Case Report

Hallervorden-Spatz disease

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Abstract

Hallervorden-Spatz disease (HSD) is a rare disorder characterized by progressive extrapyramidal 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. Here we present four HSD cases with different clinical pictures.

Key Words: Extra pyramdal sign, Hallervorden-Spatz Disease, dystonia, dementia

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INTRODUCTION

Hallervorden-Spatz disease (HSD) is a rare disorder characterized by progressive extrapyramidal 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, instead of HSD, eventually came to be used for this condition;[1] although, the most recent term for the disorder is pantothenate kinase (PANK2)- associated neurodegeneration.[2]

Onset most commonly occurs in late childhood or early adolescence. The classic presentation is in the late part of the first decade or the early part of the second decade, when the individual is between ages 7 years and 15 years. However, the disease has been reported in infancy, and cases with adult onset have been described as well.[3-5]

HSD is relentlessly progressive. The course is characterized by progressive dementia, corticospinal signs (e.g., spasticity, hyper-reflexia), and extrapyramidal signs, including rigidity, dystonia, and choreoathetosis. The course of the disease usually proceeds over 10-12 years and affected individuals typically die in the second or third decade, but case reports describe patients surviving 30 years.[6,7]

The disease can be familial or sporadic. When familial, HSD is inherited recessively; it has been linked to chromosome 20.[8] A mutation in the PANK2 gene on band 20p13 has been described in patients with typical HSD.[9]

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CASE REPORTS

Case 1

A 19-year-old girl was relatively asymptomatic until the age of 15 years when she started developing dysphagia, dysarthria, and dysphonia. These abnormalities progressed over 4 years with anarthria, severe dysphagia and abnormal movement of tongue [Video 1].

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There is no impairment of higher cortical functions. No visual abnormalities were detected. No significant family history was obtained. Neurological examination revealed sever slurred speech; sever tongue dystonia, mild bilateral rigidity on lower limbs, hyperreflexia, and auto babinski. Laboratory investigations including serum copper and ceruloplasmin levels were normal. Magnetic resonance imaging (MRI) scan revealed small hyper intensity in the inner part of both GP, surrounded by the hypo-intense rim peripherally on T2 [Figure 1].

Drugs: Tetrabenazine 25 BID, Ammoral Bid

Case 2

A 20-year-old girl was relatively asymptomatic until age of 14 years when she started walking on toes and unsteady gait. Gradually, she developed motor difficulties in hands, dysphagia, and dysarthria.

She has positive family history for nearly similar symptoms in her cousin. Neurological examination revealed hyper-extension in neck muscles and because of that she was unable to look downward. No visual abnormalities were detected. She had slurred speech and difficulty in chewing. Dystonia was present on both upper and lower limbs. Axial rigidity was prominent finding. She had generalized rigidity. Deep tendon reflexes were exaggerated and babinski sign was positive [Video 2].

Lab data were negative for Wilson serology. MRI scans revealed small hyper intensity in the inner part of both GP, surrounded by the hypo-intense rim peripherally on T2 [Figure 2].

Drugs: Pimozide 4 BID, Orlept 200 BID, Triphen 2 eight, Baclofen BID

Case 3

A 34-year-old woman who presented with limb tremor and mild slurring in speech. She was asymptomatic until age 17 when she developed dysarthria and right hand tremor. Gradually, the symptom worsened and it propagated to left foot and then left hand and right foot involved too [Video 3].

Her family history was positive.

Neurological examination revealed mild dysarthria, no rigidity or spasticity was detected. She had severe asymptomatic twisting tremor in hands. In lower limbs, tremor was more severe on the left side. Serology for Wilson disease was negative. MRI scan revealed small hyper intensity in inner part of both GP, surrounded by the hypo-intense rim peripherally on T2 [Figure 3].

After 5 years of disease start she had a successful pregnancy, but after that her symptoms worsened.

Drugs: Isicome 250/25 ½ QID, Gabapentine 100 BID, Triphen 2 BID, Ammoral 100 BID

Case 4

A 22-year-old man presented with dysphagia, motor difficulties, and speech problems. His symptoms started 6 years ago with mild dysphagia and unsteady gait and abnormal posture of the right hand. In a short time, his dystonia propagated to other limbs and dysphagia worsened and he developed incomprehensive speech. When After start walking, a sudden severe pain pop out in both lower limbs and by standing and short resting it get resolved fast.

Neurological examination revealed marked diffuse rigidity (both pyramidal and extra pyramidal). Tone was increased. Deep tendon reflexes were brisk. Babinski sign was positive. After seating for a short time, he was unable to maintain upright posture and bending posture is produced.

Because of severe dystonia in limbs and tongue muscles, he was unable to eat easily as you can see in

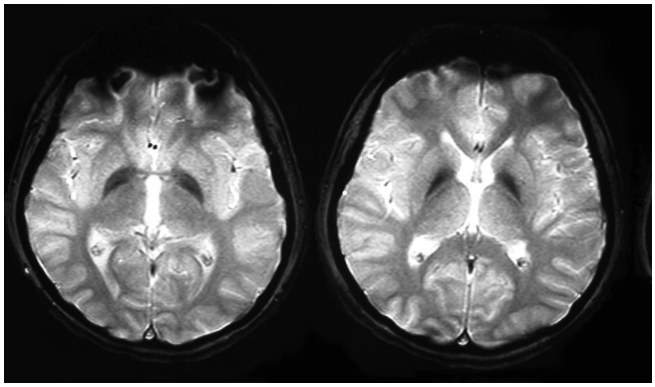

Figure 1: Bilateral basal ganglia hypodensity

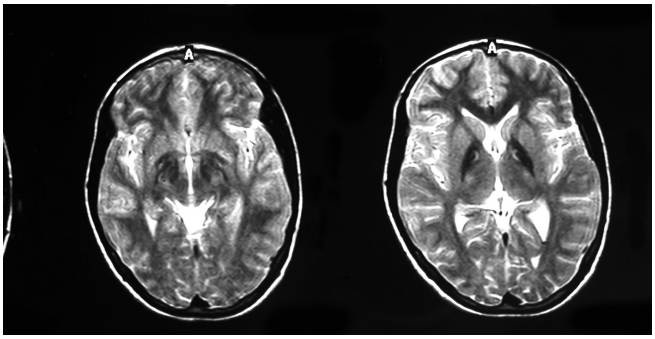

Figure 2: Magnetic resonance imaging revealed small hyper intensity in inner part of both GP, surrounded by hypointense rim peripherally on T2

movie. Serum copper and ceruloplasmin levels were normal. MRI scan revealed small hyper-intensity in inner part of both GP, surrounded by the hypo-intense rim peripherally on T2 [Figure 4].

Drugs: Isicom 250/25 1/2BID, Baclofen BID, Triphen BID, Tetrabenazine 25 BID, Na Valproate 200 BID

Etiology

The exact etiology of HSD is not known. One suggestion states that abnormal peroxidation of lipofuscin to neuromelanin and deficient cysteine dioxygenase lead to abnormal iron accumulation in the brain. While portions of the globus pallidus and pars reticulata of the substantia nigra (SN) have high iron content in healthy individuals, individuals with HSD have excess amounts of iron deposited in these areas.

However, the exact role of iron in the etiology of this disease remains unknown. However, whether the deposition of iron in basal ganglia in HSD is the cause or consequence of neuronal loss and gliosis is not clear. Decreased activity of the enzyme cysteine di-oxygenase was demonstrated in 1 affected child.[10] This was postulated to lead to accumulation of cysteine in the basal ganglia, since cysteine can chelate iron and thus result in its deposition. However, these findings were not confirmed in adult patients.

A role for mutation in the PANK2 gene (band 20p13) in the etiology of HSD has been proposed. Deficiency of PANK2 may lead 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.[11] Mutations in the PANK2 gene account for most HSD cases. Such mutations result in an autosomal recessive inborn error of coenzyme A metabolism called PANK2– associated neurodegeneration.[12-15]

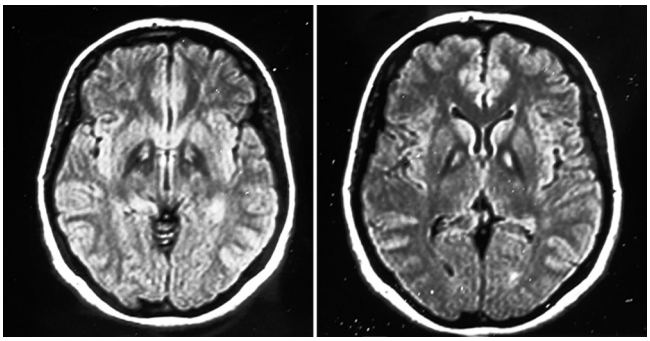

Figure 3: Eye-of-the-tiger sign in T2 image

Pathologic evaluation reveals characteristic rust-brown discoloration of the globus pallidus and SN pars reticulata secondary to iron deposition.[16,17]

History

Symptoms in HSD include the following:

- Dystonia – A prominent and early feature
- Significant speech disturbances – Can occur early
- Dysphagia – A common symptom; caused by rigidity and corticobulbar involvement
- Dementia – Present in most individuals with HSD
- Visual impairment – Caused by optic atrophy or retinal degeneration; not uncommon and can be the presenting symptom of the disease, although this is rare
- Seizures – Have been described.[16]

Clinical manifestations of HSD vary from patient to patient. The symptoms usually begin in the first decade with a motor disorder of extrapyramidal type and gait difficulty. Symptoms dominating the clinical picture include rigidity of extremities, slowness of movement, dystonia, choreoathetosis, and tremor.

In some patients, extrapyramidal dysfunction may be delayed for several years as spasticity and dysarthria may be the presenting symptoms.

Physical examination

Physical examination reveals signs consistent with extrapyramidal and corticospinal dysfunction. In addition to rigidity, dystonia, and chorea, patients may experience spasticity, brisk reflexes, and extensor plantar responses.

Based on the common clinical features, the following diagnostic criteria for HSD have been proposed.[16] All of the obligate findings and at least 2 of the corroborative

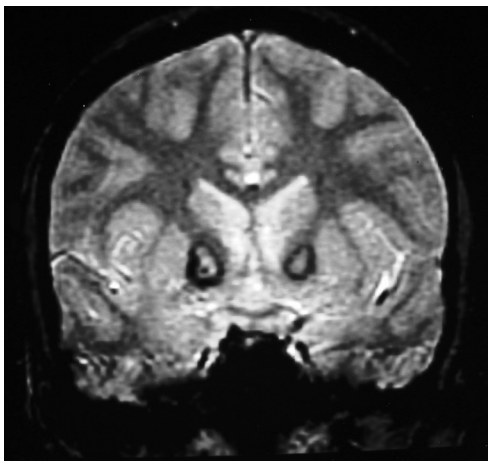

Figure 4: Eye of tiger sign in coronal view

findings should be present. None of the exclusionary factors should be present.

Obligate features of HSD include the following:
- Onset during the first 2 decades of life
- Progression of signs and symptoms
- Evidence of extrapyramidal dysfunction, including 1 or more of the following: Dystonia, rigidity, choreoathetosis.

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

Diagnostic considerations

The differential diagnosis of HSD includes other diseases presenting with extrapyramidal-pyramidal-dementia complex.
- Wilson disease
- Wilson disease
- Juvenile form of Huntington disease
- Juvenile neuronal ceroid lipofuscinosis
- Machado-Joseph disease
- Neuroacanthocytosis
- Hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration HARP syndrome.
- GM gangliosidoses.

Approach considerations

No biochemical markers have been found in HSD. Levels of copper, ceruloplasmin, lipids, amino acids, and acanthocytes typically are measured in the blood to exclude other conditions. Radionuclide scan reveals increased uptake of iron by the basal ganglia.[18]

Cultured skin fibroblasts have been reported to accumulate iron (^{59}Fe) transferrin, but the isotope is no longer available for human use.

Increased platelet monoamine oxidase – B activity has been reported.[19] Bone marrow histiocytes and peripheral lymphocytes may demonstrate the presence of abnormal cytosomes, including fingerprint, granular, and multilaminated bodies.[20,21] The characteristics of the material suggest the presence of ceroid lipofuscin.

Computed tomography (CT) scanning

CT imaging is not very helpful in the diagnosis of HSD but may exhibit hypo-density in the basal ganglia and some atrophy of the brain. Calcification in the basal ganglia in the absence of any atrophy also has been described.

Single-photon emission computed tomography (SPECT) scanning

Iodine-123 (^{123}I)-beta-carbomethoxy-3beta-(4-fluorophenyl) tropane (CIT) SPECT scanning and (^{123}I)-iodobenzamide (IBZM)-SPECT scanning also have been used in making the diagnosis of HSD.[22]

MRI

MRI has increased the likelihood of antemortem diagnosis of HSD.[23-25] The image below depicts the typical MRI appearance in HSD, revealing bilaterally symmetrical, hyperintense signal changes in the anterior medial globus pallidus, with surrounding hypo-intensity in the globus pallidus, on T2-weighted scanning. These imaging features are fairly diagnostic of HSD and have been termed the eye-of-the-tiger sign.[26-28]

A study by McNeill *et al*. concluded that in most cases of HSD, different subtypes of neurodegeneration associated with brain iron accumulation can be reliably distinguished with T2 and T2, fast – spin echo brain MRI.[25]

The hyper-intensity represents pathologic changes, including gliosis, demyelination, neuronal loss, and axonal swelling, and the surrounding hypointensity is due to the loss of signal secondary to iron deposition.

Treatment

The treatment of patients with HSD remains directed toward symptomatic findings. Tremor in patients with HSD responds best to dopaminergic agents. The anticholinergic agent benztropine helps rigidity and tremor. Benzodiazepines have been tried for choreoathetotic movements.

Hypertonia is usually a combination of rigidity and spasticity and may be difficult to treat. Dopamine agonists and anticholinergics may help to reduce rigidity. Baclofen in moderate doses relieves the stiffness and spasms and can reduce dystonia.

Symptoms such as drooling and dysarthria can be troublesome. Treat excessive drooling with a medication such as methscopolamine bromide. Dysarthria may respond to medications used for rigidity and spasticity. Speech therapy also may be useful, and computer-assisted devices may be employed in the treatment of patients with advanced cases. Gastrostomy feeding may be necessary in advanced cases of dysphagia.

A multidisciplinary team approach involving physical, occupational and speech therapists may be needed in selected patients with a protracted course to improve functional skills and communication.

Systemic chelating agents, such as desferrioxamine have been used in an attempt to remove excess iron from the brain, but these have not proved beneficial. Dementia is progressive, and no treatment has proved clearly effective.

Medication

As previously mentioned dopaminergic agents, such as levodopa and bromocriptine can produce modest improvements in dystonia. If dopaminergic agents are not effective against dystonia, anticholinergics can be used, but they offer only transient relief. Botulinum toxin injections also can improve dystonic muscles.

Agents used to relieve rigidity and spasticity may prove effective against dysarthria while methscopolamine bromide can deter excessive drooling.

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