Hallervorden–Spatz syndrome

Variable imaging findings

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ABSTRACT

Authors describe clinical features, CT scan and MRI findings of 4 Egyptian boys (3 brothers from one sibship and a sporadic case) with Hallervorden-Spatz syndrome (HSS). These patients presented around the age of 10-years-old with rigidity, dystonia, dysarthria, mental deterioration with loss of previously acquired skills and choreoathetotic movements. The 3 brothers developed seizures around the age of 16 and the older brother died at the age of 20. Although, the CT scan of the 3 brothers showed bilateral symmetrical calcification of the basal ganglia, the MRI of the 4 cases demonstrated bilateral symmetrical hyperintense areas surrounded by hypointense areas in the globus pallidus giving the characteristic "eye-of-the-tiger" sign. Based on the clinical and MRI picture, these 4 cases could be the atypical type of HSS. However, calcification of globus pallidus is an associated finding in these cases. This is the second report in the literature with this association. In addition, we present the results of the use of antioxidants, L-dopa and Botulinum toxin injections in the management of these cases.

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Hallervorden-Spatz syndrome (HSS) was first described in 1922 by progressive dystonia, extrapyramidal manifestations, dementia and death in the second or third decades of life.[1] It is a rare autosomal recessive neurodegenerative disorder. Although mutations in the gene located on chromosome 20p13 encoding pantothenate kinase 2 enzyme (PANK2) were reported recently in patients with the classic form and one third of cases of the atypical form, the rest of the patients did not show these mutations.[2] This enzyme plays a major role in the biosynthesis of coenzyme A. Deficiency of this enzyme enhances iron deposition and subsequently gliosis mainly in the globus pallidus and substantia nigra. Further, histopathological examination confirmed iron deposition in these areas. In normal brain, abundant iron is found in the globus pallidus and substantia nigra and in aged brain iron-reactive spheroids and granules in macrophages are seen quite frequently in these areas as well, similar to those in HSS, although, not associated with a specific disease. Other gray matter nuclei of the brain, such as the red nucleus and the dentate nucleus, are equally rich in iron. However, in HSS the iron deposition is pathologically intensified, while iron levels in blood and cerebrospinal fluid remain normal.[3] The characteristic neuroaxonal swelling and iron deposition in the globus pallidus could be detected in the MRI as a hypointense area in the globus pallidus, and sometimes as a hyperintense area in the anteromedial part surrounded by a hypointense area in the globus pallidus and these changes are termed as the "eye-of-the-tiger" sign.[4] In addition, calcification of the globus pallidus was described once as an occasional finding among cases with HSS.[5]

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Recently, Hayflick et al classified this syndrome, based on the clinical, imaging and genetic make-up, into 2 forms (classic and atypical) and provided evidence that the mutations of the PANK2 are related to the type of the disease and the MRI findings.[2] The reported familial cases were present in approximately one half of the core group of patients.[1,6] In this report, we present 2 Egyptian families, the first had 3 sibs and a sporadic case in the other. The clinical and MRI findings are suggestive of the diagnosis of the atypical form of HSS. The 3 brothers showed calcification of the globus pallidus, in addition to the "eye-of-the-tiger" sign confirming that calcification could be an associated finding in cases with HSS. This paper highlights the importance of MRI in the evaluation of any case with calcification of the basal ganglia and discusses the different trends in the treatment of this syndrome.

Case Report. ***Family 1.*** The 3 brothers were born to first-degree consanguineous healthy parents. Their eldest brother is healthy, married and has a normal female baby. The 3 brothers presented around the age of 10 years with rigidity, dystonic posture of neck and limbs, dysarthria and gradual loss of previously acquired skills (cannot control urination and defecation). At the age of 16 years, they developed epilepsy in the form of generalized tonic-clonic seizures and increased stiffness of the legs with decreased mobility. At the age of 18 years, the older brother became bed ridden and died at the age of 20 (we examined him before his death). Now the middle brother is 18-years-old, and has dystonic posture of neck and limbs with rigidity and choreoathetotic movements. He can speak only a few words, but he could not walk and he is bed ridden. The youngest brother (16-years-old) showed impaired mental function, slowing of voluntary movements, shuffling gait, but he could walk. He had dysarthria, but he could speak. He had a peculiar brownish-grey pigmented area in the right upper half of the face. The 3 brothers were referred to our Clinical Genetics Department, at the National Research Centre for further evaluation. They had no special facial features. Their mental abilities were severely impaired. They had severe dystonic posture of neck and limbs with rigidity, however, the reflexes were intact, Babinski showed planter flexion response, abdominal reflexes and superficial sensations were present. Choreoathetotic movements were also noted. Complete blood picture, metabolic screening in blood and urine using thin layer chromatography, screening for organic acids, ceruloplasmin and copper level in serum and urine, pyruvate and lactate levels in blood were normal. Eye examination showed normal fundus examination and slit lamp did not manifest Kayser-Fleisher ring. An EEG showed epileptogenic focus. A brain CT scan for the 3 brothers showed bilateral symmetrical calcification in the globus pallidus **(Figure 1)**. Unexpectedly, MRI showed bilateral symmetrical hyperintense areas surrounded by prominent hypointense areas in the globus pallidus giving the characteristic "eye-of-the-tiger" sign. Antioxidant tablets, L-dopa tablets and Botulinum toxin injections in the neck were tried with the youngest brother over one year to ameliorate the condition and to improve the dystonia. These medications until now have not shown any significant improvement.

Family 2. A 13-year-old boy, the first boy born to consanguineous healthy parents. The father has normal healthy children from a previous marriage. The boy showed within normal developmental milestones and entered primary school. Three years ago, the condition started with difficulty in walking and writing. Then the parents noticed the abnormal

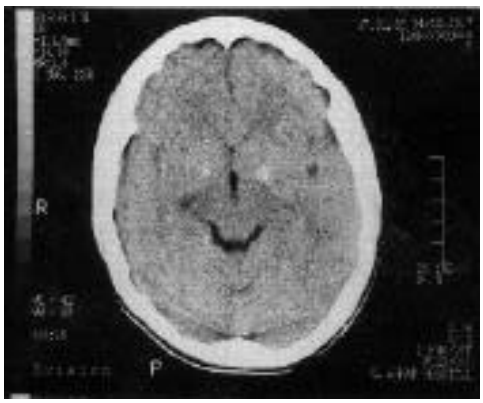

Figure 1 - A CT scan of the youngest brother of family one shows bilateral symmetrical calcification of the globus pallidus.

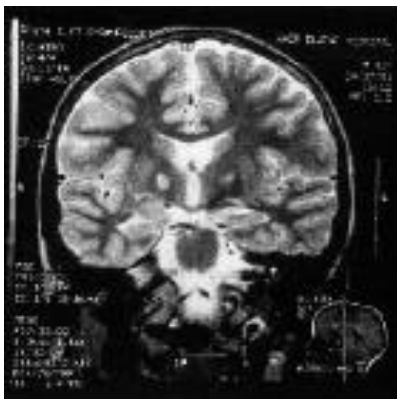

Figure 2 - Coronal cranial MRI scan of the sporadic case of family 2 revealed bilateral symmetrical hyperintense areas surrounded by prominent hypointense areas in the globus pallidus of lentiform nucleus giving the "eye-of-the-tiger" sign.

choreoathetotic movements and dementia. The condition deteriorated progressively, and he had dysarthria and rigidity but he has no epilepsy. By examination he has no dysmorphic features. Weight, height and head circumferences were around the mean. He could speak, but with difficulty. He also could walk, but with shuffling gait. In addition, he had dystonic posture of limbs, choreoathetotic movements and rigidity, however, the reflexes were present, Babinski showed planter flexion response, abdominal reflexes and superficial sensations were intact. Complete blood picture, metabolic screening in blood and urine using thin layer chromatography, screening for organic acids, ceruloplasmin and copper level in serum and urine, pyruvate and lactate level in blood were normal. Eye examination showed normal fundus and retina and slit lamp did not manifest Kayser-Fleisher ring, an EEG was normal. Brain CT scan was normal, however, MRI showed bilateral symmetrical hyperintense areas surrounded by prominent hypointense areas in the globus pallidus giving the characteristic "eye-of-the-tiger" sign **(Figure 2)**. Antioxidant and L-dopa tablets were tried with this patient for over 2 years to ameliorate the condition or to stop the progress of the disease. However, these medications neither showed improvement of the patient's condition nor prevented the progression of the disease.

Discussion. The diagnosis of HSS encompasses several disorders that share the common features of neurodegeneration and iron accumulation in the brain, including HARP syndrome (hypobetalipoproteinemia, acanthocytosis, retinitis pigmentosa and pallidal degeneration), idiopathic hemochromatosis and carbon monoxide poisoning. The normal blood picture, blood chemistry and negative history of gas exposure made the diagnosis of these syndromes a remote possibility. In addition, causes of extrapyramidal symptoms and signs and dementia could be Wilson's disease, Huntington's chorea, olivopontocerebellar atrophy, Leigh's disease, mitochondrial encephalopathies, myoclonic dystonia and neuronal ceroid-lipofuscinosis. These syndromes were excluded throughout the history and investigations in all the cases by the normal ceruloplasmin and copper level in blood, negative family history of chorea, no cerebellar atrophy in the MRI, normal level of pyruvate and lactate in the blood, no myoclonic epilepsy and normal fundus examination. These extrapyramidal symptoms and signs and dementia are the main manifestations of HSS. The clinical manifestations, course of the disease and the imaging findings of our patients distinguish this syndrome from other neurodegenerative and extrapyramidal conditions. The onset, as well as the clinical manifestations of HSS, varies from patient to patient. In our series, the age of onset of the disease was around 10 years. The early onset and rapid progression are originally reported to be the classic form of HSS. In contrast, many authors have reported late adult onset[7-9] suggestive of the atypical form of the disease.[2]

The classic form of HSS is characterized by progression to death at least by early adulthood. Although, some patients undergo slowly progressive changes or even plateau for many years and continue to function until the third decade of life.[10] Alternately, the atypical form of HSS is reported to have a slower course of progression of the disease.[2] In our patients, the older brother showed progressive course of the disease with death within 10 years from onset. The sporadic case in our series also showed rapid progressive course suggesting that these cases could be the classic type of HSS.

The hallmark of the disease is the characteristic MRI finding, called the "eye-of-the-tiger" sign.[4] It is in the form of bilateral symmetrical hypointense areas in the globus pallidus due to iron deposition. The central high signal intensity of the globus pallidus in HSS has been attributed to gliosis, demyelination, increased water content and axonal swelling and neuronal loss with disintegration, vacuolization, and cavitation of the neuropil. These processes lengthen T2-weighted images, which produce high signal intensity on T2-weighted images. The finding of hyperintensity within the hypointense region of the medial globus pallidus may be also due to tissue rarefaction in the internal part of the nucleus.[5,11] This sign could even precede the clinical features of the disease.[12] In our cases, the MRI showed typically the "eye-of-the-tiger" sign. The MRI detection of the "eye-of-the-tiger" sign has the potential to shed more light on the presence of the PANK2 mutations in patients with HSS.[2] Although, absence of this sign does not rule out the diagnosis of HSS,[8,9] Hayflick et al considered these cases as the atypical form of HSS and these authors found that only one third of atypical cases of HSS had PANK2 mutations.[2]

The important finding in this study is the presence of bilateral symmetrical calcification in the globus pallidus in the CT of the 3 brothers. This rare sign was described as an occasional sign reported only once in cases with HSS.[5] It seems unlikely that calcium deposition contributes in the mineralization process of the basal ganglia in HSS. However, it could be secondary to the degenerative process. Interestingly, the brownish-grey pigmentation presented in the youngest brother was similarly to that described by Hallervorden and Spatz in 1922 in their first description of HSS in 2 twin girls.[1] This could be attributed to deposition of iron in the skin. The accumulation of iron in the skin in cases with HSS was a matter of debate. The accumulation of ^{59}Fe-transferrin in cultured skin fibroblasts has

previously been reported, although other authors have not found this.[13,14] Authors have found difficulties in the explanation of the wide variability of clinical features that have been associated with the pathology of HSS.[2,6,9] The presence of early dystonia, rigidity in all the 4 cases and the severe neurological manifestations are all in accordance with the classic type of HSS. The absence of the corticospinal tract manifestations, spasticity and hyperreflexia, does not rule out the diagnosis as these manifestations are present in 25% of cases with classic HSS and 18% of cases with atypical HSS. In addition, Hayflick et al noticed that extrapyramidal defects developed in 73% in the atypical group and dysarthria could be the only presenting symptom in this group. Our patients had extrapyramidal signs in the form of choreoathetotic movements and all of them had dysarthria with the progression of the disease.

Seizures were reported to occur in 21.4% among patients with HSS,[10] with none in the classic cases of HSS.[2] Optic atrophy is also a common feature and is often accompanied by retinitis pigmentosa and 68% of patients with classic HSS developed this sign.[2,7,10] However, retinopathy may develop with the progress of the disease instead of at the onset. According to Hayflick et al's classification, our cases had the onset, course, clinical picture and MRI findings in accordance with the classic type of HSS, although none of them had optic atrophy and the 3 brothers had seizures[2] which is in favor of the atypical type of HSS. The question is, are these cases the atypical form of HSS with PANK2 mutations or are they the classic form of the disease with seizures, extrapyramidal signs and no optic atrophy? This question awaits confirmation by DNA analysis.

The increase in the oxidative stress in the basal ganglia due to redox cycling of iron complexes that leads to dopamine overflow and psychomotor dysfunction has attracted the attention of many authors to think about antioxidants as beneficial in slowing the progression of the disease.[9,14] In addition, Hickman et al added L-dopa and Botulinum toxin to reduce the dystonia in the management of a case with HSS.[9] In contrast, others showed improvement of dystonia after stereotactic pallidotomy in cases affected with HSS.[15] In our study, treatment with antioxidants, L-dopa and injection of Botulinum toxin did not show significant improvement of dystonia or even stopped the progression of the disease.

The recent discovery of PANK2 mutations and the new classification of patients with HSS has suggested that supplemental pantothenate (vitamin B5) could compensate for the partial enzymatic deficiency in these patients with classic disease, possibly ameliorating or preventing the progression of symptoms.[2] However, this new trend has not yet been evaluated.

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