Clin Neuroradiol (2017) 27:481–483
DOI 10.1007/s00062-017-0605-9

CORRESPONDENCE

# Clinical and Imaging Presentation of a Patient with Beta-Propeller Protein-Associated Neurodegeneration, a Rare and Sporadic form of Neurodegeneration with Brain Iron Accumulation (NBIA)

**Elke Hattingen[1] · Nikolaus Handke[2] · Kirsten Cremer[3] · Sabine Hoffjan[4] · Guido Matthias Kukuk[2]**

Received: 26 March 2017 / Accepted: 9 June 2017 / Published online: 22 June 2017


**Abstract** Neurodegeneration with brain iron accumulation (NBIA) is a heterogeneous group of inherited neurologic disorders with iron accumulation in the basal ganglia, which share magnetic resonance (MR) imaging characteristics, histopathologic and clinical features. According to the affected basal nuclei, clinical features include extrapyramidal movement disorders and varying degrees of intellectual disability status. The most common NBIA subtype is caused by pathogenic variants in *PANK2*. The hallmark of MR imaging in patients with *PANK2* mutations is an eye-of-the-tiger sign in the globus pallidus. We report a 33-year-old female with a rare subtype of NBIA, called beta-propeller protein-associated neurodegeneration (BPAN) with a hitherto unknown missense variant in *WDR45*. She presented with BPAN's particular biphasic course of neurological symptoms and with a dominant iron accumulation in the midbrain that enclosed a spotty T2-hyperintensity.

**Keywords** Substantia nigra · Beta-propeller protein-associated neurodegeneration (BPAN) · Neurodegeneration with brain iron accumulation (NBIA) · Static encephalopathy in childhood with neurodegeneration in adulthood (SENDA)

✉ Elke Hattingen
Elke.Hattingen@ukb.uni-bonn.de

[1] Department of Radiology, Neuroradiology, University Hospital of Bonn, Sigmund-Freud Straße 25, 53127 Bonn, Germany

[2] Department of Radiology, University Hospital of Bonn, Bonn, Germany

[3] Department of Human Genetics, University Hospital of Bonn, Bonn, Germany

[4] Department of Human Genetics, Ruhr-University Bochum, Bochum, Germany

## Background

Neurodegeneration with brain iron accumulation (NBIA) occurs rarely with an estimated prevalence of less than 1/1000000 [1].

Ten subtypes have been detected including idiopathic NBIA based on their corresponding gene mutations. Pantothenate kinase-associated neurodegeneration (PKAN) represents almost 35–50% of all clinical NBIA cases, followed by PLA2G6-associated neurodegeneration (PLAN), mitochondrial membrane-associated neurodegeneration (MPAN) and BPAN [2]. Currently therapy focusses on symptoms.

Iron accumulation, mainly in the form of ferritin, is a physiological aging process and is seen as hypointense areas in T2-weighted (w) images, and as prominent signal loss on T2*-w images [3].

PKAN is caused by compound heterozygous or homozygous pathogenic variants (autosomal recessive inheritance) in the *PANK2* gene [4]. Classic PKAN often begins with gait abnormalities in childhood followed later by rapidly progressive extrapyramidal signs, whereas atypical PKAN phenotypes include an adult onset with speech difficulties and psychiatric disturbances and a slower clinical progression. Characteristic finding in T2-weighted images is the so-called eye-of-the-tiger sign, a hyperintense signal central in the globus pallidus surrounded by a hypointense area. Hypointensity is caused by excessive iron accumulation and hyperintensity was supposed to be related to gliosis, neuronal loss and elevated water content [5].

BPAN is the only X-linked, very rare form of NBIA. BPAN represents with a particular biphasic clinical course, which begins with a relatively stable encephalopathy in childhood and changes into a progressive neurodegeneration with corresponding neurological deterioration in early adulthood. Therefore, BPAN is also known as "SENDA", meaning static encephalopathy in childhood with neurodegeneration in adulthood. Until now, only 7% of cases in NBIA have been diagnosed with BPAN [1]. BPAN is caused by heterozygous or hemizygous pathogenic variants in the WD repeat-containing protein 45 (WDR45) gene, located at Xp11.23. All categories of variants have been reported, most of them are private mutations in exon 3–12 [6]. *WDR45* mutations are linked to dysfunctional autophagy resulting in neuronal dyshomeostasis [7, 8]. To date, most of the affected individuals have been female assuming an X-linked dominant mode of inheritance. Presumably, males with germline WDR45 mutations are nonviable. Variable expression or reduced penetrance in females and the fact of surviving males, who are affected similar to females, are explained by somatic mosaicism in males and females and skewing of X chromosome inactivation in females [6]. The vast majority of patients with BPAN are simplex cases. Clinical symptoms often include development delay, ataxic gait, seizures and spasticity in childhood and a neurological deterioration in early adulthood (mean 25.3 years) with dystonia, parkinsonism and further cognitive impairment [1, 9]. In contrast to other variants of NBIA, iron accumulation firstly occurs in the substantia nigra, resulting in a stronger iron deposition compared to the globus pallidus [1]. MRI of BPAN patients reveals hypointensities on T2-weighted images in the globus pallidus and substantia nigra as well as cerebral and cerebellar atrophy. Furthermore, T1-weighted images show hyperintensity with a central hypointense band in substantia nigra [2, 9].

## Case Presentation

A 33-year-old woman presented at our hospital with gait disturbance and spontaneous drops without adverse-effects reflexes, resulting in injuries of the face and teeth. She had a parkinsonian gait with short and shuffling steps and body rotation was impaired. Furthermore, she showed increasing oral motor dysfunction with dysphagia.

Medical history revealed global developmental delay in childhood with mild spasticity and language impairment. She had seizures with loss of consciousness and absences, which started at the age of 3 and decreased considerably in frequency without ceasing completely. During adolescence, neurological impairments were stable until the age of 27, when deterioration of gait disturbance occurred.

No other family member had similar symptoms, the patient had two healthy brothers and a healthy mother, her father and grandfather died of aortic rupture of unknown cause.

MR imaging at the age of 33 years revealed a marked T2-hypointensity in the substantia nigra which was more pronounced than in the globus pallidus (Fig. 1). In these hypointense areas, susceptibility-weighted images (SWI) showed excessive signal loss, also known as "blooming", caused by the iron deposition. In addition, there was a bilateral central small T2-hyperintense spot within the hypointense area of the midbrain. We interpreted these symmetrical small spots as a comparable pathology to the more pronounced "eye" in the pallidum of PKAN patients, al-

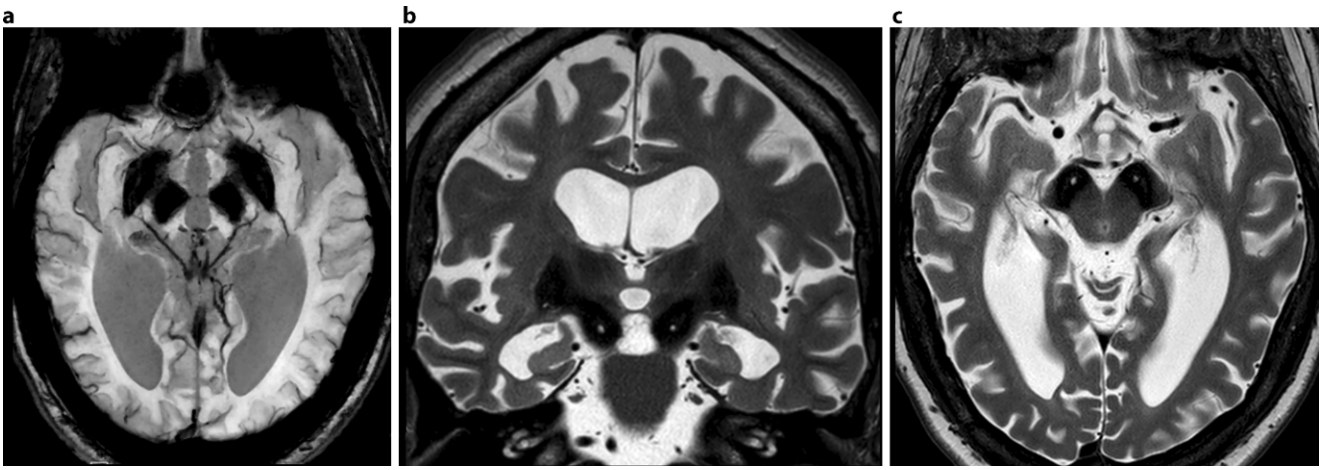


**Fig. 1** **a** Axial susceptibility-weighted image (SWI) shows excessive iron deposition in the substantia nigra and in the globus pallidus due to neurodegeneration. **b** Coronal T2-weighted image presents two hyperintense tiny spots in the substantia nigra surrounded by hypointense signal. In contrast, the globus pallidus lacks central hyperintensities. Also note that there is a global atrophy of the brain, with enlargement of the ventricles, the Sylvian fissure, and the sulci of the convexity and of the mesiotemporal region. **c** Corresponding axial T2-weighted slice shows the hypointense regions that enclose a small and rounded T2-weighted hyperintense spot on each side

though we cannot rule out that these spots are only enlarged Virchow robin spaces included by the iron depositions. However, their exactly symmetric location, the round form, and the absence of adjacent dilated spaces argue against this hypothesis. The previously reported T1-hyperintensity with a central hypointense band in substantia nigra was missing [2, 9].

Mutational analyses were done by high resolution melting (HRM) followed by direct sequencing of atypical curves showing that the patient was carrying a previously not described heterozygous missense variant in the *WDR45* gene, which was strongly suspected to be pathogenic [10].

The mutation was not identified in patient's mother as the only living parent, so that this mutation was assumed to be de novo.

In conclusion, patients with biphasic extrapyramidal symptoms and cognitive impairments starting in childhood and deteriorating in young adulthood should be tested for BPAN. MRI can identify iron deposits which are typical for NBIA, while the enclosing T2-hyperintensity in the pallidum is typically absent or, as in our BPAN patient, may occur as small spots in other deep brain nuclei.

**Conflict of interest** E. Hattingen is a consultant for the Fraunhofer Institut Frankfurt. N. Handke, K. Cremer, S. Hoffjan and G.M. Kukuk declare that they have no competing interests.

## References


1. Hogarth P. Neurodegeneration with brain iron accumulation: diagnosis and management. J Mov Disord. 2015;8:1–13.
2. Gregory A, Hayflick S. Neurodegeneration with brain iron accumulation disorders overview. In: GeneReviews(R). Seattle: University of Washington; 2016.
3. Drayer BP. Magnetic resonance imaging and extrapyramidal movement disorders. Eur Neurol. 1989;29(Suppl 1):9–12.
4. Hartig MB, Hortnagel K, Garavaglia B, Zorzi G, Kmiec T, Klopstock T, Rostasy K, Svetel M, Kostic VS, Schuelke M, Botz E, Weindl A, Novakovic I, Nardocci N, Prokisch H, Meitinger T. Genotypic and phenotypic spectrum of PANK2 mutations in patients with neurodegeneration with brain iron accumulation. Ann Neurol. 2006;59:248–56.
5. Guillerman RP. The eye-of-the-tiger sign. Radiology. 2000;217: 895–6.
6. Haack TB, Hogarth P, Kruer MC, Gregory A, Wieland T, Schwarzmayr T, Graf E, Sanford L, Meyer E, Kara E, Cuno SM, Harik SI, Dandu VH, Nardocci N, Zorzi G, Dunaway T, Tarnopolsky M, Skinner S, Frucht S, Hanspal E, Schrander-Stumpel C, Héron D, Mignot C, Garavaglia B, Bhatia K, Hardy J, Strom TM, Boddaert N, Houlden HH, Kurian MA, Meitinger T, Prokisch H, Hayflick SJ. Exome sequencing reveals de novo WDR45 mutations causing a phenotypically distinct, X-linked dominant form of NBIA. Am J Hum Genet. 2012;91:1144–9.
7. Dall'Armi C, Devereaux KA, Di Paolo G. The role of lipids in the control of autophagy. Curr Biol. 2013;23:R33–R45.
8. Lu Q, Yang P, Huang X, Hu W, Guo B, Wu F, Lin L, Kovács AL, Yu L, Zhang H. TheWD40 repeat PtdIns(3)P-binding protein EPG-6 regulates progression of omegasomes to autophagosomes. Dev Cell. 2011;21:343–57.
9. Hayflick SJ, Kruer MC, Gregory A, Haack TB, Kurian MA, Houlden HH, Anderson J, Boddaert N, Sanford L, Harik SI, Dandu VH, Nardocci N, Zorzi G, Dunaway T, Tarnopolsky M, Skinner S, Holden KR, Frucht S, Hanspal E, Schrander-Stumpel C, Mignot C, Héron D, Saunders DE, Kaminska M, Lin JP, Lascelles K, Cuno SM, Meyer E, Garavaglia B, Bhatia K, de Silva R, Crisp S, Lunt P, Carey M, Hardy J, Meitinger T, Prokisch H, Hogarth P. β-Propeller protein-associated neurodegeneration: a new X-linked dominant disorder with brain iron accumulation. Brain. 2013;136:1708–17.
10. Tschentscher A, Dekomien G, Ross S, Cremer K, Kukuk GM, Epplen JT, Hoffjan S. Analysis of the C19orf12 and WDR45 genes in patients with neurodegeneration with brain iron accumulation. J Neurol Sci. 2015;349:105–9.