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Beta-propeller protein associated neurodegeneration (BPAN); the first report of three patients from Iran with de novo novel mutations

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Beta-propeller protein associated neurodegeneration (BPAN) is classified among the neurodegeneration with brain iron accumulation (NBIA) diseases. It is the only one with an X-linked dominant mode of inheritance resulting from mutations in the *WDR45* gene at Xp11.23 [1,2]. Most patients are females and to date all detected mutations have been de novo [1].

Herein we report clinical, genetic and imaging of three Iranian cases of BPAN. All cases underwent thorough neurologic examination and brain MRI. *WDR45* mutation screening was performed to confirm the diagnosis. Evaluation of brain parenchyma and brainstem structures was performed using Transcranial Sonography (TCS).

BPAN1. A 24-year-old woman with three episodes of unprovoked generalized tonic-clonic seizures followed by developmental delay starting at nine months of age. Her situation was stable for the following years until she manifested slowing of movements and recurrent falls in the past year. Neurologic examination revealed a coarse and masked face. Speech was unintelligible. There was hypokinesia and rigidity of limbs and mild dystonia of right foot (Videos 1 & 2). Her brain MRI showed iron deposition in pallidum and substantia nigra (SN) on T2 and FLAIR with a halo sign on T1. Her brain CT scan showed a thin rim of hyperdensity in both cerebral peduncles at the level of SN (Fig. 1A).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.11.012.

BPAN2. This 39-year-old woman was initially diagnosed with cerebral palsy due to mental retardation and mild gait disturbance since early childhood. At the age 32 she developed progressive slowing of movements, festination and freezing of gait. Levodopa and amantadine were started a couple of years earlier leading to mild improvement of symptoms.

Neurologic examination revealed an akinetic rigid Parkinsonism and mild dystonic posture of right fingers and shuffling gait. Her brain MRI showed the same findings as the BPAN1 (Fig. 1B).

BPAN3. A 22-year-old woman with progressive slowing of movements and dysphagia started five years ago. She was not able to stand or walk unaided in the recent years. She had one episode of generalized tonic-clonic seizure when she was one-year-old.

On examination, she was awake and alert, but not able to talk or obey commands. There was prominent dystonic posturing of hands and legs. All limbs were rigid and hypokinetic. She had severe postural instability and walked slowly with bilateral support (Videos 3 & 4).

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Brain CT scan revealed hyperdensity in globus pallidi (Fig. 1C).

A summary of the clinical features of the patients was presented in Table S1.

On TCS we found increased echogenicity of SN and increased diameter of third ventricle in all cases. The echogenicity of Lentiform nucleus (LN) was increased in one patient (Table S2 and Fig.S1).

Regarding the genetic results in total, three novel candidate disease-causing variations were detected in the *WDR45* gene, which were not observed in the public databases and predicted to have deleterious effects on protein structure. All variations were heterozygous de novo mutations and were not detected in their parents (Table S1 and Fig.S2).

BPAN was formerly known as static encephalopathy of childhood with neurodegeneration in adulthood (SENDA) is a biphasic disease, patients present with developmental delay and mental insufficiency in early childhood and develop severe neurologic deterioration mainly characterized by Parkinsonism and further cognitive decline in adolescence or early adulthood. The patients are stable between these two phases. Other clinical features of BPAN are language dysfunction, epilepsy and Rett-like behaviours [2,3].

Abbreviations: NBIA, Neurodegeneration with brain iron accumulation; BPAN, Beta propeller protein associated neurodegeneration; SENDA, Static encephalopathy of childhood with neurodegeneration in adulthood; TCS, Transcranial sonography; SN, Substantia nigra; LN, Lentiform nucleus

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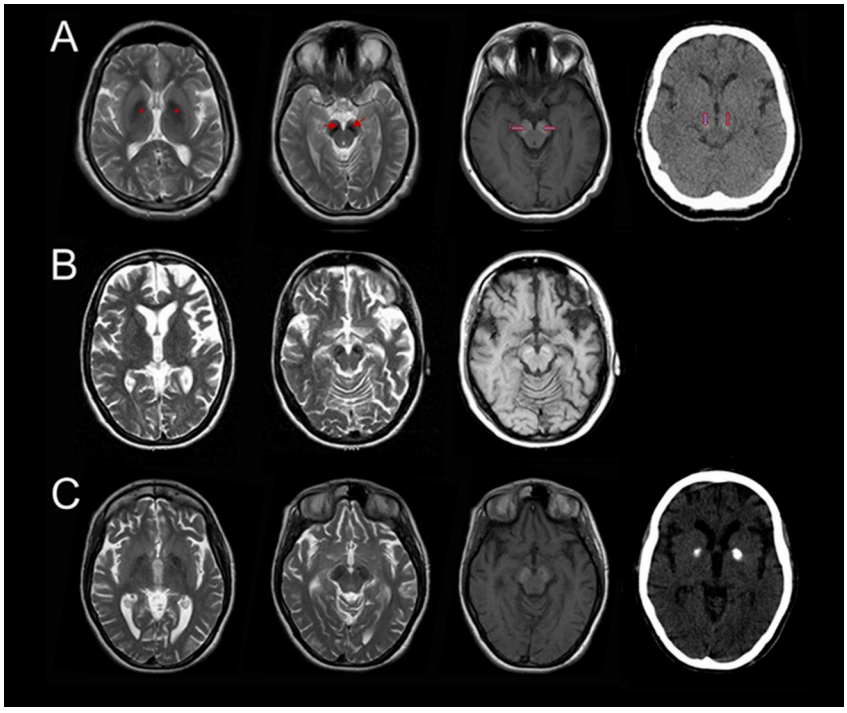

Fig. 1. Brain Imaging of cases BPAN1 (A), BPAN2 (B) and BPAN3 (C). Axial T2 MRI sequences showing mild hypointensity of globus pallidus (first column, red stars) and significant hypointensity of substantia nigra (second column, red arrows). Axial T1 MRI sequences demonstrate Halo sign in cerebral peduncles (third column, right and left arrows). Brain CT scan of BPAN1 shows hyperdensity of bilateral substantia nigra and BPAN3 showing hyperdensity of both pallidi (fourth column, down arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Like all NBIAs, the brain MRI in BPAN displays signal changes in the basal ganglia which corresponds to iron deposition; but in contrast to other NBIAs, with greater signal changes in the SN rather than the globus pallidus (GP), and a distinct midbrain signal on T1-weighted images called the halo sign [1,3]. There are two case reports showing calcification of basal ganglia in patients with BPAN [4]. BPAN1 and BPAN 3 showed calcification of SN nigra and globus pallidus on CT scan respectively.

There are few case studies on TCS in two subgroups of NBIAs showing increased echogenicity of SN and LN in Pantothenate Kinase-Associated Neurodegeneration (PKAN) and LN in Mitochondrial-membrane Protein-Associated Neurodegeneration (MPAN) patients [5]. We used TCS in our cases which is a relatively simple procedure which looks an appropriate modality for detection of iron deposition in the basal ganglia and midbrain.

In conclusion we report the first three cases of BPAN from the Middle East. All had novel mutations in *WDR45* gene with typical clinical features and brain MRI. TCS showed increased diameter of third ventricle (DTV), and hyperechogenicity of the SN while LN was hyperechogenic in only one of our patients.

We declare that written informed consent has been provided from the patients' parents to the publication of their photographs and videos, in both the printed and online modalities.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.11.012.

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Parkinsonism and Related Disorders 61 (2019) 231–233

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