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Late-Onset Myopathy and Recurrent Rhabdomyolysis Case Report: Compound Heterozygosis and Novel Thymidine Kinase-2 Mutation

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Abstract

Thymidine kinase 2 deficiency myopathy is a rare autosomal recessive disease with a broad spectrum of severity. The thymidine kinase 2 gene encode for mitochondrial thymidine kinase, which phosphorylates the pyrimidine nucleosides thymidine and deoxycytidine. The most frequent mutation is p.Lys202del and compounds heterozygous forms have been reported. We report a 50-year-old female with recurrent rhabdomyolysis, bilateral ptosis, and girdle limb weakness. Muscle biopsy presented frequent, red-raged fibers and dystrophic changes. The most severely affected muscles in magnetic resonance imaging axial T1-weighted sequences were the gluteus maximus, sartorius and tensor fasciae latae muscles. We found a compound heterozygous mutation in the thymidine kinase 2 gene (pathogenic mutation in [c.323C>T p.(Thr108Met)] and novel mutation in [c.268C>T p.(Arg90Cys)]). Deoxynucleoside therapy was offered.

Keywords: Thymidine kinase 2; Myopathy; Rhabdomyolysis; Mitochondria

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Introduction

Thymidine Kinase 2 (TK2) deficiency myopathy is an autosomal recessive disease, due to mitochondrial DNA (mtDNA) depletion [1,2]. The mtDNA encodes less than 0.1% of the proteins regulating mitochondrial activity, most encoding genes remain unknown [3,4]. TK2-deficiency myopathy is specifically caused by defects in the replication, maintenance, and repair of mitochondrial DNA by TK2, which is the first and limiting step in the phosphorylation of deoxypyrimidine nucleosides [1]. Several mutations have been described in the TK2 gene that leads to the myopathic form [3-5].

TK2-related myopathy clinical picture is heterogeneous, and three forms have been described: infantile (<1 year), childhood (1 to 12 years), and late-onset myopathy (>12 years), the latter being the most unusual (17.4%) and with a relatively better prognosis [6]. In the late-onset group, the mean age of symptoms onset is between 17 and 31 years [6,7], with a similar prevalence among gender, and mean survival is 19.8 to 23.0 years [6,7].

Muscle clinical manifestations are characterized by proximal weakness, ptosis, facial diplegia, ophthalmoparesis and dysphagia [6,7]. The natural progression of the disease evolves to respiratory failure at 10 years of presentation, requiring non-invasive mechanical ventilation [6,7]. Creatine Kinase (CK) may be normal, although it usually is elevated between 190 U/L to 6500 U/L [6,7]. Serum lactate is a nonsensible test and is elevated in only 25% of cases [7].

The genetics profile of TK-2 patients shows that p.Lys202del is the most frequent mutation in the TK2 gene in late-onset patients [7]. In recent years, compound heterozygosis has been described in TK-2 related children's onset myopathy [8,9].

Herein, we report a novel compound heterozygosis mutation late onset TK2- deficiency

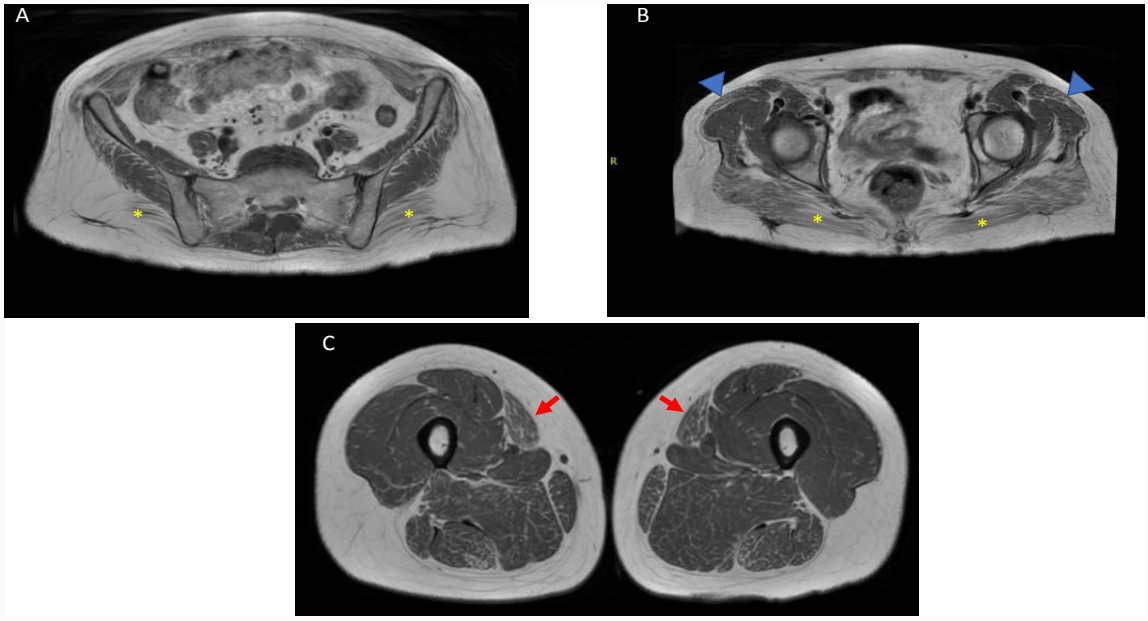

Figure 1: Muscle MRI. T1W images at pelvic girdle (A and B) and thighs (C). The gluteus maximus muscles (asterisks) show severe fatty infiltration and tensors fasciae latae (arrowhead) and sartorius (arrows) show moderate involvement.

myopathy.

Case Presentation

We report a 50-year-old female, with no neuromuscular, cardiac, or diabetic family history. During her childhood, the patient had exercise intolerance without muscle weakness. At 36 years old, after a long flight, the patient presented an acute episode of limb girdle weakness, myalgias and a 25,000 U/L in serum CK. This episode lasted three days, then she returned to being asymptomatic, and CK returned to normal values.

The patient started a progressive girdle limb muscle weakness one year after the first rhabdomyolysis episode and slightly elevated CK (600 U/L to 900 U/L). At 47 and 50 years, she had new episodes of rhabdomyolysis (CK 15.000 and 17.000 U/L) episodes with no precise trigger. She was admitted to our hospital due to the last episode of rhabdomyolysis.

On examination, there was bilateral ptosis, orbicular oculi, and limb-girdle weakness. Venous blood lactate was elevated (18.9 mg/dl) and no other abnormalities were documented in the laboratory exams. No deafness and cardiopathy was found in audiometry and echocardiography, respectively.

Electromyography registered myopathic changes in both orbicularis oculi and gluteus maximum. Muscle Magnetic Resonance Imaging (MRI) of the lower limbs showed fatty infiltration predominantly in the gluteus maximus, sartorius and tensors fasciae latae. The other muscles of the pelvis, thighs, and legs had significantly less involvement (Figure 1). Deltoid muscle biopsy unveiled increased muscle fiber internal nuclei, several small rounded muscle fibers and scattered pale. There was a focus of endomysial inflammatory cells and necrotic fibers. Also, frequent cyclooxygenase negative and red raged fibers were found.

Next-Generation Sequencing (NGS) neuromuscular panel revealed a pathogenic heterozygous mutation of the TK2 gen [c.323C>T p.(Thr108Met)] and [c.268C>T p.(Arg90Cys)] mutation, both associated with mitochondrial DNA depletion syndrome (Table 1). Genetic counselling was done, and a NGS TK-2 gen was performed on her asymptomatic son, showing only one allele with c.268C>T p.(Arg90Cys) mutation.

The patient responded satisfactorily to intravenous fluids therapy without renal or respiratory involvement. Deoxynucleoside therapy was offered, and the patient was discharged.

Discussion

Recessive mutations in the TK2 gene are responsible for diverse clinical presentations mainly characterized by progressive muscle weakness, dysphagia, and respiratory involvement with a broad spectrum of severity and onset [7-12]. Recurrent rhabdomyolysis is a rare presentation form of late-onset TK-2 myopathy, only one clinical case was reported in the literature [13].

The most frequent mutation is p.Lys202del. Moreover, there are multiple pathogenic mutations described in the literature [7,10,11]. Compound mutations have been described [8,9], expanding the spectrum of possible mutated combinations. Generally, adult onset TK-2 deficiency myopathy is less severe than pediatric forms. This may be due to better maintenance of the muscle mtDNA content, differing from late-onset pediatric forms, which have an increased mtDNA expression [11]. Compound mutations have been increasingly described in different forms of TK2 deficiency myopathies [9,11,12]. These combinations can produce the symptomatic form while homozygous (NM_004614.4:c.323C>T), or compound (NM_004614.4:c.268C>T) [11].

Muscle fat infiltration on lower-limb muscle MRI is an important clinical clue to the diagnosis. Gluteus maximus is the most severely affected muscle, and sartorius, a muscle which is usually spared in many genetic muscle diseases (even in late stages), was also affected. Interestingly, these MRI fits with a pattern previously described in late-onset TK2 patients [7].

Muscle biopsies in late-onset TK-2 deficiency myopathy showed

Table 1: Patient compound mutations in whole exome sequencing test.

Gene	Coordinates	Amino acid change	SNP identifier	Zygosity
TK2	NM_004614.4:c.323C>T	p.(Thr108Met)	rs137854431	Heterozygous
TK2	NM_004614.4:c.268C>T	p.(Arg90Cys)	rs281865489	Heterozygous

Abbreviations: TK2: Thymidine Kinase 2; SNP: Single Nucleotide Polymorphism

the typical findings of mitochondrial dysfunction described in most mitochondrial myopathies. However, other TK2 deficiency forms also revealed dystrophic features distinct from most other mitochondrial myopathies [7]. Our patients show dystrophic and mitochondrial features on the muscle biopsy.

This case reinforces that rhabdomyolysis should be included in the myopathy phenotypic spectrum of TK-2 deficiency, similar to what was published in a previous case report [13].

Conclusion

A compound heterozygous mutation in TK2-gene (pathogenic mutation in [c.323C>T p.(Thr108Met)] and novel mutation in [c.268C>T p.(Arg90Cys)]) are associated to recurrent rhabdomyolysis and late-onset myopathy.

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