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Case Report

A rare cause of epileptic encephalopathy: a beta-propeller protein associated neurodegeneration case with a new mutation and literature review

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ABSTRACT

In this report, detailed clinical features of a female patient and a new mutation that was not previously identified in the WD repeat-containing protein 45 (WDR45) gene are presented in order to contribute to the information in the literature on the phenotype as well as genotype of Beta-Propeller Protein Associated Neurodegeneration. Whole Exome Sequencing (WES) analysis was done since etiology could not be determined. Our case was admitted to the hospital due to epilepsy, growth retardation and autism. Her family history was unremarkable except consanguineous marriage. She had tonic seizures twice at the age of 7 and 12 months and had continual seizures after 16 months. At the time, electroencephalography and brain MRI were performed twice were determined to be normal. Brain MRI Spectroscopy was also found to be normal at 35 months of age. Metabolic screening tests (acyl carnitine profile, urine organic acids, plasma amino acids, a very long chain fatty acid profile, etc.) were also normal. Genetic screening of the epilepsy panel for epileptic encephalopathies was negative. WES analysis revealed heterozygous previously unreported variant in intron 6 of the WDR45 gene, c.344+5G>A. In conclusion; Beta-Propeller Protein Associated Neurodegeneration should be considered as an option in the diagnosis of female patients with clinical findings of epilepsy, growth retardation and autism, with unspecified etiology.

Key words: beta-propeller protein associated neurodegeneration, WDR45 gene mutation, epileptic encephalopathy.

Beta-Propeller Protein Associated Neurodegeneration (BPAN), also known as Neurodegeneration with Brain Iron Accumulation type 5 (NBIA5) (OMIM # 300894) is an X-linked transient disease, mostly caused by de novo mutation in the WD repeat-containing protein 45 (WDR45) gene.[1-3] Mitochondrial abnormalities, autophagic defects, decrease in lysosomal functions, cellular iron accumulation and increase in oxidative stress can develop in the patient. The prevalence of NBIA group disorders is estimated to be less than 1/1.000.000.[4] The clinical course of the disease consists of two phases. The first phase begins in childhood and early-onset seizures, developmental retardation, cognitive impairment, speech disorder, motor dysfunctions such as ataxia, and behavioral disorders specific to autism spectrum can be seen. The second phase is subacute and begins in adolescence or early adulthood, presenting with neurological deterioration characterized by parkinsonism, dystonia and dementia.[5,6]

The diagnosis of suspected BPAN is based on clinical findings and hypo-intensity, suggestive of iron accumulation in brain magnetic resonance imaging (MRI).[7,8] The definitive diagnosis is established by means of molecular testing, identifying a heterozygous WDR45 pathogenic variant in females, and a hemizygous WDR45 pathogenic variant or deletion of WDR45 in males. Somatic mosaism has been reported rarely in girls.[1]

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There is no definite cure of BPAN. Supportive treatment is given for seizures and movement disorders.[9]

In this report, detailed clinical features of a female patient with non-syndromic epileptic encephalopathy, growth retardation, autism, and a new mutation that was not previously identified in the WDR45 gene are presented, in order to contribute to the information in the literature on the phenotype as well as genotype of the disease.

Case Report

Clinical History

A 40-month-old girl presented with epilepsy and growth retardation. After an eventless pregnancy, she was born at 37 weeks, weighted 3000 gram and without asphyxia. Developmental milestones: head control at 5 months, sitting without support at 11 months, walking at 21 months, first word at 25 months of age. Her parents had consanguineous marriage. She had two healthy brothers, 5 and 6 years old. No family history of any neurological disease was determined. She had the first seizure at the age of 7 months, when she had a fever. She was found to be staring at a fixed point and then having myoclonic jerks. She had a second seizure, similar to the first, at 12 months of age, again when she had a fever. Electroencephalogram (EEG) taken at that time and brain MRI taken to investigate growth retardation were normal. Febrile seizure was considered and that's why an antiepileptic drug was not prescribed. When the patient was 16 months old, phenobarbital (6 mg/kg/day, in 2 doses) was initiated upon having an attack of clonic contractions following fixed gaze in a fever-free period. She had absence, myoclonic and/or tonic seizures for 5-6 times per month despite phenobarbital. Then, pyridoxine (vitamin B6) was initiated. As it failed too, Sodium Valproate was given and continued for 2 months at increased doses (40 mg/kg/day (2 doses)). Afterwards, Sodium Valproate was discontinued and levetiracetam was started, due to the increase in seizures. With levetiracetam (60 mg/kg/day, 2 doses) and phenobarbital combination, her seizures were reduced to 2-3 times per month but increased again to 3-4 per month when she was 35 months of age. When the patient was 36 months old, phenobarbital was discontinued and clobazam (1 mg/kg/day, 2 doses) was started. Two months after starting clobazam, levetiracetam and clobazam combination stopped the seizures completely. The patient had already applied to the child psychiatry department due to speech delay, lack of communication skills, and stereotypic movements at 30 months of age and since then she was followed up with a diagnosis of autism. In the latest examination, her speech was consistent with 36 months of development although her calendar age was 52 months, and her ability to communicate and meet individual needs was consistent with 32 months (Denver Developmental Screening Test). She had gait ataxia, eye contact, moderate mental and speech delay and stereotyped movements. Currently she receives special education support and has had no seizure in 14 months. For this study, written informed consent was obtained from her parents after parents were fully informed.

Laboratory and Imaging

EEG and brain MRI taken when she was 13 months were reported as normal. Brain MRI Spectroscopy was also found to be normal at 35 months of age. Metabolic screening tests (acyl carnitine profile, urine organic acids, plasma amino acids, a very long chain fatty acid profile, etc.) were also normal. Genetic screening of the epilepsy panel for epileptic encephalopathies was negative. Since etiology could not be determined, Whole Exome Sequencing (WES) was requested. No pathological discharge was detected in EEGs repeated at 35 and 45 months of age.

The patient was confirmed as BPAN by means of WES and brain MRI taken repeatedly including T2 axial gradient sequence at 45 months of age. There was no signal change supporting iron accumulation in brain MRI (Fig. 1).

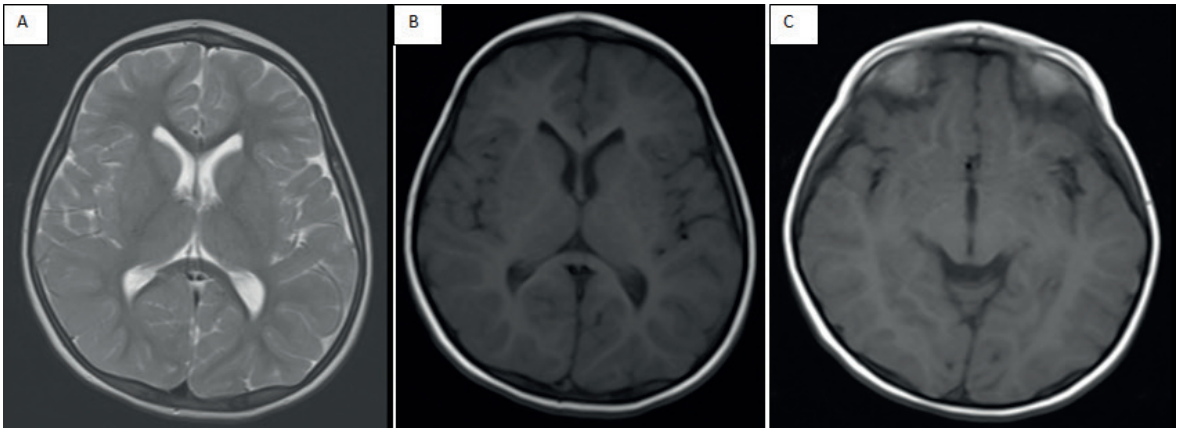

Fig. 1. Brain MRI at 45 months of age shows no evidence of iron deposition. A: T2 Axial Globus Pallidus section, B: T1 Axial Globus Pallidus section, C: T1 Axial Substanti Nigra section.

Genetic Analysis

Genomic DNA was isolated from peripheral blood samples using the QIAamp DNA Blood Mini kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer's instructions. WES analysis revealed heterozygous previously unreported variant in intron 6 of the WDR45 gene, c.344+5G>A (g.48934299C>T) (Centogene, Germany). Detected variant was also analysed and confirmed by Sanger sequencing according to the manufacturer's protocols. Sanger sequence analysis image is shown in Figure 2. The amplicons were analyzed by direct sequencing with ABI 3500 (Life Technologies, Waltham, Massachusetts, USA). Analysis of sequence results was done by Mutation Surveyor Programme (SoftGenetics, USA).The mutation was considered as *de novo* because the genetic analyses of the parents were normal.

Discussion

BPAN is a rare disease with 68 cases reported in the literature so far.[10] Here, we present the case of a female patient presenting with clinic findings of epileptic encephalopathy with a previously unidentified mutation.

The development and common use of the techniques such as MRI, Next-Generation Sequencing (NGS) and WES, facilitated the early diagnosis of the disease and contributed to its awareness.[11] Although iron deposition in the brain has been often described in globus pallidus, it can be seen as hypointensity in areas such as cerebellum and substantia nigra on T2-weighted images, depending on the type of the disease.[7,8] As an additional and specific finding, hyperintense halo can be seen in T1-weighted images of substantia nigra and

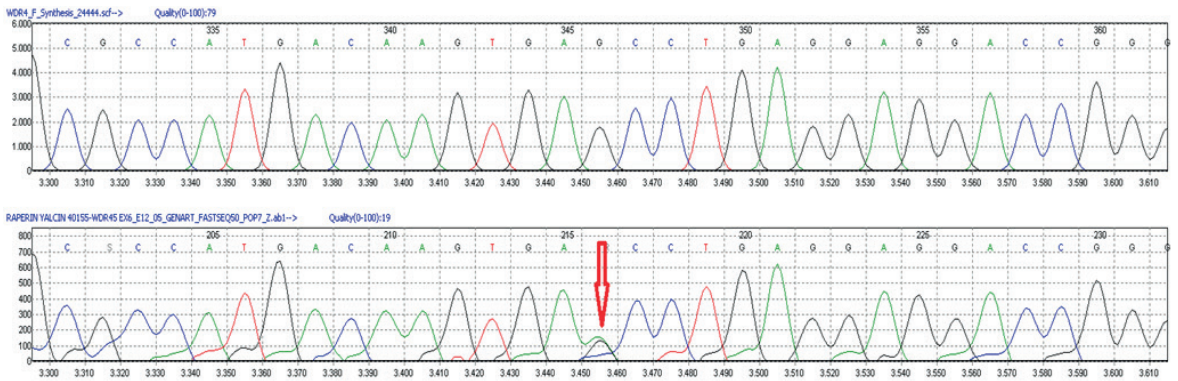

Fig. 2. Sanger sequence analysis of the detected mutation.

cerebral peduncle.[12] However, brain MR can be normal especially in early childhood, as it was in our patient. In some patients, significant signs may develop on brain MRI results in the late period when movement disturbances begin.[1,13] NGS and WES enabled early diagnosis without significant clinical findings and/or iron accumulation in basal ganglia.[1,14]

The clinical presentation of BPAN may show significant phenotypic variance. However, its main characteristic clinical features in childhood are usually early onset seizures with poor treatment response, speech, motor and mental delay. Initially febrile seizures are seen and then non-provocative, tonic, tonic-clonic, absence or myoclonic seizures.[8,15] Epilepsy is usually most severe in childhood and gets mild in later years. Multiple types of seizures can be seen in the same patient.[1] The clinic findings of our patient was consistent with epileptic encephalopathy[16], revealing itself with continuous epileptic activity and neurological and cognitive impairment. Her initial seizures were febrile, then afebrile, absence, tonic-clonic and myoclonic seizures. The decrease in seizures after clobazam may be due to the effect of the drug or the natural course of the disease, alleviating epilepsy at later ages. Another interesting feature in our patient was, despite her frequent seizures, epileptic discharge or ground rhythm irregularity was not detected on the interictal EEG, taken three times. Although the prevalence of NBIA group disorders having neurodegeneration is estimated to be less than one in a million[4], it is probably higher. In a series of 655 patients who had epileptic encephalopathy clinic findings and negative results for known pathogenic variant genes, Carvill et al.[17] screened the patients for the WDR45 gene using the NGS method and determined 7 BPAN patients, where all were females and four of them had previously unspecified mutations.

Morikawa et al.[18] reported 6 patients (2 females and 4 males), having a mutation in the WDR45 gene and a history of infantile spasm. Infantile spasms started before the age of one in 5 patients, and at 46 months of age in one. Only two patients had iron accumulation in the brain. Female patients had milder phenotypic features.[18]

Of the cases published in the literature to date, 85.9% are girls, 67.7% had epileptic seizures, that usually started in childhood, and 90.2% displayed no iron accumulation on brain MR.[10]

As far as we know, this is the first BPAN case in childhood age group, reported from Turkey. Upon mutation database search, the c.344+5G>A mutation detected in the WDR45 gene has not been previously reported. The mutation was considered de novo because of the normal genetic analysis of the parents. Our case contributes to the information in the literature, regarding phenotype with epilepsy, growth retardation and autism, comprising most of the symptoms seen in the first stage of the disease, and also regarding genotype with the new mutation.

In conclusion, BPAN should be considered as an option in the diagnosis of female patients having clinical findings of epilepsy, growth retardation and autism, with unspecified etiology.

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