DYNC1H1 de novo mutation, spinal muscular atrophy and attention problems☆

Mutación *de novo* en *DYNC1H1*, atrofia muscular espinal y problemas atencionales

Dear Editor:

The *DYNC1H1* gene, located on chromosome 14q32,[1] encodes the cytoplasmic dynein heavy chain, part of a motor complex with multiple subunits that plays an essential role in retrograde axonal transport and other intracellular functions.[2]

DYNC1H1 mutations are associated with a broad spectrum of diseases, including intellectual disability, epileptic encephalopathy, malformations of cortical development, Charcot-Marie-Tooth disease, hereditary spastic paraplegia, microcephaly, and spinal muscular atrophy with lower limb involvement.[1–5]

We present the case of an 8-year-old boy with a de novo missense mutation of *DYNC1H1*, who was clinically diagnosed with spinal muscular atrophy (predominantly affecting the lower limbs) and predominantly inattentive attention-deficit/hyperactivity disorder.

The patient was the son of young, healthy, non-consanguineous parents. The reason for consultation was inattention and excess motor activity, mainly affecting academic performance and peer relationships. Pregnancy and delivery were uneventful. He had personal history of generalised hypotonia; psychomotor developmental delay, with free ambulation at 30 months and good language development; suspected ataxia since 36 months of age; coeliac disease; and eosinophilic oesophagitis. Regarding family history, his maternal grandmother presented amyotrophic lateral sclerosis. Physical examination detected no pigmentation alterations or dysmorphic features; he presented generalised hypotonia with wide-based gait and predominantly lower-limb weakness. Stretch reflexes were hypoactive and plantar reflex was flexor. The patient did not present dysmetria.

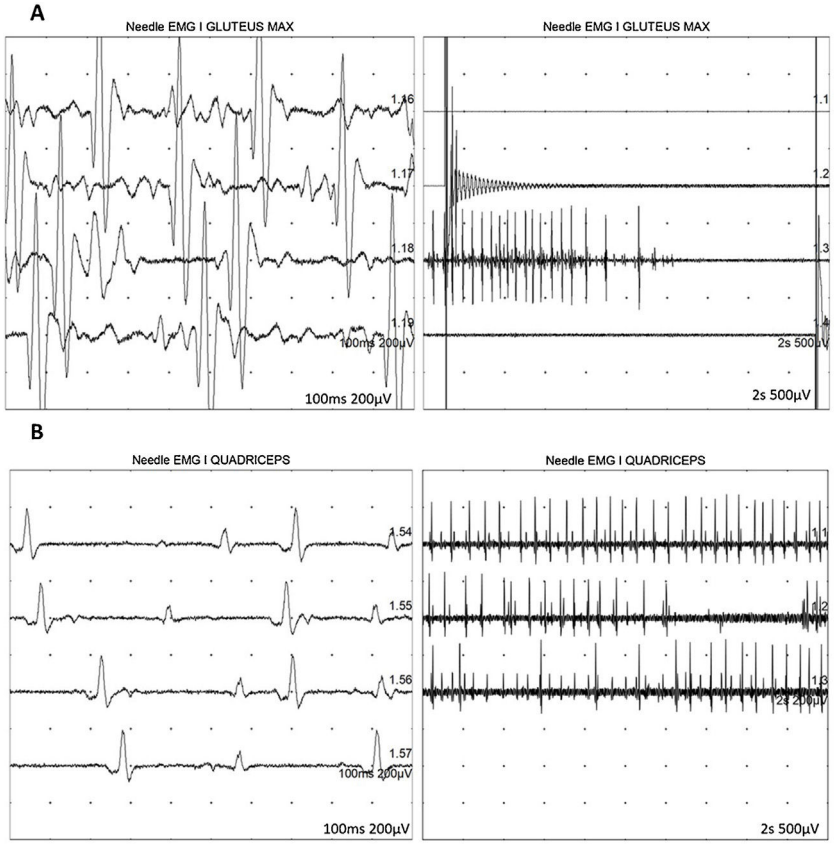

Figure 1 Neurophysiological study showing severe, chronic, axonal neurogenic changes in proximal regions of the lower limbs. Electromyography studies of the left gluteus maximus (A) and quadriceps muscles (B) show increased motor unit potential duration and decreased recruitment, indicating loss of motor units.

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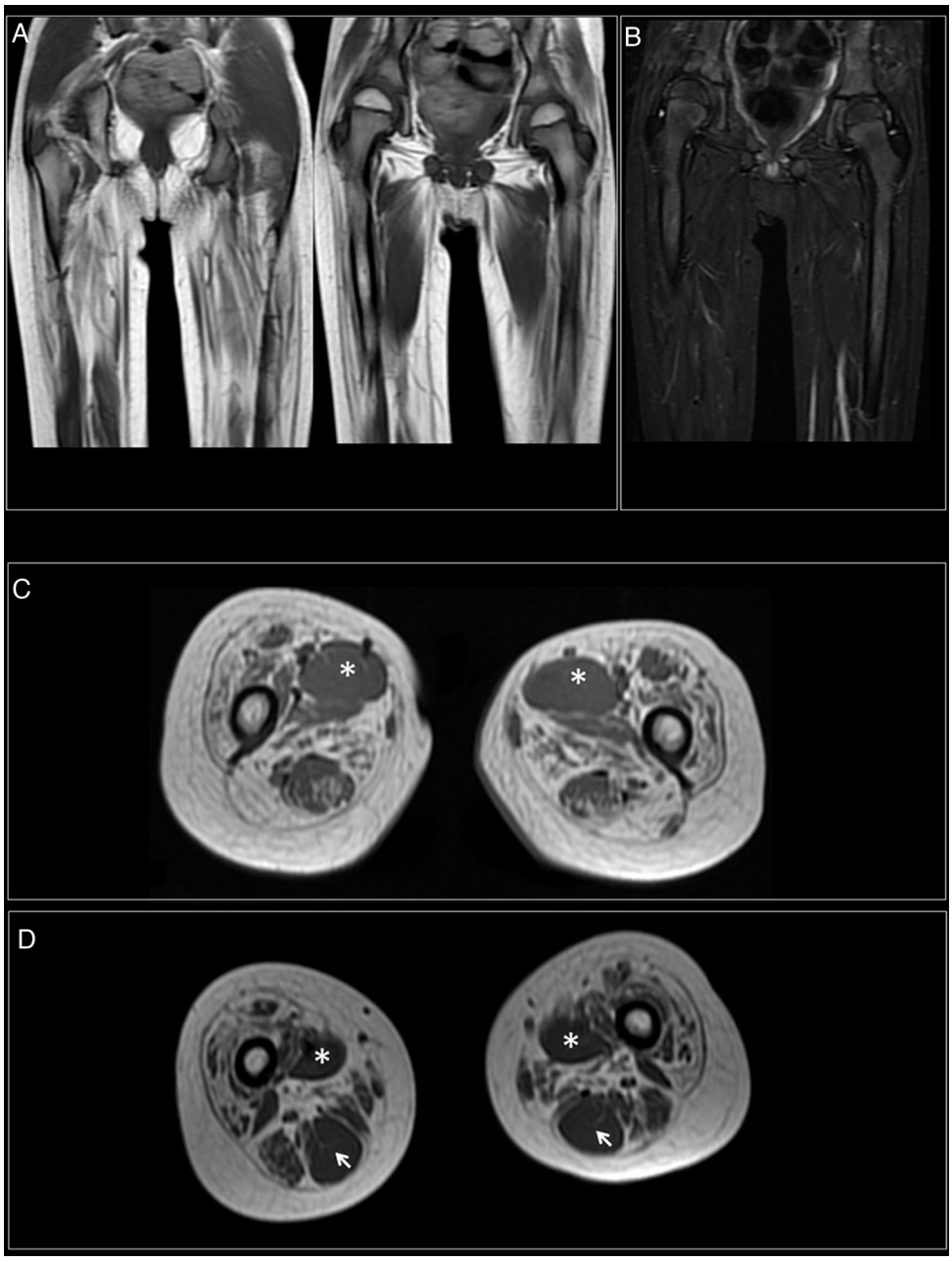

Figure 2 Muscle MRI. (A) Coronal T1-weighted sequence showing fatty replacement of the proximal muscles of both lower limbs; involvement is symmetrical and bilateral. (B) T2-weighted sequences showed no signs of acute denervation. (C) Symmetrical fatty replacement, with particular involvement of the anterior (quadriceps) and medial (adductor magnus) compartments. The adductor longus is preserved (asterisk). (D) Partial fatty replacement of the ischiotibial muscles in the posterior compartment, with the exception of the semitendinosus (arrow).

When the patient was 3 years old, he underwent a genetic study with a targeted panel for ataxias, as well as an electromyography and electroneurography study; all results were normal. A brain and spinal MRI study revealed reduced thickness of the right parasagittal anterior cranial fossa with adaptation of the right inferior frontal and olfactory gyri and the right uncinate fasciculus.

Due to the patient's academic difficulties, at the age of 6 years he underwent a neuropsychological evaluation, which revealed a total IQ of 85 in the Wechsler Intelligence Scale for Children-V, scoring low (5 points) for the digit span; in continued execution tasks, he presented high scores for errors of omission and variable attention (higher than percentiles 95-99). His score for manual dexterity in the Movement Assessment Battery for Children-2 was in the first percentile. Clinical records completed by the patient's parents and teachers were consistent with the neuropsychological evaluation results, indicating pronounced attentional difficulties.

At 7-and-a-half years old, when he consulted at our department, the genetic study was expanded with trio whole exome sequencing, which revealed a *DYNC1H1* mutation (c.751C > T; p.Arg251Cys); we repeated the neurophysiological study (Fig. 1), detecting severe, stable, chronic, axonal neurogenic changes in proximal regions of the lower limbs (gluteal/crural muscles). We also performed an MRI study of the lower limbs (Fig. 2), which revealed complete fatty replacement of the proximal muscles in both legs; symmetrical bilateral involvement was observed on coronal T1-weighted sequences, whereas T2-weighted sequences showed no signs of acute denervation.

Our patient's clinical phenotype is similar to those previously described in the literature.[6] Spinal muscular atrophy is a group of hereditary diseases that cause progressive muscle degeneration and weakness secondary to the loss of spinal or bulbar motor neurons. Most cases are associated with mutations in the *SMN1* gene.[7] In recent reports, cases have been associated with such other genes as *UBA1*, *DYNC1H1*, and *BICD2*.[4,8,9] With regard to the *DYNC1H1* gene, an article from 2018 by Chan et al.[6] reported 4 unrelated patients with the missense mutation c.751C > T in heterozygosis, with a phenotype coinciding with that observed in our patient: predominantly lower-limb muscle weakness, learning difficulties in 2 cases and intellectual disability in the other 2, mild brain MRI alterations, and evidence of spinal muscular atrophy in lower-limb MRI studies. The authors also note that muscle MRI (a non-invasive test) is more specific than muscle biopsy in the diagnosis of this disease.[6] In 2012, Tsurusaki et al.[4] described a different *DYNC1H1* mutation (c.917A > G) in 2 patients with spinal muscular atrophy. Cognitive problems have also been reported; we recommend the article by Fiorillo et al.,[10] who describe attentional problems similar to those of our patient. Initially, mutations in the first domains of this gene were associated with lower motor neuron involvement, whereas mutations at the N-terminal end were associated with cognitive problems or malformations of cortical development[4,11,12]; however, more recent studies and detailed analysis of international data have raised doubts about this genotype-phenotype correlation.[13] The study by Chan et al.[6] demonstrates how an identical mutation in the tail domain of *DYNC1H1* can indistinctly be associated with intellectual disability or learning difficulties. Similarly, mutations in the tail or motor domains have been associated with malformations of cortical development. Thus, phenotypic variability may be influenced by the domain affected, but conditioned by other genetic or even environmental factors.

This case underscores the importance of whole-genome sequencing techniques, which offer greater diagnostic yield than panels or arrays and are recommended as the first-line study in current guidelines; trio sequencing (proband plus parents) further increases sensitivity.[14] We would stress that the combination of both techniques may constitute a potential tool for individuals with undiagnosed neurodevelopmental disorders,[15] as well as the importance of properly interpreting genetic study results. The diagnostic yield and value of these studies are known to increase when they are interpreted in the hospital context by professionals with access to the patient and to the results of complementary studies.[16]

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Antineuronal antibodies: Anti-recoverin in neurological syndromes without retinopathy. SARS-CoV2 infection as a trigger☆

Anticuerpos antineuronales: anti-recoverina en síndromes neurológicos sin retinopatía. Infección por SARS-CoV2 como desencadenante

Dear Editor:

Central and peripheral nervous system diseases associated with presence of antibodies against neuronal epitopes are increasingly frequent. Researchers first identified autoantibodies targeting intracellular antigens, and subsequently autoantibodies targeting synaptic and cell surface proteins. These autoantibodies may appear in the context of tumours, as part of an indirect immune-mediated response,[1,2] or in the context of central nervous system infection.[2]

We present the cases of 3 patients with varying levels of neurological involvement who tested positive for anti-recoverin autoantibodies.

The first patient was a 77-year-old man who was admitted due to diplopia, lower limb weakness, and constitutional symptoms progressing over the course of one month. He also reported episodes of disorientation and sleep-wake cycle alterations. The examination revealed left fourth cranial nerve palsy, proximal paresis of the left lower limb, fasciculations in the quadriceps muscle, and hyperreflexia.

A brain MRI scan detected no alterations. A chest radiography revealed a solid mass in the right upper lobe. Core needle biopsy diagnosed squamous cell carcinoma, and a CT scan ruled out metastasis. Assessment by the ophthalmology department detected no signs of retinopathy.

Symptoms progressed, with the patient presenting more severe weakness, complex ophthalmoplegia, and hypophonia. CSF analysis yielded normal results. Antineuronal antibody testing detected anti-recoverin, anti-Ki67, and anti-GAD65 antibodies. A neurophysiological study showed signs compatible with left polyradiculopathy or left lumbosacral plexopathy. Treatment with immunoglobulins and steroids was ineffective.

The second patient was a 45-year-old man who was admitted due to bilateral pneumonia secondary to SARS-CoV-2 infection and pulmonary thromboembolism, requiring ventilatory support at the intensive care unit. From admission, he presented altered level of consciousness, with alternating episodes of psychomotor agitation and low level of consciousness. A brain MRI scan with contrast detected no alterations, and CSF analysis yielded normal results. EEG revealed desynchronisation and generalised background slowing, with no interhemispheric asymmetry. A 5-day cycle of immunoglobulins failed to achieve a clinical improvement. Ten days later, in view of the impossibility of extubating the patient due to agitation, we administered methylprednisolone dosed at 500 mg/day for 5 days. A subsequent CSF analysis revealed mildly elevated protein levels (61 mg/dL) and presence of leukocytes (31 cells/μL: 68% neutrophils, 29% lymphocytes) and erythrocytes (16 900 cells/μL). The patient improved progressively several days after finishing corticosteroid therapy; sedatives were withdrawn and he was transferred to a ward bed. Antineuronal antibody testing detected anti-recoverin and anti-titin antibodies in the blood. At discharge, the patient presented normal mental state and EEG activity. A PET-CT scan detected no signs of malignancy, an ophthalmologic examination detected no signs of retinopathy, and antibody testing yielded negative results.

The third patient was an 82-year-old man who had recently undergone surgery for a bladder tumour; he was admitted due to status epilepticus consisting of focal clonic seizures affecting the right side of the body, progressing to

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