

# Pantothenate Kinase Associated Neurodegeneration (Hallervorden – Spatz Syndrome)

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**Abstract.** Hallervorden–Spatz syndrome is a rare autosomal recessive hereditary condition characterized by early onset of progressive movement alteration that include dystonia, rigidity and choreoathetosis usually associated with pyramidal signs and mental deterioration. We report two sisters where diagnosis was missed till MRI showed classic imaging findings. Mutation analysis in one, revealed homozygous mutations in the PANK 2 gene. The need for clinical recognition of this entity and differentiation of this form from other static and progressive neurological illnesses is emphasized.

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**Key words:** Pantothenate kinase associated neurodegeneration; Hallervorden-spatz syndrome; PANK 2 gene

Hallervorden – Spatz syndrome (HSS) [OMIM 234200] is an autosomal recessive neurodegenerative disorder associated with iron accumulation in the basal ganglia. Clinical features include early onset of progressive dystonia and intellectual impairment. Pigmentary retinopathy, choreoathetosis, pyramidal signs, optic atrophy, acanthocytosis have also been described.<sup>1</sup> Neuroimaging studies often reveal a heterogeneous signal intensity in the basal ganglia, which constitutes a feature highly suggestive of this disorder. Until recently the diagnosis depended upon clinical features and classic MRI abnormalities. In 2001, Zhou *et al* linked HSS with a defect in the gene (PANK2) on the short arm of chromosome 20 (20p13) encoding the enzyme Pantothenate Kinase 2 which is important in Coenzyme A synthesis.<sup>2</sup> Hence this disorder was renamed Pantothenate Kinase associated neurodegeneration (PKAN). We describe 2 sisters in whom the diagnosis of PKAN was made only after MRI revealed classic findings, the diagnosis in one being confirmed by the demonstration of homozygous mutation in PANK 2 gene.

## CASE REPORTS

### Case 1

A seven-year-old girl was born to a 6<sup>th</sup> gravida 32-year-old mother married to her first cousin. There had been 2 spontaneous abortions at 3 and 5 months gestation and she had 2 elder sibs aged 13 and 10 years who were apparently normal. The delivery and postnatal period had

been uneventful. Language and motor developmental delay had been noted at 10 months of age and she had attained walking unaided at 2.5 years of age. Frequent falls were noted thereafter. At 4 years she had developed stiffness but was able to interact with parents, feed and partially dress herself. She was being followed at a tertiary care center but no conclusive diagnosis was forthcoming. Six weeks prior to admission she had developed abnormal posturing of limbs and trunk associated with arching. No seizures had been witnessed and she had lost her ability to sit and stand.

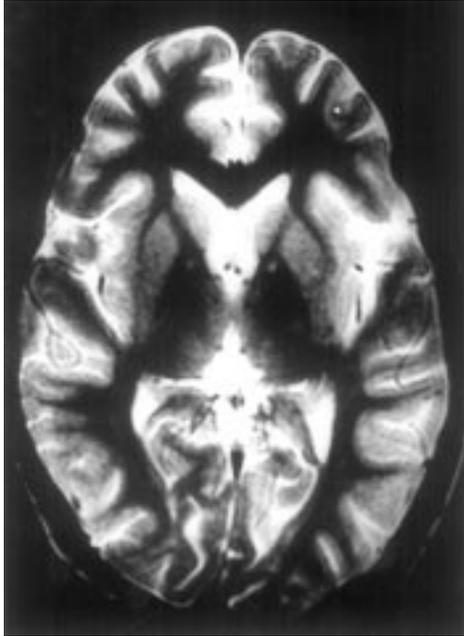
Clinical examination revealed marked dystonic posturing, brisk deep tendon reflexes and positive babinskis. Her speech had become dysarthric and old healed hematomas were evident. Fundoscopy revealed bilateral pigmentary retinopathy. Laboratory investigations, which included urine metabolic screening, urine copper and serum ceruloplasmin were within normal limits. Her peripheral smear showed acanthocytosis. Occasional lymphocytes showed cytoplasmic vacuolation. Bone marrow examination revealed occasional histiocytes having pale blue homogeneous cytoplasm. MRI done revealed the classic 'eye of tiger' appearance (Fig 1).

Using PCR amplification and sequencing the analysis of her genomic DNA revealed homozygous 2 base pair deletion in Exon 2 of the PANK gene (692-693 deletion) leading to frameshift and premature truncation of the protein. In view of existing consanguinity this offers sufficient molecular diagnosis for confirmation of PKAN.

### Case 2

Her younger sib aged 6 years was also examined. Her

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**Fig. 1.** MRI scan of the patient showing hyperintensity in the medial globus pallidus on Axial T2 image, "Eye of Tiger" appearance

development in the first two years had been normal except for delayed walking, which she had attained at 2 years. She had relatively infrequent but well documented episodes of dystonic posturing of foot and trunk. Her symptoms had become more frequent for the last 1 year. She had a slow gait and had developed contractures of the tendo achilles. She had rigidity with brisk reflexes and positive babinski's on both sides. Her speech had minimal spontaneity and was dysarthric and sluggish. Her MRI also had similar findings. Her ophthalmic examination has revealed pigmentary retinopathy. Her peripheral smear also disclosed vacuolated cymphocytes. Due to monetary constraints, her genomic DNA for analysis could not be send.

## DISCUSSION

Hallervorden Spatz Syndrome (HSS) is a rare inherited neurodegenerative disorder with childhood, adolescent and adult onset.<sup>3</sup> Patients with HSS have a combination of motor symptoms in the form of dystonia, parkinsonism, choreoathetosis, corticospinal tract involvement, optic atrophy, pigmentary retinopathy and cognitive impairment. Swaiman has described the clinical course as follows: (1) early onset childhood types; those with diagnosis before 10 years of life, either rapidly or slowly progressive (Type Ia and Ib), (2) Late onset types in which the diagnosis becomes apparent between 10 and 18 years and (3) adult types. According to him most of the patients harboring the slowly progressive, early onset childhood type of disease become symptomatic after 5 years of age, although the disease can manifest as early as 1 year of

age. Our cases are similar to those described by Peña *et al*<sup>4</sup> where the onset was early but diagnosis was missed till MRI revealed the classic findings. It must be emphasized that individual clinical variations are frequent in patients affected by the early onset HSS and a high index of suspicion should be maintained.

After the discovery of the PANK 2 gene and owing to the unethical activities of Julius Hallervorden and Hugo Spatz, the disorder is better named as PKAN.<sup>5</sup> In a recent review by Hayflick<sup>6</sup> *et al* who reviewed 123 patients from 98 families, the following interesting observations have been made.

All patients with the classic early onset disease and one third of those with atypical late onset disease had mutations in the PANK2 gene. In all patients with mutation in the PANK 2 gene whether classic or atypical had classic MRI features, suggesting thereby that MRI served as an important tool to predict mutation status. We thereby assume that the second sib would test positive for a mutation in the PANK 2 gene. The age at onset in their series for classic disease was less than 6 years with a mean age of  $3.4 \pm 3.0$  years. Dystonia, dysarthria, rigidity and choreoathetosis was seen in 98% of cases, cortical tract signs in 25%, cognitive decline in 29%, retinopathy in 68%, optic atrophy in 3% cases and acanthocytosis in 3%. Seizures had not been reported in any patient with the classic disease. Eighty five percent patients became nonambulatory within 15 years of onset of disease. Patients with atypical disease were older ( $13.7 \pm 5.9$  years), had difficulty in speech including palilalia and dysarthria. Psychiatric symptoms reminiscent of frontotemporal dementia were present in 30% cases along with preservative behavior and movements with freezing during ambulation specially while turning corners or encountering uneven surfaces. Thomas *et al*<sup>7</sup> observed that of the 34 affected individuals from 10 families, the presence of mutations in the PANK2 gene were associated with younger age at onset and higher frequency of dystonia, dysarthria and intellectual impairment and gait disturbance. Parkinsonism was commonly seen in adult onset whereas dystonia in childhood onset cases. Pigmentary degeneration of retina was observed early in classic disease and was unlikely to develop later in cases when not present at time of diagnosis.

PKAN is the first identified disorder of Pantothenate metabolism. PANK 2 genes are expressed ubiquitously in retina and infant basal ganglia. They code for an essential enzyme Pantothenate Kinase which plays a key role in Coenzyme A synthesis.<sup>8</sup> Konstanze Hörtnagel and his group postulate that the symptoms observed in pantothenate kinase-associated neurodegeneration are caused by a deficiency of the mitochondrial isoform of the enzyme and postulate the existence of a complete intramitochondrial pathway for *de novo* synthesis of coenzyme A.<sup>9</sup> High concentration of iron is the pathologic hallmark of the disorder, hence it was also called

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neurodegeneration associated with iron accumulation. It has been proposed by Zhou *et al*<sup>2</sup> that oxidative stress due to accumulation of cysteine in the absence of pyrophosphopantothenate perpetuates damage. Identification of the basic defect may in future lead to development of treatment strategies.

To conclude, PKAN should be considered in the differential diagnosis of early onset cognitive impairment and dystonia. The classic finding of “eye of tiger” appearance suggests the presence of mutations in PANK 2 gene. If mutations are identified the disorder is amenable to prenatal diagnosis.

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