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Case report

ACTA1-myopathy with prominent finger flexor weakness and rimmed vacuoles

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Abstract

Actinopathy is a group of clinically and pathologically heterogeneous myopathies due to mutations in the skeletal muscle sarcomeric α-actin 1-encoding gene (*ACTA1*). Disease-onset spans from prenatal life to adulthood and weakness can preferentially affect proximal or distal muscles. Myopathological findings include a spectrum of structural abnormalities with nemaline rods being the most common. We report a daughter and father with prominent finger flexors and/or quadriceps involvement. Muscle biopsies revealed rimmed vacuoles in both patients, associated with type 1 fiber atrophy in the daughter, and nemaline rods in the father. Next generation sequencing identified a novel dominant *ACTA1* variant, c.149G>A (p.Gly50Asp) in both individuals and no abnormal variants in vacuolar myopathy-associated genes. Our findings expand the clinico-pathological spectrum of actinopathy.

Keywords: *ACTA1*; Congenital fiber type disproportion; Finger flexor weakness; Inclusion body myositis; IBM; Nemaline myopathy; Rimmed vacuoles.

1. Introduction

Mutations in the skeletal muscle sarcomeric α-actin 1-encoding gene (*ACTA1*) cause autosomal dominant or less commonly recessive congenital myopathies with a wide range of clinical phenotypes and pathological findings [1]. Weakness generally occurs prior to teenage years, but adult-onset weakness has been reported [1]. The pattern of weakness varies from limb-girdle, scapuloperoneal [2] to the recently described distal phenotype [3]. Muscle biopsy may show classic nemaline rods or less commonly actin filament aggregates, caps, cores, fiber type disproportion, myofibrillar pathology, or zebra bodies [3].

Herein, we report a daughter and her father with a childhood-onset of the weakness and prominent finger flexor and/or quadriceps involvement due to a novel dominant *ACTA1* variant. Muscle biopsies revealed no inflammatory exudate but rimmed vacuoles in both patients. This family expands the clinical and pathological spectrum of actinopathy.

2. Case reports

The proband is a 39-year-old woman with congenital joint hypermobility, congenital cyanotic heart defect requiring surgical repair and delayed motor milestones. She was a slow runner since childhood and had difficulty keeping up with her peers. At age 33, she noted inability to do sit-ups due to abdominal muscle weakness and, three years later, difficulty climbing stairs and getting up from the floor, dyspnea and orthopnea. She denied myalgia, pigmenturia or complications from exposure to anesthetics. Creatine kinase

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Table 1
Clinical findings in proband and father.

Characteristics	Proband	Father
Age at presentation	39	69
Motor milestones	Delayed	Normal
Age at onset (years)	Early childhood	11
Symptoms at onset	Slow runner	Slow runner and frequent falls
Progression	Abdominal wall weakness (at age 33); proximal leg weakness, dyspnea at rest and orthopnea (at age 36)	Gait difficulty and dyspnea on exertion (at age 40)
Facial weakness	++	+
Neck flexor weakness	+	+
Upper extremity weakness		
– Proximal	+/− triceps; + others	+ shoulder external rotators, elbow flexors, and elbow extensors; +/− shoulder abductors
– Distal	++ left thumb flexors and + right thumb flexors; + finger extensors; +/− other muscles	+ finger flexors; +/− finger extensors and intrinsic hand muscles
Abdominal wall muscle weakness	++	Not tested
Characteristics	**Proband**	**Father**
Lower extremity weakness		
– Proximal	Nl knee extensors; ++ hip flexors; + others	++ left knee extensors and + right knee extensors; ++ left hip flexors and + right hip flexors; + left knee flexors; − others
– Distal	++ toe extensors; − plantar flexors and foot invertors; + others	++ right foot evertors and + left foot evertors; + ankle dorsiflexors; − ankle dorsiflexors
Other features	High arched palate; left scapular winging; scoliosis; distal joint hyperlaxity	No scapular winging or joint hyperlaxity

Nl, normal strength (MRC grade 5); +/−, very mild weakness (MRC grade 4+); +, mild weakness (MRC grade 4); ++, moderate weakness (MRC grade 3); +++, severe weakness (MRC grade 1–2); ++++, very severe weakness (MRC grade 0).

(CK) was mildly elevated at 222 U/L (normal <173 U/L). The patient's father carried the diagnosis of sIBM despite the onset of weakness around age 11. His weakness started worsening after age 40. The proband's 36-year-old sister is asymptomatic. Table 1 summarizes the key clinical features of the proband and affected father. Weakness of finger flexors was present in the proband and in the father. In addition, the father had also quadriceps weakness and atrophy. The proband's two daughters, age 3 and 6 years, respectively, had axial hypotonia and joint hypermobility at birth; the oldest had delayed motor development and now has difficulty rising up from the floor while the youngest is unable to fully close her eyelids while sleeping.

Nerve conduction studies and 2 Hz repetitive stimulation of spinal accessory and peroneal nerves were normal. Needle EMG revealed short duration, low amplitude motor unit potentials with early recruitment in proximal and distal muscles, and rare fibrillation potentials in proximal lower limb muscles. EKG, echocardiogram, and overnight oximetry were normal. Blood acid alpha-glucosidase level and genetic studies for myotonic dystrophies type 1 and 2, and facioscapulohumeral dystrophy type 1, performed prior to our evaluation, were normal. Right triceps biopsy showed findings consistent with congenital fiber type disproportion but also rimmed vacuoles (Fig. 1(A)–(C)), one of which contained congophilic material. Inflammatory changes, cytochrome c oxidase-negative fibers, core formations and nemaline rods were absent. No ectopic accumulation of α-actinin, myotilin and other Z-disk associated proteins was detected by immunohistochemical studies. In light of the patient's clinical history and observed myopathological findings not suggestive of an immune-mediated myopathy, MHC-I immunostaining was not performed.

The proband's father (now age 69) had undergone quadriceps biopsy at age 54 and diagnosed with sporadic inclusion body myositis (sIBM) elsewhere, mainly on the basis of his pattern of weakness, despite the early onset of the weakness. His muscle biopsy slides showed nearly end-stage muscle, groups of atrophic fibers, numerous pyknotic nuclear clusters, fiber splitting, increase in internalized nuclei, and rare fibers with rimmed vacuoles or nemaline rods (Fig. 1(D) and (E)). Inflammatory changes and cytochrome c oxidase-negative fibers were absent. MHC-I immunostaining was not performed. Subsequent epon sections for light and electron microscopy studies confirmed the presence of nemaline rods (Fig. 1(F) and (G)) and did not identify tubulofilamentous inclusions.

Next generation sequencing (NGS) of 74 myopathy genes (*Supplementary material 1A*) showed 2 novel heterozygous variants, one in exon 3 of *ACTA1* (NM_001100.3), c.149G>A (p.Gly50Asp), and one in exon 2 of the GAA (NM_000152.3), c.109C>G (p.Leu37Val). In silico analysis predicted that the *ACTA1* variant is deleterious and the GAA variant tolerated. The proband's father carries the same *ACTA1* variant. Additional NGS in the proband revealed no abnormal variants in genes causative of vacuolar myopathies and multisystem proteinopathy (*Supplementary material 1B*).

3. Discussion

Although both proband and father developed symptoms early in life, they did not seek medical attention until their

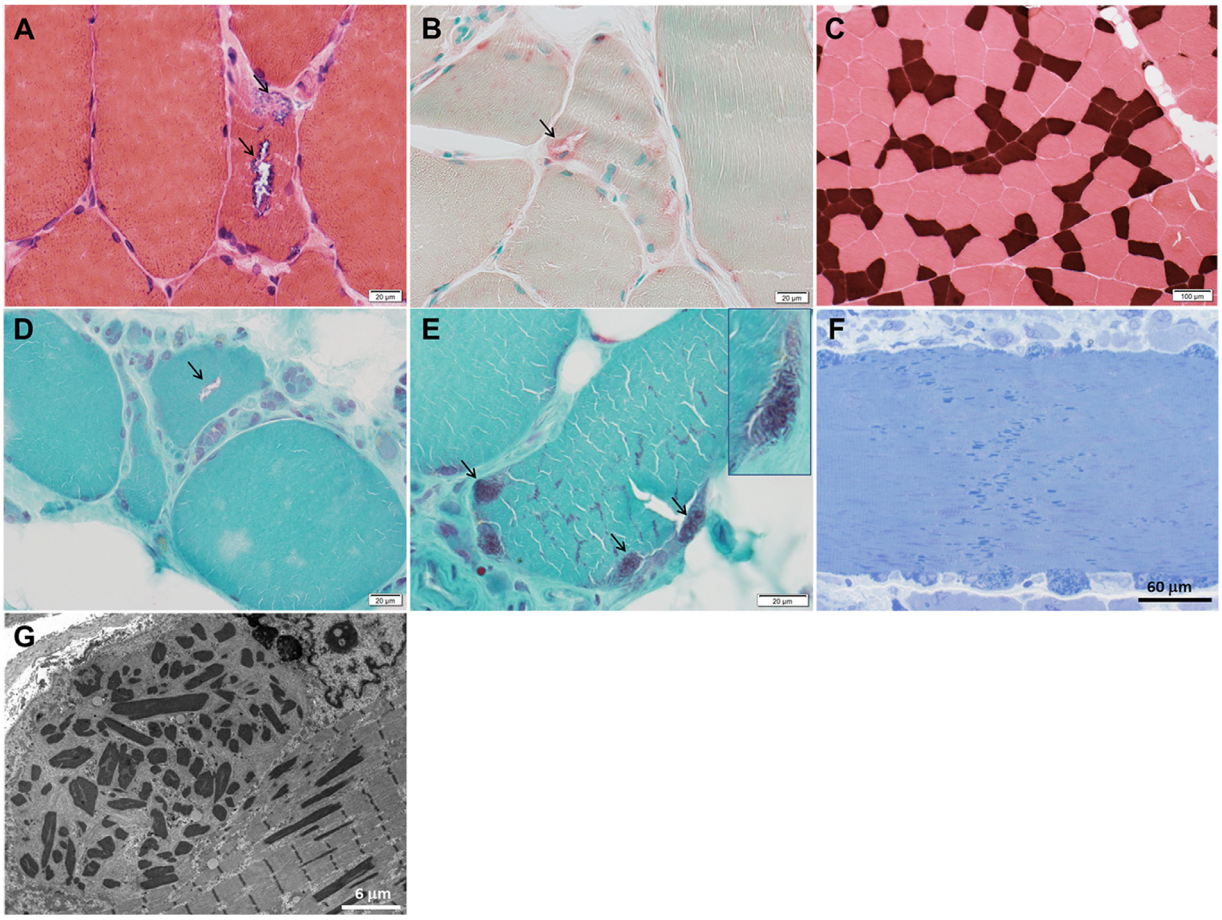

Fig. 1. Muscle biopsies of proband and her father. Proband's biopsy photographs (A–C) depicting fibers with rimmed vacuoles (arrows) overreactive for acid phosphatase (A, hematoxylin-eosin; B, acid phosphatase) and type 1 fiber atrophy (darkest fibers; C, ATPase pH 4.2). Proband's father's muscle biopsy photographs (D–G) showing a fiber with rimmed vacuole (arrow, D) in the midst of numerous pyknotic nuclear clusters and fatty replacement, and nemaline rods (arrows, E) as seen in Gomori trichrome. In the epon 1 µm sections (F, toluidine blue; G, electron microscopy), the nemaline rods are identified in subsarcolemmal groups and amidst sarcomeres across the entire diameter of some muscle fibers.

mid-30s or early 40s, when the weakness became progressive and started impacting their activities of daily living. Thumb or finger flexors were weaker than finger extensors in proband and father; knee extensors and hip flexors were equally weak in the father. This pattern of weakness resembles the classic features of sIBM [4], and, indeed, in combination with the rimmed vacuoles on biopsy, had led to the misdiagnosis of sIBM in the father, despite his young age of disease onset arguing against sIBM [5]. The early disease-onset and family history of autosomal dominant trait were the main elements that prompted the search of an alternative diagnosis also in the father. In light of the presence of rimmed vacuoles in the muscle biopsy of both proband and father, the possibility of other hereditary muscle diseases featuring rimmed vacuoles was considered, but not supported by the molecular analysis. No pathogenic variants were found in known genes causative of myopathies with rimmed vacuoles. Recently, predominant finger flexor weakness was reported in patients with *GNE*-myopathy and in two subjects carrying a heterozygous VCP variant, one meeting clinical and pathological criteria of sIBM and one with possible sIBM [6,7]. Prominent finger flexor involvement can also occur in other hereditary muscle diseases, including myotonic dystrophy type 1 and 2 [8], autosomal dominant filamin C-distal myopathy [9], glycogen storage disease type 2 [10], and now also in ACTA1-myopathy.

ACTA1 is a highly conserved protein and any amino acid change is likely to be pathogenic [11]. The novel *ACTA1* variant, p.Gly50Asp, affects a highly conserved residue and is predicted to be deleterious. It also co-segregates with the vacuolar myopathy and prominent finger flexor weakness in this family with autosomal dominant myopathy. The detection of nemaline rods in the father's biopsy, despite being nearly end-stage, and the type 1 muscle fiber atrophy in the proband's biopsy also support the pathogenicity of the p.Gly50Asp variant, in addition to underscoring the intrafamilial pathological variability of ACTA1-myopathy. A different missense mutation at the same codon, p.Gly50Cys, was reported in the online Leiden Open Variation Database (https://databases.lovd.nl/shared/genes/ACTA1), but its pathogenicity was not confirmed.

ACTA1-myopathy can present with various patterns of weakness. Distal weakness was not considered a prominent feature of ACTA1-myopathy until recently, when we reported

a family of autosomal dominant distal myopathy with early finger extensor involvement due to a novel p.Gly253Arg mutation [3]. To our knowledge, the present family is the first ACTA1-myopathy with predominant finger flexor weakness. Nemaline rods are the classic pathological findings of ACTA1-myopathy, but other pathological findings do occur as mentioned above [3]. We have now shown in two patients that also rimmed vacuoles can accompany ACTA1-myopathy. Rimmed vacuoles in ACTA1-myopathy had been previously described in a single patient with zebra body myopathy [12]. That patient's biopsy showed also myofibers containing nemaline rods and sarcoplasmic hyaline materials on trichrome stained sections, resembling myofibrillar pathology.

The present family broadens the phenotypic spectrum of ACTA1-myopathy to include the prominent finger flexor weakness and vacuolar pathology.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2019.02.012.

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