Parkinsonism and Related Disorders 81 (2020) 45–47

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Correspondence

Intermediate phenotype of ATP13A2 mutation in two Chilean siblings: Towards a continuum between parkinsonism and hereditary spastic paraplegia

ARTICLE INFO

Keywords
ATP13A2
Kufor-Rakeb syndrome
Spastic paraplegia
SPG78
Parkinsonism

ATP13A2 mutations have been implicated in juvenile parkinsonism (PARK9) and neuronal ceroid lipofuscinosis [1]. Recently, association with complicated hereditary spastic paraplegia (HSP) and an amyotrophic lateral sclerosis-like phenotype have been reported [2,3].

We describe two siblings from a non-consanguineous Chilean family with no Ashkenazi ancestry, affected by an intermediate phenotype combining parkinsonism and HSP. Mutation screening identified two mutations in *ATP13A2* in both patients. A literature review of patients with prominent HSP is provided.

The index patient is a 23-year-old man with delay in motor and language milestones, who presented with instability while running at age 14 years, and soon after presented progressively dysarthria, dysphagia, cognitive impairment, and bilateral rest and postural tremor. In the next 10 years, he progressively developed upper limb amyotrophy, mild levodopa-unresponsive parkinsonism and severe lower limb spasticity accompanied by ataxic movements. The 22-year-old sister started with ataxic gait, dysarthria, and cognitive impairment at 17 years of age. Delusional thoughts associated with visual and auditory hallucinations occurred few years later in association with mild levodopa-unresponsive parkinsonism and severe lower limb amyotrophy and spasticity. Unlike her brother, she did not show tremor. Both siblings are wheelchair-dependent and none exhibited gaze palsy, oculogyric spasms or facial-faucial-finger mini-myoclonus. Brain MRI in both patients showed diffuse cerebellar atrophy without signs of iron accumulation (Supplementary material 1 Fig. S1). Electromyogram unraveled signs of lower motoneuron disease in lower limbs.

Friedreich's ataxia and Wilson's disease were excluded by targeted mutation analysis. Whole exome sequencing revealed two pathogenic variants (c.2529+1G > A and c.3057delC) in *ATP13A2* in a compound heterozygous state (for details see Supplementary material 2).

The clinical picture of both patients resembled an intermediate phenotype between classical parkinsonian and complicated HSP [1,2]. Noteworthy, HSP symptoms were also reported in the original Chilean family carrying mutations in *ATP13A2* [1]. In 2017, Estrada-Cuzcano et al. assigned *ATP13A2* a novel HSP locus (SPG78) based on five patients with complicated HSP carrying mutations in *ATP13A2*, though one patient presented also parkinsonism [2]. As shown in Table 1, 13 out of 19 patients with prominent HSP presented also signs of parkinsonism. HSP or parkinsonism can be present either at disease onset or develop at later stages.

As the number of clinical phenotypes explained at the genetic level growth, it becomes clear that intermediate phenotypes are part of a phenotype continuum connecting clinical entities that were otherwise regarded as different (Supplementary material 1 Fig. S2). This observation has been made for several neurodegenerative diseases and their causative genes, e.g. *POLR3A*, *ATP1A3*, and *PLA2G6* [4,5]. Table 1 illustrates the presence of a varied plethora of clinical manifestations in patients with *ATP13A2* mutations supporting a continuum between different phenotypes rather than separate syndromes or allelic conditions (PARK9 and SPG78). The latter suggests additional modifier genes or alleles contributing to the phenotype which might relate to the protein network involved in both parkinsonism and HSP [6].

Our report highlights that an intermediate phenotype between a prominent parkinsonian (Kufor-Rakeb syndrome; PARK9) and a complicated HSP (SPG78) clinical spectrum exists, which favors the concept of a single genetic entity or condition with heterogeneous and overlapping clinical features rather than separate allelic disorders with a different nomenclature or classification. This is supported by shared pathogenic pathways among HSP-associated mutations, similarly to the ones causing Kufor-Rakeb syndrome and neuronal ceroid lipofuscinosis that ultimately impair the lysosomal and mitochondrial function [2]. Based on our observations, we propose to use the term *ATP13A2*-associated disorder to any phenotype that results from pathological variants in the *ATP13A2* gene because mutations in *ATP13A2* might lead to a wide range of connected phenotypes.

Funding sources

This work was supported by the European Community's Seventh Framework Programme (FP7/2007–2013) under Grant Agreement n° 2012–305121 "Integrated European –omics research project for diagnosis and therapy in rare neuromuscular and neurodegenerative diseases (NEUROMICS)".

https://doi.org/10.1016/j.parkreldis.2020.10.004
Received 6 July 2020; Received in revised form 24 September 2020; Accepted 4 October 2020
Available online 6 October 2020
1353-8020/

Table 1
Summary of clinical findings of patients with ATP13A2 mutations and prominent HSP phenotype.

Patient	Reference	Gaze palsy	Lower limbs spasticity or spastic gait	Pyramidal signs	Amyotrophy	Ataxia	Parkinsonism	Cognitive impairment	Psychosis
Patient 1	This report	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Patient 2	This report	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
V-1	Eiberg (2012) [S1]	Yes	Yes	Yes	(NR)	Yes	Yes	Yes	Yes
Proband (family 41)	Kara (2016) [S2]	Yes	Yes	(NR)	(NR)	Yes	No	Yes	(NR)
Patient 17	van de Warrenburg (2017) [S3]	Yes	Yes	(NR)	(NR)	(NR)	Yes	Yes	(NR)
HSP84.II.1	Estrada-Cuzcano (2017) [2]	No	Yes	Yes	No	Yes	No	Yes	No
HSP84.II.3	Estrada-Cuzcano (2017) [2]	No	Yes	Yes	No	Yes	No	No	No
HSP84.II.4	Estrada-Cuzcano (2017) [2]	No	Yes	Yes	No	Yes	No	Yes	No
HIH21480.II.3	Estrada-Cuzcano (2017) [2]	Yes	Yes	Yes	No	Yes	No	Yes	No
HIH22132.II.1	Estrada-Cuzcano (2017) [2]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Patient 1	Noch (2017) [S4]	Yes	Yes	Yes	(NRNR)	(NR)	Yes	Yes	(NR)
Patient 2	Noch (2017) [S4]	Yes	Yes	Yes	(NR)	Yes	Yes	Yes	(NR)
II-2	Inzelberg (2018) [S5]	Yes	Yes	Yes	(NR)	Yes	Yes	Yes	Yes
II-3	Inzelberg (2018) [S5]	Yes	Yes	Yes	(NR)	Yes	Yes	No	No
Patient 2	Erro (2019) [S6]	Yes	Yes	Yes	(NR)	Yes	Yes	Yes	(NR)
Patient 8	Wei (2019) [S7]	(NR)	Yes	Yes	(NR)	(NR)	(NR)	(NR)	(NR)
Patient A	Estiar (2020) [S8]	(NR)	Yes	Yes	(NR)	Yes	Yes	Yes	(NR)
Patient B	Estiar (2020) [S8]	(NR)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Patient C	Estiar (2020) [S8]	(NR)	Yes	Yes	(NR)	Yes	Yes	Yes	Yes

(NR) Not reported – References S1 to S8 can be found in Supplementary Material 2.

Ethical statement

This study was approved by the local Institutional Review Board and informed consent was obtained. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Authors' contributions

All authors made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Declaration of competing interest

None.

Acknowledgments

We thank the patients and their family for their willingness to participate in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2020.10.004.

References

[1] A. Ramirez, A. Heimbach, J. Gründemann, et al., Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase, Nat. Genet. 38 (2006) 1184–1191, https://doi.org/10.1038/ng1884.
[2] E. Estrada-Cuzcano, S. Martin, T. Chamova, et al., Loss-of-function mutations in the ATP13A2/PARK9 gene cause complicated hereditary spastic paraplegia (SPG78), Brain 140 (2017) 287–305, https://doi.org/10.1093/brain/aww307.
[3] R. Spataro, M. Kousi, S.M.K. Farhan, et al., Mutations in ATP13A2 (PARK9) are associated with an amyotrophic lateral sclerosis-like phenotype, implicating this locus in further phenotypic expansion, Hum. Genom. 13 (2019) 19, https://doi.org/10.1186/s40246-019-0203-9.
[4] M. Minnerop, D. Kurzwelly, H. Wagner, et al., Hypomorphic mutations in POLR3A are a frequent cause of sporadic and recessive spastic ataxia, Brain 140 (2017) 1561–1578, https://doi.org/10.1093/brain/awx095.
[5] B. Ozes, N. Karagoz, R. Schüle, et al., PLA2G6 mutations associated with a continuous clinical spectrum from neuroaxonal dystrophy to hereditary spastic paraplegia, Clin. Genet. 92 (2017) 534–539, https://doi.org/10.1111/cge.13008.
[6] G. Novarino, A.G. Fenstermaker, M. Zaki, et al., Exome sequencing links corticospinal motor neuron disease to common neurodegenerative disorders, Science 343 (2014) 506–511, https://doi.org/10.1126/science.1247363.

Marcelo Miranda[1]
Fundación Diagnosis, Santiago, Chile
Department of Neurology, Clinica Las Condes, Santiago, Chile

Florian Harmuth[1]
Institute of Medical Genetics and Applied Genomics, University of Tuebingen, Tuebingen, Germany

M. Leonor Bustamante
Fundación Diagnosis, Santiago, Chile
Human Genetics Program, Biomedical Sciences Institute, Faculty of Medicine, University of Chile, Santiago, Chile
Department of Psychiatry and Mental Health, North Division, Faculty of Medicine, University of Chile, Santiago, Chile

Malco Rossi
Movement Disorders Section, Neuroscience Department, Fleni, Buenos Aires, Argentina
Argentine National Scientific and Technological Research Council (CONICET), Buenos Aires, Argentina

Marc Sturm
Institute of Medical Genetics and Applied Genomics, University of Tuebingen, Tuebingen, Germany

Ólafur Th Magnusson
deCODE Genetics, Sturlugata 8, 101 Reykjavik, Iceland

Peter Bauer
Institute of Medical Genetics and Applied Genomics, University of Tuebingen, Tuebingen, Germany

Centogene AG, Am Strande 7, Rostock, Germany

Thomas Klockgether
Department of Neurology, University of Bonn, Bonn, Germany
German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

Alfredo Ramirez*
German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany
Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry and Psychotherapy, University of Cologne, Medical Faculty, Cologne, Germany
Department of Neurodegenerative Diseases and Geriatric Psychiatry, University of Bonn, Bonn, Germany

* Corresponding author. Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry and Psychotherapy, University of Cologne, Medical Faculty, Kerpener Strasse 62, D-50937, Cologne, Germany.
E-mail address: alfredo.ramirez@uk-koeln.de (A. Ramirez).

[1] These authors contributed equally to the work.