Case Report

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Spinocerebellar ataxia type 2 presenting with involuntary movement: a diagnostic dilemma

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Abstract

Spinocerebellar ataxia type 2 (SCA2) is a rare disease characterized by slowly progressive ataxia, dysarthria, ophthalmoplegia, and slow saccade. SCA2 can present with a complex combination of hyperkinetic and hypokinetic movement disorders. Here, we describe a patient with SCA2 that partly mimicked the clinical manifestations of Huntington's disease; similar symptoms had previously occurred in the patient's family members. The findings in this report indicate that, when a patient exhibits choreiform movement (i.e., accompanying cerebellar ataxia), an SCA2-related mutation could be responsible for the onset of disease. In addition, this knowledge of the potential for extrapyramidal involvement in such patients is critical for clinicians.

Keywords

SCA2, chorea, China, cerebellar ataxia, rare diseases, dysarthria, spinocerebellar ataxias, movement disorders

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Introduction

Spinocerebellar ataxia type 2 (SCA2) is autosomal dominant cerebellar ataxia with genetic anticipation, which shows earlier onset and more severe phenotype in successive generations, due to expanded CAG repeats; it exhibits probable paternal transmission. Within the causative gene *ATXN2*, the pathological repeat size that is

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responsible for SCA2 onset is >33.[1] The pathological mechanism of SCA2 is similar to that of Huntington's disease (HD), due to the expansion of polyglutamine-encoding CAG repeats in the corresponding genes. Patients with SCA2 exhibit complicated clinical heterogeneity, including cerebellar ataxia, slow saccade, extrapyramidal symptoms, and possible dementia. Choreiform movement in patients with SCA2 has been described in a previous case report;[2] however, this rare phenotype is generally poorly characterized, although SCA2 is one of the most common types of SCA in China. Here, we describe a Chinese patient with SCA2 manifesting as generalized chorea, which had been present in other members of the patient's family.

Case report

A 44-year-old right-handed man presented to the Neurology Department at the Second Affiliated Hospital, Zhejiang University School of Medicine with a 5-year history of involuntary movement in the upper extremities and head. Over the prior 3 years, abnormal movement, slurred speech, and gait disturbance had developed in a progressive manner, along with occasional dysphagia when drinking. In particular, the patient experienced occasional involuntary movement in the bilateral upper extremities, especially when he experienced anxiety and fatigue. Because this movement initially did not influence his daily activities, he did not consult a physician. Subsequently, the involuntary movement progressively worsened, and spread to his head. Therefore, he presented to our hospital for diagnosis and treatment. At that time, he did not receive a definite diagnosis, and symptomatic treatment, including haloperidol and clonazepam, did not significantly alleviate his complaints.

After 3 years of disease progression, the patient's dysarthria began to cause difficulties in routine communication, and his clinical symptoms became increasingly complex. His unsteady gait and dysphagia occurred when he engaged in fast movement and drinking, respectively, frequently leading to falls and coughing. He denied use of a dopamine-blocking agent, but reported a prominent family history of these manifestations in his elder sister, mother, aunt, and grandfather (Figure 1a). Neurological examinations revealed dysarthria and dysphagia. Relatively slow saccadic eye movement was detected in the patient and his elder sister. Moreover, an increased tendon reflex was observed in the patient. The finger to nose test, heel to shin test, and rapid alternating movements revealed marked abnormal findings, indicating probable cerebellar malfunction. Muscle force, tension, and sensory examinations demonstrated normal findings. His median score was 18 on the Scale for the Assessment and Rating of Ataxia, while his total motor score was 26 on the Unified Huntington's Disease Rating Scale. Brain magnetic resonance imaging of the patient revealed obvious cerebellar atrophy (Figure 1b). During 12 years of follow-up, the patient's ataxia and choreiform movements gradually worsened and he died of probable respiratory disease and nutritional deficiency at 56 years of age.

Genetic diagnosis

The patient in this report exhibited progressive cerebellar ataxia and chorea. His phenotype, neurologic examination results, and magnetic resonance imaging scans indicated probable impairment of the cerebellum and extrapyramidal tract. Based on these findings, as well as the patient's positive family history, the following potential causative genes were screened: *HTT*, *SCA1*, *SCA2*, *SCA3*, *SCA6*, *SCA7*, *SCA12*, *SCA17*, *SCA31*, and *DRPLA*. All genes revealed negative mutation findings. Therefore, we

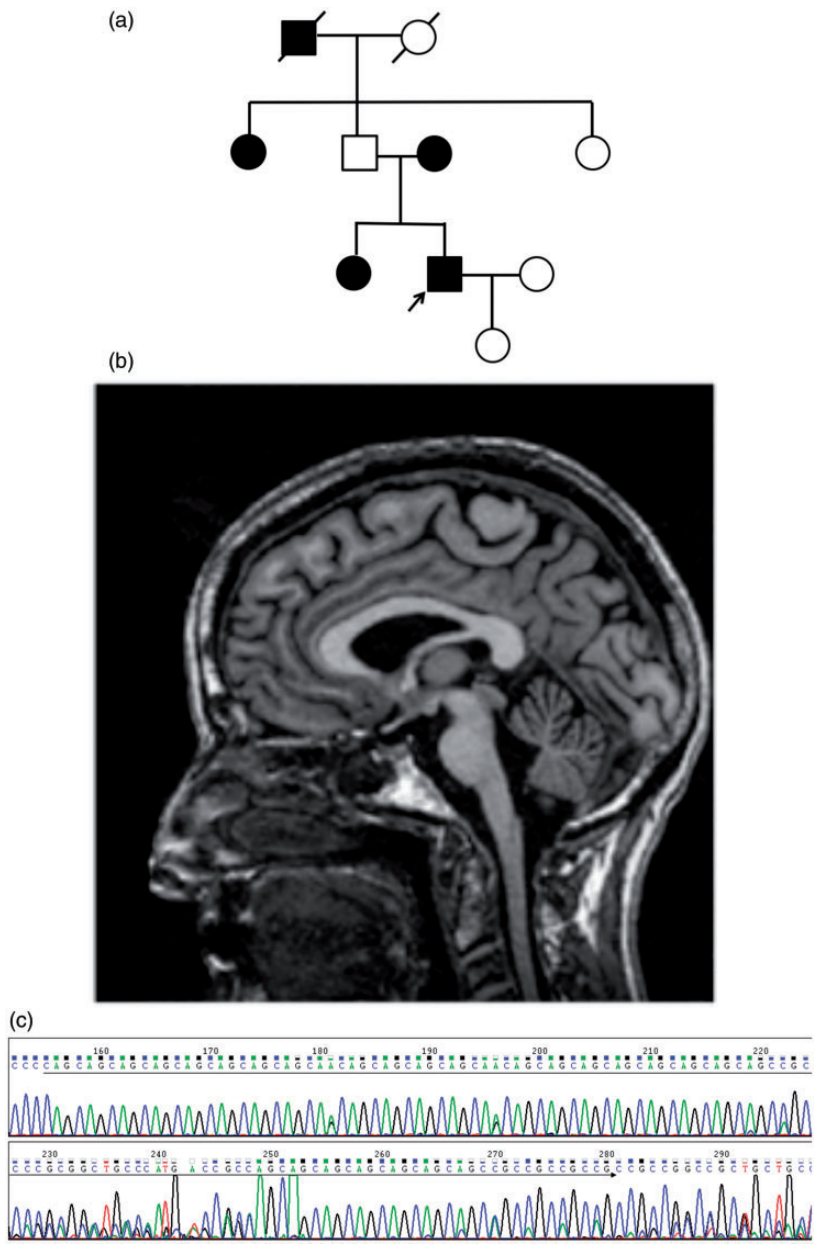

Figure 1. Findings in a Chinese patient with SCA2. a) SCA2 pedigree of the patient's family; arrow indicates the index patient. b) Sagittal brain magnetic resonance imaging scan of the index patient, which demonstrates marked cerebellar atrophy. c) Chromatogram of CAG repeats within the *ATXN2* gene in the index patient; arrow indicates the expanded allele. The normal allele of the index patient is 22 CAG repeats, while the expanded allele is 42 CAG repeats. SCA2, Spinocerebellar ataxia type 2.

Table 1. Overview of studies depicting patients with SCA2 who exhibit choreiform movement.

Study	Country	Phenotype	Onset age (years)	Year	No. of patients
Sasaki et al.[17]	Japan	Essential tremor, choreiform movement, and ataxia	Not reported	1996	2 of 12
Bhalsing et al.[2]	India	Ataxia and involuntary movement	38	2013	1 (case report)
Avelino et al.[18]	Brazil	Motor development delay, involuntary movement, and dystonia	Near 2	2014	1 (case report)
Pedroso et al.[19]	Brazil	Ataxia, dysarthria, and choreoathetotic movements	44	2014	1 of 35
Pedroso et al.[20]	Brazil	Dystonia, parkinsonism, and chorea	Not reported	2016	5 of 33

SCA2, Spinocerebellar ataxia type 2.

screened for *ATXN2* mutations in the patient and his family members. Sanger sequencing showed 22 and 42 CAG repeats within the normal and expanded alleles of the *ATXN2* gene, respectively (Figure 1c), which confirmed the diagnosis of SCA2.

Discussion

Unstable CAG expansions within the *ATXN2* gene are responsible for SCA2, which is a type of polyglutamine spinocerebellar ataxia.[3] SCA2 mainly manifests as slowly progressive ataxia, dysarthria, slow saccadic eye movements, and polyneuropathy.[4–6] It is the second most common SCA subtype worldwide, only surpassed by SCA3.[7] Although SCA2 shares clinical symptoms with other SCA subtypes, it is characterized by the clinical hallmark of slow saccadic eye movement, which is distinct from the movement of other common SCA phenotypes.[8,9]

Complex phenotype and genotype variations are typically observed in patients with SCAs, including diverse combinations of hyperkinetic and hypokinetic movement abnormalities.[10,11] Among the subtypes of SCA, various extracerebellar manifestations could appear as the presenting, dominant, or isolated disease characteristics.[12] Movement disorders have been observed in patients with other SCAs, including SCA3 and SCA1.[13] In patients with SCA2, typical magnetic resonance imaging findings show extensive atrophy in the olivopontocerebellar system and cerebral cortex.[14] In contrast, marked striatal atrophy, as well as regional or whole-brain gray and white matter changes, have been identified in patients with symptomatic HD.[15] These imaging variations could help to differentiate between a diagnosis of early SCA2 or early HD.

Similar to patients with other SCAs, patients with SCA2 mainly present with progressive cerebellar syndrome, which is sometimes associated with dystonia, parkinsonism, and myoclonus.[16] Only a few reports mentioned that patients with SCA2 could present with choreiform movements; these reports are summarized in Table 1.[2,17–20] Hyperkinetic movements may serve as the sole presenting symptom during the course of SCA2, as well as one of the complicated combinations of diverse symptoms. Although involuntary movement is a particularly common feature of

SCA17 and DRPLA, other SCA subtypes, including SCA1, SCA2, and SCA3, may also include the onset of chorea.[21] To the best of our knowledge, this is the first report of a Chinese patient with SCA2 presenting with symptoms suggestive of HD. The pathophysiology of choreiform movement in patients with SCA2 is unknown. Pathological studies of patients with SCA2 have shown involvement of the basal ganglia, thalamus, substantia nigra, and motor cortex, as well as the cerebellum, which is common to patients with all types of SCAs.[1,22] Because patients with SCA2 have a neuropathology similar to that of patients with HD, the extrapyramidal involvement could explain the increased incidence of diverse movement disorders in patients with SCA2.

There have been few clinical studies of movement disorders in patients with SCA2 owing to the rarity of the disease and the complicated clinical heterogeneity among affected patients.[1,23] Autopsies of patients with SCA2 have shown significant nigral degeneration.[24] Some experiments have also demonstrated that deep brain stimulation of the subthalamic–thalamic region could significantly alleviate postural tremor in patients with SCA2,[25] while anticholinergics and dopaminergic drugs have also been reported to improve movement disorders in patients with SCA2.[26] Thus, although medication and surgical treatment cannot slow disease progression, these treatments have been shown to improve the quality of life for patients with SCA2.

In conclusion, we have described the diverse clinical characteristics of a Chinese patient with SCA2, which partly mimicked the clinical phenotype of HD; similar symptoms had previously occurred in the patient's family members. Epigenetic factors and probable modifying genes should be further studied to explore the heterogeneity of this disease. Additionally, when confronted with a patient with choreiform movement, accompanying cerebellar ataxia or without ataxia, clinicians should screen for a variety of SCA2-related mutations, especially when negative results are reported for well-known SCA causative genes.

Ethics approval and consent for publication

The study was approved by the Ethics Committee for Human Research in Second Affiliated Hospital of Zhejiang University School of Medicine. Informed consent for publication was obtained from the patient's legal surrogates prior to publication of this report.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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