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A Rare Case of Spinocerebellar Ataxia

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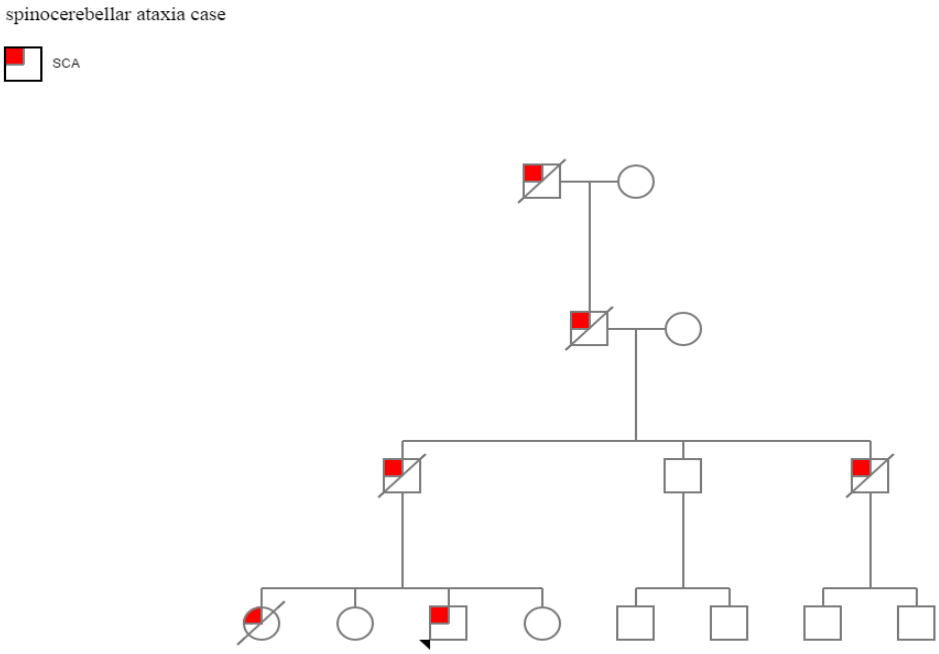
Introduction

Spinocerebellar ataxias although rare, are among the most common causes of heritable ataxias. They are inherited in autosomal dominant fashion. We encountered one such case and wish to discuss the same.

Case Report

A 30 yr male, mechanic, Right handed individual from Bihar (India) came to the hospital with complaints of loss of balance since 4yr and slurring of speech since 4 years. Patient was apparently asymptomatic 4 yr ago when he started getting unsteadiness of gait in the form of loss of balance without any side predilection. This complaint was insidious in onset, gradually progressive. It was seen initially only while running but later on progressed over to loss of balance while walking and standing. It was not associated with postural change. He also noticed difficulty in performing skilled activities, particularly performing screwing movements. There is no history suggestive of proximal or distal muscle weakness. He had also noticed stiffness in all 4 limbs. There was no history suggestive of jerky movements in any of the limbs. There was a history of involuntary grimacing. There was no history of muscle fasciculation or wasting. Patient had noticed spastic speech which was insidious in onset and progressively increasing. There was no history suggestive of cranial nerve involvement, bowel bladder involvement or sensory involvement. No history suggestive of visual abnormalities. No history of trauma. No history suggestive of any systemic illness. There is no past history of epilepsy/ forgetfulness/ abnormal behaviour/ abnormal limb movements. No history suggestive of any cardiac illness. Family history was significant in the sense that his Grandfather, Father paternal uncle and elder sister had similar complaints. Father and grandfather had origin of complaints in sixth decade of life while elder sister and paternal uncle had earlier onset in 4th and 5th decade respectively, all expired. No history of consanguineous marriage. No history of addictions.



On examination general examination was unremarkable. Spine examination was within normal limit. CNS examination suggested normal cognitive, memory and intelligence function. Speech was found to be spastic. Eye movements showed slow saccadic eye movements and normal Pursuit. No evidence of nystagmus. Rest of the cranial nerve examination was within normal limits. Nutrition and power was normal. Spasticity was present in all 4 limbs and deep tendon reflexes were exaggerated. Wide based stance and ataxic gait was noted. Positive finger nose test, dysmetria, dyssynergia, disdiadochokinesia and impaired knee heel test was noticed bilaterally. Rest of the systemic examination was within normal limits.

On the basis of these clinical features a possibility of an Autosomal dominant familial ataxic disorder was considered. And work up was advised accordingly.

Routine laboratory investigations

Parameters	Values	
Hb	12 mg/dL	
Total leukocyte count	4000/ mm3	
Platelet count	2,30,000/ mm3	
Urea	40	
Creatinine	0.8	
Na+	140	
K+	4	
Bilirubin total	1.1	
Bilirubin direct	0.4	
SGPT	70	
SGOT	50	
Total Proteins	6.5	
Albumin	3.4	
Ceruloplasmin	40 mg /dl	(N 20-50mg/dL)
24 urinary copper	50 mcg	(N 20-50mcg/dL)

ECG, CXR, Fundus examination was within normal limit. FLP was within normal limit.

MRI brain suggested diffuse cerebral and cerebella atrophy. Brainstem was unremarkable. SPECTROSCOPY Biopsy and PET scan were not performed.

SCA1 gene mapping whole blood was sent, CAG repeats 28/49 was detected with full penetrance. Method- DNA PCR, CAG repeat expansion in ATXN1 gene in SCA1 determined by PCR and capillary electrophoresis on DNA sequencer f/b Fragment analysis using gene map per software. Was also tested for SCA 2, SCA 6, and SCA 3.

Discussion

In view of a familial progressive cerebellar ataxia with brisk deep tendon reflexes and extensor plantar reflexes, following differential diagnosis were considered.

Friedreich's ataxia is the most common type of hereditary ataxia. Neurological features are progressive ataxia of gait and limb ataxia were features in favour of Friedreich's. Age of onset in most of the cases Friedreich's ataxia is less than 25 but late onset also known. Other systemic manifestations like cardiomyopathy that might be expected in Friedreich's ataxia were not present in this case. Also absent was bulbar dysfunction. The Autosomal dominant inheritance goes against the diagnosis of Friedreich's ataxia.

Dentatorubral-pallidolusyian atrophy is characterised clinically by ataxia, dementia, myoclonic epilepsy and choreoathetosis. Absence of above features and relative rarity outside African ethnicity made this diagnosis unlikely.

Cerebellar infarct was ruled out on the basis of normal MRI scan.

Multi System Atrophy is characterised by cerebellar ataxia, autonomic dysfunction sometime additional autonomic dysfunction. Pyramidal signs and extensor plantar response may also be present. However characteristic neuroimaging features of the disease like, atrophy in putamen, pons, middle cerebellar peduncles or hot cross bun sign on T2 weighted MRI were not present.

Amyotropic Lateral Sclerosis is characterised by UMN type of neurological features in presence of progressive atrophy and fasciculation's. Ataxia is uncommon in ALS.

Wilson's disease is a progressive disorder characterised by neuropsychiatric manifestations and liver failure. Absence of features suggestive of liver cell failure and normal 24 hour urinary copper excretion ruled out Wilson's disease.

Fragile X associated tremor/ataxia syndrome typically begins after 50 years of age and characteristically has inheritance similar to x-linked disorders. These features made the diagnosis unlikely. Approximately one to two individuals in 100,000 develop SCA1.

Worldwide SCA1 is seen in about 6% of individuals with autosomal dominant cerebellar ataxias but There is a considerable variation among these figures based on geographic location and ethnic background [1]. For example, SCA1 represented 6% of autosomal dominant ataxia in a North American study as seen by Moseley et al 1998, 34% in Serbia by Dragasevic et al 2006, 22% in India by Mittal et al 2005, and no cases in a Korean study by Jin et al 1999.

SCA1 was also known as *olivopontocerebellar atrophy in the past*. A term abandoned in favor of spinocerebellar ataxia mainly as the later was found out to be consisting of a group of multiple disorders in genetic studies. Clinical features of these disorders are as described below

Presentation in early or middle adult life with progressive cerebellar ataxia of the limbs and trunk, imbalance and gait disturbance, Bradykinesia, scanning speech, nystagmus, and oscillatory tremors of the head and trunk is common. Dysphagia, Dysarthria, and oculomotor and facial palsies are also known to occur. The reflexes are mostly normal, but knee and ankle jerks can be lost, and plantar reflexes can be extensors. Rigidity, an immobile face, and parkinsonian tremor are the extrapyramidal features that might be encountered. Dementia may

be noted but is usually mild. Urinary and fecal incontinence is known. Cerebellar and brainstem atrophy can be seen on MRI [1]. Marked shrinking of the ventral half of the pons, disappearance of the olivary eminence on the ventral surface of the medulla, and cerebellar atrophy are features seen on postmortem inspection. Histological features are loss of Purkinje cells, reduced numbers of cells in the molecular and granular layer, middle cerebellar peduncular demyelination and the cerebellar demyaelination. Severe loss of cells in the pontine nuclei and olives may be found. Degenerative changes in the putamen, and pigmented cell loss in the substantia nigra can be seen if extrapyramidal features are present clinically. More widespread degeneration in the central nervous system (CNS) may often present.

SCA1 encodes a gene product called *ataxin-1* its function is not known. 40 CAG repeats within the coding region characterize a mutant genotype, while a normal allele has 36 repeats [1]. A few patients with milder disease are known to have 38–40 CAG repeats. A larger number of repeats correlates with earlier age of onset for SCA1 and anticipation is present in subsequent generations. Transgenic mice carrying SCA1 were seen to have developed ataxia with Purkinje cell abnormalities. Nuclear localization of ataxin-1 appears to be required for cell death initiated by the mutant protein but exact function is not known.

Consistent with this information, our patient had a family history of disease with anticipation. Hence, a slowly progressive familial cerebellar ataxia with long tract motor signs in presence of cerebellar atrophy on neuroimaging and positive DNA PCR for multiple CAG repeats in ATXN1 gene (SCA1) lead us to conclusion that the patient is suffering from spinocerebellar ataxia.

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