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Clinical Report

Early manifestations of epileptic encephalopathy, brain atrophy, and elevation of serum neuron specific enolase in a boy with beta-propeller protein-associated neurodegeneration

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ABSTRACT

Mutations in *WDR45* are responsible for beta-propeller protein-associated neurodegeneration (BPAN), which is an X-linked form of neurodegeneration with brain iron accumulation. BPAN mainly affects females and is characterized by seizures and developmental delay or intellectual disability until adolescence or early adulthood, followed by severe dystonia, parkinsonism, and progressive dementia. However, rare male patients have recently been reported with hemizygous germline mutations in *WDR45* and severe clinical manifestations, such as epileptic encephalopathies. We report here a 4-year-old boy presenting with profound developmental delay, non-syndromic epileptic encephalopathy, and early brain atrophy. The level of serum neuron specific enolase (NSE) was elevated, but the level of serum phosphorylated neurofilament heavy chain was not detectable. Targeted next-generation sequencing identified a *de novo* hemizygous splice donor site mutation, c.830+1G > A in *WDR45*, which resulted in a splicing defect evidenced by reverse transcriptase-PCR. Mutations in *WDR45* should be considered as a cause for epileptic encephalopathies in males with profound developmental delay and brain atrophy. Furthermore, elevation of serum NSE may contribute to early diagnosis of BPAN.

1. Introduction

Mutations in *WDR45*, an autophagy-related gene located at Xp11.23, are responsible for beta-propeller protein-associated neurodegeneration (BPAN, OMIM#300894), which is a subtype of neurodegeneration with brain iron accumulation (Haack et al., 2012; Hayflick et al., 2013; Saitsu et al., 2013). BPAN is characterized by early-onset seizures and developmental delay or intellectual disability until adolescence or early adulthood, followed by severe dystonia, parkinsonism, and progressive dementia in early adulthood. Brain magnetic resonance imaging (MRI) showed characteristic findings typically after late childhood, including iron deposition in the bilateral globus pallidus (GP) and substantia nigra (SN), hyperintensity of the SN with a central band of hypointensity in T1-weighted images, and brain atrophy. Previously, it was suggested that BPAN is inherited in an X-linked dominant pattern with presumed male lethality because of apparent bias of the male-to-female ratio and evidence of a male patient with somatic mosaicism for a mutation in *WDR45* presenting with the same symptoms as female patients (Haack et al., 2012). However, rare male patients have recently been reported with hemizygous germline mutations in *WDR45* who are more severely affected than female patients (Abidi et al., 2016; Nakashima et al., 2016; Zarate et al., 2016) (Table 1). Patients with BPAN have also been reported to develop epileptic encephalopathies (EEs), including West syndrome (WS) (Epi4K Consortium et al., 2013; Xixis and Mikati, 2015; Abidi et al., 2016; Nakashima et al., 2016). It is becoming apparent that a wide spectrum of BPAN ranges from mild cognitive delay to EEs (Long et al., 2015).

Previously, it was reported that the serum level of neuron specific enolase (NSE) was elevated in three girls and a boy with BPAN

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Table 1
Male patients with BPAN.

	Epileptic encephalopathies						Non-epileptic encephalopathies				
Patient	Present patient	Epi4K et al., ND30965	Abidi et al.	Nakashima et al. Patient 1	Nakashima et al. Patient 2	Nakashima et al. Patient 3	Hayflick et al., 63 708	Hayflick et al., 49 841	Hayflick et al. HS463	Zarate et al.	Spiegel et al., 2016
Age (years)	4	NA	5	1	2	7	37	31	31	20	2
***WDR45* mutation**	c.830+1G > A splicing defect	c.882_883 del p.Gln295fs	19.9 kb deletion involving *WDR45*	c.131-1G > A splicing defect	c.248G > A p.Trp83*	c.400C > T p.Arg134*	c.228_229 del p.Glu76fs	c.19dup p.Arg7fs	c.1025_1034 delinsACATATT p.Gly342fs	c.161_163del p.Val54del	c.1007_1008del p.Tyr336fs
Inheritance	*de novo*	*de novo*	*de novo*	*de novo*	*de novo*	maternal[a]	*de novo*	NA	NA	maternal[a]	*de novo*
Somatic mosaicism	– [b]	NA	–	–	–	–	NA	NA	+	–	+
Present neurological findings											
DD or ID	+	NA	+	+	+	+	+	+	+	+	+
Speech	nonverbal	NA	nonverbal	nonverbal	nonverbal	nonverbal	limited	limited	limited	nonverbal	nonverbal
Motor	bedridden	NA	bedridden	bedridden	bedridden	bedridden	NA	NA	NA	wheelchair-bound	bedridden
Age at regression	1.3 yrs	NA	–	–	–	–	27 yrs	28 yrs	26 yrs	–	–
Sleep disturbance	–	NA	NA	NA	NA	NA	–	+	–	sleep apnea	NA
Rett-like features	–	NA	NA	NA	NA	NA	–	–	–	NA	NA
Spasticity	quadriparesis	NA	quadriplegia	–	–	lower extremities	NA	NA	NA	quadriplegia	NA
Hypotonia	+	NA	+	–	–	+	NA	NA	NA	NA	+
Extrapyramidal signs	–	NA	+	–	–	–	+	+	+	NA	NA
Eye problems	optic disc atrophy	NA	cortical blindness	NA	NA	Leber congenital amaurosis	–	increased VEP latency	–	myopia, astigmatism	NA
Microcephaly	–	NA	–	NA	NA	NA	NA	NA	NA	–	NA
Epilepsy	+	+	+	+	+	+	–	+	+	+	–
Onset	14 mos	6 mos	3 mos	6 mos	5 mos	5 mos	–	NA	NA	3 yrs	–
Diagnosis	non-syndromic EE	WS	EOEE	WS	WS	WS	–	febrile Sz	absence or atonic Sz	NA	generalized encephalopathy
Brain MRI											
Brain atrophy	+ at 4 mos	NA	+ at 7 mos	+ at 7 mos	+ at 8 mos	+ at 8 mos	+	+	+	+ at 3 yrs	+
Myelination delay	–	NA	NA	+	+	+	NA	NA	NA	NA	–
Iron deposition (image)	– (T2WI) at 3 yrs	NA	+ GP, SN, RN (SWI) at 5 yrs	–	–	+ GP, SN (SWI) at 4 yrs	+	+	+	+ GP, SN (T2WI) at 20 yrs	–
Serum NSE (ng/mL)	83, 96	NA	NA	NA	NA	69.4	NA	NA	NA	NA	NA

WDR45: NM_007075.3, DD: developmental delay, ID: intellectual disability, yrs: years, mos: months, NA: not available, EE: epileptic encephalopathy, EOEE: early-onset epileptic encephalopathy, WS: West syndrome, Sz: seizure, GP: globus pallidus, SN substantia nigra, RN: red nucleus, SWI: susceptibility-weighted imaging, T2WI: T2-weighted imaging.

[a] Maternal somatic mosaicism.

[b] Tested in peripheral leukocytes.