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【 CASE REPORT 】

Diagnostic Challenges Posed by Preceding Peripheral Neuropathy in Very Late-onset Spinocerebellar Ataxia Type 3

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Abstract:
Peripheral neuropathy is a common extracerebellar manifestation of spinocerebellar ataxia type 3 (SCA3). However, to date, only a few SCA3 case reports have described the development of neuropathy before the emergence of apparent cerebellar signs. We herein report a case of very late-onset SCA3 in which preceding peripheral neuropathy seemingly concealed cerebellar signs, with seven years lapsing from the onset to the diagnosis. Horizontal gaze-evoked nystagmus and brain magnetic resonance imaging (MRI) findings prompted genetic testing, which confirmed the diagnosis of SCA3. A careful follow-up of neurological findings, such as nystagmus, and brain MRI are imperative for such cases.

Key words: Machado-Joseph disease, neuronopathy, hot cross bun sign, magnetic resonance imaging, sensory ataxia

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Introduction

Spinocerebellar ataxia type 3 (SCA3), also known as the Machado-Joseph disease (MJD), is an autosomal-dominant inherited neurodegenerative disorder caused by the expansion of CAG repeats in exon 10 of *ATXN3* (1). Depending on the age of onset, the three main types of SCA3 are as follows: (a) "Type 1" disease, which begins earlier and is characterized by pyramidal and extrapyramidal features; (b) "Type 2" disease, which begins in young to mid-adult years presents with ataxia and pyramidal signs; and (c) "Type 3" disease, which is the later-onset form characterized by ataxia and neuropathy. Peripheral neuropathy is a common and well-known extracerebellar manifestation of SCA3 affecting up to 60% of patients (2, 3). However, to date, only a few SCA3 case reports have described the development of neuropathy before the emergence of cerebellar signs (4-6). The diagnosis of SCA3 in such cases may be complicated by the ability of sensory ataxia to mask characteristic cerebellar symptoms.

We herein report a case of very late-onset SCA3 in which preceding peripheral neuropathy seemingly concealed cerebellar signs, with seven years lapsing from the onset to the diagnosis.

Case Report

A 75-year-old Japanese woman first developed distal extremity paresthesia at 68 years of age. Her symptoms gradually worsened, and she slowly developed a progressive unsteady gait. Although her medical history comprised appendicitis and osteoporosis, there was no apparent history of SCA3 in the family. Her mother died of stomach cancer at 74 years of age, and her father died of acute leukemia in his fifties. She had 2 children in their 40s and 4 younger brothers, none of whom had neurological symptoms similar to hers. During her first admission at 72 years of age, ophthalmoplegia, nystagmus, bulging eyes, dysarthria, and dysphagia were not observed. In addition, she exhibited no

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Table. Results of Nerve Conduction Studies.

	Motor nerve				Sensory nerve	
	Distal latency (ms)	Conduction velocity (m/s)	CMAP (mV)	F-wave latency (ms)	Conduction velocity (m/s)	SNAP (μV)
First examination (at 71 years of age)						
L. Median nerve	4.7 (<4.5)	49 (>48)	4.9 (>5.0)	28.3 (<31.4)	40 (>43)	3 (>11.3)
L. Ulnar nerve	3.0 (<3.6)	52 (>46)	8.2 (>4.7)	27.8 (<31.7)	50 (>40)	1 (>8.8)
L. Superficial radial nerve					50 (>48)	4 (>14.3)
L. Tibial nerve	3.9 (<5.9)	40 (>36)	9.1 (>5.6)	46.9 (<56.8)		
L. Sural nerve					45 (>37)	2 (>3.4)
Final examination (at 74 years of age)						
L. Median nerve	4.4 (<4.5)	45 (>48)	3.9 (>5.0)	28.3 (<31.4)	41 (>43)	3 (>11.3)
L. Ulnar nerve	3.1 (<3.6)	58 (>46)	7.2 (>4.7)	27.1 (<31.7)	39 (>40)	2 (>8.8)
L. Superficial radial nerve					52 (>48)	6 (>14.3)
L. Tibial nerve	4.5 (<5.9)	37 (>36)	7.6 (>5.6)	44.3 (<56.8)		
L. Sural nerve					51 (>37)	2 (>3.4)

All studies were performed in the left extremities (L.).
CMAP: compound muscle action potential
All sensory studies were antidromically measured.
Abnormal values are indicated with underline. Normal limits are indicated in parentheses (our laboratory data).

muscle weakness at that time, and limb ataxia was not present in the upper extremities, although her deep tendon reflexes were diminished in the upper extremities and absent altogether in the lower extremities. Babinski's sign was absent. She exhibited paresthesia in all distal limbs, and superficial sensations (touch or pain) were preserved; the position sense was reduced at the toe, and the vibration sense was moderately reduced at the ankle joint and mildly reduced at the knee. Romberg's sign was positive, and her gait was ataxic. She was unable to perform tandem gait walking. She did not consume alcohol and used no medication or drugs that could explain her polyneuropathy.

The outcomes of routine blood tests, including a full blood count and analyses of the fasting glucose and electrolyte levels, renal profile, liver function, and levels of vitamins B1, B12, and folic acid, were normal. Comprehensive screening for autoimmune diseases yielded negative tests for antinuclear, anti-neutrophil cytoplasmic, anti-Ro/SSA, and La/SSB antibodies and cryoglobulins, and M protein was not detected. Serologic tests for syphilis, viral hepatitis B and C, human T-cell lymphotropic virus, and HIV were negative. A cerebrospinal fluid analysis revealed normal protein levels with no pleocytosis. A lip biopsy revealed no evidence of Sjögren's syndrome. In addition, no orthostatic hypotension was observed in the head-up tilt test, and the sympathetic sweat response and skin vasomotor reflex on the palm were preserved. However, nerve conduction studies revealed a reduced sensory nerve action potential amplitude (Table). These findings indicated chronic sensory ataxic neuropathy. High-dose intravenous immunoglobulin did not improve her condition.

On her second hospital admission at 73 years of age, the patient exhibited bilateral horizontal gaze-evoked nystagmus in both directions in addition to the neurological abnormalities observed during the first admission. However, cerebellar ataxia was not noted at this admission either. Abdominal fat aspiration and gastroduodenal biopsies revealed no evidence of amyloid deposition. In addition, needle electromyography performed in the right first dorsal interossei, iliopsoas, and tibialis anterior muscles revealed fibrillations in the first dorsal interossei. All tested muscles exhibited high-amplitude and polyphasic motor unit potentials.

At 74 years of age, the patient underwent brain magnetic resonance imaging (MRI), which revealed cerebellar atrophy. T2-weighted imaging (T2WI) showed linear high-intensity areas along the medial margin of the internal segment of the right globus pallidus and the pons midline as well as other non-specific high-intensity signals in the cerebral white matter (Fig. 1). Her horizontal gaze-evoked nystagmus and MRI abnormalities led us to consider a diagnosis of spinocerebellar ataxia with peripheral neuropathy. A genetic analysis with informed consent revealed an expanded CAG trinucleotide repeat (64/27) in *ATXN3* (Fig. 2).

Discussion

We herein report a case of very late-onset and non-familial SCA3 in which preceding peripheral neuropathy may have masked cerebellar signs and rendered the diagnosis challenging. Although horizontal gaze-evoked nystagmus and brain MRI findings suggested the possibility of SCA in the differential diagnosis, seven years lapsed from the onset to the eventual diagnosis. Retrospectively, the progress of the peripheral neuropathy is unclear against the background progression of unsteady gait throughout the disease course. Thus, it seems imperative to consider other causes of ataxia,

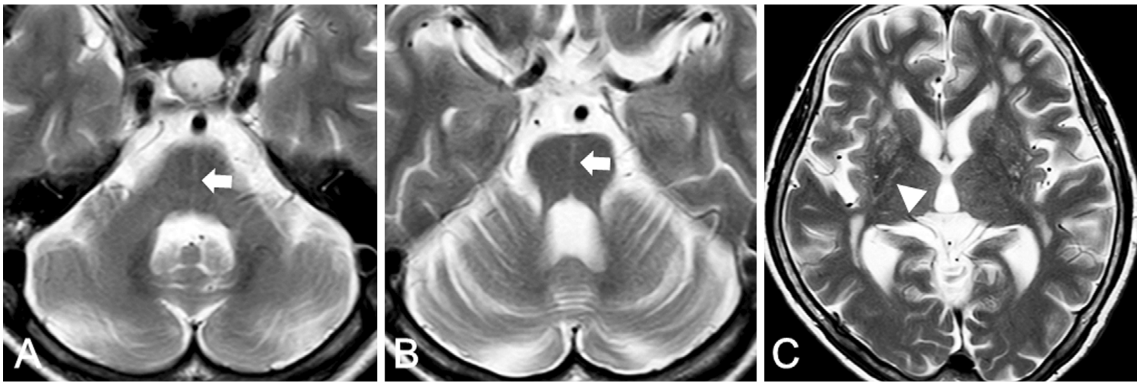

Figure 1. **Brain magnetic resonance imaging. Axial T2-weighted magnetic resonance images depicting a midline linear high-intensity area in the pons (arrows), cerebellar atrophy (A, B), and a linear high-intensity area along the medial margin of the internal segment of the right globus pallidus (arrowheads) (C).**

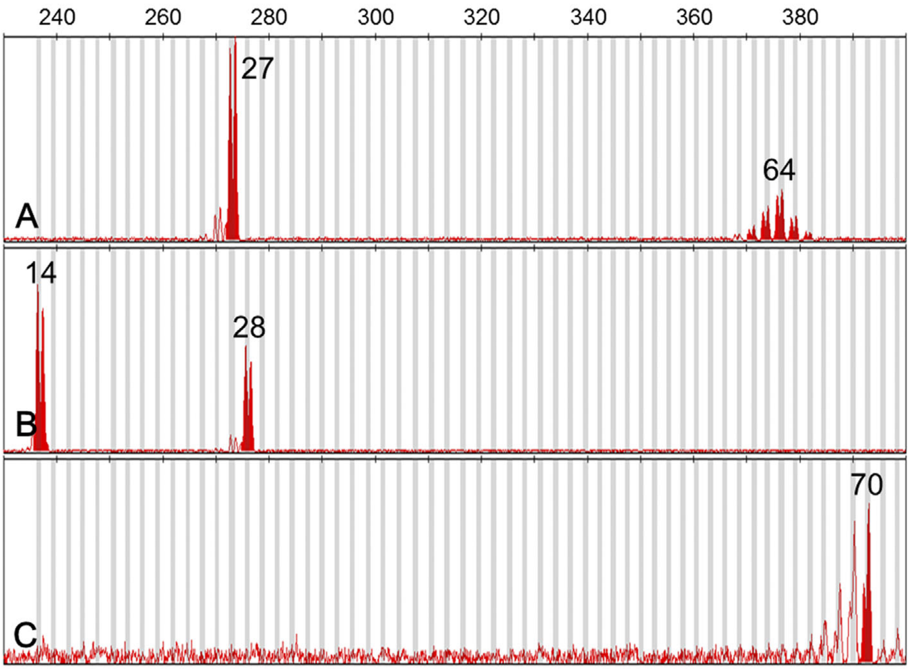

Figure 2. **Detection of *ATXN3* trinucleotide repeat expansions. Peaks of *ATXN3* gene (CAG) n expansions by PCR and a fragment analysis in the patient (A), normal features in a healthy control with 14 and 28 trinucleotide repeats (B), and a positive control with 70 trinucleotide repeats (C). The numbers of trinucleotide repeats in the controls were determined by Sanger sequencing. Each number written above the peaks refers to the trinucleotide repeat count. The number of trinucleotide repeats was determined by a comparison with healthy and positive controls.**

such as compressive myelopathy and SCA, in cases such as this.

We believe that the peripheral neuropathy in the present case was a symptom of SCA3 because of the known association of peripheral neuropathy with SCA3 (excluding other etiologies of peripheral neuropathy) and electrophysiological similarities of these conditions. As in our case, a previous nerve conduction study revealed reduced motor and markedly reduce sensory potential amplitudes in SCA3 (3). Neuronopathy and axonal dying-back neuropathy have been postulated as mechanisms underlying the axonal damage associated with SCA3 (3, 7). In our case, the sural/radial amplitude ratio of >0.3 in nerve conduction studies and chronic denervation of the proximal muscles in electromyography studies suggested neuronopathy rather than length-dependent axonopathy as the mechanism underlying the axonal damage.

Only a few cases of SCA3 with peripheral neuropathy without or prior to cerebellar manifestation have been reported. A previous report described a man who experienced peripheral neuropathy for 6 years before the appearance of cerebellar signs at 52 years of age; in addition, the case confirmed a 62-repeat trinucleotide expansion (6). In addition, two other reports have described cases with intermediate CAG repeat lengths in which patients presented with peripheral neuropathy without or prior to the manifestation of cerebellar signs [coexistence of diabetes and monoclonal gammopathy of undetermined significance in one case (4) and no data excluding other causes of neuropathy in another (5)]. Consistent with those cases, our case shares the common features of short repeat lengths and middle-aged or elderly patients; these features may thus be related to the unusual presentation. Genotype-phenotype studies have indicated that SCA3 patients with longer CAG repeat lengths are more severely affected and have an earlier disease onset and more rapid progression than those with small expansions (8). In contrast, peripheral neuropathy is reported more frequently in patients with small CAG expansions and a late disease onset (3). Two multiple regression analysis-based studies demonstrated that, rather than the length of the CAG repeat, the duration over which the SCA3 mutation exerts its effect is the primary determinant of peripheral neuropathy (3, 9). Thus, peripheral neuropathy might be a prominent sign and symptom in middle-aged or elderly patients with short CAG repeat lengths.

In the present case, cerebellar atrophy observed on brain MRI suggested the possibility of SCA as a differential diagnosis. In addition, linear high-intensity areas along the medial margin of the internal globus pallidus and the midline of the pons on T2WI prompted us to perform a genetic test for SCA3. A previous report described a linear high-intensity area along the medial margin of the internal globus pallidus on T2WI in SCA3 patients (10). A midline linear high-intensity area in the pons is a change heralding the "hot cross bun sign," which is the typical sign of multiple-system atrophy. This finding is observed in patients with SCA, including SCA3 (11).

In conclusion, the present case highlights the fact that axonal-mediated peripheral neuropathy can precede and conceal cerebellar signs in SCA3, particularly in cases of late-onset disease. In such cases, the close follow-up of neurological findings (e.g. nystagmus) and adequate imaging tests are imperative for obtaining an accurate diagnosis, particularly when the progression of peripheral neuropathy is masked by various symptoms.

The authors state that they have no Conflict of Interest (COI).

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