Parkinsonism and Related Disorders 62 (2019) 239–241

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Correspondence

Neurodevelopmental disorder associated with *IRF2BPL* gene mutation: Expanding the phenotype?

ARTICLE INFO

Keywords:
IRF2BPL
Brain iron accumulation
Epileptic encephalopathy
Dystonia
Ataxia

Recently mutations in IRF2BPL gene with a complex neurological phenotype including combination of progressive neurodevelopmental delay, seizures, cerebellar ataxia, dystonia and pyramidal signs were reported in 2 independent studies [1,2].

We report a 36 years old female, who was born from third uneventful pregnancy and after normal delivery. All motor milestones in childhood were normal. She started speaking at the age of 3 years and her mental development was slightly delayed, resulting in later admission to regular school. Her academic performance was sufficient during first 3 years of school, however, since the age of 11 years she started developing progressive mental retardation. At 10 years she developed generalized photosensitive and myoclonic epilepsy. Currently, her seizures are clinically well controlled with medication. The patient currently presents with severe mental retardation, cerebellar syndrome, dysarthria, markedly reduced ocular saccades in both planes associated with insuppressible head movements, generalized choreodystonia, increased tendon reflexes and positive Babinski sign bilaterally (see Suppl. video; informed consent for online publication of the video has been obtained from parents of the subject). Recently performed EEG shows irregular theta activity, frequent sharp theta waves and complexes of sharp and slow waves over the left hemisphere with incomplete synchronization. Basic metabolic screening was normal, the patient was initially tested negative for NPC1, NPC2, DRPLA, MERRF, Unvericht-Lundborg and Lafora body disease.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.01.017.

Her MRI shows severe generalized brain atrophy. In addition, there is a signal drop apparent in the deep gray matter (DGM) nuclei on T_2-weighted images suggestive of increased iron deposits (see Fig. 1). Therefore, we performed quantitative T_2 relaxometry and compared the mean T_2 values in the patient with four age-matched healthy controls. This analysis confirmed decreased mean T_2 relaxation time in globus pallidus (GP), striatum, substantia nigra (SN), thalamus, and dentate nucleus (DN) presumably caused by increased iron content (see Suppl. Table 1).

Whole exome sequencing revealed novel nonsense variant in *IRF2BPL* (hg19 g.chr14:077493763G > A, M_024496.3: p. Gln125*/c.373C > T) which on family testing was shown to be a *de novo* event (Supplemental Data, Supplemental Fig. 1 and Fig. 2). The mutation is similar to those previously reported, in particular it is predicted to truncate the *IRF2BPL* protein similar as p.Gln121*, p.Gln126* and p.Gln127*.[1,2] There were no plausible (freq. < 0.05 in available databases) exonic/splicing variants in genes so far associated with brain iron accumulation (incl. REPS1, CRAT, COASY, C19orf12, FTL, PANK2, PLA2G6, WDR45). Apart from the *IRF2BPL* mutation, four ultrarare variants in other potentially relevant genes were studied but all were found to be inherited (see Suppl. Table 2).

Similar to our subject, previous reports [1,2] have described cerebral and cerebellar atrophy in their series of patients. In addition, our patient at the age of 35 years presented also with mildly increased brain iron concentration diffusely in the DGM nuclei, what may, if confirmed in other cases with *IRF2BPL* mutation, present an important diagnostic clue for this condition. The observed pattern of iron accumulation is different, and the magnitude is lower compared to typical findings in core neurodegeneration with brain iron accumulation (NBIA) syndromes. While we have observed approximately 5–15% drop in T_2 values in the DGM nuclei of this patient, pantothenate kinase-associated neurodegeneration (PKAN) patients typically exhibit 35% drop in T_2 relaxation time in GP [3]. Moderate diffuse involvement of the DGM is rather non-specific; similar findings were described in Wilson disease [4], multiple sclerosis and other disorders. Therefore, the mechanism of iron accumulation is likely not directly related to IRF2BPL dysfunction but together with diffuse brain atrophy is a marker of widespread neurodegenerative and/or neuroinflammatory changes in *IRF2BPL* mutation carriers. Iron accumulation observed in our patient but not in previous cohorts may be related to the long disease duration and comparatively older age of this case.

While other disorders traditionally associated with neurodevelopmental delay, like Rett syndrome, neuronal ceroid lipofuscinosis or X-linked adrenoleukodystrophy are typically not associated with increased brain iron accumulation, this clinical phenotype along with brain iron accumulation may be present in cases with beta-propeller protein-associated neurodegeneration caused by WDR45 mutations [5]. In the latter, gradual iron buildup, particularly in SN and GP, is observed after occurrence of clinical symptoms and may be mild in the initial stages. Nevertheless, compared to MRI findings in our subject,

https://doi.org/10.1016/j.parkreldis.2019.01.017
Received 28 October 2018; Received in revised form 13 January 2019; Accepted 22 January 2019

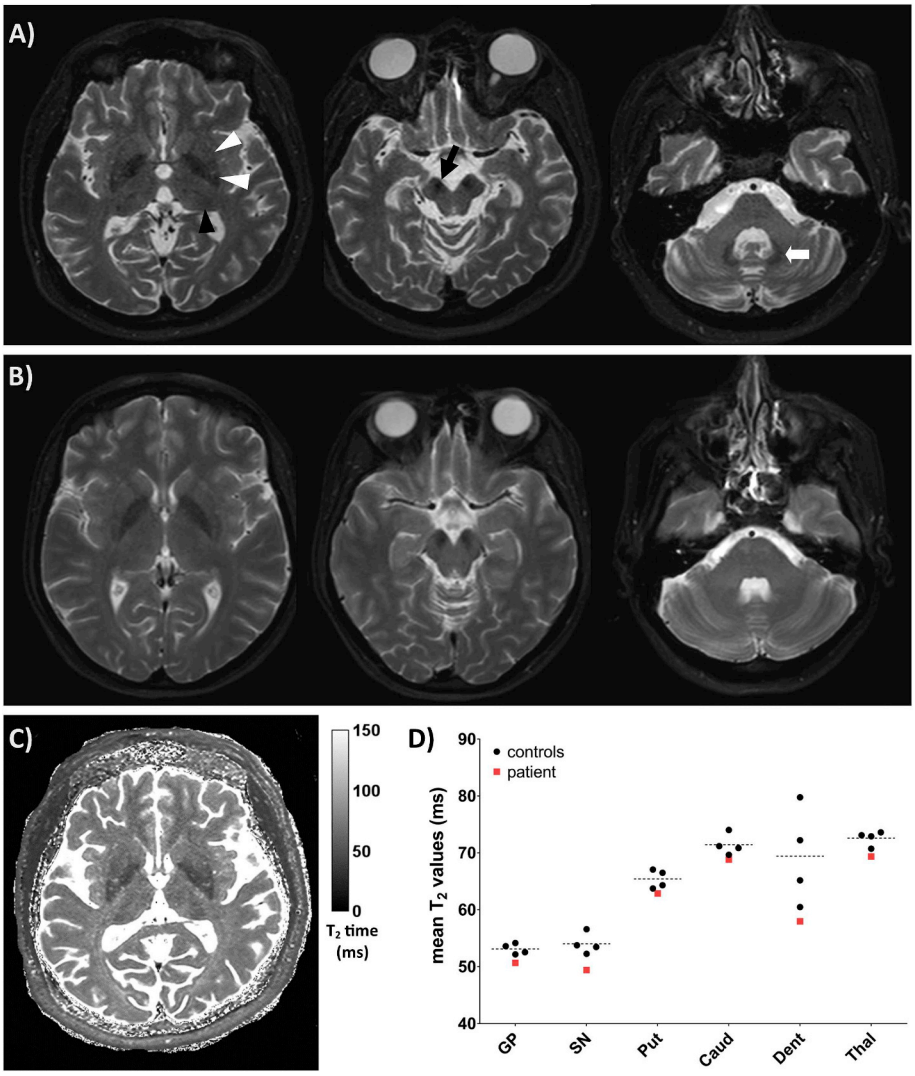

Fig. 1. Comparison of T_2-weighted MRI image A) in the patient and B) healthy female aged 37 years acquired using the same parameters (TR/TE = 2355/80 ms). T_2 signal drop was noted in the putamen (white arrowheads), thalamus (black arrowhead), SN (black arrow), and dentate nucleus (white arrow). C) T_2 parametric map of the patient at the level of basal ganglia; MRI was performed on a 3.0T system (Phillips Healthcare, Amsterdam, Netherlands); the imaging protocol included a 2D multi-echo spin-echo pulse sequence (TR = 2355 ms, 5 equidistant echoes with TE = 20–100 ms, spatial resolution = 0.4 × 0.4 × 2.0mm^3). T_2 parametric maps were reconstructed using the MRI processor plugin (D.Prodanov, 2009) for ImageJ (NIH, MD, USA). Mean T_2 values were measured in the patient and four control subjects (2 m/2f; mean age 35.3, range 34–37 years) in the GP, putamen, caudate nucleus, SN, dentate nucleus, and thalamus. D) Dot graph comparing T_2 values in the patient (red rectangles) and controls (black dots). The values in the patient are lower than those of controls in all examined regions. Dashed lines in the graph represent group means. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
Abbreviations: TR - repetition time, TE - echo time, GP – globus pallidus, SN – substantia nigra, Put – putamen, Caud – caudate nucleus, Dent – dentate nucleus, Thal – thalamus.

subjects with WDR45 mutations ultimately develop severe iron deposition accompanied by T_1 hyperintense halo surrounding SN, what may distinguish these 2 conditions. In conclusion, we present one of the oldest cases with IRF2BPL mutations manifesting with a complex progressive clinical phenotype and signs of mild diffuse brain iron accumulation in the deep gray matter.

Author roles

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft; B. Review and Critique;

Matej Skorvanek – 1ABC, 2C, 3A; Petr Dusek - 1AC, 2AB, 3A; Malgorzata Rydzanic – 1C, 2C, 3B; Anna Walczak – 1C, 2C, 3B; Joanna Kosinska – 1C, 2C, 3B; Grazyna Kostrzewa – 1C, 2C, 3B; Malgorzata Brzozowska – 1C, 2C, 3B; Vladimir Han – 1C, 2C, 3B; Petra Dosekova – 1C, 2C, 3B; Zuzana Gdovinova – 1C, 2C, 3B; Zdenka Lehotska – 1C, 2C, 3B; Pawel Lisowski – 1C, 2C, 3B; Rafal Ploski – 1ABC, 2C, 3B.

Acknowledgements

This work was supported by the National Science Centre Poland, grant 2017/27/B/NZ1/02401 to PL. The Slovak Research and Development Agency, grant APVV-14-0415.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.01.017.

Conflicts of interest and financial disclosures

The authors declare no conflict of interests in regards to this manuscript.

References

[1] P.C. Marcogliese, V. Shashi, R.C. Spillmann, et al., IRF2BPL is associated with neurological phenotypes, Am. J. Hum. Genet. 103 (2018) 245–260.
[2] F. Tran Mau-Them, L. Guibaud, L. Duplomb, et al., De novo truncating variants in the intronless IRF2BPL are responsible for developmental epileptic encephalopathy, Genet. Med. (2018), https://doi.org/10.1038/s41436-018-0143-0 [Epub ahead of print].
[3] M. Dezortova, V. Herynek, M. Krssak, et al., Two forms of iron as an intrinsic contrast agent in the basal ganglia of PKAN patients, Contrast Media Mol. Imaging 7 (2012) 509–515.
[4] P. Dusek, D. Skoloudik, J. Maskova, et al., Brain iron accumulation in Wilson's disease: a longitudinal imaging case study during anticopper treatment using 7.0T MRI and transcranial sonography, J. Magn. Reson. Imag. 47 (2018) 282–285.
[5] Y. Ichinose, M. Miwa, A. Onohara, et al., Characteristic MRI findings in beta-propeller protein-associated neurodegeneration (BPAN), Neurol Clin Pract 4 (2014) 175–177.

Matej Skorvanek[*,1]
Department of Neurology, Faculty of Medicine, P. J. Safarik University, Kosice, Slovak Republic
Department of Neurology, University Hospital of L. Pasteur, Kosice, Slovak Republic
E-mail address: matej.skorvanek@upjs.sk.

Petr Dusek[1]
Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic
Department of Radiology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic

Malgorzata Rydzanicz, Anna Walczak, Joanna Kosinska
Department of Medical Genetics, Medical University of Warsaw, Warsaw, Poland

Grazyna Kostrzewa, Malgorzata Brzozowska
Department of Forensic Medicine, Medical University of Warsaw, Warsaw, Poland

Vladimir Han
Department of Neurology, Faculty of Medicine, P. J. Safarik University, Kosice, Slovak Republic
Department of Neurology, University Hospital of L. Pasteur, Kosice, Slovak Republic

Petra Dosekova
Department of Neurology, Faculty of Medicine, P. J. Safarik University, Kosice, Slovak Republic

Zuzana Gdovinova
Department of Neurology, Faculty of Medicine, P. J. Safarik University, Kosice, Slovak Republic
Department of Neurology, University Hospital of L. Pasteur, Kosice, Slovak Republic

Zdenka Lehotska
Department of Radiology, University Hospital of L. Pasteur, Kosice, Slovak Republic

Pawel Lisowski[***]
Institute of Genetics and Animal Breeding, Polish Academy of Sciences, Jastrzebiec, Magdalenka, Poland
Max Delbrück Center for Molecular Medicine (MDC) in the Helmholtz Association, Berlin, Germany
E-mail address: lisowski884@gmail.com.

Rafal Ploski[**]
Department of Medical Genetics, Medical University of Warsaw, Warsaw, Poland
E-mail address: rploski@wp.pl.

[*] Corresponding author. Department of Neurology, Safarik University and L. Pasteur University Hospital, Trieda SNP 1, 04066, Kosice, Slovakia.
[***] Corresponding author. Department of Medical Genetics, Warsaw Medical University, ul Pawinskiego 3c, 02-106, Warsaw, Poland.
[**] Corresponding author. Department of Medical Genetics, Warsaw Medical University, ul Pawinskiego 3c, 02-106, Warsaw, Poland.
[1] Both authors contributed to the manuscript equally as first authors.