis brevis; ADM, abductor digiti minimi; AH, abductor hallucis; EDB, extensor digitorum brevis; FH, fibular head
*reference value (Kimura), †reference value (Shin J. Oh)

Table 1-2. Electrophysiologic Study of Patient 1 at Her Age of 4 Months

Muscles	Spontaneous activity*		MUAP	Recruitment pattern
	Fib	PSW		
Gastrocnemius, right	3+	3+	polyphasic	reduced
Flexor carpi radialis, right	3+	3+	polyphasic	reduced
Tibialis anterior, right	3+	3+	polyphasic	reduced

Abbreviations : Fib, fibrillations; PSW, positive sharp waves; MUAP, motor unit action potential
*grading of abnormal spontaneous activities (0 : no abnormal spontaneous activities, 1+ : persistent/unsustained single trains in at least two muscle regions, 2+ : moderated numbers in three or more muscle areas, 3+ : many in all muscle regions, 4+ : baseline obliterated with abnormal spontaneous activities on all muscle regions)

extremity power was grade 2 symmetrically. There were no deep tendon reflexes. Tongue fasciculation was observed. His serum creatinine kinase level was 575 IU/L. There were abnormal spontaneous activities on electromyography. In a motor nerve conduction study, there was no compound muscle action potential in the left median and right common peroneal nerves. Furthermore, reduced amplitudes and delayed conduction velocities were noted in the right ulnar and both tibial nerves. On the electrodiagnostic study (Medelc Synergy, Oxford Ltd., UK) sensory nerve action potentials were found in the right median, left superficial peroneal, and both sural nerves (Table 2-1, 2-2). SMA type 1 was confirmed by detecting the deletion of exons 7 and 8 of the SMN gene.

At the age of 4 months, he could not control his head. His respiration was progressively distressed. He was admitted with respiratory distress and frequent aspiration. On examination, he showed a bell-shaped chest, weak cry, and areflexia. He is now supported by a mechanical ventilator.

Discussion

SMA is one of the most common genetic neuromuscular diseases, after Duchenne muscular dystrophy. It is autosomal recessive inherited and is caused by the loss of the telomeric copy of the survival motor neuron gene (SMN1) on human chromosome 5q13[2, 4]. Expression of the SMN gene is prevalent in many kinds of neurons, but motor neurons are exclusively affected in SMA. These motor neuron defects cause the pathologic change of SMA[1, 5].

Classic infantile SMA was believed to be a purely motor disorder, affecting neurons of the spinal anterior horn and nuclei of the lower cranial nerves[6]. In the early reports, no sensory abnormalities were found in this disease[7, 8]. However, a few patients with pathologic evidence of sensory involvement have been reported [9, 11]. Subsequently, 6 cases of SMA with pathologically proven sensory nerve involvement[3] were reported. The authors of that report reviewed the pathologic results of 9 autopsied SMA patients. At that time, molecular diagnosis was not available. Thus, they confirmed the diagnosis of SMA by the demonstration of the anterior horn cell loss seen on autopsy of those patients. Of the 9 patients, 6 showed pathological changes in sensory pathways [3].

Recently, another group reported that, in 7 unrelated infants

Table 2-1. Electrophysiologic Study of Patient 2 at His Age of 2 Months

	Stimulation site	Lat. (ms)	Amp. (mv)	NCV (m/s)
Motor Nerve				
R Median (APB)	Wrist/Elbow	no response/no response		
R Ulnar (ADM)	Wrist/Elbow	2.9/4.65	0.6/0.4	45.7
R Peroneal (EDB)	Ankle/FH	no response/no response		
R Tibial (AH)	Ankle/Knee	3.55/6.9	0.1/0.1	29.9
Sensory Nerve				
R Median	Wrist	no response		
R Ulnar	Wrist	2.25	2.6	24.3
R Sup. peroneal	Lateral leg	3.6	19.4	
R Sural	Calf	no response		

Lat, latency; Amp, amplitude; NCV, nerve conduction velocity; F, F wave; L, left; R, right; B, both; APB, abductor pollicis brevis; ADM, abductor digiti minimi; AH, abductor hallucis; EDB, extensor digitorum brevis; FH, fibular head

Table 2-2. Electrophysiologic Study of Patient 2 at His Age of 2 Months

Muscles	Spontaneous activity*		MUAP	Recruitment pattern
	Fib	PSW		
Gastrocnemius, left	2+	2+	Polyphasic	Reduced
Vastus medialis, left	3+	3+	Polyphasic	Reduced
1st dorsal interossei, left	3+	3+	Polyphasic	Reduced

Abbreviations : Fib, fibrillations; PSW, positive sharp waves; MUAP, motor unit action potential
*grading of abnormal spontaneous activities (0, no abnormal spontaneous activities; 1+, persistent/unsustained single trains in at least two muscle regions; 2+, moderated numbers in three or more muscle areas; 3+, many in all muscle regions; 4+, baseline obliterated with abnormal spontaneous activities on all muscle regions)

with SMA type 1, axonal degeneration of the sural nerve was noted[6]. The diagnosis of SMA was confirmed by the presence of a homozygous deletion of the SMN1 gene in all patients[6]. There was a marked axonal loss of the sural nerve in the patients with severe and classic SMA type 1 that was confirmed electrophysiologically, by light and electron microscopy, and by morphometry[6]. Patients with SMA type 2 or 3 did not show peripheral nerve pathology. The amount of SMN protein seems to be sufficient to maintain sural nerve function in milder forms. There is another report of 2 patients with SMA type 1 whose nerve conduction study and electromyography suggested more extensive sensory involvement than classically described with SMA[2].

In our patients, we strongly suggested the diagnosis of SMA type 1 on clinical impression. However, electromyography and nerve conduction study aroused the possibility of motor sensory neuropathy. Molecular genetic studies confirmed the diagnosis of SMA in our patients. We did not perform sural nerve biopsies, because conventionally, it is not necessary for the workup examination of SMA.

In the formerly reported 2 cases, 1 patient did not show a deletion of the SMN1 gene[2]. There might be some possibility of congenital neuropathies. The congenital axonal neuropathies have phenotypes that can be indistinguishable clinically from children with infantile SMA[2]. They have conventionally been distinguished from SMA by the presence of significant sensory involvement on biopsy and electromyography[2]. Now some SMA patients, including ours, for whom diagnosis was confirmed by molecular genetics studies, have shown sensory peripheral nerve involvement by pathologic or electrophysiological study. Thus, sensory involvement is not an exclusion factor in SMA. It has been suggested that there might be a continuous diagnostic spectrum between congenital neuropathies and SMA type1 [2].

It has been proposed that a lack of the SMN1 gene alone can be responsible for peripheral nerve involvement, as no large deletion involving the NAIP gene and multicopy markers was found in 1 patient who had sensory involvement[6]. However, unless the structure of the SMA region on chromosome 5q is not entirely identified, further genotypephenotype correlations remain speculative[6].

As in our patients, the question of whether infantile SMA can be indistinguishable from hereditary motor and sensory neuropathy has become of increasing interest after reports of SMA clinically similar to congenital amyelination or hypomyelination[12]. In patients in whom electrical stimulation yields no recordable action potentials, differential diagnosis includes congenital hypomyelination as well as congenital axonal neuropathy. Delayed conduction velocities can be caused not only by demyelination, but also by relevant axonal loss[6]. As motor and sensory nerve action potentials may be reduced or absent in peripheral neuropathies and in SMA with sensory involvement, it is sometimes difficult to differentiate these entities based on electrophysiological findings[6]. Recently, molecular genetic testing for the SMN gene has been much developed and the diagnostic dilemma from the overlapping phenotypes of congenital axonal neuropathy and SMA type I is usually resolvable[2]. However, because the usual SMN gene mutation is not detectable in 10% of patients with SMA, there is still some diagnostic uncertainty[2]. Therefore, if the SMN gene defect is not found in clinically indistinguishable cases of peripheral neuropathy and SMA type 1, the diagnosis is difficult.

We propose that genetic diagnosis should be performed if clinical symptoms suggest the possibility of SMA, even though sensory deficits are shown in the electrophysiological or pathologic studies.

한 글 요 약

광범위한 감각신경 침범을 동반한 척수성 근위축증 2예

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척수성 근위축증은 상염색체 열성으로 유전되며 사지 및 몸통 근위부와 원위부의 광범위한 근력약화를 특징으로 한다. 5번 염색체 장완(5q11.2-13.3)에 위치한 survival motor neuron (SMN) 유전자의 결손이 그 원인이다. 척수성 근위축증은 순수하게 운동신경만 침범하는 것으로 알려져 있다. 분자유전학적 방법으로 유전자의 결손을 증명하므로써 진단할 수 있다. 저자들은 아주 이른 영아시기부터 심한 근긴장도 저하와 잦은 폐흡인을 보였고, 분자유전학적 검사로 척수성 근위축증을 진단한 2명의 환아에서 신경전도 검사상 광범위한 감각신경을 침범한 경우를 경험하여 보고하는 바이다. 본 증례는 감각 신경을 침범한 척수성 근위축증에 대해 국내에서는 첫번째 보고로 생각한다.

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