We describe a child with pathologically proven Hallervorden Spatz disease. He presented with extrapyramidal symptoms and characteristic “eye-of-the-tiger” sign on magnetic resonance imaging. He was given the possible benefit if any of deep brain stimulation with no much improvement. Pathological examination of the brain showed iron deposition in bilateral globus pallidi, spongiform change and neuron axonal degeneration (spheroids).

Key Words: Hallervorden Spatz disease, movement disorder, pantothenate kinase 2 deficiency

Introduction

Hallervorden Spatz disease (HSD) is a rare neurodegenerative disorder of basal ganglia and is characterized by extrapyramidal symptoms, mental deterioration, dementia, and retinal degeneration. Both familial and sporadic cases have been reported. Only six cases have been reported from India, clinical diagnosis based on clinical and magnetic resonance imaging characteristics,[1-4] (Table 1). We report a pathologically proven case of HSD from India.

<table>
<thead>
<tr>
<th>Authors and Years</th>
<th>Age/ Sex</th>
<th>Clinical features</th>
<th>Family History</th>
<th>Radiology</th>
<th>Others</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaushik et al 1995</td>
<td>9 yr/M</td>
<td>Involuntary movements, Dystonia, Retinitis Pigmentosa</td>
<td>Elder brother died at 9 yrs</td>
<td>Not Done</td>
<td>RBC-</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Singh and Mitra 1997</td>
<td>7 yr/M</td>
<td>Dystonia, GTC</td>
<td>2 siblings died at 13.87 yrs</td>
<td>T1 W hypointense</td>
<td>—</td>
<td>1 year</td>
</tr>
<tr>
<td>Shah et al 1999</td>
<td>7 yr/M</td>
<td>Mental retardation</td>
<td>Parental uncle died at 13 yrs</td>
<td>Eye-of-the-tiger-sign</td>
<td>—</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>23 yr/M</td>
<td>Tremors, gait impairment</td>
<td>-</td>
<td>Eye-of-the-tiger-sign</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>11 yr/F</td>
<td>Mental retardation</td>
<td>-</td>
<td>Eye-of-the-tiger-sign</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Rao et al 2003</td>
<td>9 mths/F</td>
<td>Dystonic movementsTorticollis</td>
<td>N.L.</td>
<td>T1 W hypointensity</td>
<td>—</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Present case</td>
<td>8/M</td>
<td>Dystonic movementsDystonic</td>
<td>N.L.</td>
<td>Eye-of-the-tiger-sign</td>
<td>Died</td>
<td></td>
</tr>
</tbody>
</table>

M – Male; F – Female; T1W1 – T1 weighted imaging; GTC generalized tonic clonic seizures
Spatz Disease was made. In view of poor response to pharmacotherapy he was given the possible benefit if any of deep brain stimulation (DBS). Electrodes were implanted in bilateral globus pallidus interna. Postoperatively he developed severe stridor and could not be extubated and needed a tracheostomy. He developed pneumonia and died three months after the procedure.

At autopsy the brain weighed 1100 grams before fixation with an unremarkable external surface. Coronal slicing of the brain showed brownish yellow discoloration of the bilateral globus pallidi. (Figure 2a). Microscopic examination of the cerebellum and different lobes of the cerebral hemispheres revealed slight prominence of melanin containing cells in the leptomeninges without any hypoxic changes. Sections examined from the globus pallidi showed brownish black color pigment deposition in the parenchyma both extracellularly and intracellularly in the neurons and astrocytes, and as mulberry-like encrustation of blood vessel wall (Figure 2b). This pigment on Pearl’s reaction proved to be iron (Figure 2c) and did not stain with the calcium stains. There was spongiosis, loss of neurons, gliosis and eosinophilic spheroids (Figure 2d) (neuron axonal dystrophy, NAD). These spheroids were immunoreactive to neurofilament. Iron deposition and spheroids were also seen in the corticostriate tracts but were not associated with demyelination or axonolysis of the tracts and white matter. Sections from the electrode site implantation revealed cyst formation and collection of foamy macrophages along with reactive gliosis of the surrounding parenchyma. These features were consistent with HSD.

### Discussion

Hallervorden Spatz Disease (HSD) is a rare autosomal recessive neurodegenerative disorder with aberrant iron metabolism in the brain, first described by Hallervorden and Spatz in 1922. It is characterized by childhood onset of extrapyramidal motor symptoms. Some patients may present with mental changes, dementia and vision disturbances. Average survival after diagnosis onset is 11.8 years. Pathological findings include iron deposition, axonal swellings or spheroids (NAD) predominantly in the globus pallidus and pars reticularis of the substantia nigra. Since the first description of this disease, little progress has been made in the treatment.

Recently, the gene for the disease has been localized to chromosome 20p12.3-13, coding for pantothenate kinase 2 which is required for the phosphorylation of pantothenic acid in the formation of coenzyme A. Due to defective phosphorylation of pantothenic acid there is under utilization of cystine which, when in excess causes chelation of iron leading to free toxic radicals production. The preferential involvement of basal ganglia is attributed to the excess of pantothenate kinase receptors. Thus, the term pantothenate kinase 2-associated neurodegeneration (PKAN) may be preferable instead of HSD.[6]

The characteristic MR finding of “eye-of-the-tiger”-sign corresponds to the pathological findings. The hypointensity on T2 weighted image is because of iron deposition and central hyperintensity is secondary to gliosis and spongiosis.[7] This is well corroborated pathologically in this case also. The other conditions in which high signal intensity, like HSD can be observed are metabolic disorders, like organic acidurias, early onset levodopa responsive Parkinsonism and cortical-basal ganglionic degeneration. The other disorder affecting basal ganglia such as Leigh’s disease, mitochondrial encephalopathies, infantile bilateral necrosis and Wilson’s disease more frequently involve the putamen rather than the globus pallidus.

The other differential diagnosis of iron deposition in the basal ganglia and “eye-of-the-tiger”-sign include aceruloplasminemia and neuroferritinopathy. These are distinct conditions of abnormal iron metabolism but unlike HSD present in adult or late life. Neuroferritinopathy is characterized by onset at 40-55 years of age and defect is localized to gene encoding ferritin light chain polypeptide at 19q13.3.
ceruloplasminemia is associated with diabetes mellitus and there is complete deficiency of ceruloplasmin protein. The gene is localized to chromosome 3q13.3. Recently, neurodegenerative diseases of brain with accumulation of iron have been classified according to the age of onset and gene defect into different groups (Table 2). Hayflick et al.[8] studied 123 cases from 98 families and classified HSD clinically as classic disease and atypical form. Classical HSD is characterized by early onset, rapid progression and presence of typical “eye-of-the-tiger”-sign with PANK2 mutations. In contrast, atypical disease is characterized by late onset with slow progression and only one-third of the cases showed PANK2 mutations. “Eye-of-the-tiger”-sign may or may not be present. They concluded that all patients with “eye-of-the-tiger”-sign, whether classic or atypical, showed PANK2 mutations and this favoured to the diagnosis of HSD.

Management is symptomatic and there is no definitive treatment of this disease. Resistance, drugs adverse effects and ineffectiveness of the medical treatment in stopping the disease progression in movement disorders has led to exploration of surgical modalities in the treatment of these disorders. The role of surgical treatment for dystonia is evolving. Stereotactic pallidotomy[9] and thalamotomy[10] have been tried with good short-term results. However, these are permanent procedures with increased risk of side effects. In contrast, DBS is a relatively newly described technique, which is reversible and is seemingly free of side effects and complications apart from the risk of infection. It is however expensive. The principle of this technique is based on the concept that high frequency stimulation of neural cells lead to suppression or modulation of their activity, without generating irreversible anatomical lesions. Bilateral DBS was tried in this case but without any benefit. 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.[11] Its potency is comparable to proteolytic iron chelator, desferal, which does not cross the blood-brain-barrier.

Thus, HSD is a rare neurodegenerative disorder characterized by iron deposition in the globus pallidus with characteristic radiological “eye-of-the-tiger”-sign. Pre- and post-natal molecular diagnosis is possible. The role of DBS needs to be evaluated on large number of patients before it is discarded.

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References


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