‘Neurodegeneration with brain iron accumulation’ (NBIA) is a clinically and genetically heterogeneous group of disorders presenting with progressive extrapyramidal dysfunction, and as a common feature, with brain iron deposition in the basal ganglia, particularly in the globus pallidus and substantia nigra (Gregory and Hayflick, 2013a). Over recent years an increasing number of mutations in novel disease genes have been identified in NBIA, facilitated by new genetic technologies. Mutations in nine different genes have been shown to cause NBIA to date, with a spectrum of overlapping clinical phenotypes (Fig. 1, Gregory and Hayflick, 2013a). The identification of novel disease genes has improved our understanding of major disease mechanisms leading to iron deposition as a potential common pathway, although the direct link between iron accumulation and clinical presentation requires further work.

The clinical ‘hallmarks’ of NBIA are progressive dystonia, dysarthria, spasticity and parkinsonism. Optic atrophy, retinal degeneration and peripheral neuropathy may be associated features in a number of NBIA syndromes. Characteristic MRI findings may be helpful in the diagnosis, but they may appear only later in the disease course. However some specific signs on MRI may facilitate the diagnosis (Fig. 1). The age of manifestation (childhood–adulthood) and the inheritance pattern (autosomal recessive in seven forms; autosomal dominant in neuroferritinopathy; and X-linked in WDR45 deficiency) may be helpful in the differential diagnosis of NBIA (Fig. 1). In a large proportion of cases (~40%), the underlying genetic basis of NBIA has yet to be defined, suggesting further genetic heterogeneity (Gregory and Hayflick, 2013a).

The first identified and most common form of NBIA is pantothenate kinase-associated neurodegeneration (PKAN, MIM 234200; formerly known as Hallervorden-Spatz disease), caused by mutations in PANK2 (Gregory and Hayflick, 2013b). PKAN typically presents with dystonia before 10 years-of-age associated with dysarthria, rigidity and pigmentary retinopathy. Infantile neuroaxonal dystrophy (MIM 256600) is a recessive early childhood-onset disorder with hypotonia, psychomotor retardation and pyramidal signs due to PLA2G6 mutations (Morgan et al., 2006). The third most common NBIA is mitochondrial membrane protein-associated neurodegeneration (MPAN, MIM 614298) due to mutations in C19orf12 (Hartig et al., 2011). The onset is in childhood or early adulthood, the spasticity may be more prominent than the dystonia, and typical features include optic atrophy and motor neuropathy with increased creatine kinase (Horvath et al., 2012). Neuroferritinopathy (MIM 604290, FTL1 gene) is more common in the UK (~75 reported cases: McNeil and Chinnery, 2012). Rare forms of NBIA are fatty acid hydroxylase-associated neurodegeneration (FAHN, MIM 612443), Kufor-Rakeb disease (PARK9, MIM 606693), aceruloplasminemia (MIM 604290) and Woodhouse-Sakati syndrome, caused by mutations in the FA2H, ATP13A2, aCP and DCAF17 genes, respectively (Gregory and Hayflick, 2013a).

In this issue of Brain, Susan Hayflick’s group—in collaboration with several international investigators—reports a large cohort of 23 patients with a recently identified form of NBIA, carrying mutations in the X-chromosomal WDR45 gene encoding a beta-propeller protein, postulated to play a role in autophagy (Hayflick et al., 2013). While two papers reported recently on the identification of WDR45 as a novel NBIA gene (Haack et al., 2012; Saitsu et al., 2013), the paper by Hayflick and colleagues (2013) provides an excellent overview on the clinical presentation. Before the identification of WDR45, the original description of some patients with this form of NBIA referred to a distinct clinical syndrome called static encephalopathy of childhood with neurodegeneration in adulthood (SENDA). The new study expands the clinical phenotype and suggests that WDR45 deficiency should be named as ‘beta-propeller protein-associated neurodegeneration’ (BPAN).

BPAN is a clinically recognizable disorder with a two-stage disease progression and most likely represents a common type of NBIA (Haack et al., 2012; Saitsu et al., 2013). Despite a high number of different mutations and variable ethnic background, the natural history of the disease is remarkably uniform and recognizable by its distinct pattern of clinical and MRI features. The first stage of the disease is global developmental delay with intellectual disability in infancy or early childhood. Most children are described as clumsy; spasticity and epilepsy—including focal, atonic, absence, generalized tonic-clonic or myoclonic seizures—are frequently reported. A second phase of the disease affects all patients and manifests in adolescent or young adult life (~25 years) with progressive dystonia, cognitive decline, speech difficulties and parkinsonism characterized by bradykinesia and rigidity, usually without tremor. The severity of parkinsonian features in some patients prompted the authors to suggest that BPAN may be also classified as a genetic form of...
prominent iron accumulation has been detected in the substantia nigra in the early phase of the disease. While nigral iron is evident in these patients, the pallidum may not appear hypointense in T2* sequences. T1-weighted signal hyperintensity with a central band of hypointensity in the substantia nigra seems to be a specific finding in BPAN. Generalized cerebral atrophy is also reported in 19 out of 23 patients, whereas cerebellar atrophy is a less common feature only being present in six individuals (Hayflick et al., 2013).

Prominent iron accumulation has been detected in the substantia nigra in the early phase of the disease. While nigral iron is evident in these patients, the pallidum may not appear hypointense on regular T1-weighted images, only on gradient-echo or T2* sequences. T1-weighted signal hyperintensity with a central band of hypointensity in the substantia nigra seems to be a specific finding in BPAN. Generalized cerebral atrophy is also reported in 19 out of 23 patients, whereas cerebellar atrophy is a less common feature only being present in six individuals (Hayflick et al., 2013).

One of the most puzzling features of WDR45 deficiency is its inheritance pattern. Although WDR45 is located on the X chromosome, clinical features of the disease do not follow the pattern typical for an X-linked disorder. All affected individuals to date are sporadic cases with no family history of NBIA and most WDR45 variants are nonsense mutations, each arising de novo (Hayflick et al., 2013). Although the significant gender bias (20 females versus three males) suggests that WDR45 mutations are lethal in most males, the phenotypes of the three affected male patients carrying nonsense mutations is clinically indistinguishable from the clinical presentation in females (Gregory and Hayflick, 2013). After excluding sex-chromosome aneuploidy, the most likely explanation is that the mutations are post-zygotic, leading to somatic mosaicism in males, and possibly in females. This mechanism could explain the similarities between genders and also the detection of exclusively de novo mutations in females; and suggests that genetic analysis of multiple tissues may be necessary to screen for WDR45 mutations in mildly affected individuals (Haack et al., 2012). A similar inheritance pattern has been observed in Rett syndrome (MIM 312750), another X-linked dominant disease (Christodoulou and Ho, 2012).

What is the disease mechanism in WDR45 deficiency and how can we link it with other forms of NBIA? WDR45 encodes a so-called WD repeat protein, which belongs to a large family of molecules with repeating units containing a conserved core of 40+ amino acids that terminate with tryptophan-aspartic acid (WD). WD40 proteins have a highly symmetrical seven-bladed beta-propeller structure that is optimal in coordinating protein–protein interactions and this unique structure most likely regulates the assembly of multi-protein complexes in diverse cellular functions, such as autophagy, transcriptional regulation and signal transduction (Saitsu et al., 2013). Dysregulation of autophagy has been suggested in various neurodegenerative conditions (Alzheimer’s or Parkinson’s disease) or other diseases with cytoplasmic aggregates where cytoplasmic materials are engulfed by membrane structures forming autophagosomes (Menzies et al., 2011). Studying autophagy in WDR45 deficiency provided the first experimental evidence that an autophagy defect is indeed associated with neurodegeneration (Saitsu et al., 2013). Abnormal autophagy as
the basic disease mechanism has also recently been implicated in a novel form of hereditary spastic paraparesis due to mutations in another beta-propeller protein, tectonin beta-propeller containing 2, TECPR2 (Oz-Levi et al., 2012). However it is still unclear how increased autophagy relates to iron accumulation. Various basic mechanisms have been implicated in NBIA (altered iron metabolism, fatty acid metabolism, apoptosis, transcriptional regulation, autophagy), but whether abnormal iron deposition is a final common pathway, directly leading to disturbed neuronal dysfunction, or a ‘biomarker’ of NBIA, facilitating disease detection remains to be established (Fig. 1). Identification of novel genetic forms of NBIA, such as the recently reported BPAN provides novel insights to answer this very important question. Better understanding of the disease mechanisms and their role in iron accumulation is essential to define whether novel therapeutic interventions should target iron deposition, or the primary defect (autophagy, fatty acid metabolism, apoptosis etc), secondarily leading to iron deposition, or both (Fig. 1). In neuroferritinopathy, signal intensity in the thalamus showed documented changes over time and good correlation with the clinical rating scale measuring dystonia severity, establishing a link between iron accumulation and clinical presentation (McNeil et al., 2012). Similar studies are urgently needed in other NBIA conditions to determine the natural history of disease and to provide the platform for therapeutic intervention.

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References


Imaging neuronal loss and recovery in compromised but viable brain tissue

Selective neuronal loss, that is necrosis or apoptosis of a portion of neurons in cerebral tissue with grossly preserved architecture (Garcia et al., 1996), is difficult to assess but can seriously impact brain function in patients with cerebrovascular disease. It has been associated with temporary cerebral ischaemia, as in reperfused penumbral tissue (Garcia et al., 1996; Baron, 2005), and with chronic cerebral hypoperfusion due, for example, to atherosclerotic disease of major cerebral arteries or ischaemic heart disease (Yamauchi et al., 2011). Selective neuronal loss may be a significant factor in cognitive impairment and limited functional recovery ability. Conventional diagnostic imaging with CT or MRI does not identify selective neuronal damage (Garcia et al., 1996;