The first Turkish case with early-juvenile-onset recessive distal titinopathy and the first case with prominent neurogenic involvement

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INTRODUCTION

Titinopathies are a heterogeneous group of disabling diseases characterized by muscle weakness with or without additional cardiac or respiratory impairment. Titinopathies are varying in the age of onset, degree of muscle involvement, severity and rate of progression, and have been associated with both dominant and recessive TTN mutations. TTN gene encodes titin, a giant sarcomeric protein that plays important functional and structural roles in the sarcomere. Interestingly mutations in TTN can cause different phenotypes and conversely, different genes can cause the same phenotypes as those of titinopathy. The pathogenicity of titin variants is very difficult to assess and many more different types of titinopathy remain to be discovered and described, as determining their effects on transcript and protein level requires relevant expertise. Recessive titinopathies are an extremely rare spectrum of diseases in which muscle weakness accompanied by contractures. Patients present with hypotonia at birth, congenital myopathy characterized by delayed motor development within the first 12 months of life, or distal or proximal myopathy with onset in childhood or later.

OBJECTIVES

Herein, we present the first case of juvenile-onset recessive titinopathy from Turkey. This case was also the first case of recessive titinopathy with marked neurogenic involvement who presented with muscle twitches and spasms in literature.

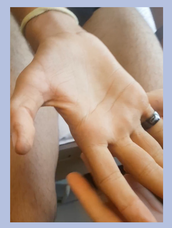


Figure 1: Thenar-hypotenar atrophy

CASE

15-year-old, male

Complaint:

- Fatigue, weakness
- Twitching and cramps in the muscles especially in the lower extremities
- Symptoms for 9 months

History:

- Tremor in hands from 7 years old
- He was investigated due to moderate creatine kinase elevation in another clinic and chronic diffuse neurogenic changes were found in the electroneuromyographic examination.
- Consanguineous parents

Examination:

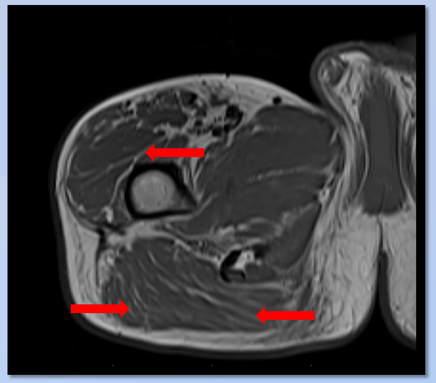
- Distal upper extremity weakness (3-4/5)
- Moderate weakness in proximal lower extremities
- Thenar-hypotenar atrophy (Figure 1)
- Resting tremor
- DTR are brisk at lower extremities
- Muscle fasciculation, pes planus
- Positive Gowers' sign

Investigations:

- CK: ***1153*** IU/L
- Plasma 3-methylhistidine and glycine elevation, not diagnostic
- SMN1/SMN2 gene analysis (another center): Negative
- SLC521A2 and ALS2: Normal
- ENMG: Chronic neurogenic changes, no denervation
- Brain MRI: Normal
- Cervical MRI: Enlargement of the central canal of the spinal cord
- Muscle biopsy: Chronic neurogenic atrophy
- Muscle MRI: Linear signal changes suggesting fat infiltration, especially in the gluteus maximus and posterior crural muscles (Figure 2)

DISCUSSION

Due to the enormous size of the 38,000 amino acid protein and the corresponding size of the large coding sequence with more than 100 kb of cDNA, the relationship of the titin gene to diseases is difficult to study. However, the new technique soon revealed a large number of titinopathy patients in the categories of congenital myopathies and muscular dystrophies. Since the proband has juvenile onset proximal weakness in the lower extremity and distal weakness in upper extremities with fasciculation. ENMG findings were consistent with lower MND and moderate CK elevation. He was investigated for SMN1 and ALS genes. However, all genetic analyses were normal. Riboflavin was initiated for treatable neuronopathies. A *novel compound heterozygous p.I5079L (c.15235A>T) and p.G16602R (c.49804G>A) (NM133378.4) mutations in the TTN gene* were detected by WES. Hosokawa et al. reported a siblings with proximal lower motor neuron findings associated with *compound heterozygous TTN variants (c.6621delG, p.W2207Cfs*28 and c.23718T>A, p.F7906L*).



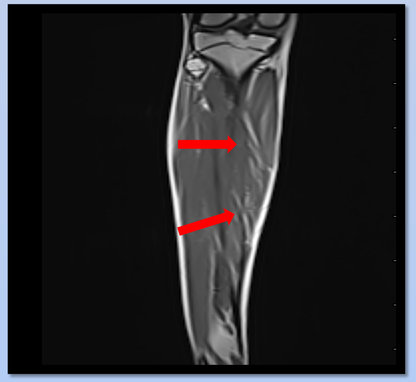


Figure 2.MRI of the right thigh and cruris: Linear signal changes suggesting fat infiltration within the muscle planes in general, most prominently in the gluteus maximus and posterior group crural muscles

CONCLUSIONS

Recessive titinopathies are myopathies with congenital and non-congenital onset, with distal or proximal involvement and accompanied by contractures. This is the first case in which neurogenic findings are prominent clinically and by ENMG and muscle biopsy. The wide variety of phenotypes among the currently known titinopathies is not surprising considering the size and complexity of the gene. Herein a *novel compound heterozygous p.I5079L (c.15235A>T) and p.G16602R (c.49804G>A) (NM133378.4) mutations in the TTN gene* associated with a new lower MND phenotype which expands the clinical spectrum of titinopathy was reported. .

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