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Case Report

First Report of A Lebanese Patient With TK2 Related Myopathic Syndrome

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Abstract

Congenital Neuromuscular disorders are individually very rare but collectively very common, particularly in societies with very high rates of consanguinity. Their diagnosis yet remains challenging and many underdiagnosed. During the infectious episodes the patients affected with these disorders present with different levels of severity especially affecting the respiratory system. Here, we report a novel mutation in a Lebanese patient presenting with an early onset mucle weakness and motor regression. By Whole Exome Sequencing, a novel likely pathogenic variant in the thymidine kinase 2 (*TK2*) gene was found confirming the diagnosis of mitochondrial DNA depletion syndrome type 2 (Myopathic type). At age of 4 years and a half, the patient was affected by COVID-19. The clinical features of this patient, in addition to its treatment during his COVID-19 infection are discussed.

***Keywords:** TK2 gene; Exome; Myopathy; Mitochondrial Disease; COVID-19*

Introduction

The clinical spectrum of TK2 deficiency stretches from infancy to childhood ranging from motor regression to early death [1]. Mutations of the thymidine kinase 2 (*TK2*) genes have been reported mainly in the myopathic form of mitochondrial diseases[1]. Up until now, few patients with the latter syndrome and 42 different *TK2* variants have been reported world wide [2] but never in Lebanese patients [3,4,5, 6].

Here, we describe the first reported Lebanese myopathic patient presenting with a novel *TK2* variant. The clinical features in addition to the clinical management during an episode of COVID-19 infection, are discussed.

Case Report

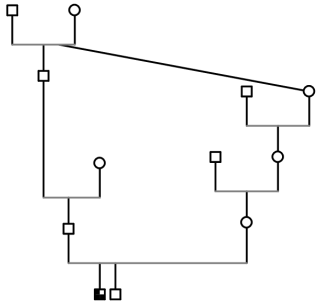

***Figure 1 :** Patient's pedigree*

Here we present the case of a 3-year-old boy, born to Lebanese first cousins once removed parents originating from northern Lebanon. He was born at term after an uneventful pregnancy. Developmental milestones were age-appropriate until 3 years of age where he started having gross motor regression. He began losing the ability to rise from a sitting position and bear his weight to walk. However, fine motor skills were preserved which enabled him to feed himself and hold a pen to scribble and paint. He was never toilet trained and his language and social skills were well maintained. The patient's weight, height and head circumference were appropriately following the growth curve at the 50th percentile. With the motor regression, the diagnosis of myopathy was raised but no work up was performed. A whole exome sequencing study didn't reveal any pathogenic variant.

The patient presented to our institution 7 months following the onset of his symptoms with a pneumonia and respiratory failure requiring intubation. The patient required six weeks hospitalization course with further regression of his motor function. Upon presentation, his physical examination showed muscle weakness more pronounced proximally with retained deep tendon reflexes. Ocular movements were normal and no ptosis was observed. A baseline work up showed a CK level of 685 IU/L, lactate 3.2 mmol/L pyruvate 0.75 mmol/L, HCO3 14mmol/L, and the rest of the metabolic work up showed no anomalies.

A skeletal muscle biopsy was performed and histological studies showed marked variation in myofibers size and shape, with many scattered necrotic myofibers, extensive fibrosis, and prominent endomysial fat infiltrates (Figure 2). Few scattered ragged red fibers (RRFs) were also noted. Oxidative enzymes stains showed a mosaic pattern of cytochrome c oxidase (COX) activity ranging from complete loss to normal activity (Figure 2). Observed pathological changes were suggestive of a mitochondrial disorder.

Biochemical studies of mitochondrial respiratory chain enzymes showed a significant decrease in all assessed isolated activities of respiratory chain complexes I, II, III, IV, V (table 1) . Mitochondrial mass was also significantly reduced as shown by the drop in the activity of the reference enzyme Citrate synthase. Normalized activities, expressed in terms of the citrate synthase level for each individual complex, were within normal limits for complexes, II, III, but not for complexes I, IV, and V indicating that their impairment is significant.

Biochemical studies as outlined were indicative of a combined mitochondrial deficiency involving specifically complexes I, IV, and V, while sparing particularly complexes II. Such a picture is commonly related to mitochondrial DNA-related abnormalities that are often genetically induced by nuclear or mitochondrial pathogenic variants.

A whole exome sequencing done earlier was revisited, which revealed a is homozygous variant in the *TK2* gene: NM_004614.4:c.504C>G p.Ile168Met. According to the ACMG recommendations, this variant was classified as Likely pathogenic. The parents were found to be carriers of the same variant at the heterozygous state. The patient was discharged on none invasive ventilation and a home based physical therapy program, and was started on carnitine 100 mg/kg/day, coenzyme Q 10 150 mg, biotin 10 mg, vitamin B2 100 mg daily. The patient showed notable motor improvement and respiratory stability.

After 7 months the patient presented again to our department with respiratory distress, hypotonia, somnolence, and decreased activity with only lactic acidosis reaching 4 mmol/L. His chest Xray showed bilateral perihilar infiltrates and his secretions PCR was positive for COVID-19 infection (Epsilon Variant). His hospital course was smooth and recovered with supportive treatment after 2 weeks of hospitalization.

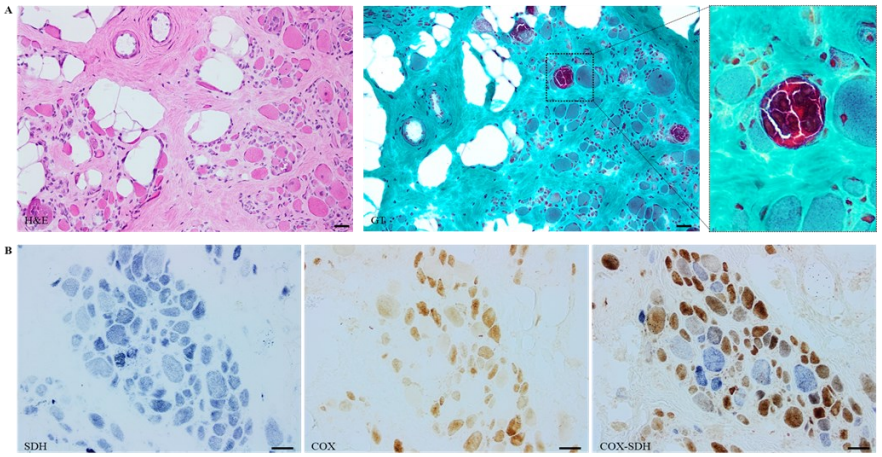

Figure 2: *Histology studies of the patient's muscle biopsy . (Panel A) Hematoxylin and eosin (H&E) and modified Gomori Trichrome (GT) stains highlighted dystrophic features characterized by a marked variation in myofibers size and shape, with prominent endomysial fibrosis, fatty infiltrates, and regenerating/degenerating muscle fibers. Few scattered raged red fibers (RRFs) were also noted throughout the sections (Inset). (Panel B). Oxidative enzymes stains show many myofibers with a variable degree of COX negativity (COX stain & COX-SDH stains) as usually observed in mitochondrial disorders. Scale bars : 50 µm.*

Table 1: Biochemical assessment of mitochondrial respiratory chain complexes activities. Respiratory chain complex I (CI; NADH dehydrogenase), complex II (CII; succinate dehydrogenase), complex III (CIII; coenzyme Q cytochrome c-oxidoreductase), complex IV (CIV; cytochrome c oxidase) and complex V (CV; ATP synthase) enzymatic activities were studied. Citrate synthase activity was used as a control for mitochondrial mass, while lactate dehydrogenase (LDH) was used as a cytosolic reference. All enzymatic activities were assessed spectrophotometrically. Values represent enzymatic activities and are expressed in nano moles of substrate transformed per minute per milligrams of proteins (nmol.min-1.mg-1).

	Activities ($nmol.min^{-1}.mg^{-1}$)	Ref. range ($nmol.min^{-1}.mg^{-1}$)
	Patient (c.2242C>G)	
CI	1.71*	[10.42-47.30]
CII	7.86*	[18.73-47.70]
CIII	25.80*	[81.28-210.86]
CIV	8.63*	[82.01-237.59]
CV	10.69*	[62.21-130.72]
Citrate Synthase	28.99*	[110.86-288.65]
LDH	985*	[2084-7317]

* Indicates activities that do not fall within our normal reference values.

Discussion

Mitochondrial diseases are clinically and genetically a heterogeneous group of disorders. Detection of all associated pathogenic variants is challenging because of their diverse genetic origin, mitochondrial and nuclear genome, and their wide clinical variability. Even though mitochondrial disorders have been originally linked to mitochondrial DNA mutations, recent advances have shown that the bulk of pathogenic variants are found within the nuclear genome with an impact on the stability and the function of the mitochondrial DNA [7]. Mitochondrial DNA maintenance defects are described by mtDNA depletion or deletion [8]. These defects can be grouped as encephalohepatopathy, encephalomyopathy, encephaloneuropathy, neurogastrointestinal encephalopathy, myopathy, ophthalmoplegia, optic atrophy, or neuropathy [8].

Currently, owing to the development of next-generation sequencing (NGS) technology, a growing number of mitochondrial-related pathogenic variants are being identified. Documenting the different types of Thymidine Kinase 2 genetic deficiencies allows a better understanding of its clinical spectrum. We describe here an unreported mutation in *TK2* gene in a Lebanese child.

TK2 myopathy clinical spectrum has three major clinical forms including an, infantile onset, childhood onset and a late onset myopathy. A retrospective review found that 41.1% of cases of TK2 deficiency present as childhood onset between the ages of 1 and 12 years of age [9]. Our patient developed at the age of 3 years, proximal muscle weakness and hypotonia which is consistent with the most presenting sign of the disease [9].

It is believed that COX-deficient fibers and red ragged fibers (RRF) are of the most common histological signs of TK2 deficiency seen on a muscle biopsy [2]. Unlike our patient, the muscle biopsy detected no RRFs but had COX-deficient fibers. Many of the patients in earlier case reports lacked RRFs and COX-deficient fibers. These can be explained by the fact that the presence of RRfs and COX-deficient fibers is dependent on the age of onset at which they present. They are usually present in older patients rather than younger. Accordingly, depending on the stage of the disease's diagnosis, they might have different laboratory and histological findings [2].

Our patient became wheelchair-bound in the first year of diagnosis compared to a study on 30 patients showing that 63% of childhood onset TK2 deficiency became wheelchair-bound within 10 years of disease onset [9]. Moreover, it showed that half of childhood onset required ventilator support similar to our patient [9]. Our patient's early loss of gait can be explained by the severity of the first respiratory infectious episode.

Our patient presented with a slowly progressive gross motor regression suggestive of myopathy, yet without a completely clear picture that led to a normal first reading of the whole exome sequencing until clinical picture was entirely revealed and WES was revisited again. The presence of an unreported mutation not described in the foreign genetic databases explains the diagnostic delay, and stresses on the importance of creating national genetic databases in the communities with high consanguinity rates.

In a large majority of patients, WES provides the possibility to get a diagnosis. It is being used more frequently in medical genetics practices due to its clinical availability. The use of WES has also led to the discovery of novel disease-causing genes, insights into the clinical and allelic heterogeneity. Nonetheless, it is imperative to understand the true limitation of WES as discussed by the retrospective study on the application of whole exome sequencing done by Shashi et al. [10] Providing the clinical and laboratory data before obtaining WES consequently re-analyzing WES will not delay the diagnosis and treatment to the patient.

The COVID-19 pandemic has the capability to severely affect patients with neuromuscular disease. Hence, at the beginning of the pandemic, guidance on the impact and management of COVID-19 infection in neuromuscular disease patients have been emerged by the national neurological associations and neuromuscular networks. The committee defined a high risk of severe course of COVID-19 infection in all forms of neuromuscular disease, with the exception of the mildest forms. A higher risk of disease was expected in patients with muscular weakness reaching the diaphragm or chest, usage of ventilation via mask or tracheostomy, oropharyngeal weakness, presence of tracheostoma, cardiac involvement, and patients taking steroids or taking immunosuppressant therapy [11]. Patients with neuromuscular diseases that do not involve swallowing or respiratory muscles and those who are not on immunosuppressants, are not considered at “high risk” of COVID-19 infection [12]. Thus, it is recommended to monitor moderate to high-risk patients with NMD for rapid deterioration in respiratory function. In a multicenter cross-sectional study in France, 84 patients with NMD and variable comorbidities were followed up during their COVID-19 infection. Within this cohort study, 58% of patients with NMD had no effect on their pre-existing disease, 31% had worsening of symptoms and 11% died. Six out of the 9 deceases patients had at least two underlying comorbidities (such as respiratory or cardiac failure, diabetes, hypertension or age above 65 years)[13].

Current data from the COVID-19 pandemic on the outcome of COVID-19 infection on patients with NMD remains unknown, certainly in the pediatric population. Reporting individual cases of rare neuromuscular diseases patients when encountering the COVID-19 germ can be very helpful in orienting the management even if case based, due to the rarity of the disorder.

Conclusion

Congenital Neuromuscular disorders present with an increased risk of morbidity and mortality with respiratory tract infections, metabolic myopathies seem to tolerate the infection better when maintain a metabolic stability. COVID-19 (Epsilon Variant) respiratory infection was well tolerated in one child with TK2 mutation. This is the first Lebanese patient to be reported as carrier of this mutation, the mutation was never reported earlier and subsided in an earlier studied whole exome sequencing, arguing with the possibility of other missed patients earlier and stressing the necessity of coupling the next generation genetic studied with the accurate clinical presentation and the necessary para-clinical pathological work up.

Conflict of interest

None of the authors has a conflict of interest with the material presented in this paper.

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