Spinocerebellar Ataxia 17: A clinical Rubik’s cube

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Introduction

Spinocerebellar ataxia 17 (SCA17) is a rare autosomal dominant cerebellar ataxia (ADCA) which is characterized by cerebellar ataxia combined with a variety of symptoms including dementia, psychiatric symptoms, pyramidal signs, movement disorders such as dystonia and chorea, choreoathetosis, parkinsonism, and epilepsy. [1] It can occur in a familial, de novo, or sporadic form, with low penetrance; hence, genetic screening is essential for diagnosis. [2] SCA17 has been recognized as one of the most heterogeneous forms of ADCA with a wide clinical spectrum at presentation. [3] There are only two previous case reports of genetically proven sporadic SCA-17 from India. [4, 5] We report a case of sporadic SCA17 from India who had Huntington disease like (HDL 4) syndrome.

Case

A 26-year-old male was presented with a 10-year history of slowly progressive slowness of activities, rigidity and impairment of gait characterized by marked postural instability and falls. During previous 5 years, he also developed dysarthria, clumsiness in upper limbs, and decline in memory. That resulted in difficulties to perform activities of daily living (ADL) which made him quit his job, and for last 2 years he needed support of family members to perform ADL. He denided any history of headaches, seizures, or visual problems. He was born of non-consanguineous marriage Hindu parents without any perinatal complications. He was youngest among siblings, rest of three siblings were asymptomatic Family history for similar illness was absent up to three generations. There was no history of prolonged exposure to toxin or drug, malabsorption or nutritional deficieny, or trauma.

On examination, there was no Kayser Fleischer ring (KF), telangiectasia or pes-cavus. His mini-mental state examination (MMSE) score was 21/30. He had deficits in orientation, registration, language, and attention. The fundus examination showed normal optic disc. Motor power and sensory system examination was normal. All deep tendon reflexes were exaggerated. He had parkinsonian features as generalized lead pipe rigidity, bradykinesia and cerebellar features as ataxic gait, dysdiadochokinesia, dysmetria, dystarthis, and hypometric saccades, severe axial asynergy during postural changes, choreiform dyskinesias. The autonomic nervous system examination was unremarkable including no postural fall of systolic blood pressure.

To summarize, we were dealing with a sporadic, juvenile onset, slowly progressive syndrome with symmetric Parkinsonism, Cerebellar ataxia, with cognitive decline without optic atrophy.

On the basis of clinical features differential diagnoses of early onset multiple system atrophy, juvenile Huntington’s disease, early onset sporadic or hereditary degenerative cerebellar ataxias, and Wilson’s disease was considered. The patient worked up for juvenile-onset Parkinsonism with cerebellar ataxia.

Investigations

Hematological, biochemical investigations including complete blood count, liver and renal function test, lipid profile, thyroid profile, were normal. Peripheral blood smear for acanthocytes was negative. Serum ceruloplasmin level was normal.

MRI brain revealed cortical atrophy, pan cerebellar atrophy and caudate head atrophy as shown in figure 1.

The nerve conduction study and other electrophysiological tests including autonomic function tests (RR interval and Sympathetic skin response) were normal. Molecular genetics studies for spinocerebellar ataxia (SCA1, SCA2, SCA3, SCA7, and SCA 12) were negative. An abnormal copy of SCA17/TBP- CAG (TATA-Box Binding Protein) expansion in disease range was (CAG 59) detected in the patient’s DNA sample confirming the diagnosis of SCA 17.
There was no symptomatic improvement with levodopa, amantadine, and Vitamin E but without any significant improvement in symptoms. At one year follow up, he had further decline in cognitive functions. His family members did not consent for molecular testing.

Discussion

Abnormal expansion of CAG in TATA-binding protein (TBP) is a single mutation but results in heterogeneous clinical syndromes depending on number of repeats and penetrance.

Syndromes resulting from abnormal CAG expansion in the TATA-binding protein (TBP) have been described in literature according to their characteristic clinical presentation. Previous researches have reported Huntington disease like, Parkinson's disease like, Creutzfeldt-Jakob disease like and Alzheimer disease like phenotypes caused by this mutation. Now a days with wide spread availability of genetic testing, positive individuals falls under the category of spinocerebellar ataxia 17. These syndromes have been observed only sporadically or in solitary individuals within a family, as observed in our case. The apparent negative family history in our case could be explained by a de novo expansion.

Our patient presented with simultaneous progressive parkinsonian features and cerebellar ataxia and cognitive decline at 16 years of age without family history. This clinical profile overlaps a Huntington’s disease-like phenotype (HDL-4) which is reported to carry SCA17 mutations. HDL-4 phenotype has been observed only sporadically or in solitary individuals within a family, as observed in our case. The apparent negative family history in our case could be explained by a de novo expansion.

SCA17 was initially reported by a Japanese group in four Japanese pedigrees with a combination of above mentioned manifestations. Abnormal CAG expansion in the TATA-binding protein (TBP) gene with 47 to 55 repeats was found in these families, whereas the normal repeat number ranged from 29 to 42. A series of studies indicated the broad clinical spectrum of the disease; with most prevalent abnormalities include cerebellar ataxia and dementia at the onset of the disease depending on penetrance and number of repeats.

Our patient had 59 CAG repeats, which falls in higher repeat number probably explains early onset and combination of Parkinsonism, cerebellar ataxia and cognitive decline since onset.

Pontocerebellar, cortical and subcortical atrophy have been reported in magnetic resonance imaging of brain in patients with SCA17. In our case cerebellar and caudate head atrophy was observed.

Dietrich Haubenberger et al reported the first Indian patient of SCA-17 in 2006. In a retrospective analysis of molecular data from India by Bhanushali et al reported SCA 2 and SCA12 to be most frequently detected ataxias whereas SCA 10 and SCA17 were the rarest forms. Hire et al reported two cases of SCA 17 presenting as HDL-4 phenotype from India.

To conclude, SCA-17 is a rare SCA-subtype with only a two case reports from India. In Indian context SCA 2 as the most common SCA sub type. SCA 2 by presence of Parkinsonism and cerebellar ataxia very closely mimic SCA 17. Thus, the screening of SCA2, SCA3, and SCA17 should be done in cases of cerebellar ataxia with Parkinsonism and evidence of other neurological systems involvement.

The wide clinical spectrum and lack of family history in sporadic cases makes it difficult to diagnose bed side and leads to inadvertent investigations. In the present era most of
the inherited disorders are now being classified genetically. We suggest knowledge and application of newer genetic classifications along with older clinical classifications (e.g. Harding et al for present case) will ease the bedside approach of such clinically heterogeneous degenerative neurological disorders. [14]

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