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Case Report

Adult-onset atypical form of Hallervorden-Spatz disease

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Abstract. Hallervorden-Spatz syndrome is a rare neurodegenerative disease, resulting from mutation in the Pantothenate kinase-2 gene, and characterized by progressive pyramidal and extrapyramidal dysfunction, dementia, retinal degeneration and optic nerve atrophy. Clinical symptoms are related to abnormal iron deposition in the globus pallidus and substantia nigra.

We present a case report of a 50-year old woman that was diagnosed as atypical Hallervorden-Spatz disease with dominant extrapyramidal symptoms and the lack of typical eye-of-the-tiger sign in brain MRI.

Key words: Hallervorden-Spatz disease, iron deposition, eye-of-the-tiger sign, neurodegeneration related to pantothenate kinase, basal ganglia

1. Introduction

Hallervorden-Spatz (HS) disease is a rare, inherited autosomal recessive neurodegenerative disorder caused by a mutation in the Pantothenate kinase 2 gene (PANK2), characterized by pigmentary degeneration of globus pallidus, substantia nigra and nucleus ruber, and presents with pyramidal and extrapyramidal signs, visual loss, and cognitive impairment (1).

The syndrome was first described by Julius Hallervorden and Hugo Spatz in 1922, and its onset is in usually late childhood or early adolescence and progression occurs over 10 years or more (2).

Most of the cases are due to mutations in the PANK2 gene on chromosome 20p13-p12.3, and associated with massive iron accumulation in the basal ganglia (3).

In this report, we aimed to present a female patient, who was diagnosed as HS disease, with prominent choreoathetoid symptoms.

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2. Case report

A 50-year-old woman was referred to our clinic with involuntary movements such as bending and twisting of legs, arms and feet of 20 years duration. The symptoms have progressed over years, and she had difficulty of making fine hand movements and walking over the last few years. There was no specialty in the personal and family history of the patient, and she had normal birth, growth and development processes.

Neurological examination revealed choreoathetoid movements in both upper and lower limbs. The fundus and pupil examination were normal. She had eye movements in all directions of gaze and sufficient convergence. The patient is found to have increased deep tendon reflexes, and bilateral extensor plantar responses. Cerebellar ataxia and Romberg's sign were positive.

Laboratory tests including a CBC, blood chemistry, ceruloplasmin and copper levels, serum iron and iron binding capacity were normal. Peripheral blood smear did not reveal acanthocytosis.

T2-weighted cranial MR images showed hypointense areas in both globus pallidus which may be associated with iron deposition (Figure 1).

Genetic sequence analysis for PANK2 mutations was recommended to confirm the diagnosis, but the patient refused, and she was diagnosed as having HS disease on clinical and radiological grounds.

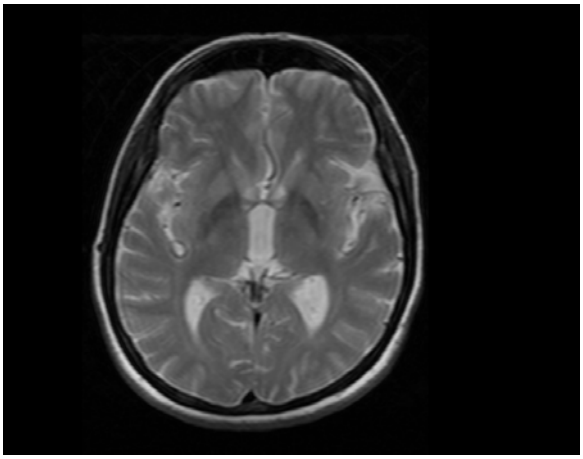

Fig. 1. T2-weighted cranial MR image showed hypointense areas in both globus pallidus.

Haloperidol was started for symptomatic treatment, and gradually increased up to 5mg/day. The patient showed a significant decrease in choreoathetoid movements after the treatment.

3. Discussion

Hallervorden-Spatz disease, also known as Pantothenate kinase-associated neurodegeneration (PKAN), is characterized by pigmentary degeneration of the basal ganglia due to iron deposition. PANK2 plays a role in the phosphorylation of pantothenic acid. PANK2 gene mutation, causing defective phosphorylation of pantothenic acid, results in pathological deposition of iron in some parts of brain, including globus pallidus, subthalamic nucleus, and substantia nigra pars reticularis, where pantothenate kinase receptors are more concentrated (1).

Clinical findings vary widely in this disorder; pyramidal symptoms including spasticity, increased tendon reflexes, and extensor plantar responses and extrapyramidal system findings such as rigidity, dystonia, parkinsonism, choreoathetosis as well as gait disturbance, dementia, visual impairment, mental retardation, and psychosis are common (2,4).

In our case, the first clinical symptom has started as extrapyramidal system findings at 30 years of age, then the clinical symptom progressed gradually with severe deterioration in walking and fine motor hand skills. The pathological findings that were observed in the physical examination such as choreoathetoid movements of the extremities, increased tendon reflexes, extensor plantar responses, cerebellar ataxia, and dysdiadochokinesia show that the features in this case are in accordance with literature data.

Although HS disease cases involve mental retardation, optic atrophy and pigmentary retinopathy (2), our case did not show these findings.

Hallervorden-Spatz disease is an inherited metabolic disorder with autosomal recessive trait. However, some HS disease cases occur sporadically, and also our case is thought to be sporadic due to lack of family history.

No specific laboratory test can be used to aid in the diagnosis of HS disease. Increased iron deposition in the basal ganglia of patients with HS disease can not be explained by serum iron level or any defect in iron metabolism. The advances in neuro-imaging methods during recent years have led to the diagnosis in the childhood period which once had been made only in post-mortem period. Classic "eye-of-the-tiger" appearance on a T2-weighted MR image is composed of hypointensity of the globus pallidus from iron deposition, medial hyperintensity secondary to gliosis and spongiosis, increased water content, and cellular degeneration. The specific PANK2 mutation is strongly linked to the specific MR appearance of the eye-of-the-tiger, and the patients with positive PKAN mutation show this sign, while those without the mutation do not have it. Although eye-of-the-tiger is a specific sign for the diagnosis of HS disease, the absence of this finding can not exclude the diagnosis, and also it was reported that it might disappear in some cases during follow-up (5).

Movement disorders in PKAN can be further classified in two phenotypes; classical form is characterized with early onset in the first decade of life, serious extrapyramidal symptoms, rapid progression (dependent walking in 10 to 15 years), eye-of-the-tiger sign, and PANK2 mutation. On the other hand, atypical form is characterized by late-onset, non-serious extrapyramidal findings, slow progression, PANK2 mutation in only 33% of patients with or without eye-of-the-tiger sign (6,7). The initial symptoms are dystonia in classical form, and parkinsonism in atypical form (8). Our case was considered as an atypical form of HS disease, who presented with late-onset neurodegenerative disease, very slow progression, extrapyramidal symptoms such as choreoathetoid movements, and lack of typical eye-of-the-tiger sign.

The other entities for differential diagnosis include aceruloplasminemia and neuro-ferritinopathy which are characterized with iron deposition in the basal ganglia and "eye-of-the-tiger" sign, organic aciduria which exists abnormal hyperintense signal, cortical basal

ganglionic degeneration, early onset levodopa-responsive parkinsonism, Wilson disease which affects lentiform nucleus and putamen rather than globus pallidus, Leigh disease, infantile bilateral necrosis, and mitochondrial encephalopathy (9).

There is no specific and effective treatment for HS disease. The aim of treatment is to relieve the symptoms. The use of chelators such as desferrioxamine to prevent iron accumulation was found to be ineffective in the treatment of this disease. Future therapeutic strategies may involve direct delivery of phosphorylated pantothenate to the cells bypassing pantothenate kinase (10).

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