

Pantothenate Kinase-Associated Neurodegeneration- Rare form of Neurodegeneration with Brain Iron Accumulation

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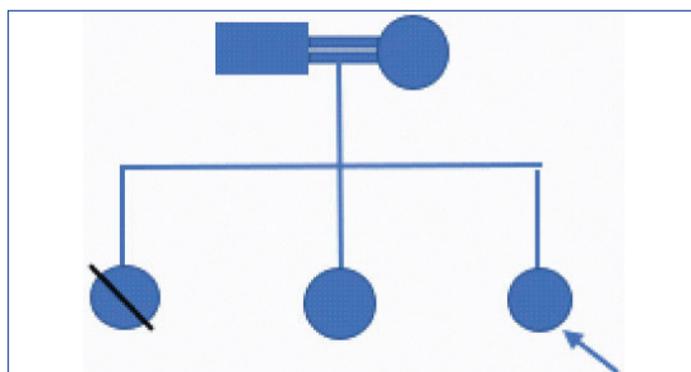
ABSTRACT

Pantothenate Kinase-Associated Neurodegeneration (PKAN), a rare autosomal recessive disorder is mainly caused by mutation in the PANK2 gene. PKAN is included in a group of disorders known as Neurodegeneration with Brain Iron Accumulation (NBIA). Magnetic Resonance Imaging (MRI) of brain demonstrates the pathognomonic appearance of “Eye of Tiger” appearance in the Globus Pallidus, which is due to abnormal brain iron accumulation. We present a rare case of PKAN with recurrent falls, development delay with bilateral retinitis pigmentosa and normal laboratory investigation. Similar complaints were present in one of the sibling who died of the illness.

Keywords: Eye of tiger, Globus pallidus, Retinitis pigmentosa

CASE REPORT

An eight-year-old girl presented to Department of Paediatrics with history of recurrent falls since two years and sustained several injuries over the head and knee due to the fall, delayed development since two years with non-attainment of developmental milestones and abnormal posturing of hands since one year. There was delayed speech and motor development. The child was born out of second degree consanguineous marriage, third child in order of birth [Table/Fig-1]. History of similar complaints was noted in elder sibling, who died at 13 years of age.

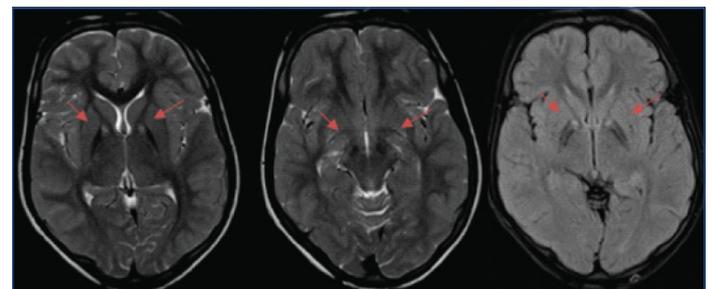


[Table/Fig-1]: Schematic representation of the pedigree chart showing the second degree of consanguineous marriage, the index case is the third child in order of birth. The chart also demonstrates the death of the eldest sibling.

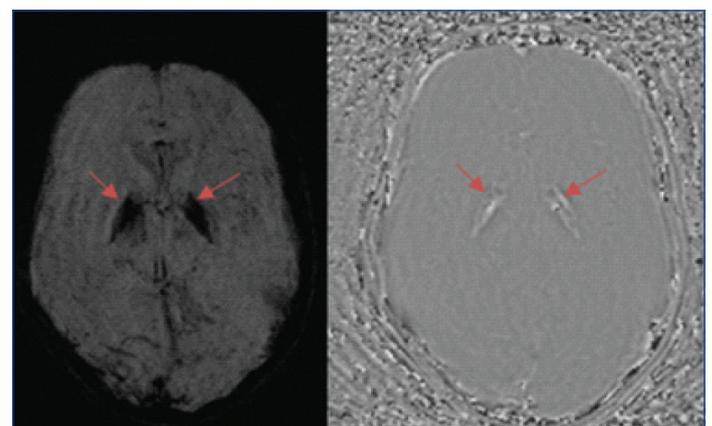
Head to toe examination revealed multiple injuries present over forehead and knee joint. The neurological examination revealed the presence of moderate dystonia. Tests for strength, coordination and sensitivity were unremarkable. No Parkinsonism, chorea or myoclonus was evident. The neuro-ophthalmologic exam, including fundoscopy revealed bilateral retinitis pigmentosa (advanced). Cortical thumb was present and patient drags right foot while walking. Power in the upper limb was reduced to 4/5. The phono audiological assessment revealed inadequate speech and language skills. Laboratory tests, including complete blood count, renal function test, liver function test and blood clotting tests were within normal limits. Serum ferritin level was normal. Peripheral blood smear revealed a normal blood picture without

any acanthocytes. Genetic testing was not done as the patient's parent were not willing for it.

The patient was referred to Department of Radio-diagnosis for MRI of brain for further evaluation. MRI scan revealed symmetrical central hyper intensity surrounded by hypo intense signal in Globus pallidus, consistent with the “eye-of-the-tiger” sign in the T2 weighted images [Table/Fig-2]. Susceptibility Weighted Imaging (SWI) sequence demonstrated low signal in corresponding areas from iron deposition [Table/Fig-3]. This finding confirmed the diagnosis of PKAN.

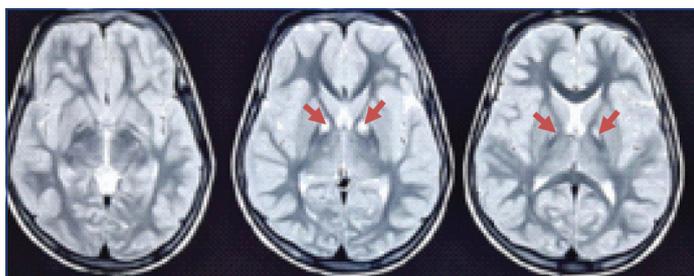


[Table/Fig-2]: T2 weighted and Fluid attenuated inversion recovery sequences (FLAIR) demonstrates symmetrical central hyper intensity surrounded by hypo intense signal in Globus pallidus, consistent with the “eye-of-the-tiger” sign (red arrows).



[Table/Fig-3]: Susceptibility Weighted Imaging (SWI) and phase sequence demonstrated low signal or blooming in bilateral Globus pallidus from iron deposition (red arrows).

Elder sibling who had similar complaints, had died at 13 years of age. MRI brain of the elder sibling revealed similar symmetrical central hyper intensity surrounded by hypo intense signal in Globus pallidus, consistent with the “eye-of-the-tiger” sign in the T2 weighted sequence [Table/Fig-4]. The screening MRI brain of the other living sibling revealed no abnormality.



[Table/Fig-4]: T2 weighted of the elder sibling demonstrates symmetrical central hyper intensity surrounded by hypo intense signal in Globus pallidus, consistent with the “eye-of-the-tiger” sign (red arrows).

Other differential diagnosis which can be included are Wilson’s disease, hepatic cirrhosis and carbon monoxide poisoning. Wilson’s disease is accumulation of copper resulting from a deficiency of ceruloplasmin, its serum transport protein. In Wilson’s disease there is T2 shortening noted in bilateral Globus pallidus and Kayser Fleishner rings in cornea. In Hepatic cirrhosis T1 weighted MR image depicts symmetric hyperintense foci in bilateral Globus pallidus and substantia nigra due to deposition of manganese which reverses after liver transplantation. In Carbon monoxide poisoning the MR imaging depicts symmetric hyperintense foci in the Globus pallidus due to T1 shortening [1]. All these were ruled out based on the characteristic MRI features.

DISCUSSION

PKAN, previously also called as Hallervorden-Spatz syndrome described in 1922 by two German neuropathologists, Julius Hallervorden and Hugo Spatz, whose studies were based on pathological specimens obtained under Nazi euthanasia programs in individuals with physical and intellectual disabilities [2,3]. The first subtype of the Hallervorden-Spatz syndrome, identified by the mutation in the PANK2 gene and specific radiological and clinical findings, was denominated as Pantothenate kinase-associated neurodegeneration or PKAN [4].

A new nomenclature for the syndrome was proposed in 2003, after the recognition of genetic mutations associated with the clinical syndrome, particularly the PANK2 gene. This gives rise to introduction of the terms NBIA and PKAN [5-7].

PKAN accounts for 50% of NBIA cases [8]. It is a rare autosomal recessive disorder associated with mutation in the PANK2 gene located on chromosome 20p13 and encodes Pantothenate kinase, it is a key regulating enzyme of coenzyme-A synthesis [9,10]. PKAN is subdivided into two main types, based on age of onset, clinical features and progression: (a) classic (b) atypical [5].

Classic disease had PANK2 mutations, patients with early-onset, rapidly progressive disease will consistently prove to have inherited defects in PANK2 gene. In patients with atypical disease, especially those with PANK2 mutations were much more likely to develop speech and psychiatric problems. Most pathognomonic finding is a one-to-one correlation between the MRI of brain eye-of-the-tiger pattern and the presence of a PANK2 mutation. The clinical descriptions of the major forms of PKAN has been described in [Table/Fig-5] [5]. The index case and the elder sibling are of classical type of PKAN. And shows inheritance, classic age of presentation and progression was also typical of the disease [11,12]. Seizures occur rarely in the classic type and was also not present in index case. Bilateral retinitis pigmentosa was also a finding in the index case [10].

Classic type of PKAN has a typical onset by three years and 90% of cases occur before six years of age. Usually presenting with

Features	Early onset, rapidly progressive disease-classic type	Late onset, rapidly progressive-atypical type
Age at onset	First decade	Second or third decade
Major neurological features	Extrapyramidal dysfunction, corticospinal tract involvement	Speech disorders, psychiatric disorders, extrapyramidal dysfunction, corticospinal tract involvement
Pigmentary retinopathy	Very common	Rare
Rate of disease progression	Loss of independent ambulation within 10-15 years after onset	Loss of independent ambulation within 15-40 years after onset
Findings on MRI brain	Eye of the tiger	Eye of the tiger

[Table/Fig-5]: Phenotypic features of PKAN.

gait difficulties [11,12]. There is marked dystonia and presence of pyramidal and extrapyramidal signs [11]. Pigmentary retinopathy, saccade and pupil abnormalities are the neuro ophthalmologic examination findings [10]. Acanthocytes may be found in peripheral blood smear of the patients.

In classic type of PKAN there can be periods of marked worsening indicating that the progression is not linear. Within 10-15 years of disease onset there is loss of walking ability [5]. Patients may evolve to death within the first decade of disease onset [8].

Atypical PKAN compared to the classic form is more heterogeneous, usually seen in second or third decade of life with slower progression, the characteristic feature being the presence of psychiatric symptoms and speech disorders [5,6,8,10]. Pigmentary retinopathy is rare [5,8]. There is less involvement of the motor system, loss of walking occurs at 15-40 years of disease onset [5,13]. In adolescents the striking clinical feature is development of dystonia, while in patients more than 20 years of age Parkinsonism is the chief clinical symptom [8].

MRI of brain is an important diagnostic tool. Eye-of-the-tiger sign, that is bilateral hypo intensity of the Globus pallidus with a central area of hyper intensity visualised on T2-weighted MR images is a pathognomonic finding. There can be hypo intense signal change in substantia nigra which is seen in some patients. On T2 sequences the areas of iron deposition appear hypo intense [14]. Pathologically the hypo intense areas correspond to abnormal deposition of iron and the central hyper intense signal change is due to neuronal loss with gliosis. Specific diagnosis can be achieved with associated MRI which helps in distinguishing the various subtypes of NBIA [Table/Fig-6].

Disorders	Iron deposition	White matter involvement	Other findings
PKAN	GP, SN Mild	No	Eye of the tiger sign
PLAN	GP, SN	Mild	Moderate cerebellar atrophy
NFT	Patchy GP, putamen, CN, dentate, thalamus	Mild, moderate	Cyst, cavitation, MILD cerebral, cerebellar atrophy
ACP	GP, putamen, CN, thalamus, red nucleus, dentate	Moderate, severe	Mild cerebellar atrophy
FAHN	GP, SN	Moderate	Ponto-cerebellar atrophy
KRS	GP, putamen, CN		Severe cerebral, cerebellar, brainstem atrophy
WSS	GP	Severe, confluent	
SENDA	SN,GP	Occasional	MIDBRAIN T1 hyperintensity

[Table/Fig-6]: Subtypes of NBIA with clinical and radiological findings.

GP: Globus pallidus; SN: Substantia nigra; CN: Caudate nucleus; ACP: Aceruloplasminemia; FAHN: Fatty acid hydroxylase-associated neurodegeneration; KRS: Kuforakeb syndrome; NFT: Neuroferritinopathy; PKAN: Pantothenate kinase-associated neurodegeneration; PLAN: Phospholipase-associated neurodegeneration; SENDA: Static encephalopathy of childhood with neurodegeneration in adulthood; WSS: Woodhouse-sakati syndrome

There is no specific treatment for PKAN. Only symptomatic treatment is the mainstay of management like other NBIA. Benzodiazepines, anticholinergics and botulinum toxin can be used to control dystonia. Spasticity is relieved by using baclofen [8,9]. The symptoms can be controlled by deep brain stimulation of internal Globus pallidus and stereotactic surgical modalities such as thalamotomy and pallidotomy, however these don't help in arresting the progression of the disease [9].

To conclude, NBIA syndromes even though rare, should be included in the differential diagnosis when the patients present with progressive extrapyramidal syndrome and abnormal iron deposition on brain MRI. The quality of life can be improved by multidisciplinary rehabilitation programs which promote satisfactory conditions in these patients [15].

CONCLUSION

MRI of brain is an important diagnostic tool in evaluating brain iron disorders and facilitates clinical diagnosis. Though iron deposition is a useful biomarker, its pathophysiologic role in NBIA is uncertain. A more specific diagnosis can be achieved with the help of associated MR imaging abnormalities which help in distinguishing the various subtypes of NBIA. The quantification of iron content in vivo and evaluation of disease progression in clinical trials are the newer applications of MRI which aid in developing treatments for these annihilating disease conditions. This case demonstrated a classic type of PKAN with similar complaint in the elder sibling.

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