Two Cases of Spinocerebellar Ataxia Accompanied by Involvement of the Skeletal Motor Neuron System and Bulbar Palsy

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Abstract

We report two patients with spinocerebellar ataxia (SCA) with cranial and spinal motor neuron involvement. They initially presented with cerebellar ataxia, followed by bulbar palsy and limb motor neuron signs. One of the patients had a brother with a allied disorder. SCA type 1 (SCA1), SCA3 and SCA6 have been reported to involve the motor neuron system, but they were excluded by DNA analyses in the present two patients. These two patients may form a distinct disease entity among SCAs.

Key words: spinocerebellar ataxia, motor neuron disease, bulbar palsy, tongue atrophy, MRI

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Introduction

Spinocerebellar ataxia (SCA) is a disease affecting the spinocerebellar, autonomic and extrapyramidal systems. Although some cases of hereditary SCA, such as SCA type 1 (SCA1), SCA2, SCA3 and SCA6, affect motor neurons (1-7), other types rarely affect them. Atrophy and fasciculation of the tongue are characteristic in motor neuron diseases such as amyotrophic lateral sclerosis (ALS), but have also been reported in some cases of SCA1 and SCA3 (6); other types of SCA rarely show these features. Here, we report two cases of SCA accompanied by motor neuron involvement, with severe atrophy and fasciculation of the tongue, in which SCA1 and SCA3 were excluded by DNA analysis.

Case Report

Patient 1. A 52-year-old man, who had a medical history of type 2 diabetes mellitus for more than 10 years, gradually developed an unsteady gait. At age 54, action tremor appeared in both upper limbs, and he found difficulty in speaking from 58 years of age. These symptoms progressed slowly, and swallowing became difficult from 61 years of age. At age 62, his tongue became atrophic. In February 2004, at age 63, he was referred to our hospital. He had a brother 15 years older (Fig. 1A; Brother 1), who had suffered unsteady gait and dysarthria from 40 years of age and had unaccounted for motor neuron disorder, and died of myocardial infarction at age 61. His parents, his other two brothers and his son were asymptomatic.

He weighed 51 kg and was 170 cm tall. Physical examination revealed no remarkable findings. Neurologically, he did not present aphasia, apraxia or agnosia. The Mini-Mental State Examination (MMSE) gave a score of 27/30, indicating an immediate memory disturbance. There were saccadic eye movements, vertical and lateral gaze limitation, scanning speech, and severe atrophy, weakness and fasciculation of the tongue (Fig. 1B). Ocular fundus was normal, and there was not blepharoptosis. He showed marked muscle atrophy and fasciculation in all extremities as well as the trunk, and his muscle tone was decreased. However, he did not have muscle weakness in the extremities or the trunk. His deep tendon reflexes were brisk in all extremities, and Hoffmann’s, Trömner and Wartenberg reflexes were all posi-
Figure 1. The family tree (A), photograph of tongue (B), muscle biopsy sample (C) and MRI images (D-F) of patient 1. (B) The tongue is atrophic. (C) Biopsy sample of left biceps brachii muscle shows small angular fiber and small group atrophy (hematoxylin-eosin stain, scale bar = 100 μm). (D) Axial T1-weighted MRI shows cerebellar atrophy (arrows). (E) Sagittal T1-weighted MRI shows atrophy of the upper region of the cerebellar vermis (large arrow), and the cervical spinal cord appeared to be slightly atrophic (arrowheads). (F) The thoracic and lumbar spinal cord appeared to be slightly atrophic by sagittal T1-weighted MRI (arrows).

**Patient 1**

tive. The plantar reflex was flexor. He showed marked truncal and limb ataxia. The sensory and autonomic systems were unremarkable.

Laboratory blood tests revealed elevation of fasting blood sugar (191 mg/dl, normal range = 65 to 105 mg/dl), total cholesterol (249 mg/dl, normal range = 130 to 220 mg/dl) and triglyceride (377 mg/dl, normal range = 50 to 150 mg/dl). His cerebrospinal fluid was normal. SCA1, SCA3, SCA 6 and X-linked spinal and bulbar muscular atrophy (SBMA) were ruled out by DNA analysis. Motor nerve conduction velocity was slightly decreased in the right tibial nerve (38 m/sec). The amplitudes of the compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) of the right median nerve were decreased (CMAP amplitude, 4.4 mV; SNAP amplitude, 7.7 μV). Electromyography (EMG) of the tongue, sternocleidomastoid muscles, upper and lower extremities, and paraspinal muscles demonstrated high-amplitude motor unit potentials (3.0-6.5 mV) with a discrete interference pattern on voluntary contraction of the muscle. The latency and amplitude of the motor-evoked potentials (MEPs) were normal in all extremities. Magnetic resonance imaging (MRI) of the brain revealed severe atrophy in the cerebellar vermis and mild atrophy in the frontal, temporal and parietal lobes, and the cerebellar hemispheres (Fig. 1D, E). The cervical, thoracic and lumbar spinal cord appeared to be slightly atrophic by MRI (Fig. 1E, F). Te-99 m ethyl cysteinate dimer (ECD) single photon emission computed tomography (SPECT) revealed hypoperfusion in the cerebellum and bilateral parietal lobe, and especially severe hypoperfusion in the upper side of the cerebellar vermis. Muscle biopsy of left biceps brachii showed small angular fiber and small group atrophy, which suggested neurogenic muscular atrophy (Fig. 1C).

**Patient 2.** A 55-year-old woman, who had a medical his-
Patient 2

![Photograph of tongue (A), external ophthalmoplegia (B) and MRI images (C-E) of patient 2. (A) The tongue is atrophic. (B) Bilateral abductive eye position (central picture), vertical gaze limitation (vertical pictures) and lateral gaze limitation with severe adductive limitation (lateral pictures). (C) Axial T2-weighted MRI shows cerebellar atrophy (arrows) and a subtle hyperintense lesion, an ‘inverted T-sign’, in the pons (arrowheads). (D) Sagittal T1-weighted MRI shows atrophy of the upper region of the cerebellar vermis (large arrow), and the cervical spinal cord appeared to be slightly atrophic (arrowheads). (E) The thoracic and lumbar spinal cord appeared to be slightly atrophic by sagittal T1-weighted MRI (arrows).](image)

Figure 2. Photograph of tongue (A), external ophthalmoplegia (B) and MRI images (C-E) of patient 2. (A) The tongue is atrophic. (B) Bilateral abductive eye position (central picture), vertical gaze limitation (vertical pictures) and lateral gaze limitation with severe adductive limitation (lateral pictures). (C) Axial T2-weighted MRI shows cerebellar atrophy (arrows) and a subtle hyperintense lesion, an ‘inverted T-sign’, in the pons (arrowheads). (D) Sagittal T1-weighted MRI shows atrophy of the upper region of the cerebellar vermis (large arrow), and the cervical spinal cord appeared to be slightly atrophic (arrowheads). (E) The thoracic and lumbar spinal cord appeared to be slightly atrophic by sagittal T1-weighted MRI (arrows).

tory of hip joint replacements for osteoarthritis at age 52, developed an unsteady gait. At age 57, she felt ataxia in both upper limbs. She found difficulty in speaking, and her gait disturbance progressed slowly from 64 years of age. At age 70, she developed double vision and difficulty in swallowing. At age 73, her tongue became atrophic. In February 2003, at age 74, she was referred to our hospital. Her parents, brothers and sons were asymptomatic.

She weighed 41 kg and was 145 cm tall. Physical examination revealed no remarkable findings. Neurologically, she did not show aphasia, apraxia or agnosia. Her MMSE score was 19/30, indicating disorientation, acalculia and an immediate memory disturbance. She showed bilateral exotropia, and vertical and lateral gaze limitation with severe adductive limitation (Fig. 2B), slurred speech, and severe atrophy, weakness and fasciculation of the tongue. The tongue atrophy was especially severe in the tongue base (Fig. 2A). Ocular fundus was normal, and there was no blepharoptosis. She showed marked muscle atrophy and slight muscle weakness in all extremities as well as in the trunk, fasciculation in bilateral lower extremities, and hypotonia in all extremities. The deep tendon reflexes were brisk in all extremities, and Hoffmann’s, Trömner and Wartenberg reflexes were all positive. Her plantar reflex was extensor. She showed marked truncal and limb ataxia. The sensory and autonomic systems were unremarkable.

Laboratory blood tests and cerebrospinal fluid were normal. SCA1, SCA2, SCA3, and SCA6 were ruled out by DNA analysis. Motor nerve conduction velocity and amplitudes of the CMAP was normal in the bilateral median and tibial nerves. The amplitudes of the SNAP of bilateral median nerve were decreased (right 5.9 μV; left 5.1 μV) and SNAP of bilateral sural nerves was not evoked. EMG of the upper and lower extremities demonstrated high-amplitude
motor unit potentials (3.0-9.5 mV) with a discrete interference pattern on voluntary contraction of the muscle. The latency and amplitude of the MEPs were normal in all extremities. The thermoregulatory sweat test revealed slight hypohidrosis in bilateral lower extremities. MRI of the brain revealed severe atrophy in the cerebellar vermis and mild atrophy in the frontal, temporal and parietal lobes, and the cerebellar hemispheres (Fig. 2C, D). An axial T2-weighted image showed a subtle hyperintense lesion, an ‘inverted T’ sign, in the pons (Fig. 2C), which suggested that the transverse pontine fibers were affected (8). The cervical, thoracic and lumbar spinal cord appeared to be slightly atrophic by MRI (Fig. 2D, E). Tc-99 m ECD SPECT revealed hypoperfusion in the cerebellar vermis and bilateral hemispheres.

**Discussion**

Patients 1 and 2 initially presented with truncal ataxia (unsteady gait) at ages 52 and 55, respectively. Ataxia of the trunk and limbs progressed insidiously in both cases. Patient 1 developed bulbar signs (dysphagia and tongue atrophy) at age 61, 9 years after the onset. Patient 2 also developed bulbar signs, at age 70, 15 years after the onset. When we saw patient 1 at 10 years after the onset, and patient 2 at 19 years after the onset, they presented with severe cerebellar ataxia, upper and lower motor neuron signs, and bulbar signs with severe atrophy and fasciculation of the tongue. Thus, we considered these two patients to be cases of SCA accompanied by cranial and spinal motor neuron involvement, in which severe atrophy and fasciculation of the tongue were characteristic. Because patient 1 had a brother 15 years older who had developed unsteady gait and dysarthria at age 40, we considered that he had familial SCA.

Some types of hereditary SCA, such as SCA1, SCA2, SCA3 and SCA6, affect the motor neuron system (1-7). About 15% of cases of SCA1 and SCA3 have been reported to involve atrophy and fasciculation of the tongue (6). A few cases of SCA2 have been reported to involve fasciculation of the tongue (9), but there are no reports of tongue atrophy. As previously reported, tongue atrophy was present in one case of SCA6 (10, 11). However, SCA1, SCA3 and SCA6 were excluded by DNA analysis in the present two patients.

SCA with involvement of motor neurons is very rare; seven cases have been reported (10-17) (Table 1). Among them, six were reported from Japan (10, 11, 13-17). The clinical features of our two patients and the six previously reported cases were ataxia as the first symptom, followed within 10 years by involvement of the motor neuron system, except for patient 2, and all cases having bulbar signs (10, 11, 13-17). Although three previously reported cases presented with atrophy and fasciculation of the tongue (10, 11, 14, 16) and severe neuronal loss from the hypoglossal nucleus in autopsy findings (10, 11, 14), which is characteristic of our patients, our patient 1 is the only familial case. This suggests that patient 1 may be the first reported case of hereditary SCA, although involvement of motor neurons was unclear in his brother. Autopsy was performed in five previous reported cases (10-15), and Bunina bodies was present in the case of Ohara et al (10, 11), and skein-like inclusions were present in the case of Suenaga et al (15) and in that of Ohara et al. Bunina bodies and skein like inclusions have been generally considered as the histological hallmark of ALS (18), but Ohara’s case was SCA6 and Suenaga’s case had clinically been considered as SCA3. Because these two cases had progressed more slowly than in ALS, it is difficult to consider that SCA and ALS coexisted by chance.

Neurological examination of patient 2 revealed bilateral exotropia, and vertical and lateral gaze limitation with severe adductive limitation (Fig. 2B), which is a unique external ophthalmoplegia. There has been no previous report of this type of external ophthalmoplegia. Because some neuropathological examinations have reported gliosis in the medial longitudinal fasciculus (MLF) and neuronal loss and gliosis in the oculomotor nuclei in SCA3 and olivoponto-
cerebellar atrophy (19, 20), we consider that disturbance of bilateral oculomotor nuclei and MLF might be the cause of the external ophthalmoplegia in patient 2.

Both SCA and ALS are rare neurodegenerative diseases. We speculate that the disease in the present patients is not a simple coincidence of SCA and ALS, because our two patients showed marked muscle atrophy in all extremities and the trunk but not muscle weakness; SCA1, SCA2 and SCA3 which affect the motor neuron system often show muscle atrophy but rarely show muscle weakness (1-6). Eight of nine cases of SCA accompanied by involvement of the motor neuron system have been reported from Japan (10, 11, 13-17) (Table 1). It is suggested that this multiple system degenerative disease might be a distinctive disorder of Japanese. If these cases are a simple coincidence of SCA and ALS, similar cases would have been reported from other countries. Although the etiology of this multiple system degenerative disease remains unclear, it might suggest a common mechanism for SCA and motor neuron disease.

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