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Facio-scapulo-humeral muscular dystrophy with early joint contractures and rigid spine

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Early joint contractures in childhood or adolescence irrespective of muscle weakness are usually found in Emery-Dreifuss muscular dystrophy and collagen-VI related diseases and only rarely in the early stages of other progressive muscular dystrophies. We report a patient presenting severe elbow contractures and a rigid-spine since his early childhood without any evident muscle weakness, who was diagnosed with facioscapulohumeral muscular dystrophy later in life. This case is interesting since there has been no report, to date, of patients with a phenotype resembling facioscapulohumeral muscular dystrophy also in association with early and prominent elbow contractures and spinal rigidity, since childhood, resembling Emery-Dreifuss muscular dystrophy. Our case further confirmed the phenotypic variability often observed in carriers of *D4Z4* reduce allele, and highlights the complexity of a definitive diagnosis in these cases.

Key words: facioscapulohumeral muscular dystrophy, Emery-Dreifuss muscular dystrophy, joint contractures

Introduction

Early joint contractures and spinal rigidity, in childhood or adolescence, more prevalent than muscle weakness, are usually associated with Emery-Dreifuss muscular dystrophy (EDMD) where there is a scapuloperoneal pattern of weakness and heart involvement (1) and with collagen VI-related myopathies (2). In contrast, in progressive muscular dystrophies joint contractures usually appear late with advanced disease and are associated with severe weakness and reduced mobility. Nevertheless, prominent joint contractures, disproportionate to muscle weakness, have occasionally been reported in early stages of some limb-girdle muscular dystrophies (LGMD), usually calpainopathies (3, 4) or other rare myopathies such as LGMD1F, associated with mutations of the *TNPO3* gene (5), in BAG3-related myofibrillar myopathy (6), in myopathy with tubular aggregates related to *STIM1* gene mutations (7) and with recessive mutations of the *TTN* gene (8).

Facioscapulohumeral muscular dystrophy (FSHD) is one of the commonest muscular dystrophies (9) with disease onset ranging from childhood to late adulthood and typical clinical presentation involving facial muscles, shoulder girdle muscles, distal lower extremities muscles and later on proximal lower extremities muscles. There is a striking left to right asymmetry in muscle involvement and there is often severe weakness of axial muscles (9). Joint contractures appear late in the course of the disease and if prominent and early they set the diagnosis into question (10). We herein report the atypical phenotype of a patient diagnosed with FSHD who presented severe, early contractures and rigidity of the spine.

Case description

A 34-year old man, born from a non-consanguineous marriage, presented to our hospital reporting impairment in upper limb abduction, due to winged scapula, since the age of 27 years and subsequently a five-year slowly progressive difficulty in climbing stairs. He had no family history of neuromuscular disease.

On examination the patient had a waddling and stepping gait, bilateral scapular winging with impaired upper limb abduction, lumbar hyperlordosis and asymmetric lower facial muscle weakness. Asymmetric right sided atrophy of pectoralis and trapezius muscles was also evident. There was no weakness on upper limbs and on lower limbs there was severe distal weakness in the anterior leg compartment (tibialis anterior muscle graded 3/5 at the MRC scale), as well as weakness of the posterior thigh compartment (hamstrings graded 2/5 at the MRC scale). There was co-existing abdominal wall muscle weakness and a positive Beevor sign. Striking was the presence of severe bilateral elbow contractures (Fig. 1), that the pa-

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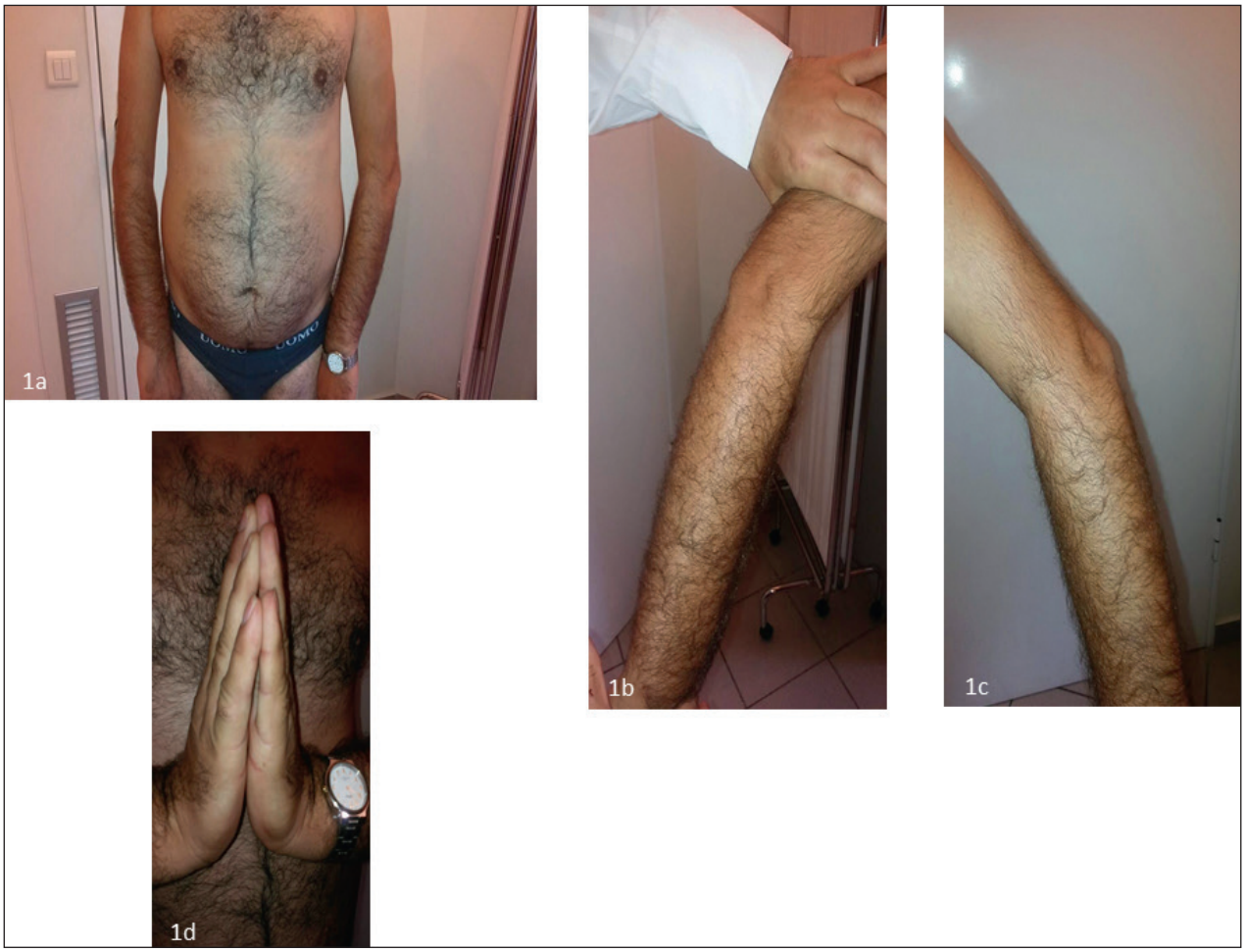

Figure 1. a) Bilateral elbows contractures; **b)** Right elbow contracture; **c)** Left elbow contracture; **d)** No "prayer sign": the patient can put the fingers close together with the elbows extended.

tient reported as being present since his early childhood, as well as of spinal rigidity, resembling an EDMD-like phenotype. Orthopedic framework at that time averred negative for an underlying bone/joint disease accounting for the contractures. His creatine kinase (CK) levels were 650 U/l (normal values 40-174 U/l). Electromyography showed myopathic traces in all examined muscles (defined as small amplitude, short duration, polyphasic motor unit action potentials, with early recruitment) as well as scarce spontaneous activity and rare myotonic discharges in biceps brachii and deltoid muscles, while nerve conduction studies were normal. A lower limb muscle MRI disclosed bilateral fatty infiltration of posterior thigh compartment as well as of tibialis anterior muscle in the lower legs.

Genetic testing was carried out for myotonic dystrophy type 1 and 2 due to the presence of myotonic discharges on electromyography and averred negative. Subsequent testing for restriction fragment at 4q35, revealed the presence of an allele with 10 *D4Z4* repeats, compatible with the diagnosis of FSHD with uncommon features (clinical category D1) (11). The patient refused to undergo further genetic testing for genes related to myopathies associated with early contractures (*LMNA, EMD, FHL1, TTN, COL6, CAPN3*) but agreed to a right tibialis anterior muscle biopsy. Muscle biopsy was processed as previously described (10) and revealed dystrophic features (muscle fiber necrosis and regeneration), no evidence of myofibrillar pathology or any abnormality in immunohistochemical studies.

Discussion

Facioscapulohumeral muscular dystrophy has a rather typical clinical presentation where joint contractures appear late in the course of the disease and if prominent and since the early stages, they set the diagnosis into question (12 13). In contrast to this concept we present the

interesting case of a young man diagnosed with FSHD, who presented with a scapuloperoneal syndrome with early and prominent elbow contractures and spinal rigidity, since childhood, resembling Emery-Dreifuss muscular dystrophy. The patient harbored a borderline contracted fragment of 10 *D4Z4* repeats in a permissive 4q35A chromosome, compatible with the diagnosis of FSHD (12). Longer *D4Z4* contractions are usually not de novo mutations (14) but often show reduce penetrance (15) probably explaining the lack of a positive family history in our patient. Unfortunately, refusal of other relatives to undertake genetic testing cannot exclude the presence of asymptomatic carriers among them. Our patient also reported early elbow contractions and rigid spine since early childhood, resembling an Emery-Dreifuss-like phenotype. Facioscapulohumeral muscular dystrophy "double trouble" condition patients are frequently reported (16) and such a "double trouble" with a co-existent myopathy associated with early contractures was not formally excluded by further genetic testing in our patient, since he refused. Nevertheless, there were no clinical or systemic manifestations reminiscent of another muscle disease. There was no family history of heart disease, nor did a meticulous cardiac evaluation disclose any heart involvement in him as it would have been expected in the case of EDMD (1). Muscular MRI didn't reveal the typical pattern we encounter in collagen VI related myopathies (17) and other typical clinical signs of collagenopathies such as keloids or prayer sign (Fig. 1d) were not found on clinical examination (2). As far as titin associated Emery-Dreifuss-like recessive muscular dystrophy it doesn't seem very likely since all previously reported cases had a childhood-onset disease (8). Calpainopathy seems not very probable since it doesn't present with a scapuloperoneal pattern of weakness and usually has higher CK levels (18) and on clinical examination we found no miosis or opthalmoparesis and the patient reported no myalgia features that are usually reported in *STIM1*-related myopathy (7, 19). In short of further genetic testing a tibialis anterior muscle biopsy was performed revealing neither myofibrillar pathology nor abnormalities in immunohistochemical staining suggestive of another coexisting myopathy that could account for his contractures.

Early contractures and spinal rigidity are usually not part of the typical clinical spectrum of FSHD (13). Nevertheless, atypical phenotypes associated with reduced *D4Z4* alleles, and completely different from the characteristic pattern of muscle involvement of the disease (12, 13) have already been described in carriers *D4Z4* reduced allele (16), especially, in patients with borderline contractions (20). Borderline *D4Z4* allele contractions have been associated with a broad myopathic spectrum, including FSHD with atypical phenotypes and it has been suggested that other factors besides *D4Z4* repeat number are involved in modulating disease penetrance, phenotype and severity in this borderline region (20). Our case confirms the large spectrum of phenotypes associated with *D4Z4* contraction, particularly with borderline alleles, highlights that early and prominent contractures and rigid spine can be found in a patient with FSHD and that if there are other signs of the disease, genetic testing should be performed. Whether this case represents a rare, underdiagnosed atypical phenotype of FSHD, or simply a "double trouble" with an underlying, second co-existing myopathic disorder needs to be further elucidated.

Conflicts of interest

None of the authors has any conflict of interest to disclose.

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