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LETTER TO THE EDITOR

First case of autosomal dominant cerebellar ataxia with deafness and narcolepsy (ADCA-DN) with confirmed *DMNT1* gene mutation in Spain. Review of the *DMNT1* mutation syndromes

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Introduction

Autosomal dominant cerebellar ataxia with deafness and narcolepsy (ADCA-DN) is an ultra-rare genetic disease caused by an autosomal-dominant mutation in the DNA methyltransferase-1 (*DNMT1*) gene [1]. This condition normally presents with the neurological triad mentioned in its name around the age of 40.

The ADCA-DN syndrome was first described in 1995 by Melberg et al. in a Swedish pedigree [2]. The actual cause was nonetheless found in 2012 by Winkelmann et al. who identified three different missense mutations in the *DMNT1* gene that affect the targeting sequence and cause a loss of function [1]. Interestingly, mutations in the same gene were previously identified by Klein et al. as the cause of hereditary sensory neuropathy with dementia and hearing loss now called hereditary sensory and autonomic neuropathy type 1E or HSAN1E [3]. These mutations are also missense, and they affect the targeting sequence. However in HSAN1E, the alterations are located in exon 20; whereas in ADCA-DN, they occur in exon 21.

Up to date, 21 families harboring the mutations that cause ADCA-DN have been identified in Europe and USA, but to our knowledge no cases have been described in Spain. Hereby, we present the first case of ADCA-DN with a confirmed *DMNT1* mutation in Spain and briefly review *DMNT1* related disorders.

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Case presentation

A 46-year-old woman complaining of gait instability was remitted to our neurology outpatient clinic. Relevant history included bilateral sensorineural deafness diagnosed at age 35. Family history stood out as her mother had narcolepsy, deafness, was wheelchair-bound by the age of 60 and died at the age of 68 with no clear diagnosis. She has a healthy 35-year-old sister and 6-year-old son.

The patient described a one-year evolution of mild gait instability. At directed anamnesis, she complained of episodes of sudden loss of tone with emotions without loss of consciousness, and a trend to fall sleep without notice. Physical exam only showed impaired tandem gait. Complementary exams included normal blood tests, electroneurogram, and polysomnography. Repeated brain magnetic resonance imaging (MRI) exams (2018, 2021, and 2022) showed non-specific, non-progressing generalized atrophy with cerebellum predominance. A multiple sleep latency test showed a median sleep latency of 2 min. but she only had 1 sleep-onset REM period, not fulfilling the criteria for narcolepsy. Lumbar puncture was rejected by the patient. A panel for hereditary ataxias (including CAG repetitions of SCA 1, 2, 3, 6, 7, and DRPLA genes) was negative. ADCA-DN was suspected by family history, so finally, a directed genetic test for mutations in *DMNT1* resulted in diagnosis of ADCA-DN with a pathogenic heterozygous mutation p.Ala570Val (NM_001130823.3:c.1709C > T).

The patient received genetic counseling, and no symptomatic treatment was initiated as symptoms were mild, and she was already using hearing aids. The DNMT1 variant was not segregated in the proband's family, as samples from her mother were not available and the patient refused to study her son and sister.

Discussion

The *DMNT1*-related disorders are believed to be different spectra of the same disease. Caused by an autosomal dominant missense mutation with 100% penetrance, the presentation is very heterogeneous, including the age of onset (median 38) and progression rate. Depending on the exon, the affected phenotype can resemble more closely ADCA-DN (Exon 21) or HSAN1E (Exon 20) [4, 5].

In ADCA-DN, symptoms of narcolepsy are usually the first presented but are frequently unnoticed, being the most common onset sensorineural deafness, which presents around the age of 20–40 s. Cerebellar ataxia appears afterwards, sometimes overlapping with the previously mentioned symptoms. HSAN1E phenotype presents with epicritic and protopathic sensory axonal neuropathy respecting cranial nerves and torso at around the same age. Sudomotor dysfunction usually follows or overlaps. In both conditions, early dementia presents around the age of 40. Patients can also present a plethora of neurological problems throughout the course of the disease, being the most common optic nerve atrophy, movement disorders such as writer's cramp or parkinsonism and epilepsy. The disease produces early death at the age of 50–60. Some complementary exams may help with diagnosis (Table 1). The diagnosis should be obtained by genetic testing. Management includes symptomatic treatment for the different manifestations and genetic counseling [4].

The NM_001130823.3:c.1709C > T mutation was identified in 2012 as the cause of ADCA-DN by Winkelmann et al. in an Italian and US pedigree [1]. The Italian proband corresponded to a de novo mutation. In the US pedigree, 13 family members were affected, but the mutation was confirmed in 2 individuals. The Italian proband developed narcolepsy–cataplexy at the age of 42 followed by hearing loss, memory problems and depression (age 43), cerebellar ataxia (age 46), peripheral sensory neuropathy (age 47), and optic atrophy (age 55). The patient was alive at the age of 57. The US proband developed narcoleptic symptoms and cataplexy at the age of 35 and 44, respectively, followed by hearing loss and cerebellar ataxia (age 48), memory loss, psychosis and dementia (age 54–56), peripheral sensory neuropathy (age 55), optic atrophy (age 57), and was alive at the age of 58 [1]. Importantly, the mutation was reported as *NM_001130823.1:c.1709G > A* in this study. However, the National Center for Biotechnology Information (NCBI) determined that the expression reported in the article could not be validated, so the Human Genome Variation Society (HGVS) expression *NM_001130823.1:c.1709C > T* is being used to retain the location and sequence consequence, with the assumption that the change reported was from the complementary strand (see note on ref. 6).

In this case, the first confirmed case of ADCA-DN in Spain, the patient reached the age of 46 with no major impairments or cognitive complaints, which demonstrate the variable expressivity of this genetic condition, but a

Table 1 Main phenotype discrepancies and similarities between ADCA-DN and HSAN1 and useful complementary exams with expected pathological result

Age of onset (years)	Phenotype (Exon affected)		Complementary exams
	ADCA-DN (Exon 21)	HSAN1E (Exon 20)	
Variable	Narcolepsy *Daytime sleepiness* *Sleep attacks* *Cataplexy*		• Multiple sleep latency test: • ≤ 8 min. of REM latency. • ≥ 2 Sleep-onset REM periods. • Electroneurogram: Large and small fibre axonal loss. • Sural nerve biopsy: Marked loss of myelinated fibres. • CSF: Low hypocretin. • Brain MRI: Non-specific bihemispheric and cerebellar atrophy. • PET-FDG and perfusion SPECT: Fronto-medial and thalamic hypometabolism.
20–40	Sensorineural deafness	Sensory neuropathy *Hiporreflexia* *Respects cranial nerves and torso* *Epicritic and protopathic*	
30–40	Cerebellar ataxia*	Autonomic neuropathy *Characteristically sudomotor dysfunction predominates*	
40	Early dementia *Executive dysfunction and behavioural disorders*		
Variable	Optic nerve atrophy, epilepsy, movement disorders, etc.		
50–60	Early death		

ADCA-DN Autosomal Dominant Cerebellar Ataxia with Deafness and Narcolepsy; *HSAN1E* Hereditary Sensory and Autonomic Neuropathy type 1E; *CSF* Cerebrospinal fluid; *MRI* Magnetic Resonance Imaging; *PET-FDG* Positron emission tomography with 18F-fluorodeoxyglucose; *SPECT* Single Photon Emission Computed Tomography

*Physical exam is very important to distinguish cerebellar versus sensory ataxia, the latter being possible to appear in HSAN1E long-term outcome will have to be evaluated to confirm this observation. To conclude, we would like to raise awareness of the *DMNT1*-related disorders. Given the expression of these disorders, they can be mistaken with early onset dementia, and the symptoms may be wrongly related to different conditions instead of being put on an adequate clinicopathological context. In this case, family history was crucial to underpin the suspicion of the disorder. An accurate identification of the disorder is especially important to offer genetic counseling for the affected patients, and facilitate further research that may lead to possible treatments in the future.

Author contribution Carlos was in charge of writing the original draft, reviewing and editing, conceptualization, visualization, methodology, and project administration. Ana, Rafael, Gemma, and Dalila helped with the conceptualization and literature review. Natalia and Miguel helped with the conceptualization, reviewing and editing, and fulfilled the role of supervisors.

Declarations

Competing interests The authors declare no competing interests.

Ethical approval Ethical approval was not required. A written consent was obtained from the patient to publish this case.

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