Hallervorden Spatz Disease/ Pantothenate Kinase Associated Neurodegeneration – A Case Report.

A. V. Kale*, Suvarna Magar** & Akshay Golwalkar***

* Professor & HOD, **Assistant professor, ***3rd year Resident, Department of Paediatrics, MGM Medical College, Aurangabad, Maharashtra India.
Corresponding Email Address: drsuvarnamagar@gmail.com

Case Report
Subject: Paediatrics

Abstract:
Hallervorden-Spatz disease (HSD) is a rare disorder characterized by progressive extra pyramidal dysfunction and dementia. Hallervorden and Spatz first described the disease, in 1922, as a form of familial brain degeneration characterized by iron deposition in the brain. The term neurodegeneration with brain iron accumulation type 1 (NBIA-1), instead of HSD, eventually came to be used for this condition, although the most recent term for the disorder is pantothenate kinase-associated neurodegeneration.

Keywords: Pantothenate Kinase associated Neurodegeneration, Eye of Tiger Sign.

Introduction:
PKAN is an autosomal recessive disorder. The parents of an affected child must both be heterozygous carriers for the disease and therefore must carry one mutant allele. The disorder is caused by a mutant PANK2 gene located at the chromosomal locus: 20p13-p12.3. Symptoms typically begin in childhood and are progressive, often resulting in death by early adulthood. Symptoms of PKAN begin before middle childhood, and most often are noticed before ten years of age. Symptoms include: dystonia, dysphagia & dysarthria, tremors, writhing movements, dementia, spasticity, Rigidity, weakness, seizures (rare), toe walking, retinitis pigmentosa. The progression of the disease usually occurs over 10-12 years, and affected individuals typically die in the second or third decade.

A role for mutation in the PANK2 gene (band 20p13) in the etiology of HSD is known. Deficiency of pantothenate kinase leads to accumulation of cysteine and cysteine-containing compounds in the basal ganglia. This causes chelation of iron in the globus pallidus and free radical generation as a result of rapid auto-oxidation of cysteine in the presence of iron [1]. Mutations in the PANK2 gene account for most inherited HSD cases. Such mutations result in an autosomal recessive inborn error of coenzyme A metabolism, which has been termed pantothenate kinase-associated neurodegeneration [2].

Case report:
A thirteen year old boy, 1st born to third degree consanguineous parents of agrawal community, presented with history of involuntary movements with dystonic posture for one and half years, and progressive deterioration in locomotion, significant speech disturbances, swallowing difficulties along with impairment of vision since last four months. Antenatal, natal and post natal periods were uneventful; Child had regression of attained milestones.

His younger brother, who is 10 years old, has similar illness. Examination revealed a normal head circumference and choreo-athetotic movements mainly involving the upper extremities, along with dystonic arching of the trunk and drooling of saliva and dysarthric speech.

There was hypertonia in all 4 limbs and lower limbs also had fixed flexion deformities at ankle. Fundus examination revealed pigmentary spicules along with attenuated Vessels and pale disc, suggestive of retinal pigmentary dystrophy without any evidence of cherry red spot. On slit lamp examination, there was no evidence of Kayser-Fleischer rings. Serum copper, ceruloplasmin, iron and electrolytes, lipoproteins and cholesterol were normal. Skull X-ray and CSF were within normal limits. EEG showed
generalized slowing without any spike wave discharge.

MRI done revealed the classic ‘eye of tiger’ appearance at basal ganglia, globus pallidum. DNA sequencing of the PANK2 gene in patient revealed a negative study as it was done on founder 5 mutation in agarwaal community i.e.215-216 insA mutation in the homozygous state in exon 1C of PANK 2 gene [3]. Full genetic sequence for PANK 2 gene was advised but patient did not follow up later.

![Figure 1: MR 1.5-T SE sequence (2000/ 28-1 00) in axial section shows marked pallidal hypointensity in T2-weighted image consistent with iron deposits and a central spot of hypointensity within the hyperintense "eye-of-the-tiger" sign (arrows).](image)

**Discussion:**

PKAN is a rare neurodegenerative disorder with aberrant iron metabolism in the brain [4]. It is classified under neurodegeneration with brain iron accumulation (NBIA). PKAN which was first described by Julius Hallervorden and Hugo Spatz [5] can be familial or sporadic. The mode of inheritance is autosomal recessive. Clinically, the disease most commonly presents as a childhood onset predominantly extra pyramidal disorder. NBIA has different clinical presentations and genetics but shares the same characteristics of iron accumulation in the brain. In recent years, several genetic causes have been identified, such as PANK2, PLA2G6, FA2H, ATP13A2, CP, and FTL [6]. Among them, the core syndromes are pantothenate kinase-associated neurodegeneration (PKAN, NBIA type 1), which was previously named Hallervorden-Spatz disease and accounts for approximately 50% of NBIA cases [7], and PLA2G6-associated neurodegeneration (PLAN, NBIA type 2).

In 2001, the causative gene of PKAN, PANK2, was first identified to be located on chromosome 20p13 [8]. Since then, more than 100 mutations have been published. PANK2 encodes a 1.85 kb transcript that includes 7 exons. A genotype and phenotype correlation study showed that all patients with classic PKAN and one-third of the atypical group had PANK2 mutations [9].

Swaiman has described the clinical course as follows: 1) early onset childhood type, those with diagnosis before 10 years of age, 1a) rapidly progressive and 1b) slowly progressive.2) late onset- when diagnosis becomes apparent between 10-18 years of age. 3) Adult type. Our case was early onset but diagnosis was done only when the MRI showed classic picture. PANK 2 genes are expressed ubiquitously in infant retina and basal ganglia. They code for essential enzyme pantothenate kinase which plays a key role in coenzyme A synthesis [10]. Pathologically there are characteristic abnormalities in the basal ganglia. Pigment deposition of mainly iron in globus pallidus and substantia nigra along with focal axonal swelling is seen. High concentration of iron is the hallmark of the disease.

In all patients with mutation in PANK2 gene, whether classic or atypical had classic MRI features suggesting thereby that MRI served as an important tool to predict mutation status.

Management of PKAN is supportive and involves physiotherapy, speech therapy and orthopedic surgeries for deformities. There is currently no established therapy for the disease. Intrathecal baclofen has been reported to improve ease of care and dystonia in PKAN patients. Deferiprone, an iron chelator, has been shown to be safe and tolerable in PKAN patients, as well as effective in reducing brain iron accumulation as measured by MRI [11].

Future therapeutic strategies may involve direct delivery of phosphorylated pantothenate to the cells bypassing pantothenate kinase. Neuroprotection by the brain permeable iron
chelator, VK 28 which inhibits both basal and Fe/ascorbate induced mitochondrial membrane lipid peroxidation has shown promising results in rats [12].

**Conclusion:**

PKAN should be considered in the differential diagnosis of early cognitive impairment, dysarthria, progressive extra pyramidal system involvement and dystonia. The classic finding of eye of tiger sign is diagnostic of disease and suggests PANK 2 gene mutation. If mutations are available the prenatal diagnosis is possible.

**References:**