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Treatment of Pantothenate-Kinase Neurodegeneration With Baclofen, Botulinum Toxin, and Deferiprone: A Case Report

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HIGHLIGHTS

- PKAN, causes motor symptoms with brain iron deposition, no established treatment.
- Baclofen, botulinum toxin, and deferiprone can improve PKAN symptoms.
- This case shows treatment efficacy in a 7-year-old with early-stage PKAN.

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Treatment of Pantothenate-Kinase Neurodegeneration With Baclofen, Botulinum Toxin, and Deferiprone: A Case Report

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The authors have no potential conflicts of interest to disclose.

ABSTRACT

Pantothenate kinase-associated neurodegeneration (PKAN) is a rare autosomal recessive disorder characterized by progressive motor symptoms, such as dystonia and spasticity. Classical PKAN is the most common subtype of neurodegeneration with brain iron accumulation (NBIA). Currently, there is no established treatment for PKAN. However, baclofen and botulinum toxin have been reported to improve motor symptoms and ease care in these patients. Additionally, Deferiprone is a well-tolerated iron chelator that has been shown to be effective in reducing brain iron accumulation. In this case report, we present the case of a seven-year-old boy who presented to our ward with spastic gait and extrapyramidal signs. Brain magnetic resonance imaging was performed, which showed features of neurodegeneration secondary to brain iron accumulation with a specific appearance of the eye-of-the-tiger sign. Genetic testing was positive for a homozygous mutation in PANK2, and the diagnosis of early-stage classical PKAN was made. This case report highlights the potent efficacy of baclofen, botulinum toxin, and deferiprone in slowing down the disease progression at an early stage and improving the severity of symptoms.

Keywords: Pantothenate Kinase-Associated Neurodegeneration; Neurodegeneration with Brain Iron Accumulation (NBIA); Movement Disorder; Genes; Muscle Rigidity

INTRODUCTION

Neurodegeneration with brain iron accumulation (NBIA) encompasses a group of heterogeneous disorders characterized by increased brain iron deposition, predominantly affecting the basal ganglia. Pantothenate kinase-associated neurodegeneration (PKAN) represents the most prevalent subtype of NBIA [1,2]. PKAN is an autosomal recessive neuroaxonal dystrophy caused by mutations in the PANK2 gene located on chromosome 20p. This gene encodes a mitochondrial enzyme crucial for coenzyme A biosynthesis, necessary for normal metabolic functions [3]. Clinical manifestations of PKAN include severe dystonia, dysarthria, rigidity, retinitis pigmentosa, limb spasticity, contractures, spinal deformity, Parkinsonism, and bulbar dysfunction. Brain magnetic resonance imaging (MRI) in PKAN typically reveals bilateral symmetrical central hyperintense signals within the medial aspect

Author Contributions

Conceptualization: Hameed M, Siddiqui F, Gangishetti PK; Data curation: Hameed M, Khan MK, Gangishetti PK; Formal analysis: Siddiqui F, Khan MK, Tadisetty S; Investigation: Hameed M, Khan MK, Gangishetti PK; Methodology: Hameed M, Siddiqui F, Gangishetti PK; Resources: Hameed M, Khan MK, Gangishetti PK; Supervision: Hameed M, Gangishetti PK; Writing - original draft: Siddiqui F, Khan MK, Tadisetty S; Writing - review & editing: Hameed M, Siddiqui F, Khan MK, Tadisetty S, Gangishetti PK.

of the globus pallidus, surrounded by a hypointense rim on T2-weighted images, creating the characteristic "eye-of-the-tiger" sign. Hyperintensity corresponds to gliosis, demyelination, and neuronal loss, while hypointensity indicates iron accumulation within the brain [3]. PKAN can be classified into classic and atypical forms. Classic PKAN usually presents with motor symptoms before the age of 6, displaying a progressive course that initially manifests as gait abnormalities such as dystonia, spasticity, and frequent falls. Atypical PKAN exhibits a slower progression, with symptom onset typically occurring after the age of ten and encompassing psychiatric features [4].

While definitive treatment for PKAN remains elusive, various pharmacological and surgical interventions are employed for palliative care. Baclofen, a gamma-aminobutyric acid (GABA) receptor agonist, constitutes one of the primary drugs utilized to alleviate dystonia severity in PKAN patients [5]. Baclofen is particularly effective in individuals experiencing pain and spasticity [6]. Its efficacy can be enhanced through concurrent administration of botulinum toxin type A (BoNT-A) injections, which function by inhibiting acetylcholine release at the neuromuscular junction. BoNT-A injections have demonstrated efficacy in the management of spasticity and dystonia across various disorders [7]. Deferiprone (1,2-dimethyl-3-hydroxypyrid-4-one or L1) is a potent iron chelator capable of crossing the blood-brain barrier to clear intracellular iron accumulation. Although a randomized controlled trial conducted in 2019 demonstrated that deferiprone slows down the progression of PKAN and is well-tolerated, the results did not reach statistical significance according to the employed scale [8].

This case report represents the first documented instance in which the combined efficacy of botulinum toxin, baclofen, and deferiprone was employed for the treatment of early-stage classical PKAN. It is noteworthy to mention that previous reports have established the effectiveness of botulinum toxin injections in the management of PKAN symptoms. Additionally, baclofen and deferiprone have been recognized as potential therapeutic options for symptom relief and disease management, respectively. However, the unique aspect of this case lies in the novel combination of these treatments, thereby contributing to the limited existing knowledge on comprehensive therapeutic strategies for PKAN.

CASE DESCRIPTION

We present a case report of a seven-year-old boy who presented to our ward with complaints of gait abnormalities, muscle spasticity, and dysarthria that had been ongoing for 7 months (**Supplementary Video 1**). The patient was born from a nonconsanguineous marriage with a positive birth history for preterm birth at 32 weeks and a neonatal ICU stay for a week. He also had a history of febrile seizures at 2 years of age and exhibited delays in psychomotor development, including delayed acquisition of motor milestones such as crawling, standing, and walking.

On general physical examination, an abnormal posture was noted, but no other significant findings were observed. Neurological examination revealed a strength of 4/5 in the upper and lower extremities, increased tone in all extremities, brisk deep tendon reflexes, and an up-going Babinski sign. The patient exhibited a spastic gait but did not require assistance while walking. The cardiovascular, respiratory, and gastrointestinal systems showed no abnormalities upon review, and the eye examination was unremarkable.

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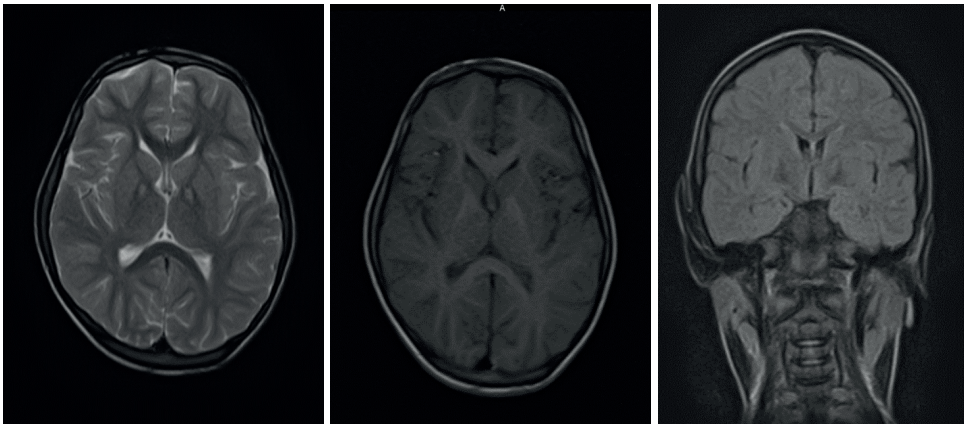

Fig. 1. Eye-of-the-tiger sign visible on axial (first two) and coronal (last) planes of brain magnetic resonance imaging.

Routine blood tests and electroencephalogram was performed, and the results were within normal limits. Brain MRI showed features of neurodegeneration secondary to brain iron accumulation, characterized by the presence of the eye-of-the-tiger sign (**Fig. 1**). Based on these findings, a suspected diagnosis of PKAN was made. Genetic testing confirmed the presence of a heterozygous mutation in the PANK2 gene, supporting the diagnosis of classical early-stage PKAN.

To manage the symptoms, the patient received a single 300-unit injection of onabotulinum toxin-A (Botox®; Allergan, Inc., Dublin, Ireland) into the gastrocnemius muscles of both legs. The injection was guided by anatomical landmarks, and the total volume injected was 6 mL (3 mL per leg). The spasticity scale was assessed using the Modified Ashworth Scale (MAS) before and after the injection, with a reduction in muscle tone observed from MAS level 3 to MAS level 1 in the gastrocnemius muscles.

Following 40 days of therapy with baclofen (20 mg/day) and botulinum toxin, there was improvement in dystonia and spasticity. Muscle tonicity normalized in the upper and lower extremities, leading to the resolution of the spastic gait. The patient's functional status was assessed using activities of daily living (ADL) and motor function tests. Specific assessments were conducted, including the Functional Independence Measure (FIM) to evaluate ADL and the Berg Balance Scale (BBS) to assess balance and mobility. Additionally, the Peabody Developmental Motor Scales (PDMS) were used to measure fine motor skills and coordination. Significant improvements were noted in ADL as measured by the FIM, with the patient achieving increased independence in self-care activities such as dressing, feeding, and personal hygiene. The BBS results showed enhanced balance and mobility, indicating improved coordination. Moreover, the PDMS assessments demonstrated notable progress in fine motor skills, showcasing enhanced dexterity and control.

Future treatment plans include initiating iron chelation therapy using deferiprone (Ferinil; Global Pharmaceuticals, Tamilnadu, India) at a dosage of 1,000 mg/day due to the presence of brain iron accumulation. Furthermore, the patient was started on low-dose iron supplementation (2 mg/kg/day) based on low ferritin levels and transferrin saturation.

Currently, the patient is following the aforementioned treatment regimen and has not reported any progression of the disease or worsening of symptoms. We obtained written

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and signed consent from the patient's guardian to create and publish this case report. Additionally, the Institutional Review Board Committee of the National Institute of Child Health approved the publication of this case report. The manuscript complies with the ethical recommendations of the Declaration of Helsinki of the World Medical Association.

DISCUSSION

PKAN is a neurodegenerative disorder that is caused by iron accumulation in the brain, which leads to extrapyramidal movement disorders and abnormal iron accumulation in the deep basal ganglia. The brain injury mainly occurs due to abnormal metabolism and accumulation of cysteine, which subsequently leads to secondary iron accumulation that causes neuronal injury due to oxidative stress [9].

The classic form of PKAN is characterized by choreoathetosis, dystonia, dysarthria, rigidity, and speech problems, with signs of upper motor neurons such as hyperreflexia, hypertonia, spasticity, and upgoing plantar reflexes also being present. Ophthalmic features can include bilateral retinopathy, retinitis pigmentosa that may lead to cataracts and acantholysis. The atypical form, on the other hand, is less aggressive and is characterized by late onset (after 10 years of age) with psychiatric abnormalities being the most prominent feature, but less cognitive decline and slower development of muscular symptoms [10,11]. There have also been cases of PKAN mimicking Tourette syndrome [12].

The diagnosis of PKAN is confirmed by brain MRI and genetic testing. The brain MRI typically shows bilateral symmetrical central hyperintense signals on the medial side of globus pallidus, with surrounding hypointensity on T2-weighted images, also known as the eye-of-the-tiger sign. However, it is important to note that the eye-of-the-tiger sign is not pathognomonic of PKAN and has been previously reported in other diseases. Therefore, MRI findings should always be clinically correlated with symptoms [13]. Genetic testing remains the gold standard for the diagnosis of PKAN [14].

The differential diagnoses of classical PKAN include X-linked intellectual disability with Dandy Walker malformation, Alpha-L fucosidosis, Leigh syndrome, and infantile neuroaxonal dystrophy. However, these disorders can be distinguished from PKAN based on their clinical and MRI features [15-18].

Currently, there is no guideline-recommended treatment for PKAN, but treatment options are divided into 2 categories: disease-modifying agents, such as deferiprone, which remove the intracellular iron accumulation in the basal ganglia, and agents supporting symptomatic relief, such as oral anticholinergics, benzodiazepines, and anti-spastic agents. Baclofen is a well-known treatment for spasticity and was the treatment recommended to our patient [19]. Botulinum toxin has also shown a great deal of symptom improvement in patients with severe dystonia. Deep brain stimulation of globus pallidus has shown improvement in motor symptoms [20].

In conclusion, the presented case highlights the clinical features and diagnostic workup of PKAN, a rare neurodegenerative disorder. The diagnosis of PKAN is challenging, and a high degree of clinical suspicion is necessary, especially when patients present with early onset extrapyramidal symptoms. Early diagnosis and treatment with disease-modifying agents and symptomatic relief medications can potentially slow down the disease progression

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and improve the quality of life for patients with PKAN. The case report emphasizes the importance of treatment options such as deferiprone, baclofen, and botulinum toxin as they have shown significant effect in slowing down the disease progression and providing symptomatic relief. Further research is needed to develop more effective treatments for this devastating disorder.

SUPPLEMENTARY MATERIAL

Supplementary Video 1

Demostration of spastic gait and rigidity in all extremities.

Click here to view

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