Pantothenate - Kinase Associated Neurodegeneration

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Abstract

Neurodegeneration with brain iron accumulation is a group of disorders, the commonest of which is PKAN (Pantothenate kinase associated neurodegeneration). We present here, a case of 18 year old boy with progressive dementia, pyramidal and extrapyramidal involvement, dysarthria, seizures and myoclonus. The patient was diagnosed as PKAN (formerly Hallervorden Spatz disease) after “eye of tiger” appearance on neuro-imaging.

Introduction

PKAN is a rare autosomal recessive disorder characterized by progressive extrapyramidal dysfunction and associated features like corticospinal involvement, intellectual impairment, retinitis pigmentosa and optic atrophy and seizures.

Case Report

We present the case of an 18 year old boy, second child of a second degree consanguineously married parents, who presented with gradual onset, progressive complaints for last 8 years. Patient had tendency to fall to start with. He had progressive decline in scholastic performance, behavioural changes and dementia. He also had history of stiffness in lower limbs followed by upper limbs (suggestive of rigidity). He had myoclonic jerks especially in morning hours and also generalised tonic clonic convulsions since last five years. The seizures were controlled with valproate. The elder brother (25 years) was completely normal.

On CNS examination, the MMSE score was nineteen (calculation and recall totally impaired). Patient had spastic dysarthria. He had rigidity and grade IV power in all four limbs with normal reflexes and bilateral extensor plantars. Coordination was normal bilaterally. Sensory system revealed no abnormality.

Ocular examination was totally normal (no KF rings, normal retina). Serum ceruloplasmin was normal (22, the range being 20 to 60). Peripheral smear was negative for acanthocytes.

MRI was suggestive of central hyperintensity surrounded by hypointense signal in globus pallidus bilaterally on T2W images giving “eye of the tiger” sign (Figure 1).

The patient was started on central anticholinergics (trihexyphenidyl) and muscle relaxants (baclofen) and valproate was continued.

Discussion

Neurodegeneration with brain iron accumulation (NBIA) encompasses a group of progressive extrapyramidal disorders characterised by iron accumulation in the brain. The term NBIA, is sufficiently broad to encompass the spectrum of disorders previously called Hallervorden–Spatz syndrome as well as additional disorders of high brain iron.\(^1\) (Figure 2 : Classification of NBIA).

PKAN accounts for approximately 50% of cases of NBIA. Pantothenate kinase is an essential regulatory enzyme in Co-A biosynthesis. Mutation in the PANK2 gene (band 20p13) leads to mitochondrial CoA deficiency hindering \(\beta\)-oxidation of fatty acids. This results in deposition of cysteine (substrate in CoA synthesis) 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.\(^1\) Recently Krue M et.al and his colleagues from, Oregon Health and Science University, Portland, USA, have identified mutations in the fatty acid hydroxylase gene FA2H, newly implicating abnormalities of ceramide metabolism in the pathogenesis of NBIA. Phenotypically the affected family members exhibited spastic quadriaparesis, ataxia, and dystonia with onset in childhood and episodic neurological decline. The phenotypic spectrum of FA2H mutations is diverse, because they have been identified in both a form of hereditary spastic paraplegia (SPG35) and a

**NBIA classification**

- **INAD, infantile neuroaxonal dystrophy; NAD, neuroaxonal dystrophy;**

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progressive familial leukodystrophy. These findings link white matter degeneration and NBIA for the first time and implicate new signaling pathways in the genesis of NBIA.

The symptoms usually begin in the first decade with a motor disorder of extrapyramidal type and gait difficulty. Symptoms include progressive rigidity of extremities (first in the lower and later in the upper extremities), slowness of movement, and involuntary movements like choreoathetosis, dystonia, and tremor, which may precede or accompany the rigidity. Both involuntary movements and rigidity may involve muscles supplied by cranial nerves, resulting in difficulties in articulation, chewing and swallowing. Mental deterioration, emaciation, severe feeding difficulties, and visual impairment occur commonly in the late stages of the disease.

PKAN is known to occur in two forms; the classical with an early onset, fast progression and pigmented retinopathy. The other form is atypical (like our patient), with late onset, slow progression, rarely retinal involvement (our patient had normal retina), presence of psychiatric symptoms.

**Hallmark features of PKAN (both typical and atypical)**

- **Obligate features**
  - Onset during the first decade for classic and second or third decade for atypical form
  - Progression of signs and symptoms and loss of ambulation within 10 to 15 years of onset for classic and 15 to 40 years of onset for atypical form
  - Evidence of extrapyramidal dysfunction including one or more of the following: dystonia, rigidity, choreoathetosis
  - MRI brain with eye of tiger appearance

- **Corroborative features**
  - Corticospinal tract involvement (spasticity, extensor toes)
  - Retinal degeneration and/or optic atrophy
  - Positive family history consistent with autosomal recessive inheritance
  - Low or absent plasma pre-beta lipoprotein fraction
  - RBC acanthocytes

- **Exclusionary features**
  - Abnormal ceruloplasmin levels and/or abnormalities in copper metabolism
  - Evidence of neuronal ceroid lipofuscinosis by electron microscopy, enzymatic assay, or the presence of a DNA mutation in any of the genes associated with this condition
  - Predominant epileptic symptoms
  - Severe retinal degeneration or visual impairment preceding other symptoms
  - Presence of familial history of Huntington chorea and/or other autosomal dominantly inherited neuromovement disorders
  - Presence of caudate atrophy on imaging studies
  - Deficiency of beta hexosaminidase A or of ganglioside monosialic acid-1 (GM1)-galactosidase
  - Pathologic evidence of spheroid bodies in the peripheral nervous system, indicative of infantile neuroaxonal dystrophy

By definition, patients with NBIA have abnormal iron accumulation in the basal ganglia. (Figure 3: Approach to a patient with suspected NBIA) The peculiar MRI feature in both classical and atypical forms of PKAN is “Eye of the tiger sign”. It is seen in the medial aspect of globus-pallidus in the form of high signal intensity in the centre surrounded by low signal intensity ring in T2W MRI images. Fe is absent from CNS in healthy adults at birth, but deposits occur throughout life with the highest concentrations in globus-pallidus in the form of metalloprotein ferritin. This Fe deposition is pathologically intensified in PKAN, while blood and CSF Fe levels are normal. This contributes to the peripheral hypointensity, whereas central high signal intensity is due to gliosis, increased water content, neuronal disintegration, vacuolisation and cavitation.

To date an absolute correlation has been found between eye-of-the-tiger sign, and the presence of mutations in PANK2. All individuals with PANK2 mutations have the ‘eye of the tiger’ sign and all individuals with the ‘eye of the tiger’ sign have at least one PANK2 mutation.

The treatment of PKAN is supportive. Dystonias can be treated with botulinum toxin, intrathecal baclofen. Trihexyphenidyl is also useful. Other therapies under investigation include high dose pantothenate, the PANK2 enzyme substrate, fish oil supplements (rich source of docosahexanoic acid) to prevent retinal complications, development of iron chelating agents that can reach the central nervous system, deep brain stimulation, ablative pallidotomy.

Current research focuses on the future use of high, in possibly alleviating symptoms as well as the further development of iron chelating agents that may be better aimed at reaching the central nervous system and working to better remove excess iron from the individual’s system.

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**References**
