Hallervorden-Spatz Syndrome in Two Siblings Diagnosed by Clinical Features and Magnetic Resonance Imaging

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Abstract

The Hallervorden-Spatz syndrome (HSS) is a rare condition characterized by extrapyramidal and pyramidal signs, dystonia, dysarthria, retinal degeneration, dementia and a progressive course. The development of magnetic resonance imaging (MRI) has increased the number of clinical and pathological reports of HSS. MRI pallidal abnormalities are called "eye of the tiger" signs. The combination of clinical features and MRI findings can be considered as highly suggestive of a diagnosis of HSS.

Patient 1 was a 28 year old man who had been well until the age of 25 years. He developed dysarthria, difficulty with his gait and dystonia in his arms at the age of 28 years. Patient 2 was a 33 year old man who was the older brother of the first patient. He developed gait difficulty, tongue dystonia and dystonia of both arms at the age of 25 years. Each patient had spastic gait, dysarthria, dystonic posturing of both arms and generalized hyperreflexia, but no Kayser-Fleischer rings or retinitis pigmentosa. Blood chemistry, urine copper, serum copper and serum ceruloplasmin were all normal. MRI of the brain showed the "eye of the tiger" sign in the globus pallidus on T2 - weighted images.

These siblings had clinical features and MRI findings consistent with HSS. They are the first to be reported in Thailand.

Key word : Hallervorden - Spatz Syndrome, Eye of the Tiger, MRI

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The Hallervorden-Spatz syndrome (HSS) is a rare condition, which is most often transmitted as an autosomal recessive trait. Its clinical manifestations usually occur during the first two decades of life[1]. The HSS is characterized by extrapyramidal and pyramidal signs, dystonia, dysarthria, retinal degeneration and dementia, and it has a progressive course[2]. Although ferrokinetic studies have demonstrated iron storage in the basal ganglia of a patient affected by HSS, to date no diagnostic biochemical test is available[3,4]. The diagnosis of HSS is made on clinical grounds and confirmed by characteristic neuropathological findings[3]. Magnetic resonance imaging (MRI) of pallidal abnormalities consist of decreased signal intensity in T2-weighted images, compatible with iron deposition, and a small area of hyperintensity in its internal segment ("eye of the tiger" sign)[5-7]. Angelini et al proposed that the combination of neurological signs and MRI findings can be considered as highly suggestive of HSS[8].

CASE REPORTS

Patient 1 was a 28 year old man who was the second son of non-consanguinous parents. He had one younger brother and one older brother. He was born at full-term after a normal pregnancy. The delivery was uncomplicated. The patient had been well until the age of 25 years old, when he developed dysarthria. In the following year, he began to have difficulty with his gait which was associated with rigidity of both legs. At the age of 28, he developed dystonic posturing of both arms. His father and mother had no history of neurological or hepatobiliary disease, but his older brother also suffered from HSS. The neurological examination revealed a spastic gait, dysarthria, limitation of lateral gaze, slow finger movements, dystonic posturing of both arms and generalized hyperreflexia. There were no Kayser-Fleischer (K-F) rings, cogwheel rigidity, cerebellar signs or retinitis pigmentosa. The patient's mood and personality were normal. Blood chemistry, complete blood count, plasma glucose, renal function, liver function, urine copper, serum copper and serum ceruloplasmin were all normal. MRI of the brain performed on a 1.5 T showed bilateral symmetrical pallidal hypointensity peripherally, hyperintensity centrally and "eye of the tiger" in T2-weighted images (Fig. 1A).

Patient 2 was a 33 year old man. He is the older brother of the first patient. The pregnancy and delivery were unremarkable. The patient's development was normal and he was in a good health until the age of 25 years old when he developed difficulty with his gait. Three years later, he developed progressive difficulty with his speech because of tongue dystonia. Over the following 2 years, a marked dystonic posturing of the arms became evident and his speech difficulty increased. Neurological examination revealed a spastic gait, marked oromandibular dystonia which was evident when speaking, severe dysarthria, dystonic posturing of the arms and generalized hyperreflexia. There were no K-F rings, cerebellar signs or retinitis pigmentosa. The patient's mood and personality were nor-

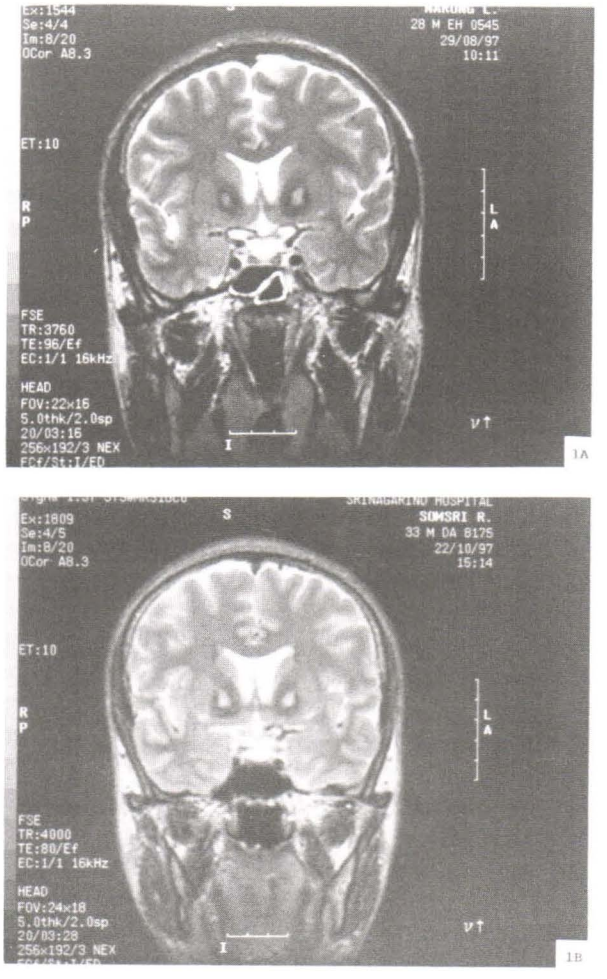

Fig. 1A, B. Coronal T2W image showed bilateral symmetrical pallidal hypointensity peripherally, hyperintensity centrally (eye of the tiger).

mal. Blood chemistry, urine copper, serum copper and serum ceruloplasmin were normal. MRI of the brain showed an "eye of the tiger" sign in the globus pallidus on T2-weighted images (Fig. 1B).

DISCUSSION

The syndrome was described by Hallervorden and Spatz in 1922[9]. The massive iron deposition in the globus pallidus and substantia nigra, autosomal recessive genetic transmission, and clinical manifestations distinguish this syndrome from other neurodegenerative and extrapyramidal diseases[1]. The pathogenesis of HSS remains unknown. The 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 in the normal brain[10]. Iron is deposited in pathologically high concentrations in the brain in several central nervous system degenerative diseases, particularly HSS[9,11-13], Parkinson's disease[14], Alzheimer's disease[15], and Pick's disease[16]. In 1991 Swaiman proposed diagnostic criteria for the diagnosis of HSS[1]. All of the obligatory findings and at least two corroborative findings should be present (Table 1). None of the exclusion factors should be present (Table 2).

All of the obligatory features proposed by Swaiman were present in our patients. Corroborative features were also present; they included corticospinal tract involvement, a positive family history consistent with autosomal recessive inheritance, and hypodense areas involving the globus pallidus on MRI. There were no exclusion features. Thus our two patients met the criteria for the diagnosis of HSS, as proposed by Swaiman.

Literature review by Med-line from 1966 to 1997 revealed 144 cases of HSS. Of these 144 cases, only 11 were reported from Asian countries (5 from Japan, 2 from Korea, 2 from Taiwan, 1 from China, and 1 from India)[17-26]. The clinical find-

Table 1. Diagnostic criteria, obligatory features and corroborative features.

Obligatory features	Corroborative features
1. Onset during the first two decades of life.	1. Corticospinal tract involvement.
	2. Progressive intellectual impairment.
2. Progression of signs and symptoms.	3. Retinitis pigmentosa.
3. Extrapyramidal dysfunction ; dystonia, rigidity, choreoathetosis.	4. Optic atrophy.
	5. Seizures.
	6. Family history consistent with autosomal recessive inheritance.
	7. Hypodense areas on MRI involving the basal ganglia, particularly the substantia nigra.
	8. Abnormal cytosomes in circulating lymphocytes and/or sea-blue histiocytes in bone marrow.

Table 2. Diagnostic criteria, exclusion features.

Exclusion features
1. Abnormal ceruloplasmin levels and/or abnormalities in copper metabolism.
2. Overt neuronal ceroid-lipofuscinosis as demonstrated by severe visual impairment and/or difficult controlling seizures which are often generalized.
3. Predominant epileptic symptoms.
4. Severe retinal degeneration or visual impairment preceding other symptoms.
5. A familial history of Huntington's chorea and/or other autosomal dominant neuromovement disorder.
6. Caudate atrophy demonstrated by imaging studies.
7. Deficiency of hexosaminidase A.
8. Deficiency of GM_1-galactosidase.
9. Non progressive course.
10. Absence of extrapyramidal signs.

ings of 8 cases from Asia are shown in Table 3. Strikingly, the number of cases reported increased after 1986 when a combination of clinical features and MRI findings, instead of autopsy findings, were required for the diagnosis. Thirty six and 88 cases of HSS were reported between 1966 and 1986, and 1987 and 1997, respectively.

Halliday has recently proposed a classification of HSS, which he divided into 6 groups[27]. The first group is HSS associated with a pediatric nuerodegenerative disorder, which was described by Hallervorden and Spatz. The first reported family had 12 children. Five of them, all girls, developed the same neurodegenerative condition between the ages of 7 and 9 years. The second group is HSS associated with neurofibrillary tangles;[28,29] the third HSS associated with acanthocytosis;[3,30-35] the fourth HSS associated with degenerative neuronal changes;[2,29,36-39] the fifth HSS associated with central nervous system malformations;[40] and the sixth a group with an adult onset[41,42]. It would be rational to reserve the term Hallervorden-Spatz disease for the pediatric cases, and the remainder to be called the Hallervorden-Spatz syndrome[27].

There is no specific treatment for HSS. Attempts have been made to remove the excess iron deposits from the brain by using desferrioxamine, but this lead to no clinical improvement or decreased iron storage in the brain. Symptomatic treatment often proves helpful. The most common movement disorder is dystonia. Therapy with levodopa or carbidopa may be effective. Our two patients were treated with levodopa. Patient 1 improved clinically. Patient 2 showed no improvement with levodopa, but improved with trihexyphenidyl.

SUMMARY

This report emphasizes that the antemortem diagnosis of HSS can be made by a combination of clinical features and MRI results. Suggestive signs include insidious walking difficulties, progressive oromandibular dystonia and clinical signs of corticospinal tract involvement. The MRI findings are very helpful for the premortem diagnosis of HSS.

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การวินิจฉัย Hallervorden–Spatz syndrome ในสองพี่น้องโดยลักษณะทางคลินิกและการตรวจด้วยคลื่นแม่เหล็กไฟฟ้าสมอง

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Hallervorden–Spatz syndrome (HSS) เป็นกลุ่มอาการที่พบได้น้อย ลักษณะทางคลินิก ประกอบด้วย pyramidal, extrapyramidal การเคลื่อนไหวผิดปกติ พูดลำบาก การเสื่อมของจอประสาทตา ความจำเสื่อมและอาการรุนแรงมากขึ้นเรื่อยๆ การตรวจด้วยคลื่นแม่เหล็กไฟฟ้าสมองช่วยให้มีการวินิจฉัยโรคได้มากขึ้น โดยพบลักษณะผิดปกติที่สมองส่วน pallidus ที่มีลักษณะคล้ายตาเสือ (eye of the tiger) วิธีวินิจฉัยโรคในผู้ป่วยที่มีชีวิตโดยลักษณะทางคลินิกและการตรวจคลื่นแม่เหล็กไฟฟ้าสมอง

ผู้ป่วยรายที่ 1 เป็นเพศชาย อายุ 28 ปี เริ่มมีอาการพูดลำบาก เดินลำบาก เมื่ออายุ 25 ปี และเมื่ออายุ 28 ปี มีอาการเคลื่อนไหวผิดปกติของมือทั้ง 2 ข้าง ผู้ป่วยรายที่ 2 เป็นพี่ชายของผู้ป่วยรายที่ 1 มีอาการเดินลำบาก ลิ้นและแขนเคลื่อนไหวผิดปกติเมื่ออายุ 25 ปี ตรวจร่างกายทางระบบประสาทของผู้ป่วยทั้ง 2 ราย พบการเดินลำบาก พูดลำบาก เกร็งของมือทั้ง 2 ข้าง รีเฟล็กซ์เอ็นลึกไว ตรวจไม่พบ Kayser–Fleischer ring และ retinitis pigmentosa ผลการตรวจเลือดหาระดับทองแดง ceruloplasmin ได้ผลปกติ และระดับทองแดงในปัสสาวะปกติ การตรวจสมองด้วยคลื่นแม่เหล็กไฟฟ้าพบลักษณะคล้ายตาเสือ (eye of the tiger) ที่บริเวณสมองส่วน globus pallidus

ได้นำเสนอผู้ป่วย HSS 2 รายซึ่งเป็นพี่น้องกันและเป็นรายงานแรกของประเทศไทย

คำสำคัญ : Hallervorden–Spatz syndrome, ตาเสือ, การตรวจด้วยคลื่นแม่เหล็กไฟฟ้า

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