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Eye-of-the-Tiger Sign: A Case Report of a Key MRI Clue to Pantothenate Kinase-Associated Neurodegeneration in an Eight-Year-Old Girl

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Abstract

Pantothenate kinase-associated neurodegeneration (PKAN) is an autosomal recessive disorder and the most common form of neurodegeneration with brain iron accumulation (NBIA), whose imaging hallmark is the "eye-of-the-tiger" sign of the globus pallidus on brain MRI.

We report the case of an eight-year-old girl, born to first-cousin parents, with a history of delayed walking and language acquisition, who presented with a four-month history of worsening gait instability and frequent falls. Neurological examination revealed dysarthria, lower-limb dystonia, postural tremor, brisk deep tendon reflexes, and bilateral extensor plantar responses.

Brain MRI at 1.5 T showed bilateral, symmetric T2 hypointensity of the globus pallidus surrounding a central hyperintense focus, consistent with the eye-of-the-tiger sign, with marked pallidal signal loss on susceptibility-weighted imaging (SWI). The substantia nigra, dentate nuclei, cerebellum, and remaining brain parenchyma were normal, as were serum copper, ceruloplasmin, and lactate levels. This combination of a progressive extrapyramidal and pyramidal syndrome with the eye-of-the-tiger sign pointed to PKAN, pending genetic confirmation.

This case shows that recognizing this sign on MRI allows the radiologist to suggest the diagnosis and guide targeted genetic testing. Although highly suggestive, the sign is not pathognomonic, and confirmation requires identification of biallelic pathogenic *PANK2* variants.

Categories: Neurology, Genetics, Pediatrics
Keywords: child, eye-of-the-tiger sign, magnetic resonance imaging, neurodegeneration with brain iron accumulation, pank2, pantothenate kinase-associated neurodegeneration, susceptibility-weighted imaging

Introduction

Neurodegeneration with brain iron accumulation (NBIA) is a clinically and genetically heterogeneous group of inherited disorders characterized by abnormal iron deposition in the basal ganglia, predominantly in the globus pallidus and substantia nigra [1,2]. Its main subtypes include pantothenate kinase-associated neurodegeneration (PKAN), PLA2G6-associated neurodegeneration (PLAN), mitochondrial membrane protein-associated neurodegeneration (MPAN), and beta-propeller protein-associated neurodegeneration (BPAN) [1].

PKAN, the most common NBIA subtype, is caused by biallelic pathogenic variants in *PANK2*, which encodes pantothenate kinase 2, a mitochondrial enzyme that catalyzes the first step of coenzyme A (CoA) biosynthesis [1,3]. Its characteristic MRI feature is the eye-of-the-tiger sign, defined as bilateral pallidal T2 hypointensity surrounding a central hyperintense focus [2,4]. In the landmark genotype-phenotype study by Hayflick et al., this pattern was found in all patients carrying *PANK2* mutations [4]; it is, however, not pathognomonic [5,6].

We report the case of an eight-year-old girl in whom the eye-of-the-tiger sign, supported by susceptibility-weighted imaging (SWI), oriented the diagnosis toward PKAN in the setting of a progressive extrapyramidal and pyramidal syndrome, and we discuss the imaging features, differential diagnosis, and diagnostic implications of this sign.

Case Presentation

An eight-year-old girl, born to first-cousin parents, was referred for gait imbalance and recurrent falls. Her developmental history was notable for delayed acquisition of walking and language. Over the four months preceding evaluation, she developed progressively worsening gait instability, resulting in frequent falls.

Neurological examination revealed dysarthria, lower-limb dystonia, a postural tremor, brisk deep tendon

reflexes, and bilateral extensor plantar responses. There was no sensory or motor deficit, rigidity, cerebellar syndrome, or dysphagia, and no behavioral disturbance or seizures were reported. Cognitive function was not formally assessed.

Brain MRI was performed on a 1.5 T scanner and included axial and coronal T2-weighted, axial fluid-attenuated inversion recovery (FLAIR), diffusion-weighted (DWI), and susceptibility-weighted imaging (SWI) sequences. T2-weighted images showed bilateral, symmetric hypointensity of the globus pallidus surrounding a central hyperintense focus in its anteromedial portion, producing the eye-of-the-tiger sign (Figure *1*). The central foci were hyperintense on FLAIR (Figure *2*). SWI demonstrated marked bilateral pallidal signal loss consistent with iron deposition (Figure *3*), and the globus pallidus also appeared hypointense on DWI. The substantia nigra, dentate nuclei, and cerebellum were normal, with no cerebellar atrophy, and the remaining brain parenchyma was unremarkable.

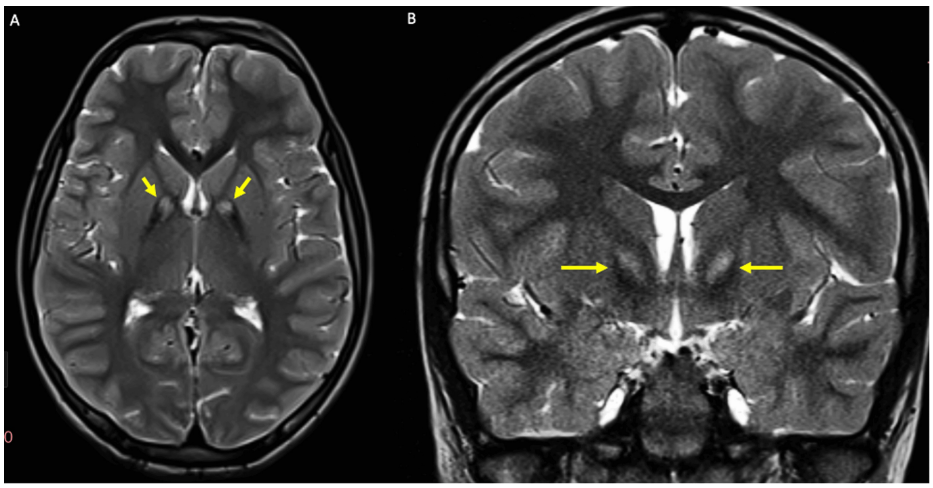

FIGURE 1: "Eye of the tiger" sign on T2-weighted MRI sequence

(A) Axial and (B) coronal T2-weighted images show bilateral, symmetric hypointensity of the globus pallidus surrounding a central hyperintense focus in its anteromedial portion (yellow arrows), producing the eye-of-the-tiger sign.

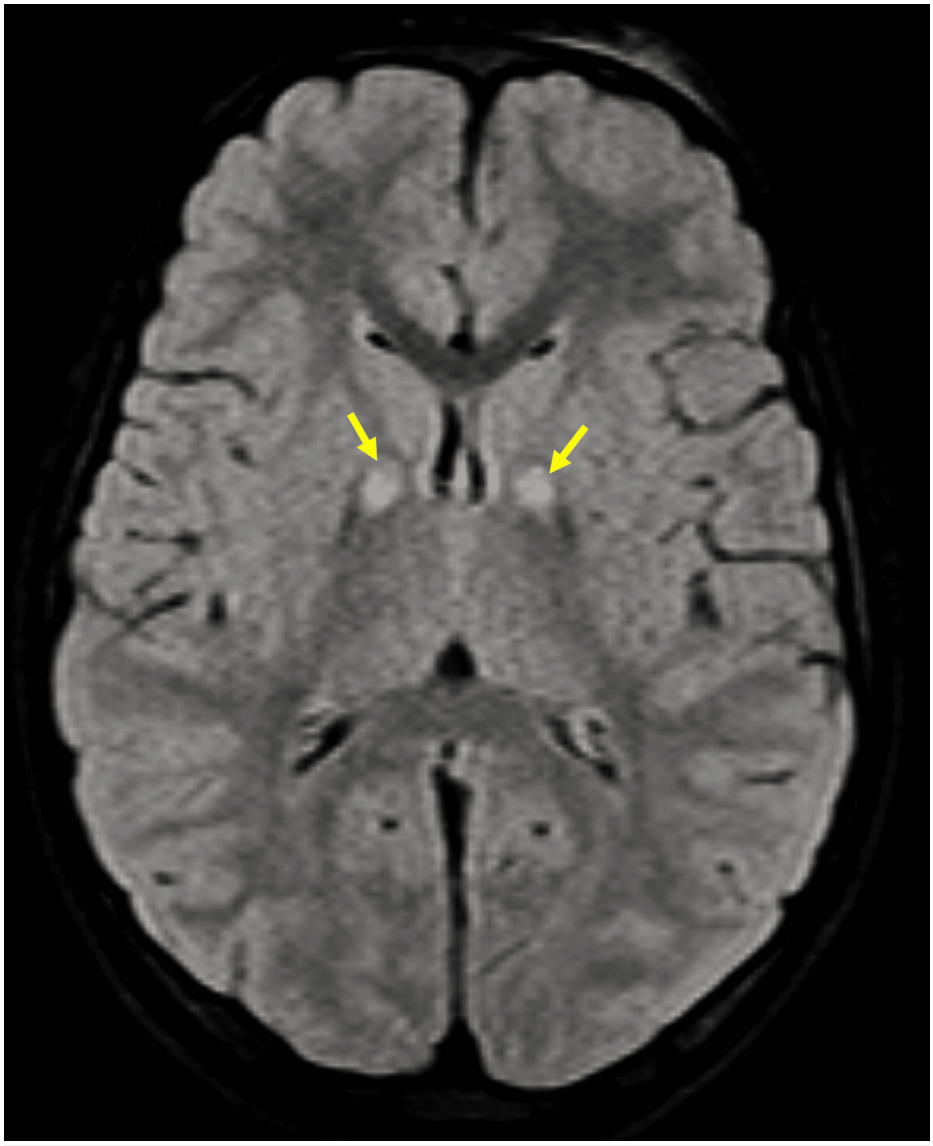

FIGURE 2: Pallidal abnormalities on FLAIR MRI sequence

Axial fluid-attenuated inversion recovery (FLAIR) image shows bilateral, symmetric hyperintense foci in the anteromedial globus pallidus (yellow arrows).

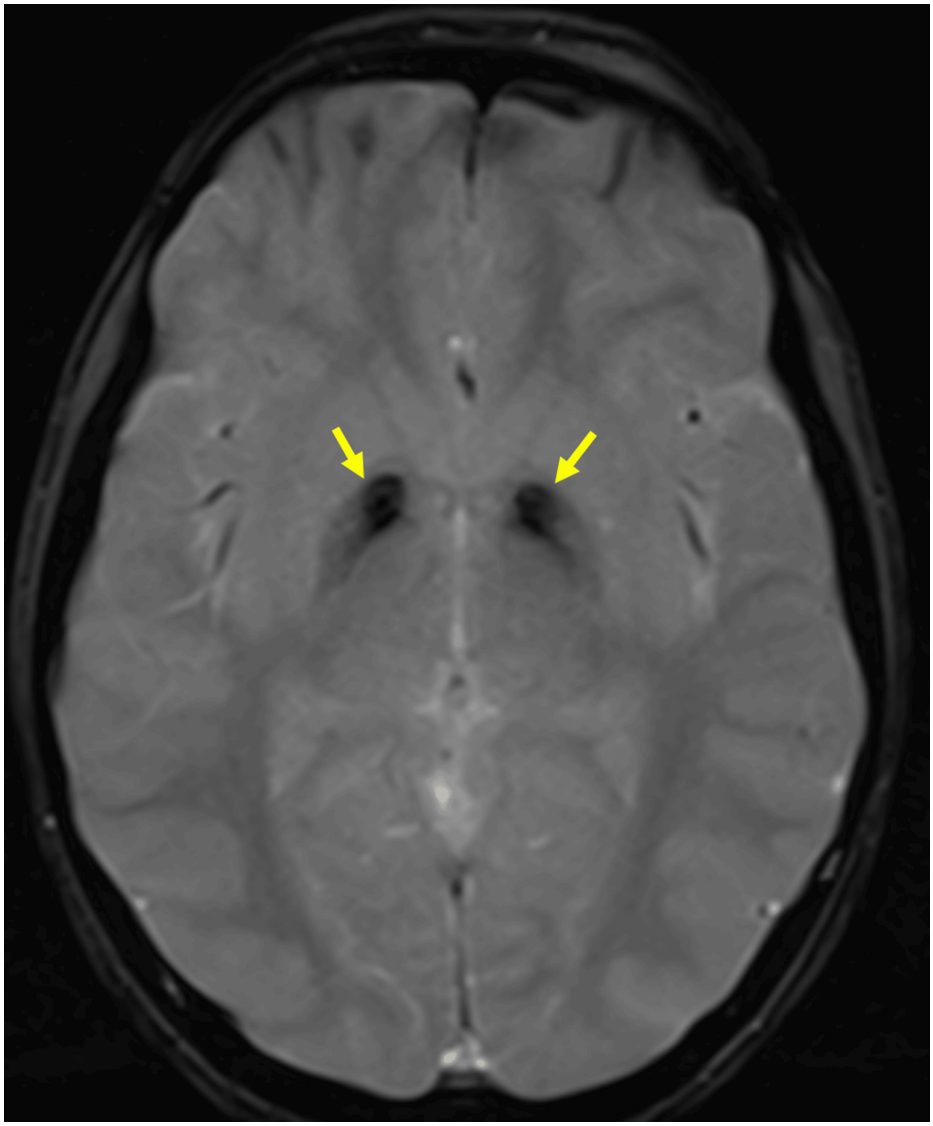

FIGURE 3: Pallidal abnormalities on susceptibility-weighted imaging sequence

Axial susceptibility-weighted image shows marked bilateral, symmetric signal loss in the globus pallidus (yellow arrows), consistent with iron deposition.

Serum copper, ceruloplasmin, and lactate levels were within normal limits. On the basis of the clinical presentation and MRI findings, PKAN was suspected. The family was referred for genetic counseling and *PANK2* molecular testing was requested; the result is pending, as testing has been delayed by the family's limited financial resources. An ophthalmological evaluation, including fundus examination, has been scheduled.

Discussion

PKAN accounts for the largest proportion of NBIA cases [1]. Pantothenate kinase 2 catalyzes the phosphorylation of pantothenate (vitamin B5), the first and main regulatory step of CoA biosynthesis [1,3]. The mechanisms linking *PANK2* deficiency to neurodegeneration and to secondary pallidal iron accumulation remain incompletely understood [1].

The clinical spectrum of PKAN is usually described as classic, typically with onset in childhood, and atypical, with later onset, although these categories represent the two ends of a continuum [1,4]. Classic PKAN usually begins in the first decade of life, often with gait disturbance, and is dominated by progressive motor dysfunction, particularly dystonia, associated with dysarthria, rigidity, spasticity, hyperreflexia, and extensor plantar responses; tremor and chorea may also occur. Progression is relatively rapid and leads to loss of independent ambulation in many patients [4,7]. Atypical PKAN begins later, usually in the second or

third decade, and progresses more slowly; speech difficulties and behavioral or psychiatric changes may precede prominent motor manifestations, whereas dystonia and parkinsonism may emerge later in the course [4,7].

Our patient's presentation, with delayed motor and language milestones followed by progressive gait instability, frequent falls, lower-limb dystonia, dysarthria, postural tremor, and pyramidal signs, is compatible with a childhood-onset neurodegenerative process and, in particular, with classic PKAN. Although clinical deterioration became evident only at eight years of age, the preceding developmental delay may reflect an earlier onset of the disease process.

Other reported manifestations of PKAN include dysphagia, sleep disturbances, and behavioral or psychiatric symptoms such as impulsivity, emotional lability, anxiety, or depression [1,8]. Cognitive function ranges from preserved to impaired, and cognitive difficulties may be more apparent in some atypical presentations [4,8]. Seizures are not a typical feature of the disease [1,8].

Visual involvement is another important feature of PKAN and should be sought before genetic confirmation, as it supports the diagnosis. Pigmentary retinal degeneration is frequent, particularly in classic disease, and may manifest as night blindness, progressive peripheral visual field loss, or reduced visual acuity [4,9]. It may be subtle or subclinical, detectable only by fundus examination or electroretinography, and can therefore be missed if visual symptoms are not specifically sought [9]. Its pathogenesis remains incompletely understood but is considered in the context of *PANK2*-related disruption of CoA-dependent metabolism in retinal neurons. Other neuro-ophthalmologic findings include pupillary abnormalities, such as Adie-like pupils, and ocular-motor abnormalities, particularly slowed or hypometric vertical saccades [9].

On MRI, the eye-of-the-tiger sign consists of bilateral pallidal T2 hypointensity surrounding a central hyperintense focus, typically located in the anteromedial globus pallidus [2,10]. The peripheral hypointensity reflects iron deposition, which shortens T2 and T2* relaxation times, whereas the central hyperintensity corresponds to tissue injury, with neuronal loss, gliosis, vacuolation, and tissue rarefaction on neuropathological examination [11]. Susceptibility-sensitive sequences, such as T2*-weighted gradient-echo imaging and SWI, amplify the effect of iron through local magnetic field inhomogeneity and increase the conspicuity of pallidal hypointensity [2,10]. In our patient, the sign was clearly depicted on axial and coronal T2-weighted images; the central foci were hyperintense on FLAIR, and SWI confirmed a marked pallidal susceptibility effect; the pallidal hypointensity on DWI most likely reflects the same susceptibility effect on echo-planar images. The normal appearance of the substantia nigra, dentate nuclei, and cerebellum was also consistent with PKAN, in which iron deposition predominates in the globus pallidus [2,6]. The appearance of the sign also varies with age: in early childhood, the central T2 hyperintensity may predominate over a still discrete peripheral hypointensity, whereas the hypointense rim becomes more extensive and marked with age and the central hyperintensity may eventually fade or disappear in adults [6].

Although highly suggestive of PKAN in a compatible clinical context, the eye-of-the-tiger sign is not pathognomonic [5,6]. Within the NBIA group, a similar pallidal appearance has been described in neuroferritinopathy and in MPAN, the latter usually associated with substantia nigra hypointensity and T2 iso- to hyperintense streaking along the medial medullary lamina; PLAN is characterized mainly by cerebellar atrophy, and BPAN by early and predominant iron deposition in the substantia nigra [2,6]. Outside the NBIA group, eye-of-the-tiger-like appearances have been reported in Wilson disease, carbon monoxide intoxication, multiple system atrophy, and fucosidosis, and even in healthy adults [5,6,12,13]. In our patient, the normal substantia nigra and cerebellum argued against MPAN, PLAN, and BPAN; normal serum copper and ceruloplasmin levels made Wilson disease unlikely; and the normal serum lactate level and absence of other parenchymal lesions reduce support for a mitochondrial disorder without definitely excluding it. The main clinical, imaging, and diagnostic features that help distinguish PKAN from other NBIA subtypes and conditions reported to mimic the eye-of-the-tiger sign are summarized in Table *1*.

Disorder	Clinical profile and course	MRI features	Other diagnostic clues and confirmation
PKAN	Usually childhood onset, although atypical later-onset forms occur. Progressive dystonia and other movement abnormalities are common; speech, gait, and balance may be affected. Retinal involvement may occur.	Bilateral pallidal T2 hypointensity with a central T2 hyperintensity, producing the classic eye-of-the-tiger appearance. Iron-sensitive sequences help assess the distribution of iron. The appearance evolves with age and disease stage.	Confirm with pathogenic variants in *PANK2*. The MRI sign is highly suggestive in the appropriate context but is not diagnostic by itself [2,5,6].
Neuroferritinopathy	Usually adult onset, with a slowly progressive movement disorder; dystonia, chorea, parkinsonism, or cognitive and behavioral changes	Iron-related signal loss in the basal ganglia, with variable involvement of the globus pallidus, putamen, and other structures. An eye-of-the-tiger-like pallidal	Associated with *FTL* variants; consider genetic testing, particularly with adult onset or a

	may occur. A family history can be informative.	appearance has been reported; putaminal involvement and cavitation may help distinguish it from PKAN.	compatible family history [2,5,6].
MPAN	Progressive motor and cognitive manifestations may coexist with psychiatric or behavioral changes. Pyramidal signs, optic atrophy, and motor neuropathy can be useful clues.	Iron accumulation in the globus pallidus and substantia nigra. A T2 iso- to hyperintense streak along the medial medullary lamina between the pallidal segments is a characteristic clue, although it is not present in every patient. Eye-of-the-tiger-like appearances have also been reported.	Confirm with pathogenic variants in *C19orf12*. The clinical combination of extrapyramidal and pyramidal signs, cognitive or psychiatric changes, and optic or peripheral nerve involvement supports consideration of MPAN [2,6].
PLAN	Phenotype varies with age. Early-onset disease may cause developmental delay or regression, gait instability, ataxia, spasticity, and speech impairment; later-onset forms may present with movement, cognitive, or psychiatric features.	Cerebellar atrophy may be prominent, especially in early-onset disease. Iron accumulation can occur, but the classic PKAN pallidal pattern is not the usual defining feature.	Confirm with pathogenic variants in *PLA2G6*. Age at onset and the presence of cerebellar or broader neurodevelopmental involvement help distinguish PLAN from PKAN [2,6].
BPAN	Typically a biphasic course: developmental delay or intellectual disability in childhood, followed after a period of relative stability by progressive dystonia-parkinsonism and cognitive decline, often in adolescence or adulthood.	Iron deposition is often prominent in the substantia nigra, with possible globus pallidus involvement. T1 hyperintensity and the substantia nigra “halo” sign may be seen; these differ from the classic pallidal eye-of-the-tiger pattern. MRI findings evolve with age.	Usually associated with pathogenic variants in *WDR45*. The characteristic developmental history followed by later movement disorder is a major differentiating clue [2,6].
Wilson disease	Often presents in adolescence or young adulthood with hepatic, neurological, psychiatric, or mixed manifestations. Movement abnormalities and behavioral or cognitive changes may occur.	Basal ganglia signal abnormalities may include a pallidal pattern mimicking the eye-of-the-tiger sign. Other regions may also be involved; the MRI should be interpreted as a whole rather than by the pallidal appearance alone.	Look for Kayser–Fleischer rings and abnormal copper studies. In the case reported in [12], the diagnosis was supported by low serum ceruloplasmin and copper, increased urinary copper excretion, and a Kayser–Fleischer ring [12,13].
Carbon monoxide intoxication	Acquired disorder; a history of exposure and an acute or delayed neurological syndrome are key. The timing of symptoms in relation to exposure helps distinguish it from a hereditary neurodegenerative condition.	Bilateral basal ganglia abnormalities, classically involving the globus pallidus, may simulate an eye-of-the-tiger appearance.	Exposure history and the acute or subacute clinical context are central to diagnosis. The cited reviews report this as a mimic but provide limited detail on specific ancillary tests [6,13].
Multiple system atrophy	Usually adult onset, with progressive parkinsonism or cerebellar features and autonomic dysfunction.	Pallidal signal changes mimicking the eye-of-the-tiger sign have been reported; this appearance is not sufficient to diagnose PKAN.	The adult-onset movement disorder and autonomic clinical features are important discriminators [5,6].
Fucosidosis	Usually presents in childhood with developmental delay or regression and progressive neurological impairment; systemic features may provide additional clues.	Symmetric pallidal hypointensity with central or curvilinear T2 hyperintensity may closely resemble the eye-of-the-tiger sign.	The case in [13] was confirmed by molecular testing demonstrating *FUCA1* variants. The metabolic and developmental phenotype should prompt consideration of a lysosomal disorder [13].

TABLE 1: Clinical, imaging, and diagnostic features distinguishing PKAN from other NBIA subtypes and conditions mimicking the eye-of-the-tiger sign

BPAN: beta-propeller protein-associated neurodegeneration; MPAN: mitochondrial membrane protein-associated neurodegeneration; NBIA: neurodegeneration with brain iron accumulation; PKAN: pantothenate kinase-associated neurodegeneration; PLAN: PLA2G6-associated neurodegeneration

There is no established routine blood or cerebrospinal fluid biomarker that confirms PKAN, and routine laboratory studies are usually unremarkable. The diagnosis relies on the combination of clinical and MRI findings and is confirmed by identification of homozygous or compound heterozygous pathogenic variants affecting both *PANK2* alleles [1,4]. Consanguinity increases the likelihood of homozygosity for a recessive variant but does not by itself establish the diagnosis. In our patient, molecular testing has been delayed by financial constraints. In such settings, recognition of the eye-of-the-tiger sign on routinely available sequences has direct practical value: it allows the radiologist to suggest the diagnosis, to direct testing toward targeted *PANK2* analysis rather than broader and costlier genetic investigations, and to initiate counseling and follow-up without delay.

Genetic counseling is essential for this consanguineous family. Once the familial variants are identified and both parents are confirmed as heterozygous carriers, each pregnancy carries a 25% risk of an affected child, a 50% chance of an asymptomatic carrier, and a 25% chance of an unaffected non-carrier. Identification of the familial variants would also allow carrier testing of relatives and prenatal or preimplantation genetic testing.

Management is currently multidisciplinary and predominantly symptomatic. Depending on the manifestations, care may include pediatric neurology, physical therapy, occupational therapy, speech and swallowing support, nutritional care, ophthalmology, psychosocial support, and mobility aids. Dystonia, spasticity, pain, dysphagia, sleep problems, and other complications are treated individually. Deep brain stimulation of the globus pallidus may be considered in selected patients with severe dystonia, although response varies and it is not curative [8].

In a randomized controlled trial, the iron chelator deferiprone reduced pallidal iron on MRI but did not significantly slow disease progression on the primary dystonia outcome [14]. Other therapeutic strategies remain investigational.

The disease course is variable. Cohort studies suggest that two predicted loss-of-function *PANK2* variants are associated, on average, with earlier onset and more rapid progression, but individual outcomes cannot be reliably predicted from genotype alone [4,7]. In our patient, follow-up is still too short to characterize the rate of progression.

Conclusions

In a child with developmental delay followed by a progressive gait disorder with dystonia, dysarthria, and pyramidal signs, the eye-of-the-tiger sign on T2-weighted MRI should prompt the radiologist to suggest PKAN. SWI strengthens the diagnosis by demonstrating pallidal iron deposition, and assessment of the substantia nigra, dentate nuclei, and cerebellum helps distinguish PKAN from other NBIA subtypes. Although highly suggestive, the sign is not pathognomonic, and confirmation requires identification of biallelic pathogenic *PANK2* variants.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Drafting of the manuscript: Houda Bennani, Lina Belkouchi

Concept and design: Nazik Allali, Latifa Chat

Critical review of the manuscript for important intellectual content: Nazik Allali, Latifa Chat, Siham Elhaddad

Supervision: Siham Elhaddad

Disclosures

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