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CASE REPORT

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# Optic atrophy as the first symptom in Hallervorden-Spatz syndrome

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**Abstract** A 16-year-old boy with the classic or postinfantile type of Hallervorden-Spatz syndrome is described. Bilateral optic atrophy with visual loss but without retinal changes was the only presenting symptom. Mild cognitive impairment, behavioural disturbances and insidious extrapyramidal involvement appeared later. MRI showed marked symmetrical hypointensity of the globi pallidi and substantia nigra. This new observation suggests that the occurrence of optic atrophy in a patient with Hallervorden-Spatz syndrome should be regarded as nonconincidental and stresses the importance of an accurate neurological work-up in all adolescents with any unusual form of progressive optic atrophy.

**Key words** Hallervorden-Spatz syndrome · Optic atrophy · Basal ganglia · Iron deposits · Magnetic resonance imaging

## Introduction

Hallervorden-Spatz syndrome (HSS) is a rare neurological disorder characterized by extrapyramidal and pyramidal signs, visual and mental deterioration.

Although the age at onset is variable, most HSS patients present in childhood or adolescence [26]. Both familial and sporadic cases have been reported [8, 26], and no specific biochemical abnormalities have as yet been found in HSS.

The diagnosis of this syndrome, until the use of magnetic resonance imaging (MRI), was based on the typical clinical picture and the characteristic pathologic central nervous system findings originally described by Hallervorden and Spatz [13]. These findings consist in iron deposition in the globus pallidus and pars reticulata of the substantia nigra, widespread gliosis, demyelination and focal axonal swelling [8]. Before the availability of MRI it was not possible to detect abnormal iron deposits in the brain in vivo [10]. In the last decade its usefulness has been definitely confirmed in the in vivo diagnosis of HSS [2, 4, 7, 11, 12, 15, 16, 18–23, 25, 27].

The authors report the case of a 16-year-old youth whose presenting sign of HSS was bilateral optic atrophy and discuss the importance of an accurate neurological work-up in all adolescents with any unusual form of progressive optic atrophy.

## Case report

A 16-year-old boy was the second child of nonconsanguineous Italian parents who had no history of neurological disease. His older brother, now 23 years old, is in good health. His mother's pregnancy, labour and delivery were normal, and his own past medical history was unremarkable. All developmental milestones were reached normally.

At the age of 14 years, during a routine screening eye examination, bilateral visual loss was detected. The patient was first admitted to our Institute of Ophthalmology and was then referred to our Paediatrics Department for a complete general and neurological work-up. A complete ophthalmological examination revealed: 20/80 corrected visual acuity in both eyes, normal intraocular pressure and anterior segment examination, and slow bilateral pupillary reflexes. Neither nystagmus nor abnormalities of extraocular muscles were found. On fundus examination the optic discs were found to be bilaterally pale and atrophic with normal retinal vessels; neither reti-

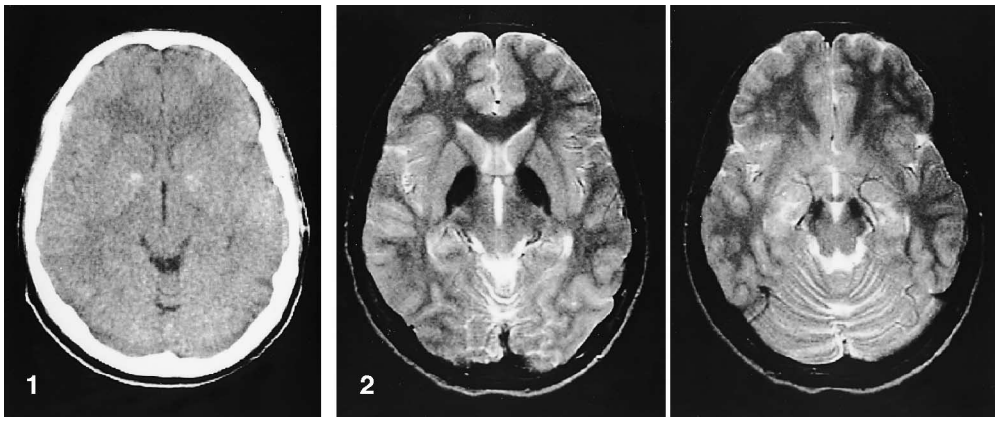


**Fig. 1** CT scan shows tiny areas of increased density bilaterally in the internal segment of the globus pallidus

**Fig. 2** Axial T2-weighted spin echo (TR 2500, TE 100) MRI. Decreased signal intensity is seen (*left*) in the globi pallidi and (*right*) in the zona reticularis of substantia nigra

nal pigmentary changes nor choroidal alterations were present. Fluorescein angiography demonstrated that both optic discs were hypofluorescent without peripapillary vascular changes; no retinal pigment alterations were observed. Colour vision, quantified with the Farnsworth-Munsell 100-hue test, was borderline. The contrast sensitivity curve was bilaterally and similarly depressed at all spatial frequencies examined. Electrophysiological testing showed normal flash electroretinogram (in both photopic and scotopic conditions) and an abnormal pattern of visual evoked potentials (VEP) with bilaterally reduced amplitude and increased latency at all spatial frequencies examined.

Neurological examination revealed an expressionless face, tremor of the limbs, hyperreflexia, gait difficulties and mild rigidity of the legs with bilateral Babinski sign. Biochemical laboratory tests were all normal, including blood and urine levels of copper, ceruloplasmin, serum creatine kinase, peripheral blood smear, liver function tests, lactate, high-resolution lipoprotein electrophoresis, vitamin E, aminoacid and organic acid screenings and lysosomal enzymes. Routine cerebrospinal fluid analyses were negative.

Electroencephalography and electromyography with motor and sensory velocity studies and also both brain stem auditory evoked potentials (BAEP) and somatosensory evoked potentials (SEP) were all within normal limits.

Brain CT scans revealed tiny and symmetrical hyperdense areas in the internal segment of both globi pallidi (Fig. 1). Axial and coronal T2-weighted high-field-strength (1.5 T) MRI showed marked symmetrical hypointensity of the globus pallidus and substantia nigra (Fig. 2), which was consistent with iron deposition.

The subsequent clinical course was characterized by progressive learning difficulties and personality changes with irritability and behavioural abnormalities. For these reasons our patient received psychological and teaching support from his school administration. At the age of 16 years the patient showed marked irritability and "nervousness," with inappropriate behaviour. He performed poorly in simple calculations and on questions of general information and judgment. A Wechsler Intelligence Scales for Children-Revised (WISC-R) assessment revealed a verbal intelligence quotient (IQ) of 74 and a performance IQ of 54 (total IQ=62). Visual acuity deteriorated to 20/100 bilaterally.

All these results were consistent with the diagnosis of classic or postinfantile HSS, which presented with bilateral loss of vision because of optic atrophy.

## Discussion

HSS is a rare disorder, and its clinical manifestations can vary from individual to individual [26]. Three subgroups of HSS have been defined, depending on the age at which symptoms first appear [18]: (a) late infantile type, which affects children under the age of 6 years; (b) classic or postinfantile type, which starts between 7 and 15 years of age; (c) adult form, which starts after the age of 22 years.

In their review, Dooling et al. [8] summarized the clinical features and post-mortem results of examination of patients affected by HSS. In their core group (42 of 64 patients) HSS developed in 81% of the patients before the age of 15 years. The first signs were related to posture and movement in 88% of the affected children, with the following distribution of different signs: spasticity and hyperreflexia in 67%, dystonia in 55%, choreoathetosis in 45% and tremors in 36% of patients. Rarer presenting signs were intellectual (10%) and visual impairment (2%). The latter was due to retinal changes classified as retinitis pigmentosa. Retinal pigmentary changes were observed in 26% of patients with fully developed HSS. In this core group the mean duration of disease was 11 years and familial involvement was present in approximately half the cases.

After a complete literature review, Newell et al. [17] concluded that the mean age at onset of HSS in patients with retinal pigmentary degeneration was 4.7 years, whereas in patients without retinal involvement it was 15 years. In the former group of patients, corresponding to the "late infantile type" of HSS, the disease has a more rapid clinical course, often leading to death in childhood.

Recently, Swaiman [26] proposed some major and minor diagnostic criteria for HSS. The main features included: onset during the first 2 decades of life, progressive course and evidence of extrapyramidal dysfunction. Corroborative features included: corticospinal tract involvement, progressive intellectual impairment, retinitis pigmentosa or optic atrophy, seizures, positive family history, and hypointense areas involving the basal ganglia seen on MRI.

The proposed exclusion criteria were: abnormal ceruloplasmin levels or copper metabolism, predominant epileptic symptomatology, severe retinal degeneration or vis-

ual impairment preceding other symptoms, and a nonprogressive course.

Neuroimaging studies are of considerable assistance in the diagnosis of HSS: previous reports have provided good documentation of some of the characteristic neuroradiological findings in this syndrome. A CT scan may show bilateral high-density lesions within the globus pallidus [2, 4, 5, 9, 15, 18, 19, 22, 28, 30, 31]. These findings are consistent either with calcifications (similar to those observed in Fahr disease, in endocrine parathyroid disorders and in mitochondrial encephalomyopathies) or with iron deposits. The latter hypothesis is suggested by negative staining for calcium and intense positivity for iron, as documented by rare pathological reports [15, 22, 23, 29]. However, these abnormalities, which are consistent with deposits of elements of high atomic number, are nonspecific findings. In a minority of reported cases CT scans have been normal [7, 15, 20, 25, 27] or shown mild diffuse atrophy of the cerebral cortex with slight ventricular dilatation [14, 16].

In contrast, MRI seems to be more specific. With this diagnostic technique abnormalities confined to the pallidum [1, 2, 4, 12, 14, 15, 18, 19, 21, 22, 25, 27] or also spreading to the pars reticulata of the substantia nigra [7, 11, 16, 18, 20, 23] and corresponding to neuropathological evidence of iron deposition have been demonstrated. According to Scott's classification [24], the latter is described as type 1, while the former belongs to type 2 HSS. High-field-intensity (1.5 T) MRI can demonstrate iron deposits because of preferential T2 proton relaxation enhancement (i.e. very low signal intensity). An area of high signal intensity is sometimes evident in the central part of the pallidum, and it is consistent with a smaller amount of iron and a greater water content [2, 11, 12, 15, 19, 21, 22]. This finding has been called the "eye-of-the-tiger" sign by Sethi et al. [24], and it is seen better on high field MRI. This finding is specific, but not always present even with 0.5-T [4, 27] or 1.5-T MRI [16, 20, 23].

It has been suggested [2, 6, 12, 23] that the changes in signal emission on MRI indicate that iron deposition is scant or absent in the early stages of the disease (normal signal), then gradually increases (diffuse low signal intensity in T2-weighted images), and may eventually culminate in central cellular degeneration and vacuolization with a central lesser amount of iron and high water content (eye-of-the-tiger sign).

However it has been shown that during normal human development the nucleus pallidus and other brain structures (e.g. red nucleus, substantia nigra, and dentate nucleus) physiologically accumulate iron [3]. This is shown by an MRI signal that is initially hyperintense compared with that from white matter (stage I), then becomes isointense (stage II) and finally hypointense (stage III). As a rule, stage III is never seen in these brain areas in patients less than 10 years old, whereas it is frequently observed in most patients by the age of 25 years or older [3]. For this reason the contribution of neuroimaging techniques to the diagnosis of HSS is strongly decisive in the paediatric age group. In recent years a few cases of young patients with HSS and optic atrophy without retinal pigmentary changes have been reported [11, 18], but optic atrophy was rarely the first presenting sign or visual impairment the only symptom before the diagnosis of HSS was made. In the case reported by Casteels et al. [7], optic atrophy with progressive visual loss was the only presenting symptom for 3 years and, as in our case, this was followed by behavioural alterations with motor abnormalities. This patient also had no retinal pigmentary changes and a normal electroretinogram. MRI features were superimposable on those observed in our case, and the eye-of-the-tiger sign was not found. All reported cases – including ours – of HSS presenting with optic atrophy without retinal pigmentary degeneration [7, 11, 18] can be classified in the type 1 subgroup of the neuropathological classification [24], with involvement of both nuclei pallidi and substantia nigra. This subgroup combines cases both of the late infantile type, with precocious onset and rapid course [18, 20, 23], and of the classic or postinfantile type, with later onset and slow clinical course [7, 11, 16]. Therefore it is still uncertain whether the different patterns identified by MRI correlate with different subgroups of HSS.

The relationship of optic atrophy without previous retinal pigmentary degeneration with other brain alterations in HSS is unknown; the same is true for the pathogenesis of optic atrophy. From this case, which confirms some previous reports, it appears that bilateral optic atrophy arising insidiously during childhood should be minutely investigated with a complete ophthalmological, paediatric and neuroradiological work-up. This could allow earlier identification of the early stages of HSS, which probably has a slower clinical course and occurs more commonly in the classic or postinfantile subgroup type.

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