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Abstract:	

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Ataxia and action myoclonus related to novel biallelic mutations in *ATP13A2* gene

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Mutations in *ATP13A2* gene have been causally associated with Kufor-Rakeb syndrome and later with neuronal ceroid lipofuscinosis and complicated forms of hereditary spastic paraplegia (SPG78) [1-3]. *ATP13A2* gene encodes a lysosomal 5P-type ATPase responsible for the selective transport of cations. Bialellic mutations in *ATP13A2* gene cause a lysosomal and mitochondrial dysfunction, leading to a neuronal apoptosis and alpha-synuclein accumulation [4]. Kufor-Rakeb syndrome, a rare autosomal recessive form of juvenile parkinsonism, was first described in 1994 in a consanguineous family from Kufor-Rakeb (Jordan). All affected members presented with the typical clinical features: juvenile-onset parkinsonism, pyramidal signs, dementia and supranuclear gaze palsy [5]. Tremor, dystonia, bulbar dysfunction, slow saccades and facial minimyoclonus were also described, as well as psychiatric manifestations [6]. Cerebellar signs were very uncommon however action myoclonus, ataxia and seizures have been reported together with parkinsonism in a single Iranian family carrying *ATP13A2* mutation [7-9]. More recently, a phenotype with late-onset ataxia and action myoclonus without parkinsonism has been reported [10].

Case Report

We report a 47-year-old male presenting with late-onset myoclonic ataxia syndrome related to biallelic mutations in the *ATP13A2* gene.

The patient was born at term in a non-consanguineous family and his family history was unremarkable. He has an unaffected younger brother. The patient had no delayed psychomotor and language milestones however, hyperactivity and poor academic performance were observed in Primary School. The symptoms started at age

39 with action myoclonus in the upper and lower limbs associated with cerebellar ataxia, which rapidly progressed to wheelchair confinement at the age of 44. Examination at age 47 showed severe action myoclonus involving both upper and lower limbs and moderate dysarthria. No resting myoclonus or tremor was noted, although there were tongue, palpebral and perioral muscle twitches which increased with motor activity. Vertical and horizontal saccades were mildly slowed and broken pursuit was observed. There was no nystagmus. Speech and breathe difficulties were noted due to the presence of diaphragmatic action myoclonus. Deep tendon reflexes were brisk with sustained ankle clonus and bilateral flexor plantar responses. He also had *pes cavus*. The patient was unable to walk or even stand upright without strong support due to severe ataxia and axial myoclonus (Video S1).

Blood examination, microbiological and serological tests values were all normal. Immunological test were performed to exclude causes of acquired ataxia including antineuronal, anti-thyroid, celiac disease and anti-GAD antibodies and were all negative. Cerebrospinal fluid analysis data were normal including absence of oligoclonal bands. Magnetic resonance imaging of the brain revealed cerebellar and brainstem atrophy with secondary dilatation of the fourth ventricle. T2-weighted images showed focal hyperintense lesions in the inferomedial region of the right cerebellar hemisphere and right parietal region related to residual encephalomalacia due to mild traumatic brain injury in childhood (Figure 1. C). Electroencephalogram showed focal irregular delta waves located in the right temporal lobe without epileptiform discharges. Nerve conduction studies evidenced a chronic axonal motor polyneuropathy. Somatosensory evoked potential showed giant potentials. Long latency reflex responses were identified in both median nerves. Back-average technique was not performed due to the absence of continuous myoclonic activity. Electromyography and

electroretinography were normal. The neuropsychological assessment demonstrated dyscalculia, executive dysfunction, and visual-perceptual, verbal memory and learning impairment.

Genetic testing for Friedreich's Ataxia and for spinocerebellar ataxia types 1, 2, 3, 6, 7, 12, 17 and *DRPLA* were negative. Analysis of ataxia and hereditary paraplegia genes by Next-Generation exome Sequencing (NGS) showed predicted pathogenic variants in compound heterozygosity, c.3135C>A; p.Tyr1045Ter and c.3469A>T; p.Lys1157Ter, within the *ATP13A2* gene. Both of these pathogenic variants are predicted to generate a premature stop codon that results in a protein truncation (Figure 1. B). To further determine these variants pathogenicity, segregation study was performed and confirmed the heterozygous carrier status of the patient's mother and sibling (Figure 1. A).

The patient was initially treated with levetiracetam, with an incomplete clinical response of the myoclonic jerks. As the disease progressed, additional anti-myoclonic drugs were tried including piracetam, zonisamide, valproate, topiramate, gabapentin and perampanel. A very modest improvement of action myoclonus was obtained combining levetiracetam, valproate and perampanel.

Discussion

Mutations in the *ATP13A2* gene were identified as the cause of Kufor-Rakeb in 2006, since then the phenotypic spectrum has been broadened with a great variety of clinical features in which parkinsonism is usually predominant [1]. Action myoclonus and cerebellar sings are very rare accompanying features, however as illustrated here, can occur in the absence of parkinsonism. No specific genetic mutation seemed to account

for this phenotype [7-9]. The presence of severe action myoclonus, pyramidal signs and giant potentials in SSEP in our patient together with early onset seizures in previous reports suggest a cortical involvement [7].

In summary, this case illustrates a new phenotype of late-onset action myoclonus and ataxia associated with novel heterozygous compound mutations in the *ATP13A2* gene.

Author contributions

1) Research project: A. Conception, B. Organization, C. Execution;

2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

3) Manuscript: A. Writing of the first draft, B. Review and Critique.

LM: 1BC, 3AB; ASR: 1C, 3B; ALPN: 1BC, 3B; MCJ: 1C, 3B (genetic diagnosis); AMD: 1C, 3B (genetic diagnosis); JI: 1ABC, 3C.

Financial disclosures for the previous 12 months

LMA, ASR, ALPN, MCJ, AMD report no conflict of interests. JI receives research support from the Fondo de Investigación Sanitaria-ISCIII (PI17/00936) and from Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), has also received speaker honoraria from Abbvie and Zambon.

Ethical compliance

Informed consent for video recording was obtained from the patient. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Video 1

Segment 1: Severe upper-limb action myoclonus is observed, together with dysmetria

Segment 2: Continuous perioral muscle twitches

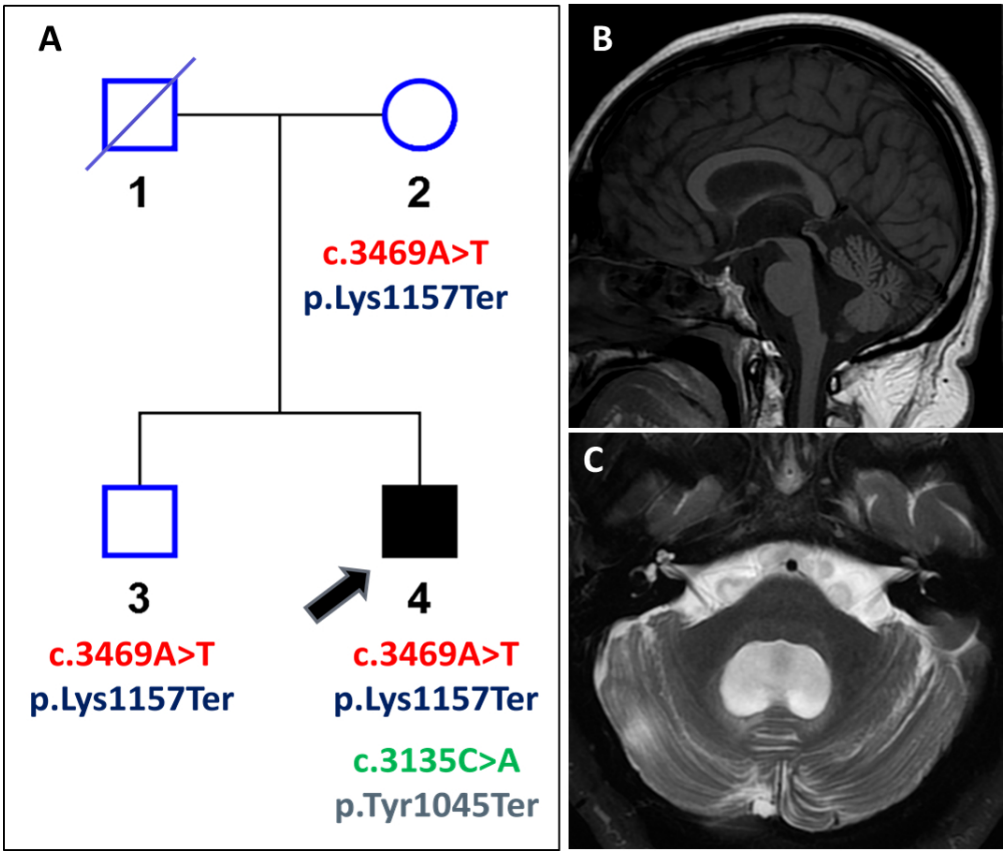
Segment 3: Severe gait ataxia accompanied by axial myoclonic jerks

Segment 4: Lower-limb ataxia

Segment 5: Axial myoclonic jerks with action

Figure 1

Pedigree and segregation analysis of the *ATP13A2* mutations (A). Sagittal T1-weighted (B) and axial T2-weighted MRI (C) showing prominent cerebellar atrophy and fourth ventricle enlargement.



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