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Newly Characterized Forms of Neurodegeneration with Brain Iron Accumulation

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Abstract

Neurodegeneration with brain iron accumulation (NBIA) comprises a group of brain iron deposition syndromes that lead to mixed extrapyramidal features and progressive dementia. Historically, many patients with clinical and radiologic features of NBIA have not had a clearly identifiable molecular cause. Recent discoveries have shown that mutations in *C19orf12* or *WDR45* can lead to NBIA. *C19orf12* mutations are inherited in an autosomal recessive manner, and lead to a syndrome similar to that caused by mutations in *PANK2* or *PLA2G6*. In contrast, *WDR45* mutations lead to a distinct form of NBIA characterized by spasticity and intellectual disability in childhood followed by the subacute onset of dystonia-parkinsonism in adulthood. *WDR45* mutations act in an X-linked dominant manner. Although the function of *C19orf12* is largely unknown, *WDR45* plays a key role in autophagy. Each of these new forms of NBIA thus leads to a distinct clinical syndrome and together they implicate new cellular pathways in the pathogenesis of these disorders.

Keywords

Neurodegeneration; brain iron accumulation; parkinsonism; dystonia; mitochondrial membrane protein-associated neurodegeneration (MPAN); beta propeller protein-associated neurodegeneration (BPAN)

Introduction

Neurodegeneration with brain iron accumulation (NBIA) defines a group of neurodegenerative diseases that share prominent extrapyramidal features, dementia, and

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Compliance with Ethics Guidelines

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Conflict of Interest

Joshua M. Doorn declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

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radiographic evidence of iron deposition in the basal ganglia. Iron deposition also occurs in sporadic forms of neurodegenerative disease such as Parkinson disease, albeit to a lesser extent. NBIA often presents in childhood or adolescence but adult-onset forms are also seen.

Mutations in *PANK2* and *PLA2G6* have been recognized as the most common forms of NBIA and contribute to the greatest burden of disease¹. *PANK2* mutations account for most cases, representing about half of NBIA cases in large cohorts. However, approximately 40% of NBIA cases do not have an identifiable molecular basis². As neuroimaging techniques such as susceptibility-weighted imaging continue to advance and awareness of NBIA grows, it will become increasingly important to distinguish NBIA from mimics that combine a neurodegenerative course with T2 hypointensity of the basal ganglia³.

Here, we describe recent insights into two newly discovered genetic causes of NBIA, summarizing clinical, neuroimaging, and pathologic features and highlighting new areas for research. A comparison of MPAN and BPAN can be found in Table 1.

Mitochondrial membrane protein-associated neurodegeneration (MPAN)

Originally identified in *PANK2*-negative Polish patients, MPAN patients share features of both *PANK2* and *PLA2G6*-associated NBIA. Among patients from Western Europe, a founder mutation in *C19orf12* (encoding for a mitochondrial transmembrane protein of uncertain function) is particularly common. This led to the estimation that MPAN may occur almost as frequently as pantothenate kinase-associated neurodegeneration (PKAN) within NBIA cohorts⁴. However, when more diverse populations are considered, MPAN has more conservatively been estimated to account for 1 in 20 NBIA cases worldwide⁵.

Clinical features

Both early childhood-onset and adult-onset have been reported for MPAN^{4,5,6}. Many patients present initially with gait impairment, which can be related to spasticity, dystonia or parkinsonism. Spasticity can preferentially affect the lower limbs or can affect the upper limbs as well. Dystonia often begins in the feet, but may spread to the hands or become generalized. Parkinsonism seems to occur predominantly in patients with later-onset disease, and includes resting tremor, rigidity, bradykinesia, and postural instability. Optic atrophy is a common feature in MPAN⁷, similar to phospholipase-associated neurodegeneration (PLAN) associated with mutations in *PLA2G6*. Dementia is common among patients with MPAN, and a wide variety of neuropsychiatric symptoms have been observed, including depression, anxiety, obsessions/compulsions, inattention, impulsivity, and psychosis with auditory or visual hallucinations. A predominantly motor axonal neuropathy is seen in a subset of patients⁸, although loss of proprioceptive function can also occur⁵. Incontinence, dysarthria, and dysphagia are additional features. Affected patients have a variable response to levodopa^{4,5}. It has been proposed that MPAN patients may have a somewhat milder course than patients with PKAN.

In some cases, rapid progression may be seen, and patients may deteriorate quickly after diagnosis⁹. Recently, mutations in *c19orf12* have also been found to lead to hereditary spastic paraplegia type 43 (SPG43) in some patients¹⁰. Interestingly, the same mutation was

described as leading to a hereditary spastic paraplegia phenotype in one family and an NBIA phenotype in another. A combined upper and lower motor neuron syndrome mimicking juvenile ALS has also been described in MPAN¹¹.

Neuroimaging

Neuroimaging is key to the diagnosis of NBIA, and can be used to distinguish among forms of the disease⁹. Hypointensity of the globus pallidus and substantia nigra on T2-weighted MRI sequences is common to several forms of NBIA and is seen in MPAN. Some patients with MPAN have also been found to have cortical and/or cerebellar atrophy^{4,5} (Figure 1).

Neuropathology

Swollen, dystrophic axons and degenerating neurons or “neuroaxonal spheroids” are a pathologic hallmark of NBIA and can be seen in the brain or can be appreciated via skin or peripheral nerve biopsy in patients with MPAN⁵. Prior to the identification of MPAN as a distinct NBIA subtype, only PLAN was known to feature neuroaxonal spheroids in peripheral tissue.

Postmortem studies of brain tissue from MPAN patients have proven instructive. α -synuclein positive Lewy bodies and Lewy neurites are extremely prominent in MPAN⁴, exceeding that seen in more common cases of Lewy body disease⁵. Tau-containing inclusions are also observed^{4,5}. Histologically, Perls’ Prussian blue stain for iron shows focal deposits in the globus pallidus and substantia nigra, mirroring neuroimaging findings. Demyelination can be seen in the optic and pyramidal tracts. Neuroaxonal spheroids are also demonstrable within the brain^{4,5}.

Genetics

DNA sequence analysis of *C19orf12* is clinically available. The most common mutation detected, particularly among those of Western European descent, is the c.204_214del11 (G69RfsX10) mutation⁴. Outside of this population, however, a number of private mutations have been observed. MPAN is an autosomal recessive disorder, although apparently symptomatic heterozygous carriers have been reported⁵. The identification of mutations in a single allele in a patient with NBIA is thus of uncertain clinical significance.

Molecular Basis of Disease

Prior to the characterization of its role in MPAN, *C19orf12* was only recognized as a predicted protein. Sequence analysis suggests that *C19orf12* is a transmembrane protein that localizes to the mitochondria. Expression analysis suggests that this mitochondrial membrane protein plays a role in lipid metabolism⁴.

Beta-propeller Protein Associated Neurodegeneration (BPAN)

Mutations in *WDR45* (a β propeller domain-containing protein) lead to beta propeller protein associated neurodegeneration (BPAN)^{13,14}. BPAN features a distinctive natural history, with early neurodevelopmental disability followed by years of clinical stability before the

onset of dystonia-parkinsonism in adulthood¹⁵. BPAN is thought to account for approximately 1–2% of all cases of NBIA and is the only form of the disease with an X-linked dominant inheritance pattern^{13,14}. Most BPAN cases are sporadic rather than familial, with mutations typically appearing *de novo*^{13,14}.

Clinical Features

BPAN follows a characteristic course¹⁶. Affected patients have a static encephalopathy in childhood. Intellectual disability is typical and many patients exhibit spastic paraplegia or quadriplegia. Some patients also have epilepsy which is typically able to be controlled with antiepileptic medications. After childhood, BPAN patients remain relatively stable for decades. During early adulthood, affected patients develop extrapyramidal symptoms, sometimes with relatively abrupt onset. Patients often begin their neurologic decline with increasingly frequent falls, followed by the appearance of dystonia and parkinsonism and worsening intellectual functioning. Patients progress to a state of akinetic mutism, sometimes within a period of a few years.

Neuroimaging

On MRI, patients with *WDR45* mutation show a characteristic T1 hyperintensity of the cerebral peduncles and substantia nigra (sometimes extending into the globus pallidus) not seen in other forms of NBIA¹⁶ (Figure 1). The pathology responsible for this signal change is not known. T2-weighted images demonstrate hypointensity of both the substantia nigra and globus pallidus¹². Interestingly, BPAN is the only form of NBIA in which the T2 hypointensity of the substantia nigra outweighs that of the globus pallidus. BPAN patients also display a unique region of hyperintensity in the substantia nigra on T1-weighted images.

Neuropathology

Although no molecularly-confirmed cases of BPAN have come to autopsy, Eidelberg and colleagues described three patients in 1987 that demonstrated iron deposition in the basal ganglia and a clinical phenotype remarkably consistent with BPAN¹⁷. The three patients, all women, had baseline intellectual disability but developed an extrapyramidal syndrome and progressive dementia in adulthood. Neuropathologic findings across these cases showed cortical atrophy and iron deposition in the globus pallidus and substantia nigra. Axonal spheroids were widespread but most prominently found in the globus pallidus and substantia nigra. Neurofibrillary tangles were prominent and seen throughout the cortex, deep gray nuclei, hippocampus, and brainstem. Additional features include granulovacuolar degeneration, and Hirano bodies. Lewy bodies were noted in one of the patients. In one patient whose spinal cord was available for analysis, motor neuron degeneration was also observed.

Genetics

BPAN is inherited in an X-linked dominant manner, and all reported cases to date have been sporadic. Disease-associated *WDR45* mutations have been postulated to represent loss of

function mutations predicted to lead to haploinsufficiency. Consistent with this idea, diverse mutations lead to diminished protein abundance, perhaps because mutant transcripts and/or proteins are degraded¹⁴.

The clear female predominance (only three males have been identified thus far with the disease) suggests that germline mutations in hemizygous males are often embryonic lethal. *WDR45* mutations may thus occur somatically during embryogenesis, and males can carry a variable mutation load, leading to either exceptionally severe or relatively mild symptoms compared to affected female patients. Heterozygous or hemizygous mutations can be detected in patients clinically suspected to have BPAN via commercially available DNA sequence analysis.

Molecular Basis of Disease

In contrast to *C19orf12*, the function of *WDR45* and its yeast ortholog Atg18 is better understood given its role as an essential part of cellular autophagic machinery¹⁸. Defective autophagy has been widely implicated in neurodegenerative disease, putatively contributing to the accumulation of abnormal proteins¹⁹. Mice deficient in core components of the autophagic machinery display a neurodegenerative phenotype²⁰. However, BPAN represents the first time that a mutation in a core component of autophagy has been linked to a human neurodegenerative disease.

WDR45 is a member of the WD-40 family. This protein family features a seven bladed β -propeller structure that regulates the formation of multimeric protein complexes by providing a scaffold facilitating protein-protein interactions. Additionally, within the β -propeller domain is a core Phe-Arg-Arg-Gly domain that binds to phosphoinositides²¹.

Atg18 is known to interact with Atg2 and Atg21 and to contribute to autophagosome formation and maturation. Analysis of BPAN patient-derived lymphoblasts has shown that enlarged LC3-II positive autophagosomes accumulate. Such structures are also positive for ATG9A, a protein that only transiently localizes to the phagophore assembly site and promotes autophagosome genesis under normal conditions, suggesting that abnormal autophagosomes accumulate with loss of WDR45¹⁴. Importantly, although autophagy was impaired in patient-derived lymphoblasts, it was not completely abolished, suggesting that perhaps some of the disease-associated phenotype could be rescued if autophagy could be upregulated. The curious natural history of BPAN patients also suggests that autophagy is critical for both early neurodevelopment (leading to a childhood static encephalopathy when impaired) as well as ongoing cellular quality control (leading to neurodegeneration in adulthood).

Conclusion

Although the exact incidence of NBIA remains uncertain, patients with forms of the disease are increasingly being recognized in populations of patients presenting for evaluation of complex movement disorders and neurodegenerative disease. The identification of MPAN and BPAN represent important steps forward in the characterization of forms of NBIA, yet a large proportion of NBIA cases still remain idiopathic.

Research priorities include studies designed to elucidate fundamental cellular functions affected by loss of *C19orf12* and *WDR45*. The generation of appropriate animal models will also be crucial to research progress. Although the characterization of causative genes for these forms of NBIA represents a crucial first step, much work remains to be done to better characterize disease pathomechanisms, particularly in the case of MPAN. Only when this is accomplished can novel therapeutic strategies be developed for these devastating diseases.

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Figure 1. Neuroimaging features of BPAN and MPAN

The top row showcases MRI features of BPAN, including hypointensity of the globus pallidus and substantia nigra on T2 weighted images, hyperintensity of these regions on T1 weighted images, and cerebral > cerebellar atrophy. The bottom row highlights features of MPAN, including T2 hypointensity of the globus pallidus and substantia nigra and cerebellar atrophy

Table 1

Comparison of clinical, neuroimaging, and pathologic features of MPAN and BPAN

	MPAN	BPAN
Eye findings	Optic Atrophy	None
Pyramidal tract signs	Present	Present
Extrapyramidal features	Dystonia, parkinsonism	Dystonia, parkinsonism
Neuropsychiatric features	Dementia, depression, anxiety, impulsivity, psychosis	Early intellectual disability, adult-onset dementia
Peripheral nerve	Motor Axonopathy	None
Neuroaxonal spheroids	Brain, peripheral nerve	Brain
MRI findings	T2 hypointensity of the globus pallidus > substantia nigra, mild cerebral/cerebellar atrophy	T2 hypointensity of the substantia nigra > globus pallidus, T1 hyperintensity of substantia nigra > globus pallidus, severe cerebral > cerebellar atrophy