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Hallevorden Spatz Disease: A Diagnosis Missed

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Abstract

Hallervorden-spatz disease is a rare neurodegenerative disorder. We describe a child who presented with regression of milestones and progressive dystonia, along with the characteristic "eye-of-the-tiger" appearance on MRI. Interestingly, the child was being treated earlier as a case of spastic paraplegia of undetermined cause with a normal MRI scan previously.

Introduction

HSD is a neurodegenerative disease of the basal ganglia and is characterized by extrapyramidal signs and symptoms, mental deterioration and dementia. Both sporadic and familial cases have been reported. Diagnosis is based on clinical presentation and characteristic Magnetic Resonance Imaging.

Case report

A 6.5 year old male presented with regression of milestones for the past 5 years and dystonic posturing of limbs for the past 3 years.

He was apparently well till 1year of age with normal psychomotor development. He was the product of non-consanguineous marriage with an uneventful antenatal and postnatal course. At 15 months of age he had a single episode of Generalized Tonic Clonic Seizure not associated with fever. This event was followed by progressive falls during ambulation which eventually over the course of one year led to complete inability to walk. By 2.5 years of post natal age he had lost the ability to sit with support. The above events were accompanied by progressively increased tone of bilateral upper and lower limbs. At the age of 3 years he developed abnormal dystonic posturing of limbs which have subsequently led to fixed contractures in bilateral lower limbs.

The child had begun to speak 1-2 words by the age of 15 months gradually developed dysarthria by the age of 2 years which has since progressed to complete loss of speech. His visual acuity has also diminished over the past year and he cannot fix on a particular object.

At present he has complete loss of locomotor ability, vision and speech.

His younger sibling who is now 3.5 years of age has also developed similar symptoms of regression of milestones and dystonic posturing for the past 8 months.

The index case has been started on Levadopa. Baclofen and Trihexyphenydyl were added with no significant improvement of his symptomatology.

On examination the child was bedridden with generalized dystonia and fixed contractures of all four limbs (Figure 1). There was no evidence of Kayser Fleischer ring or Retinitis Pigmentosa. Serum Ferritin and Ceruloplasmin levels were normal. The peripheral blood picture did not reveal any acanthocytes. The MRI of the patient at the age of 3.5 years was normal. Repeat MRI done at our centre when the patient was xx years old showed hypointensity with an area of central hyperintensity in the bilateral Globus Pallidi (Eye of the Tiger Sign, Figure 2) on T2 weighted imaging.

Based on the clinical and MRI findings a diagnosis of Hallevorden Spatz Disease was made.

MRI of the younger sibling was performed at our centre which showed normal imaging.

Discussion

Hallervordan-spatz disease is a rare disorder characterized by progressive extrapyramidal dysfunction and dementia. The disease has its onset in late childhood or adolescence. The disease can be familial or sporadic, when familial; it is inherited recessively and has been linked to chromosome 20.[1]

Our case was initially treated as spastic quadriplegia of undetermined etiology. The MRI done initially at the age of 3.5 years was essentially normal and misled the clinicians. The younger sibling of the patient has also started

developing similar symptomatology demonstrating a familial inheritance pattern. However interestingly his T2W MRI picture is also normal. The mutational analysis could not be performed due to financial constraints.

Hallervorden and Spatz first described the disease in 1922 as a form of familial brain degeneration characterized by iron deposition in brain. A mutation in Pantothenate kinase gene (PANK2) on band 20p13 has been described in patients with typical HSD.[2]

The term Neurodegeneration with brain iron accumulation type 1 (NBIA-1) has been used in more recent publication.[3]The newest terminology for this condition is Pantothenate kinase-associated neurodegeneration.[4]
HSD is relentlessly progressive. The course is characterized by progressive dementia, corticospinal signs (spasticity, hyperreflexia) and extrapyramidal signs including rigidity, dystonia and choreoathetosis. Seizures have also been described in few patients. Affected individuals typically die in the second or third decade. The course of the disease usually proceeds over 10-12 years but case reports describe patients surviving 30 years.
Based on the common clinical features, the following criteria have been proposed. (Table 1)[5]

Table 1: All the obligatory findings and at least two of the corroborative findings should be present. None of the exclusionary features should be present

Obligate features
Onset in the first 2 decades of life.
Progression of signs and symptoms
Evidence of extrapyramidal dysfunction including one or more of the following: dystonia, rigidity, choreothetosis

Corroborative features
Corticospinal tract involvement
Progressive intellectual impairment
Retinitis pigmentosa and/or optic atrophy Seizures
Positive family history consistent with autosomal recessive inheritance
Hypointense areas on the MRI involving the basal ganglia
Abnormal cytosomes in the circulating lymphocytes and/or sea-blue histiocytes in the bone marrow.

Exclusionary features
Abnormal ceruloplasmin levels and/or abnormalities in copper metabolism.
Presence of overt neuronal ceroid lipofuscinosis
Predominant epileptic symptoms
Severe retinal degeneration or visual symptoms preceding other symptoms
Presence of family history of Huntington chorea or other autosomal dominant inherited movement disorders.
Presence of caudate atrophy on imaging studies
Deficiency of hexosaminidase A
Deficiency of GM 1 galactosidase
Nonprogressive course
Absence of extrapyramidal signs

The differential diagnosis includes Wilson's disease, Juvenile ceroid lipofuscinosis, Huntington's disease and Neuroacanthocytosis. There is no specific biochemical marker for Hallervorden-spatz disease; MRI (T2W) shows hyper intensity (tissue necrosis, edema) surrounded by hypointensity (abnormal iron accumulation) in the region of Globus Pallidus. This is called the "eye of the tiger" appearance. A one to one correlation between this pattern and PANK2 mutation has been observed.

Management is predominantly supportive, including levadopa, bromocriptine and trihexyphenidyl for dystonia. Botulinum toxin has also been tried. The role of surgical treatment for dystonia is evolving. Stereotactic pallidotomy [6]and Thalamotomy [7]have been tried with good short term results. Deep Brain Stimulation is a relatively newly
described technique, which is seemingly free of side effects.

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 has shown promising results in rats,[8] with potency comparable to desferal which does not crosss the blood-brain-barrier.

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