구척수근위축증에서 감각신경병의 단면적 및 종적 연구

명지병원 신경과, 이화여자대학교 의학전문대학원 신경과학교실*,
연세대학교 의과대학 신경과학교실**, 선우&조 신경과***

김지영 · 박기덕* · 김승민** · 선우일남***

– Abstract –

Cross-sectional and Longitudinal Features of Sensory Neuropathy in Bulbospinal Muscular Atrophy

Jee Young Kim, M.D., Kee Duk Park, M.D.*, Seung-Min Kim, M.D., Ilnam Sunwoo, M.D.*****

Department of Neurology, Myongji Hospital
*Department of Neurology, Ewha University School of Medicine**
*Department of Neurology, Yonsei University School of Medicine***
*Sunwoo & Cho Neurology Clinic****

Objectives: Bulbo-spinal muscular atrophy (BSMA) is an inherited motor neuronopathy, but it is known that subclinical sensory neuropathy can be found. The objective of this study is to clarify the features of sensory neuropathy by cross-sectional and longitudinal studies.
Method: We analyzed the clinical and electrodiagnostic data of 41 BSMA patients who were genetically confirmed. Follow-up studies were performed in 10 patients among them.
Results: Of 41 patients, 11 complained of sensory symptoms (26.8%), such as numbness or paresthesia of distal extremities. However, sensory neuropathy was observed in 23 patients (56.1%) with nerve conduction study (NCS). Reduced amplitude of action potentials was the most remarkable finding of the group with sensory neuropathy. For 10 patients with follow-up NCS, the mean follow-up interval was 8 years. There was no significant temporal change between the first and the follow-up sensory NCS.
Conclusion: Subclinical sensory neuropathy was found in 56.1% of BSMA patients. The longitudinal study shows that subclinical sensory neuropathy in BSMA may not progress over time.

Key Words: Bulbospinal muscular atrophy, Neuronopathy, Sensory, Action potentials

INTRODUCTION

Bulbospinal muscular atrophy (BSMA) is well-known as inherited motor neuronopathy, characterized by slowly progressive proximal and bulbar muscular weakness and atrophy. It usually begins between late thirties and early forties, with tremor, cramp or fasciculation, especially in perioral area. Although most BSMA patients do not

Address reprint requests to **Jee Young Kim, M.D.**
Department of Neurology 55, Hwasu-ro 14beon-gil, Deogyang-gu, Goyang-si, Gyeonggi-do, Korea
TEL: 82-31-810-5446, FAX: 82-31-969-0500, E-mail: nrkjy55@gmail.com
투고일: 2014년 3월 26일, 1차 수정일: 2014년 4월 9일, 2차 수정일: 2014년 4월 12일, 게재확정일: 2014년 4월 12일

complain sensory symptoms, it is reported that subclinical sensory neuropathy can be found.[1-5] However, the pathomechanism and characteristics of sensory neuropathy has not been clear.

Previous studies showed the electrodiagnostic features for sensory neuropathy of BSMA.[1-5] However, most of reports were based on the cross-sectional study and did not describe the sequential change of electrodiagnostic features. The aim of this paper is to clarify the characteristics of sensory neuropathy in BSMA patients who were genetically confirmed through cross-sectional and longitudinal studies.

MATERIALS AND METHODS

A total of 41 patients (36 families) with the diagnosis of BSMA confirmed by genetic analysis were included in this study. Genetic test was performed by polymerase chain reaction for the detection of the number of CAG triplet repeats in the androgen receptor (AR) gene. Their clinical and electrodiagnostic data were retrospectively analyzed.

Motor and sensory nerve conduction studies (NCS) were performed by using a standard method with surface electrodes. In motor study of upper extremity, the median and ulnar nerves were stimulated sequentially at wrist, elbow and axilla, recording over the abductor pollicis brevis and abductor digiti quinti muscles with the belly-tendon method. In motor study of lower extremity, the peroneal and tibial nerves were stimulated sequentially at ankle and knee, recording over the extensor digitorum brevis and abductor hallucis muscles. In sensory study of arm, the median and ulnar nerves were stimulated at the second finger for median and the fifth one for ulnar recording over the wrist, elbow and axilla with an orthodromic method. Sensory nerve action potential (SNAP) values of the finger to wrist segment were used for statistical analysis. In sensory study of leg, sural nerve was stimulated at the posterior-lateral calf, recording over posterior to the lateral malleolus with an antidromic method. The electrodiagnostic study was performed in at least one arm and leg in all of 41 patients. Thus a total of 164 motor nerves and 123 sensory nerves were examined. Follow-up NCS were performed in 10 patients among them. Amplitude of the motor and sensory action potentials was measured by peak-to-peak method. The measured amplitude and conduction velocity (CV) were defined as abnormal if the value were less than 2 standard deviations of normal values. Statistical analysis was performed using a SPSS 14.0 software package. The result was considered statistically significant if a p-value was found to be less than 0.05.

RESULTS

The clinical and electrodiagnostic data of 41 patients (36 families) were analyzed. Among them, 4 subjects were included in one family and other two subjects were included in another. The mean age of patients at the first electrodiagnostic study was 51.4 ± 10.8 years, ranged from 29 to 72 years. Of 41 patients, 11 patients complained of sensory symptoms (26.8%), such as numbness or paresthesia of feet or hands. In neurologic examination, decreased sensation of distal parts was observed in 7 of 41 patients (17.1%). Of the 41 patients, 10 patients had diabetes. Nobody had history of toxin exposure or alcoholics. Abnormalities of sensory NCS were observed in 23 of 41 patients (56.1%). The mean age of 23 patients with sensory neuropathy was 53.8 ± 10.7 years and older than the other (48.3 ± 10.5 years), although it was statistically insignificant. In the group with sensory neuropathy, 7 patients were diabetic (7/23, 30.4%) and the other group had 3 patients with diabetes (3/18, 16.7%).

The results of NCS were compared between two groups (Table 1). Reduced amplitude of SNAPs was the most remarkable finding of the group with sensory neuropathy. The SNAP amplitudes of median, ulnar and sural nerves were significantly reduced in the group with sensory neuropathy (16.2 ± 6.0 vs. 9.9 ± 4.7 for median, 12.5 ± 4.5 μV vs. 5.1 ± 2.9 μV for ulnar, 12.5 ± 4.2 μV vs. 4.8 ± 3.3 μV for sural nerve). Sensory conduction in the ulnar and sural nerves was significantly slow in the group with sensory neuropathy (44.8 ± 3.3 m/s vs. 39.8 ± 9.9 m/s for ulnar, 38.3 ± 4.2 m/s vs. 31.3 ± 12.8 m/s for sural nerve).

For 10 patients who had undergone follow-up NCS, the mean interval between the first and the follow-up studies was 8.0 years, ranged from 1 to 17 years. In the serial sensory NCS, there was no statistically significant difference of amplitudes and CVs ($p>0.05$, Table 2).

DISCUSSION

In 1968, Kennedy described 11 patients of 2 families, who showed slowly progressive spinal and bulbar weakness, and defined their clinical features of progressive

Table 1. The Comparison of NCS Results between 18 Patients without Sensory Neuropathy and 23 Patients with Sensory Neuropathy

	Normal Sensory NCS (n=18)	Abnormal Sensory NCS (n=23)
Age at the first examination [range]	48.3 ± 10.5 [29-63]	53.8 ± 10.7 [40-71]
Median nerve		
CMAP (μV)	10361.1 ± 3993.3	11087.0 ± 4648.8
MCV (m/s)	58.8 ± 6.6	57.0 ± 4.7
SNAP (μV)	16.2 ± 6.0	9.9 ± 4.7*
SCV (m/s)	46.1 ± 3.6	44.4 ± 3.1
Ulnar nerve		
CMAP (μV)	11261.1 ± 3293.7	11474.0 ± 4312.3
MCV (m/s)	60.0 ± 3.1	56.2 ± 4.6†
SNAP (μV)	12.5 ± 4.5	5.1 ± 2.9†
SCV (m/s)	44.8 ± 3.3	39.8 ± 9.9*
Peroneal nerve		
CMAP (μV)	5171.1 ± 2968.0	4377.8 ± 3218.9
MCV (m/s)	47.1 ± 4.4	43.0 ± 5.1*
Tibial nerve		
CMAP (μV)	17912.3 ± 8019.5	18142.6 ± 7320.8
MCV (m/s)	47.8 ± 3.7	46.1 ± 4.6
Sural nerve		
SNAP (μV)	12.5 ± 4.2	4.8 ± 3.3†
SCV (m/s)	38.3 ± 4.2	31.3 ± 12.8†

Data are expressed as a mean ± standard deviation.
CMAP: compound muscle action potential, MCV: motor conduction velocity, SNAP: sensory nerve action potential, SCV: sensory conduction velocity
*$p < 0.05$, †$p < 0.01$

Table 2. The Summary of Serial Sensory Nerve Conduction Studies in 10 BSMA Patients

Case	Test year	Median nerve		Ulnar nerve		Sural nerve	
		SNAP (μV)	SCV (m/s)	SNAP (μV)	SCV (m/s)	SNAP (μV)	SCV (m/s)
1	2001	10.9	41.1	6.6	38.0	5.6	31.9
	2008	6.6	42.6	3.3	40.7	5.5	28.6
2	1991	10.8	43.6	6.4	41.1	np	np
	2000	7.8	43.5	4.0	38.2	np	np
3	2007	13.3	46.8	3.9	41.1	8.8	36.4
	2008	12.9	47.5	4.4	43.6	7.0	34.9
4	1987	20.0	46.1	20.0	44.0	15.0	39.3
	2000	14.4	41.1	27.6	44.0	13.0	35.8
5	1999	2.2	40.8	2.2	40.9	3.0	41.5
	2008	2.8	40.6	3.3	40.4	2.4	40.2
6	2000	18.8	41.3	17.2	43.5	12.8	31.1
	2005	16.0	46.9	18.4	45.5	12.8	41.8
7	1997	12.0	51.9	10.0	47.0	14.8	42.9
	2009	20.4	51.9	19.7	50.0	20.9	38.3
8	1994	12.5	51.2	8.7	47.8	7.9	47.3
	2009	14.5	44.8	12.8	40.5	6.5	37.3
9	2006	13.4	45.3	2.9	33.0	5.4	36.4
	2008	12.6	46.0	3.8	38.1	10.0	39.3
10	1999	16.0	47.8	10.0	40.4	np	np
	2005	7.8	35.2	6.3	36.9	np	np

SNAP: sensory nerve action potential, SCV: sensory conduction velocity, np: no potential

proximal spinal and bulbar muscular atrophy of late onset with sex-liked recessive trait.[6] Some of those described by Kennedy had sensory impairment, but it was not regarded as one of clinical features. Since Harding reported absent or small SNAPs were found in most of their BSMA patients, subclinical abnormalities of SNAPs have been considered as one of features.[7] Although sensory symptoms or signs are usually undetectable clinically, it has been reported that SNAPs abnormalities are found in many BSMA patients.[2-4] Of our 41 patients, SNAPs abnormalities were found in 23 patients (56.1%). This group was older and had more diabetic patients than the other one. A combination of these factors might contribute to subclincal sensory neuropathy. In most previous reports, reduced or absent SNAPs were described as the distinctive features of sensory involvement in BSMA.[1-5] Similarly, decreased SNAPs amplitude or unobtainable SNAPs were the most remarkable findings in our patients with sensory dysfunction. Reduction or absence of SNAPs might present axonal process due to degeneration of primary sensory neurons or dorsal root ganglia demonstrated by the previous histopathologic studies.[3,8]

The longitudinal NCS of sensory nerves for 10 patients indentified that electrodiagnostic features of sensory nerves had not progressed over the years although motor deficits of patients had been aggravated. It suggests that sensory abnormalities may not be related with disease duration or progression. It is thought that the pathomechanism affecting the sensory system may be different from that affecting the motor system. Suzuki et al. showed that a shorter CAG repeat was more closely linked to the sensory-dominant phenotype and suggested that CAG repeat size might influence the electrophysiologic phenotypes in BSMA.[5] Doyu et al. identified that mutant AR gene with increased size of tandem CAG repeat was directly transcribed in various tissues of the patients with BSMA.[9] There might be tissue-specificity in expression of mutant AR gene.

Our study has several limitations. First, we could not show whether electrodiagnostic results and the number of CAG repeats are related or not, because this study is a retrospective study and we do not have the exact number of CAG repeats. Second, the number of cases with serial NCS is too small to fully describe temporal changes of electrodiagnostic features. However, this study shows that a substantial number of BSMA patients have subclinical sensory impairment, although proximal muscular weakness is a key characteristic of BSMA. And the longitudinal NCS presents that sensory neuropathy of BSMA patients might be stationary even if disease has progressed.

CONCLUSIONS

This study presents that sensory neuropathy of BSMA patients might be stationary. These results suggest that the pathologic process involving the sensory system might be different from that affecting the motor system, in a tissue-specific manner. It might result from the tissue-specificity in expression of mutant AR gene. Further studies for AR gene may clarify these clinical questions.

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