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Spinocerebellar ataxia type 2 (SCA2) with white matter involvement

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Abstract

Two sisters presented with olivopontocerebellar atrophy, neuronal loss in the substantia nigra, intranuclear ubiquitin-, ataxin-2-positive inclusions in neurons, and severe demyelination and axon loss of the cerebral white matter with no accompanying inflammatory pathology. The genetic study demonstrated a 22/36 CAG triplet expansion in the SCA2 gene in one of the sisters; SCA1, SCA3, SCA6, SCA7, SCA8, SCA12, SCA17 and DRPL were ruled out in this patient. The present report shows that severe cerebral white matter pathology may occur in the context of SCA2.

Keywords: Spinocerebellar ataxia; CAG expansion; White matter; SCA2; Demyelination

Spinocerebellar ataxia type 2 (SCA2) is an autosomal dominant ataxia caused by a CAG trinucleotide expansion in the codon region of the chromosome 12q23-24.1 that encodes the protein ataxin-2 [1,5–7]. The normal allele of the SCA2 gene comprises 14–31 CAG triplets interrupted by 1 to 3 repeats of CAA. The mutated allele is expanded to a sequence of 35–59 CAG repeats and consists of a pure stretch of CAG [1,8,12,14]. SCA2 is manifested as slowly progressive ataxia and dysarthria associated with tremor, nystagmus, slow saccadic eye movements and ophthalmoparesis. Tendon reflexes, which are brisk during the first years of life, are absent later. The disease is manifested in some patients as parkinsonism that responds to levodopa or dopamine agonists [4,14]. Pathological findings reveal severe neuronal loss in the pons and cerebellum (mainly Purkinje cells), and marked degeneration in the substantia nigra, inferior olive, and dorsal columns of the spinal cord. Other nuclei are also affected including caudate, putamen and globus pallidus, thalamus, subthalamus and periaqueductal grey matter; the cerebral cortex is involved in some cases [3]. Intranuclear neuronal inclusions are commonly seen in SCA2 [9,11,14]. The cerebellar peduncles and cerebellar white matter are usually involved, but the cerebral white matter is currently preserved.

SCA2 was found in two sisters with olivopontocerebellar atrophy and severe white matter involvement. The detection of CAG expansion mutation, performed by PCR in post-mortem tissue in one of them, showed a genotype 22/36. No other members of the family were apparently affected. The patients descended from consanguineous parents. Eleven siblings were born alive; two died in the first days of live and one died at the age of 7 years. No neurological symptoms, excepting for probable Alzheimer's disease, have been recorded in other members of this family (Fig. 1).

The initial neurological symptoms in the first patient appeared at the age of 27 years and were characterized by dysarthria and difficulties in walking, coincidental with the pregnancy of a single girl. Neurological deficits progressed slowly during the following 10 years when bruxism, screaming and agitation episodes were observed. MRI studies at the

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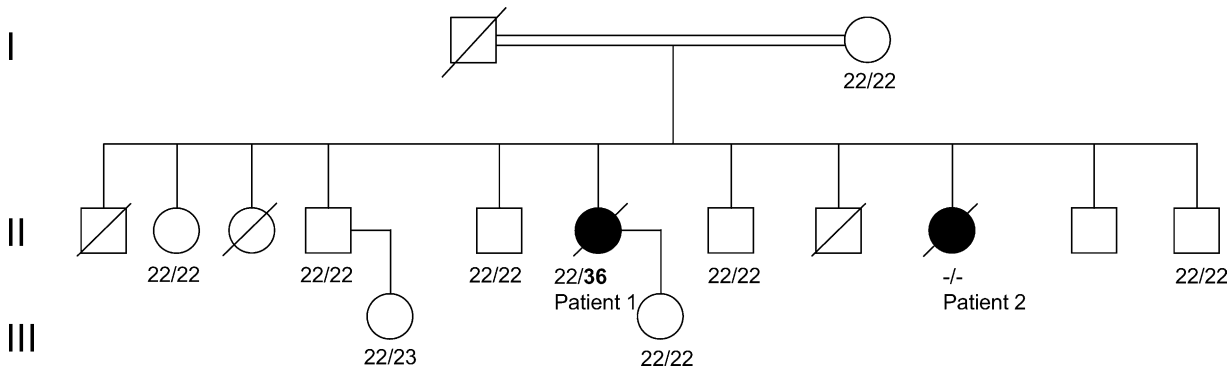

Fig. 1. Patients 1 and 2 are indicated by filled circles. The numbers below each case show the number of CAG repeats.

age of 42 showed vermian and hemispheric cerebellar atrophy, pontine atrophy and severe cerebral leucoencephalopathy. The patient evolved rapidly with tetraparesia in flexion, myoclonic jerks, urinary and faecal incontinence, and mental deterioration and dementia. She died at the age of 46.

A younger sister with diabetes mellitus, diagnosed at the age of 25 years, started with difficulties in walking, dysarthria and bruxism at the age of 31. The disease progressed rapidly, with practical impossibility of walking 5 years later, together with mental impairment, anosognosia, hypersexuality, aggressiveness, choreoathetosis and severe language deterioration. MRN studies disclosed vermian and hemispheric cerebellar atrophy and bilateral hyperintensities in the subcortical white matter. She died at the age of 40. No electrophysiological studies are available in these patients.

The brains were fixed by immersion in 10% buffered formalin for 2 or 3 weeks. The neuropathological study was carried out on de-waxed 4-μm thick paraffin sections. In addition, DNA from the two patients was extracted from paraffin-embedded brain tissue. DNA was amplified in a mixture containing 200 μM of each deoxynucleotide, 200 ng primer SCA2a and 40 ng labeled primer SCA2b-FAM [12], 1.25 U Expand High Fidelity PCR system (Roche), and 2 mM Tris–HCl, pH 7.5 (25 °C), 10 mM KCl, 0.1 mM DTT, 0.01 mM EDTA, 0.05% Tween-20, 0.05% Nonidet P40, 5% glycerol and 2.5 mM $MgCl_2$, in a final volume of 10 μl. The PCR amplification protocol was as follows: 5 min denaturation, 30 cycles at 94 °C, 1 min; 58 °C, 30 s; and 74 °C, 1 min; and final extension at 72 °C for 7 min. Runs were done on Genescan 3.1 (PE Biosystems) and results were analyzed with the Genotyper 2.5.

Genetic analysis showed the presence of 22 CAG triplets in the normal allele and a sequence of 36 CAG repeats in the mutated alleles in the first patient. Genetic studies showed no abnormalities in SCA1, SCA3, SCA6, SCA7, SCA8, SCA12, SCA17 and DRPL genes. The available material was not suitable for analysis in the second patient because of DNA degradation. Other family members were also studied following informed consent; the two members of the third generation were aged 22 and 21 years at the time of the genetic study. Expanded alleles within the normal range were present in all cases examined (Fig. 1). Direct sequencing was successfully done in the majority of subjects of the family except for patients 1 and 2, and for one brother who rejected the genetic study. All examined family members presented $(CAG)_{22}$ interrupted by two CAA: $(CAG)_8$ CAA $(CAG)_4$ CAA $(CAG)_8$, which conferred a stable transmission of the repeats. [1,2]. No material for study was available from the father and we cannot rule out the possibility that the father might have carried out the mutation. Other possibility is that the father could have had large normal alleles [15]. A low level of CAG repeat expansions in SCA2, as observed in this case, is not new. Sanpei et al. [13] reported a patient with a 35 CAG repeat allele, while Cancel et al. [1] reported a patient with a 36 CAG repeat expansion. Moreover, cases with small expansions may appear as sporadic or recessive cases [15]. Interestingly, the daughter of the first patient showed normal alleles, implying that she had inherited the normal allele of her mother (22 repeats) instead of the mutant, pathological allele of 36 repeats.

The neuropathological study revealed similar findings in the two cases. The macroscopic examination showed marked cerebellar atrophy, moderate atrophy of the pons (mainly in patient 1) and inferior olivary nucleus, and reduced pigmentation of the substantia nigra. The microscopic study revealed loss of Purkinje neurons (Fig. 2A), together with axonal torpedoes (axonal swellings) in many remaining Purkinje cells (Fig. 2B). Marked neuronal loss and gliosis were observed in the inferior olivary nuclei (Fig. 2C), dentate nuclei, pontine nuclei and substantia nigra. This was accompanied by atrophy of the cerebellar peduncles. Mild neuron loss and gliosis was also present in the gracilis and cuneatus nuclei, trigeminal nuclei and Clarke's column. The dorsal columns of the spinal cord were demyelinated and reduced numbers of myelin fibers were seen in the nucleus dorsalis of Clarke, dorsal spinocerebellar tracts, cuneate and gracilis fascicles, medial lemniscus and trigeminal tracts. Slight neuron loss and gliosis was noticed in the ventral anterior, ventral medial and ventral posterior nuclei, mediodorsal, pulvinar and reticular nuclei of the thalamus, and in the subthalamus. Moderate neuron loss and gliosis was present in the caudate and putamen. Neuron loss was observed in the pal-