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Correspondence

Atypical late presentation of BPAN in a male: A case report

Dear Editor,

Beta-propeller protein-associated neurodegeneration (BPAN), the only currently known X-linked dominant neurodegeneration with brain iron accumulation (NBIA) syndrome, is characterized by severe intellectual disability in infancy, including infantile seizure disorders and pervasive behavioural disturbances. Movement disorders and dementia typically occur years after this initial static phase of developmental delay [1,2].

Despite having been recognized as a clinico-radiological syndrome for a number of years [3], the causative mutation in the *WDR45* gene was only recently identified through exome sequencing [2]. The gene encodes a WD40 repeat protein, which regulates the assembly of multiprotein complexes involved in normal cerebral development and autophagy.

Given the X-linked dominant inheritance, male lethality *in utero* was initially presumed and indeed the majority of cases reported have been females with heterozygous germline mutations. A recent review of published literature found 64 genetically confirmed cases, nine of which were in males [4]. Most of the male cases presented with more severe features but a few had clinical phenotypes which were undistinguishable from the female patients; this is thought to be due to two mechanisms. Firstly, males with post-zygotic mutations exhibit somatic mosaicism [2], with the severity of the phenotype depending on the time-point at which the mutation occurred during embryogenesis. Secondly, skewed X-chromosome inactivation in females [2] leads to heterozygous females being functionally mosaic and explains the variability in phenotype. The vast majority of cases are de novo mutations; however, a germline mutation has been described causing a severe phenotype in a male and a milder presentation in his sister, with the asymptomatic mother found to be mosaic for the same mutation [5]. One male with somatic mosaicism has thus far been confirmed [2].

We report the case of a 44-year old man with a one-year history of slowing of movement. He was the product of a normal pregnancy, although reportedly suffered perinatal respiratory problems requiring resuscitation. Family history was unremarkable, including non-consanguineous parents and 3 healthy siblings. He exhibited moderate developmental delay, acquiring speech at a late age (6–7) despite achieving grossly normal motor function. This was attributed to cerebral palsy secondary to presumed perinatal hypoxia. He developed gait hesitation and freezing at the age of 43, as well as a left-sided postural tremor and impaired dexterity. There were no new cognitive or behavioural changes. Examination revealed mild facial hypomimia, normal eye movements and moderate axial rigidity. Speech output was reduced but he was not dysarthric. He had marked asymmetrical bradykinesia and rigidity in upper and lower limbs (**video**), with stooped posture, reduced stride length, frequent episodes of gait freezing most marked on turning, and loss of postural reflexes. He had globally brisk reflexes but the neurological examination was otherwise unremarkable. L-dopa replacement was titrated up to 450mg/day with modest anti-parkinsonian benefit.

The patient's brain MRI demonstrated low T2 and gradient echo signal changes in the region of the substantia nigra, as well as less prominent pallidal hypointensity on gradient echo sequences (Fig. 1). No T1-weighted sequences were obtained. This prominence of nigral changes, in comparison to the preferential basal ganglia involvement in other NBIA syndromes, is characteristic of BPAN [1,4]. There was mild global atrophy but no hypoxic-ischaemic changes. No calcification was seen on CT brain imaging. Ancillary laboratory tests including copper and caeruloplasmin were within normal limits.

Next generation sequencing (NGS) of a peripheral blood sample of genomic DNA using a panel of 28 genes associated with dystonia and parkinsonism, showed a frameshift mutation in exon 9 of the *WDR45* gene (Reference sequence: NM_007075.3, c.[601_602 = /601_602del], p.[Leu201 = /Leu201Lysfs*21]), predicted to result in premature protein truncation. The mutation was confirmed by Sanger sequencing (Fig. 1). An adjacent two base-pair mutation leading to the same amino acid change has been previously described and deemed likely pathogenic in a female patient with BPAN [6]. The NGS data (Fig. 1F) demonstrated around 475 reads in the areas adjacent to the deletion and 120 reads in the deleted area. Given that the reads outside the deletion are made up of both mutant and wild-type sequences, the overall ratio of normal:mutant sequence (350:120) is compatible with somatic mosaicism. Mutation status was confirmed negative by Sanger sequencing in the mother.

The genetic panel analysis ruled out mutations in genes associated with three other NBIA syndromes, namely *PANK2, FA2H* and *FTL*.

Our case enriches the current understanding of BPAN in several important ways. Firstly, it widens the clinical spectrum of this rare disease, to now encompass milder phenotypes arising in middle-aged males. To our knowledge, our patient displays the oldest reported onset for movement disorders amongst male cases of BPAN, and he is also atypical through absence of childhood seizures, only moderate learning disability and preserved albeit limited verbal expression. Secondly, this is only the second confirmed case of somatic mosaicism in a male, likely accounting for this milder phenotype. Thirdly, and perhaps of most practical importance in daily practice, this case underscores the need to maintain a high index of clinical suspicion in patients who bear the often empirical label of ‘cerebral palsy’.

Disclosures

The authors report no relevant disclosures.

Declarations of interest

None.

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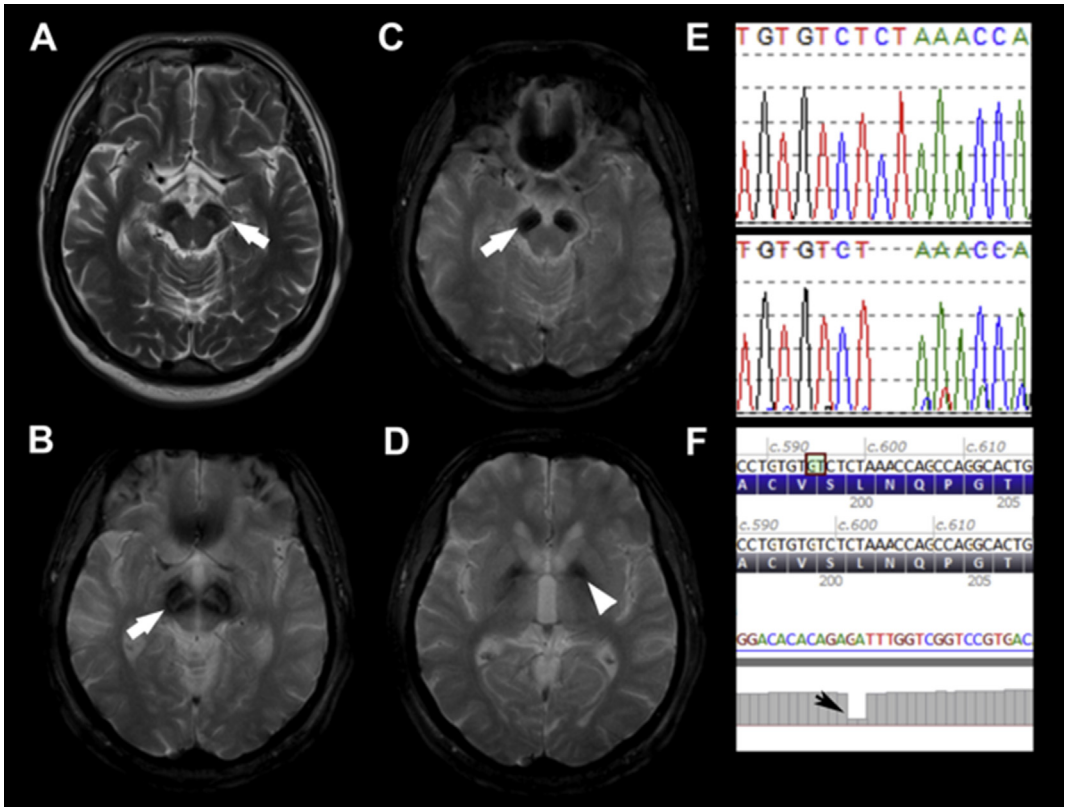

Fig. 1. Axial magnetic resonance images showing bilateral low signal in the midbrain (arrows) and basal ganglia (arrowhead) on (A) T2-weighted and (B, C, D) gradient echo sequences. (E) Sanger sequencing result on control subject (top) and proband (bottom) showing a deletion of bases 601–602 in exon 9 of the WDR45 gene. (F) Next-generation sequencing data showing the presence of both normal and mutant sequence (arrow points to the location of the deletion). Mutation analysis software used: Alamut Visual v2.9.

Written consent

We confirm that the patient has given written informed consent for the publication of his data and video including online publication on the journal website.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.09.010.

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Mihaela Boca*, Amit Herwadkar
Greater Manchester Neuroscience Centre, Salford Royal Hospital, Salford Royal NHS Foundation Trust, Stott Lane, Salford, M6 8HD, UK
E-mail address: mihaela.boca@srft.nhs.uk (M. Boca)

Kate Garrard, Nicholas Beauchamp
Sheffield Diagnostic Genetics Service, Sheffield, UK

Catherine Breen
Manchester Centre for Genomic Medicine, St Mary's Hospital, Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, UK
Division of Evolution and Genomic Sciences, School of Biological Science, University of Manchester, Manchester, UK

Monty Silverdale, Christopher Kobylecki
Greater Manchester Neuroscience Centre, Salford Royal Hospital, Salford Royal NHS Foundation Trust, Stott Lane, Salford, M6 8HD, UK
Division of Neuroscience and Experimental Psychology, University of Manchester, Manchester, UK

* Corresponding author.