Spinocerebellar ataxia type 7: Report of an Indian family

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Abstract

Spinocerebellar ataxia type 7 (SCA7) is a form of autosomal dominant cerebellar ataxia which is associated with pigmentary retinal degeneration. It is known for its world-wide rarity except in the Scandinavian countries. It is very rarely reported from India and the neighbouring Asian countries**.** The present report describes the neurogenetic findings of a family of SCA7, from the northern part of Karnataka in South India. It documents the wide intrafamilial phenotypic variability, which could be correlated with the CAG repeat counts and phenomenon of anticipation. Genotype phenotype correlation highlighted certain disparities in comparison with the previous studies. The report highlights the need for multiethnic population studies and the role of genetic counseling and prenatal testing in SCA7 patients.

Key Words

Autosomal dominant cerebellar ataxia, neurogenetics, pigmentary retinal degeneration, spinocerebellar ataxia type 7

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Introduction

Spinocerebellar ataxia type 7 (SCA7) is a form of autosomal dominant neurodegenerative disease, which is known for its world-wide rarity except in Sweden and Finland.[1] Its unique feature is the occurrence of pigmentary retinal degeneration along with degeneration of the cerebellum, brainstem and the cervical spinal cord. The clinical manifestations of SCA7 include motor manifestations dominated by cerebellar ataxia and progressive vision loss with variable temporal profile.[2] It is caused by the expansion of CAG trinucleotide repeat in the chromosome 3p.[3] The phenotypic expressions may vary widely based on the CAG repeat count and age of onset.[2] The condition has been rarely reported from India.[4,5] The present report describes a family of SCA7, consisting of six affected members, from the Belgaum region of Northern Karnataka in South India.

Patients and Methods

This study was initiated following the examination of the proband who presented with features of progressive ataxia followed by vision loss and provided a family history of similar illness. Nine members of this family [Figure 1] were studied genetically after obtaining clearance from the Institutional Ethics Committee. Deoxyribonucleic acid-polymerase chain reaction (DNA-PCR) technique followed by agarose gel electrophoresis was used for the molecular diagnosis of SCA7. The number of repeats was estimated by analysis of the length size of the amplimer, in conjunction with a molecular weight marker.

The genetically proven living members [as indicated by darkened circles and squares in the pedigree chart, Figure 1] were evaluated clinically to assess genotype phenotype correlation. Apart from documenting the findings of standard neurological examination, the ataxic features were quantified using the brief ataxia rating scale (BARS) with a total rating score of 30. This scale is derived from the modified international ataxia rating scale.[6] Ophthalmic evaluation included detail clinical examination with special reference to visual acuity, color vision and funduscopic examination.

Imaging of the brain was performed in all the genetically proven cases; magnetic resonance imaging (MRI) in four and computerized tomography (CT) scanning in one. Comparative electroretinogram (ERG) using eyelid electrodes were performed in the proband (III-4) and one gene proven asymptomatic (III-2) case. Similarly, ocular coherence tomography (OCT) was used to determine the retinal nerve fiber layer thickness in the same two cases.

In addition to the data obtained from the gene proven cases, clinical data of a sib (III-7) belonging to this family who died

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at the age of 3 years is also discussed. This sib was examined by the author 4 years ago as an independent case with a provisional diagnosis of hypotonic cerebral palsy. He was retrospectively considered to be an infantile form of SCA7 based on the positive family history.

Results

Out of the nine members who underwent genetic testing for SCA7, five proved to be positive for the disease. Figure 1 shows the pedigree chart of the family indicating the position of the affected members. The following data analysis and discussion relates to these five genes proven and one clinically diagnosed case of infantile onset SCA7.

Out of the total six affected members five were males and one was female. The clinical presentation of these 6 cases was variable. Two cases (III-2 and III-5) were asymptomatic whithree cases (II-1, III-3 and III-4) had clinical presentation of varying severity and the single genetically non-proven case (III-7) suffered the fatal infantile form. Table 1 shows a summary of the demographic data, CAG repeat counts, neurological, ophthalmic and neuroimaging findings of these cases.

Case Reports

Following is the brief descriptive summary of each of the six affected cases.

Case no. 4 (III-4)

This male proband aged 22 years (CAG count 59, BARS score: 14/30) who presented with 4 years history of progressive symptoms was found to have ataxic gait, dysarthria, bulbar paresis, slowing of saccades and bilateral pyramidal signs. He had a loss of central vision, poor color vision, pale optic discs and moderately severe pigmentary dystrophy of the retina [Figure 2]. The visual symptoms had appeared about 2 years following the neurological symptoms.

ERG showed no recognizable standard wave forms with pattern reversal stimulation suggestive of severe retinal dysfunction. OCT showed evidence of gross thinning of the fovea as well as thinning of the retina nerve fiber layers dominantly affecting the inner layers [Figure 3b]. MRI of the brain showed evidence of moderate atrophy of the cerebellum and brainstem [Figure 4b].

Case no. 3 (III-3)

This elder brother of proband, aged 24 years (CAG count 67, BARS scores 29/30) was symptomatic from the early age of 12 years. At the time of examination 12 years later he was chair bound and required help of two people to mobilize him. He had gross head, truncal and limb tremors even at rest along with severe bilateral pyramidal signs. He had moderately severe bulbar palsy along with mild bifacial weakness. External ocular movements were grossly limited and he was legally blind for 2 years. Pupils were dilated and fixed. Fundoscopy revealed gross pallor of the optic disc and severe pigmentary dystrophy of the retina. The visual symptoms had appeared 4 years following the neurological symptoms. CT scan of the head showed evidence of severe atrophy of the cerebellum and brainstem along with involvement of the perisylvian cortex [Figure 4c].

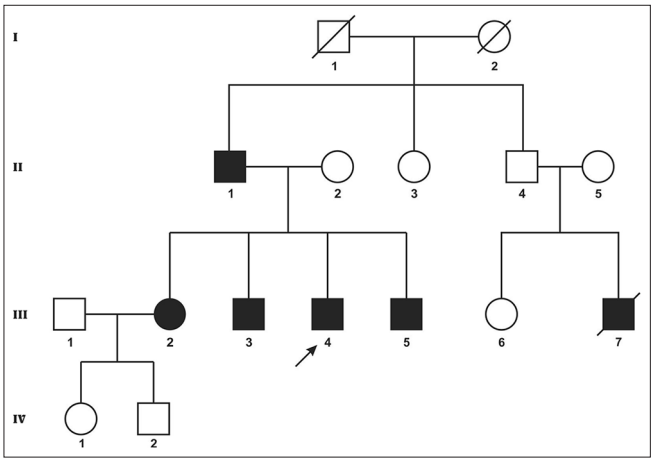

Figure 1: Pedigree chart of the family indicating the affected members (shaded dark)

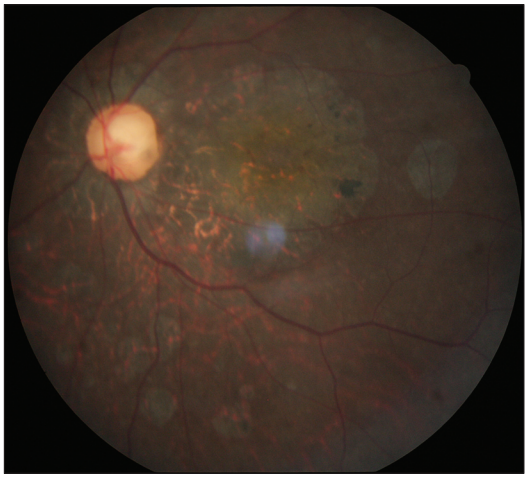

Figure 2: Fundus photography of the proband demonstrating the pigmentary retinopathy along with optic atrophy

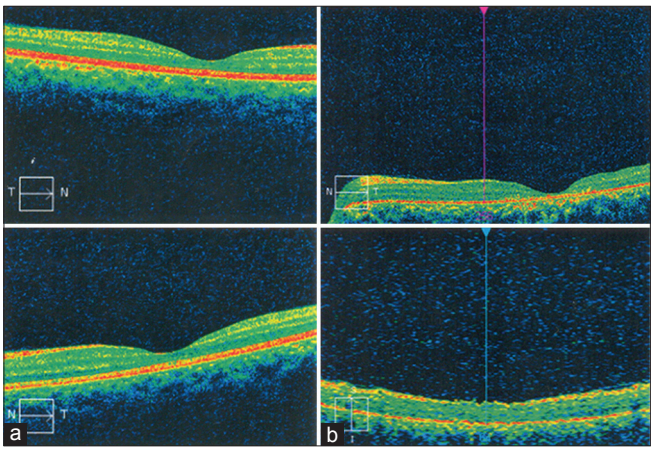

Figure 3: Ocular coherence tomography images: (a) (III-2; gene proven asymptomatic case) Shows normal retinal fiber layer thickness; (b) (III-4 with the visuo-cerebellar form of the disease) Showing gross thinning of the fovea along with thinning of the retinal nerve fiber layers dominantly involving the inner layers

Table 1: Summary of neurological and ophthalmic features along with CAG repeat counts

Parameter	Case no. 1 (II-1)	Case no. 2 (III-2)	Case no. 3 (III-3)	Case no. 4 (III-4)	Case no. 5 (III-5)	Case no. 6 (III-7)
CAG count	46	49	67	59	49	ND
Onset age (years)	47	NA	12	18	NA	Infantile
Duration (years)	3	NA	12	4	NA	3 (dead)
Ataxia (BARS)	7/30	0/30	29/30	14/30	0/30	Truncal wobbling
Oculomotor abnormality	Mild	None	Severe	Mild	None	Moderate
Bulbar weakness	None	None	Severe	Mild	None	Severe
Pyramidal signs	None	None	Gross	Moderate	None	None
Visual acuity	Normal	Normal	Blind	Poor	Normal	Blind
Color vision	Normal	Normal	Affected	Affected	Normal	ND
Retinal dystrophy	None	None	Gross	Moderate	None	ND
ImagingM (cerebello-brainstem atrophy)	Mild	None	Gross	Moderate	None	ND

ND=Not done (deceased infantile case), NA=Not applicable (asymptomatic cases), BARS=Brief ataxia rating scale

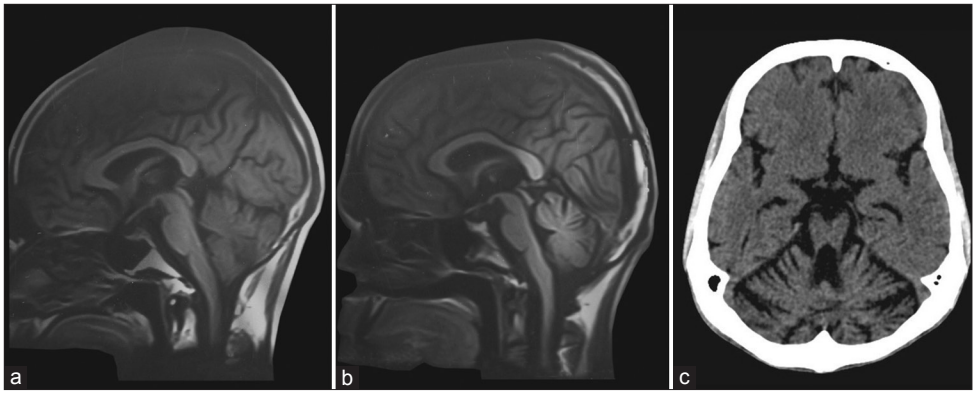

Figure 4: Brain images of II-1 (mild ataxic disease), III-4 (the proband with moderate disease) and III-3 (severe disease) respectively. While (a) (magnetic resonance imaging) shows evidence of mild cerebellar atrophy; (b) (MRI) Shows evidence of moderate cerebellar, and brainstem and upper cervical cord atrophy; (c) (computerized tomographic scan) Shows evidence of gross atrophy of the cerebellum and the brainstem. There is evidence of atrophy of the perisylvian cortex as well

Case no. 1 (II-1)

Father of proband, aged 54 years (CAG repeat count 46, BARS score: 7/30) had slowly progressive symptoms for about 3 years. He had mild features in the form of gait ataxia, dysarthria and slow saccades. He never complained of visual symptoms. Fundoscopy was normal. MRI of the brain showed evidence of mild cerebellar atrophy [Figure 4a].

Case no. 2 (III-2)

This 28-year-old elder sister of proband (CAG repeat count 49, BARS score: 0/30) was asymptomatic. Neurological examination, funduscopy and MRI scan of the brain showed no abnormality. Her ERG wave forms were normal. OCT showed normal thickness of the retinal nerve fiber layer [Figure 3a].

Case no. 5 (III-5)

This 20-year-old youngest brother of proband (CAG repeat count: 49, BARS score: 0/30) was asymptomatic for symptoms of SCA7. However, he had astigmatism along with amblyopia in the right eye with poor vision on that side. Funduscopy did not reveal either retinal dystrophy or any other contributory finding related to the amblyopia. MRI of the brain was normal.

Case no. 6 (III-7)

This 3 years boy had presented with history of delayed developmental milestones, poor sucking and vision. Examination revealed generalized hypotonia, inability to sit erect due to truncal wobbling and poor cough reflex. The external ocular movements, which were tested with passive head movements, were asymmetrically limited in all directions. The pupils were dilated and fixed and visual tracking was not possible. A provisional diagnosis of hypotonic cerebral palsy was considered. He died of aspiration pneumonia a month later before genetic, neuroimaging or ophthalmic investigations could be performed.

Discussion

The clinical and genetic profile of SCA7 is derived mostly from the Scandinavian studies[2,7-10] and a few recent Asian studies.[5,11,12] Almost all previously published studies suggest that there is a strong correlation of clinical presentation to CAG repeat counts. Some common undisputed genotype phenotype correlations are listed below.

- There is a strong negative correlation between the age of onset and size of the CAG repeat expansion[2]
- In patients with 59 repeats or more visual impairment is the most common initial symptom while in those with less than 59 repeats ataxic symptoms predominate. However, exceptions do occur[10]
- Large expansions are associated with earlier onset and a more severe and rapid clinical course while very large

expansions are usually seen in cases with early/infantile onset with fatal outcome.[2,7,8]

The present family consisted of examples of almost all types of phenotypic presentation of SCA7, which can be explained on the basis of CAG repeat counts and anticipation. Examples of asymptomatic, isolated ataxic, visuo-ataxic and fatal infantile onset cases existed.

The gene proven asymptomatic cases (III-2 and III-5) had no detectable subclinical ophthalmic or radiological findings suggestive of SCA7. This observation indicates that genetic survey of suspected SCA7 families should include clinically "unaffected cases" for genetic analysis to avoid under diagnosis. A similar asymptomatic case has been mentioned by Han *et al*., in a Chinese family.[11] Such asymptomatic cases need long-term clinical follow-up and are ideal cases for genetic counseling.

The gene proven symptomatic cases presented either with isolated ataxic disorder of late onset (II-1) or with the visuo-ataxic syndrome of moderate (III-4) or severe degree (III-3). Interestingly, both latter cases had ataxia as the initial symptom followed by visual symptoms. This temporal profile is atypical when compared with cases reported from the Scandinavian countries where visual onset is more common.[3] However, cases with ataxic onset are not uncommon in the asian literature. In the Chinese study the ataxic, visual and mixed onset cases were equal in number.[11] A Korean case of SCA7 reported by Kim *et al*., had ataxia without retinal degeneration.[12] A single case of SCA7 reported from Assam in India had pure ataxic syndrome.[5] This observation may reflect the differing population genetics between the Scandinavian and Asian regions.

The single genetically untested infantile onset fatal case of SCA7 in this family had presentation similar to the cases described by previous authors.[7,8] Families with such cases need appropriate genetic counseling and prenatal genetic testing.

The gene positive symptomatic cases of this family confirmed the well-recognized genotype phenotype correlation as described previously. Cases with larger CAG repeats had earlier onset illness associated with more severe ataxic/ophthalmic symptoms [Table 1].

This study poses some unusual disparate phenotypic expressions:

Firstly, two cases (III-2 and III-5) who had CAG repeat count of 49 remained asymptomatic while their father (II-1) with a CAG repeat count of 46 was symptomatic with the ataxic features of classical middle age onset. Secondly, all the gene positive symptomatic cases had ataxia as the initial symptom followed by ophthalmic symptoms. While one case (II-1) had only ataxic features, two cases (III-3 and III-4) had ataxic symptoms followed by the ophthalmic symptoms by 4-2 years respectively in spite of having CAG counts 59 and above (i.e. 67 and 59 respectively).

Similar observations have been made by Horton *et al*.[10] Two of their cases with CAG repeat counts of 41 remained asymptomatic at ages 46 and 58 years. These authors also observed that the onset of visual symptoms preceded the onset of motor symptoms in three cases with <59 repeats. Such disparities indicate the presence of yet unknown genetic factors, which influence the phenotypic expression.

This study adds new neurogenetic information about SCA7 to the Indian literature. The temporal profile of the symptomatology of Asian SCA7 cases may differ from the Scandinavian cases.

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