Hallervorden-Spatz Syndrome in Two Siblings Diagnosed by the Clinical Features and Magnetic Resonance Imaging (MRI)

Dong Wook Kim, M.D., Young in Choi, M.D., Ki Joong Kim, M.D., Tae Sung Ko, M.D.,
Yong Seung Hwang, M.D., In Won Kim*, M.D.,

Department of Pediatrics and Radiology*, Seoul National University Children's Hospital and
Seoul National University College of Medicine, Seoul, Korea
Department of Pediatrics, Dongguk University Pohang Hospital+, Pohang, Korea

Hallervorden-Spatz syndrome (HSS) is a heredodegenerative disorder characterized by both progressive pyramidal and extrapyramidal signs, dysarthric speech, and mental deterioration. No diagnostic biochemical test is yet available, and diagnosis of HSS can be confirmed only at autopsy by the characteristic neuropathology including abnormal iron storage, disordered myelination, and loss of brain substance. We present two siblings with clinical features consistent with HSS, in whom magnetic resonance imaging (MRI) demonstrated the deposition of iron in the globus pallidus and the substantia nigra thus allowing an antemortem diagnosis of HSS.

INTRODUCTION

Hallervorden-Spatz syndrome (HSS) is a rare condition, most often transmitted as an autosomal recessive trait, which usually becomes evident during the first two decades of life (Swaiman et al., 1983; Swaiman, 1991). To date no diagnostic biochemical test is available, although ferrokinetic studies demonstrate iron storage in basal ganglia of children affected by HSS (Swaiman et al., 1983; Tanfani et al., 1987; Galluci et al., 1990). So the diagnosis of HSS is made on the basis of a suggestive clinical picture and has to be confirmed by the characteristic neuropathological findings (Tanfani et al., 1987).

The principal clinical features are (a) occurrence at a young age; (b) motor disorders, mainly of the extrapyramidal type (dystonic postures, muscular rigidity, involuntary movements, choreoathetosis, or tremor), and signs of corticospinal system in-

volvement; (c) mental changes indicative of dementia; and (d) a relentlessly progressive course. The neuropathological changes are mainly represented by (a) bilateral, symmetrical, partially destructive lesions of the globi pallidi, especially their internal segment, and of the pars reticulata of the substantia nigra, associated with demyelination and focal axonal swelling; (b) widely disseminated spheroids; (c) accumulation of pigment, much of it iron containing, in the regions most affected (Galluci et al., 1990).

Drayer et al. have recently reported that high field strengh (1.5 T) MRI is able to reveal distribution of brain iron in normal subjects as hypointense areas on T2-weighted images using the spin-echo (SE) sequence (Drayer et al., 1986). Based on this observation, MRI offered the possibility of detecting iron deposit abnormalities in the brain and suggested its usefulness for the in vivo diagnosis of HSS (Tanfani et al., 1987; Galluci et al., 1990). Therefore, a number of reports have often, but not uniformly, demonstrated hypointensity of the basal ganglia, particularly the substantia nigra on T2-weighted SE images, indicating an increased iron deposition in such patients with HSS (Littrup et al., 1985; Drayer et al., 1986; Rutledge et al., 1987; Tanfani et al., 1987; Mutoh et al., 1988; Sethi et

Address for correspondence: Yong Seung Hwang, Department of Pediatrics, Seoul National University Children's Hospital, 28 Yongon-dong, Chongno-gu, Seoul, 110-744, Korea. Tel 02-760-3570,3676
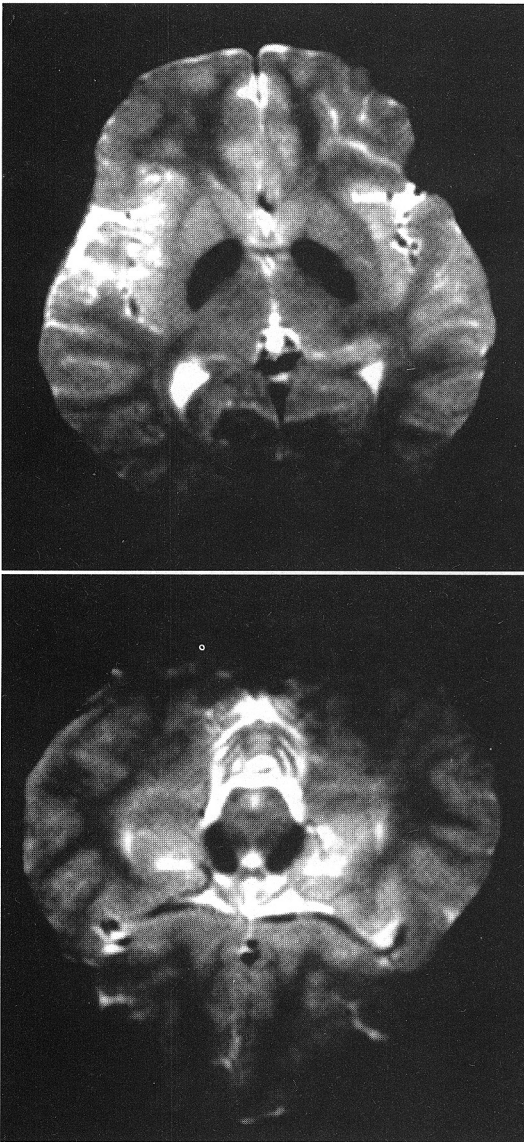
Fig. 1. Magnetic resonance scan T2-weighted images (2.0 T) of patient 1 shows prominent low signal intensities bilaterally in the globus pallidus and the substantia nigra.
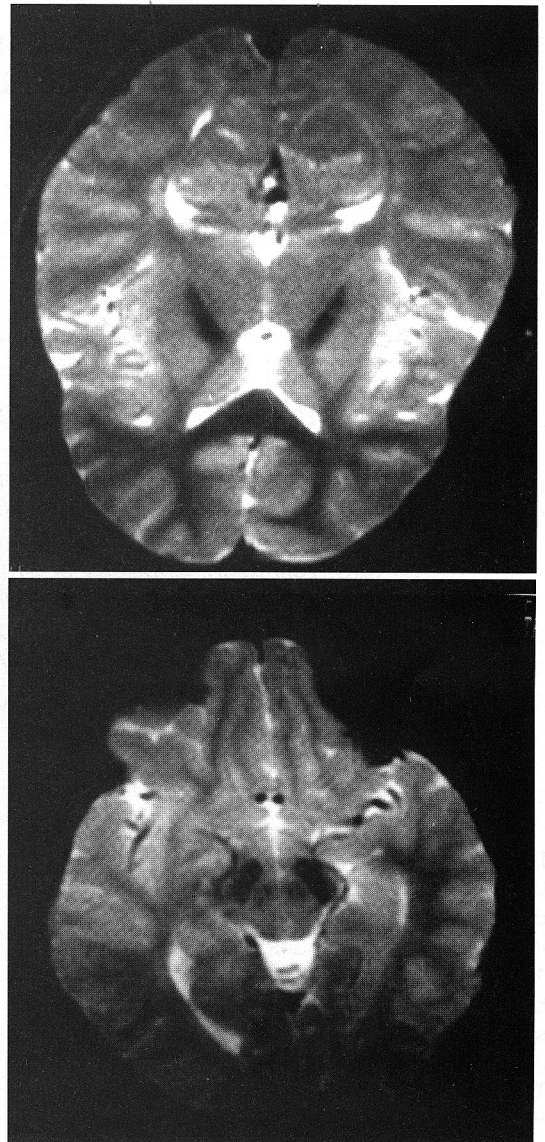
Fig. 2. Magnetic resonance scan T2-weighted images (2.0 T) of patient 2 discloses bilateral markedly decreased signal intensities in the globus pallidus and the substantia nigra.

al., 1988; Schaffert et al., 1989; Galluci et al., 1990; Swaiman, 1991). The scans should be performed on equipment using fields of 1.5 T or greater (Swaiman, 1991).

We report two siblings with clinical features consistent with HSS in whom MRI demonstrated the deposition of iron in the substantia nigra as well as in the globus pallidus.

CASE REPORTS

Patient 1

A 7-year-old boy presented with a progressive gait disturbance. He was the second child of unrelated parents. His father was a 57-year-old farmer and had no history of neurologic disease. His mother, 27 years old, was mentally retarded with-

out any other neurologic deficit. His younger brother, now 6 years old, was in good health. However, his 8-year-old sister had a similar neurologic deficit. The patient's birth and early development were normal. From the age of 2 years, he began to show abnormal gait with a tendency to intrarotation of the feet and toe walking. In the following years, the gait disturbance steadily progressed associated with frequent falls, and impairments of speech and intelligence were noted.

On admission, he walked on his toes with a mild equinovarus posture of the legs. His general apperance looked dull. Physical examination revealed intention tremor, rigidity, and exaggerated deep tendon reflexes, but there was no Babinski sign. There was no pigmentation of the skin or hepatosplenomegaly. Dysarthric speech and dysdiadochokinesia were noted. There was no Kayser-Fleischer ring. Laboratory examination results were all normal including serum copper, ceruloplasmin, and urinary copper excretion. Electromyography (EMG) and nerve conduction velocity (NCV) revealed no abnormalities. Psychometric evaluation showed that his social age was 2.6 years old and his capacity of social adaptation was 37 %. MRI scan was performed with a SE sequence on a 2.0 T. Prominent low signal intensities were noticed bilaterally in the globus pallidus and the substantia nigra on T2-weighted images (Fig. 1).

Patient 2

This 8-year-old girl was the elder sister of patient 1. Her birth and infancy were unremarkable. She could walk alone at the age of 1 year. But she began to show gait disturbance with a tendency to toe walking from the age of about 3 years. Subsequently, her motor performances progressively deteriorated and she became unable to walk at age 5. Clinical examination revealed a dull appearance, generalized rigidity, hyperreflexia, and speech impairment. She was not able to walk alone, could move only with crawling, and spoke only a few single words. The high field strength (2.0 T) MRI disclosed bilateral excessive decrease of signal in the globus pallidus and the substantia nigra on T2-weighted images using the SE sequence (Fig. 2).

DISCUSSION

The normally comparatively high concentrations of iron in the globus pallidus, the pars reticulata of the substantia nigra, and a few other brain areas are well recognized (Hallgren et al., 1958; Swaiman, 1991). Iron is deposited in pathologically high concentrations in the brain in several central nervous system degenerative diseases, particularly HSS, Parkinson disease, Alzheimer's disease, and Pick's disease (Hallervorden et al., 1922; Hallervorden, 1924; Lhermitte et al., 1924; Akelaitis, 1944; Goodman, 1953; Rojas et al., 1965; Szanto et al., 1966; Earle, 1968; Swaiman et al., 1983; Youdim et al., 1989; Swaiman, 1991).

Hallervorden and Spatz described an illness in five siblings with the characteristic clinical features of dystonic posturing, rigidity, choreoathetosis, and progressive dementia in 1922 (Hallervorden et al., 1922). There were striking neuropathological changes, mainly affecting the globus pallidus and the pars reticulata of the substantia nigra, consisting of abnormal accumulations of iron-containing pigment, decreased myelin in the globus pallidus, and widely distributed focal axonal swellings in the pallidonigral system and cortex. Since then, a spectrum of the conditions subsumed in attempts to provide meaningful subclassifications. Although the basic pathophysiology of HSS remains unknown, the massive iron deposition in the globus pallidus and substantia nigra, the presumably autosomal recessive genetic transmission, and the clinical manifestations distinguish this disorder from other neurodegenerative and extrapyramidal diseases (Swaiman, 1991).

In general, the clinical manifestations of patients with HSS vary from individual to individual. The classic form is characterized by onset in the middle or late portion of the first decade of life and the presence of corticospinal impairment (eg, spasticity, hyperactive deep tendon reflexes, clonus, and extensor toe signs). Signs and symptoms of extrapyramidal dysfunction may be delayed for 1 to several years and usually occur in the form of dystonia; however, rigidity, choreoathetosis, and tremor also may be present. Intellectual retardation or decline is present in most but not all patients. Optic atrophy is also a common feature and is often accompanied by retinitis pigmentosa. Although progression to death at least by early adulthood is described, it has become obvious that the clinical course is variable. Some patients undergo slowly progressive changes or even plateau for many years and continue to function in the third decade of life. Other patients undergo rapid deterioration with profound dystonia and rigidity, difficult chewing and swallowing, and respiratory compromise; they die within 1 to 2 years

after onset of the first symptoms (Dooling et al., 1974; Swaiman, 1991).

Although ferrokinetic studies demonstrate iron storage in basal ganglia of children affected by HSS, no diagnostic biochemical test is available to date. So, the in vivo diagnosis has been problematic. Swaiman has recently proposed some noteworthy criteria for the in vivo diagnosis of HSS (Swaiman, 1991). According to his proposal, all of the following obligate features, at least two of the corroborative features, and none of the exclusionary features should be present for the diagnosis of HSS. Obligate features include onset during the first two decades of life; progression of signs and symptoms; and evidence of extrapyramidal dysfunction, including one or more of dystonia, rigidity, and choreoathetosis. Corroborative features include corticospinal tract involvement, ie, spasticity and/or extensor toe signs; progressive intellectual impairment; retinitis pigmentosa and/or optic atrophy (usually associated with visual evoked response and electroretinogram abnormalities); seizures; positive family history consistent with autosomal recessive inheritance; hypodense areas on MRI involving the basal ganglia, particularly the substantia nigra (most obvious in children during the first decade of life); and abnormal cytosomes in circulating lymphocytes and/or sea-blue histiocytes in bone marrow (Swaiman et al., 1983). Exclusionary features include abnormal ceruloplasmin levels and/or abnormalities in copper metabolism; the presence of overt neuronal ceroid-lipofuscinosis as demonstrated by severe visual impairment and/or difficult-to-control seizures often of the generalized type (ie, atypical absence, generalized tonic-clonic); predominant epileptic symptoms; severe retinal degeneration or visual impairment preceding other symptoms; presence of family history of Huntington chorea and/or other autosomal dominantly inherited neuromovement disorders; presence of caudate atrophy as demonstrated by imaging studies; deficiency of hexosaminidase A; deficiency of GM1-galactosidase; nonprogressive course; and absence of extrapyramidal signs.

In our cases, all of the obligate features proposed by Swaiman are present. Corroborative features are also present, which include corticospinal tract involvement, progressive intellectual impairment, positive family history consistent with autosomal recessive inheritance, and hypodense areas on MRI involving the basal ganglia. There is no evidences of exclusionary features. So these features meet the criteria for the in vivo diagnosis of HSS, recently proposed by Swaiman.

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