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Case Report

A novel emerin gene mutation in Emery Dreifuss muscular dystrophy patient with spontaneous chordae tendinae rupture

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ABSTRACT

Emery Dreifuss muscular dystrophy (EDMD) is an inherited myopathy characterized by early contractures, slow progressive muscle weakness and cardiac involvement. To date at least seven genes have been associated to EDMD with different inheritance patterns, being emerin gene responsible for the X-linked form of the disease. We report a 40-year-old man who was referred for severe gait difficulty. At age 6 years the patient presented with a waddling gate, lumbar lordosis and heel contractures. Both electrophysiology and muscle biopsy were consistent with a neurogenic disorder and he received a diagnosis of spinal muscular atrophy type 3. At the age of 30 the patient developed heart involvement with junctional escape rhythm and, eight years later, had a spontaneous chordae tendinae rupture. A new clinical examination showed severe muscular weakness and atrophy in scapulohumeroperoneal pattern with significant involvement of the lower facial and intrinsic hand muscles and on a second muscle biopsy emerin was absent by immunohistochemistry and by immunoblot analysis. Sequence analysis of EMD gene revealed the presence of a novel mutation represented by an out-of-frame deletion spanning from the beginning of exon 1 to the half of intron 2 (p.Asp6Glyfs*27). Our study expands the clinical and molecular spectrum of X-linked EDMD.

1. Introduction

Emery Dreifuss muscular dystrophy (EDMD) is a rare inherited myopathy characterized by the clinical triad of early multi-joint contractures, slowly progressive muscle weakness and wasting with a humeroperoneal distribution, and cardiac involvement leading to conduction defects, dilated cardiomyopathy and sudden death [1]. At least seven genes have been associated to EDMD with different inheritance patterns, being emerin (*EMD*) the most frequent gene for the X-linked form of the disease (EDMD1) [1]. Here we report on a patient with EDMD presenting with atypical clinical features and a novel *EMD* mutation.

2. Case report

A 40-year-old man was admitted to our Department after he dropped out from the neurological follow-up for over 20 years. His motor milestones were normal, but at the age of 6 years he underwent a first neurological evaluation for waddling and asymmetrical stepping gait without limitations in running and daily activities. On clinical examination the patient had Gowers sign, diffuse mild muscle wasting without a distinctive pattern of distribution, lumbar lordosis and shortening of both Achilles tendons. Deep tendon reflexes were absent. Family history was significant for gait disturbance and sudden cardiac death in his maternal grandfather, whose three brothers presented walking impairment too (Fig. 1A). Serum CK values were elevated up to three times the upper limit of normal value and electrocardiogram (ECG) was normal. An electromyography (EMG) revealed myopathic features including small, polyphasic units and fast recruitment but four years later a second EMG recorded neurogenic motor units potentials (MUPs). A muscle biopsy showed neurogenic features including isolated atrophic fibers with angular borders and type grouping. Based on clinical and laboratory findings, the patient was diagnosed with spinal muscular atrophy (SMA) type 3. At 30 years of age, the patient was found to be in asymptomatic junctional escape rhythm at 46 beats per minute and he was referred for full cardiac assessment including 24 -h Holter monitoring and echocardiography every sixth months. At the age 38 he required mechanical mitral valve replacement for severe acute

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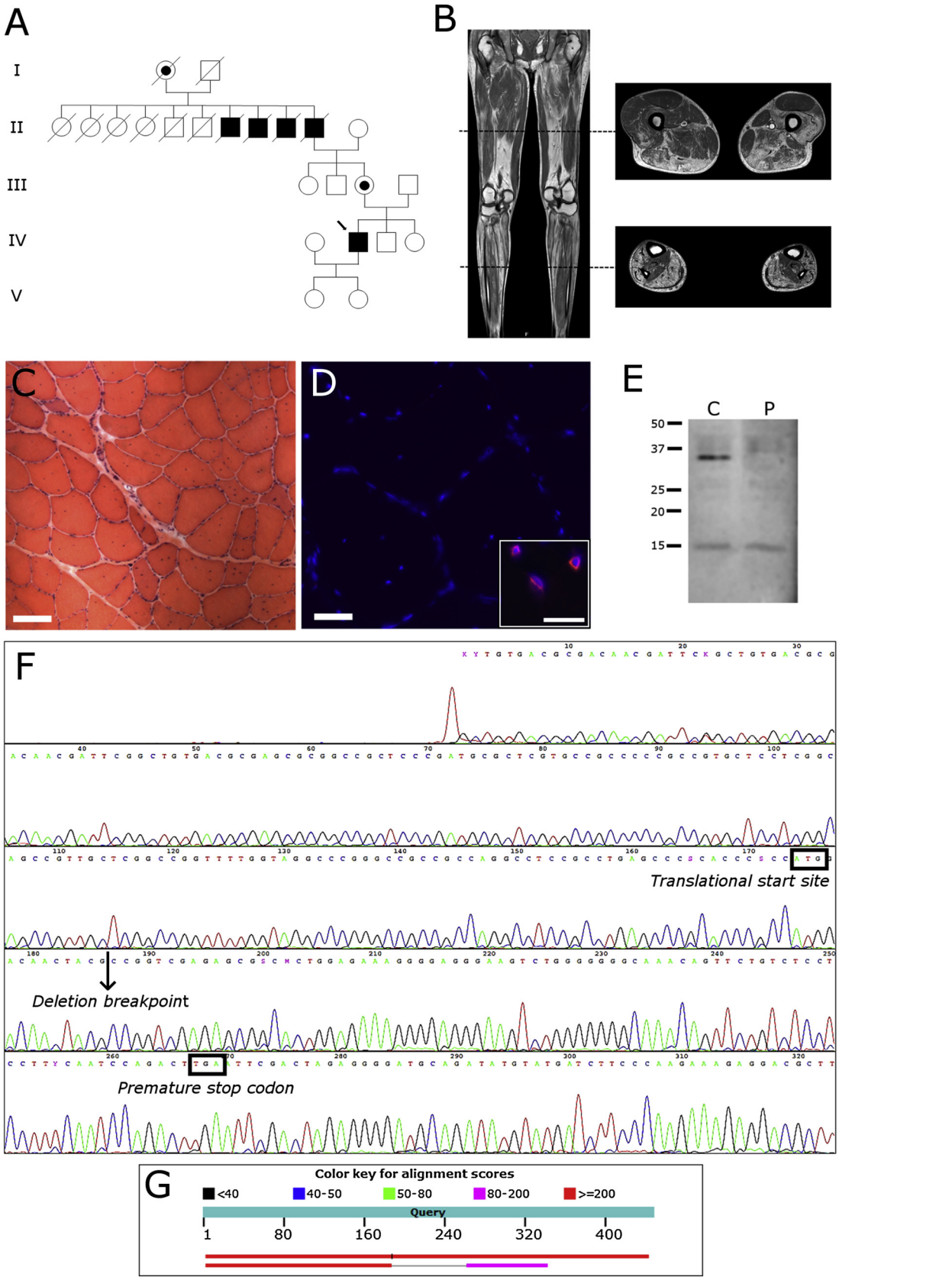

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Fig. 1. A, Pedigree of the family. Arrow indicates the patient. **B,** Muscle MRI of lower limbs. Severe fatty infiltration predominantly in the posterior compartment of the thigh muscles and in the anterior compartment of the leg muscles. **C,** Light microscopy of muscle biopsy specimen. Hematoxylin and eosin stain shows increased variation in fiber size and several fibers with internal nuclei. Bar: 50 μm. **D,** Immunofluorescence for emerin. Immunoreaction of emerin is absent at the nuclear membrane. Bar: 50 μm. Inset, emerin staining of control muscle. Bar: 20 μm. Nuclei are stained with DAPI. **E,** Immunoblot analysis of emerin. Emerin is detected as a band of approximately 35 kDa in control muscle (C) but is absent in muscle of patient (P). **F and G,** Sequence analysis of amplification product obtained amplifying *EMD* from exon 1 to exon 3, showed the presence of a genomic deletion involving part of exon 1, intron1, exon 2 and part of intron 2. (F) Chromatogram of *EMD* mutated sequence. Boxes highlight the canonical translation start codon in exon 1 and the premature stop codon generated by the deletion. Arrow indicates the deletion breakpoint joining exon 1 to intron 2. (G) Scheme of result obtained by Alignment Sequences Nucleotide BLAST (https://blast.ncbi.nlm.nih.gov/Blast) with genomic reference sequence (NG_8677.1).

mitral regurgitation due to spontaneous chordae tendinae rupture.

On admission the patient presented a waddling and toe walking gait. There was moderate to marked weakness and atrophy of scapula fixators, pectoralis, deltoid, triceps, biceps brachii and intrinsic hand muscles, mild to moderate weakness and atrophy of hip flexor and biceps femoris muscles, and marked weakness and wasting of tibialis anterior. A moderate weakness of the orbicularis oris muscle was also observed. Deep tendon reflexes were absent and sensory exam was normal. Bilateral contractures of both elbows and ankles were evident. Based on these new clinical features an alternative diagnosis was considered. ECG confirmed a junctional escape rhythm and echocardiography showed only mild left atrial dilatation. EMG recorded a chronic neurogenic pattern without spontaneous activity at the deltoid, brachial triceps, biceps brachii, tibialis anterior and rectus femoris muscles. Nerve conduction studies of upper and lower limbs including median, radial, ulnar. tibial, peroneal and sural nerves were normal. Lower limb muscle MRI documented severe fatty infiltration of muscles predominantly in the posterior compartment of the thigh and in the anterior compartment of the leg with relative preservation of the gracilis, sartorius, soleus, tibialis posterior, extensor hallucis longus, vastus medialis, obturator and ilio-psoas (Fig. 1B). Spirometry and videofluoroscopic swallow study were normal. An open biopsy of the left vastus lateralis muscle showed dystrophic features with marked fiber size variation, many fibers with internal nuclei, few necrotic fibers and endomysial fibrosis (Fig. 1C). Immunohistochemistry documented absent nuclear staining for emerin (Fig. 1D) but normal immunoreactivity for all other tested antibodies including dystrophin, α-, β- and γ-sarcoglycan, α-dystroglycan, caveolin-3, dysferlin, laminin α2 and spectrin. Emerin was not detected by immunoblot analysis (Fig. 1E). Mutation analysis identified a never reported genomic deletion with an extension of 367 nucleotides, spanning from exon 1 to intron 2, resulting in a frameshift mutation (c.14_187 + 71del) in the *EMD*, leading to the recognition of a premature stop codon (p.Asp6Glyfs*27) (Fig. 1F).

3. Discussion

Our patient is of clinical interest for a number of reasons. First, he presented cardiac involvement with junctional escape rhythm at age 30 and, eight years later, had a rupture of mitral chordae tendinae without potential underlying causes such as mitral valve prolapse, local myxomatous degeneration, subacute endocarditis, rheumatic heart disease, connective tissue abnormalities, blunt chest trauma, hypertrophic cardiomyopathy and ischemic heart disease [2]. Junctional escape rhythm is a common ECG finding in patients with X-linked EDMD [3,4] but there are no reports of spontaneous chordae tendinae rupture in EDMD patients. Although primary rupture of mitral chordae tendineae is relatively frequent, mostly among male adults over fifty [2], we cannot conclude definitively whether in our patient it represents a phenotypic manifestation of the disease or is either a coincidental event. The second interesting clinical aspect is the distribution of the muscle weakness and atrophy. Beside the distinctive scapulohumeroperoneal pattern of weakness, our patient at the age of 40 years presented a significant involvement of the lower facial muscles and of the intrinsic hand muscles, which are usually mildly and later affected in the course of the disease [5–7]. Finally, the missed diagnosis of EDMD which in our patient was reached only in his adult life. This delay may be due to different reasons. At the first neurological examination the clinical picture was characterized by a waddling gait, suggesting a proximal muscle weakness of lower limbs, associated with the more typical peroneal involvement, and the classical tendineous contractures, usually predating symptomatic weakness, became relevant in the second decade. Repeated EMGs recorded neurogenic features during the follow-up and the first muscle biopsy was consistent with a primary neurogenic process which led to the diagnosis of SMA type 3. Cardiac manifestations were underdiagnosed for a number of years. Lastly, and most important, the lack of a regular clinical and laboratory follow-up.

4. Conclusion

In conclusion, our patient with a novel *EMD* mutation showed chordae tendinae rupture, an atypical cardiac manifestation within the context of X-linked EDMD.

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Declaration of Competing Interest

We declare no conflicts of interest.

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