

## Progressive Gait Abnormalities With Features Suggestive Of PKAN: A Case Report

Xing Yan Choo<sup>1\*</sup>, Sangita Kuparasundram<sup>1</sup>, Chiew Sern Ong<sup>1,2</sup>, Adeline Mee Leh Chuo<sup>1</sup>

<sup>1</sup>Department of General Medicine, Sengkang General Hospital, Singapore

<sup>2</sup>Department of Neurology, National Neuroscience Institute, Singapore

\*Corresponding Author: Xing Yan Choo, Department of General Medicine, Sengkang General Hospital, Singapore.

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### Abstract

#### Background

Pantothenate Kinase Associated Neurodegeneration (PKAN) is a form of Neurodegeneration with Brain Iron Accumulation (NBIA). It is a rare neurological disorder with a genetic basis with classic and atypical conditions. We present a case of a patient with progressive gait difficulties who was found to have an MRI brain scan with features suggestive of possible PKAN.

#### Case Presentation

59 years old Malay male patient presented with broad-based gait, inconsistent freezing episodes with difficulties with the initiation of speed, and intermittent shuffling patterns and retropulsion. He also had behavioral issues. MRI brain scan showed T2 FLAIR hyperintense foci in bilateral globus pallidus with a hypointense rim resembling the 'eye of the tiger' sign.

#### Conclusion

A growing body of literature regarding the varied clinical presentation of atypical PKAN, including psychiatric and neuropsychological symptoms. MRI brain scan findings may not necessarily be pathognomonic for this condition. However, genetic testing may be helpful for confirmation of diagnosis. Treatment is not curative and is focused on symptomatic management, and we hope to add to the literature on this rare condition with this case report. However, further research about treatment is underway.

**Keywords:** Pantothenate Kinase Associated Neurodegeneration (PKAN), the eye of the tiger, Neurodegeneration with Brain Iron Accumulation (NBIA), neurodegeneration

### Introduction

#### Background

Neurodegeneration with Brain Iron Accumulation (NBIA) is a group of rare neurological disorders with a genetic basis in which iron accumulates abnormally in the basal ganglia and substantia nigra. This can present as progressive extrapyramidal movement disorders. Pantothenate Kinase Associated Neurodegeneration (PKAN) is a subtype of NBIA and can present in classic or atypical forms. Classic PKAN usually has a childhood onset with the more rapid development of gait abnormalities with increased muscle tone

(spasticity or dystonia). Retinal degeneration with visual symptoms can also occur. Atypical PKAN progresses more slowly. A growing body of literature regarding the atypical presentation of PKAN, including psychiatric and neuropsychological symptoms [1]. In this case report, we present a patient with progressive gait difficulties who was found to have MRI brain scan features suggestive of possible PKAN. Further elaboration as to the significance and management of these findings are discussed.

#### Case Presentation

The patient is a 59-year-old Malay male with a medical history of hypertension, hyperlipidemia, ischaemic heart disease, chronic alcohol dependence, and Hepatitis C. He was previously incarcerated for sexual offenses in 2019 and is estranged from his family. He currently lives in a private community home. He had a previous admission 2018 for subjective complaints of lower limb weakness, which was investigated with an MRI scan of the spine that did not reveal any significant abnormalities.

He had progressive difficulties with gait over the preceding 1-2 years and was admitted in Oct 2022 for further evaluation. While he could ambulate for short distances with a walking stick for support, he mostly preferred to use a wheelchair for mobilization. He was able to manage his activities of daily living with modified independence from a seated position. He reported a fear of falling and was observed to have freezing episodes during ambulation. The sheltered home staff, such as a prior episode of sexual disinhibition, also noted behavioral issues.

On examination, he was alert, communicative, and could follow instructions easily. There were no cranial nerve deficits. Reduced facial expression was noted though there were no other overt features of parkinsonism, such as resting tremors. There was no rigidity, spasticity, or dystonia. No choreoathetosis or different abnormal movement patterns were present. He had full motor muscle strength in all four limbs with no sensory deficits or issues with coordination. Gait assessment showed a wide-based apraxic gait pattern with difficulties initiating gait and freezing episodes, which occurred inconsistently. At times he would have a shuffling way with occasional retropulsion, though he did not display turning by numbers. Romberg's test was negative. He achieved a total score of 10 out of 10 on an abbreviated mental test. However, he scored 21 out of 28 on a modified Mini-Mental State Examination assessment with deficits in orientation, attention, and memory.

As part of the investigations, an MRI brain scan was performed, which showed T2 FLAIR hyperintense foci in bilateral globus pallidus with a hypointense rim resembling the "eye of the tiger" (see **Figure 1**). There were also features of chronic microvascular ischemia (Fazekas grade 2) and cerebral volume loss disproportionate to the patient's age. The patient also had an elevated erythrocyte sedimentation rate (ESR) of 62 mm/h (upper limit of normal: 10 mm/h). An MRI of the lumbosacral spine showed degenerative changes but was otherwise unremarkable. A nerve conduction study showed sensorimotor, demyelinating polyneuropathy. Further workup with a myeloma panel screen and autoimmune markers were negative.

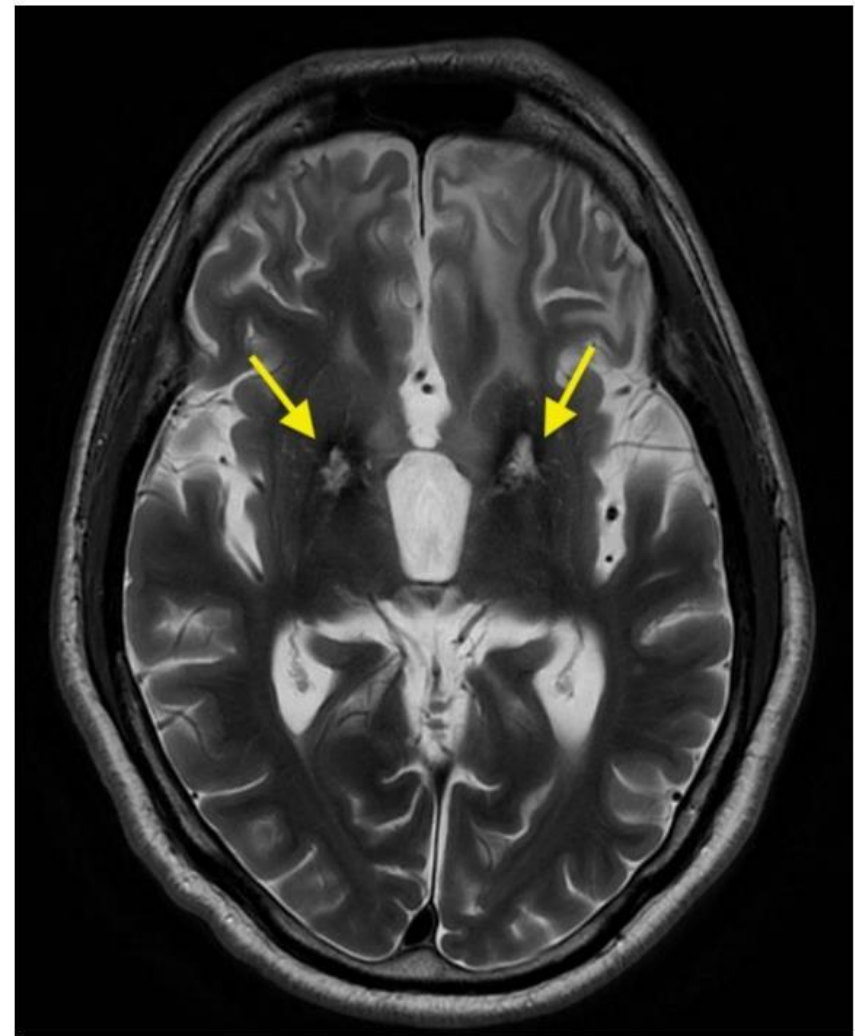
## Discussion and Conclusion

PKAN is a rare condition, with some studies reporting a prevalence of 1 to 3 cases per million [2]. Males and females are equally affected, and while it occurs across all age groups, the racial distribution is unclear.

The presentation of atypical PKAN can be varied, especially with later adult-onset; parkinsonism and dystonia can be common characteristics [3]. Tomic et al. reported features of dystonia (oromandibular and generalized), dysarthria, dysphagia, gait difficulties, and postural instability in a series of nine patients. These developed in the first 4.6 years of the disease course and were followed by the development of skeletal deformities after about 7 years [4]. Lee et al. found further heterogeneity in clinical presentation among the Korean population. Twelve out of 15 patients had gait and balance abnormalities. Two patients had dystonic gait, one patient had a combination of dystonic pace with freezing, and one patient had isolated freezing of gait. All patients were able to walk through some required walking aids for assistance [1].

In addition to motor symptoms, cognitive dysfunction has been reported. A case study of two Japanese siblings also reported evidence of executive and frontal lobe dysfunction on neuropsychological

He was given a trial of Madopar 62.5mg TDS (given freezing episodes, shuffling gait pattern, retropulsion, and hypomimia) but without significant effect. His progress with therapy remained largely static, although he responded better (though inconsistently) with visual cues.



**LEGENDS**  
Figure 1: MRI Brain T2 weighted scan showing bilateral globus pallidus hypointense rim with central hyperintense foci showing the "eye of the tiger" sign.

assessment [5]. Another case series of three females with PKAN showed evidence of impaired attention, fluency, inhibition, and mental flexibility. They also postulated that these may link with behavioral issues such as attention deficit hyperactivity disorder [6]. Palmeri et al. reported a case that initially presented with problems with balance and was noted to have executive dysfunction with impaired problem-solving. He also displayed inappropriate behavior with sexual ideation [7]. There have also been case reports of patients with predominant psychiatric features, such as a 48-year-old patient with mania and psychosis with delusions and hallucinations [8] and another with a history of paranoia and agitation in his 30s, who then developed extrapyramidal symptoms at age 54 years [9].

It is noted that late-onset cases tend to display these psychiatric or neuropsychological features. Though not established, this patient may have also had similar behavioral issues based on previous reports. He did not show abnormal behavior during admission; communication was grossly functional. There are postulations that these behavioral issues can be related to disruptions of the thalamocortical circuits of the limbic system [7]. Formal neuropsychological assessment may have been beneficial in further characterizing cognitive deficits.

Regarding MRI brain imaging features, previous studies have shown a 94% correlation between the presence of the "eye-of-the-tiger" sign and the PANK2 (pantothenate kinase 2) genetic mutation for PKAN. All cases with PANK2 mutations had this MRI brain finding [10]. However, there were cases with a negative sign for the genetic mutation, most of which were late or adult-onset [10].

The "eye of the tiger" sign occurs due to the hypointense appearance of the Globus pallidus from abnormal accumulation of iron, with the central high signal from gliosis [11]. This radiological finding differentiates PKAN NBIA from non-PKAN NBIA. NBIA results from pathologies such as neuroferritinopathy, multiple system atrophy, corticobasal degeneration, multiple sclerosis, previous intracranial hemorrhage, amyloid angiopathy, and multiple cavernomas [10,11]. Abnormal iron deposition can also be found in otherwise healthy adults as part of a normal aging process.

Genetic tests may help confirm the diagnosis of PKAN. Identifying biallelic pathogenic variants in PANK2 via molecular genetic testing confirms the diagnosis if the clinical features are inconclusive. However, this condition is not curable, and treatment focuses on relieving symptoms and is individualized to the patient. For relief of disabling dystonia, baclofen, clonazepam, and benzhexol can be used. Intramuscular botulinum toxin may be considered for focal dystonia.

**Ethics Approval and Consent To Participate:** Not Applicable

#### **Consent For Publication**

The patient has provided written informed consent and verbally consented to the use of their health information for the purpose of this case report. All identifiable information has been removed to maintain confidentiality. The patient has been fully informed of the purpose, potential benefits, and risks of the study.

**Availability of Data and Materials:** Not Applicable

**Competing Interest:** The authors declare that they have no competing interests.

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Levodopa/carbidopa may help some PKAN patients, and amantadine is effective for patients with gait dysfunction, postural instability, and freezing of gait [12]. Drugs that reduce iron levels in the body (iron chelation) have been tried but are ineffective and can cause anemia [13]. Oral pantothenate (vitamin B5) has been suggested as a possible supplement in patients with deficient levels of pantothenate kinase activity. In recent years, disease-specific treatments have been developed, but most of these treatments (Coenzyme A, Fosmetpantothenate, Pantethine, Pantazine, 4'-Phosphopantetheine) are still in preclinical studies and focus on using alternative substrates to bypass the PANK2 enzyme defect [14].

Pallidotomy and thalamotomy have been investigated to control dystonia, but relief appears to be temporary. Deep brain stimulation of the globus pallidus has shown promising results and has gained favor over ablative procedures [15].

The utility of diagnosis may be for prognostication purposes and to make necessary provisions regarding care arrangements given the progressive nature of this disease. Poor social support for this case, in particular, may significantly impact this area as a private home may have difficulty continuing the patient's care as his care needs increase.

#### **Authors' Contribution:**

Xing Yan and Sangita contributed to the drafting of the case report. Adeline and Chiew Sern reviewed and revised the manuscript. All authors were involved in the final revision of the manuscript and approved its submission. All authors were also responsible for the medical care and management of the patient.

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