Parkinsonism and Related Disorders xxx (2015) 1–3

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Letter to the Editor

Timely diagnosis of Wilson's disease using whole exome sequencing

Keywords:
Wilson's disease
Neurogenetics
ATP7B gene
Next-generation-sequencing
Exome sequencing

1. Main text

Wilson's disease (WD) is a rare inborn error of copper metabolism caused by mutations in *ATP7B* gene. Although there is no genetic heterogeneity in WD etiology, the widespread clinical presentation of WD makes its diagnosis not always straightforward, particularly when atypical symptoms are present and a number of differential diagnoses must be considered [1]. Since it is a potentially treatable disorder, the prognosis of WD rests in a confirmatory and timely diagnosis leading to prompt therapy [1,2]. Exome sequencing has proved to be useful for the diagnosis of several neurogenetic disorders, enhancing the ability to identify the causative genetic defect in patients with complex phenotypes. Moreover, the cost and time needed to reach a proper diagnosis is reduced [3]. We report the phenotype and genotype of a patient with WD who, by means of exome sequencing, was diagnosed with the disease, with two novel *ATP7B* mutations being identified.

A 25- year-old woman, born of non-consanguineous parents, was admitted to our center with a 6-month history of progressive irritability, personality changes, depression, emotional liability, unmotivated laughter and slow speech. Involuntary movements in the left hand, abnormal posture of lower limbs and impairment of gait were also observed. On neurological examination, the patient was alert, with Mini-Mental State of 23/30 and Montreal cognitive assessment test (MOCA) of 20/30. Speech was slow; a moderate-severe dysarthria was present. Except for slow conjugate eye movements and square wave jerks, cranial nerves were normal. We found increased deep tendon reflexes in lower limbs, bilateral Hoffman's sign, left ankle clonus and a mild right brachio-crural paresis. She presented slow and rhythmic involuntary movements in the left upper limb, suggestive of stereotyped movements and a dystonic posture in internal rotation of both lower limbs (video: segment 1).

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2015.09.031.

A decreased ceruloplasmin (18 mg/dl) and a mildly increased urinary copper excretion (84.80 ug/24 h) in the presence of normal total serum cooper levels (71.1 ug/dl) were found. The rest of routine laboratory tests were normal. Ophthalmologic evaluation did not show the presence of Kayser-Fleischer's rings. The MRI showed increased signal intensity on T2/FLAIR bilaterally and symmetrically in putamen, caudate nucleus, posterior limb of the internal capsule, tectum mesencephalon, pons and red nucleus. A remarkable diffusion restriction in both putamen and red nucleus was observed (Fig. 1).

Based on radiological findings - albeit atypical but suggestive of WD- and the evidence of low serum cooper as well as an increased urinary cooper excretion, a probable diagnosis of WD was postulated. Empirical treatment with D-Penicilamine was initiated. In order to confirm the diagnosis, we performed a targeted *ATP7B* sequencing, looking for the presence of the common *His1069Gln* mutation. However, the mutation remained undetected. Consequently, a so-called rapid exome sequencing was performed using an ampliseq assay in an Ion Proton platform, revealing compound heterozygosity for two *ATP7B* novel mutations *(NM_000053: c.2165T > A:p.L722Q and c.3704G > A:p.G1235D)*. A month after penicillamine therapy onset, the patient showed an improvement in cognitive functions, gait and dysarthria in concordance with an adequate decoppering (video: segment 2).

We have presented a WD patient with predominant psychiatric symptoms and a wide spectrum of neurological manifestations without Kaiser Fleisher rings. The patient's MRI showed atypical neuroimaging findings characterized by the so-called giant panda sign but with restriction in DWI. We illustrate how exome sequencing was useful for confirming a molecular diagnosis, which allowed a prompt therapy. Previous reports have shown the presence of restriction in the DWI of WD patients, correlating diffusion changes with clinical severity. On the other hand, restricted diffusion may be seen at early stages of the disease, with a return to normal diffusivity after necrosis and spongiform degeneration have occurred [4]. The observed pattern on MRI, along with the absence of Kaiser-Fleisher rings, is likely to reveal early stages of the disease in our patient. Delays in the diagnosis of WD are more frequent in patients with neuro-psychiatric presentations than in those with hepatic affection. A mean time to diagnosis of about 3 years has been reported in patients showing neuropsychiatric symptoms at onset. Early diagnosis leading to prompt therapy is crucial in stopping the progression of the disease [2]. Exome sequencing can be performed in a few days at a cost no greater than what it takes to sequence a small number of candidate genes [3,5]. In summary, we have highlighted the use of next generation sequencing as a fast tool for confirming a WD diagnosis and have reported two novel *ATP7B* mutations, thus expanding the spectrum of mutations causing WD.

http://dx.doi.org/10.1016/j.parkreldis.2015.09.031
1353-8020/

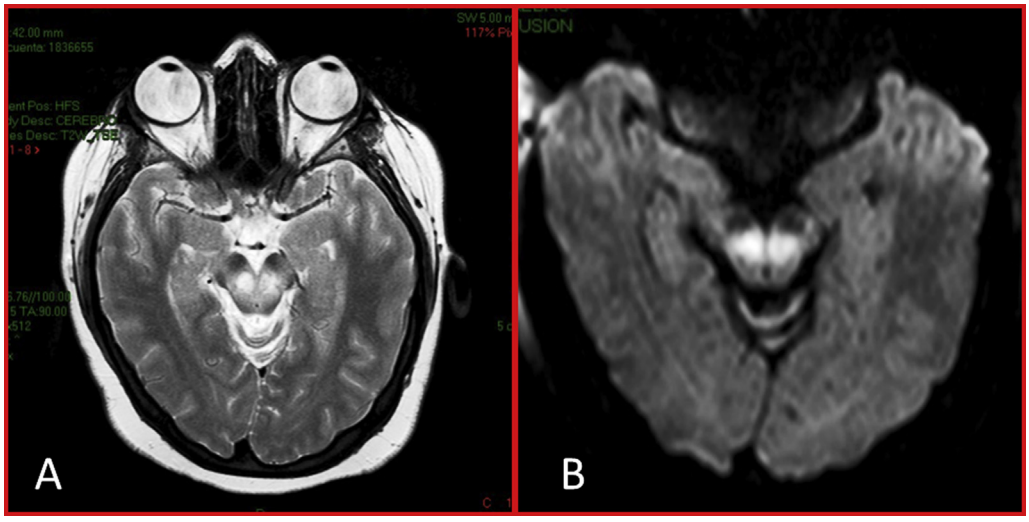

Fig. 1. Brain MRI showing high signal on axial T2 (A) with a noteworthy diffusion restriction (B) in both red nucleus (Bright Panda Sign). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Declaration of interest

Marcelo Kauffman is researcher in CONICET and Gobierno de la Ciudad de Buenos Aires. Sergio Rodríguez-Quiroga has a fellowship from Gobierno de la Ciudad de Buenos Aires.

The rest of the authors declare that they have no conflict of interest.

Author's contributions

Protocol draft and execution: SRQ, JR, TA, MC, DGM, NM, NG, MK.

Manuscript draft: SRQ, JR, TA, NG, MK.

Review and Critique: SRQ, JR, TA, MC, DGM, NM, NG, MK.

Acknowledgments

We thanks Professor Francisco Cardoso (Md, PhD), for his valuable contribution in the evaluation and discussion of the patient.

References

[1] EASL, Clinical practice guidelines: Wilson's disease, J. Hepatol. 56 (2012) 671–685.
[2] E.A. Roberts, M.L. Schilsky, Diagnosis and treatment of Wilson disease: an update, Hepatology 47 (2008) 2089–2111.
[3] K. Lohmann, C. Klein, Next generation sequencing and the future of genetic diagnosis, Neurotherapeutics 11 (2014) 699–707.
[4] P. Favrole, H. Chabriat, J.P. Guichard, F. Woimant, Clinical correlates of cerebral water diffusion in Wilson disease, Neurology 66 (2006) 384–389.
[5] T.J. de Koning, J.D. Jongbloed, B. Sikkema-Raddatz, R.J. Sinke, Targeted next-generation sequencing panels for monogenetic disorders in clinical diagnostics: the opportunities and challenges, Expert Rev. Mol. Diagn. 15 (2015) 61–70.

Sergio A. Rodríguez-Quiroga
Consultorio y Laboratorio de Neurogenética, Centro Universitario de Neurología "José María Ramos Mejía" y División Neurología, Hospital JM Ramos Mejía, Facultad de Medicina, UBA, Argentina

Área de Trastornos del Movimiento, Centro Universitario de Neurología "José María Ramos Mejía" y División Neurología, Hospital JM Ramos Mejía, Facultad de Medicina, UBA, Argentina
E-mail address: sergiorodriguez@dr.com.

Julieta Rosales
Consultorio y Laboratorio de Neurogenética, Centro Universitario de Neurología "José María Ramos Mejía" y División Neurología, Hospital JM Ramos Mejía, Facultad de Medicina, UBA, Argentina

Área de Trastornos del Movimiento, Centro Universitario de Neurología "José María Ramos Mejía" y División Neurología, Hospital JM Ramos Mejía, Facultad de Medicina, UBA, Argentina
E-mail address: julietarosales1987@gmail.com.

Tomoko Arakaki
Área de Trastornos del Movimiento, Centro Universitario de Neurología "José María Ramos Mejía" y División Neurología, Hospital JM Ramos Mejía, Facultad de Medicina, UBA, Argentina
E-mail address: tomokoarakaki2@gmail.com.

Marta Cordoba
Consultorio y Laboratorio de Neurogenética, Centro Universitario de Neurología "José María Ramos Mejía" y División Neurología, Hospital JM Ramos Mejía, Facultad de Medicina, UBA, Argentina
E-mail address: martacordoba.genomics@gmail.com.

Dolores González-Morón
Consultorio y Laboratorio de Neurogenética, Centro Universitario de Neurología "José María Ramos Mejía" y División Neurología, Hospital JM Ramos Mejía, Facultad de Medicina, UBA, Argentina

Consultorio de Neurooftalmología, Centro Universitario de Neurología "José María Ramos Mejía" y División Neurología, Hospital JM Ramos Mejía, Facultad de Medicina, UBA, Argentina
E-mail address: doloresgm@gmail.com.

Nancy Medina
Consultorio y Laboratorio de Neurogenética, Centro Universitario de Neurología "José María Ramos Mejía" y División Neurología, Hospital JM Ramos Mejía, Facultad de Medicina, UBA, Argentina
E-mail address: genesisnan2020@gmail.com.

Nélida S. Garretto
Área de Trastornos del Movimiento, Centro Universitario de Neurología "José María Ramos Mejía" y División Neurología, Hospital JM Ramos Mejía, Facultad de Medicina, UBA, Argentina
E-mail address: nsgarretto@hotmail.com.

Please cite this article in press as: S.A. Rodríguez-Quiroga, et al.Timely diagnosis of Wilson's disease using whole exome sequencing, Parkinsonism and Related Disorders (2015), http://dx.doi.org/10.1016/j.parkreldis.2015.09.031

Marcelo A. Kauffman*
Consultorio y Laboratorio de Neurogenética, Centro Universitario de Neurología "José María Ramos Mejía" y División Neurología, Hospital JM Ramos Mejía, Facultad de Medicina, UBA, Argentina

IBCN "Eduardo de Robertis", Facultad de Medicina, UBA-CONICET, Argentina

* Corresponding author. Consultorio de Neurogenética, División Neurología, Hospital JM Ramos Mejía, Urquiza 609, 1221, Buenos Aires, Argentina.
E-mail address: marcelokauffman@marcelokauffman.info (M.A. Kauffman).

5 July 2015