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Pantothenate kinase associated neurodegeneration (PKAN) presenting as a seizure disorder

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Abstract

Pantothenate kinase associated neurodegeneration (PKAN) is an uncommon degenerative disease of the basal ganglia caused by mutations in the PANK2 gene. We describe a 19-years-old man with clinically and radiologically diagnosed case of PKAN, who presented with generalized tonic clonic seizures 2 years preceding other classical extrapyramidal features of the disease. PKAN presenting with seizure has not, to our knowledge, been reported previously.

INTRODUCTION

Pantothenate kinase associated neurodegeneration (PKAN) or Hallervorden Spatz disease is a rare familial recessive neurodegenerative disorder, characterized clinically by pyramidal and extrapyramidal symptoms and signs, and radiologically by reduced signal intensity with central hyperintensity in globus pallidus.[1] We herein report a case of a 19-years-old male with PKAN who presented with generalized seizures long before developing classical features of the disease.

CASE REPORT

A 19-years-old man presented with 3 years history of generalized tonic clonic seizures (GTCS) and on and off myoclonic jerk of limbs which was well controlled on 1000mg/day of sodium valproate. All the episodes were similar in semiology, consisting of sudden onset loss of consciousness followed by generalized tonic clonic movements in all four limbs associated with frothing from mouth with each episode lasting for 1-2 minutes. Each episode was followed by postictal confusion lasing for 5-15 minutes. For the past one year, the family members noticed progressively worsening hand tremors disturbing his day to day activities and gait impairment. When informed by his physician that all of his symptoms could result from sodium valproate, he stopped it abruptly and had recurrence of one episode of GTCS. Following this, he presented to our Institute, and was found to have additional symptoms of progressive slurring of speech, abnormal posturing of right ankle, frequent abnormal gesturing of hands, progressive cognitive decline, drooling of saliva from mouth and features suggestive of social disinhibition for the past one year. The examination was remarkable for poor scoring on Mini Mental Status Examination (23/28) with poor performance on parameters like recall and calculation. He also had spasticity, hyperreflexia, right ankle flexion dystonia and bilateral cerebellar signs with dysarthria. Family history revealed second degree consanguineous marriage in parents as depicted in the pedigree chart (Figure 1). One of his sisters had symptoms suggestive of spastic paraparesis and dystonia in both feet but she was not brought for medical examination. There was no history to suggest seizures in her or any other family member.

Investigations revealed normal hemogram including peripheral smear negative for acanthocytes, liver function tests, renal function tests, 24-hour urinary copper, serum ceruloplasmin level, cerebrospinal fluid (CSF) analysis, lactate levels (both CSF and blood) and iron-profile including serum iron and ferritin levels and total iron binding capacity (TIBC). Slit-lamp examination for Kayser-Fleischer ring was negative and there was no evidence of retinal pigmentation on fundoscopy. Human immunodeficiency virus (HIV) serology was non-reactive. Electroencephalogram (EEG) was normal. Cranial Magnetic resonance imaging (MRI) showed hypointensity with an area of central hyperintensity (Eye-of-the-tiger sign) in both globus pallidi on T2 weighted imaging (figure 2). Based on the clinical features and MRI findings, a diagnosis of PKAN was made. The patient was discharged on trihexiphenydyl,

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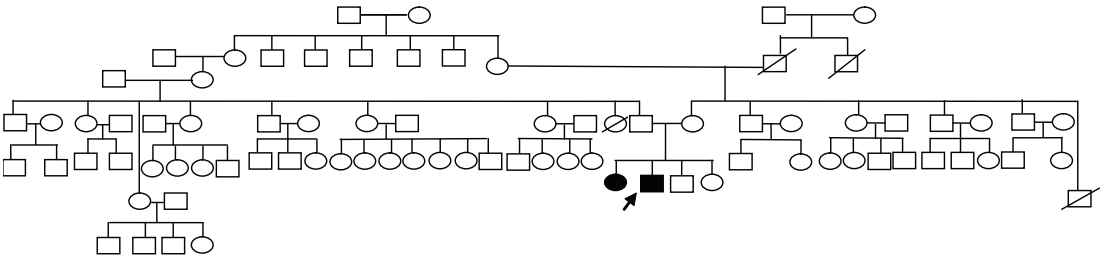

Figure 1. Pedigree chart of the patient showing consanguinity in parents.

clonazepam, baclofen and levetiracetam. At two months of follow-up there was no recurrence of seizures, and other symptoms had improved partially. PANK2 mutation analysis could not be done initially as this investigation was not available in our Institute. When it was later planned to be done elsewhere, unfortunately he was lost to follow-up.

DISCUSSION

PKAN is a rare neurodegenerative disorder with aberrant iron metabolism in the brain.[1] It is classified under neurodegeneration with brain iron accumulation (NBIA). PKAN which was first described by Julius Hallervorden and Hugo Spatz[2], can be familial or sporadic. The mode of inheritance is autosomal recessive. Clinically, the disease most commonly presents as a childhood onset predominantly extrapyramidal disorder. In few patients, psychiatric symptoms, dementia and visual disturbances can be the presenting manifestations. The other features of the disease include spasticity, hyperreflexia, tremors, choreoathetosis, seizures, dysphagia, dysarthria, cerebellar signs, optic atrophy and pigmentary degeneration of the retina.[1] Hayflick *et al* classified PKAN into classic disease and atypical form. The classical PKAN has an early onset, rapid progression and 'eye of the tiger sign' in those with positive PANK2 mutations, whereas atypical form is characterized by late onset, slow progression and PANK2 mutation in only one third of patients.[3] Although, seizure is a well known feature of PKAN, our case is unusual in that the first presentation of the disease was seizures. The other clinical features of the disease manifested after an interval of 2 years. However, we acknowledge that the seizure in our patient might have occurred coincidentally, though we could not identify another symptomatic cause.

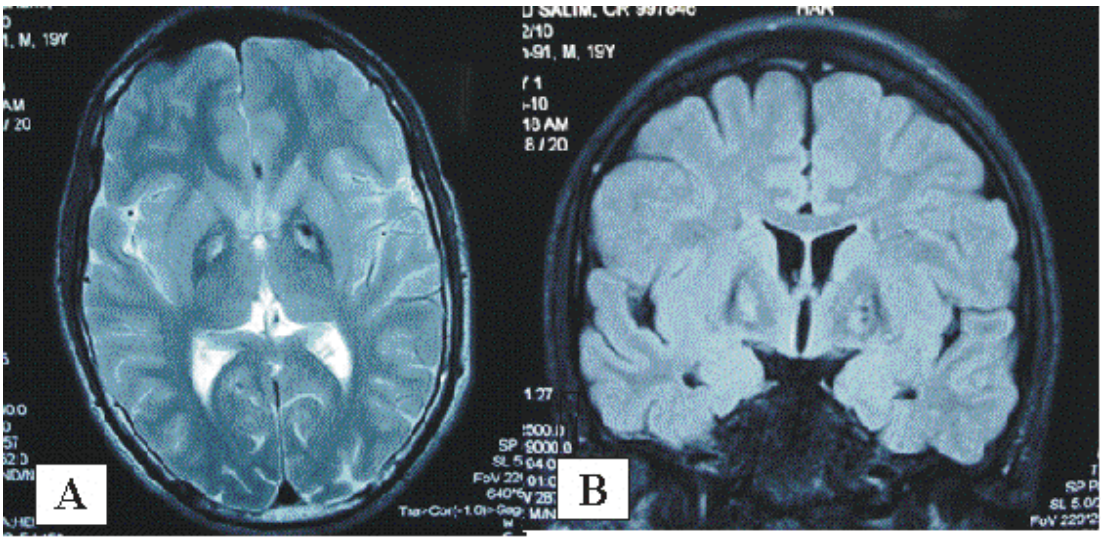

Figure 2. (A) Axial T2W imaging and (B) Coronal T2 FLAIR imaging showing hypointensity with central area of hyperintensity in both globus pallidi (Eye-of-the-tiger sign).

PKAN presenting with seizure has not, to our knowledge, been reported previously. Although the sister was having clinical symptoms suggestive of PKAN, the diagnosis of PKAN was not considered in the brother until he developed the full fledged manifestations of the disease.

Previously, dopamine-neuromelanin system was postulated to be involved in the basic pathogenesis.[4] However, recently Zhou *et al* have identified a 7-bp deletion in the coding sequence of a gene called PANK2 that has homology to murine pantothenate kinase. Gene mapping has localized the defect to chromosome 20p12.3-13.[5] After the advent of imaging techniques like computed tomography (CT) scan and MRI, the diagnosis is increasingly being made antemortem.[6] CT scan usually shows hypodensity in both basal ganglia, along with mild to moderate atrophy of the brain and basal ganglia. On MRI, initially hyperintense signals are seen chiefly in the globus pallidi and are symmetrical. As the disease progresses, a hypointense rim develops around the hyperintense area due to excess iron accumulation. Hyperintense signals are attributed to gliosis, increased water content and neuronal loss. When the disease advances the central hyperintensity is also lost due to further iron accumulation.[7]

The differential diagnosis includes dopa-responsive dystonia, infantile neuroaxonal dystrophy, juvenile Huntington's disease, neuroacanthocytosis, neuronal ceroid lipofuschinosis, HIV encephalopathy and early Alzheimer's disease.[1,8] The mean survival after diagnosis is 11.8 years. Management of PKAN involves physiotherapy, speech therapy and control of abnormal movements and dystonia. The trials of stereotactic pallidotomy and thalamotomy, and deep brain stimulation have been disappointing.[9-11]

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