

# Hallervorden-Spatz disease

Mohammed O. Alotaibi, MD, Ahmed R. Alrumyan, MRCP, Hussain M. Aljawad, FRCP(C).

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## ABSTRACT

We describe fluid attenuated inversion recovery sequence MRI and proton MR spectroscopy appearances of the brain in a 7-year old Saudi boy who presented with the clinical features of Hallervorden-Spatz disease to King Fahad National Guard Hospital, Riyadh, Kingdom of Saudi Arabia.

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**H**allervorden-Spatz disease (pantothenate kinase associated neurodegeneration [PKAN] with brain iron accumulation) is a rare, inherited, neurological movement disorder characterized by progressive degeneration of the nervous system. Symptoms vary greatly among patients and usually develop during childhood. Most patients experience periods of rapid deterioration lasting 1-2 months, with relatively stable periods in between. The rate of progression correlates with the age at onset, thus, children with early symptoms tend to fare more poorly. Chromosomal analysis is the definitive way of diagnosis, but lately imaging has played a role in detection of early onset disease. Our objective in presenting this case is to reinforce the fact that the MRI appearance of PKAN, (described previously)<sup>1</sup> may be characteristic and provide us with an additional tool towards imaging diagnosis of this disabling neurodegenerative disorder prompting chromosomal analysis.

**Case Report.** A 7-year-old Saudi boy presented to our institution with delayed developmental milestones since birth. Lately, the child had shown deterioration of his motor skills and developed speech difficulties. The child was the product of a full term normal delivery and had no peri-natal problems. However,

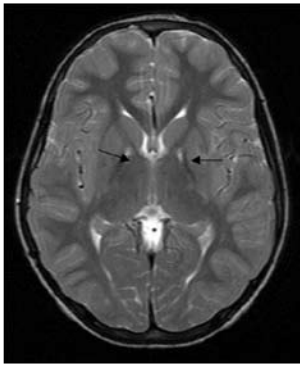
problems with locomotion occurred early and the child has never been able to walk independently. Increased muscle tone in the upper and lower limbs had been recorded since birth. He was also able to string sentences together, but over the previous 6 months, both his walking and speech had deteriorated. Examination revealed an alert well-oriented child with a good memory. He had dysphasia and apraxia although his speech was understandable. He had choreoathetoid movements and generalized muscle spasticity. An MRI of the brain (1.5 Tesla) depicted low T2 intensity of the globus pallidi bilaterally with small central areas of increased intensity likened to an eye-of-a-tiger (**Figure 1**). This finding was even more striking on the fluid attenuated inversion recovery (FLAIR) sequence (**Figure 2**). An MR spectroscopy over the globus pallidi revealed a marked decrease in N-acetyl aspartate (NAA) with increased creatine and a low NAA/creatine ratio (**Figure 3**). An MR spectroscopy was also performed on the deep white matter of the left frontal lobe, depicting a normal spectrum on FLAIR images (**Figure 2**). An MR spectroscopy of the deep white matter of the left frontal lobe revealed a decreased NAA but normal myoinositol (**Figure 4**).

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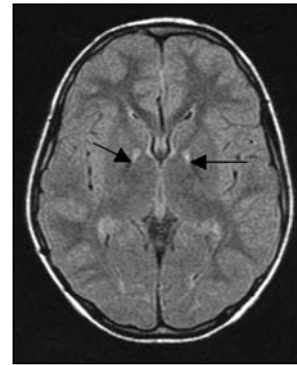
From the Department of Radiology (Alotaibi, Aljawad), and the Department of Pediatrics (Alrumyan), Neurology Section, King Fahad National Guard Hospital, Riyadh, Kingdom of Saudi Arabia.

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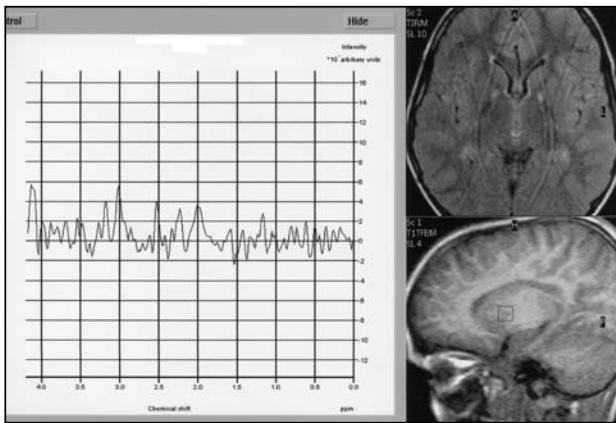
Address correspondence and reprint request to: Dr. Mohammed O. Alotaibi, PO Box 421, Riyadh 11323, Kingdom of Saudi Arabia. Tel. +966 (1) 2482037. Fax. +966 (1) 2520088 Ext. 1411. E-mail: shaher55@yahoo.com



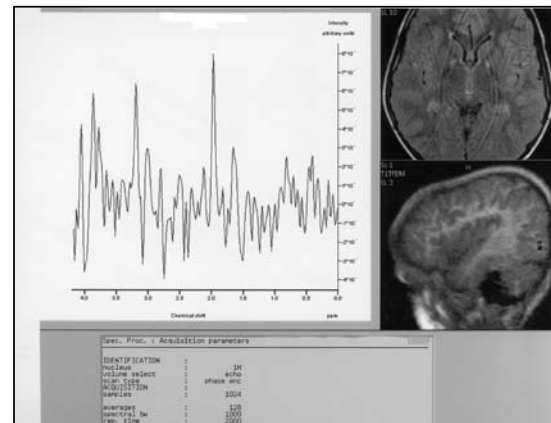
**Figure 1** - T2WI MRI showing low T2 intensity of the globus pallidi bilaterally with small central areas of increased intensity giving the of eye of the tiger appearance (arrows).



**Figure 2** - FLAIR image shows more classical eye of the tiger appearance (arrows).



**Figure 3** - MR spectroscopy over the globus pallidus shows a marked decrease in N-acetyl aspartate (NAA) with increased creatine and low NAA/CREATINE ratio.



**Figure 4** - MR spectroscopy over the deep white matter revealed a decreased N-acetyl aspartate (NAA) but normal myoinositol.

**Discussion.** Hallervorden and Spatz first described PKAN in 1922 as a form of familial brain degeneration due to iron deposition in the brain. The disease is characterized by neuronal degeneration that usually begins in childhood and involves progressive muscle rigidity, weakness, and movement disorder. Most cases are due to a mutation in the gene responsible for making a protein, pantothenate kinase 2. Patients with this gene anomaly accumulate iron in the brain, especially the basal ganglia. It manifests itself as extrapyramidal dysfunction and dementia. The onset is most commonly in late childhood or early adolescence, but cases with adult onset have been described.<sup>2</sup> The disease can be familial or sporadic. When familial, it is inherited recessively and has been linked to chromosome 20.<sup>3</sup> Recently, a mutation in the pantothenate kinase (PANK2) gene on band 20p13 has been described in patients with typical PKAN.<sup>4</sup> The pathophysiology of PKAN is not known. One theory of pathogenesis proposes that abnormal peroxidation of lipofuscin

to neuromelanin and deficient cysteine dioxygenase leads to abnormal iron accumulation in the brain. The globus pallidus and pars reticulata of substantia nigra normally have high iron content in healthy individuals, but patients with PKAN have excess amounts of iron deposited in these areas. However, the role of iron in the pathogenesis of this disease remains unknown. More recently, a role for mutation in the PANK2 gene (band 20p13) in the pathogenesis of the disease has been proposed. The deficiency of pantothenate kinase may lead to accumulation of cysteine and cysteine-containing compounds in the basal ganglia. This causes chelation of iron in the globus pallidus and free radical generation as a result of rapid auto-oxidation of cysteine in the presence of iron.<sup>5</sup> Symptoms, which vary greatly among patients and usually develop during childhood, may include slow writhing, distorting muscle contractions of the limbs, face, or trunk, choreoathetosis, muscle rigidity, spasticity, ataxia, confusion, disorientation, seizures, stupor, and dementia. Other less common

symptoms may include painful muscle spasms, dysphasia, mental retardation, facial grimacing, dysarthria, and visual impairment. The course of the disease is relentless and usually proceeds over 10-12 years with progressive neurological problems, but case reports describe patients surviving 30 years.<sup>6</sup> Affected individuals typically die in the second or third decade. Gross pathological findings are those of characteristic rust-brown discoloration of the globus pallidus and SN pars reticulata secondary to iron deposition.<sup>7-9</sup> This is associated with generalized brain atrophy and a reduction in the size of the caudate nuclei, SN, and tegmentum. Microscopically, the characteristic changes include the following: variable loss of neurons, myelinated fibers, and gliosis in globus pallidus and SN, which may appear spongiotic when severe. Iron deposition may be found both intracellular and extracellular and frequently is centered on vessels. These changes are found to a lesser degree in other parts of the brain and in the spinal cord. The CT appearances are not specific but may exhibit hypodensity in the basal ganglia and some atrophy of the brain. Calcification in the basal ganglia in the absence of any atrophy also has been described. The MRI holds the promise of early detection of PKAN.<sup>5,10,11</sup> The typical MRI appearance is of bilaterally symmetric high signal changes in the anterior medial globus pallidus with surrounding low signal in the globus pallidus on T2-weighted sequences. These imaging features are fairly diagnostic of PKAN and have been termed the “eye-of-the-tiger” sign.<sup>12</sup> The high signal changes can be explained on the basis of gliosis, demyelination, neuronal loss, and axonal swelling, and the surrounding low signal is due to ferromagnetic property of iron deposition. Iodine 123 (123I)-beta-carbomethoxy-3beta-(4-fluorophenyl) tropane (CIT) single-photon emission computed tomography (SPECT) and (123I)-iodobenzamide (IBZM)-SPECT also have been used in making the diagnosis of this disease.<sup>13</sup>

In conclusion, we report the MR spectroscopy appearance of PKAN, thus providing us with an

additional tool towards imaging diagnosis of this disabling neurodegenerative disorder.

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