Novel WDR45 Mutation and Pathognomonic BPAN Imaging in a Young Female With Mild Cognitive Delay

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abstract

β-propeller protein-associated neurodegeneration (BPAN) is a recently identified X-linked dominant form of neurodegeneration with brain iron accumulation caused by mutations in the WDR45 gene. BPAN commonly presents as global developmental delay in childhood with rapid onset of parkinsonism and dementia in early adulthood and associated pathognomonic changes seen on brain MRI. In this case report, we present a pediatric patient with mild cognitive delay and pathognomonic MRI changes indicative of BPAN preceding neurologic deterioration who is found to have a novel de novo mutation in the WDR45 gene.

Neurodegeneration with brain iron accumulation (NBIA) is a genetically and clinically heterogeneous group of disorders with the common feature of iron deposition in the basal ganglia and substantia nigra. β-propeller protein-associated neurodegeneration (BPAN) is a recently identified, X-linked dominant form of NBIA characterized by 2 phases of disease: intellectual disability and global developmental delay in childhood with rapid progressive onset of parkinsonism, dystonia, and dementia in early adulthood. Previously referred to as static encephalopathy of childhood with neurodegeneration, BPAN involves de novo mutations in the WDR45 gene, which plays a critical role in autophagy through a WD40 repeat protein with a β-propeller platform structure. In this case report, we present a young woman with MRI changes preceding clinical progression who possesses a novel, heterozygous mutation in WDR45: c.251A>G (p.Asp84Gly).

PATIENT PRESENTATION

We report an 18-year old young woman born from nonconsanguineous parents who was referred for neurologic assessment at age 17 for a long-standing history of mild speech development issues and cognitive difficulties. Before the publication of this case report, fully informed written consent was provided by the family.

Pregnancy and birth history were unremarkable. Gross and fine motor developmental milestones were achieved at appropriate times during childhood; however, her mother reported a long-standing history of expressive and receptive language difficulties requiring speech language therapy until grade 8. She continued to struggle with sentence structure, grammar, and articulation at the time of assessment. Cognitive difficulties were first identified at age 6, and she was subsequently placed into a special education program. Previous psychoeducational testing results were unavailable. Her mother reported no history of developmental regression but did feel her language skills plateaued at age 14. At age 17, she was completely independent in her activities of daily living and was...
functioning in a basic stream in her age-appropriate school grade. There was no history of seizures, headaches, or visual disturbances. There were also no reported autistic features or other neurologic abnormalities. She was described as a restless sleeper. Sleep evaluation was normal. At age 16, she was referred to a metabolic clinic for hypercholesterolemia on routine blood testing, which was thought to be exacerbated by isotretinoin for acne treatment.

Family history included maternal history of polycystic kidney disease and paternal history of hypercholesterolemia and possible learning disorder. Maternal ethnicity was Welsh and French, and paternal ethnicity was unknown. There was no history of neurologic disease in the family.

Physical examination revealed a well-looking female with no dysmorphic features. Her demeanor was pleasant and affect appropriate. She had articulation difficulties but was able to convey her thoughts. Growth parameters included weight 52.7 kg (>10th centile), height 150.5 cm (3rd centile), and BMI 23 (>50th centile). Head circumference was 53.3 cm (25th centile). Neurologic examination was completely unremarkable with no clear dysarthria, spasticity, dystonia, or parkinsonian features.

Given her long-standing history of intellectual and language difficulties without concrete neurologic findings, initial testing consisted of fragile X testing and comparative genomic hybridization microarray, which were normal. Electroencephalography was normal. The patient received her first brain MRI at this point, which demonstrated bilateral prominent T2 hypointensity in both the globus pallidus and substantia nigra, with relatively increased hypointensity in the substantia nigra (Fig 1). Furthermore, on sagittal T1, there were mildly increased streaks of hyperintensity in these areas. There was no cortical atrophy observed on imaging.

On the basis of her clinical features and the findings on brain MRI, BPAN was suspected, and a WDR45 gene

FIGURE 1
A and B, Susceptibility-weighted angiography demonstrating striking hypointensity in bilateral globus pallidi and substantia nigra. C and D, Axial T2-weighted images with globus pallidi only minimally more hypointense to white matter. E, Coronal gradient echo image demonstrating subtle T1 hyperintensity in the substantia nigra (arrows), the “halo sign.”
analysis was performed, revealing a heterozygous mutation (c.251A>G; p.Asp84Gly). Her mother did not have this mutation, and her father was unavailable for genetic testing. The findings were discussed with the patient and her family, and the prognosis provided regarding possible future neurodegeneration was guarded given the limited data available in the literature.

**DISCUSSION**

This is the first patient reported with the previously mentioned WDR45 gene mutation. She presented with only mild cognitive and language difficulties and pathognomonic MRI findings preceding neurodegeneration in the context of a BPAN diagnosis. This report further expands the WDR45 phenotype. The diagnosis was suggested by typical brain MRI findings in a female child with cognitive delay and no other clinical features and emphasizes the need to consider WDR45 gene sequencing in pediatric patients (especially females) with history of cognitive delay and such MRI findings, regardless of severity.

The gene responsible for BPAN was recently identified in 2012, and there are currently only 29 cases described in the literature including this report.\(^3\)\(^-\)\(^5\) WDR45 belongs to the family of WD40 proteins that are crucial to protein–protein interactions in autophagy, a process thought to be defective in many neurodegenerative conditions.\(^6\) The exact mechanism through which WDR45 mutations cause clinical features is currently unknown. There have been a few reported cases of males with the same condition, but in general BPAN is thought to be lethal in males.\(^1\)

Neuroimaging in BPAN patients reveal striking basal ganglia and substantia nigra pathology with the distinguishing feature of a bright halo on T1-weighted imaging in the cerebral peduncles and substantia nigra due to iron deposition in these areas.\(^3\)

In a report of 23 patients with BPAN, Hayflick et al found that all subjects were diagnosed with global developmental delay in early childhood and severe limitations in expressive language skills.\(^3\) For our patient, it is interesting to note that her long-standing cognitive and language difficulties were classified as mild on multiple medical assessments, and there was no history of delay in attaining social and gross and fine motor developmental milestones. In fact, her mother faced significant challenges in obtaining a neurologic assessment for her daughter given the lack of severity of her symptoms. Furthermore, Haack et al found that some patients with BPAN exhibited spasticity, disordered sleep, ocular defects, epilepsy, and ataxia, and Ohba et al presented a case report of a BPAN patient with clinical findings of Rett syndrome (regression, loss of acquired purposeful hand movements, gait abnormalities).\(^5\)\(^-\)\(^6\) These features were all absent in our patient. She did have a history of hypercholesterolemia, but there have been no reports in the literature to date linking lipid metabolism and BPAN; thus, this finding was felt to be secondary to her acne medication.

In previous case reports, brain MRI findings that resulted in the subsequent diagnosis of BPAN was triggered by neurologic deterioration and the development of dysarthria, dystonia, and Parkinsonism in affected patients.\(^7\) These MRI findings were consistent with evidence of increased iron accumulation in the substantia nigra and globus pallidus and occasional generalized cerebral atrophy at the time of neurologic degeneration. The youngest patient reported with these MRI findings is a 6-year-old girl with Rett syndrome–like features diagnosed by whole exome sequencing.\(^8\) In contrast, although our patient underwent her first brain MRI as part of a diagnostic workup for cognitive delay at age 17, which revealed striking findings consistent with BPAN, she did not display any signs or symptoms of neurologic or psychiatric degeneration seen in previously reported subjects with the same MRI findings.

Currently, there is no known effective prevention or treatment of neurologic decline in BPAN. In previous reports, medical therapy with levodopa resulted initially in significant improvements in patients’ motor function and affect; however, these benefits were short-lived with early recurrence of dystonia and development of disabling dyskinesias.\(^1\) Continued deterioration of motor and language skills with subsequent severe, progressive dementia are common features in previous case reports of patients with BPAN, leading to early death in the third through fifth decade of life due to secondary complications from dysphagia and severe parkinsonism.

As authors of previous BPAN case reports have suggested, we recommend that the diagnosis of BPAN should be considered in all children with global developmental disabilities, especially when accompanied by seizures, disordered sleep, or Rett syndrome–like symptoms. However, as demonstrated through our case, BPAN deficiency can present as nonspecific cognitive delays, making the diagnosis difficult to ascertain unless a brain MRI or gene sequencing is performed. We recommend that WDR45 testing should also be considered in cases of isolated cognitive and language delays, regardless of severity if MRI findings are suggestive. Early diagnosis of BPAN is of utmost importance, providing families with a direction for possible management and prognosis and preventing further unnecessary diagnostic testing. In addition, early identification of WDR45 mutation may lead to a better understanding of the pathophysiology of BPAN and result in the
development of novel therapeutic interventions for preventing or delaying the onset of neurodegeneration for pediatric patients. Finally, gaining insight into the role of autophagy dysfunction in the development of BPAN will likely advance our understanding of common disorders thought also to be related to autophagy dysregulation, such as Huntington disease, Alzheimer disease, and Parkinson disease.

**ABBREVIATIONS**

BPAN: β-propeller protein-associated neurodegeneration

NBIA: neurodegeneration with brain iron accumulation

**REFERENCES**


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