LETTER TO THE EDITOR

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PNKP mutation in a child: is there a firm line between MCSZ and AOA4 phenotype?

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To the Editors

Mutations in the PNKP (polynucleotide kinase 39-phosphatase) gene are linked with the spectrum of neurodegenerative diseases such as ataxia-oculomotor apraxia (AOA) and neurodevelopmental dysfunction- microcephaly with early onset seizures (MCSZ) [1]. The PNKP gene, one of the genes associated with the AOA spectrum, is involved in DNA repair pathways. PNKP-related disorders show phenotypic heterogeneity, which can be influenced by multiple factors, such as gene-pleiotropism, geographical origin, changes in DNA kinase or DNA phosphatase PNKP-effect, and environment [1].

Neurodegenerative features in AOA are triggered by impaired repair of DNA single strand breaks (SSBs) and reduced DNA kinase activity, while neurodevelopmental dysfunction is caused by PNKP malfunction in DNA double-strand breaks (DSBs) and reduced DNA phosphatase activity [2]. Nevertheless, studies have shown that reduced SSB repair is included in both neurodevelopmental and neurodegenerative pathology in PNKP-mutated diseases, and the extent of this defect might influence phenotypic variation and disease severity [2]

We present the case of a patient with homozygous PNKP mutation with AOA4 features. Our case report shows that there is a broad spectrum within AOA4 and MCSZ syndromes, pointing out that there is no clear delineation within PNKP-related diseases. The clinical picture of our patient is in unison with the fact that MCSZ and AOA4 represent a clinical spectrum rather than separate phenotypes.

Our patient is a 15-year-old girl of Balkan origin with an early onset progressive ataxia, developmental delay, MRI-verified cerebellar atrophy, and endocrinological abnormalities. Her parents are of Balkan origin and live in Serbia. They reported consanguinity, although they did not know the degree of consanguinity. The family history is unremarkable for neurological diseases. The girl was born two weeks before term, and developmental delay was noted early in her life: unassisted walking was achieved by the age of one, with her first words being spoken at the age of two. She went to a speech therapist and was attending a school for special needs children. In the first decade, her gait became unsteady and by the age of ten progressed to an inability to walk or sit without assistance. Her first neurological examination at age of eight showed minor dysmorphological cranial features with elongated midface, short philtrum, hypotelorism and microcephaly, with head circumference below 5th percentile. Speech was nasal and dysarthric, gait was broad-based and ataxic, with cavus foot deformity, mild dorsiflexion weakness and leg areflexia. There was an impression of moderate cognitive delay. Eye examination revealed broken smooth pursuit and nystagmus, but an absence of oculomotor apraxia (OMA). Her body mass index was within the normal range. MRI of the head and spine showed extensive cerebellar volume loss, volume reduction of middle cerebellar peduncles, enlargement of the fourth ventricle, and microcephaly (Fig. 1). EEG examination showed slow encephalopathic activity without epileptiform changes. Routine biochemical analysis revealed combined hyperlipoproteinemia without elevated liver enzymes and no

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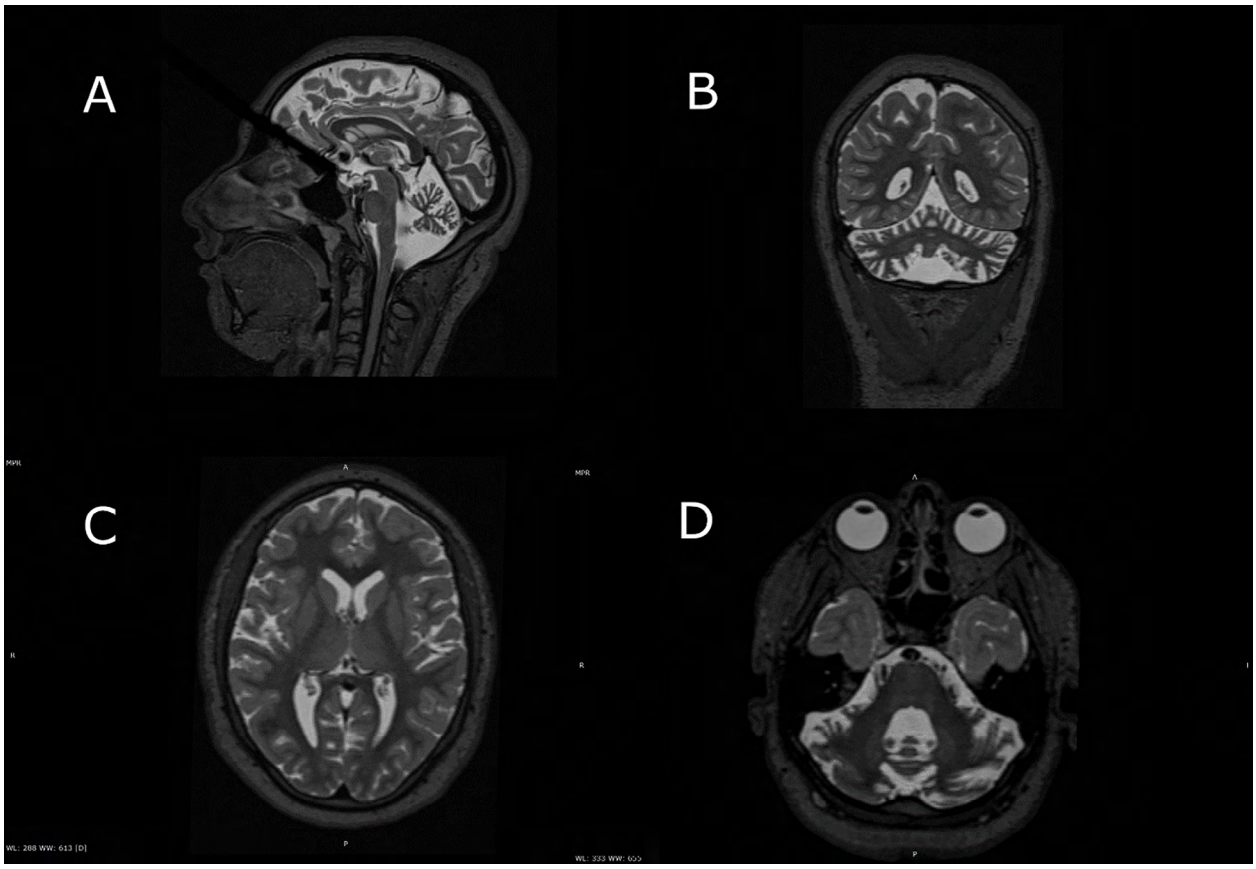

Figure 1. Brain MR imaging findings in 15-year-old female patient with pathogenic PNKP-gene mutation and ataxia-oculomotor apraxia; sagittal (A), coronal (B) and axial (C, D) multiplanar reconstructions of 3D T2-weighted images show global and extensive cerebellar volume loss, involving both vermis and cerebellar hemispheres (A, B, C), along with moderate volume reduction of both middle cerebellar peduncles (C) and subsequent enlargement of fourth ventricle. (A, B, C). Furthermore, axial image at level of gangliocapsular region (C) reveals microcephaly without clearly abnormal gyral pattern or other associated structural abnormalities

other abnormalities. Karyotype and neurometabolic testing were normal. The levels of alpha fetoprotein and IgM were increased. No other immunological abnormalities were found. Electroneurography revealed combined demyelinating axonal polyneuropathy. The patient was followed up by a multidisciplinary team and was treated with speech, occupational and physical therapy. Her parents reported disease progression in the repeated examinations.

At the age of fifteen, the girl was unable to walk, and sitting was possible only with support, mainly due to severe truncal and extremities ataxia; feeding was followed by nasal regurgitation and signs of dysphagia. Yet her body weight was increasing; endocrinological and gynaecological examination indicated polycystic ovary syndrome (PCO): obesity, combined hyperlipoproteinemia, hyperglycaemia, hypertrichosis, and secondary amenorrhea. Pathological hepatogram was registered and abdominal ultrasound showed hepatic steatosis. Repeated brain MRI was without progression. Clinical exon sequencing detected homozygote pathogenic variant of c.1253-1269dup p. (THr424GlyfsTer49)-, a frameshift mutation in the PKNP gene.

This is the first pathogenic PNKP-gene mutation to be reported in the Balkan region. This mutation seems to be common in various European heritages (it has been reported in Norway, the Netherlands [3], Germany, and Belarus [4]), and Asian heritages (Iranian, Japanese and Palestinian origins) [5]. The PNKP mutation is the most common cause of AOA in Portugal [1]. However, additional studies are needed to determine whether this is also the case in other populations. The latest data suggest that in patients with mixed MCSZ-AOA4 phenotype, SSB repair is reduced and requires both kinase and phosphatase domain of PKNP to be intact [2].

In contrast to the Portuguese study, we do not report dystonia as a first symptom, but we noted marked gait disturbance with time to wheelchair in the preadolescent period, differently to slower progression in the literature (with mean age at being bound to a wheelchair occurring in adolescence) [1]. Also, we report an absence of OMA but the presence of striking obesity leading to PCO rather than previously reported biochemical abnormality. The same frameshift p. Thr424Glyfs mutation, followed by progressive neurodegeneration, cerebellar atrophy, cognitive deterioration, and no ocular signs was found in the

cases of Dutch brothers [3]. However, in our case, the diagnosis of epilepsy was not reported and the predominant sign was ataxia rather than polyneuropathy. The same haplotype of chromosome 19 has been mapped in Palestinian patients with MCSZ, but with no AOA4 features [5]. Consanguinity was likewise reported in that case. Two Belarus families provided the first observed AOA4 in Slavic countries with PNKP mutation, which differ from our case in the absence of cerebellar atrophy, but with signs of early onset epilepsy and AOA [4]. The distinctive feature of our patient is mixed MCSZ-AOA4 phenotype that has some variance from typical AOA (absence of oculomotor apraxia) and from typical MCSZ (absence of epilepsy). A possible molecular explanation for this phenotypic variability is a reduced role played by this protein in the repair of both SSBs and DSBs [2].

Future studies clarifying PNKP regulation and interaction with other repair enzymes might help explain these clinical characteristics.

We have presented the case of a 15-year-old Serbian patient with detected pathogenic homozygous mutation in the PNKP gene. Our case report unifies the symptoms of two PNKP-related autosomal recessive diseases (AOA and MCSZ), and points out that there are no firm lines in the spectrum of PNKP diseases. This acknowledgment demands an early genetic diagnosis and continuous follow up of the patient.

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References

1. Bras J, Alonso I, Barbot C, et al. Mutations in PNKP cause recessive ataxia with oculomotor apraxia type 4. Am J Hum Genet. 2015; 96(3): 474–479, doi: 10.1016/j.ajhg.2015.01.005, indexed in Pubmed: 25728773.
2. Kalasova I, Hailstone R, Bublitz J, et al. Pathological mutations in PNKP trigger defects in DNA single-strand break repair but not DNA double-strand break repair. Nucleic Acids Res. 2020; 48(12): 6672––6684, doi: 10.1093/nar/gkaa489, indexed in Pubmed: 32504494.
3. Poulton C, Oegema R, Heijsman D, et al. Progressive cerebellar atrophy and polyneuropathy: expanding the spectrum of PNKP mutations. Neurogenetics. 2013; 14(1): 43–51, doi: 10.1007/s10048-012-0351-8, indexed in Pubmed: 23224214.
4. Rudenskaya GE, Marakhonov AV, Shchagina OA, et al. Ataxia with Oculomotor Apraxia Type 4 with Common „Portuguese" and Novel Mutations in Two Belarusian Families. J Pediatr Genet. 2019; 8(2): 58–62, doi: 10.1055/s-0039-1684008, indexed in Pubmed: 31061747.
5. Shen J, Gilmore EC, Marshall CA, et al. Mutations in PNKP cause microcephaly, seizures and defects in DNA repair. Nat Genet. 2010; 42(3): 245–249, doi: 10.1038/ng.526, indexed in Pubmed: 20118933.