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Atypical Pantothenate-Kinase Associated Neurodegeneration (PKAN) in Two Iranian Patients

Pantothenate kinase- associated neurodegeneration (PKAN) or Hallervorden-Spatz syndrome is a rare autosomal recessive disorder characterized by dystonia, Parkinsonism, and iron accumulation in the brain. There are two types of this disease: the classic disease which is characterized by an early onset and rapid progression, and the atypical disease which is characterized by later onset and slow progression.

Clinical diagnosis is based on clinical and characteristic magnetic resonance imaging findings.

We report two Iranian cases of atypical PKAN, the diagnosis of which was missed till MRI showed classic imaging findings.

Keywords: Pantothenate Kinase-Associated Neurodegeneration, Nerve Degeneration, Magnetic Resonance Imaging

Introduction

Pantothenate kinase-associated neurodegeneration (PKAN), formerly known as Hallervorden-Spatz syndrome, is a rare neurodegenerative disorder first described in 1922.[1] The pattern of inheritance is autosomal recessive.[2] PKAN is characterized by childhood onset of extrapyramidal motor symptoms. Some patients may present with mental changes, dementia, and vision disturbances. Average survival after the initial diagnosis is 11.8 years.[3] The exact etiology of the syndrome remains unknown,[4] but it has been linked to a defect on the PANK2 gene on chromosome 20 (20p13) which has a significant role in coenzyme A synthesis.[2] There are two major types; the classic early-onset type and the atypical late-onset type. The classic early-onset type is characterized by rapid progression and signs of gait impairment which causes restriction of normal activities by mid-adolescence. In the atypical late-onset variant, the accumulation of iron occurs later in the course and the disease is slowly progressive.[4] In patients with PANK2 mutations, the major imaging modality for diagnosis is MRI which displays the classic "eye of the tiger" sign.

This is, to our knowledge, the first PKAN image finding report from Iran.

Case Presentation

Case 1

This case was a 14-year-old male without a previous family history of a similar disorder. His mother's gestational period and his neonatal history were uneventful. The neurological and mental development of the patient was normal until the age of 7, then he presented abnormal choreoathetoid movements, rigidity, and after that dysarthria. Fundoscopy was normal. The patient's intellectual capacity was reduced (IQ=65). Laboratory tests: routine CBC, blood

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smear, FBS, urea, creatinin, ESR, CRP and liver function tests, serum copper, iron, ceruloplasmin, and ferritin were within normal limits. The genetic test for fragile x syndrome and other significant abnormalities was negative.

Then MRI was performed with General Electric (USA) 1.5 tesla Scanner in sagittal, coronal, and axial sections with T1, T2, and FLAIR sequences.

T1 weighted fast spin echo revealed an abnormal high signal in the anteromedial part of the globus pallidus. It showed higher signal intensity in T2 weighted and FLAIR images with peripheral, especially posterolateral low signal, producing the classic "eye of the tiger" sign (Figs. 1A and B). Five years before that, lower field MR imaging only showed these abnormalities in T2 weighted image while the T1 weighted image was completely normal (Figs. 1C and D).

Case 2

Our other patient is a 17-year-old girl with no previous family history of PKAN. Her mother's pregnancy and her neonatal history were unremarkable. During childhood and up to early adolescence, her neurological symptom development and milestone attainment were normal. She presented initially with dysarthria and thereafter declining academic ability at the age of 14. Fundoscopy revealed bilateral pigmentary retinopathy. Routine lab tests carried out for the patient including CBC, FBS, urea, creatinin, serum copper, iron, ceruloplasmin, and ferritin, ESR, CRP and liver function tests, were unequivocal.

MRI was performed with the same machine and the same sequences as the first case and the same findings were revealed (Figs. 2A-C).

Discussion

PKAN or Hallervorden-Spatz syndrome is a rare autosomal recessive condition associated with iron accumulation in the basal ganglia.

In Hallervorden-Spatz syndrome, histopathologic studies have revealed iron deposits in the perivascular spaces, walls of the lenticulostriate vessels, axonal spheroids, microglia, and macrophages in the neuropil.[5]

In the study carried out by Hayflick and colleagues, no episode of seizure was reported in patients suffering from the classic form of the disease and 85% of these patients had become nonambulatory within 15 years of disease onset. The mean age of onset in the classic type was 3.4 ± 3.0 years, whereas the mean age in the late-onset type was 13.7 ± 5.9 years. Among 30% of patients suffering from the atypical form of the disease, psychiatric symptoms simulating frontotemporal dementia together with preservative behavior and freezing were noted.[4]

The atypical variant of the disorder is particularly heterogeneous and has multitude manifestations; as mentioned before, it is slowly progressive and patients suffering from this variant who reach middle age should not automatically be assumed to have progressive dementia. These cases may be affected by abnormal behavioral problems with obsessions and compulsions.[6]

Both of our cases were atypical due to the late onset of their symptoms. Our first case presented with abnormal choreoathetoid movements, rigidity and subsequently dysarthria; similar to the classical type of PKAN but with slower progression and higher mean age of onset. The second case was initially presented with dysarthria, and thereafter with declining academic ability which is similar to the reported symptoms of atypical PKAN.

Both classic and late-onset types are associated with iron accumulation in the basal ganglia. In genetic examinations carried out by researchers, 100% of the patients with the classic variant and about one third of the patients with the atypical late-onset form had PANK2 mutations.[4]

The most characteristic finding on MRI imaging is bilateral diffuse low signal intensity of the globus pallidus together with a focus of high intensity on T2 MRI; this creates the characteristic "eye of the tiger" sign.[7] The hypointensity on the T2 weighted image is the result of iron deposition, and the central hyperintensity is secondary to gliosis and spongiosis.[8]

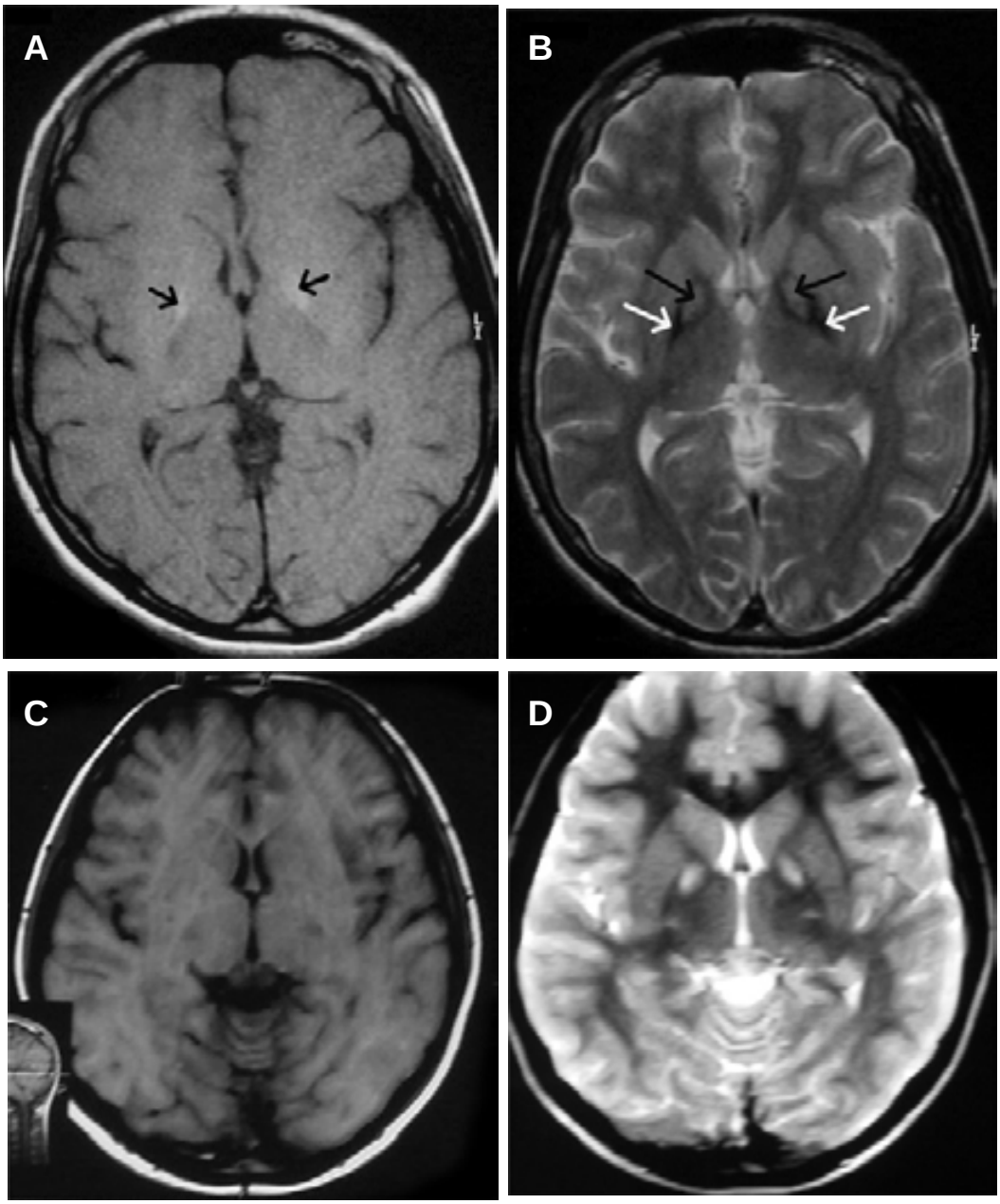

Fig. 1. A 14-year-old male presented with abnormal choreoathetoid movements and dysarthria**.**

A. T1 weighted fast spin echo shows bilateral high signal area in the anteromedial part of both globus pallidi (black arrows).

B. T2 weighted fast spin echo shows the characteristic "eye of the tiger" sign with high signal in the anteromedial (black arrows) and peripheral low signal in the posterolateral part of globus pallidus (white arrows).

C. T1 weighted image of the same patient five years ago with lower magnetic field MR does not show any abnormality in globus pallidus.

D. T2 weighted image of the same patient five years ago shows "eye of the tiger" sign.

All patients with PKAN displayed the "eye of the tiger" appearance on T2 MRI whether they were early or late-onset.[4] However, this pattern was not observed in those lacking the PANK2 mutations.[4] Baumeister and his group later noted that the "eye of the tiger" sign may be lost during the course of the disorder in patients initially having the sign.[9] But the first case showed this sign after 5 years from the initial MRI. Sener noted existence of marked low signal intensity in the globus pallidi on the fluid-attenuated inversion recovery images of his case. marked low signal intensity in the globus pallidi in his patient was seen due to presence of iron deposition Because of known less sensitivity to susceptibility effects in FLAIR imaging. He noted that the eye of the tiger appearance cannot be detected on FLAIR images.[7]

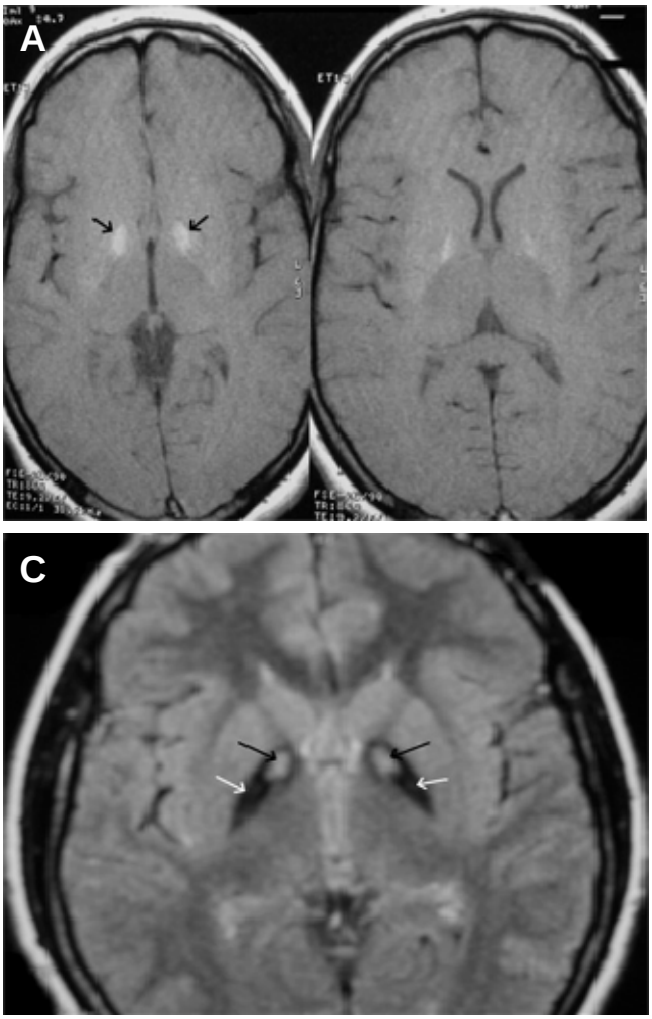

Fig. 2. A 17-year-old girl presented initially with dysarthria and thereafter declining academic ability at the age of 14 and bilateral pigmentary retinopathy in fundoscopy.

A. T1 weighted fast spin echo shows bilateral high signal area in the anteromedial part of both globus pallidus (black arrows).

B. T2 weighted fast spin echo shows the characteristic "eye of the tiger" sign with high signal in the anteromedial (black arrows) and peripheral low signal in the posterolateral part of globus pallidus (white arrows), black arrowhead shows incidentally noted enlarged perivascular space.

C. FLAIR sequence of the same case shows the characteristic "eye of the tiger" sign with high signal in the anteromedial (black arrows) and peripheral low signal in the posterolateral part of globus pallidus (white arrows)

But Frangel et al. noted the eye of the tiger in FLAIR sequence in their case.[10]

We also noted this sign in FLAIR sequence which was even more prominent than T2 weighted in both of our cases.

The other differential diagnosis of iron deposition in the basal ganglia and "eye of the tiger" sign include neuroferritinopathy and aceruloplasminemia. These are distinct conditions of abnormal iron metabolism, but, unlike Hallervorden-Spatz disease (HSD), are present in adolescence or late life. Neuroferritinopathy is characterized by onset at 40-55 years of age, and aceruloplasminemia is associated with diabetes mellitus and there is complete deficiency of ceruloplasmin.[3] Serum ceruloplasmin, ferritin, iron, and copper in our cases were normal.

The detection of PANK2 mutation enables genetic diagnosis and allows presymptomatic testing of family members. Yet, after accurate history taking and performing a complete physical examination, an MRI can still be considered as the "gold standard" in the diagnosis of early-onset PKAN.[4] It has also been brought to attention that the MRI findings may precede the onset of symptoms in the classic form, and even before the characteristic MRI findings abnormalities outside the globus pallidus -such as cerebellar and cerebral atrophy- were both more common and more severe in cases that did not harbor PANK2 mutations. Generally speaking, there were no specific imaging abnormalities in the latter group.[11]

Currently, there is no specific therapeutic measure to counter this disease; the efficacy of pentothenate supplementation in ameliorating symptoms should still be proved. Despite this, the administration of levodopa, anticholinergics, and intrathecal baclofen have apparently improved the quality of life of the patients.[1]

As a conclusion, we can say that observing the "eye

of the tiger" appearance on T2 MRI is the choice imaging modality in helping us diagnose classic PKAN at present. There are no imaging or genetic criteria for the definitive diagnosis of atypical (late-onset) patients without PANK2 mutations.[4]

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