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A novel *TTN* variant in a patient with distal myopathy of lower limbs and dilated cardiomyopathy☆

Una nueva variante en el gen de la titina en un paciente con miopatía distal de miembros inferiores y miocardiopatía dilatada

Dear Editor:

Titin is a sarcomeric protein expressed in the cardiac and skeletal muscles. It is encoded by a single gene, *TTN*, located on the long arm of chromosome 2.[1] *TTN* gene mutations have been associated with a wide range of cardiomyopathies and skeletal muscle disorders (late-onset tibial muscular dystrophy, early-onset recessive distal titinopathy, autosomal recessive limb-girdle muscular dystrophy-10, etc).[2] Tibial muscular dystrophy (TMD), also known as Udd distal myopathy (late-onset, type 2a), is characterised by late onset (between the ages of 35 and 55 years) and slow progression, and usually only affects the muscles of the anterior compartment of the lower limbs.[3] These patients present normal or slightly elevated serum creatine kinase levels, with EMG results suggestive of myopathy.[3,4] Muscle biopsy results reveal variability in fibre size, central nuclei, necrosis, fibroadipose tissue, and rimmed vacuoles.[5] Muscle MRI reveals selective fat replacement in the muscles of the anterior compartments of the lower limbs.

We present the case of a 37-year-old man with lower limb weakness and muscle atrophy affecting the peroneal and tibialis anterior muscles and the extensor muscles of the toes. He had no history of diabetes mellitus, cancer, or connective tissue disorders. A cardiac comorbidity was also detected, and the patient was diagnosed with dilated non-ischaemic cardiomyopathy. His parents were non-consanguineous, and he had family history of muscle disease of unknown origin in a maternal uncle, who presented weakness and muscle atrophy in the lower limbs. To date, his parents have not consulted due to neurological or cardiac symptoms.

The neurological examination revealed atrophy and weakness in the muscles of the anterior compartment of the lower limbs, with asymmetric weakness of ankle dorsiflexion (right, 1/5; left, 3/5). He was unable to toe walk as a result of the poor dorsiflexion.

A blood analysis including muscle enzymes and a mitochondrial respiratory chain enzyme assay yielded normal results. Electroneurography showed no alterations, and the EMG study revealed low-amplitude polyphasic motor unit potentials with early recruitment of the tibialis anterior muscles; these findings are compatible with a chronic myopathic process. A biopsy study of the quadriceps revealed myopathic alterations with nuclear centralisation and vacuolar degeneration, with no ragged red fibres and normal COX staining.

An MRI scan of the muscles of the lower limbs (Fig. 1) revealed atrophy with fat replacement in the extensor muscles (tibialis anterior, extensor digitorum longus, and extensor hallucis longus, predominantly on the right side). A cardiac MRI scan revealed biventricular dilatation with moderate systolic dysfunction affecting both ventricles, and dilatation of both atria; these findings are compatible with non-ischaemic cardiomyopathy.

Massive sequencing of 8 genes associated with muscular dystrophies (*ANO5*, *DMD*, *DYSF*, *EMD*, *FHL1*, *LMNA*, *SYNE1*, and *SYNE2*) detected no pathogenic mutations. A subsequent sequencing study of 22 genes, including *TTN*, revealed loss of heterozygosity, affecting at least exons 32 to 364 of the gene. The study detected the c.86581T>A (p.Trp28861Arg) *TTN* variant in homozygosis. Cosegregation analysis detected the same variant in heterozygosis in both parents.

TTN mutations have been associated with various muscle diseases, cardiomyopathies, or a combination of both. The first mutation (an 11-bp insertion/deletion) was reported in 2002, and was called FINmaj.[6] A dominant missense mutation in exon 364 (c.107840T>A p.Ile35947Asn) was subsequently detected in a Belgian family.[5] In 2008, Hackman et al.[4] described 3 novel mutations in 2 Spanish families and 2 French families (2 deletions, g.292998delT and g.293376delA) and a nonsense mutation (g.293379C>T [p.Q33396X]). A more recent study describes the phenotype of an Italian family with TMD and a new heterozygous mutation, g.293326A>C, which predicts the amino acid substitution p.His33378Pro.[7] Algahtani et al.[8] report the heterozygous nonsense mutation c.85652C>G (p.Pro28551Arg) in a Saudi patient with bilateral facial weakness.

We describe a novel variant of *TTN* in homozygosis in a Spanish patient with TMD and cardiomyopathy. The patient

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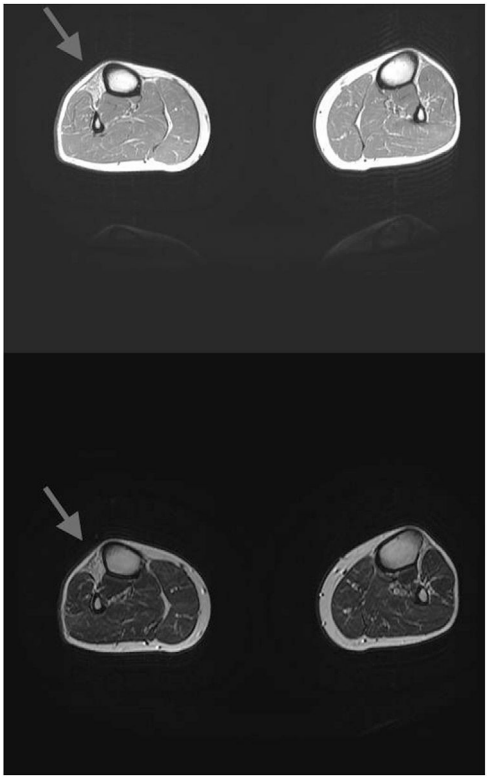

Figure 1 Muscle MRI (axial plane, T2-weighted sequence): atrophy with fat replacement in the extensor muscles of the lower limbs.

presented nucleotide variant c.86581T>A (p.Trp28861Arg), apparently in homozygosis, in exon 341 of *TTN*. This variant causes the substitution of tryptophan for arginine at position 28861 of the polypeptide chain; these 2 amino acids have moderately different physicochemical properties. The change is located in a residue of the fibronectin type III domain, a conserved protein domain widely found in animal proteins. This variant has not previously been described in the literature, nor is it included in the ClinVar, dbSNP, ExAC, or ESP databases.

The presence of weakness affecting the muscles of the anterior compartment of the lower limbs suggests that this novel homozygous variant of *TTN* is pathogenic, and potentially involved in the pathogenesis of TMD and cardiomyopathy.

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Spontaneous spinal epidural hematoma and nonaneurysmal subarachnoid haemorrhage in patient with eosinophilic granulomatosis with polyangiitis☆

Hematoma epidural espinal espontáneo y hemorragia subaracnoidea no aneurismática en paciente con granulomatosis eosinofílica con poliangitis

Dear Editor:

Eosinophilic granulomatosis with polyangiitis (EGPA) is a type of systemic necrotising vasculitis affecting small- and medium-sized vessels, which belongs to the spectrum of anti-neutrophil cytoplasmic antibody (ANCA)—associated vasculitis. Disease progression presents 3 phases, which may or may not be sequential: an allergic phase (asthma, rhinitis, and nasal polyposis), an eosinophilic phase (eosinophilia in peripheral blood or lung or gastrointestinal tissues), and a vasculitic phase, which may involve multiple organs, including the peripheral and, rarely, the central nervous systems (CNS). In 1990, the American College of Rheumatology created a set of diagnostic criteria (asthma, eosinophilia > 10% in peripheral blood, mono- or polyneuropathy, non-fixed pulmonary infiltrates, paranasal sinus abnormalities, and extravascular eosinophilia), with diagnosis being established in patients meeting 4 of the 6 criteria; these criteria have sensitivity of 85% and specificity of 99.7%[1]. Treatment includes corticosteroids and such immunosuppressants as cyclophosphamide in refractory cases. Current series suggest a clear improvement in survival rates, increasing from 70% to 90% at 5 years[2]. Cardiac involvement is the main cause of death in patients with EGPA, followed by brain haemorrhage.

We report the case of a 54-year-old man diagnosed with EGPA due to history of severe cortico-dependent asthma, paranasal polyposis, eosinophilic dermatitis, peripheral eosinophilia, and recently diagnosed axonal sensory polyneuropathy. He was treated exclusively with prednisone, dosed at 5 mg/day.

The patient was assessed at the emergency department due to a 48-h history of spontaneous, sudden-onset low back pain, developing into progressive weakness of the left leg, paraesthesia in the left thigh, pollakiuria, and constipation. Physical examination identified no fever, and arterial blood pressure was 157/111 mm Hg. Neurological examination revealed proximal weakness (3/5) in the left leg, hypoaesthesia at the L1 level, exaggerated left patellar and Achilles reflexes, and left Babinski sign. At baseline, laboratory results (glycaemia, ions, liver and kidney function) and coagulation were normal. A complete blood count revealed leukocytosis (20 000 cells/μL; normal range: <10 200) and eosinophilia (1300 cells/μL [14.8%]; normal range, 500 [<5% of total]). A chest radiography displayed no abnormalities. A thoracolumbar MRI study (Fig. 1A) identified epidural haemorrhages at the T8-L1 and S1-S2 levels; emergency T12-L1 laminectomy and evacuation of the haemorrhages were performed. A spinal cord arteriography performed 24 h after the procedure revealed normal findings.

On the third day after admission, the patient presented a sudden decrease in the level of consciousness; a head CT scan (Fig. 1B) detected a spontaneous subarachnoid haemorrhage (SAH), classed as grade IV on the Fisher scale. A subsequent CT angiography identified no relevant alterations. A brain arteriography performed 36 h later yielded normal findings. The patient died on day 6 after admission.

Our patient meets diagnostic criteria for EGPA of 3 years of progression; given the recent diagnosis of polyneuropathy, it may be classified as being in the vasculitic phase[3].

CNS involvement is reported in 6%—10% of cases of EGPA[4], with ischaemic stroke and brain haemorrhages being particularly common; multiple strokes may occur, and stroke may be the first sign of the disease[4—12]. Spinal haemorrhages are much rarer[13,14].

The largest series of haemorrhagic complications involving the CNS in patients with EGPA is probably that reported by Sabio et al.[3] Of 28 patients diagnosed with EGPA, 14 (50%) presented spontaneous SAH, 13 (46%) presented intraparenchymal haemorrhage, 5 (17.9%) presented intraventricular haemorrhage, and 3 (10.7%) presented spinal haematomas. Ross et al.[14] report 6 cases of EGPA with spinal complications, including 4 with subdural or subarachnoid haemorrhage.

Our patient initially presented a spontaneous spinal epidural haematoma (SSEH), as observed in the neuroimaging study and confirmed during surgery, and subsequently a spontaneous SAH.

It has been suggested that spontaneous SAH in the context of EGPA may be explained both by vasculitis, with disruption of the internal elastic lamina, and by rupture of the post-stenotic dilatation caused by granuloma formation

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