

# Neurodegeneration Associated with Pantothenate Kinase. Case report

## *Neurodegeneração Associada a Pantotenato Quinase. Relato de caso*

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### ABSTRACT

*Neurodegeneration with Brain Iron Accumulation (NBIA) belongs to a group of disorders characterized by the predominant involvement of the basal ganglia. Patients may present psychiatric symptoms, extrapyramidal signs and cognitive decline. Few cases of this disease have been reported in Brazil. We present a typical NBIA case. This case has the classical signs and symptoms of NBIA in a woman with advanced/end-stage disease, in addition to the presence of cerebral atrophy, which is not a common finding.*

**Key-words:** Neurodegeneration; Iron; Pantothenate kinase; PANK2; NBIA

### RESUMO

*A neurodegeneração cerebral com acúmulo de ferro (NBIA) pertence a um grupo de distúrbios caracterizados pelo envolvimento predominante dos gânglios da base. Esses casos podem se manifestar com sintomas psiquiátricos, manifestações extrapiramidais e declínio cognitivo. Poucos casos desta doença foram relatados no Brasil. Apresentamos um caso de NBIA típica. Este caso destaca a evolução clínica dos sinais e sintomas característicos da NBIA em uma mulher com estágio avançado/final da doença, além da presença de atrofia cerebral, que não é um achado comum.*

**Palavras-chave:** Neurodegeneração; Ferro; Pantotenato quinase; PANK2; NBIA

## INTRODUCTION

Pantothenate-associated neurodegeneration (PKAN) is part of a subset of progressive and hereditary neurological disease called Neurodegeneration with Brain Iron Accumulation (NBIA), a term introduced by Hayflick et al. in 2003 to cover all neurological disorders with progressive extrapyramidal symptoms, intellectual disability and magnetic resonance imaging with evidence of excessive iron deposition in the brain, especially in the basal ganglia<sup>5</sup>. The disease occurs in two clinical forms: one typical, more common in children in the first decade of life, and the other atypical, which predominantly affects young adults. The pathophysiological processes leading to NBIA disorders have not been elucidated yet, nor is it known whether iron plays a causal role or neurodegeneration<sup>6</sup>. The diagnosis is made based on the clinical history and MRI findings, and lately – especially in developed countries – there is an increasing use of genetic sequencing for a more accurate and faithful diagnosis<sup>4</sup>.

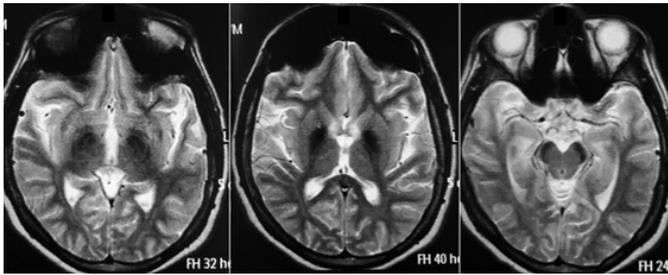
## CASE REPORT

A 23-year-old female patient with normal neuropsychomotor development until the age of 2 when she started with difficulty walking and lost this ability at 8 years of age; also presented dystonia and choreoathetosis. Two years later she developed progressive upper limb paresis associated with loss of vision - with funduscopy identifying retinal pigmentary degeneration - and saccadic eye movements. She progressively presentedodynophagia and worsened visual acuity. At the age of 17, she began treatment for dystonic storms, using phenobarbital, without improvement, and carbamazepine, with partial improvement. She was brought to our service one year later. Upon admission, the patient was essentially restricted to a wheelchair, noncommunicative and nonresponsive. Pupils were equal and constricted from 3 to 2 mm with light. The motor exam showed grade 3 strength in the four limbs, according to the modified scale of the Medical Research Council (mMRC), spasticity and extensor plantar response bilaterally. Based on the previous medical history and physical examination we requested

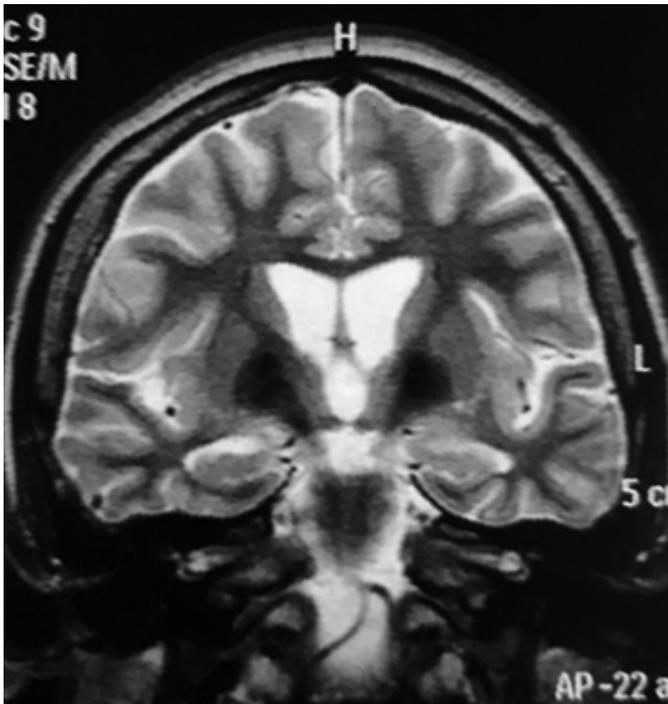
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a MRI of the brain, which identified findings compatible with iron accumulation in topography of globus pallidum and substantia nigra bilaterally associated with encephalic volume reduction (Fig. 1). The lesion presented a hyperintense center with hypointense halo in T2 sequences characterizing the “eye-of-the-tiger” sign (Fig. 2). At the age of 20, Baclofen was started, due to the worsening of dystonia, and gastrostomy was performed. Currently, with 23-years-old, she is in a vegetative state and clinically stable.



**Figure 1.** MRI of the brain, T2-weighted, axial, showing hypodensity in the topography of globus pallidum and substantia nigra bilaterally. There is also diffuse brain atrophy with enlargement of Sylvian fissures.



**Figure 2.** MRI of the brain, T2-weighted, coronal, showing hypodensity in the topography of globus pallidum bilaterally and adjacent white matter.

## DISCUSSION

Pantothenate-associated neurodegeneration (PKAN) has a prevalence estimated at 1-3: 1,000,000 and represents the most

common subtype within neurodegeneration with cerebral iron accumulation (NBIA)<sup>5</sup>. NBIA exhibits marked genetic heterogeneity, and at least ten genes have been associated with different subtypes of NBIA. The PANK2 gene, present in the mitochondria and in the nucleus, catalyzes phosphorylation of pantothenate in the bioavailability of coenzyme A (CoA). Mutations at this gene cause the most common NBIA disorder, PKAN2, which accounts for 50% of NBIA cases<sup>5</sup>. When PKAN is suspected, genetic testing is recommended in order to confirm the diagnosis. Sequencing and deletion/duplication analyses of the PANK2 gene, which is mutated in PKAN, are needed for a complete analysis<sup>7</sup>, however, in the case in question, no such tests were carried out.

It is a rare autosomal recessive disease associated with the mutation in the PANK2 gene located on chromosome 20p13 and encodes the pantothenate kinase, a key regulatory enzyme of coenzyme-A synthesis. This is essential for energy metabolism, fatty acid synthesis, degradation and synthesis of multiple neurotransmitters and glutathione, which is an antioxidant that prevents cellular damage caused by reactive oxygen species (ROS). Deficiency in energy production can lead to the formation of ROS and result in cellular damage. Thus, tissues with high metabolic demand, such as the basal ganglia and the retina, are the most affected<sup>5</sup>. In addition, cysteine, a substrate of PANK2, may play a central role in iron accumulation, since in those patients with absent/hypofunctioning PANK2 there was an intracellular increase in cysteine and iron chelate leading to iron accumulation in the brain<sup>3,5</sup>. The classic PKAN, corresponding to the case, refers to the disease of early onset, ataxia and postural difficulties that started in the first decade of childhood. In our case, such symptoms were perceived at 2 years. This is followed by additional progressive extrapyramidal symptoms: dystonia, chorea and parkinsonism<sup>1</sup>. The presence of dystonic opisthotonus or oromandibular dystonia suggests the inclusion of PKAN as a differential diagnosis<sup>8</sup>, which only supported our diagnostic hypothesis, since our patient had these symptoms.

This motor regression is accompanied by cognitive decline and dementia. Neuro-ophthalmologic examination may reveal pigmented retinopathy and saccadic and saccular abnormalities<sup>1,2</sup>, as it was also evidenced in our case, although it is not a common finding. Atypical PKAN is more heterogeneous than the classical form, emerging in the second or third decade of life with slower evolution. Psychiatric symptoms and speech disturbances are common. The pattern of MRI of the brain observed in PKAN is

distinct and usually diagnostic. In the T2-weighted sequences, the globus pallidum shows a central hyperintense signal region circled by hypointense signal, as was demonstrated in our case. This pattern in the coronal section was termed the “eye of the tiger”<sup>1,5,7,8</sup>. The appearance of the tiger’s eye is characterized by bilateral hypointensity located in the globus pallidum, and black substance with a central area of hyperintensity, best demonstrated in T2WI and other iron-sensitive sequences. The hypointensity observed in these sequences is secondary to the susceptibility effects related to the highly increased paramagnetic iron accumulation. Within the zone of hypointense there is typically a central region of hyperintensity T2, which serves to complete the general appearance of an eye. The central zone of T2 hyperintensity is caused by neuronal loss, gliosis, and neuropil cavitation<sup>5</sup>. The treatment of PKAN is symptomatic so far. Tremors usually respond to dopaminergic agents. For rigidity and spasticity, dopamine agonists and anticholinergic agents may be used alone or in combination. Intrathecal or oral baclofen in moderate doses relieves stiffness and spasms and can reduce dystonia, being used with some success in our case to relieve the dystonic storms. The intramuscular botulinum toxin has also been used for the relief of hypertonicity. Benzodiazepines have been used for choreoathetotic movements<sup>1,7</sup>. Several groups are developing therapies that aim to supply an intermediate pathway as a substrate substitute for CoA synthesis. By circumventing the major regulatory enzyme, this approach would have the potential to flood the cell with CoA. One of the challenges of this approach is the extremely rigid regulation under which pantothenate kinase 2 is maintained, suggesting that normal cell function requires a delicate titration of CoA levels or that the cellular “cost” of CoA synthesis is high<sup>4</sup>.

## CONCLUSION

This report aimed to expose a rare disease that manifested in its typical form in the first years of life and leads the patient to a vegetative state. The clinical signs demonstrated by our case, corroborated with the typical PKAN finding on MRI. However, as the neurological signs and symptoms presented may be common to other neurological disorders, such as Huntington’s disease and Wilson’s disease, the presence of the “tiger eye” in the MRI, characteristic of the disease, was essential for the diagnosis.

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**Conflict of interest: The authors have no conflicts of interest to disclose.**

**Case report organized according CARE guideline (consensus-based clinical case reporting)**