Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 29 (2019) 678–683

www.elsevier.com/locate/nmd

Case report

X-linked Emery–Dreifuss muscular dystrophy manifesting with adult onset axial weakness, camptocormia, and minimal joint contractures

Marion Brisset[a], Rabah Ben Yaou[b,c], Robert-Yves Carlier[d,e], Anaïs Chanut[f], Guillaume Nicolas[a,e], Norma B. Romero[b,c,f], Karim Wahbi[g], Camille Decrocq[i], France Leturcq[h], Pascal Laforêt[a,e], Edoardo Malfatti[a,e,*]

[a] *APHP, Department of Neurology, Raymond Poincaré Hospital, Centre de Référence de Pathologie Neuromusculaire Nord-Est-Ile-de-France, 104 Bld Raymond Poincaré, 92380 Garches, France*

[b] *APHP, Centre de Référence de Pathologie Neuromusculaire Nord-Est-Ile-de-France, Institut de Myologie, G.H. Pitié-Salpêtrière, F-75013 Paris, France*

[c] *Université Sorbonne, INSERM U974, Center of Research in Myology, Institut de Myologie, G.H. Pitié-Salpêtrière Paris F-75013, France*

[d] *APHP, Medical imaging Department, Raymond Poincaré teaching Hospital, GHU GH HUPIFO, 104 Bld Raymond Poincaré, 92380 Garches, France*

[e] *Service de Neurologie, U1179 UVSQ-INSERM Handicap Neuromusculaire: Physiologie, Biothérapie et Pharmacologie appliquées, UFR Simone Veil-Santé, Université Versailles-Saint-Quentin-en-Yvelines, Pôle neuro-locomoteur, Hôpital Raymond Poincaré, Paris-Saclay, 104 boulevard Raymond Poincaré, 92380 Garches, France*

[f] *Unité de Morphologie Neuromusculaire, Institut de Myologie, Groupe Hospitalier Universitaire La Pitié-Salpêtrière, Paris, France*

[g] *APHP, Department of Cardiology, Cochin Hospital, 75015 Paris, France*

[h] *APHP, Laboratoire de Génétique et Biologie moléculaire, HUPC Cochin, Paris, France*

[i] *Department of Physiology, Foch Hospital, 40 Rue Worth, 92150 Suresnes, France*

Received 28 February 2019; received in revised form 1 June 2019; accepted 14 June 2019

Abstract

Emery–Dreifuss muscular dystrophy is an early-onset, slowly progressive myopathy characterized by the development of multiple contractures, muscle weakness and cardiac dysfunction. We present here the case of a 65-year-old male patient with a 20 year history of slowly progressive camptocormia, bradycardia and shortness of breath. Examination showed severe spine extensor and neck flexor muscle weakness with slight upper limb proximal weakness. Cardiologic assessment revealed slow atrial fibrillation. Whole body MRI demonstrated adipose substitution of the paravertebral, limb girdle and peroneal muscles as well as the tongue. Emerin immunohistochemistry on patient muscle biopsy revealed the absence of nuclear envelope labeling confirmed by Western Blot. Genetic analysis showed a hemizygous duplication of 5 bases in exon 6 of the *EMD*, *emerin,* gene on the X chromosome. This is an unusual presentation of X-linked Emery–Dreifuss muscular dystrophy with adult onset, predominant axial muscles involvement and minimal joint contractures. Diagnosis was prompted by the analysis of emerin on muscle biopsy.

Keywords: *EMD* gene; Emerin; Emery–Dreifuss muscular dystrophy; Muscular dystrophy; Muscle biopsy; Emerin immunohistochemistry; Whole body MRI.

1. Introduction

Emery–Dreifuss muscular dystrophy (EDMD) is an early-onset, usually in the first decade, slowly progressive myopathy [1]. EDMD is mainly caused either by mutations in *EMD* gene encoding emerin in X-linked EDMD (X-EDMD) [2], or mutations in *LMNA* gene encoding lamins A and C in autosomal dominant and recessive forms [3]. EDMD clinical presentation includes the classical triad of symptoms with early joint contractures involving the Achilles, elbows and the neck tendons, progressive muscle weakness and wasting beginning in the humeral and peroneal regions, and cardiac disease combining cardiac arrhythmias, conduction defects and cardiomyopathy [4,5]. Mean age of onset is reported to

* Corresponding author at: Service de Neurologie, U1179 UVSQ-INSERM Handicap Neuromusculaire: Physiologie, Biothérapie et Pharmacologie appliquées, UFR Simone Veil-Santé, Université Versailles-Saint-Quentin-en-Yvelines, Pôle neuro-locomoteur, Hôpital Raymond Poincaré, Paris-Saclay, 104 boulevard Raymond Poincaré, 92380 Garches, France.

E-mail address: edoardo.malfatti@gmail.com (E. Malfatti).

https://doi.org/10.1016/j.nmd.2019.06.009

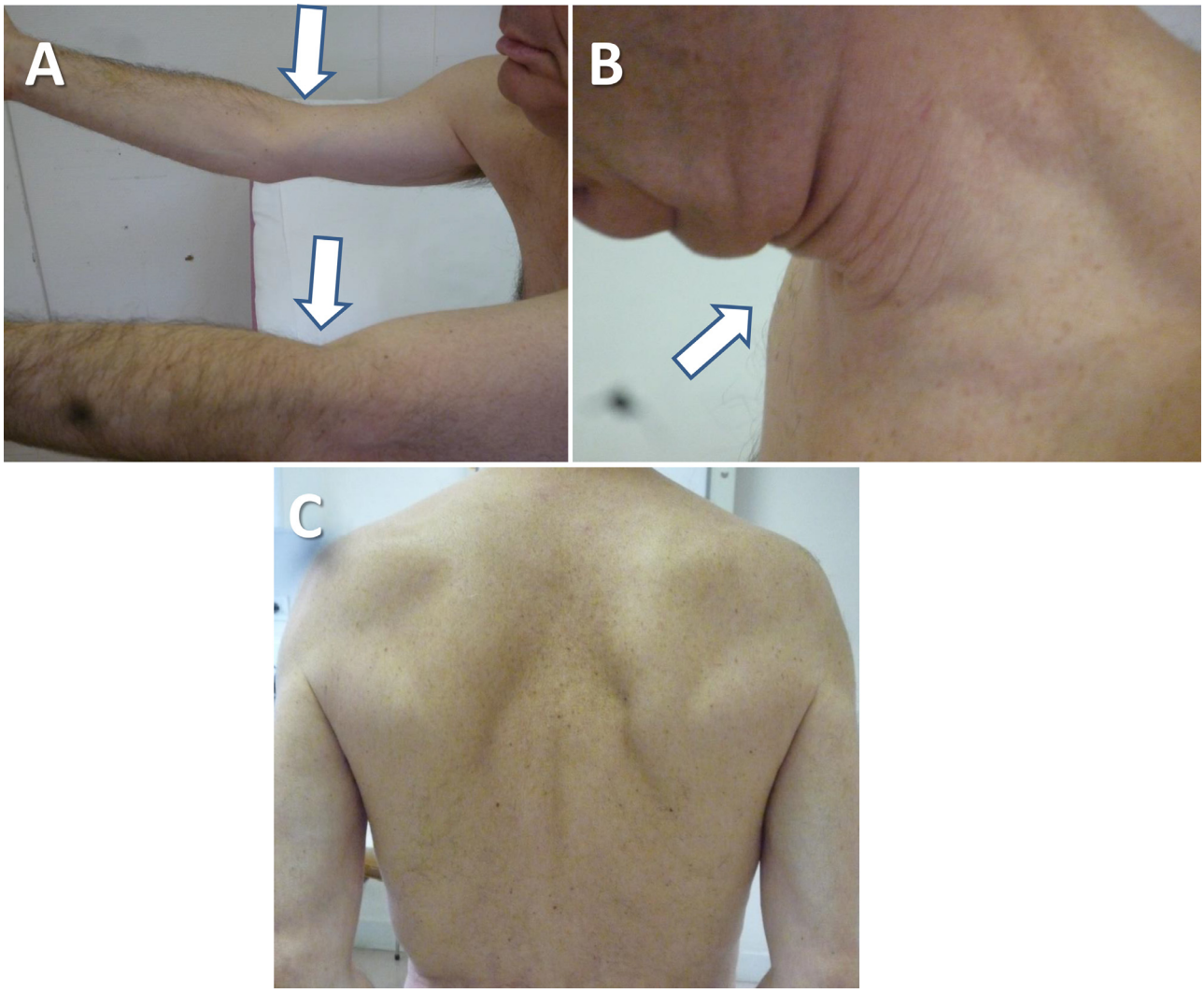

Fig. 1. *Patient's pictures.* (A) Mild elbow contractures (arrows). (B) Mild neck contractures (arrow). (C) Scapular winging.

be 5.6 years (4.2–6.9) in EDMD patients carrying an out of frame *emerin* gene mutation [6]. In another large series of 20 *emerin* mutated patients, Astejada et al. [7] found a higher range of age of onset (10.1 ± 9.5 years) distributed along the first and second decades of life. Symptoms of onset were usually joint contractures before the development of any significant muscle weakness, lower limb muscle weakness, or isolated heart conduction blocks.

We report here a man with X-linked EDMD showing unusual age of onset and muscle phenotype. Muscle immunohistochemistry allowed orientating the genetic screening toward the *EMD* gene.

2. Case report

The proband is a 65-year-old man of North African origin, born to non-consanguineous parents, a diving instructor. He had experienced mild difficulties with sporting activities from childhood and used orthopedic insoles. His mother wore a corset in adulthood and died at 65 years of unknown cause. The patient developed asymptomatic sinus bradycardia detected from 25 years of age. From age 45, he progressively showed camptocormia during walking, dyspnea on exertion, and difficulty carrying heavy weights. For example, he needed help to lift an oxygen bottle out of the water. His first physical examination at 65 years revealed a waddling gait, hyperlordosis, camptocormia with progressive worsening during walking, and slight elbow (Fig. 1(A)) and neck contractures (Fig. 1(B)). Additional features included mild facial weakness consisting of inability to puff out his cheeks and evert his lower lip; scapular winging (Fig. 1(C)) and atrophy of the biceps brachii and left calf. Manual muscle testing showed a mild proximo-distal upper limb weakness involving wrist extensors, elbow flexors and extensors, shoulder flexors, and interossei muscles (graded 4/5 on MRC scale). There was marked axial weakness involving trunk flexors and extensors, with difficulties in rising up from supine position.

CK level was normal (131 UI/L). ENMG needle electrode examination revealed pseudo neurogenic pattern with fast

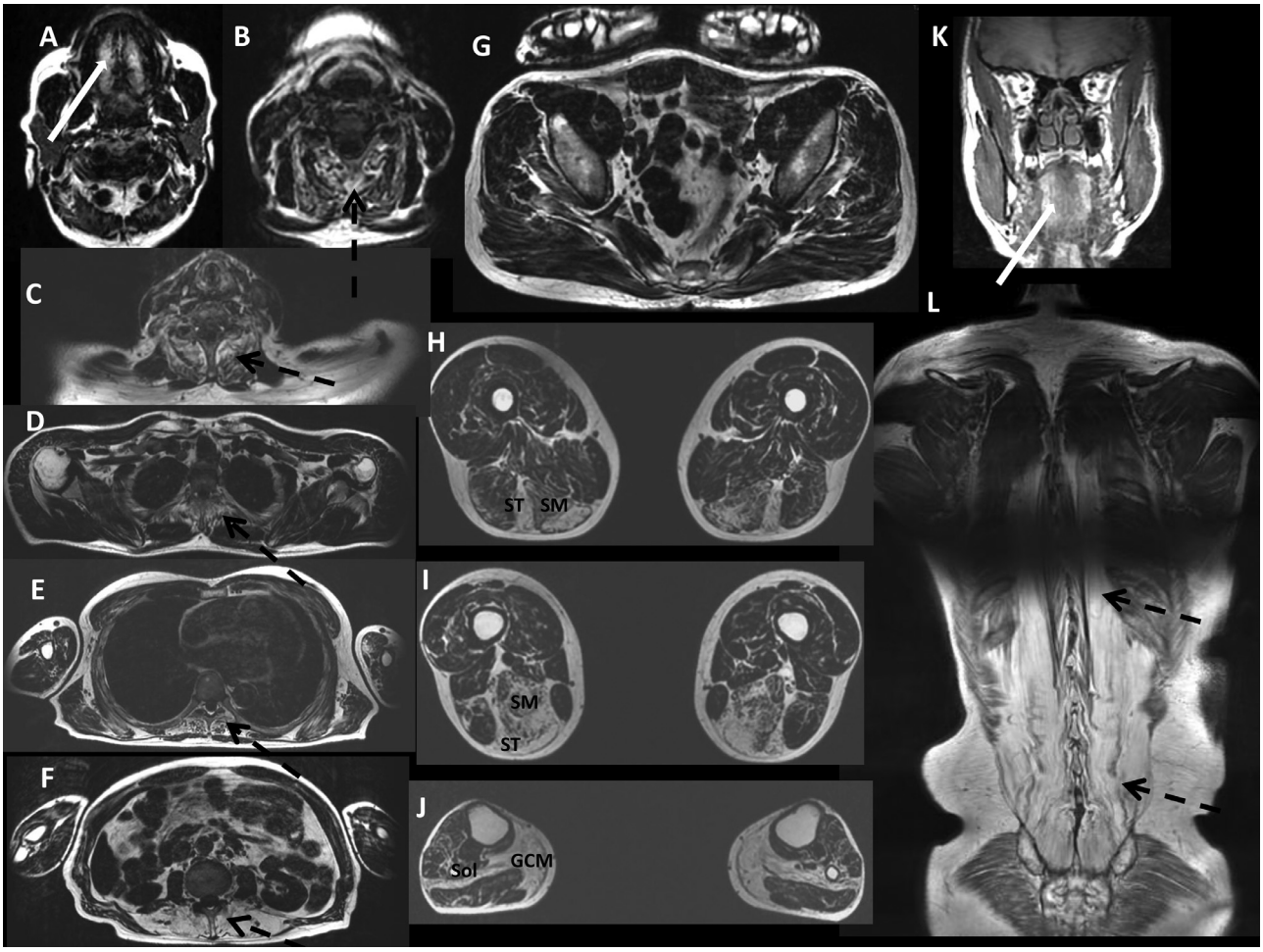

Fig. 2. *Whole body muscle MRI.* Axial sections of the 3 points DIXON sequence fat images from head to calves (A)–(J). Coronal T1 weighted sections of the face (K) and of the thoraco-lumbar muscles of the back (L). Masticatory muscles are well visible and preserved but the tongue is partly fatty infiltrated (white long arrow, (A) and (K)). Muscles of the back in cervical, thoracic and lumbar areas are heavily fatty infiltrated (black discontinuous arrows). In thighs and legs the posterior compartments are predominantly affected with atrophy and fat infiltration especially of the semi-tendinous and the semi-membranous (ST/SM) in thigh and gastrocnemius medialis (GCM) and soleus (Sol) in leg.

firing rate and high size motor unit potentials in deltoid anterior, brachioradialis, biceps brachialis, and tibialis anterior muscles. Whole body MRI showed marked fat replacement and atrophy of the tongue, trapezius, spine extensors, biceps brachialis, semi-tendinous and semi-membranous, medial gastrocnemius (Mercuri score 3) and soleus (Mercuri score 4) muscles. Fat replacement was also present but less severe in teres major, anterior serratus, deltoid and latissimus dorsi (Mercuri score 2) (Fig. 2). EKG revealed spontaneously slow atrial fibrillation, with a mean heart rate of 45 b.p.m, without QRS enlargement and cardiac electrophysiology but displayed nodal conduction bock without infrahissian conduction delay. Left ventricular dimensions and systolic function were normal on echocardiography and both atria were dilated. Forced vital respiratory capacity (FVC) was normal (100%).

A deltoid muscle biopsy showed nonspecific muscle abnormalities including a moderate number of fibers with internalized nuclei, rare atrophic fibers (Fig. 3(A) and (B)) and absence of type 2B fibers demonstrated by immunofluorescence studies using myosin alpha and beta-slow heavy chain, fast 2A heavy chain, and 2X myosin heavy chain (BA-D5, SC-71, and 6H1, Developmental Studies Hybridoma Bank, University of Iowa, Iowa City, USA) that showed the absence of 2X myosin heavy chain expression (Fig. 3(C)). A comprehensive battery of immunohistochemical reaction was carried out and immunostaining study using an antibody against emerin (NCL-Emerin, Novocastra, Newcastle, England) showed a complete absence of the normal nuclear labeling compared to a normal control (Fig. 3(D)). Western blot analysis of patient muscle homogenate using monoclonal MANEM8-7B9 anti-emerin and anti-lamins A/C antibodies confirmed the absence of emerin compared to a normal control muscle (Fig. 3(E)).

Direct sequencing of the *EMD* gene revealed a pathogenic hemizygous duplication of 5 bases c.650_654dup: p.Gln219Trpfs*20, leading to a premature frame shift.

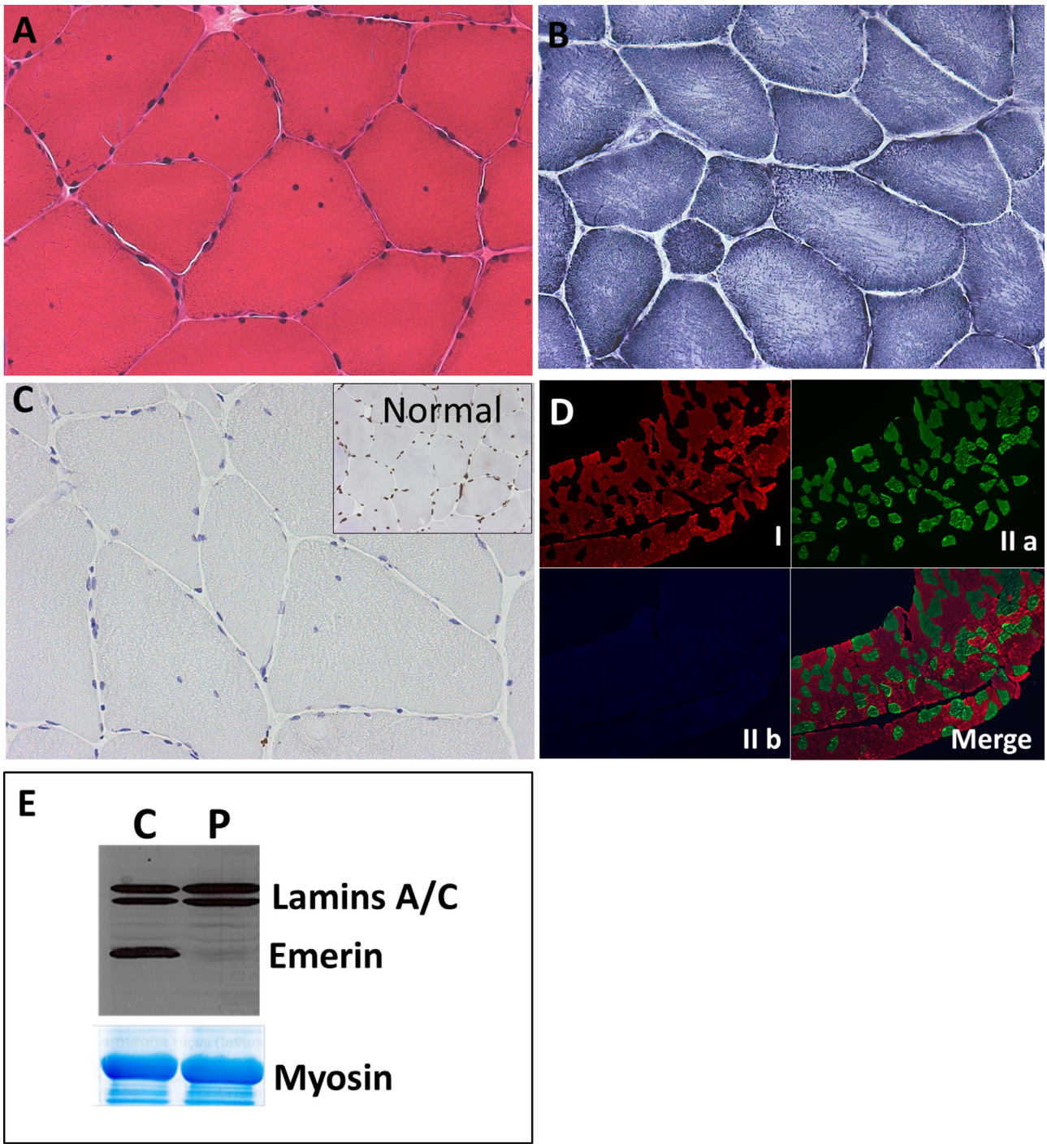

Fig. 3. *Deltoid muscle biopsy study and protein studies*. (A) HE. Some fibers harbor internalized nuclei. (B) NADH staining showing the presence of few atrophic fibers and mild disorganization of the structure. (C) Immunohistochemical analysis with an anti-emerin antibody showing complete absence of nuclear staining. The insert shows a normal nuclear emerin staining on a control muscle. (D) Immunofluorescence analysis using myosin alpha and beta slow heavy chain, fast IIa heavy chain, and 2X myosin heavy chain and merge. The absence of type IIb fibers is demonstrated by the absence of blue staining corresponding to type IIb fibers. The merged image confirms this finding. Magnification 16X. (E) Western Blot studies on muscle homogenate. C: control. P: patient. Note the complete absence of emerin band at the normal molecular weight (35 kDa) in patient's muscle. The LMNA/C, lamins A/C, bands are normally present in both patient and control. Myosin is used as loading control.

3. Discussion

The X linked Emery-Dreifuss muscle dystrophy (EDMD) was described as a childhood onset progressive myopathy with early joint contractures, followed within the third decade by supraventricular arrhythmias and cardiac conduction defects potentially evolving toward complete atrioventricular block and sudden death [1,5,8]. The mutated gene, *EMD*,

within the Xq28 [2] encodes for a 254-aminoacid protein named emerin, an inner nuclear membrane integral protein.

Mean age of onset is reported to be in the first decades [6,7,9]. Remarkably our patient only reported mild sport difficulties during infancy without any significant contracture. He developed an overt progressive axial weakness of paraspinal muscle leading to camptocormia during walking in adulthood. To our knowledge, both onset and clinical features of our patient are highly unusual. Interestingly camptocormia had never been reported before as a predominant symptom in EDMD [1,7,10,11]. Camptocormia is a frequent symptom in old patients and is frequently related to movement disorders [12]. Rare myopathic form exists, often idiopathic [13]. Concerning the myopathies related to defect in proteins of the nuclear envelope, there is a rare phenotype of severe congenital muscular dystrophy with axial involvement associating dropped head with distal limbs contractures and rigid spine due to *LMNA* gene mutations [10].

In our patient only a careful clinical examination revealed the presence of mild contractures of neck and elbows (Fig. 1), without any spine rigidity. The presence of mild contractures in X-linked EDMD have been previously reported [7,14,15]. However, in EDMD patients the contractures are one of the core clinical features and patients start developing them during childhood beginning from Achilles tendons [5,11] extending to elbows and to spine extensor muscles in the second decade [10]. Rigid spine syndrome (RSS) is the consequence of spinal contractures [5]. Myopathies with prominent spine contractures are rare in adulthood. Early onset myopathies such as congenital muscular dystrophies (e.g., *LMNA, LAMA2* and Collagen VI related myopathies) and rare congenital myopathies such as *SELENON, FHL1* related reducing body myopathy, *BAG3* myofibrillar myopathies and *titin* related myopathies may be associated with RSS [10]. The distribution of spinal rigidity is variable among different entities and can help in the differential diagnosis [10]. However, the absence of prominent contractures and rigid spine did not help to reach the diagnosis in our patient.

Whole body MRI in EDMD patients has been rarely reported. Mercuri et al. investigated nine patients including four with *EMD* mutation and found that especially the medial head of the gastrocnemius muscle had prominent atrophy [16]. In a Spanish study conducted in 42 EDMD patients including 10 X-linked EDMD, the MRI or CT scan (from trunk to feet) showed fatty infiltration in paravertebral, glutei, quadriceps, biceps, semitendinosus, semimembranosus, adductor major, soleus, and gastrocnemius but peroneus muscle was involved in 88% of patients with mutations in the *EMD* compared to only 40% of patients with mutation in the *LMNA* gene [17]. Whole body MRI of our patient showed marked symmetric fatty replacement and atrophy of the tongue, trapezius, all the spine extensors, biceps brachialis, semitendinous and semimembranous, medial gastrocnemius and soleus as previously described [16]. To a lesser extent, we also noted fatty infiltration in teres major, anterior serratus, deltoid and latissimus dorsi. In contrast, alterations of glutei, adductor major, quadriceps and biceps of the thighs, and peroneous muscles were only subtle, compared to what reported [17]. Previous studies of whole body MRI in *LMNA/C*-EDMD revealed distinctive patterns helping distinguishing *LMNA/C*-EDMD with rigid spine presentation [18,19]. As a whole, our patient showed a pattern evocative of laminopathy with a lesser atrophy compared to younger *LMNA/C* patients.

According to the online UMD-EMD database (see http://www.umd.be/EMD/), at least 230 male patients (156 families) carrying 103 *EMD* different mutations have been reported. The majority (66.6%) harbor truncating mutations (out-of-frame large or small deletions/insertions, nonsense mutations) causing absent or rarely faint emerin (out-of-frame large or small deletions/insertions, nonsense mutations) with western blot studies. The mutation harbored by our patient is a 5 nucleotides (TGGGC) duplication introducing a frame shift after aminoacid 218, was already reported in 6 affected individuals from 3 families of German, Japanese and Israeli origin [20–22]. None of them had camptocormia. These patients presented a typical EDMD phenotype with elbows and ankles contractures [20] in association with stiff neck in one case [22]. Cardiac involvement was always present, varying from 1st degree to complete atrio-ventricular block requiring pacemaker with supraventricular arrhythmias and heart dilation. It is noteworthy that any muscular condition associated with cardiac arrhythmias in early adulthood should guide to diagnosis of conditions affecting the nuclear membrane and other arrhythmogenic cardiomyopathies. Among the 6 reported patients, 2 had muscle biopsy that, similarly to our patient, showed non dystrophic findings including atrophic muscle fibers [22], type grouping and type 1 fiber predominance [20] with absent emerin [21]. Of note we describe the absence of type 2B fibers that was not reported previously. This finding is difficult to explain and could be secondary to the absence of emerin. Concordantly, it was a comprehensive battery of immunohistochemical reactions that allowed to reveal the absence of emerin thus suggesting EMD molecular study. One could argue that facing a non-specific myopathy a large gene panel would have been performed before proposing a muscle biopsy. However muscle specific study should have been performed to validate the pathogenicity of the known *EMD* mutation in such an atypical case.

In conclusion, this observation enlarges the clinical spectrum of X-linked EDMD by reporting a patient with adult onset axial weakness, camptocormia, and very mild contractures. Muscle biopsy followed by emerin immunohistochemistry directed *EMD* gene sequencing.

We stress the importance of a systematic diagnostic algorithm including muscle biopsy and muscle imaging in patients presenting myopathies with atypical clinical features.

Acknowledgments

We are thankful to the techinical team of Laboratoire Risler from the Myology Institute for the technical analysis

of muscle biopsy and to Dr Marie Christine Durand for contributing to clinical observation and technical team of 'myopahies team' of the "Laboratoire de génétique et Biologie moléculaire (HUPC, Cochin).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2019.06.009.

References

[1] Emery AEH. Emery–Dreifuss muscular dystrophy – a 40 year retrospective. Neuromuscular Disord 2000;10(4–5):228–32.
[2] Bione S, Maestrini E, Rivella S, Mancini M, Regis S, Romeo G, et al. Identification of a novel X-linked gene responsible for Emery–Dreifuss muscular dystrophy. Nat Genet 1994;8(4):323–7.
[3] Bonne G, Barletta MRD, Varnous S, Bécane H-M, Hammouda E-H, Merlini L, et al. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery–Dreifuss muscular dystrophy. Nat Genet 1999;21(3):285–8.
[4] Koch AJ, Holaska JM. Emerin in health and disease. Semin Cell Dev Biol 2014;29:95–106.
[5] Bonne G, Quijano-Roy S. Emery–Dreifuss muscular dystrophy, laminopathies, and other nuclear envelopathies. Pediatric neurology part III. Elsevier; 2013. p. 1367–76.
[6] Yates JRW, Bagshaw J, Aksmanovic VMA, Coomber E, McMahon R, Whittaker JL, et al. Genotype-phenotype analysis in X-linked Emery–Dreifuss muscular dystrophy and identification of a missense mutation associated with a milder phenotype. Neuromuscular Disord May 1999;9(3):159–65.
[7] Astejada MN, Goto K, Nagano A, Ura S, Noguchi S, Nonaka I, et al. Emerinopathy and laminopathy clinical, pathological and molecular features of muscular dystrophy with nuclear envelopathy in Japan. Acta Myol 2007;26(3):159–64.
[8] Emery AE, Dreifuss FE. Unusual type of benign x-linked muscular dystrophy. J Neurol Neurosurg Psychiatr 1966;29(4):338–42.
[9] Brown CA, Scharner J, Felice K, Meriggioli MN, Tarnopolsky M, Bower M, et al. Novel and recurrent EMD mutations in patients with emery–dreifuss muscular dystrophy, identify exon 2 as a mutation hot spot. J Hum Genet 2011;56(8):589–94.
[10] Eymard B, Ferreiro A, Ben Yaou R, Stojkovic T. Muscle diseases with prominent joint contractures: main entities and diagnostic strategy. Rev Neurol (Paris) 2013;169(8–9):546–63.
[11] Hausmanowa-Petrusewicz I, Madej-Pilarczyk A, Marchel M, Opolski G. Emery–Dreifuss dystrophy: a 4-year follow-up on a laminopathy of special interest. Neurol Neurochir Pol 2009;43(5):415–20.
[12] Abe K, Uchida Y, Notani M. Camptocormia in Parkinson's disease. Parkinsons Dis 2010;2010(6):1–5.
[13] Ali F, Matsumoto JY, Hassan A. Camptocormia: etiology, diagnosis, and treatment response. Neurol Clin Pract 2018;8(3):240–8.
[14] Vohanka S, Vytopil M, Bednarik J, Lukas Z, Kadanka Z, Schildberger J, et al. A mutation in the X-linked Emery–Dreifuss muscular dystrophy gene in a patient affected with conduction cardiomyopathy. Neuromuscular Disord 2001;11(4):411–13.
[15] Ura S, Hayashi YK, Goto K, Astejada MN, Murakami T, Nagato M, et al. Limb-Girdle muscular dystrophy due to emerin gene mutations. Arch Neurol 2007;64(7):1038.
[16] Mercuri E, Counsell S, Allsop J, Jungbluth H, Kinali M, Bonne G, et al. Selective muscle involvement on magnetic resonance imaging in autosomal dominant Emery–Dreifuss muscular dystrophy. Neuropediatrics 2002;33(1):10–14.
[17] Díaz-Manera J, Alejaldre A, González L, Olivé M, Gómez-Andrés D, Muelas N, et al. Muscle imaging in muscle dystrophies produced by mutations in the EMD and LMNA genes. Neuromuscular Disord 2016;26(1):33–40.
[18] Gómez-Andrés D, Dabaj I, Mompoint D, Hankiewicz K, Azzi V, Ioos C, et al. Pediatric laminopathies: whole-body magnetic resonance imaging fingerprint and comparison with Sepn1myopathy. Muscle Nerve 2016;54(2):192–202.
[19] Tordjman M, Dabaj I, Laforet P, Felter A, Ferreiro A, Biyoukar M, et al. Muscular MRI-based algorithm to differentiate inherited myopathies presenting with spinal rigidity. Eur Radiol 2018;28(12):5293–303.
[20] Ifergane G, Al-Sayed I, Birk O, Harel T, Wirguin I. Co-morbidity of Emery–Dreifuss muscular dystrophy and a congenital myasthenic syndrome possibly affecting the phenotype in a large Bedouin kindreditor. Eur J Neurol 2007;14(3):305–8.
[21] Funakoshi M, Tsuchiya Y, Arahata K. Emerin and cardiomyopathy in Emery–Dreifuss muscular dystrophy. Neuromuscul Disord 1999;9(2):108–14.
[22] Klauck SM, Wilgenbus P, Yates JR, Müller CR, Poustka A. Identification of novel mutations in three families with Emery–Dreifuss muscular dystrophy. Hum Mol Genet 1995;4(10):1853–7.