CHAPTER FOUR

BPAN: The Only X-Linked Dominant NBIA Disorder

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Abstract

Beta-propeller protein-associated neurodegeneration (BPAN) is the most recently identified subtype of neurodegeneration with brain iron accumulation (NBIA), being unique with respect to the underlying disease genetics, the associated clinical presentation, and the suggested pathomechanism. Mutations in X-chromosomal WDR45 arise de novo; however, the dominant pattern of inheritance is unusual for an X-linked disorder and additional mechanisms such as X-inactivation or somatic mosaicism are likely to contribute to the phenotype that is indistinguishable between males and females. The course of the disease is two-staged with developmental delay and intellectual disability in childhood and a second phase of rapid neurological deterioration characterized by parkinsonism and dementia occurring in adolescence or early adulthood. At this time, neuroimaging findings are characteristic and provide excellent diagnostic guidance. There is increasing evidence that human WDR45 deficiency impairs autophagy, thereby raising the possibility that this rare disorder will offer insights into more common neurodegenerative disorders such as Parkinson or Alzheimer disease.
1. INTRODUCTION

Beta-propeller protein-associated neurodegeneration (BPAN) is a recognizable NBIA disorder based on the clinical features, the MRI pattern, and the natural history of disease. The recent discovery of causative mutations in \textit{WDR45} has provided a beginning to investigate the biological basis of this rare disorder. \textit{WDR45} localizes to the X chromosome; hence, the genetic factors that underlie this disorder and its manifestation are complex, multifaceted, and yet to be fully understood. Nevertheless, most clinicians can recognize patients likely to have BPAN and confirm the diagnosis with clinical genetic testing.

2. CLINICAL FEATURES

The phenotype of BPAN was first recognized by Hogarth, Gregory, and Hayflick in 2002. Several idiopathic NBIA patients were examined and found to have a similar clinical picture and pattern of disease progression that differed from that observed in other NBIA disorders. The typical pattern is normal birth history with a diagnosis in early childhood of developmental delay and intellectual disability. In adolescence or early adulthood, patients undergo a period of neurological regression with onset of parkinsonism and cognitive decline from their already abnormal baseline. The regression typically prompts a brain MRI, which shows iron accumulation in the basal ganglia. Patients continue to deteriorate with worsening parkinsonism, leading to death by middle age.

Children with BPAN may be recognizable prior to the period of clinical deterioration. In addition to manifesting global developmental delay, these children usually show expressive language delay disproportionate to their other disabilities. Epilepsy is frequently part of the clinical picture, with complex partial, atonic, absence, or generalized tonic–clonic seizures all observed and with some children exhibiting multiple seizure types. Rett-like behaviors and stereotypedies are common; many children who are eventually diagnosed with BPAN carry an initial diagnosis of atypical Rett syndrome. Some overlap with atypical Angelman syndrome is evident, as well. Individuals with features of Rett or Angelman syndromes and lacking a genetic or chromosomal abnormality to explain their disease should be tested for BPAN. Other features of BPAN that are evident in childhood include dysfunctional sleep and ocular defects.
Regression in BPAN usually occurs in adolescence or early adulthood and begins with bradykinesia, freezing of gait, and rigidity. The onset of parkinsonism may be subtle, but over time, clear signs and symptoms are evident. The parkinsonism in BPAN is responsive to L-DOPA; however, the duration of benefit lasts usually only a few years and is limited by the development of disabling dyskinesias. With disease progression, patients typically have progressive cognitive decline with loss of limited expressive language skills, as well. Further details of the clinical phenotype and natural history can be found in a recently published paper (Hayflick et al., 2013). Brain MRI done after the onset of regression will show iron accumulation in the basal ganglia and prompt suspicion of one of the NBIA disorders.

3. BRAIN IMAGING

The natural history of BPAN is unusual, and the pattern of abnormalities seen on brain MRI is also distinctive. Iron appears as hypointense signal on T2-weighted imaging. In BPAN, iron is abundant in the substantia nigra and globus pallidus once there are clinical manifestations of parkinsonism (Fig. 4.1). On T1-weighted imaging, the substantia nigra/cerebral peduncles show a hyperintense “halo,” which is very distinctive and can be very helpful in guiding diagnostic genetic testing. These changes are found after clinical deterioration. The early MRI in BPAN either is normal or shows only nonspecific cerebral atrophy.

Figure 4.1 Brain MRI in BPAN showing hypointense signal on T2-weighted sequence representing iron in globus pallidus (A) and substantia nigra (B) and T1-weighted sequence showing the hyperintense “halo” in substantia nigra.
4. HISTOPATHOLOGY

Macroscopic neuropathological findings of a female BPAN patient included mild cerebellar atrophy, thinned cerebral peduncles, and dark gray-brown aspects of the substantia nigra and the globus pallidus. Microscopic work-up confirmed marked iron deposition in the substantia nigra and globus pallidus in co-occurrence with siderophages, axonal spheroids, and severe neuronal loss. While Lewy bodies and amyloid-beta plaques were absent, numerous tau-positive tangles were observed in various brain regions. For details, see Hayflick et al. (2013).

5. DIAGNOSIS

BPAN should be suspected when the characteristic natural history, clinical features, and brain MRI changes are observed. Clinical genetic testing is available to confirm a suspected diagnosis. While the BPAN phenotype represents the spectrum of disease as we currently recognize it, there are compelling reasons to expect this spectrum to broaden and to include patients with more mild and more severe manifestations. The basis for this derives from the interesting genetics of BPAN, including X chromosome linkage, somatic cell mosaicism, and skewing of X chromosome inactivation.

6. GENETICS

X-chromosomal WDR45 de novo mutations were identified in an exome sequencing study investigating a group of 14 NBIA index cases selected for distinct clinical presentation (Haack et al., 2012). Data analysis based on a recessive model of inheritance failed to identify mutations in known NBIA disease genes or obvious candidates. In contrast, considering dominant-acting mutations as a potential pathomechanism, a search for heterozygous mutations detected pathogenic mutations in WDR45 in 13 individuals. Subsequent screening of unresolved NBIA cases revealed WDR45 mutations in an additional 10 patients (Hayflick et al., 2013). Another study applied exome sequencing to investigate two index cases together with healthy family members enabling a search for de novo variation. WDR45 mutations were detected in both individuals, and subsequent mutation screening revealed pathogenic mutations in an additional three index cases (Saitsu et al., 2013). Together, a total of 28 simplex cases have been reported to date.
Only two patients share the same mutation. Of the 27 different disease alleles, apart from three missense mutations affecting evolutionarily highly conserved amino acid residues, the remaining alleles are predicted loss-of-function mutations. With WDR45 located on the X chromosome, one would expect to see mainly male affected in case of a recessive pattern or no gender bias in a dominant model of inheritance. In agreement with a dominant model, all mutations are known or suspected to be de novo. However, 25 out of 28 patients were females, suggesting that WDR45 mutations are lethal in most males. Consistently, in at least one male patient, the mutation occurred postzygotic leading to somatic mosaicism (Haack et al., 2012). Somatic mutations in males and females together with skewing of X chromosome inactivation in females could on one hand explain the similar phenotype in both genders and would on the other hand predict a much broader range of phenotypes still found to be associated with WDR45 mutations.

7. BIOLOGY

WDR45 belongs to the large family of WD40 proteins that share a conserved motif of about 40 amino acids terminating with tryptophan-aspartate (W–D) (Li & Roberts, 2001). WD40 proteins promote protein–protein interactions and play a role in various cellular processes including cell cycle control, translation regulation, signal transduction, and autophagy. WDR45 has a beta-propeller tertiary structure and a conserved domain for interaction with phospholipids. It has been shown to physically interact with the autophagy factors ATG2A and ATG2B (Behrends, Sowa, Gygi, & Harper, 2010). Knockdown studies and investigation of the WDR45 ortholog epg6 in Caenorhabditis elegans suggested a crucial role in the formation of the autophagosome with epg6 silencing leading to an accumulation of early autophagic structures (Lu et al., 2011). Saitsu et al. showed that patient-derived lymphoblast cell lines have a decrease in autophagic flux compared to controls and accumulate early autophagic structures. While an involvement of autophagy makes perfectly sense also with respect to pathomechanisms discussed in more common neurodegenerative disorders such as Parkinson or Alzheimer disease, other functions of WDR45 yet to be characterized might also contribute to the disease phenotype. More extensive investigations of patients’ brain samples or animal models might be valuable tools to address these questions. These future studies might also provide clues why involvement of the very basic pathway autophagy via WDR45
mutations predominantly affects the brain, unlike recessive mutations in another autophagy-related factor, EPG5, which causes a multisystemic disorder, Vici syndrome, characterized by callosal agenesis, cataracts, cardiomyopathy, combined immunodeficiency, and hypopigmentation (Cullup et al., 2013). The role of defective autophagy in NBIA might also be substantiated by assigning the molecular genetic basis of so far idiopathic NBIA cases to this pathway.

REFERENCES


