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De Novo Mutation in a Rare Case of Neurodegeneration with Brain Iron Accumulation

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ABSTRACT

Neurodegeneration with brain iron accumulation (NBIA) encompasses rare genetic disorders characterized by iron accumulation in the basal ganglia. Beta-propeller protein-associated neurodegeneration (BPAN) represents an extremely rare X-linked dominant subtype, with only 500 cases reported globally. We present a 5-year-old female with genetically confirmed BPAN, manifesting as early-onset refractory epilepsy beginning at three months of age. The patient exhibited global developmental delay followed by progressive neuroregression starting at age three. Clinical examination revealed microcephaly, distinctive dysmorphic features, and significant neurological impairment including spasticity, dystonia, and cognitive deterioration. Neuroimaging demonstrated cerebral atrophy with characteristic iron deposition in the globus pallidus and substantia nigra. Genetic analysis revealed a de novo mutation in the WDR45 gene, resulting in premature protein truncation.This case represents an atypical BPAN presentation with predominant epileptic encephalopathy rather than the classical movement disorder phenotype. The early onset and severity of symptoms expand our understanding of the clinical spectrum of BPAN. While primarily supportive care remains the mainstay of treatment, this case emphasizes the importance of considering BPAN in the differential diagnosis of early-onset epileptic encephalopathy and highlights the need for comprehensive genetic evaluation in similar presentations.

Keywords: *Neurodegeneration with Brain Iron Accumulation (NBIA), Beta-Propeller Protein-Associated Neurodegeneration (BPAN), Epileptic Encephalopathy, WDR45 Gene Mutation, Iron Deposition in Basal Ganglia, Early-Onset Neuroregression*

1. INTRODUCTION

Neurodegeneration with brain iron accumulation (NBIA) encompasses a group of rare genetic disorders characterized by progressive nervous system dysfunction and abnormal iron accumulation in the basal ganglia[1]. With an estimated prevalence of 1-3 per million population, NBIA presents with a spectrum of clinical manifestations including progressive dystonia, dysarthria, spasticity, parkinsonism, neuropsychiatric abnormalities, and visual loss[2]. While pantothenate kinase-associated neurodegeneration (PKAN) represents the most common subtype, beta-propeller protein-associated neurodegeneration (BPAN or NBIA type 5) is an extremely rare X-linked dominant variant with only 500 cases reported globally[3].

BPAN is caused by mutations in the WDR45 gene, which encodes the WIP14 protein crucial for cellular autophagy and iron homeostasis. The disorder typically manifests in childhood with global developmental delay, ataxia, and seizures, followed by a static phase before progressing to parkinsonism and spasticity in adulthood[3]. We present a unique case of genetically

confirmed BPAN in a 5-year-old female child presenting with early-onset refractory epilepsy, neuroregression, and distinct clinical features that deviate from the classical phenotype of movement disorders typically seen in NBIA.

2. CASE PRESENTATION

A 5-year-old female child presented with global developmental delay, refractory epilepsy, and progressive neuroregression. The patient was the second child born to non-consanguineous parents, with an uneventful perinatal history. The clinical course began at 3 months of age with the onset of epilepsy, manifesting as multiple seizure episodes that proved resistant to conventional antiepileptic medications, necessitating polypharmacy.

At the age of 3 years, the patient experienced a significant deterioration in her developmental trajectory, marked by progressive regression of previously acquired milestones. The regression affected multiple domains of development. At present, the patient exhibits severe neurological impairment characterized by complete loss of neck control, inability to maintain an upright posture, and is completely bedridden. Notably, the patient has lost the ability to recognize her mother and demonstrates significant difficulties with speech and swallowing. Cognitive assessment reveals marked impairment. There was no significant family history of similar conditions or other neurological disorders.

Physical examination revealed several distinctive features. The patient presented with microcephaly and characteristic dysmorphic facial features (figure 1), including hypertelorism, retrognathia, a short philtrum, bulbous nasal tip, and large posteriorly placed ears. Neurological examination demonstrated the presence of squint, generalized spasticity affecting all four limbs with associated dystonia, and exaggerated deep tendon reflexes. Bilateral ankle contractures were noted. The remainder of the systemic examination was unremarkable.

Fig 1: Case representation

Electroencephalography (EEG) revealed multifocal epileptiform discharges with frequent generalization (Figure 2A) and burst suppression pattern(Figure 2B), consistent with epileptic encephalopathy.

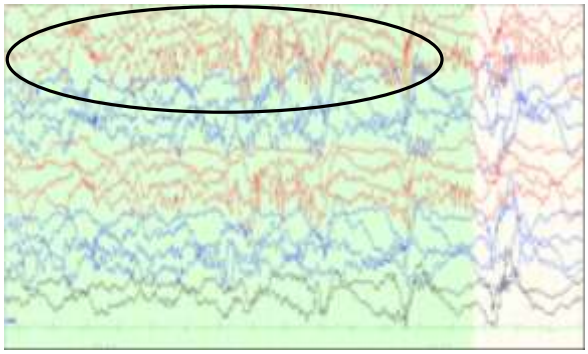

Figure 2A:

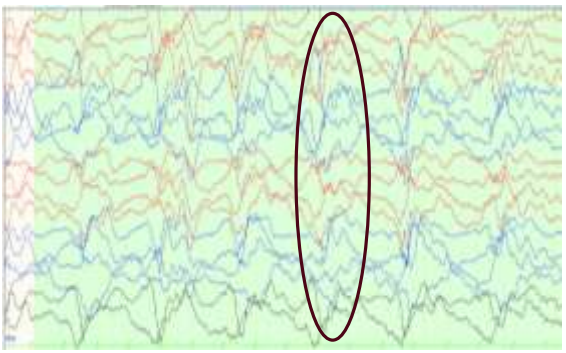

Figure 2B:

Magnetic Resonance Imaging (MRI) demonstrated (figure 3) significant cerebral atrophy with thinning of the corpus callosum. Notably, susceptibility-weighted imaging sequences revealed blooming artifacts in the bilateral globus pallidus and substantia nigra, with characteristic hypointensity noted in the bilateral globus pallidus, findings consistent with iron deposition characteristic of NBIA.

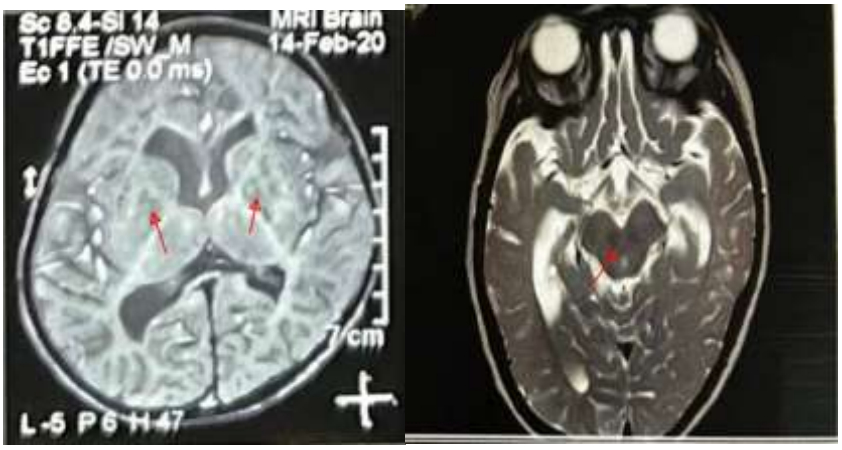

Figure 3: MRI Scan

The patient is currently undergoing regular neurorehabilitation along with continued antiseizure medication management. With the current therapeutic regimen, the patient has achieved seizure freedom, though the overall prognosis remains guarded. This case represents an atypical presentation of BPAN, with predominant refractory epilepsy taking precedence over the movement disorder phenotype typically associated with NBIA variants.

Gene	Location	Variant	Zygosity	Disease	Inheritance	Classification
WDR45	Exon 3 ChrX	c.52C>T; p. Gln18Ter	Heterozygous	Neurodegeneration with brain iron accumulation 5	X-linked dominant	Pathogenic

Sanger sequencing results of Mrs [redacted] (Mother of index child)

Gene	Location	Clinical condition	Variant detected in index child	Status of variant tested in Mother
WDR45	ChrX Exon 3	Neurodegeneration with brain iron accumulation 5	c.52C>T; p.Gln18Ter	Not Detected

Sanger sequencing results of Mr [redacted] (Father of index child)

Gene	Location	Clinical condition	Variant detected in index child	Status of variant tested in Father
WDR45	ChrX Exon 3	Neurodegeneration with brain iron accumulation 5	c.52C>T; p.Gln18Ter	Not Detected

Figure 4: Whole exome sequencing report

3. DISCUSSION

Beta-propeller protein-associated neurodegeneration (BPAN) represents a distinct and rare subtype of neurodegeneration with brain iron accumulation (NBIA), accounting for only 1-2% of all NBIA cases[1]. Our case presents several noteworthy features that both align with and deviate from previously reported cases in the literature, offering valuable insights into the phenotypic spectrum of this rare disorder.

The genetic basis of our case involves a mutation in the WDR45 gene, which encodes the WIP14 protein, a critical component in cellular autophagy pathways. This mutation results in the generation of a premature stop codon at position 18, leading to protein truncation[2]. Similar molecular findings have been reported by Hayflick et al. in their seminal paper describing BPAN as a distinct NBIA subtype[3]. The WDR45 gene's role in autophagy and iron metabolism explains the characteristic iron accumulation observed in the basal ganglia, particularly in the substantia nigra and globus pallidus, as evidenced in our patient's neuroimaging.

Our case is particularly distinctive in its presentation pattern. While the classical BPAN phenotype typically manifests as global developmental delay, ataxia, and seizures in childhood, followed by a static phase before progressing to parkinsonism and spasticity in adulthood[4], our patient demonstrated an unusually early onset of severe symptoms. The presentation of refractory epilepsy at three months of age, requiring multiple anticonvulsants, represents an earlier and more severe seizure burden than typically reported. This aligns with recent literature suggesting a broader phenotypic spectrum of BPAN than initially recognized[5].

The neuroimaging findings in our case mirror those reported in the literature, with characteristic iron deposition in the globus pallidus and substantia nigra visible on susceptibility-weighted imaging[6]. However, the degree of cerebral atrophy and corpus callosum thinning observed at such a young age is noteworthy and may correlate with the severity of the clinical presentation.

The dysmorphic features observed in our patient, including hypertelorism, retrognathia, short philtrum, and bulbous nasal tip, add to the growing literature on phenotypic manifestations of BPAN. While facial dysmorphism has been reported in some cases, the specific constellation of features in our patient contributes to the understanding of the disorder's variable expressivity[7].

The early onset of neuroregression at age three, coupled with the loss of previously acquired milestones, represents a more aggressive disease course than typically described. This raises important questions about genotype-phenotype correlations in BPAN and suggests the possibility of additional genetic or environmental modifiers affecting disease severity[8].

Treatment remains primarily supportive, focusing on seizure control and neurorehabilitation, as there are currently no disease-modifying therapies available for BPAN[9]. Our patient's response to antiepileptic medication, achieving seizure freedom, provides hope for symptomatic management, though the overall prognosis remains guarded.

This case highlights the importance of considering BPAN in the differential diagnosis of early-onset epileptic encephalopathy, even when the classical movement disorder phenotype is not the predominant feature. It also underscores the need for continued research into the pathophysiology of BPAN to develop targeted therapies for this devastating disorder.

4. CONCLUSION

This case highlights a unique presentation of Beta-propeller protein-associated neurodegeneration (BPAN) characterized by early-onset refractory epilepsy and rapid neuroregression, diverging from the typical movement disorder phenotype commonly associated with NBIA disorders. The presence of early-onset seizures at three months of age, coupled with progressive developmental regression and distinctive neuroimaging findings, expands our understanding of the phenotypic spectrum of BPAN. While current management remains primarily supportive, focusing on seizure control and neurorehabilitation, this case emphasizes the importance of early genetic testing in cases of refractory epilepsy with developmental regression. Furthermore, it underscores the need for continued research into targeted therapies for this rare but devastating disorder, while highlighting the critical role of genetic counseling and supportive care in improving quality of life for affected individuals and their families.

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