



Musculoskeletal and Emergency Imaging

Magnetic Resonance Imaging characteristics in case of TOR1AIP1 muscular dystrophy[☆]

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ABSTRACT

Mutations in the torsinA-interacting protein 1 (TOR1AIP1) gene result in a severe muscular dystrophy with minimal literature in the pediatric population. We review a case of *TOR1AIP1* gene mutation in a 16-year-old Caucasian female with a long history of muscle weakness. Extensive clinical workup was performed and MRI at time of initial presentation demonstrated no significant muscular atrophy with heterogenous STIR hyperintensity of the lower extremity muscles. MRI findings seven years later included extensive atrophy of the lower extremities, with severe progression, including the gluteal muscles, iliopsoas, rectus femoris, and obturator internus. There was also significant atrophy of the rectus abdominis and internal and external oblique muscles, and iliacus muscles. The MRI findings showed more proximal involvement of lower extremities and no atrophy of the tibialis anterior, making *TOR1AIP1* the more likely genetic cause. Muscle biopsy findings supported *TOR1AIP1* limb-girdle muscular dystrophy. Though rare, TOR1AIP1 gene mutation occurs in pediatric patients and MRI can aid in diagnosis and help differentiate from other types of muscular dystrophy. Genetic and pathology workup is also crucial to accurate diagnosis and possible treatment of these patients.

1. Introduction

Muscular dystrophies are a heterogeneous group of hereditary muscle disorders with progressive muscular degeneration and weakness. Genetic analyses have been able to identify new causes of muscular dystrophy with a lack of associated radiological findings in the literature [1,2]. Mutations in the torsinA-interacting protein 1 (TOR1AIP1) gene result in a severe muscular dystrophy. There is minimal literature describing this myopathy or imaging findings in the pediatric population [3–5]. We present a case of a *TOR1AIP1* gene mutation presenting to the Unknown Diagnosis Network (UDN). The patient was evaluated using a multi-disciplinary approach including genetics, pathology, and radiology, and the MRI findings helped differentiate between two possible genetic causes.

2. Case report

The patient is a 16-year-old Caucasian female with a history of progressive muscle weakness due to an unknown etiology. She was the product of a full term pregnancy born to a 22 year old mother. Development in first few years of life was reported as normal, however,

she was never completely able to run or jump as expected for her age. She initially presented to Neurology at the age of 8 with gradually progressive lower extremity weakness. At that time she was unable to pull herself onto a horse, had trouble getting into and out of the car, had a waddling gait and could not throw a softball. Her CK level was elevated at 10,000. She had an extensive workup including two muscle biopsies which showed mild myopathy without inflammation, EMG studies showing irritable myopathy, and non-diagnostic genetic testing including a multigene muscular dystrophy and dystroglycanopathy panel.

MRI at time of initial presentation at the age of 10 years, demonstrated minimal atrophy of the gluteus medius and minimus muscles, otherwise, no significant atrophy of the pelvis or lower extremities, with heterogenous STIR hyperintensity of the lower extremity muscles (Fig. 1). MRI findings at time of presentation to UDN included extensive atrophy of the lower extremities, with severe progression in seven years comparing to her initial MRI, including the gluteal muscles, iliopsoas, rectus femoris, and obturator internus (Fig. 2). There was also significant atrophy of the rectus abdominis, internal and external oblique muscles, and iliacus muscles. Within the thighs, there was significant bilateral symmetric atrophy of the medial and posterior compartments



Fig. 1. Initial presentation: MRI of the lower extremities.

Axial T1 through the pelvis (A) and lower extremities (B) show minimal atrophy of the gluteus medius and minimus muscles, otherwise, no significant atrophy of the muscles. Axial STIR (C) at the level of the femur show heterogeneous hyperintensity throughout the muscles.

with relative sparing of the anterior compartment. Within the posterior compartment the most significant atrophy was noted within the biceps femoris and semitendinosus muscles with less involvement of the semimembranosus. Within the medial compartment, the adductor muscles and gracilis were involved. There was mild atrophy of the anterior compartment muscles including the rectus femoris and vastus intermedius, vastus lateralis, and vastus medialis. Below the knee, there was

no significant atrophy. Heterogeneous T2 hyperintensity involving the muscles was increased compared to the initial MRI. Similar signal abnormality was present within the muscles of the initial MRI thigh and pelvis seven years ago.

She was referred at the age of 14 to the Undiagnosed Diseases Network (UDN). At the time of her symptoms had progressed to an extent that she was using a wheel chair most of the time. She could still

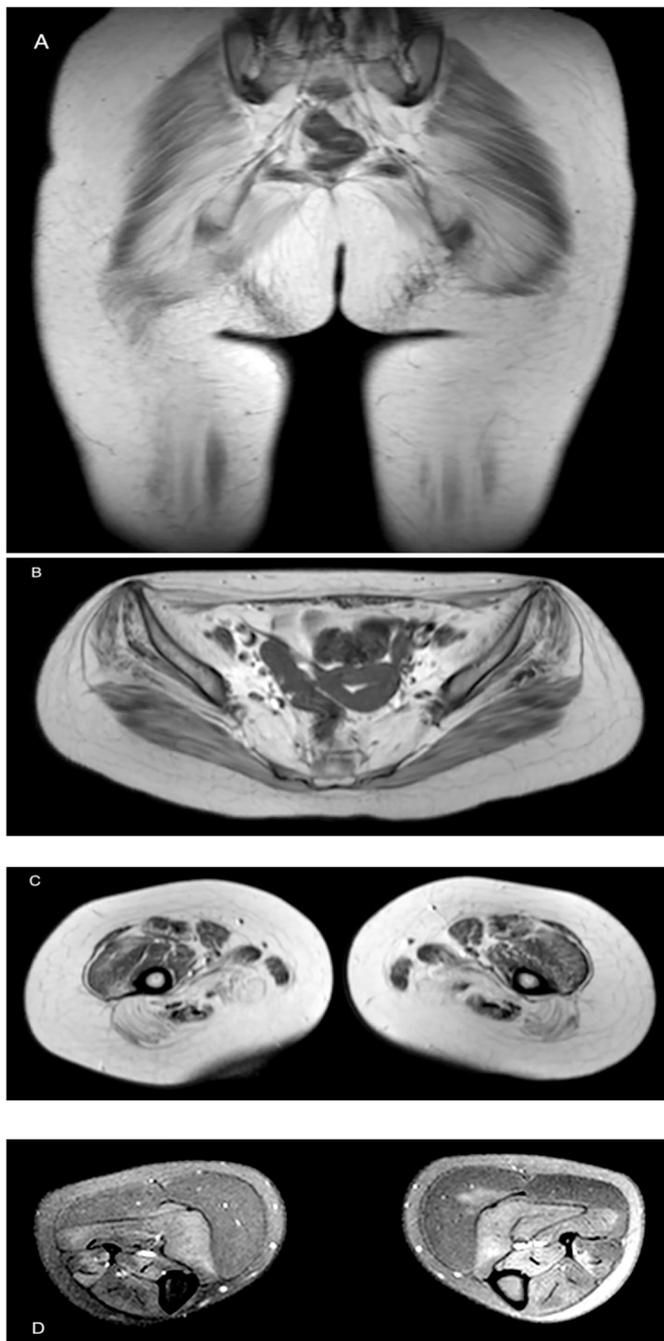


Fig. 2. MRI of the lower extremities seven years after initial presentation. MRI findings Coronal and axial T1 (A, B) show severe atrophy of the gluteal muscles, iliopsoas, rectus femoris, obturator internus, rectus abdominis and internal and external oblique muscles, iliacus muscles. (C) Axial T1 of the thighs demonstrated bilateral symmetric atrophy of the medial and posterior compartments, including biceps femoris and semitendinosus muscles with less involvement of the semimembranosus. Within the medial compartment, the adductor muscles and gracilis are involved. Mild atrophy of the anterior compartment muscles including the rectus morris and vastus intermedius, vastus lateralis, and vastus medialis. (D) Axial T2FS below the knee with no significant atrophy. Heterogeneous T2 hyperintensity throughout the muscles.

ambulate but could not walk for more than 25–50 ft and not on uneven surfaces. She had significant fatigue and tired easily. She could not manage climbing stairs and could not lift her hands above her shoulders. Her facial muscles were unaffected. Her clinical phenotype also includes dysphagia of liquids, respiratory insufficiency with decreased spirometry, vital capacity and inspiratory capacity, urinary

incontinence and abnormal lactate dehydrogenase activity (> 802 U/L, normal range = 60–170 U/L), elevated hepatic enzymes (ALT > 390 U/L, normal 7–56 U/L) (AST > 208 U/L, normal 5–40 U/L), and elevated aldolase levels (> 99.5 U/L, normal = 1–14.5 U/L).

As part of her UDN evaluation she underwent whole genome sequencing (WGS). WGS analysis found a rare missense variant in *myosin heavy chain 7 (MYH7)* and compound heterozygous rare variants in the *TOR1AIP1* gene; both could explain part of her phenotypic presentation. We then proceeded with further phenotyping of the patient to determine if a rare variant in one of these candidate genes was responsible for the clinical presentation.

Muscle biopsy was done and frozen and formalin-fixed sections stained with H&E showed wide variation in fiber size due to the presence of scattered atrophic and hypertrophic fibers. Numerous muscle fibers undergoing necrosis or regeneration were observed (see Fig. 3a). Rare fibers contained rimmed vacuoles. Several small foci of perimysial and endomysial lymphocytic inflammation were also seen. The fiber type distribution appeared normal on ATPase preparations (pH 10.4 and 4.5). No ragged-red fibers were identified on Gomori trichrome stain, and endomysial fibrosis was focal and mild. None of the pathologic findings reported in *MYH7* mutation-associated myopathy [6,7], including hyaline inclusions/bodies, type I fiber predominance, or relative type I fiber smallness were seen.

Immunofluorescence studies showed normal staining for the dystrophin-glycoprotein complex, collagen VI/perlecan, merosin, and spectrin. Caveolin-3 and dysferlin were reduced at the sarcolemma and increased in the cytoplasm of some muscle fibers, a nonspecific pattern seen in a wide range of myopathies. Many fibers expressed embryonic myosin heavy chain, a marker of regeneration, and muscle fiber expression of MHC class I was multifocal. Frequent muscle fibers showed complement C5b-9 deposition at the sarcolemma. Nuclear envelope immunostains (emerin and lamin A/C) showed complex irregularities of many nuclei (Fig. 3b and c).

Ultrastructural analysis showed nuclear envelope splitting or blebbing (Fig. 3d and e). Core-like structural abnormalities were found by light microscopy on toluidine blue-stained sections, and were also seen by electron microscopy (Fig. 3f). Autophagic debris was present, sometimes associated with muscle fiber nuclei (Fig. 3e). EM also showed basal lamina duplication (Fig. 3e), a nonspecific phenomenon in myopathies with increased autophagy and complement deposition [8].

3. Discussion

The *TOR1AIP1* gene encodes lamina-associated peptide 1 (LAP1), a transmembrane protein ubiquitously expressed in the inner nuclear envelope membrane [5]. Recessive mutations in the *TOR1AIP1* gene may result in reduced expression of LAP1 in striated muscle resulting in limb-girdle muscular dystrophy type 2Y (LGMD 2Y) [3–5]. LGMD 2Y initially presents as proximal limb weakness in childhood, progressing to distal weakness with contractures, as well as cardiomyopathy and spinal rigidity in adulthood.

This case demonstrated significant atrophy involving the bilateral pelvic muscles, as well as the posterior and medial compartments of the thigh with minimal involvement of the anterior compartment of the thigh. There was no significant atrophy of the muscles below the knee, however, there was abnormal heterogeneous signal within these muscles suggesting myositis and precursor to further atrophy.

Molecular genetic analysis by whole exome sequencing narrowed the potential causes to two candidate genes, *TOR1AIP1* and *MYH7*. Rare variants in *MYH7* can cause a number of myopathic disorders with associated muscle weakness, such as myosin storage myopathy, Laing distal myopathy, and scapuloperoneal myopathy (OMIM 608358, 255160, 181430, 160500). *MYH7* is also associated with types of cardiomyopathy (OMIM, 613426, 192600, 613426). *TOR1AIP1* can cause limb-girdle muscular dystrophy type 2Y (OMIM 614512). Rare variants

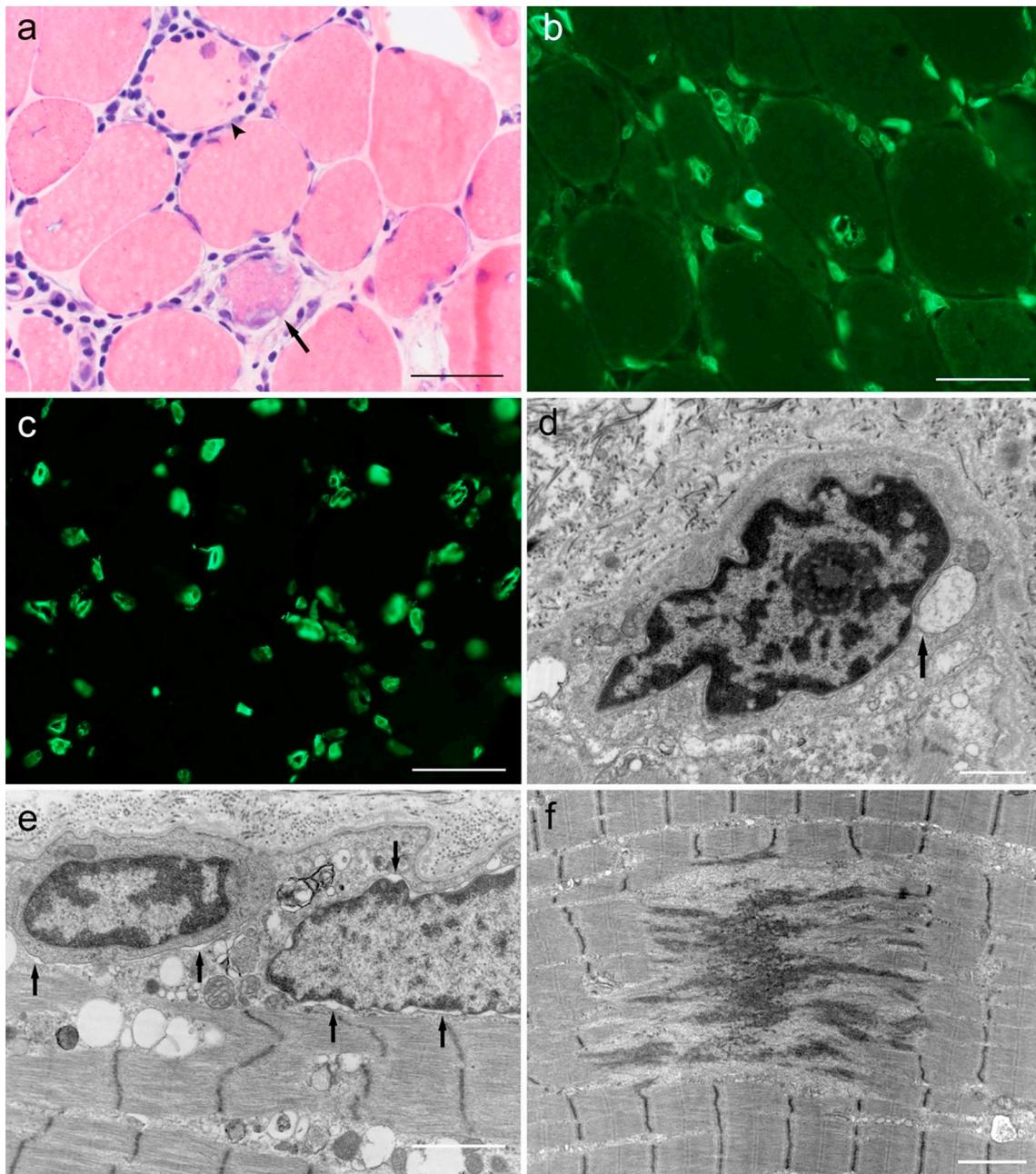


Fig. 3. a) Numerous muscle fibers are undergoing necrosis (arrowhead) or regeneration (arrow). Several small foci of endomysial and perimysial lymphocytic inflammation are observed (H&E cryosection, scale bar equals 50 μm). Immunofluorescence studies for the nuclear envelope proteins b) emerin and c) lamin A/C show complex irregularities of many nuclei (scale bar equals 50 μm). Ultrastructural analysis reveals d) and e) nuclear envelope blebbing or splitting (single arrows). Perinuclear and intersarcomeric autophagic debris is present. Foci with core-like ultrastructural pathology (f) are also observed. Scale bars in electron micrographs equal 3 μm .

in *TOR1AIP1* are associated with an autosomal recessive limb girdle muscular dystrophy type 2y. The literature described *MYH7* mutations typically involving the tibialis anterior and progressing from distal to proximal involvement of the extremities [6]. The MRI findings showed more proximal involvement of lower extremities and no atrophy of the tibialis anterior, making *TOR1AIP1* the more likely genetic cause.

A diagnosis of *TOR1AIP1* limb-girdle muscular dystrophy was also supported by histopathologic features observed in the muscle biopsy. The typical features of *MYH7*-associated myopathy were absent. Instead, the histopathology was that of a necrotizing process with inflammatory changes and abnormalities of nuclear envelope morphology, findings similar to those seen in dystrophies due to mutation in the nuclear envelope protein-encoding gene LMNA [9].

4. Conclusion

Genetic testing and clinical evaluation are crucial to making accurate diagnoses in patients with muscular dystrophies. Radiology also plays an important role in describing the muscles involved and, in this case, making an essential contribution to the diagnosis of *TOR1AIP1* gene mutation.

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