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Case Report

Ataxic gait and dysarthria in a child: pantothenate kinase-associated neurodegeneration as a diagnosis

Amine Naggar*, Khadija Laasri, Mohamed Fadil, Nazik Allali, Siham El Haddad and Latifa Chat

Radiology Department, Children's Hospital of Rabat, Mohammed V University, Rabat, Morocco

*Correspondence address. Mother-Child Radiology Department, Children's Hospital of Rabat, Mohammed V University, Lot Sanabil, Route Mehdia, Salé, Rabat, Morocco. Tel: +212 644089480; E-mail: Amine.Naggar@gmail.com

Abstract

Pantothenate kinase-associated neurodegeneration (or previously known as Hallervorden-Spatz syndrome) is a very rare disorder that typically manifests in a child with neurological signs such as gait difficulties, dysarthria, and hyperreflexia, associated potentially with psychiatric symptoms such as cognitive decline. It demonstrates on MRI the typical 'eye of the tiger' appearance, which is due to gliosis and accumulation of iron in the globi pallidi. Other differentials can mimic this appearance on MRI, it is therefore important to search for the involvement of other basal ganglia nuclei and the cerebral cortex, and also to consider the clinical and biological context.

Keywords: pantothenate kinase-associated neurodegeneration, brain iron accumulation, globus pallidus, ataxia, MRI

INTRODUCTION

Pantothenate kinase-associated neurodegeneration (PKAN) is a rare autosomal recessive disorder, with an estimated prevalence of 1 to 3 cases per million. It represents the most common form of childhood-onset neurodegeneration with brain iron accumulation (NBIA) [1].

A mutation in the PANK2 gene on chromosome 20, which codes for the pantothenate kinase 2 enzyme involved in regulating the synthesis of mitochondrial coenzyme A and that catalyzes the phosphorylation of pantothenate (vitamin B5), is found in the majority of patients [1, 2]. This mutation consequently leads to the buildup of its substrates, namely pantetheine and cysteine. The latter, known for its effective iron chelation, results in iron buildup and neuronal damage due to oxidative stress [1], with neurodegeneration primarily affecting the basal ganglia. This intracerebral iron accumulation, particularly in the basal ganglia, can be illustrated both radiologically and histologically [2].

CASE REPORT

A 6-year-old girl, with no personal nor family history and with no consanguineous parents, has been presenting with ataxic gait, repeated falls, and dysarthria since the age of 3. Physical examination revealed a negative Romberg sign (which makes cerebellar lesions less likely), hyperreflexia with a positive plantar reflex (translating upper motor neuron damage), and dystonia. The rest of the examination was unremarkable including ophthalmic examination which showed no visual fields abnormalities nor retinal degeneration. Laboratory tests, electroencephalogram, and cerebral CT scan showed no abnormalities.

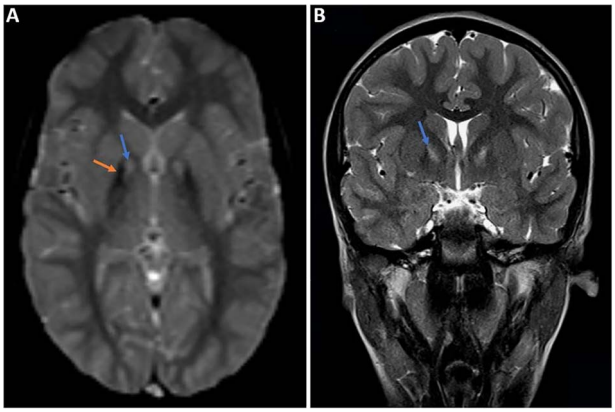

Figure 1. Brain MRI images in axial T2* sequence (**A**), coronal T2 sequence (**B**), showing at the level of both globi pallidi a hypersignal (vertical arrow) surrounded by a hyposignal (horizontal arrow), creating the 'eye of the tiger' appearance, more easily visible on the T2* sequence (**A**).

A magnetic resonance imaging (MRI) was performed, showing an 'eye of the tiger' appearance in both globi pallidi (Fig. 1), suggestive of PKAN. Genetic testing confirms the diagnosis by revealing a mutation in the PANK2 (pantothenate kinase 2) gene.

DISCUSSION

PKAN has two distinguishable clinical forms:

- The classic PKAN: typically presents in the first decade of life with an average age of three years of life. The most frequent

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signs include difficulties in walking or posture, extrapyramidal disorders comprising dystonia, dysarthria, and choreoathetosis. Involvement of the corticospinal tract is frequent, with hyperreflexia, spasticity, and a positive plantar reflex. Deterioration in cognitive abilities is also common. And the presence of retinopathy, either clinically or through electroretinographic assessments, is a relatively common occurrence [3]. While past accounts have often linked intellectual deficits to this condition, it remains uncertain if this is an inherent feature.

- The atypical PKAN: observed in older patients with an average age of 13.7 years, presenting with spasticity, hyperreflexia, and other signs of involvement of the corticospinal tract, dystonia, episodes of freezing of gait, speech difficulties, including palilalia and dysarthria, as well as deterioration in cognitive abilities and psychiatric signs including mainly a depressive disorder and lack of impulse control [3].

The evolution of classic PKAN is rapidly progressive, with significant incapacitation by the age of 20, leading to an early death, unlike atypical PKAN, which has a slower progression [3].

MRI is a fundamental diagnostic tool, nevertheless, it may be normal in the initial period of the illness. The first abnormality to appear is a hyperintense signal affecting the globi pallidi bilaterally (caused by loss of nerve cells and gliosis). Subsequently, a hypointense signal abnormality (due to the presence of iron buildup) appears around the hyperintense area, giving the characteristic 'eye of the tiger' appearance. These hypointensities become more pronounced as the disease progresses [4]. This sign is visible on T2 sequences and can be even more clearly visible on T2* and susceptibility-weighted imaging (SWI) [5, 6].

Associated involvement with hypointense signal abnormalities in the substantia nigra and the dentate nuclei is possible, although the latter is rarer. However, if other locations are found, this should prompt alternative diagnoses, primarily neuroferritinopathy [5].

The eye of the tiger sign is highly specific for PKAN. However, it has also been reported in other forms of NBIA, notably neuroferritinopathy [5], and mitochondrial membrane protein-associated neurodegeneration (MPAN) where the hyperintense signal abnormality presents a more linear rather than nodular form [7]. This sign has also been reported in Wilson's disease, carbon monoxide poisoning, organophosphate poisoning, as well as other neurodegenerative diseases beyond NBIA, such as multiple system atrophy, pure akinesia, and corticobasal degeneration [7–9]. Therefore, this sign should not be assessed in solitude; the search for associated lesions of other basal ganglia nuclei and the cerebral cortex, along with consideration of the clinical and biological context, is necessary, especially in adults [5].

To date, the majority of therapeutic approaches are palliative in nature, limited to symptom relief, aimed at improving the quality of life [1]. It necessitates a multidisciplinary team, involving a pediatrician, internist, neurologist, ophthalmologist, psychiatrist, and a geneticist. Spasticity and dystonia and can be treated with anticholinergics and benzodiazepines. When dystonia is predominant, trihexyphenidyl is to be suggested first, and intramuscular botulinum toxin is recommended for focal dystonia. If spasticity is dominant, baclofen should be considered. Additionally, speech therapy aids in improving communication [10].

CONFLICT OF INTEREST STATEMENT

No conflicts of interest to be declared.

FUNDING

None.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

No ethical approval is required for de-identified single case reports based on our institutional policies.

CONSENT

Written informed consent was obtained from the patient's legally authorized representatives.

GUARANTOR

Dr. Amine Naggar is the guarantor for this publication.

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