CASE REPORT

Pantothenate kinase-associated neurodegeneration (PKAN) in a child with Down syndrome. A case report and follow-up with MRI

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ABSTRACT

Neurodegeneration with brain iron accumulation (NBIA) is a subtype of inherited metabolic disorders. It includes pantothenate kinase-associated neurodegeneration (PKAN), which is a rare autosomal recessive disorder caused by the mutation of pantothenate kinase 2-gene (PANK2). It affects the deep grey matter nuclei causing progressive extrapyramidal motor impairment. We present a case of genetically proven PKAN in a child with mosaic trisomy 21 in which T2- hyperintensity of the basal ganglia was seen followed by the classic eye-of-the-tiger sign in a follow-up MRI.

CASE REPORT

A daughter of unrelated healthy parents was referred to our radiology department at the age of 27 months owing to afebrile seizures. MRI showed a symmetrically increased T2 signal intensity in the basal ganglia of undetermined aetiology (Figure 1), for which a long-term follow-up was advised. Shortly after the MRI, a karyotyping was performed and showed 47, XX, +21 in 8 of 20 cells (mosaic trisomy 21).

Furthermore, the parents had noticed a slight psychomotor developmental delay in their daughter since her first year of life. She did not start walking until the age of 2 years and speech was also delayed; furthermore, there was regression of her previously learnt vocabulary. By her fourth year, dystonia was first noticed in the form of contractions of both hands. Difficulty in swallowing was also noticed early on.

A follow-up MRI was performed at the age of 5 years and showed a persistent bilateral hyperintense signal in the medial globus pallidus (GP) (Figure 1). A surrounding hypointense signal, especially in T2* gradient recalled echo (GRE), not seen on the previous MRI, was newly detected (Figure 1) as well as the combined signals in the basal ganglia resembling the eye-of-the-tiger (Figure 2). Neither diffusion restriction nor enhancement was noticed.

Owing to this characteristic appearance of the eye-of-the-tiger pattern, the radiological diagnosis strongly suggested PKAN. A molecular genetic test was performed and confirmed the diagnosis by the presence of missense mutation in the PANK2 gene [c.683T>C (p. F228S) in exon 4 and c.1561G>A (p. G521R) in exon 8]. Genetic testing of the mother was then performed and showed her to be an asymptomatic carrier (heterozygote) by presence of the same mutation, c.683T>C (p. F228S).

At present, the child is being managed with anti-epilepsy medication. Iron chelation therapy with deferiprone is scheduled.

DISCUSSION

In 1922, a disease with extrapyramidal symptoms, in which the basal ganglia were involved, was described. Currently, this disease is usually classified as a neurodegenerative disorder with brain iron accumulation (NBIA) and includes 10 subtypes that represent different mutations. The PANK2 gene, which is found in chromosome 20p12.3–13, and its mutation is responsible for PKAN being the most frequent form of NBIA.1,2

PATHOGENESIS

The PANK2 gene is responsible for production of the pantothenate kinase 2 enzyme, which regulates the formation of coenzyme A (CoA). The deficiency of CoA is supposed to increase synthesis of oxygen free radicals, eventually leading to destruction of the phospholipid membrane, especially in the basal ganglia and retina, followed by iron accumulation.
Iron accumulation leads to the characteristic rust-brown discolouration and this is why the disease is sometimes called pigmentary degeneration of the GP. Generalized atrophy may be noticed. Microscopic features include loss of neurons with gliosis, vacuoles and presence of spheroids, which are non-nucleated structures that represent swollen axons.1

CLINICAL PRESENTATION
The two main forms of clinical presentations are a classical form, which involves a rapid progression of symptoms that develop in the first decade of life, and an atypical form, which, by comparison to the classical form, is slowly progressive and commences after the age of 10 years. Symptoms include dystonia, dysarthria, rigidity, choreoathetosis and cognitive decline. Visual impairment may occur owing to pigmentary retinopathy.1,3

IMAGING FINDINGS
The use of MRI for diagnosis was first reported by Tanfani et al.4 Owing to accumulation of iron, T2-weighted images demonstrate hypointense signal in GP and substantia nigra (SN). Owing to tissue gliosis and vacuolization in the medial aspect of the GP, a central hyperintensity appears medially within the hypointensity. This appearance was described by Sethi as the “eye-of-the-tiger” sign. The decreased signal owing to iron accumulation is more obvious in GRE and susceptibility weighted imaging (SWI) sequences. No diffusion restriction or enhancement occurs. Diffusion tensor imaging...
Other types of NBIA should be considered but differenci-
ated. In 1992, Okano described a case of Down syndrome in which
hydroxylase-associated neurodegeneration and PANK2 mutation.
However, the sign may be found in other diseases, such as cortical gan-
glonic degeneration, early-onset levodopa responsive parkin-
sonism and progressive supranuclear palsy.6 The sign has also
been reported in a healthy individual.7

DIAGNOSIS
The presence of severe T2 shortening and blooming on T2* 
sequences in a child should raise the suspicion of NBIA. Not
every case will show the eye-of-the-tiger sign.5 In the early 
course of the disease, isolated hyperintensity without the full pic-
ture involving the presence of the eye-of-the-tiger may be 
observed. In these cases, with the presence of suggestive clinical 
features, genetic testing is necessary. The complete MRI features 
may even precede the clinical symptoms.8

TREATMENT
As yet, there is no definitive treatment. The management has 
been principally symptomatic. Treatments under investigation
include iron-chelating agents that cross the blood–brain barrier
and deep brain stimulation of the GP.1

In 1992, Okano described a case of Down syndrome in which
progressive neurological deficit occurred with the morphological
picture of Hallervorden–Spatz syndrome on MRI. To our
knowledge, our case is the first one describing genetically proven
PKAN in a patient with mosaic trisomy 21.

The imaging features in our patient are characteristic of PKAN.
Although basal ganglion changes are reported in patients with
Down syndrome, in our case, there is no evidence of contribu-
tion of the trisomy 21 mosaicism in the imaging features. The
simultaneous presence of these two different genetic conditions
in a single patient gives this case its remarkable medical value.

LEARNING POINT
Although the eye-of-the-tiger sign, in the appropriate clinical
settings, is indicative of PKAN, it may develop at a variable point
in the disease process. The presence of uncertain bilateral
changes in the basal ganglia in an infant with symptoms suggest-
tive of the disease should be further investigated.

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