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Clinical and Genetic Analysis of Spinocerebellar Ataxia in Mali

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Abstract

Autosomal dominant cerebellar ataxia, currently denominated Spinocerebellar ataxia (SCAs) represents a heterogeneous group of neurodegenerative disorders affecting the cerebellum and its connections. We describe clinical and molecular findings in sixteen patients originating from Malian families, who suffer from progressive cerebellar ataxia syndrome. Molecular analysis allows genetic profiles of spinocerebellar ataxia to be distinguished. In seven patients, SCA type 2 (CAG) mutation was expanded from 39 to 43 repeats. SCA type 7(CAG)mutation was confirmed in six patients .Mutations were expanded from 49 to 59 repeats. In three patients, SCA type 3 was diagnosed and CAG mutation was expanded to 73 repeats.

Conclusions—Our data suggests that the most frequent types of SCA are SCA2 and SCA7. However, further studies are needed to confirm these preliminary results.

Keywords

Spinocerebellar ataxia- genetic; inherited disorders- Malians

Introduction

Autosomal dominant cerebella ataxias, currently denominated Spinocerebellar ataxia (SCAs) represent a heterogeneous group of neurodegenerative disorders affecting the cerebellum and its connections [1–2].This broad clinical heteregeneity is associated with a great genetic heterogeneity. Nearly 30 genetic loci have been identified. The more common SCAs: SCA1, SCA2, SCA3 or Macado-Joseph disease, a n d SCA6 belong to a larger group of polyglutamine disorders that also include SCA7, SCA17, dentatorubral-pallidoluysianatrophy, Huntington disease and spinobulbar muscular atrophy (Kennedy disease) [3]. The relative frequencies of different ataxias vary among different ethnic and geographic groups [3–4]. In African continent, specifically in the West African region including Mali, data concerning SCA are very scarce [5–7].

In this present report, we describe our clinical and molecular findings in five large families originating from Mali with SCAs. To our knowledge, we provide the first documentation of SCA genotypes in the Malian population.

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Methods

Five Malian families (AI-1 e A1-2),(B1-1) ,(C1-1 C1-2) with confirmed cases of Spinocerebellar ataxia, between February 2005 and November 2008, are included in this report. The presence of progressive cerebellar ataxia has been considered as necessary for inclusion in the affected group. Patients with ataxia caused or associated with abuse of alcohol or other substances and diseases were excluded. Clinical and genetic examination was performed with the informed consent of the subjects.

Mutation detection

After obtaining patient's consent, blood samples were drawn for molecular testing. The presence or absence of increased number of CAG repeats in the SCA gene was determined using the polymerase chain reaction amplification of the gene from the individual's genomic DNA. Each gene product was sized by high resolution electrophoresis in order to determine the number of CAG tandem repeats in each allele. The study was approved by the Ethic committee of Medical school of Mali.

Results

Molecular genetic analysis confirmed the presence of an expanded number of CAG repeats typical of SCA in at least one individual in each family.

SCA2/FAMILIES

Family SCA2-A1-1. The proband was a 41 year old man who presented at 34 years of age a progressive cerebellar syndrome. A CT Scan of the brain showed cerebellar atrophy.

His oldest brother was 50 year old man who had a progressive cerebellar syndrome manifested at 39 years of age. His brain CT Scan showed cerebellar atrophy.

The mother, aged 68 years, showed similar features of ataxia with onset at 59 years of age. The proband and his oldest brother were available for SCA2 genetic testing, which showed 39 to 40 CAG triplets.

In the second family (SCA2-Ai-2), the proband presented at 34 years of age with severe postural and head tremor. She had dysarthria and developed progressive gait ataxia. Her child and brother showed similar features of progressive cerebellar ataxia, with onset at 10 and 18 years of age, respectively. In both the siblings and the boy, a brain CT Scan showed cerebellar atrophy. Genetic testing for the proband and brother showed expansions ranging from 42 to 43 CAG triplets.

SCA3 Family: SCA3- B1-1

The proband was a 34 year old man, noted the insidious onset and gradual progression of difficulty walking, and a pain in the hip since 29 years of age. His mental examination showed a mild mental impairment. A brain CT Scan showed severe cerebellar atrophy.

His sister aged 30 years old presented similar features of gait difficulty and balance, with onset at 27 years of age. Their younger sister manifested gait difficulty and leg stiffness at 18 years of age. In both siblings, a CT Scan showed cerebellar atrophy.

The mother was reported to be affected with similar clinical features. Molecular analysis performed on proband showed 73 CAG triplets repeats expansions.

SCA7 Family

In family SCA7-CI-1, the proband was a 37-year-old man who presented at 34 years of age with progressive difficulty walking, loss of balance and visual impairment. A CT Scan of the brain showed cerebellar atrophy. In this family, two other brothers were also affected. The disease started at 23 and 17 years of age respectively. Genetic testing was available for them, which showed expansions ranging from 49 to 56 CAG triplets.

In the second family (SCA7-CI-2), the proband was a 21-year-old man who had presented vision difficulty since 15, and gait difficulty at 17 years of age. Clinical findings at the time of our examination included broad based gait, intention tremor and dysarthria. Fundus inspection showed pigmentary degeneration. A CT Scan of the brain showed atrophy of the cerebellum and brainstem. His mother presented at 44 years of age with progressive gait ataxia, dysarthria. The proband, available for SCA7 genetic testing, showed 59 CAG repeats triplets.

Discussion

This study describes the molecular findings and the clinical features in ataxias patients. The subjects tested positive for the mutations revealed SCA2, SCA7 and SCA3 in descending order of frequency. Spinocerebellar ataxia type 3 is the most common spinocerebellar ataxia in the world [4]; however, it is estimated to be rare in Africa. In South Africa, the prevalence of SCA3 was reported to be 3.7% .In our study, SCA 3 was detected in only one family, a total of three patients. Although generally considered rare, SCA7 has a wide geographic distribution. In South Africa, the frequency of SCA7 (22.2%) was considered as one of the highest frequencies reported in the world. In addition, the SCA7 mutations have only been found in populations of Black ethnic origin [7]. It is the most commonly identified form in Sweden and Finland [8]. The frequency of SCA7 (37.50%) in this study showed that SCA7 was not rare. We have a similar finding for SCA2 in Malian populations (43.75%).With sixteen cases diagnosed in our center in less than three years, we expect that more cases of SCA will be diagnosed in the future. Abnormal alleles in patients in our study showed CAG repeats that ranged in copy number from 39 to 43 in patients with SCA2. The expanded CAG repeats of patients with SCA7 ranged from 49 to 59, and SCA3 had 73 CAG triplets repeats expansions. Due to the few number of patients studied, we could not determine the correlation between the expanded CAG repeats and clinical symptoms and the severity of disease. Chronic pain was frequently reported among patients with SCA3 [9]. This symptom has been observed with SCA3/MJD patients in this study.

Conclusion

Our findings suggested that the frequency of SCA2 and SCA7 was significantly higher than that of SCA3/MJD in Malian patients. Further studies will be necessary to confirm these preliminary results. Molecular testing should be extended to cover the other forms of ataxia of which a large number are not found in Africa.

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Table 1

Clinical features of patients

	Patients	Age (in yr) at Onset	Age (in yr) at Exam-ination	Cerebellar signs	Dysarthria	Pyramidal signs	Postural and action tremor	Visual defects and Ophthalmople-gia	Extra Pyramidal signs	Fasciculation	Hypophonic	Dysphagia	Mental Status
SC A_2 A_1 $^{-1}$	IV 5	34	41	+	+	+	+	−	+	−	−	−	Normal
	IV 1	39	50	+	+	+	+	−	+	−	−	−	Normal
	III 2	59	68	+	+	+	+	+	+	−	−	−	+
SC A_2 A_1 $^{-2}$	III 1	32	34	+	+	+	+	−	−	−	−	−	Normal
	IV 1	10	13	+	+	+	+	−	+	−	−	−	Normal
	III 2	18	28	+	+	+	+	−	−	−	−	−	+
	II 1	59	65	+	+	+	+	−	−	−	−	−	Normal
SC A_3 B_1 $^{-1}$	IV 1	29	34	+	+	+	−	+	+	+	+	−	Normal
	IV 3	27	30	+	−	+	−	−	+	+	+	−	+
	IV 8	18	24	+	−	+	−	−	+	+	+	−	Normal
SC A_7 C_1 $^{-1}$	II 2	34	37	+	+	+	+	+	+	−	−	−	Normal
	II 8	17	23	+	+	+	+	+	−	−	−	−	Normal
	II 10	23	28	+	+	+	+	+	−	−	−	−	Normal
	I 1	54	67	+	+	+	−	+	−	−	−	−	Normal
SC A_7	III 3	15	21	+	+	+	+	+	−	−	−	−	Normal
	II 2	24	44	+	+	+	+	+	−	−	−	−	Normal