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CASE REPORT

Presence of the Eye-of-the-tiger Sign on Magnetic Resonance Imaging in a Subject with Atypical Hallervorden-Spatz Syndrome Lacking Pantothenate Kinase 2 Mutation

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Hallervorden-Spatz syndrome (HSS) is generally considered to be a rare neurodegenerative disorder associated with autosomal recessive pantothenate kinase-associated neurodegeneration or neurodegeneration with brain iron accumulation. The most well-known hallmark of the syndrome is the eye-of-the-tiger sign on the brain magnetic resonance imaging (MRI) scan. Previous studies have highlighted a one-to-one correlation between the MRI findings of the eye-of-the-tiger sign and the presence of a pantothenate kinase 2 (*PANK2*) mutation, postulating that the MRI appearance is a good diagnostic tool for identifying *PANK2* mutation-positive cases. We report an atypical HSS patient without a *PANK2* mutation, who had an eye-of-the-tiger sign on MRI, therefore strengthening the notion of genetic and radiological heterogeneity in HSS.

1. Introduction

Hallervorden-Spatz syndrome (HSS) is a heterogeneous group of neurodegenerative disorders characterized by dystonia, parkinsonism, and iron accumulation in the basal ganglia.[1] This syndrome is classified by clinical presentations to be either the classic or atypical form. In classic HSS, the disease is usually evident by 10 years of age with rapid progression to severe disability by 20 years of age. The predominant neurological features are dystonia, dysarthria, and rigidity. Cognitive decline and retinal changes are also constant features. In atypical HSS, the onset of extrapyramidal defects is later and the progression is slower. All patients with classic HSS and one-third of those with atypical disease have pantothenate kinase 2 (*PANK2*) mutations, and are said to have pantothenate kinase-associated neurodegeneration. Hayflick et al reported a one-to-one correlation between the magnetic resonance imaging (MRI) findings of the eye-of-the-tiger sign and the presence of a *PANK2* mutation and postulated that the MRI appearance is a good diagnostic tool for identifying *PANK2* mutation-positive cases.[2] Herein, we report an atypical HSS patient without a *PANK2* mutation, who had an eye-of-the-tiger sign on MRI.

2. Case report

A 38-year-old woman had progressively unsteady gait and frequent instances of falling in the past 5 years. The patient also developed mental deterioration and lost the ability to take care of her son. She later experienced depressive mood and suicide attempts. Her past medical and family histories were otherwise unremarkable. The neurological examination showed cognitive impairment, limb hyperreflexia, postural instability and bilateral feet dystonia. The patient had a normal peripheral blood smear, hemogram, biochemical and lipid profile, and serum copper and ceruloplasmin. A 1.5-T brain MRI scan showed abnormal iron deposition in the bilateral globus pallidi and substantia nigra. Within the globus pallidi, there was a central hyperintense signal demonstrating an eye-of-the-tiger sign on T2-weighted images (Figure 1). Screening the entire coding sequence of the *PANK2* gene revealed no mutation.

3. Discussion

The eye-of-the-tiger sign on the MRI scan contributed to a diagnosis of HSS for this patient. Early in the course of the disease, the

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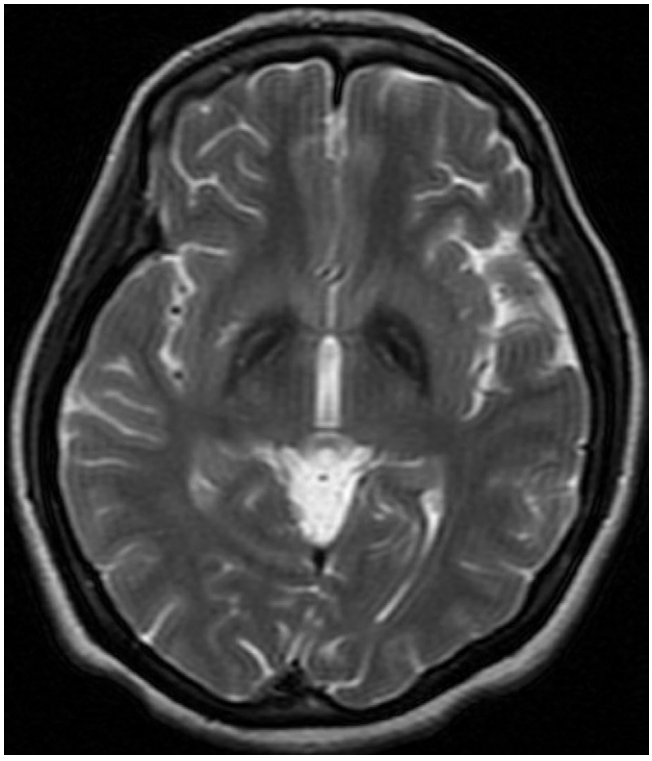

Figure 1 T2-weighted magnetic resonance image of the patient showing hypointensity with central hyperintensity lesions in the medial globus pallidi.

medial globus pallidi appear hypointense bilaterally on T2-weighted images as a result of iron deposition. The classic eye-of-the-tiger sign is generally present when symmetrical T2 hyperintensity develops, superimposing upon the hypointense background, presumably due to gliosis, increased water content, and neuronal loss with disintegration, vacuolization, and cavitation of the brain tissue.[3,4] The pathologic findings of HSS demonstrate that there are areas with different tissue densities within the globus pallidi. The first consists of a rather dense tissue containing dystrophic axons, reactive astrocytes, and residual neurons. The second pattern is associated with a rather loose tissue in which the above elements are separated by vacuoles. The area of loose tissue with vacuolization and lesser amounts of iron in the medial part of the globus pallidi corresponds to the area of high signal intensity in the T2-weighted images.[5] Baumeister et al reported a classic HSS patient who had lost the eye-of-the-tiger sign during the course of the disease and postulated progressive atrophy leading to resorption of the cavitated areas.[6] We speculate that the presence or absence of T2 hyperintensity in the medial globus pallidi is determined by a dynamic process between the degree of iron deposition and vacuole formation in this loose area. During the course of the disease, the eye-of-the-tiger sign is present in conditions of less iron deposition and more vacuole formation, and absent in conditions of more iron deposition and less vacuole formation.

Hayflick et al studied 123 patients from 98 families with a diagnosis of HSS, concluding that all patients with MRI findings of the eye-of-the-tiger sign, whether classic or atypical, had *PANK2* mutations.[2] However, Valentino et al reported a classic HSS patient who, despite having the eye-of-the-tiger sign, lacked the *PANK2* mutation.[7] Thus, the one-to-one correlation between *PANK2* mutations and the eye-of-the-tiger sign can no longer be accepted in classic HSS patients. Mutations in the *PANK2* gene lead to a deficiency of cysteine dioxygenase and subsequent cysteine accumulation and iron deposition in the globus pallidi, resulting in free radical generation and oxidative damage in the brain.[8,9] However, the relationship between *PANK2* mutations, iron deposition, and vacuolization in the medial part of the globus pallidi is not clear and awaits further study. Our findings illustrate that the eye-of-the-tiger sign is also not always associated with mutations in the *PANK2* gene in patients with atypical HSS, and strengthen the phenotypic and genetic heterogeneity of HSS.

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