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A Case Report on Pantothenate Kinase -Associated Neurodegeneration [PKAN]

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Abstract:- Pantothenate kinase- associated neurodegeneration (PKAN), formerly known as Hallervorden-Spatz syndrome, is a rare inherited autosomal recessive disorder. It is a neurological movement disorder, is mainly caused by mutation in the PKAN2 gene. PKAN is the most common type of neurodegeneration with brain iron accumulation (NBIA).On magnetic resonance imaging (MRI) of brain, demonstrates eye-of-the-tiger" sign in the globus pallidus ,which is due to abnormal iron accumulation. We present a case of a male child with PKAN presented with delayed milestones predominantly language, abnormal movements of upper limbs, gait disturbances, intellectual decline. Similar complaints were present in his elder sister and she was proven case of pantothenate kinase 2 [PKAN2] gene mutation.

Abbreviations: PKAN-Pantothenate kinase associated neurodegeneration; NBIA-Neurodegeneration with Brain Iron Accumulation; MRI- Magnetic Resonance Imaging.

Keywords:- *Hallervorden-Spatz syndrome, Eye of tiger appearance, Dystonia, Neurodegeneration, PKAN, dystonia, dementia.*

I. CASE REPORT

An 11-year-old male presented to Our Radiology department with history of delayed development since 4years, rigidity, slowed movements (bradykinesia), tremor, or dystonia since three years. There was dysarthria and choreoathetosis predominantly in the upper limbs. The child was born out of third-degree consanguineous marriage, second child in order of birth. No relevant family history was present. CNS examination shows generalized increase in limb tone, dystonia, and hyperreflexia with extensor plantar responses. Ophthalmic examination was normal. History of similar complaints were noted in his elder sister when she was at the age of 6 years age and her whole exome sequence analysis report shows homozygous pathogenic missense mutation in PANK2 gene (c.C856T: p.R286C chr20:3908153C>T) in Exon 2.

Laboratory tests for Serum ceruloplasmin, copper & iron levels were within normal limits. Peripheral blood smear revealed a normal blood picture without any acanthocytes.

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 hypointense signal in Globus pallidus, consistent with the "eye-of-the-tiger" sign in the T2W, T2 FLAIR images [Fig-1]. Susceptibility Weighted Imaging (SWI) sequence demonstrated low signal in corresponding areas from iron deposition [Fig-2]. This finding confirmed the diagnosis of PKAN.

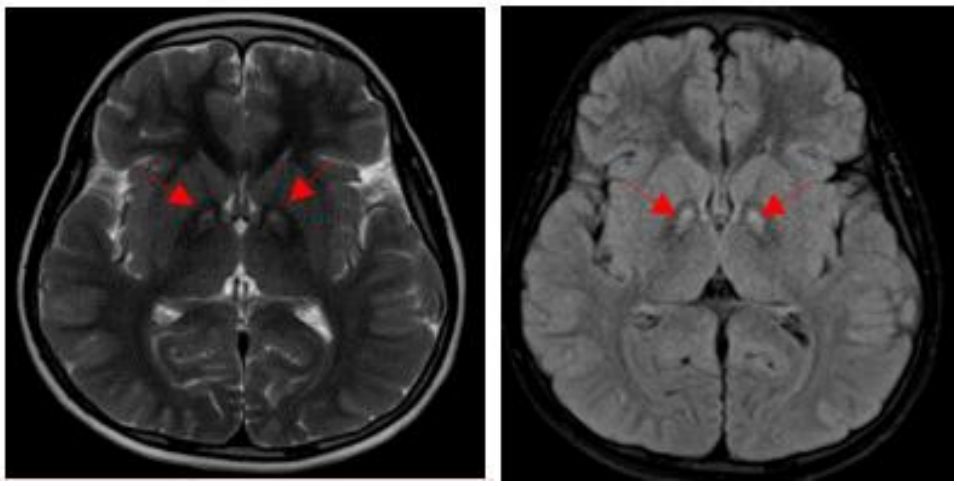

Fig 1 T2 weighted and fluid attenuated inversion recovery sequence (FLAIR) demonstrates symmetrical central hyper intensity surrounded by hypointense signal in globus pallidus, consistent with the Eye-of-the-tiger appearance [red arrows]

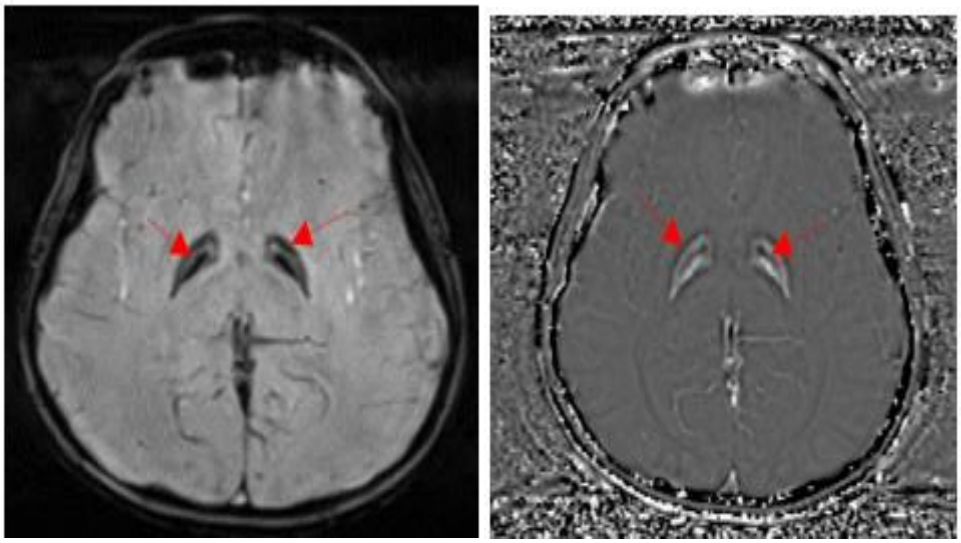

Fig 2 Susceptibility weighted imaging [SWI] and phase sequence demonstrated low signal or blooming in bilateral globus pallidus from iron deposition [red arrows]

Elder sibling who was 2 years elder than the patient had similar complaints, when she was at the age of 6years.Her symptoms got worse over time. MRI films 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 [Fig-3].

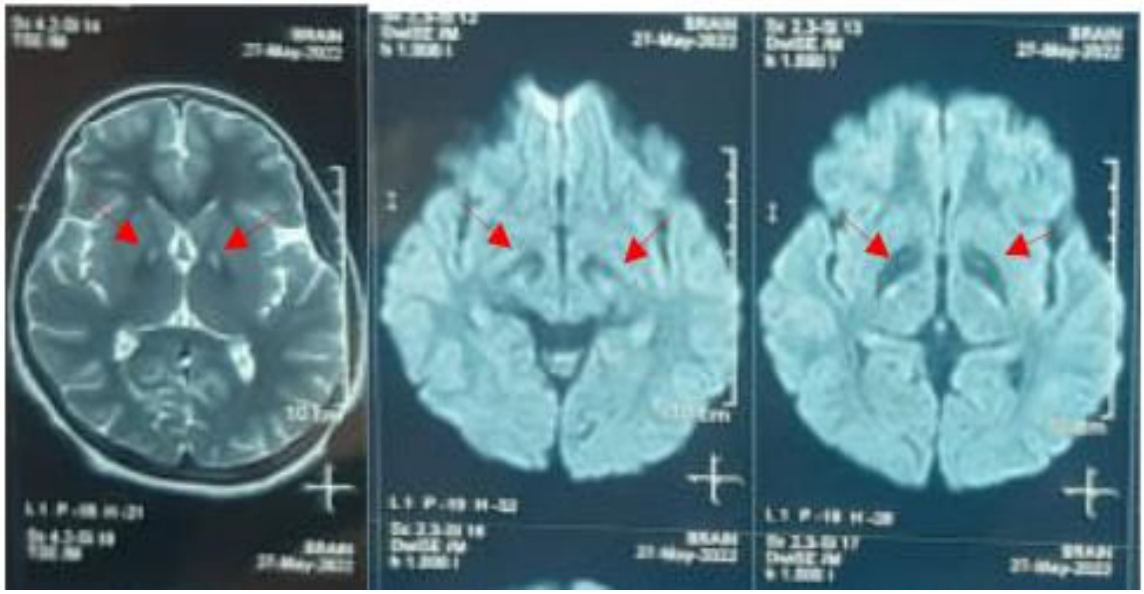

Fig 3 T2 weighted image of elder sibling demonstrated symmetrical central hyper intensity surrounded by hypo intense signal in globus pallidus, consistent with the Eye-of-the-tiger appearance [red arrows]

Differential diagnosis include Wilsons disease, carbon monoxide poisoning, methyl malonyl acidemia. In Wilson disease there is deposition of copper results from deficiency of ceruloplasmin .Wilson disease show hyperintensity in caudate and putamen not in the GP and kayser fleshner rings also found in the cornea. Carbon monoxide[CO] poisoning shows increased T2 signal in the GP followed by hemorrhagic necrosis. Methyl malonyl academia shows increased T2 signal in the GP with or without involvement of periventricular white matter .physiological iron accumulation can be also found in the healthy individual while aging[1].

II. DISCUSSION

PKAN, previously also known as Hallervorden-Spatz syndrome described by two German neuropathologists, Hallervorden and Spatz and their studies were based on pathological specimens obtained under Nazi euthanasia programs in individuals with physical and intellectual disabilities. Later the name Hallervorden-Spatz syndrome removed and A new nomenclature for the syndrome was proposed in 2003 [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]. Prevalence of PKAN estimated around 1-3 per million [5].

PKAN shows autosomal recessive inheritance, it has been linked to PANK2 gene located on chromosome 20p13. This gene encodes the pantothenate kinase 2 enzyme, which regulates the formation of coenzyme A (CoA). The deficiency of CoA leads to energy and lipid dyshomeostasis , results in increased synthesis of oxygen free radicals, eventually leading to destruction of the phospholipid membrane, especially in the basal ganglia and retina, followed by iron accumulation[4]. Pantothenate kinase associated neurodegeneration (PKAN) is the commonest form of NBIA (50%) [14]. PKAN is characterized by motor abnormalities both corticospinal (spasticity, hyperreflexia, Babinski sign) and extrapyramidal (rigidity, dystonia and choreoathetosis) features, intellectual development and pigmentary retinopathy.

Clinical classification of PKAN into, i.e., classic (75%) and atypical (25%) [7-9]. Classic PKAN shows an early onset (mean age: 3 years) and rapidly progressing course. Most common symptoms include dystonia ,dysarthria , rigidity ,choreoathetosis ,cognitive decline and pigmentary retinopathy [In 66% of cases][7-9]. Individuals with Classic disease will consistently show mutations in PANK2 gene in patients showing progressive disease. Atypical PKAN shows late onset (13-14 years) and slower progression [7-9].In atypical PKAN psychiatric and speech disturbances predominate [10], and are later followed by extrapyramidal symptoms [9].

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 [11]. Patients may evolve to death within the first decade of disease onset [6].

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 [11,6]. Pigmentary retinopathy is rare [11,6]. There is less involvement of the motor system, loss of walking occurs at 15-40 years of disease onset [11,12]. 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 [6].

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 . 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-4]. 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.

There is no definitive treatment for individuals with PKAN. Only symptomatic management can be possible. Spasticity and dystonia respond to anticholinergics, benzodiazepines. Botulinum toxin injections also provide relief of spasticity and dystonia. Baclofen can also be used as antispastic agent [11].

Iron chelating agents have been attempted to treat individuals with PKAN, but there is no measurable benefit in outcome of the disease [14].

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[13].

Table 1 Subtypes of NBIA with clinical and radioogical findings

NBIA subtypes	Gene	Chromosomal position	Location of iron deposition	Characteristic imaging findings
PKAN	PANK2	20p13	GP, SN	Eye-of-the-tiger due to bilateral symmetrical rarefaction of central GP, No white matter involvement.
PLAN	PLA2G6	22q12	GP, SN, STN	Predominant cerebellar atrophy [diffuse brain atrophy, optic atrophy with various degree of white matter involvement].
FAHN	FA2H	16q23	GP	Thinning of corpus callosum and progressive atrophy of brainstem and cerebellum [moderate to severe white matter abnormalities].
MPAN	C19orf12	19q12	GP&SN	T2 hyper intensity involving the medial medullary lamina between GP and externa [Mild diffuse brain atrophy].
KRS	ATP13A2	1p36	Putamen and caudate	Severe cerebral, cerebellar, brainstem atrophy.
Aceruloplasminemia	ACP	3q23	GP, putamen, CN, thalamus, red nucleus, dentate	Mild cerebellar atrophy.
NFT	FTL	19q13	Patchy GP, putamen, CN, dentate, thalamus	Bilateral symmetrical cystic degeneration of GP, putamen, head of the caudate nuclei, SN& deep cerebellar nuclei, cavitation, mild cerebral, cerebellar atrophy.

Subtypes of NBIA with clinical and radiological findings. GP: Globus pallidus; SN: Substania nigra; STN; Sub thalamic nucleus; CN: Caudate nucleus; ACP: Aceruloplasminemia; FAHN: Fatty acid hydroxylase-associated neurodegeneration; KRS: Kuforrakeb syndrome; NFT: Neuroferritinopathy; PKAN: Pantothenate kinase-associated neurodegeneration; PLAN: Phospholipase-associated neurodegeneration; MPAN: Mitochondrial membrane protein-associated neurodegeneration.

III. CONCLUSION

MRI of brain is an important diagnostic tool in evaluating brain iron disorders and facilitates clinical diagnosis. PKAN commonly seen in children and adolescents but if adults presented with progressive extra pyramidal symptoms we should considered it as differential diagnosis. This report is to sensitize clinicians regarding this entity and to differentiate it from other static and progressive neurological illnesses. As the radiographic findings in this illness is utmost characteristic, genetic testing should be done if the iron accumulation found in MRI. Ideal treatment strategies are not known, and at the current time therapies should be directed at the specific symptoms of the disease. This case demonstrated a classic type of PKAN with similar complaints in his elder sister.

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