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Machado-Joseph disease/SCA3 and myotonic dystrophy type 1 in a single patient

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ABSTRACT

We report here, for the first time, the case of a 41-year-old man with both Machado-Joseph disease (MJD)/spinocerebellar ataxia type 3 (SCA3) and myotonic dystrophy type 1. The patient noted dysarthria at 14 years of age and unsteady gait at 30 years of age. Similar sized expansions of the CAG trinucleotide repeats in one allele of the *ataxin-3* (*ATXN3*) gene were found in both the patient and his father, although in the other allele the length of the CAG repeats was shorter in the father compared with the patient. In the *dystrophia myotonica protein kinase* (*DMPK*) gene the CTG repeats were much more expanded in the patient compared with his father. Thus it is possible that, in the farther, the short CAG repeat in the non-expanded *ATXN3* allele delayed the onset of cerebellar symptoms, and/or that the expanded CTG repeat in the *DMPK* gene in the patient accelerated the pathogenesis of MJD/SCA3.

1. Introduction

Machado-Joseph disease (MJD), also known as spinocerebellar ataxia type 3 (SCA3) is an autosomal dominant disorder of cerebellar ataxia that is variably accompanied by other neurological features, such as pyramidal signs, extra-pyramidal signs, eyelid retraction, bulging eyes, blepharoptosis, ophthalmoplegia, nystagmus, faciolingual myokymia, tongue atrophy, muscular atrophy, sensory disturbance, and urinary disturbance [1,2]. SCA3 is caused by the expansion of CAG trinucleotide repeats in the *ataxin-3* (*ATXN3*) gene, which is located on chromosome 14q (MIM 109150) [3,4]. Myotonic dystrophy type 1 (DM1) is an autosomal dominant myopathy with myotonia that is variably accompanied by cardiac conduction impairment, cataracts, and endocrinological disorders (MIM 160900) [5]. The cause of DM1 is the expansion of CTG trinucleotide repeats in the 3′ untranslated region (3′-UTR) of the *dystrophia myotonica protein kinase* (*DMPK*) gene on chromosome 19q13.3 [6,7]. In general, SCA3 and DM1 are categorized in different classes of trinucleotide-repeat diseases and, to date, there have been no reports of patients with both diseases. Here, we report the first case of both SCA3 and DM1.

2. Case report

2.1. Case 1 (the proband)

A 41-year-old married man who had no children had noted dysarthria at 14 years of age and gait disturbance at 30 years of age. These symptoms gradually progressed. At presentation, pitting edema in the distal portion of the lower limbs was observed bilaterally. Mild blepharoptosis and frontal alopecia were also found. Neurological examination revealed mild to moderate muscle weakness in the face, neck and tongue, but no cognitive impairment or dysphagia were observed. He also showed horizontally overshooting eye movement, severely slurred speech, and moderate truncal ataxia. Mild to moderate muscle weakness was observed in the distal portion of the upper limbs and in the proximal portion of the lower limbs. Deep tendon reflexes in the four extremities were all decreased or absent, and pathological reflexes were not observed. Grip myotonia in the hands and myotonic discharge, assessed by needle electromyography (EMG), were found. Sensation was normal and Gowers' sign was positive. Mild lordosis was observed. The autonomic system was normal. Serum creatinine kinase (CK) level was normal (274 U/l; normal 62–287). HbA1c was normal (5.7%; normal <5.8) but the serum cholesterol level was elevated (252 mg/dl; normal 128–220). Cerebrospinal fluid was normal. Brain roentgenogram showed thickened cranial bone and a narrowed Turkish saddle. Head magnetic resonance imaging (MRI) demonstrated mild cerebral atrophy with FLAIR/T2-high lesions in

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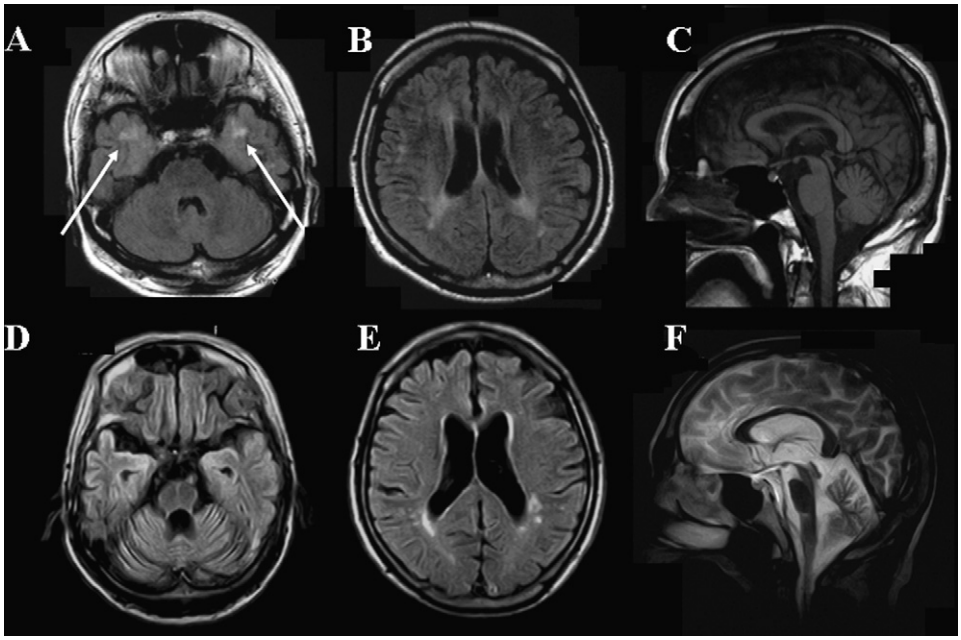

Fig. 1. Brain MRI studies of cases 1 and 2. (A–C) FLAIR MRI of case 1; (D–F) FLAIR (D and E) and T2-weighted MRI (F) of case 2. Note FLAIR/T2-high lesions in the subcortical white matter of the temporal tip (A, arrows), periventricular FLAIR/T2-high lesions (B), mild cerebellar atrophy in the anterior lobe (C), no lesions in the white matter of temporal tip (D), mild periventricular FLAIR/T2-high lesions (E), and marked atrophy of the cerebellum and brainstem (F).

the white matter of the temporal tip (Fig. 1A) and in the periventricular white matter (Fig. 1B). Mild atrophy in the anterior lobe of the cerebellum was found (Fig. 1C).

2.2. Case 2 (the proband's father)

A 73-year-old man developed unsteady gait at 40 years of age. His gait disturbance progressed gradually, and he had to walk with aid at 62 years of age. Bilateral pitting edema was found in the distal lower limbs. Neurological examination revealed horizontal gaze-evoked nystagmus, mild impairment of upward gaze, bilateral hypoacusia, severe dysarthria, severe limb and truncal ataxia, and severe bathyhypesthesia in the lower limbs with distal dominance. In contrast to case 1, all muscle power was normal and grip myotonia was not observed. Deep tendon reflexes were absent. The serum CK level was normal (54 U/l). Head MRI showed no FLAIR/T2-high lesions in the white matter of the temporal tip (Fig. 1D), but a few lesions were observed in the periventricular white matter (Fig. 1E). Apparent cerebellar and brainstem atrophy was observed (Fig. 1F).

3. Genetic analyses

Expansion of CAG repeats in the *ATXN3* gene and CTG repeats in the *DMPK* gene was examined by polymerase chain reaction (PCR) and Southern blot analysis, respectively. The number of CAG

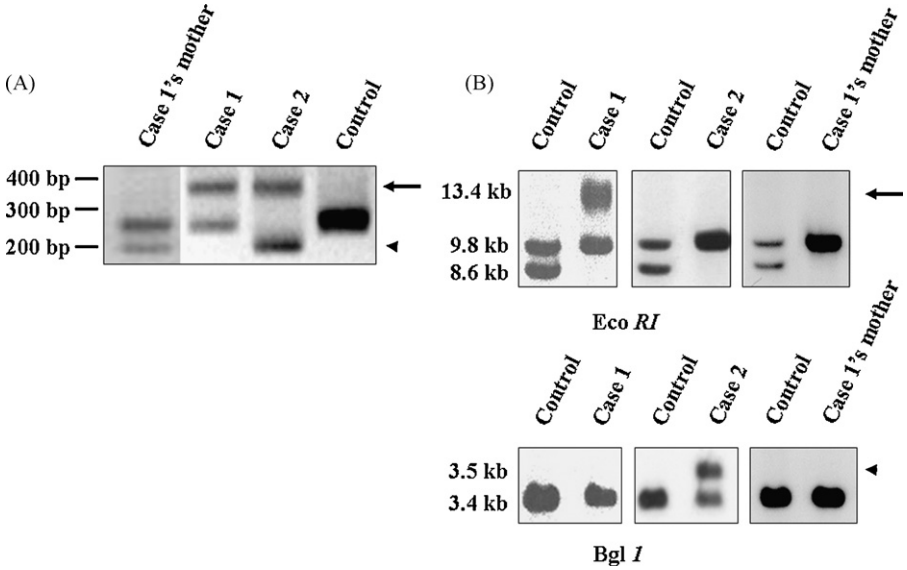

Fig. 2. PCR analysis of the *ATXN3* gene (A) and Southern blot analysis of the *DMPK* gene with EcoRI (B, upper panel) and BglI (B, lower panel). The arrow in (A) indicates expanded CAG repeats in both cases 1 and 2. The arrowhead in (A) indicates the shorter CAG repeat in the second allele of case 2. The arrow and arrowhead in (B) indicates expanded CTG repeats in cases 1 and 2, respectively. The case 1's mother did not show expansion of trinucleotide repeats in *ATXN3* or *DMPK*, respectively (A and B).