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Short communication

# Atypical pantothenate kinase-associated neurodegeneration: Clinical description of two brothers and a review of the literature

*S. Mahoui* *, *A. Benhaddadi*, *W. Ameur El Khedoud*, *M. Abada Bendib*, *M. Chaouch*

*Department of neurology, university hospital of Ben Aknoun, Algiers, Algeria*

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ABSTRACT

Two clinical forms of pantothenate kinase-associated neurodegeneration (PKAN) have been described: typical PKAN and atypical PKAN. Atypical PKAN has later onset and a slower course of disease. This report describes two siblings with the atypical form of PKAN, combining dystonia, irritability and a dysmorphia syndrome. In addition, a review of the literature was carried out for all published cases of atypical PKAN to gather descriptions of its various clinical presentations, age of onset and MRI findings, and to highlight the different treatments used for PKAN patients.



## 1. Introduction

Pantothenate kinase-associated neurodegeneration (PKAN) is a rare autosomal-recessive disorder caused by mutations in the *pantothenate kinase 2 gene* (*PANK2*) on chromosome 20p [1]. PKAN is characterized by dystonia, parkinsonism and iron accumulation in the brain, and accounts for around half of cases of neurodegeneration with brain iron accumulation (NBIA), a group of progressive neurodegenerative disorders characterized by high levels of iron, and the presence of axonal spheroids, usually limited to the brain and central nervous system [2]. In PKAN patients, magnetic resonance imaging (MRI) displays the 'eye of the tiger' sign, a specific pattern of hyperintensity within the hypointense medial globus pallidus on T2-weighted sequences. Two clinical forms have been described. Typical PKAN usually arises before 6 years of age in 88% of cases, and is characterized by a rapid and progressive course of dystonia and spasticity, leading to loss of ambulation within 10–15 years of disease onset. In addition, 68% of these

* *Corresponding author*. Department of Neurology, university hospital of Ben Aknoun, chemin des Deux-Bassins, Ben Aknoun, 16000 Algiers, Algeria.
*E-mail address:* Mahoui.soulaimane@gmail.com (S. Mahoui).

*Abbreviations:* PKAN, pantothenate kinase-associated neurodegeneration; NBIA, neurodegeneration with brain iron accumulation; MRI, magnetic resonance imaging.

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patients have retinopathy [1,3]. Atypical PKAN has a later onset, usually during the second or third decades of life (mean age: 14 years), a slower course of disease and slower progression of neuropsychiatric features, in addition to movement disorders [1,3].

Our present report is of two cases of atypical PKAN in a consanguineous family that combines dystonia and a dysmorphic syndrome. The two affected brothers had the benefit of extensive exploration, whereas a sister, who underwent brain MRI for screening purposes, was revealed to be normal.

## 2. Observations

### 2.1. Case 1

At the age of 16, the elder sibling presented with difficulty moving his tongue and, as a consequence, had elocution and swallowing difficulties accompanied by excessive salivation. His ears, nose and throat examinations were normal. However, 2 years later, shaking appeared in his right arm as well as paroxysmal oropharyngeal spasms. Now, at the age of 21, the patient's speech difficulties have worsened and the tremor has spread to his left arm. Neurological examination showed segmental dystonia, postural tremor in both arms, irritability and a dysmorphia syndrome that associates misalignment of the teeth with a high arched palate, and hollow feet (pes cavus; Fig. 1). The characteristic eye of the tiger sign was also detected on MRI (Fig. 2, left). Neuroelectromyography performed in the patient was free of abnormalities (no peripheral neurogenic damage), and there was no retinopathy on ophthalmic examination. Serum ceruloplasmin, copper excretion, serum ferritin and lipidogram tests were also performed, and all levels were normal. There was no acanthocytosis. A molecular study was not performed, as such a test is not available in Algeria.

### 2.2. Case 2

The younger sibling, who is now 18 years old, presented at the age of 10 with writing difficulties, followed a few years later by an unsteady gait, including walking on tiptoe and rocking his trunk. During the examination, he presented with generalized dystonia affecting both his upper and lower limbs and trunk, with a dystonic tremor of the arms, irritability and a dysmorphia syndrome associating hollow feet with a high arched palate. Again, brain MRI revealed the eye of the tiger sign at the basal ganglia level (Fig. 2, right). There was no retinopathy on ophthalmic examination; the workup included serum ceruloplasmin, copper excretion, serum ferritin and lipidogram tests, and showed no abnormalities. There was no acanthocytosis. A molecular study was again not performed due to the lack of its availability in Algeria.

## 3. Discussion

To determine the various clinical presentations and ages of onset for atypical PKAN, a review of the literature was carried out to identify all published cases with positive *PANK2* mutations (Table 1) [4–22]. It is worth noting that optic atrophy, dysmorphia syndrome and a weak atrophic tongue are uncommon presentations of atypical PKAN; the most common one is dystonia and, often, craniocervical dystonia, leading to dysarthria and swallowing difficulties. More than 100 mutations have been identified in the *PANK2* gene. Missense mutations that preserve partial *PANK2* activity are associated with atypical forms of PKAN [1], but no specific genotype–phenotype correlations have been identified until now. Hayflick et al. [1] established a correlation, one by one, between the presence of the eye of the tiger sign on MRI and the presence of *PANK2* mutations, although sometimes, it cannot be seen on initial imaging [7].

To date, there is no approved treatment for NBIA, which means that treating PKAN patients remains a challenge for clinicians. The first-line drugs that are usually the most effective for PKAN are trihexyphenidyl, clonazepam and baclofen [23]. Alpha-tocopherol (vitamin E), selenium and idebenone should be avoided as they may worsen symptoms, as has been reported in the case of three siblings with atypical PKAN [23]. However, pilot trials investigating deferiprone for the treatment of PKAN have found the drug to be safe and tolerable, as well as effective in reducing brain iron accumulation [24]. A *Drosophila* model of PKAN showed that pantethine

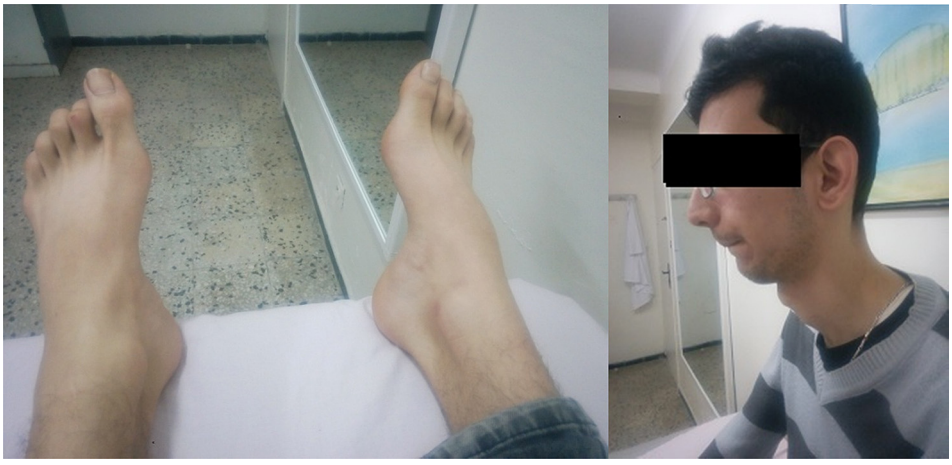

**Fig. 1 – Dysmorphia syndrome: hollow feet (pes cavus) and misalignment of teeth.**

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