A Novel *WDR45* Mutation in a 9-Month-Old Male Infant with Epileptic Spasms

Wan-Ting Liu[1], Qian Chen[1], Zhi-Jie Gao[1], Xin-Na Ji[1], Ke-Ming Xu[1], Yan-Yan Cao[2]

[1]Department of Neurology, Capital Institute of Pediatrics, Beijing 100020, China
[2]Department of Genetics, Capital Institute of Pediatrics, Beijing 100020, China

To the Editor: Neurodegeneration with brain iron accumulation (NBIA) comprises a group of disorders that manifest as early- or late-onset parkinsonism, dystonia, spasticity, and cognitive impairment.[1] One subtype of NBIA, β-propeller protein-associated neurodegeneration (BPAN), is caused by mutation of the *WDR45* gene. To date, 59 novel *WDR45* mutations have been reported. The literature indicates that it is difficult to detect the disorder in early childhood because no specific clinical or imaging features exist. In this report, we describe the case of a 9-month-old male Chinese infant with a novel mutation (c.977-1 C>T) in the *WDR45* gene.

The patient was a 9-month-old male infant who was born to nonconsanguineous parents and who had a healthy elder sister. He was born at full term, with an uneventful delivery without asphyxia and a birth weight of 3400 g. There was no family history of other hereditary or neurological disorders. At the age of approximately 3 months, the patient first presented with epileptic spasm, manifesting as bilateral eye gazing toward the right or left with head deviation, followed by generalized tonic-clonic seizures, which lasted several minutes and occurred in clusters of 2–4 per day with approximately four spams per cluster. Developmental delay was not observed until the age of 6 months, at which time he demonstrated a lack of head control, poor eye contact, and lower limb hypertonia. At the age of 9 months, he was referred to our hospital for etiologic diagnosis. His height was 73 cm, weight was 3400 g, and occipitofrontal circumference was 43 cm, with a closed fontanel. Physical examination identified a series of dysmorphic features, including epicanthal folds, a flat nasal bridge, bilaterally low-set ears, and orbital hypertelorism. Neurological examination revealed no head control, poor eye contact, no social smile, and lower limb hypertonia.

Laboratory tests revealed mild elevation in the following parameters: serum aspartate transaminase, 110.8 U/L (normal range: 0–40 U/L); lactate dehydrogenase, 431 U/L (normal range: 80–300 U/L); and α-hydroxybutyrate dehydrogenase, 375 U/L (normal range: 120–260 U/L). Levels of other liver enzymes were within normal range. No abnormalities were detected in the liver, heart, or muscles on abdominal ultrasound, echocardiogram, and electrocardiogram. Video electroencephalogram revealed hypsarrhythmia consisting of bilateral high-amplitude irregular slow waves mixed with multifocal spikes or polyspikes in the interictal period, and clusters of spasms and transient tonic attacks were recorded. Brain magnetic resonance imaging (MRI) revealed global atrophy, leukomalacia, and thinning of the corpus callosum [Figure 1a]. No iron accumulation could be detected on T1- and T2-weighted MRI, and we did not perform T2-weighted imaging, which have greater sensitivity for detecting iron accumulation. Visual evoked potentials presented with increased latency. The left auditory brainstem response (ABR) threshold was 50 dB (16–20 dB), while the threshold of the right ABR was normal. The latencies of waves I, II, and V were increased within the left ABR, especially for wave I, the latency of which also increased within the right ABR. The latencies of remaining waves of the right ABR were normal. Ranger sequencing analysis revealed a novel heterogeneous splicing mutation (c.977-1 C>T) in *WDR45* (transcript variant 1, NM_00707) [Figure 1b].

To the best of our knowledge, the present report describes the case of the youngest patient ever diagnosed as having BPAN. In addition to the typical clinical phenotypes such as developmental delay, nonspecific dysmorphic features, and global brain atrophy on neuroimaging, the patient presented with epileptic spasm as the initial symptom. Exome sequencing revealed a novel *WDR45* mutation, which resulted in a definitive diagnosis of BPAN. Thus, this report describes the course and clinical features of the early phase of this disorder, which might enable early detection of this disease.

Xixis and Mikati first reported epileptic spasms as a clinical phenotype of BPAN.[1] To date, BPAN manifesting with epileptic spasms has been diagnosed in only five patients.[1,2] The present patient displayed his first epileptic spasm at the age of 2 months, which is before psychomotor delay generally becomes noticeable. Thus, epileptic spasm might be an initial clinical phenotype in patients with BPAN. In addition, Okamoto *et al*.[3] and Takano *et al*.[2] also reported facial features and mild elevation of serum enzymes, which are consistent with the findings in the present case.

Address for correspondence: Dr. Qian Chen, Department of Neurology, Capital Institute of Pediatrics, Beijing 10020, China
E-Mail: chenqianxhl@163.com

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.247216

Received: 07-09-2018 **Edited by:** Qiang Shi
How to cite this article: Liu WT, Chen Q, Gao ZJ, Ji XN, Xu KM, Cao YY. A Novel *WDR45* Mutation in a 9-Month-Old Male Infant with Epileptic Spasms. Chin Med J 2018;131:2991-2.

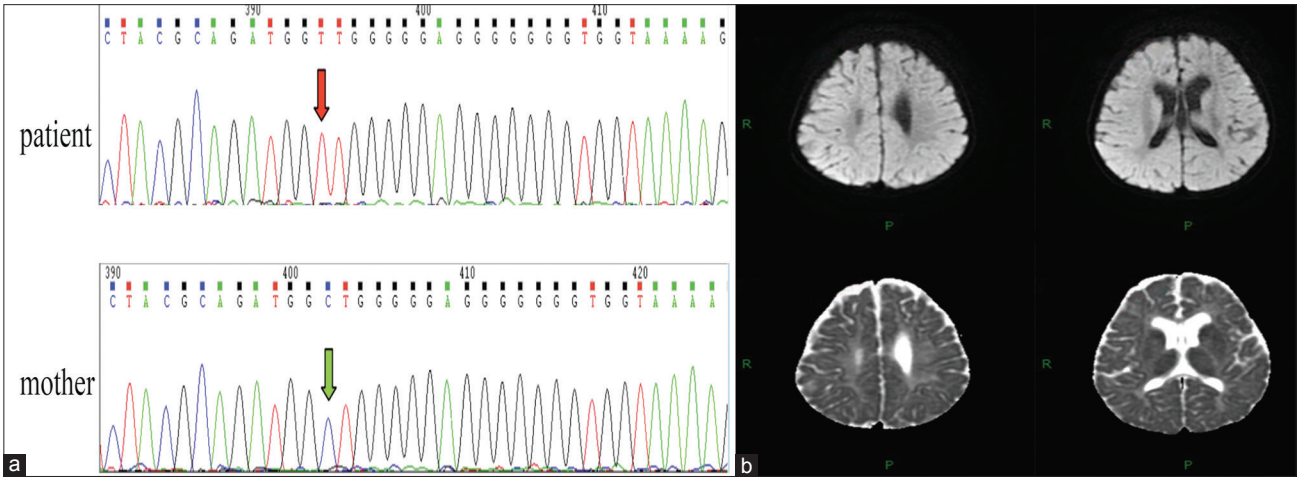

Figure 1: (a) Brain MRI performed at 9 months of age revealed a global loss of brain volume, leukomalacia, and thinning of the corpus callosum. No iron accumulation could be detected on T1- and T2-weighted MRI. (b) Sanger sequencing of WDR45 revealed a novel mutation (c.977-1 C>T) in the patient but not his mother. MRI: Magnetic resonance imaging.

These symptoms might help clinicians screen suitable candidates for genetic testing.

In previous literature, hearing defects have not been reported. The left ABR threshold of our patient was 50 dB (16–20 dB), which is a new clinical phenotype of BPAN. Moreover, the latencies of ABR waves I, III, and V were increased within the left ABR, especially for wave I, which indicates dysfunction of the peripheral auditory neurological system.

The low incidence of BPAN in males is caused by male lethality and the existence of somatic mosaicism.[1] According to published reports, nine male patients have been identified with BPAN, including our patient.[3] While seven of them presented with seizures, five of them presented with their first seizure before the age of 6 months. It indicates that male patients tend to have more severe phenotypes in early childhood. Although genetic testing of peripheral blood lymphocytes from the patient's mother revealed no mutation, somatic mutation cannot be excluded.[4]

To date, there is no effective treatment for BPAN. One case reveals that ketogenic diet is effective in controlling the epileptic spasms; however, more cases are needed to confirm this effect.[3]

In conclusion, we report the case of a 9-month-old male infant with a definitive diagnosis of BPAN and a novel *WDR45* mutation. In addition to the typical developmental delay, we also noted clinical features such as early-onset epilepsy, dysmorphic features, and cerebral atrophy on MRI. These findings should be considered when screening patients for early exome sequencing of *WDR45* mutation, which could lead to a reduction in unnecessary clinical examinations.

Declaration of patient consent

The authors certify that they have obtained all appropriated patient consent forms. In the form, the parents have given their consent for the patient's images and other clinical information to be reported in the journal. They understand that the patient's name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

This work was supported by a grant from the Capital Development Funds (No. 2016-2-2103).

Conflicts of interest

There are no conflicts of interest.

References

1. Xixis KI, Mikati MA. Epileptic spasms: A previously unreported manifestation of WDR45 gene mutation. Epileptic Disord 2015;17:467-72. doi: 10.1684/epd.2015.0784.
2. Takano K, Shiba N, Wakui K, Yamaguchi T, Aida N, Inaba Y, *et al.* Elevation of neuron specific enolase and brain iron deposition on susceptibility-weighted imaging as diagnostic clues for beta-propeller protein-associated neurodegeneration in early childhood: Additional case report and review of the literature. Am J Med Genet A 2016;170A: 322-8. doi: 10.1002/ajmg.a.37432.
3. Okamoto N, Ikeda T, Hasegawa T, Yamamoto Y, Kawato K, Komoto T, *et al.* Early manifestations of BPAN in a pediatric patient. Am J Med Genet A 2014;164A: 3095-9. doi: 10.1002/ajmg.a.36779.
4. Zhao YG, Sun L, Miao G, Ji C, Zhao H, Sun H, *et al.* The autophagy gene wdr45/Wipi4 regulates learning and memory function and axonal homeostasis. Autophagy 2015;11:881-90. doi: 10.1080/15548627.2015.1047127.