Clinical history

18-year-old male with cognitive developmental delay and ataxia since early childhood, that had been slowly progressing until early adolescence, when he had a rapid progression of dementia and parkinsonism.

MRI findings:
• T2 hypointensity in globus pallidus.
• T1 hyperintense halo surrounding a central linear band of hypointensity in the substantia nigra and cerebral peduncles.
**Gross findings**

Brain weight (fixed): 887 g
Mild cortical atrophy involving the frontal, parietal, and temporal lobes.
Dark-brown discoloration of globus pallidus and substantia nigra, more prominent in the latter.
Discussion

• Differential diagnosis

• Further workup
Differential diagnosis:

• Neurodegeneration with brain iron accumulation

• Wilson’s disease ?

• Hemochromatosis ?
Substantia nigra x20
Iron stain
Additional microscopy findings

• Tau immunohistochemistry revealed neurofibrillary tangles and dystrophic neurites in the cerebrum and basal ganglia

• Alpha-synuclein immunohistochemistry revealed relatively rare Lewy bodies and neurites in the cerebrum and basal ganglia

• No beta-amyloid deposits identified

• No lesions of TDP-43
Antemortem genetic testing revealed a pathogenic mutation in the WDR45 gene located on the X chromosome.
FINAL NEUROPATHOLOGIC DIAGNOSIS:
Beta-propeller protein-associated neurodegeneration (BPAN)
Beta-propeller protein-associated neurodegeneration (BPAN) is one of the several neurodegenerative disorders with brain iron accumulation (NBIA).

NBIA has similar pathologic changes that are observed in selectively vulnerable brain regions, which suggests similar pathophysiology.

The main clinical features of NBIA include: progressive dystonia, dysarthria, spasticity, parkinsonism, optic atrophy

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Estimated prevalence per million</th>
<th>Inheritance</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAN</td>
<td>2-3</td>
<td>X-linked dominant</td>
<td>Global developmental delay, epilepsy, dystonia, parkinsonism in adulthood</td>
</tr>
<tr>
<td>PKAN</td>
<td>2</td>
<td>Autosomal recessive</td>
<td>Classic: severe, progressive dystonia, retinal degeneration</td>
</tr>
<tr>
<td>PLAN</td>
<td>1</td>
<td>Autosomal recessive</td>
<td>Atypical: speech disorders, dystonia, psychiatric symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>INAD: psychomotor regression, ataxia, dystonia, spasticity, optic atrophy</td>
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<td></td>
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<td>aNAD: speech delay, developmental regression, dystonia, spasticity, optic atrophy</td>
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<td></td>
<td></td>
<td></td>
<td>PLA2G6-related dystonia-parkinsonism: parkinsonism, dystonia, cognitive decline,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>psychiatric changes</td>
</tr>
<tr>
<td>MPAN</td>
<td>1</td>
<td>Autosomal recessive</td>
<td>Impaired gait, spasticity, weakness, dystonia, psychiatric changes, optic atrophy,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>parkinsonism</td>
</tr>
<tr>
<td>FAHN</td>
<td>&lt;1</td>
<td>Autosomal recessive</td>
<td>Spasticity, dysarthria, optic atrophy, intellectual impairment</td>
</tr>
<tr>
<td>CoPAN</td>
<td>&lt;1</td>
<td>Autosomal recessive</td>
<td>Spasticity, oromandibular dystonia, dystasia, neuropathy, parkinsonism</td>
</tr>
</tbody>
</table>

NBIA, neurodegeneration with brain iron accumulation; BPAN, beta-propeller protein-associated neurodegeneration; PKAN, pantothenate kinase-associated neurodegeneration; PLAN, PLA2G6-associated neurodegeneration; INAD, infantile neuroaxonal dystrophy; aNAD, atypical neuroaxonal dystrophy; MPAN, mitochondrial membrane protein-associated neurodegeneration; FAHN, fatty acid hydroxylase-associated neurodegeneration; CoPAN, COASY protein-associated neurodegeneration.

Diagnostic evaluation

A diagnosis of NBIA is often suspected based on brain MRI evidence for increased basal ganglia iron along with characteristic clinical features.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Major clinical features</th>
<th>MRI features</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKAN</td>
<td>Dystonia, parkinsonism, spasticity, pigmentary retinopathy, acanthocytosis, neuropsychiatric features</td>
<td>T2 hyperintense signal surrounded by hypointense signal in globus pallidus, less involvement of substantia nigra, representing the “eye of the tiger” sign</td>
</tr>
<tr>
<td>PLAN</td>
<td>Psychomotor regression, ataxia, autism, dystonia, parkinsonism, optic atrophy</td>
<td>Iron seen later in disease, affecting globus pallidus and substantia nigra equally, cerebellar atrophy and gliosis, less often cerebral atrophy</td>
</tr>
<tr>
<td>MPAN</td>
<td>Spasticity, dystonia, dementia, peripheral nerve involvement</td>
<td>Iron affecting globus pallidus and substantia nigra equally, prominent medial medullary lamina streak on T2 sequences</td>
</tr>
<tr>
<td>BPAN</td>
<td>Intellectual disability, little to no language, mixed seizure types, juvenile parkinsonism, autism</td>
<td>T2 hypointense signal in substantia nigra even greater than globus pallidus, T1 bright “halo” in substantia nigra/cerebellar peduncles, changes may be seen in early childhood</td>
</tr>
</tbody>
</table>

T₁ imaging demonstrates the hyperintense halo surrounding a central linear band of hypointensity in the substantia nigra and cerebral peduncles in a patient with BPAN.
BPAN is an X-linked dominant disorder caused by mutations in WDR45 gene.

The human *WDR45* gene encodes a WDR45 protein which has a β-propeller structure.

WDR45 belongs to a large family of WD40 repeat protein and is believed to be an important regulator of autophagy.

So far, 93 patients carrying a WDR45 variant have been conclusively associated to BPAN. 84 of them are females while only 9 are male.
WDR45 function

The precise cellular function of WDR45 is still largely unknown, but deletions or conventional variants in WDR45 can lead to autophagy defects, malfunctioning mitochondria, endoplasmic reticulum stress and unbalanced iron homeostasis.

**Mutations in WDR45**

- Impairs autophagy
- Alters endoplasmic reticulum morphology and quality control
- Changes mitochondrial morphology and functions
- Unbalances iron homeostasis

Take Home Messages

BPAN is a hereditary neurodegenerative disease due to mutation in WDR45, affecting younger patients.

It has a distinct clinical and radiologic features.

Pathology is remarkable for iron accumulation, tau and alpha-synuclein positive neuronal inclusions. There is also a large component of axonal dystrophy, not seen in many other diseases.

There is link between WDR45 with BPAN, but the exact pathogenesis is still not clear.
References


