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Paucisymptomatic hyperCKaemia due to a mutation in the *ANO5* gene☆

HiperCKemia paucisintomática secundaria a mutación en el gen ANO5

Dear Editor:

Asymptomatic/paucisymptomatic hyperCKaemia is a frequent reason for consultation at neuromuscular disorders units. Elevated creatine kinase (CK) levels, or hyperCKaemia, may be caused by multiple factors, including hereditary myopathies. One such hereditary myopathy is anoctaminopathy secondary to mutations in the *ANO5* gene (11p14.3). Recessive *ANO5* mutations cause a wide range of clinical phenotypes, including limb-girdle muscular dystrophy type 2 L, Miyoshi myopathy 3, and isolated hyperCKaemia or hyperCKaemia associated with exercise intolerance.[1]

We present the case of a 41-year-old man with no relevant medical history except for hyperCKaemia of 6 years' progression, detected in a routine blood test (1200—4500 U/L). He practised both aerobic and anaerobic exercise, and had developed exercise intolerance over the previous year. He had never presented choluria or rhabdomyolysis. The examination revealed no muscle weakness, amyotrophy, or myotonia. An electromyography study showed motor unit potentials with myopathic features in the muscles of both lower limbs, with no pathological spontaneous activity. A muscle MRI scan revealed asymmetric fatty infiltration in the semimembranosus and medial gastrocnemius muscles (Fig. 1), with myoedema in the semimembranosus, biceps femoris, and gastrocnemius muscles on STIR sequences (Fig. 2), despite the lack of clinical evidence of weakness. A transthoracic echocardiogram and Holter electrocardiography found no alterations. A muscle biopsy revealed a dystrophic pattern, with variations in fibre size, marked nuclear internalisation, and signs of necrosis and regeneration. An immunohistochemical study and Western blot analysis detected no alterations in dystrophin, sarcoglycans, calpain, dysferlin, or caveolin.

In view of the nonspecific dystrophic alterations revealed by the MRI and biopsy studies, we requested a next-generation sequencing analysis of a panel of genes associated with neuromuscular disorders. The analysis identified a homozygous variant, c.1982 T > C, in exon 8 of *ANO5* (reference sequence: NM_213599), which causes amino acid substitution p.Leu661Pro. This variant is registered in the gnomAD database with a frequency of 0.00003230, but had not previously been associated with any disease. A genetic study of the patient's relatives revealed that both parents were heterozygous carriers of the mutation. After over 8 years of follow-up, the patient has developed no further symptoms besides mild exercise intolerance.

We present a case of paucisymptomatic hyperCKaemia secondary to a mutation in the *ANO5* gene; diagnosis was reached with massive DNA sequencing of a pre-established group of genes associated with our patient's symptoms. As mentioned previously, the aetiology of hyperCKaemia is multifactorial. Several diagnostic algorithms can be used, which include different complementary tests[2,3]; gene panel sequencing is not currently included. Among the initial tests performed in our patient, muscle MRI and biopsy

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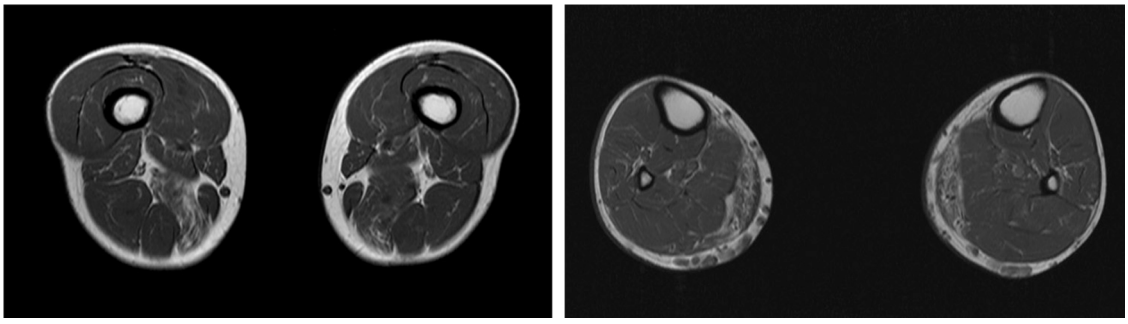

Fig. 1 T1-weighted MRI scan of the thighs and calves, axial plane. Asymmetric fatty infiltration in the semimembranosus and medial gastrocnemius muscles.

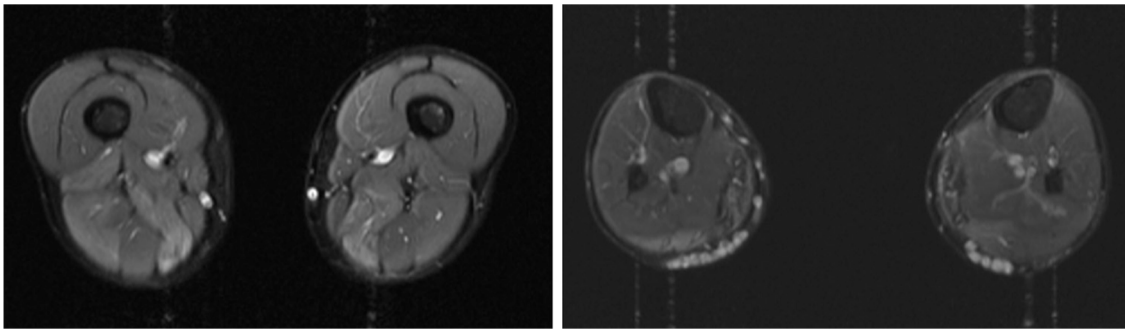

Fig. 2 MRI scan. STIR sequence revealing hyperintensity in the biceps femoris, semimembranosus, and gastrocnemius muscles.

results suggested an underlying dystrophy, but not the specific type. Muscle MRI revealed a pattern compatible with anoctaminopathy, given the asymmetric involvement of the posterior compartment of the thigh and calf.[4] However, this finding is nonspecific, and such other complementary tests as muscle biopsy are required. Although amyloid deposition[5] and necrotising myopathy[6] have been observed in patients with anoctaminopathy, no histopathological markers currently available for use in muscle biopsy provide diagnostic certainty. In view of the above, we requested next-generation sequencing of a panel of genes, reaching a definitive diagnosis. Our results are consistent with those from recent studies into patients with asymptomatic/paucisymptomatic hyperCKaemia, many of whom presented *ANO5* mutations.[7]

DNA sequencing technologies have evolved considerably in recent years; the full genome can be sequenced rapidly and at relatively low cost thanks to such techniques as next-generation sequencing.[8] Due to the considerable genetic heterogeneity of neuromuscular disorders, a comprehensive study of all possible mutations is not always possible. Given that molecular diagnosis must take clinical factors into consideration, analysing panels of genes associated with a specific condition, such as hyperCKaemia in our patient, seems to be the most cost-effective strategy.[9] In the light of the above, it seems reasonable to include gene panel sequencing in the diagnostic algorithm for asymptomatic/paucisymptomatic hyperCKaemia, particularly when the results of previous tests (eg, MRI, muscle biopsy) suggest an underlying myopathy.

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Coma blisters. A key to neurological diagnosis☆

Ampollas por coma. Una clave para el diagnóstico neurológico

Dear Editor:

Coma blisters are bullous skin lesions appearing in patients with low levels of consciousness. They were first described in 1812 by Larrey, a surgeon serving in the French army during Napoleon Bonaparte's rule, in soldiers with carbon monoxide poisoning.

We present the case of a 53-year-old male smoker with poorly controlled arterial hypertension who visited the emergency department due to sudden loss of strength in the right limbs and impaired consciousness. A CT scan revealed an intracerebral haemorrhage measuring 57 × 34 mm in the left basal ganglia, in the context of a hypertensive crisis. The patient's level of consciousness progressively worsened (Glasgow Coma Scale score of 8), and he required orotracheal intubation and sedation with propofol and fentanyl. The patient also presented abnormal movements and tremor, which resolved within 2 days with levetiracetam dosed at 1000 mg every 12 h.

In this context, he presented skin lesions in such pressure areas as the posterior surface of the arms (Fig. 1A), the gluteal area, and the lateral surface of the thighs (Fig. 1B), but also in areas not receiving pressure, such as the anterolateral surface of the left thigh (Fig. 1C). The lesions were tense, clear blisters containing a yellowish fluid; some appeared over erythematous plaques. A biopsy of skin tissue from one of the lesions revealed a subepidermal blister with sparse inflammatory infiltrate (Fig. 1D).

These findings led to a diagnosis of coma blisters (Table 1).

Coma blisters are tense blisters appearing on healthy skin and/or erythematous macules and plaques in patients with impaired consciousness. Blisters vary in size, and may measure up to 4—5 cm; their content is usually serous and rarely bloody. They usually appear 24 hours after initiation of drug treatment, and 48—72 hours after onset of coma.

Coma blisters have traditionally been associated with overdose of CNS depressants, particularly barbiturates, tricyclic antidepressants, hypnotics, opiates, antipsychotics, and alcohol. Other less frequent scenarios include carbon monoxide poisoning; neurological conditions including cerebrovascular disease, head trauma, and viral encephalitis; and such metabolic alterations as hypoglycaemia, diabetic ketoacidosis, hypercalcaemia, and hepatic encephalopathy. Coma blisters have also been reported in non-comatose patients with severe neurological disease.[1—5]

In most cases, clinical findings are sufficient for diagnosis. In case of doubt, skin biopsy[1,4] helps differentiate coma blisters from such other skin lesions as friction blisters and bullous drug eruptions. Table 1 lists the main conditions to be considered in the differential diagnosis of coma blisters.

We initially suspected that our patient's lesions were caused by drug toxicity[3] secondary to a pathogenic mechanism similar to that associated with other drug-induced skin reactions.[6] This hypothesis is supported by the fact that these lesions often appear in the context of sedative overdose; these drugs are normally excreted through the sweat glands, which are typically necrotic in biopsy studies.[4] However, as we mentioned previously, not all cases of coma blisters are drug-induced.[1—5] It seems clear that pressure, friction, and local hypoxia are also involved, since most lesions appear in pressure sites and show vascular damage without significant inflammatory infiltrate.[1,4] However, in some cases, as in the one presented here, lesions appear in areas receiving minimal pressure.

Direct immunofluorescence usually yields negative results; however, some patients display immunoglobulin and complement deposition both in the walls of dermal vessels and in keratinocytes. However, these pathogenic mechanisms are not considered to be immune-mediated, but

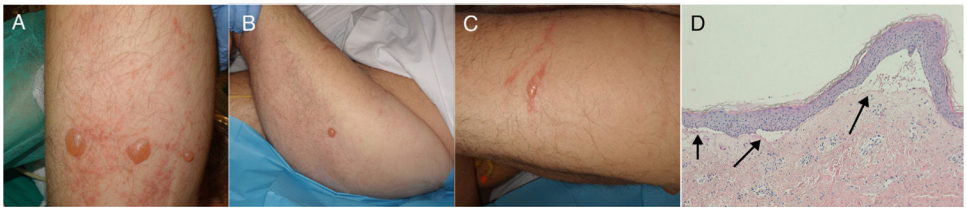

Fig. 1 a) Blisters on the dorsal surface of the right arm, surrounded by erythema. B) Isolated blister on healthy skin on the lateral surface of the left thigh. C) Blister on the anterolateral surface of the left thigh. D) Biopsy of a lesion with haematoxylin-eosin staining (×10), showing the dermoepidermal junction (arrows), with sparse inflammatory infiltrate.

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