Three Spinocerebellar Ataxia Type 2 Siblings with Ataxia, Parkinsonism, and Motor Neuronopathy

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Abstract

Spinocerebellar ataxia type 2 (SCA2) represents a family of dominant neurodegenerative disorders that result from CAG expansion repeat mutations. The phenotype consists of some common features, most notably progressive ataxia. We describe three siblings with SCA2, manifesting parkinsonism and ataxia in the first sibling, juvenile parkinsonism in the second and motor neuronopathy in the third. Genetic examination revealed expansion to 42, 43, and 42 CAG repeats. There was no relationship between the number of repeats and phenotype. The SCA2 gene should be studied in families with heterogeneous neurodegenerative disorders, including motor neuron disease.

Key words: SCA2, motor neuron disease, parkinsonism, ataxia, neurodegenerative disorders


Introduction

Autosomal dominant cerebellar ataxia type 2 is caused by CAG expansion in the coding region of the ataxin 2 gene on chromosome 12q23-24.1. The normal range of CAG repeats usually extends from 14 to 32 repeats, while it ranges from 35 to 50 or more in affected persons (1, 2). The clinical hallmark of spinocerebellar ataxia type 2 (SCA2) with juvenile onset is cerebellar gait and limb ataxia associated with slow eye movements and hyporeflexia. However, it has been shown recently that the phenotype of SCA2 is wider than previously believed. Patients may present with either a typical L-dopa-responsive parkinsonism or an atypical parkinsonism including signs of ataxia (3). There may be considerable intra- and interfamilial variation of clinical signs (4). We describe three siblings with SCA2 CAG expansion, one sibling presented with parkinsonism and ataxia, the second one with juvenile parkinsonism, and the third one with motor neuronopathy. We investigated the relationship between phenotype and genotype.

Case Report

Three siblings were examined after obtaining permission to use their photographs and informed consent was obtained to take blood sampling for genetic study. Genomic DNAs were isolated from peripheral blood lymphocytes using the DNA Extractor WB kit (Wako, Japan). The regions containing the SCA2 CAG repeats were PCR-amplified using previously described gene-specific primers (5´-CCCTCACCATGTCGCTGAAGC-3´ and 5´-3´) (5). The number of the repeats in the fluorescent-labeled PCR products was estimated by Gene Scan analysis using an ABI PRISM 310 automated DNA sequencer (Applied Biosystems, Foster City CA USA), then, determined through the PCR products sequencing on an ABI PRISM 310 Genetic Analyzer using a Big Dye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems).

The proband (case 1: III-13) is a 59-year-old man. He had been well until 42 years of age, when he noticed gait difficulties. At 45 years, he was diagnosed with PD. His mother (II-8), sister (case 2: III-14), uncles (II-4,5) and aunts (II-2,7) of the mother’s side had been treated under the diagno-
sis of Parkinson’s disease. The family history suggested they were affected by hereditary parkinsonism with autosomal dominance (Fig. 1). He showed mild rigidity and bradykinesia. No limb or gait ataxia was noted. Levodopa/carbidopa was prescribed with marked benefit. The medication allowed him to perform activities of daily living. He kept his job as a local government employee until the age of 56. However, his symptoms progressed gradually. At the age of 57, he developed dysarthria and trunkal ataxia. Brain magnetic resonance imaging (MRI) study revealed brainstem and cerebellar atrophy (Fig. 2a).

Case 2 (III-14) is the younger 58-year-old female sibling of the proband (III-13). At age 39, she developed resting tremor and rigidity, and bradykinesia. She was diagnosed with juvenile PD. She responded to levodopa very well, keeping her job perfectly for 15 years as an office worker for an insurance company. She sometimes showed mild trunkal and leg dyskinesia during “ON” time with levodopa treatment. She did not show ataxia, abnormal eye movements, pyramidal signs, nor significant dysautonomia except for constipation. Brain MRI revealed no abnormalities. The ratio of myocardial 123I-metaiodobenzylguanidine (MIBG) scintigraphic uptake in regions of interest in the heart to that in the mediastinum (H/M ratio) was reduced (early 1.26, delay 1.09) (6). Her phenotype was indistinguishable from idiopathic PD.

Case 3 (III-12) is the elder 64-year-old male sibling of the proband (III-13). Marginal muscle weakness and atrophy in the upper limbs was noted at 14 years of age. The muscle weakness was slowly progressive. However, he could manage everything in his life as a business person up to the age of 60 years. He did not show signs or findings suggestive of poliomyelitis or exposure to toxic substances that cause muscle weakness. Neurological examination disclosed muscle atrophy in the neck, shoulder girdle, and limbs (Fig. 2b). He did not show ataxia, parkinsonism, or pyramidal signs. Brain MRI revealed no abnormalities. Electrophysiological findings were consistent with a chronic neurogenic pattern. Nerve conduction study was normal with no evidence of conduction block. Compound muscle action potential was low, which was consistent with muscle atrophy.

The siblings had a normal allele with 22 repeats that sequencing showed glutamines were encoded by (CAG)1 (CAA)(CAG)8. The expanded allele of case 1 had 43 glutamine repeats encoded by (CAG)34(CAA)(CAG)8. The number of repeats was increased by two in case 1 compared to case 2 and case 3, and there were no differences between case 2 and case 3 in the genetic investigation.

**Discussion**

This family had been noticed as being affected by hereditary PD with autosomal dominance. The proband case showed ataxia 12 years after the development of parkinsonism and was shown to have SCA2 mutation on gene analysis. Case 2 showed parkinsonism but did not develop ataxia until 19 years after PD onset, when she showed balance disturbance and CT scan confirmed mild cerebellar atrophy. MRI study did not show cerebellar atrophy. MIBG study revealed a decreased H/M ratio which is compatible with parkinsonism, while the other 2 cases (1 and 3) showed H/M ratio values of 2.1 and 1.9, respectively, which are normal. Case 3 developed bilateral muscular atrophy of the arms. Cases with SCA2 exhibiting muscular atrophy and cerebellar ataxia or rigidity have been previously reported (7, 8). Case 3 started to develop muscle weakness and atrophy of the arms at 14 years of age, which worsened very slowly. He was not affected by poliomyelitis, with his serum titer being lower than the detectable limit. Nerve conduction velocity was normal, but there was a suggestion of spinal cord motor neuron degeneration. The CAG repeat expansion in SCA2 gene was detected in case 3. Pathological...
study has previously revealed cases of SCA2 showing motor neuron degeneration (9). Case 3 (III-12) may be a phenotype of SCA2 and should be followed up for the possible development of ataxia or parkinsonism. Pathological study will be recommended for the motor neuronopathy in the future.

Patients with parkinsonism-predominant SCA2 without ataxia have been recently described to respond dramatically to levodopa therapy. These cases are reported in Asians, but rarely in Caucasians. The present cases are compatible with these reports of PD (3, 4, 7). CAG repeats which were in the low expansion range and interrupted by CAA were associated with SCA2-related parkinsonism (10, 11). Another finding about SCA disease is the large variation of the phenotype. SCA2 has been classified by OPCA, and its phenotype seems to be related to the length of CAG repeats (12, 13). However there was no difference in the length on CAG repeats or the gene sequence in our siblings. Their phenotype varied and they were diagnosed as different disorders clinically. There may be other factors apart from the length or sequence of CAG repeats that determine SCA2 phenotype. CAG repeat size can be different between tissues such as cerebellum, pons, or spinal cord (14). Genotypic examination for SCA2 should be considered more widely because of the varied phenotype (15).

In conclusion, we have described three siblings with SCA2, who developed juvenile parkinsonism, parkinsonism/
ataxia, and motor neuronopathy. Motor neuron symptoms and signs may be a manifestation in SCA2. The SCA2 gene should be studied in families with heterogeneous neurodegenerative disorders, including motor neuron disease.

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

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