News Release

Title

Clinical features of female carriers and prodromal male patients with spinal and bulbar muscular atrophy

Key Points

- Spinal and bulbar muscular atrophy (SBMA) is an adult-onset X-linked neuromuscular disease caused by the expansion of a trinucleotide CAG repeat within the first exon of the A*ndrogen Receptor* gene.
- Most patients with SBMA first notice muscular weakness in their mid-forties, which is preceded by early-stage signs such as hand tremors and muscle cramps emerging more than ten years before the onset of subjective weakness.
- In this study, we investigated the clinical and electrophysiological features of female carriers and the early-stage male subjects with SBMA to elucidate the early pathophysiological changes of SBMA.
- Our findings clarified that female carriers of SBMA have early-stage signs and mild muscular weakness, particularly in the neck muscles. Their muscular weakness is associated with neurogenic changes. The pathophysiological changes of female carriers might be similar to those of pre-puberty subjects with SBMA.

Summary

According to research published online on September 30, 2022, in Neurology®, the medical journal of the American Academy of Neurology, a group of researchers, headed by Prof. Masahisa Katsuno, Department of Neurology, and Associate Prof. Atsushi Hashizume, Department of Clinical Research Education, Nagoya University Graduate School of Medicine, have revealed the clinical and electrophysiological features in female carriers and early-stage subjects with SBMA.

SBMA is an adult-onset X-linked neuromuscular disease which chiefly affects adult males. SBMA is caused by the expansion of a trinucleotide CAG repeat within the first exon of the androgen receptor (AR) gene. Both neurogenic and myogenic changes underlie the pathogenesis of SBMA. The main symptoms are muscular atrophy, limb weakness, and fasciculation of facial, bulbar, and limb muscles, which manifest between 30 and 60 years of age. In most cases, hand tremors and muscle cramps are noticed more than ten years before the emergence of limb weakness.

In this study, we assessed the clinical and electrophysiological features of female carriers and early-stage male subjects with SBMA to elucidate the early pathophysiological changes of the disease. The results of motor functional scales, motor unit number estimation, dual-energy X-ray absorptiometry, and peripheral blood tests were compared between female carriers and healthy female controls and between SBMA subjects and healthy male controls. Female carriers experienced early-stage symptoms such as muscle cramps more frequently than healthy female controls. Decreased motor unit number estimation and electromyography abnormalities, including high amplitude or polyphasic potentials, were observed in female carriers with mild muscle weakness in neck flexion and a slow walking speed. Changes in muscle-related markers, including

serum creatine kinase and dual-energy X-ray absorptiometry, were detected in male early-stage subjects with SBMA but not in female carriers.

Our findings indicate that female carriers of SBMA manifest mild muscular weakness associated with changes in neurogenic biomarkers. Conversely, male patients showed neurogenic and myopathic changes even at the early stage. These results suggest testosterone-independent neurodegenerative pathophysiology in female SBMA carriers.

Research Background

SBMA is an adult-onset X-recessive neuromuscular disease. The main symptoms are muscular weakness, muscular atrophy, and bulbar dysfunction, which manifest between 30 and 60 years of age; however, prodromal symptoms such as hand tremors or muscle cramps usually precede for more than ten years. As for the pathomechanism of SBMA, the testosterone-dependent nuclear accumulation of pathogenic AR protein is thought to be crucial in neural cell dysfunction and eventual degeneration and underlies the sex-dependent manifestation of SBMA. In addition to motor neuron degeneration, some previous studies suggested that myogenic components also contribute to the pathogenesis of SBMA. There is a pressing need to elucidate the initial pathophysiological changes of patients with SBMA.

Research Results

This study investigated 21 female carriers and 17 age-matched female controls, 11 early-stage SBMA subjects, and 14 age-matched healthy male controls. The prevalence of muscle cramps, one of the clinical features in early-stage male subjects, was higher in female carriers than in healthy controls (Table 1). The values of the motor functional measures were low in female carriers. Remarkably, there were statistically significant differences in the neck score of the MMT and the mQMG (Table 1).

Table 1 Comparison of the early-stage signs and the motor functions between female carriers and healthy controls

	Female carriers	Healthy females	*p*-value
	n = 21	*n* = 17	
Early-stage signs			
Hand tremors (number)	4	0	0.057[a]
Muscle cramps (number)	15	2	**<0.001**[a]
Motor functions			
MMT			
Neck flexion	4.6 ± 0.5	5.0 ± 0.0	**0.002**[b]
Upper limbs[a]	29.0 ± 1.5	29.8 ± 0.8	0.072[b]
Lower limbs[b]	29.0 ± 1.3	29.8 ± 0.8	0.090[b]
mQMG score			
Head lifted	0.67 ± 0.66	0.24 ± 0.44	**0.021**[b]
Arm outstretched[c]	0.24 ± 0.63	0.0 ± 0.0	0.096[b]
Leg outstretched[d]	0.38 ± 0.81	0.12 ± 0.49	0.222[b]

Data are shown as the mean ± standard deviation
[a]Chi-square test, [b]Student t-test
MMT, manual muscle testing; mQMG score, the modified quantitative myasthenia gravis score

Male SBMA subjects demonstrated altered myopathic markers, including CK, creatinine, ALST mass, and skeletal muscle mass index (Figure 1A-D). In female carriers, only serum CK levels were slightly higher than controls, but the average values were within the normal range (41–153 IU/L), much lower than in male subjects.

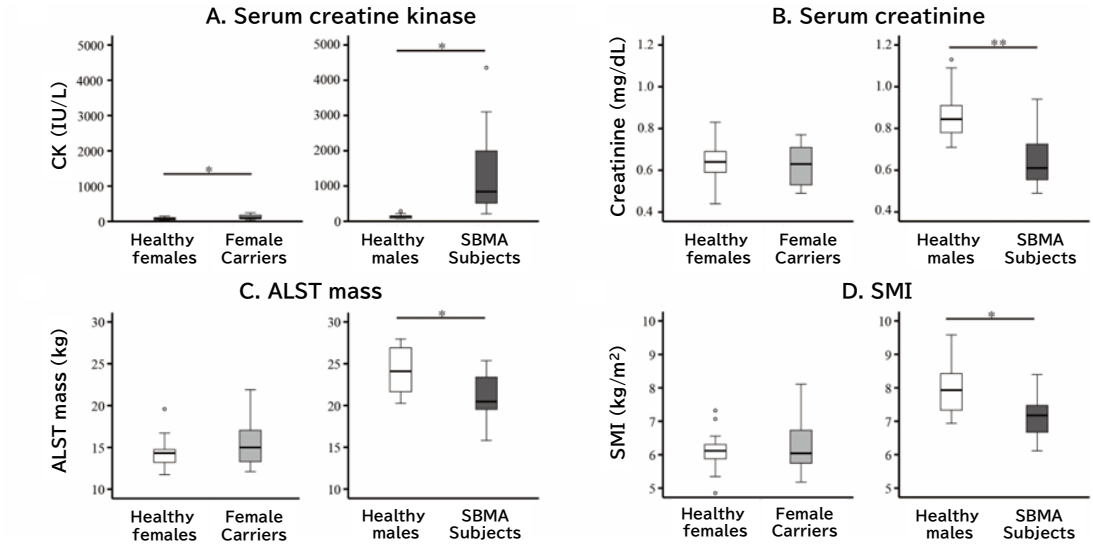

Figure 1 Comparison of myopathic markers between female carriers or male subjects with SBMA and healthy controls

MUNE values were significantly lower in female carriers than in controls for the amplitude and area methods (Figure 2A-B). Maximum CMAP was almost the same in both groups, but the average SMUP was significantly larger in controls than in female carriers, suggesting motor unit remodeling without subjective weakness (Figure 2C-D).

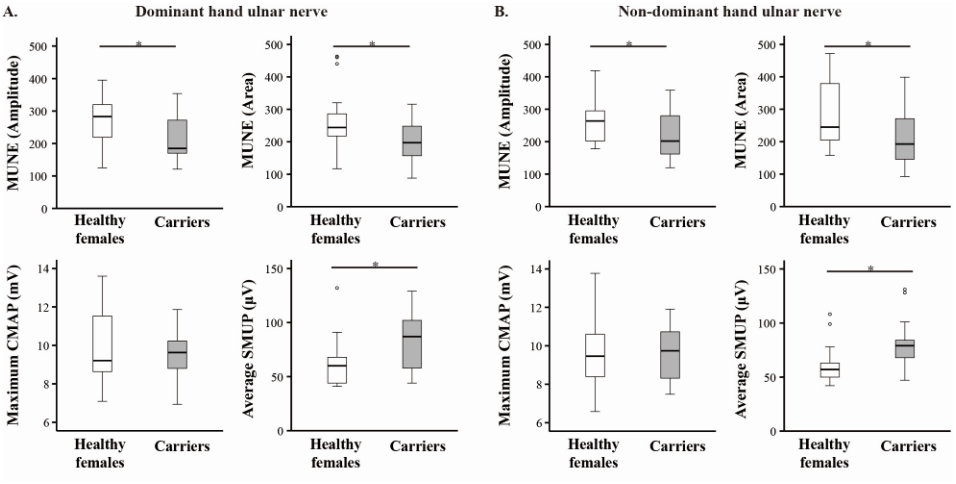

Figure 2 Comparison of the results of the electrophysiological examination between female carriers and healthy controls

As for electromyography performed on 12 female carriers, no acute denervation potentials were observed. However, chronic denervation potentials such as high amplitude motor unit potentials and polyphasic potentials were observed in eight and three of the 12 carriers, respectively, indicating chronic neurogenic changes (Table 2).

Table 2 Electromyography finding in female carriers

Subject number	Tongue			Biceps			Quadriceps		
	Denervation potentials[#]	High amplitude motor unit potentials	Polyphasic	Denervation potentials[#]	High amplitude motor unit potentials	Polyphasic	Denervation potentials[#]	High amplitude motor unit potentials	Polyphasic
1	-	+	-	-	-	-	-	+	-
2	-	-	+	-	-	-	-	-	-
3	-	+	+	-	-	-	-	-	-
4	-	-	+	-	-	-	-	-	-
5	-	+	+	-	-	-	-	+	-
6	-	-	+	-	-	-	-	-	-
7	-	-	+	-	-	-	-	+	+
8	-	-	+	-	-	-	-	+	+
9	-	-	+	-	-	-	-	+	-
10	-	-	-	-	-	-	-	+	-
11	-	-	-	-	-	-	-	+	-
12	-	-	-	-	-	-	-	-	+

[#]Denervation potentials: any of fibrillation, positive sharp waves, or fasciculation was observed

Research Summary and Future Perspective

In conclusion, female carriers of SBMA had early-stage signs and mild muscular weakness, particularly in the neck muscles. Their muscular weakness was associated with neurogenic changes, but myopathic changes were inconspicuous. The pathophysiological changes of female carriers might be similar to those of pre-puberty subjects with SBMA (Figure 3). Further studies are needed to clarify the initial pathophysiological events in SBMA.

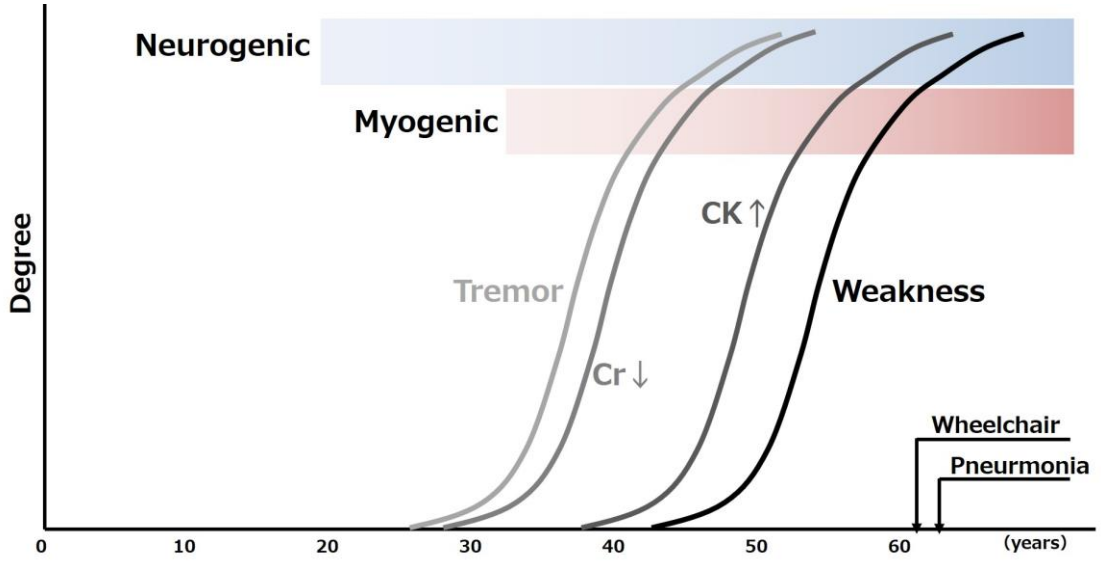

Figure 3 Hypothetical progression of SBMA

Publication

Ryota Torii, Atsushi Hashizume, Daisuke Ito, Yoshiyuki Kishimoto, Hideyuki Moriyoshi, Tomonori Inagaki, Ryoichi Nakamura, Tomohiko Nakamura, Tameto Naoi, Mitsuya Morita and Masahisa Katsuno

"Clinical features of female carriers and prodromal male patients with spinal and bulbar muscular atrophy" *Neurology*, in 2022.

doi: 10.1212/WNL.0000000000201342

Japanese ver.

https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Neu_221027.pdf