CARTA AO EDITOR/LETTER TO THE EDITOR

DOK7-Associated Congenital Myasthenic Syndrome: A Differential Diagnosis of Core Myopathies?

Síndrome Miasténico Congénito por Mutação no Gene *DOK7*: Diagnóstico Diferencial das Miopatias com Cores?

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Downstream-of-kinase (DOK) 7 is a postsynaptic protein associated with the acetylcholine receptor clustering pathway. *DOK7* mutations cause neuromuscular transmission failure, accounting for 10%–15% of all congenital myasthenic syndromes (CMS).[1] While CMS-DOK7 patients may present with classic CMS symptoms, atypical clinical and pathological findings may also be observed.

We report the case of a 22-year-old male who presented with a 3-year history of progressive proximal limb weakness. Despite an unremarkable medical history and achievement of normal motor milestones, he reported difficulty running as a child. There was no familial consanguinity or history of neuromuscular disease. Neurological examination disclosed bilateral facial weakness without ptosis or ophthalmoparesis, bilateral sternocleidomastoid muscle atrophy, proximodistal tetraparesis (G2-3/5UL G4/5LL), mild waddling gait and no clinical myotonia. There was no bulbar weakness or impairment of respiratory function. Creatine kinase (CK) levels were normal and needle electromyography revealed myopathic motor unit potentials in the evaluated muscles. As the first suspected diagnosis was a myopathy, a muscle biopsy was performed and it revealed myopathic features, with type-2 fibre atrophy and rare, discrete core-like areas devoid of oxidative enzyme staining **(Fig. 1)**, leading to the differential diagnosis of a core myopathy. Upon genetic testing (congenital myopathy gene panel), homozygosity for the frameshift mutation c.1124_1127dupTGCC (p.Ala378Serfs*30) in the *DOK7* gene was identified, which is the most common pathogenic mutation associated with CMS-DOK7. Repetitive nerve stimulation was performed afterwards and showed a significant and reproducible decremental response in the spinal accessory nerve. The patient started salbutamol with moderate clinical improvement.

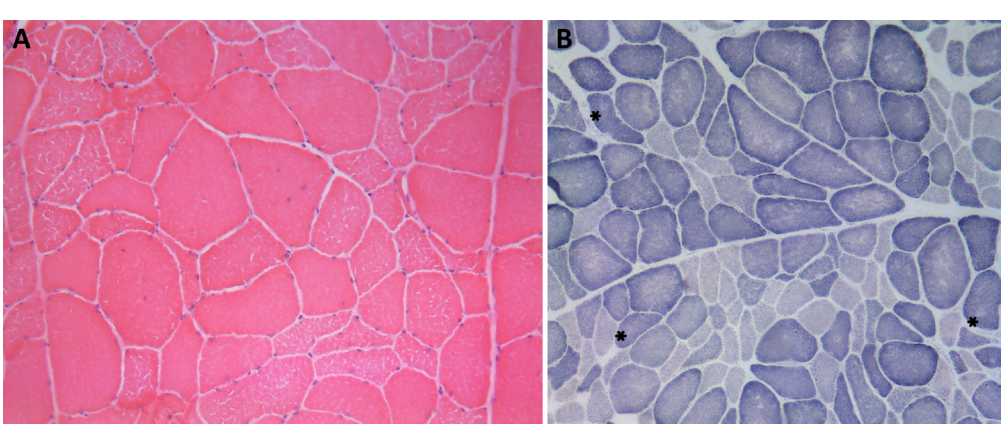

Figure 1. Muscle biopsy. (A) Fibre diameter variability with atrophy and hypertrophy. Haematoxylin and eosin stain, 200X. (B) Rare core-like areas (*) devoid of oxidative enzyme stain. Succinic dehydrogenase (SDH) stain, 100X.

Although its clinical picture may be diverse, most patients with *DOK7* mutations presenting in adulthood display a limb-girdle pattern of weakness and ptosis without ophthalmoparesis. Our patient had predominant UL limb-girdle weakness, which could be a nonspecific clue for CMS diagnosis, but no ptosis or ophthalmoparesis. Exercise-dependent weakness and daytime fluctuation of symptoms are not always present and symptoms may fluctuate over longer periods. Most patients have a slowly progressive course of disease, as presented in our case.[2] So far, no obvious correlation between the clinical symptoms and the location of the mutations could be established, but in a review of the phenotypical spectrum of 14 patients, the patients with late onset of symptoms were all homozygous for the frameshift mutation c.1124_1127dupTGCC, the causative mutation in our patient.[2]

A predominant limb-girdle distribution at this age implies a differential diagnosis with congenital myopathies or muscular dystrophies. In patients with predominant proximal weakness, electrodiagnostic testing is used to evaluate myopathic changes and also to identify neuromuscular junction disease. CMS with this presentation may be easily missed if repetitive nerve stimulation is not performed. As a specific treatment exists for some CMS, an inaccurate or delayed diagnosis hampers patients; access to proper and prompt treatment.[3] Repetitive nerve stimulation should be included as part of the investigation of limb-girdle weakness, especially in young patients.

Biopsy results may be misleading in cases like the one we present. Muscle histology on light microscopy in CMS-DOK7 patients often shows non-specific myopathic changes, that may lead to an erroneous diagnosis of congenital myopathy.[1,3,4] Additionally, rare reports of minicores[3,5] and cores[1,5] in CMS-DOK-7 patients were published over the last decade showing that *DOK7* mutations may predispose to the development of core-like areas in the muscle. Classically, the presence of core-like areas on muscle biopsy was synonym of core myopathies, which are clinically, pathologically, and genetically heterogeneous muscle diseases and an important differential diagnosis of limb-girdle CMS. The finding of core-like areas in CMS-DOK7 patients; biopsies expands the spectrum of its pathological features, although the pathogenesis of these core-like areas in CMS remains unknown. We propose the inclusion of *DOK7* mutations in the differential diagnosis of core myopathies, as the presence of myopathic features in electrophysiologic studies or muscle biopsy does not exclude CMS from the differential diagnosis. ■

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