

Spinocerebellar Ataxia Type 2 (SCA2): Clinical Features and Genetic Analysis

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Summary

Spinocerebellar ataxia type 2 (SCA2) is an autosomal dominant neurodegenerative disease that results from the expansion of an unstable trinucleotide CAG repeat encoding for a polyglutamine tract. In normal individuals, alleles contain between 14 and 31 CAG repeats, whereas the pathological alleles have more than 35 CAG repeats. The clinical phenotype of SCA2 includes a progressive cerebellar ataxia with additional features such as ophthalmoplegia, extra-pyramidal or pyramidal signs and peripheral neuropathy.

We report a SCA2 large African family with several affected individuals. A major pathological allele carrying 43 CAG repeats was identified in the proband. To our knowledge, this is a first report of a SCA disorder described in Central African patients, thus indicating the need to consider this diagnosis in young African ataxic patients.

Key words: Spinocerebellar ataxia 2, autosomal dominant, CAG repeats, Central African patients.

Introduction

The spinocerebellar ataxias (SCAs) form a clinically and genetically heterogeneous group of autosomal dominant progressive ataxia disorders. Their clinical phenotypes vary substantially between and within spinocerebellar ataxia families, making clinical classification extremely difficult [1].

Up to now, 15 different loci (SCA1–8, 10–14, 16 and 17) have been found in association with SCAs [2–8]. All mutations that have been identified so far are expanded repeats. In six of them, SCA1, 2, 3, 6, 7 and 17, the mutation is an unstable translated CAG repeat coding for an elongated polyglutamine tract within the respective proteins.

SCA2 is one of the most frequent forms, accounting for 50–70% of all families with dominant ataxia (OMIM, 183090). Clinically, SCA2 usually presents with progressive ataxia accompanied by a variety of additional symptoms such as dysarthria, ophthalmoplegia, extra-pyramidal or pyramidal signs, slow eye movements and peripheral neuropathy. In the present report, we describe a SCA2 large family

from Central Africa with several affected subjects. In addition, the SCA2 causing mutation was identified in the index case.

Material and Methods

Subjects

The proband was a 14-year-old female from a large family with several affected individuals (Fig. 1). This patient was evaluated for the first time in clinical genetics consultation at Kigali Teaching Hospital in Rwanda in December 2005. She had history of progressive cerebellar ataxia since the age of 12. She presented cerebellar limb ataxia associated with dysarthria, dystonia and mild akinesia. Clinical examination revealed slow eye movements, lower limb decreased reflexes, supranuclear ophthalmoplegia with horizontal nystagmus, facial myokimia, postural tremor with fasciculation, amyotrophy in the lower limbs and proximal weakness in the upper limbs. She had mild pyramidal signs but there was no mental deterioration. She could not walk unassisted. The family pedigree showed that other family members presented similar symptoms with a decreasing age at the onset of symptoms in four successive generations, but unfortunately most of them had died (Fig. 1). These conditions were consistent with an autosomal dominant spinocerebellar ataxia disorder.

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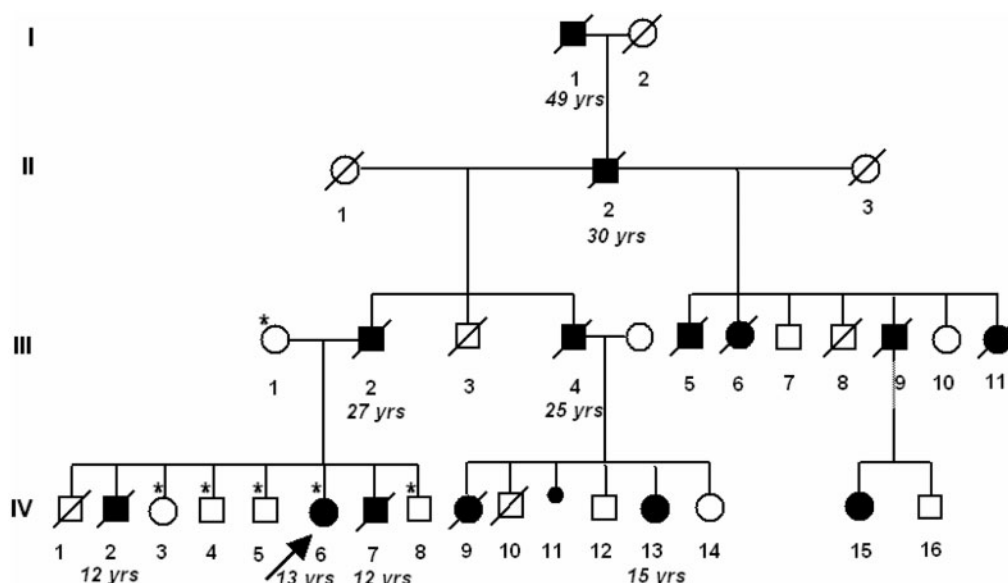


FIG. 1. Pedigree of a SCA2 large African family showing 14 affected subjects over 4 generations. Slashed symbols represent deceased individuals. An asterisk is placed above individuals for whom a DNA sample was obtained and analysed. The age of the disease onset is indicated below affected individuals. The index case is indicated by an arrow.

In order to confirm the diagnosis, blood sample was collected from the index case after informed consent, as well as from five asymptomatic family members (III.1, IV.3, IV.4, IV.5, IV.8, Fig. 1).

SCA1, SCA2, SCA3, SCA6, SCA7 gene analysis

Genomic DNAs were isolated from peripheral blood leukocytes using the Qiagen kit (QIAGEN, SA, France). The regions containing the SCA1, SCA2, SCA3, SCA6 and SCA7 CAG repeats were PCR-amplified using previously described primer sets [9]. The exact size of the repeats in the fluorescently labelled PCR products was determined by Gene Scan analysis using an ABI 3100 automated DNA Sequencer (Applied Biosystems).

Results

The family clinical history and the pedigree revealed that 14 subjects over four generations were affected by the disease (Fig. 1). Almost all patients had progressive cerebellar ataxia. The clinical transmission pattern in this family was consistent with an autosomal dominant inheritance. There was a vertical transmission of the disease trait, and approximately one-half of the offspring were affected. The age at the onset of disease symptoms decreased markedly in the successive generations ranging from 49 to 12 years and almost all cases followed a paternal transmission suggesting an instability of the CAG repeat length.

Molecular analysis of SCA2-CAG expansion in the proband revealed one major CAG pathological expansion allele (CAG¹⁹/CAG⁴³, for a normal range between 14 and 31 CAG repeats). Moreover, an abnormal trinucleotide (CAG) repeat expansion was not detected in the SCA1, SCA3, SCA6 and SCA7 genes.

Discussion

SCAs of different types show similar clinical features and are therefore not or hardly distinguishable. Generally, the SCAs typically manifest in adulthood. However, the age of the disease onset in SCA2 varies, occurring between early childhood and late adulthood with features of anticipation. On average, the disease starts around the age of 35 years. All SCA2 patients suffer from a progressive cerebellar syndrome with ataxia of gait, ataxia of limb movements and dysarthria. Saccade slowing is a highly characteristic feature that is observed in the majority of SCA2 patients. Cerebellar oculomotor abnormalities are rarely found in SCA2. Typically, tendon reflexes are absent or decreased. Pyramidal tract signs are present in <20% of the patients. Vibration sense is decreased in most patients [10–12].

It has been shown in a previous study of 89 autosomal dominant cerebellar ataxia families that the SCA2 mutation was the most frequent cause of SCA, accounting for 40% of all SCAs, as compared

with SCA1 and SCA3 which account for 35 and 15%, respectively [13].

In the present report, the disease onset occurred earlier in the index case than in her relatives (I.1, II.2, III.2, III.4) (Fig. 1), suggesting an anticipation. Indeed, as in other disorders caused by expansions of CAG repeats in the coding region an anticipation can be observed in families with a SCA2 mutation [14]. The anticipation is the onset of the symptoms at decreasing ages in successive generations, together with an increasing severity of the clinical signs. This feature is linked to an increased length of the repeat expansion. Indeed, it has also been shown that the frequency of dystonia, myoclonus and myokymia increased with the size of the CAG repeat, while ophthalmoplegia, mental impairment, dysarthria and axonal neuropathy are correlated with disease duration [14]. In a study of nine Chinese families, Zhou *et al.* [15] showed a strong inverse correlation between the age of onset and the number of repeats. A remarkable family was reported by Babovic-Vuksanovic *et al.* [16], in which a child with more than 200 CAG repeats had a neonatal onset of hypotonia followed by retinitis pigmentosa and optic atrophy. Moreover, an increasing repeat number is statistically associated with an earlier disease onset and more severe symptoms. However, an individual prognosis based on the size of the expansion is not possible.

In SCA2, transmission of the CAG repeat from mother to child is usually stable, but there is a significantly higher paternal instability of the CAG repeat length [13], thus explaining that for this disease the anticipation is linked to paternal transmission.

In conclusion, clinical signs, ages at onset and durations of the SCA2 disease vary substantially between and within affected families. The CAG repeat instability at SCA2 locus explains this extensive clinical variability and the anticipation.

For genetic counselling purposes, one has to consider that paternal transmission is at high risk for significant anticipation, and earlier onset of the disease in children due to the instability of the CAG repeats, while a maternal transmission can occur but is associated with a stable mutation size.

To the best of our knowledge, this is the first clinical and molecular diagnosis of SCA2 in Central African patients. Our findings showed that this neurogenetic disorder could be considered among other neurological pathologies in this population and that a particular attention should be given to young patients in affected families. Further epidemiological studies on large cohorts are required in order to establish the frequency of all SCA disorders in African populations.

References

1. Burk K, Abele M, Fetter M, *et al.* Autosomal dominant cerebellar ataxia type I clinical features and MRI in families with SCA1, SCA2 and SCA3. *Brain* 1996;119(Pt 5):1497–505.
2. Orr HT, Chung MY, Banfi S, *et al.* Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. *Nat Genet* 1993;4:221–6.
3. Kawaguchi Y, Okamoto T, Taniwaki M, *et al.* CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1. *Nat Genet* 1994;8:221–8.
4. Sanpei K, Takano H, Igarashi S, *et al.* Identification of the spinocerebellar ataxia type 2 gene using a direct identification of repeat expansion and cloning technique, DIRECT. *Nat Genet* 1996;14:277–84.
5. Zhuchenko O, Bailey J, Bonnen P, *et al.* Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the alpha 1A-voltage-dependent calcium channel. *Nat Genet* 1997;15:62–9.
6. Klockgether T, Evert B. Genes involved in hereditary ataxias. *Trends Neurosci* 1998;21:413–8.
7. Herman-Bert A, Stevanin G, Netter JC, *et al.* Mapping of spinocerebellar ataxia 13 to chromosome 19q13.3-q13.4 in a family with autosomal dominant cerebellar ataxia and mental retardation. *Am J Hum Genet* 2000;67:229–35.
8. Yamashita I, Sasaki H, Yabe I, *et al.* A novel locus for dominant cerebellar ataxia (SCA14) maps to a 10.2-cM interval flanked by D19S206 and D19S605 on chromosome 19q13.4-qter. *Ann Neurol* 2000;48:156–63.
9. Pulst SM, Nechiporuk A, Nechiporuk T, *et al.* Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2. *Nat Genet* 1996;14:269–76.
10. Orozco Diaz G, Nodarse Fleites A, Cordoves Sagaz R, *et al.* Autosomal dominant cerebellar ataxia: clinical analysis of 263 patients from a homogeneous population in Holguin, Cuba. *Neurology* 1990;40:1369–75.
11. Riess O, Laccone FA, Gispert S, *et al.* SCA2 trinucleotide expansion in German SCA patients. *Neurogenetics* 1997;1:59–64.
12. Moseley ML, Benzow KA, Schut LJ, *et al.* Incidence of dominant spinocerebellar and Friedreich triplet repeats among 361 ataxia families. *Neurology* 1998;51:1666–71.
13. Giunti P, Sabbadini G, Sweeney MG, *et al.* The role of the SCA2 trinucleotide repeat expansion in 89 autosomal dominant cerebellar ataxia families. Frequency, clinical and genetic correlates. *Brain* 1998;121(Pt 3):459–67.
14. Cancel G, Durr A, Didierjean O, *et al.* Molecular and clinical correlations in spinocerebellar ataxia 2: a study of 32 families. *Hum Mol Genet* 1997;6:709–15.
15. Zhou YX, Wang GX, Tang BS, *et al.* Spinocerebellar ataxia type 2 in China: molecular analysis and genotype-phenotype correlation in nine families. *Neurology* 1998;51:595–8.
16. Babovic-Vuksanovic D, Snow K, Patterson MC, *et al.* Spinocerebellar ataxia type 2 (SCA 2) in an infant with extreme CAG repeat expansion. *Am J Med Genet* 1998;79:383–7.