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Clinical Study

Postural leg tremor in X-linked spinal and bulbar muscular atrophy

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ABSTRACT

X-linked spinal and bulbar muscular atrophy (SBMA) is an adult-onset neuromuscular disorder caused by a CAG repeat expansion in the androgen receptor gene. Postural hand tremor is well known as a non-motor neuron sign, but to our knowledge postural leg tremor has not been reported. We studied the occurrence and physiological features of postural leg tremor in 12 male patients (38–64 years old) with genetically proven SBMA. Three patients had postural leg tremor with a frequency of 4–7 Hz. In these patients, sensory nerve action potential (SNAP) was not detected in the lower limbs. There were significant differences between the patients with postural leg tremor and those without postural leg tremor in both the SNAP of the sural nerve and the length of the CAG repeat. Phenotypical differences between shorter CAG repeats, which indicate a sensory-dominant phenotype, and longer CAG repeats, which indicate a motor-dominant phenotype, have been previously reported. In the present study, 60% of patients with shorter CAG repeats (<47) showed leg tremor and none of the patients with longer CAG repeats (⩾47) did. Postural leg tremor could be a clinical feature that predicts shorter CAG repeats of the androgen receptor gene.

1. Introduction

X-linked spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is a rare, adult-onset neuromuscular disorder characterized by slowly progressive proximal muscle weakness, fasciculation and bulbar weakness [1,2]. Genetically, the expansion of CAG repeats in the first exon of the androgen receptor gene is associated with SBMA [3]. Postural hand tremor is the most important non-motor neuron symptom because it is frequently documented as the initial symptom of SBMA [4,5]. Postural hand tremor has been described as being associated with an alteration of peripheral signaling [6]. In contrast, as postural leg tremor has rarely been documented in the literature, both the occurrence and pathological mechanism remained unknown. To clarify whether postural leg tremor is associated with the dysregulation of sensory nerve networks, as is the case for postural hand tremor, we performed a clinico-electrophysiological assessment of our SBMA patients.

2. Method

Twelve male patients with SBMA, aged 38 to 64 years, were recruited between October 2003 and September 2012. The average age of onset with demonstrated muscle weakness was 45.3 ± 8.3 (standard deviation) (range, 30–61) years. Gene analyses of the first exon of the androgen receptor gene were obtained from all patients and its CAG expansions (45–51 repeats) were entirely compatible with the Japanese SBMA population (40–57 repeats) [4]. Hand tremor was examined with arms outstretched horizontally and leg tremor in the Mingazzini maneuver posture, raising the lower limbs with the hip and knee in a 90° flexed position [7]. Clinical records of disease onset, neurological examination, nerve conduction studies (NCS) and surface electromyography (s-EMG) were collected. Briefly, in s-EMG, waves were detected from two cup electrodes placed on the skin separated by a 2.5 cm gap above the muscles concerned including the forearm muscles (first interosseus dorsalis, extensor digitorum communis, abductor digiti minimi) and lower limb muscles (vastus medialis, tibialis anterior). Sensory nerve conduction velocities were measured using standard surface stimulating and recording techniques in the sural nerve [8]. The data are shown as mean ± the standard error of the mean. The result was analyzed by Mann-Whitney *U* test or Fisher's exact test on GraphPad Prism version 6 (GraphPad Software, San Diego, CA, USA).

3. Result

Postural leg tremor was detected in three patients and all patients had postural tremor in the forearm and/or finger muscles (Table 1). Sensory disturbances or subjective sensory symptoms were only documented in Patient 2 and 10. Patient 2 showed decreased vibration sense and Patient 10 felt cold and numb in his

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Table 1
Demographic, clinical and electrophysiological characteristics of spinal and bulbar muscular atrophy patients

Patient	Age, years	Age at onset	CAG expansion (repeats)	Hand tremor	Leg tremor	Muscle strength (MMT)				Sural nerve SNAP (μV)	Sensory disturbance
						QF	Hamstrings	TA	Calf		
1	42	41	45	−/+*	+	5/5	5/5	5/5	5/5	Not evoked	–
2	63	61	45	+	+	4/4	4+/4+	5/5	5/5	Not evoked	Decreased vibration sense in feet
3	64	56	45	+	+	5/5	5/5	5/5	5/5	Not evoked	–
4	57	42	45	+	–	5/4+	5/4+	4+/5	5/5	Not tested	–
5	52	47	46	+	–	3/3	4/4	5/5	5/5	4.2	–
6	57	53	47	+	–	4/4	4/4	5/5	5/5	4.4	–
7	42	42	47	+	–	5/5	4+/5	5/5	5/5	Not tested	–
8	43	40	48	+	–	4/4	5/5	5/5	5/5	6.1	–
9	52	45	49	+	–	3/3	4/4	5/5	5/5	Not tested	–
10	55	46	49	+	–	3/3	3/3	4/4	4/4	2.8	Numb and cold in feet
11	45	41	50	+	–	4+/4+	4+/4–	5/5	5/5	3.0	–
12	38	30	51	+	–	4/4	4–/4–	5/5	4+/4+	Not tested	–

MMT = manual muscle testing, QF = quadriceps femoris, SNAP = sensory nerve action potential, TA = tibialis anterior, + = present, – = absent.
* Patient demonstrated finger tremor but no hand tremor.

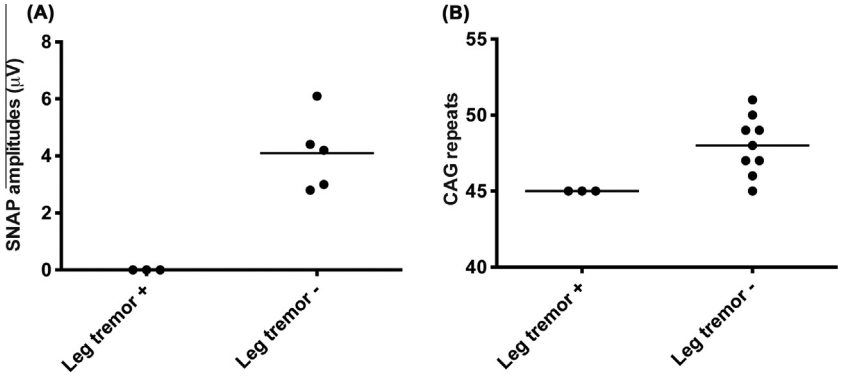

Fig. 1. (A) Sensory nerve action potential amplitudes of eight patients and (B) CAG repeat expansion in 12 patients with spinal and bulbar muscular atrophy. SNAP = sensory nerve action potential, + = present, – = absent.

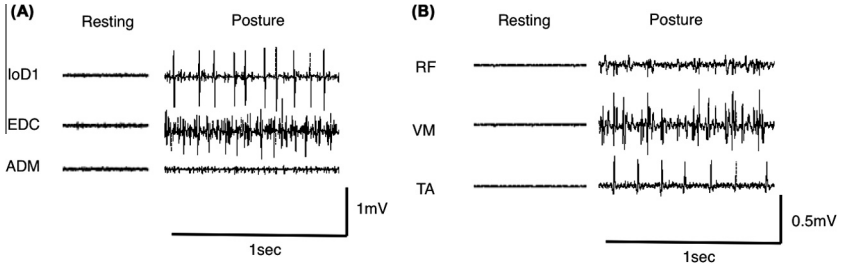

Fig. 2. Surface electromyography (s-EMG) obtained from Patient 2 from (A) the right upper limb muscles (first interosseus dorsalis muscle, extensor digitorum communis and abductor digiti minimi) when the arms were stretched outward horizontally, and (B) from the right lower limb muscles (rectus femoris, vastus medialis and tibialis anterior muscle) at rest and in the Mingazzini position. ADM = abductor digiti minimi, EDC = extensor digitorum communis, IoD1 = first interosseus dorsalis, RF = rectus femoris, TA = tibialis anterior, VM = vastus medialis.

feet. The SNAP of the sural nerve was evaluated in eight of the 12 patients. It was not detected in patients with leg tremor, while the amplitudes were 4.1 ± 1.3 μV in the group without leg tremor ($p < 0.05$) (Fig. 1A).

According to a previous study, patients with fewer than 47 CAG repeats (normal population, <40 repeats) show a sensory dominant phenotype [9]. Three of the five patients with shorter repeats (<47) presented leg tremor (Table 1). Conversely, the CAG repeats of patients with leg tremor were significantly shorter than those of the patients without leg tremor ($p < 0.05$, Fig. 1B). There were no significant differences in age, disease onset, disease duration, or muscle strength between the two groups of those with or those without leg tremor. The patients with leg tremor are presented below.

3.1. Patient 1

A 42-year-old man without a family history of SBMA or other motor neuron disease noticed difficulty in climbing stairs 1 year