Parkinsonism and Related Disorders 64 (2019) 342–345

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Correspondence

PNKP deficiency mimicking a benign hereditary chorea: The misleading presentation of a neurodegenerative disorder

ARTICLE INFO

Keywords:
PNKP
Benign hereditary chorea
Polyneuropathy
Pediatric movement disorders

ABSTRACT

PNKP gene encodes for a kinase/phosphatase involved in DNA damage response, controlled and stabilized by ATM phosphorylation. *PNKP* deficiency, thus far described in 40 subjects, has been associated with a complex neurological phenotype encompassing microcephaly, seizures, developmental delay, ataxia, oculomotor apraxia and polyneuropathy. We report a new case expanding the clinical phenotype of this rare disorder. This 25 years old girl presented with chorea at the age of 2 years and remained stable up to the adult age when the emergence of fatigability and asthenia of lower limbs prompted a new examination disclosing a sensory-motor axonal demyelinating neuropathy. Clinical exome sequencing revealed two previously described variants in *PNKP* gene. This case highlights the phenotypic variability of *PNKP* associated disorders, showing that an early onset apparently non progressive chorea can be the presenting symptoms of this rare condition.

PNKP deficiency is an autosomal recessive condition belonging to a family of neurodevelopmental and neurodegenerative disorders related to genome instability. *PNKP* gene encodes for the polynucleotide kinase/phosphatase (PNKP), a bifunctional protein critical for DNA damage repair. PNKP phosphorylation, mediated by ATM protein in response to DNA damage, prevents its ubiquitylation dependent proteasomal degradation, ensuring a proper recruitment to the damaged DNA sites and timely repair [1]. Here we report a phenotypic expansion of *PNKP* deficiency in a patient presenting with a pure chorea in childhood and a severe progressive polyneuropathy in adult age.

This 25 years old girl was born at term after an uneventful pregnancy and delivery from non-consanguineous and healthy parents; birth growth parameters were normal, including occipito-frontal circumference (OFC).

After a normal psychomotor development, she presented at the age of 2 years with subacute onset chorea. On examination at the age of 7 years she was a girl with normal intellectual development and school performances with mild microcephaly (OFC -2SD), generalized chorea, and hypotonia, mimicking Sydenham chorea (video segment 1). Neuroimaging, rheumatological and metabolic diagnostic work-up resulted inconclusive. Chorea remained stable for several years, with relapses and partial remissions, and was well controlled by pimozide. She has never presented ocular motility disorders. At the age of 19 she presented with mild residual chorea, subtle cervical dystonia, and progressive fatigability and asthenia of lower limbs (video segment 2). Clinical and neurophysiological assessment revealed a sensorimotor

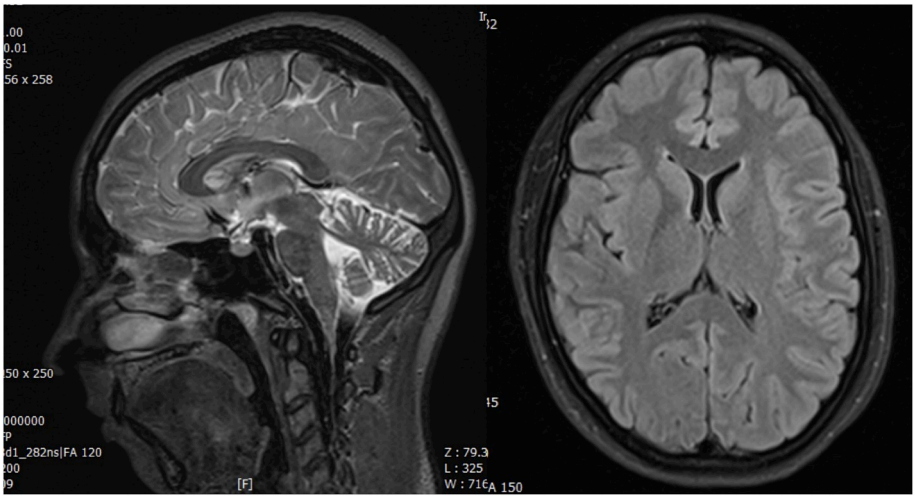

Fig. 1. Brain MRI at the age of 22 years showing mild cerebellar atrophy.

https://doi.org/10.1016/j.parkreldis.2019.03.012
Received 3 January 2019; Received in revised form 15 March 2019; Accepted 18 March 2019

Table 1
Clinical, biochemical, neuroradiological, and genetic data of reported patients with PNKP deficiency.

Family/sex	Onset/last examination	Presentation	Ataxia	Oculomotor apraxia	Microcephaly	Seizures	Neurophaty	DD/ID	Movement disorder	MRI	Biological Markers	Genotype	Reference
I/M	birth/deceased at 25 yrs	Microcephaly DD	+	–	+	+	+	+	–	Cerebellar atrophy	n.a.	c.1250_1266dup (homozygous)	Poulton, 2013
I/M	3 mo/18 yrs	microcephaly DD	+	–	+	+	+	+	–	Cerebellar atrophy, thin CC, reduced WM volume	n.a.	c.1250_1266dup (homozygous)	Idem
II/M	birth/21 yrs	microcephaly	–	–	+	+	n.a.	+	–	n.a.	–	975G > A (homozygous)	Shen, 2010
II/M	birth/6 yrs	microcephaly	–	–	+	+	n.a.	+	–	n.a.	–	975G > A (homozygous)	Idem
III/M	birth/n.a.	microcephaly	–	–	+	+	n.a	+	–	n.a.	n.a.	975G > A (homozygous)	Idem
III/F	birth/n.a.	microcephaly	–	–	+	+	n.a.	+	–	n.a.	n.a.	975G > A (homozygous)	Idem
IV/M	birth/4,5 yrs	microcephay	–	–	+	+	n.a.	+	–	thin CC, cerebellar atrophy, reduced WM volume	–	975G > A (homozygous)	Idem
IV/M	birth/21 mo	microcephaly	–	–	+	+	n.a.	+	–	thin CC, cerebellar atrophy, reduced WM volume	–	975G > A (homozygous)	Idem
V/F	birth/12 yrs	microcephaly	–	–	+	+	n.a.	+	–	Simplified gyral pattern, thin CC, cerebellar atrophy, reduced WM volume	n.a.	1250_1266dup (homozygous)	Idem
V/F	birth/12 yrs	microcephaly	–	–	+	+	n.a.	+	–	Simplified gyral pattern, thin CC, cerebellar atrophy, reduced WM volume	n.a.	1250_1266dup (homozygous)	Idem
VI/F	1 mo/n.a.	microcephaly/ seizures	–	–	+	+	n.a.	+	–	Simplified gyral pattern, thin CC, reduced WM volume	n.a.	1250_1266dup (homozygous)	Idem
VII/F	birth/14 yrs	microcephaly	–	–	+	+	n.a.	+	–	Simplified gyral pattern, thin CC, cerebellar atrophy, reduced WM volume	n.a.	526C > T 1250_1266dup	Idem
VII/M	Prenatal period/3,5 yrs	microcephaly	–	–	+	+	n.a.	+	–	Simplified gyral pattern	n.a.	526C > T 1250_1266dup	Idem
VIII/F	4 mo/8 yrs	seizures	–	–	+	+	n.a.	+	–	reduced WM volume	n.a.	1250_1266dup 17 bp deletion (intron 15)	Idem
VIII/M	4 mo/18 mo	seizures	–	–	+	+	n.a.	+	–	thin CC	n.a.	1250_1266dup 17 bp deletion (intron 15)	Idem
IX/M	birth/13 yrs	microcephaly	–	–	+	+	+	+	–	Cerebellar atrophy	n.a.	c.1133A > C (homozygous)	Entezam, 2018
IX/F	n.a./30 yrs	microcephaly	–	–	+	+	+	+	–	n.a.	n.a.	c.1133A > C (homozygous)	Idem
IX/F	n.a./27 yrs	microcephaly	–	–	+	–	+	+	–	n.a.	n.a.	c.1133A > C (homozygous)	Idem
IX/F	n.a./18 yrs	microcephaly	–	–	+	–	+	+	–	n.a.	n.a.	c.1133A > C (homozygous)	Idem
IX/F	n.a./5,8 yrs	microcephaly	–	–	+	–	+	+	–	n.a.	n.a.	c.1133A > C (homozygous)	Idem
IX/F	n.a/3 yrs	microcephaly	–	–	+	–	+	+	–	n.a.	n.a.	c.1133A > C (homozygous)	Idem
X/M	5 yrs/n.a.	dystonia	+	+	–	–	+	+	+	Cerebellar atrophy, brainstem atrophy	↑ AFP	c.[1123G > T] [1253_1269dup	Bras, 2015
X/F	9 yrs/n.a.	dystonia	+	+	–	–	+	+	+	Cerebellar atrophy, brainstem atrophy	↑ AFP	c.[1123G > T] [1253_1269dup	Idem
XI/F	6 yrs/n.a.	dystonia	+	+	–	–	+	+	+	Cerebellar atrophy	↑ AFP ↓ albumin	c.[1123G > T] (homozygous)	Idem
XII/F	3 yrs/n.a.	ataxia	+	+	–	–	+	+	dystonia	Cerebellar atrophy	↓ albumin ↑ cholesterol	c.[1221_1223del] [1549_1550insTGTACTGC]	Idem
XIII/M	1yrs/n.a.	dystonia	+	+	–	–	+	–	+	Cerebellar atrophy	↓ albumin	c.[1221_1223del] [1315_1329delinsGGGT]	Idem
XIV/F	3 yrs/n.a.	ataxia	+	+	–	–	+	–	dystonia	Cerebellar atrophy	↑ AFP ↓ albumin	c.[1123G > T] (homozygous)	Idem

(*continued on next page*)

Table 1 (*continued*)

Family/sex	Onset/last examination	Presentation	Ataxia	Oculomotor apraxia	Microcephaly	Seizures	Neurophaty	DD/ID	Movement disorder	MRI	Biological Markers	Genotype	Reference
XV/F	4 yrs/n.a.	ataxia	+	+	–	–	+	–	–	Cerebellar atrophy	↑ AFP ↑ cholesterol	c.[1123G > T 1322_1323insAGCCG]	Idem
XVI/F	4 yrs/n.a.	oculomotor apraxia	+	+	–	–	+	–	dystonia	Cerebellar atrophy	AFP (N) albumin and cholesterol (n.a.)	c.[1123G > T] (homozygous)	Idem
XVI/M	7 yrs/n.a.	oculomotor apraxia	+	+	–	–	+	+	–	Cerebellar atrophy	AFP (N) albumin and cholesterol (n.a.)	c.[1123G > T] (homozygous)	Idem
XVII/F	2 yrs/n.a.	dystonia	+	+	–	–	+	+	+	Cerebellar atrophy	↓ albumin ↑ cholesterol	c.[1123G > T] (homozygous)	Idem
XVII/M	3 yrs/n.a.	dystonia	+	+	–	–	+	+	+	Cerebellar atrophy, brainstem atrophy	↓ albumin ↑ cholesterol	c.[1123G > T] (homozygous)	Idem
XVIII/F	5 yrs/28 yrs	dystonia chorea	+	–	–	–	+	+	+	Cerebellar atrophy	↓ albumin ↑ cholesterol ↑ AFP	c.1196T.C c.1385G.C	Paucar, 2016
XIX/F	6 yrs/50 yrs	gait unsteadiness, motor clumsiness	+	+	–	–	+	+	–	Cerebellar atrophy, pontine atrophy, reduced WM volume	↓ albumin ↑ cholesterol	c.1196 T > C c.1393_1396del	Tzoulis, 2017
XX/F	7 yrs/n.a.	impaired balance	+	–	–	–	+	+	–	Cerebellar atrophy	↓ albumin ↑ cholesterol	c.1253_1269dup c.1545C > G	Scholz, 2018
XXI/M	1 yrs/17 yrs	gait abnormalities feet deformities	+	–	–	–	+	–	–	Cerebellar atrophy	n.a.	c.1221_1223delCAC (homozygous)	Pedroso, 2015
XXII/M	third decade/ 55 yrs	neuropathy	–	+	–	–	+	–	–	Cerebellar atrophy	n.a.	c.1549C > T c.1221_1223del	Leal, 2018
XXIII/M	third decade/ 26 yrs	neuropathy	+	+	–	–	+	–	–	Cerebellar atrophy	↓ albumin ↑ cholesterol ↑IgE	c.1549C > T c.1221_1223del	Idem
XXIV/F	third decade/ 59 yrs	neuropathy	–	–	–	–	+	–	–	Cerebellar atrophy	n.a.	c.1549C > T (homozygous)	Idem
XXV/F	third decade/ 55 yrs	neuropathy	–	–	–	–	+	–	–	Cerebellar atrophy	n.a.	c.1549C > T (homozygous)	Idem
XXVI/F	2 yrs/25 yrs	chorea	–	–	+	–	+	–	+	Cerebellar atrophy	↓ albumin ↑ cholesterol ↑IgE↓ IgA	c.1253_1269dup c.1196T > C (NM_007254; NP_009185)	Present case
XXVII/M	birth/49 yrs	severe microcephaly	+	–	+	+	+	+	–	Cerebellar atrophy, reduced WM volume	↑cholesterol ↑ triglycerides ↓ albumin	c.196C > G c.1253_1269dup	Unpublished case (V Leuzzi)

Legend: **mo**, months; **yrs**, years; **DD**, development delay; **ID**, intellectual disability; **MRI**, magnetic resonance imaging; **n.a.,** not available; **CC**, corpus callosum; **WM,** white matter; **AFP**, alfa fetoprotein; **N**, normal.

axonal demyelinating neuropathy (video fragment 3). Brain MRI disclosed cerebellar atrophy (Fig. 1). In the few following years the neuropathy spread to the upper limbs with a distal to proximal progression pattern, and presently she is able to walk only with orthosis (video segment 3). Blood examination showed slight hypercholesterolemia, hypoalbuminemia, low levels of IgA, and increased IgE. Alpha fetoprotein was normal. Clinical exome sequencing revealed two previously reported *PNKP* mutations [c.1253_1269dup (p.Thr424Glyfs*49); c.1196T > C (p.Leu399Pro)] (NM_007254; NP_009185) inherited from her unaffected parents [2,3].

Supplementary video related to this article can be found at doi:10.1016/j.parkreldis.2019.03.012.

PNKP deficiency, thus far described in 40 subjects (Table 1), has been associated with two main clinical syndromes: congenital microcephaly with early onset intractable seizures (MCSZ) and developmental delay and ataxia with oculomotor apraxia (AOA4). Overlapping phenotypes encompassing a variable association of microcephaly, epilepsy, developmental delay, polyneuropathy, and ataxia, have been described. Polyneuropathy has been reported as a late disease course feature in patients with ataxia with oculomotor apraxia and in cases with mild epilepsy [4]. Adult presentation of prominent polyneuropathy resembling an axonal form of Charcot-Marie-Tooth disease has been recently described [5].

Hyperkinetic movement disorders were the presenting symptom in 7 out of 40 patients so far reported; all of them later developed ataxia with or without oculomotor apraxia [6,7]. Six out of 7 presented with isolated dystonia, one patient presented with chorea and dystonia. As in other disorders of DNA repair such as ataxia teleangiectasia and ataxia with oculomotor apraxia type 1 (*APTX* gene deficiency) and 2 (*SETX* and *PIK3R5* gene deficiency) a variable association of hypercholesterolemia, hypoalbuminemia and high levels of AFP can be detected (Table 1) [3,5–7]. Immunoglobulin pattern abnormalities including IgA deficiency have been reported in ataxia teleagiectasia, while increased IgE levels have been reported in a single case of *PNKP* deficiency [5].

In our patient chorea remained isolated up to the adult age, anticipating of several years the progressive polyneuropathy which dominated the late disease course. Taking this into account, to avoid a frustrating unexpected clinical outcome, *PNKP* gene should be considered in the differential diagnosis of each early onset choreic syndrome.

The association of chorea, microcephaly, and normal cognitive development represents a unique clinical trait suggesting *PNKP* mutation. A variable association of hypoalbuminemia, hypercholesterolemia, and increased alpha fetoprotein levels, could be an important biochemical clue to the diagnosis.

Declarations of interest

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Final disclosures

All authors have approved the final article. They also declare no conflicts of interest. Vincenzo Leuzzi has served on scientific advisory boards for Nutricia and BioMarin. No funding has been received for this study.

Ethical approval and informed consent

All authors declare that the manuscript is in accordance with the statement of ethical standards for manuscripts submitted to *Parkinsonism and related disorders*. All authors declare that the patient consented for video publication and provided a signed release form authorizing the offline and/or online distribution of this video material.

Author roles

CC: 1,2.
TM: 1.
GS: 1,2.
IM: 1.
CC (Carducci):1.
AA: 1.
LV: 2,3.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.03.012

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