Case Report

Pantothenate Kinase Deficiency Related Neurodegeneration (PKAN) – An Ultra Rare Inherited Metabolic Disorder

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Abstract: Pantothenate Kinase-related Neurodegeneration (PKAN) is an Autosomal Recessive (AR) inherited disease identified by focal iron accumulation in the basal ganglia. Formerly recognized as Hallervorden-Spatz disease. PKAN is now considered to be one of several diseases that clinically presents with Neurodegeneration due to deposition of iron in brain (NBIA). Here, we describe an eleven-year-old boy identified as typical PKAN.

Keywords: Neuroregeneration, Eye of tiger sign, Brain iron accumulation, PANK2 gene mutation, Autosomal recessive, Dystonia.

INTRODUCTION

PKAN is classified under a group of disorders known as Neurodegeneration due to iron deposition in the brain. The exact prevalence of PKAN is yet unknown, but it has an estimated prevalence of 1–3/million with a general population carrier frequency of 1/275–500. The clinical manifestation generally starts before the age six years and is recognized by expeditiously intensifying dystonia, rigidity, and choreathetosis. Initially described by two German pathologists in 1922 as Hallervorden-Spatz disease with clinical description of a progressive extrapyramidal signs that occurred due to accumulation of iron in the Basal ganglia [1], later on it was renamed as a disorder of brain iron accumulation (NBIA) in 2003. After the report of first genetic mutation in the Pantothenate Kinase 2 (PANK2 gene) on chromosome 20p 12.3-p13 in 2001 [2], the NBIA cases with this mutation were relegated under the new disorder Pantothenate kinase-related neuroregression (PKAN). They are considered ultra-rare with a combined estimated prevalence of 1–3 per 1,000,000 [3].

The clinical presentation of PKAN widely differs from early childhood to adulthood. Different varieties of PKAN have been reported in the literature according to time of onset of clinical symptoms. Generally childhood form, which presents before the age of ten years with awkward gait followed by dystonia and spasticity. In some cases, there is period of quiescence of clinically symptoms but dystonia and other movement disorders, (ballism, chorea, tremors) subsequently follow with speedy evolution. Most of the cases lost ambulation by the age of 10-15 years and become bed confined. The complications of the eyes; retinitis pigmentosa and other retinal abnormalities eventually results in blindness. The brain MRI in PKAN demonstrate classic findings of the "eye-of-the-tiger" sign. To date, all patients with typical MRI findings have been observed to have a mutation in the PKAN2 gene.

CASE REPORT

An eleven-year-old boy was brought to our pediatric neurology clinic with delayed development from the start. Currently he has developed new symptoms which include; frequent falls while walking, episodic posturing of the limbs and regression of his achieved developmental milestones. He also had gradual disturbance of cognition and language, associated with visual disturbance, especially at night for the past three years.

He is outcome of first degree consanguineous Saudi parents, 3rd in birth order. He was delivered at term through normal spontaneous vaginal delivery and had no natal or peri-natal or postnatal complications. On clinical examination his weight was 14 kg below 5th centile, head circumference (OFC) 51.5cm at 50th centile. His vital signs were stable, there was no neurocutaneous stigmata, and no visceromegaly.

On physical examination generalized dystonia associated with dysarthria was noted, his speech was not clear due to difficulty in articulation. He also had generalized hypertonia associated with choreiform movements. His Babinski sign showed extensor planter response. Fundoscopic examination revealed bilateral retinal pigmentary changes.

Brain MRI showed hypointense signals on T2 weighted image in both globi pallidi bilaterally with small central areas of hyper intensity, give picture of "eye-of-a-tiger" (Fig. **1A**). These findings were more obvious on the FLAIR weighted image (Fig. **1B**). Magnetic Resonance Spectroscopy (MRS) in the region of

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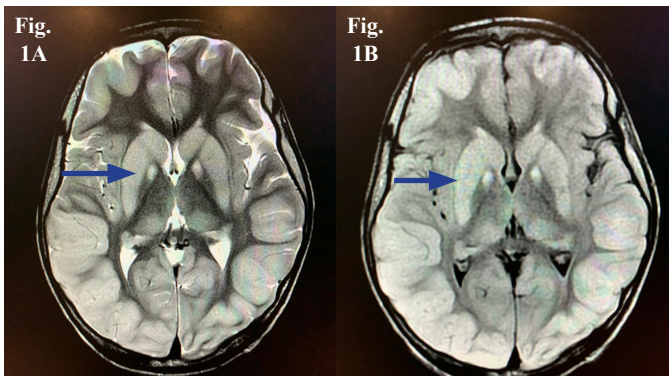
globus pallidus showed low in N-acetyl aspartate (NAA) with high creatine peaks and a decrease NAA/creatine ratio (Fig. **2**). His peripheral blood film did not show acanthocytes. On the basis neurological examination and MRI/MRS pictures diagnosis of pantothenate kinase deficiency neurodegenerative disorder was suspected.

Based on the characteristic findings "eye-of-the tiger" on MRI, Whole Exome Sequencing (WES) for PANK2 gene mutation was done, which verified the diagnosis of PKAN by the presence of missense mutation in the PANK2 gene [c.1150 C >T (p. Pro 384 Ser). Genetic testing for both parents revealed carrier for that homogygous mutation.



Figs. (1A, B): Brain MRI T2 and FLAIR Axial Sections: Showing "Eye of Tiger Sign"

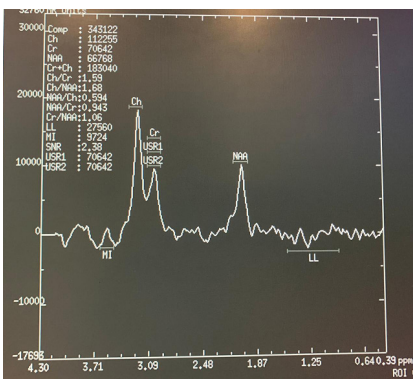


Fig. (2): Magnetic Resonance Spectroscopy (MRS).

He was put on trihexyphenidyl to treat dystonia and baclofen for spasticity. Patient was also referred for physiotherapy and occupational therapy.

DISCUSSION

PKAN is a rare AR neurodegenerative disorder. It was first described in 1922 and currently, PKAN is customarily categorized as a psychomotor regressive disorder with deposition of iron in the brain (NBIA) [1, 3]. The PANK2 gene is situated on chromosome 20p12.3–13 and this gene is responsible for producing coenzyme A in mitochondria. In the absence or abnormal function of PANK2 gene that will result in cumulation of N-pantothenyl cysteine and free cysteine. Cysteine causes iron chelation and can result in secondary iron deposition in the brain that will exaggerate neuronal injury by inducing oxidative stress [4, 5].

The 1561G>A missense mutation is the most prevalent cause of PKAN universally, and homozygotes have classic PKAN [5]. In the classic form, the first clinical presentation manifests between the age of three and four years, and disease process advance speedily [5,6]. The clinical manifestation is identified by intensifying extrapyramidal dysfunction and is characterized by rapidly progressive dystonia, rigidity, and choreoathetosis, as seen in our patient. The disease process continue to progress gradually over years. Spasticity, extensor planter response, dysarthria, and deterioration of cognition become more prominent in early adulthood. Patient loses ambulation within 5 to 15 years of onset of symptoms.

There is deposition of iron pigment in globi pallidi bilaterally which show hypointense signals on T2 weighted images and hyperintense signals in the anteromedial area, which is due to necrosis and edema that results in classical radiological sign known as "eye-of-the-tiger" sign. Histopathological examination shows intemperate deposition of iron-containing pigments in the globi pallidi and substantia nigra. In our patient, MRI brain was performed at the age of seven years which showed the classic "eye-of-the-tiger" sign. When the full "eye-of-the-tiger" sign is present on MRI in childhood, 100% of such cases have the PANK-2 mutation [7].

CONCLUSION

To confirm the diagnosis of this disorder, the PANK2 gene testing is the gold standard. Whole exome sequencing (WES) was performed in our patient which revealed a missense homozygous mutation in PANK2 gene. One similar patient was reported by Fasano *et al*. in 2017 [8]. Currently, there is no curative treatment for this disorder. Current management strategies focus mainly on symptomatic medical treatment for movement disorders and surgical symptom palliation to improve the quality of life [9, 10].

CONFLICT OF INTEREST

Declared none.

ACKNOWLEDGEMENTS

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