

Cox10 Novel Variant in a Lebanese Female Patient with Congenital Cataracts

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Abstract

Mitochondrial disorders can present with a very wide clinical variability depending on the affected gene. Novel mutations in mitochondrial diseases are being identified more frequently than the past decades in the Lebanese population, where these disorders rank as the most common inborn errors of metabolism. Here we describe a novel COX10 variant in a female patient from south Lebanon, presenting with congenital cataracts, failure to thrive, microcephaly, global developmental delay and behavioral problems. The patient carries a not reported before missense mutation in the COX10 gene (c.514A>G p.(Thr172Ala)), confirming the diagnosis of a homozygous COX10 variant, in favor of Leigh syndrome. The cataracts finding. This is to our knowledge the first reported patient with COX10 mutation presenting with congenital cataracts; thus, adding to the clinical spectrum of this disease.

Keywords: Mitochondrial disease, Leigh Syndrome, COX10, Congenital cataracts, Microcephaly.

Introduction

With the recent advances in molecular genetic studies, novel variants are being described more and more specially in closed consanguineous populations. The Lebanese population still suffers from a high rate of consanguinity [1] and the mitochondrial diseases rank among the most common inborn errors of metabolism in Lebanon based on the recent publications [2]. The clinical presentation of mitochondrial disorders bears a wide spectrum of variability depending on the affected gene and on the mitochondrial heteroplasmy. Here we report a novel mutation in the COX10 gene, in a female child presenting with congenital cataracts, a sign previously unreported earlier in patients with the same mutation.

Case Presentation

We hereby report the case of a 15-year-old girl, who first presented at the age of 2 years for failure to thrive and neurodevelopmental delay. She was born to third degree consanguineous parents (figure 1), from South Lebanon, at term by C-section for preeclampsia, with a low birth weight of 1.6kg.

Her height and head circumference were also below the 5th percentile. The patient had a left eye cataract that was operated successfully at 1 year of age. During her first year of life the patient had significant regression of her growth whereby her height, weight and head circumference dropped below the 3rd percentile at the age of 4 months.

The patient started to say her first words at the age of 8 months and began to walk assisted at the age of 1 year.

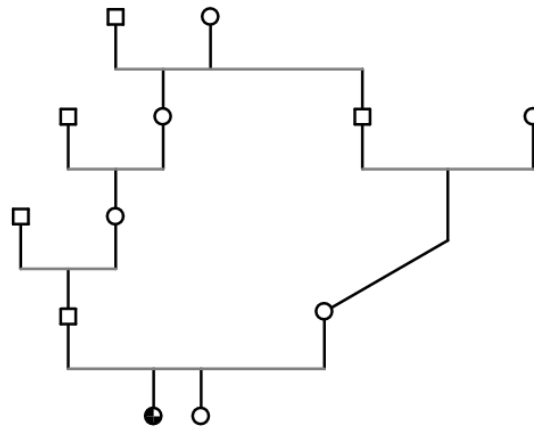


Figure 1: Family's Pedigree.

At 2 years of age, patient's neurological and motor functions started to regress. She first refused to walk, and she had stagnation of language development as she was only saying few words repetitively, with inability to form sentences. Physical exam was remarkable for right eye strabismus and bilateral lower limb spasticity with normal reflexes and a persisting failure to thrive with a weight and head circumference at the 3rd percentile. Gastroscopy, colonoscopy, and biopsies were performed to rule out malabsorption disorders and celiac disease, and all turned out negative. The patient tested negative for cystic fibrosis mutations. Endocrinology workup was also done including bone age, TSH, IGF-1 and karyotype and revealed to be normal. Cardiac ultrasound showed a mild mitral insufficiency.

Brain MRI/Spectroscopy revealed minimal sequelae of periventricular leukomalacia with no MRS abnormalities and no brain calcifications.

The patient started to be followed at a specialized center with regular psychomotricity and speech therapy sessions, she started to show some improvement: she became more tonic; however, she crawls more than walks, and she started saying much more words.

At the age of 5 years, patient started walking alone. She was more active, able to climb up and down stairs. She started attending a specialized school and was saying more than 20 words. She was doing better contact and interaction with good appetite and improving weight. She was suffering from recurrent upper respiratory tract infections and otitis media. Hearing test done and was found to be positive for bilateral sensorineural hearing impairment. Rett syndrome test was done by analysis of MECP2 gene was found to be negative.

At the age of 7 years the patient was still doing all activities and good interactions. She was able to say many words but can stay 3 to 4 days without speaking.

A muscle biopsy was performed and showed Myofibers that varied mildly in size, with few scattered shrunken fibers, mean fiber diameter ranging from 20 to 50 Mm. Focal myolysis was noted. Lipid globules were slightly increased in size and density within some of the myofibers. No storage vacuoles, no specific inclusions, no rods and no cores were seen within myofibers. Small clusters of granular histiocytes, CD68+, were present within connective tissue of perimysium, nonspecific. No complement deposits were seen. Multifocal subsarcolemmal mitochondrial accumulations and a rare ragged-red fiber were noted. Mitochondrial enzymes were well expressed, but COX was absent from muscular walls of perimysial arterioles. ATPase shows good differentiation of type I and II fibers, with mild Type I predominance, and small clusters of myofibers type I grouping. ATP synthase immunohistochemistry showed absence of this enzyme within small groups of large rounded myofibers, and good staining of residual fibers.

The muscle biopsy was confirmed by a whole-Exome Sequencing (WES) test that showed a novel missense mutation in the COX10 gene (c.514A>G p. (Thr172Ala)), confirming the diagnosis of a newly described COX10 homozygous variant, in favor of Leigh syndrome.

Discussion

Even though occupying a geographical position on the crossroad of multiple civilizations, the Lebanese population still suffers from a high rate of consanguinity and rare disorders are not an abnormal finding in patients with neurometabolic symptoms [3]. The mitochondrial diseases are the most common inborn error of metabolism identified in the Lebanese population with multiple specific variants of the mutations [4,5,6]

Here we present the case of a female patient presenting with congenital cataracts, failure to thrive, global cognitive delay, and a muscle biopsy showing the lack of Cytochrome C oxidase expression in muscle walls of perimysial arterioles, and a molecular study showing a novel mutation in the COX10 gene. To our knowledge this is the first reported patient with COX10 mutation presenting with congenital cataracts.

Leigh syndrome is a devastating neurodegenerative disorder primarily affecting the central nervous system, with an estimated incidence of 1 in 40,000 live births [7]. It is characterized by the progressive leukodystrophy, leading to motor and cognitive impairments. Mitochondrial dysfunction plays a central role in the pathogenesis of Leigh syndrome, affecting critical energy-producing processes such as electron transport chain and ATP synthesis [8].

Cytochrome c oxidase (COX) deficiency is one of the many causes of Leigh syndrome. This enzyme, which is known as complex IV, is the terminal component of the mitochondrial respiratory chain and plays a pivotal role in catalyzing the transfer of electrons from reduced cytochrome c to molecular oxygen. Dysfunction of complex IV leads to reduced energy production and increased production of reactive oxygen species, which can cause cellular damage [9].

COX is a member of heme-Cu oxidases [10]. It is a complex assembly of 13 subunits, three of which form the catalytic subunits encoded by genes within the mitochondria and are primarily responsible for electron transfer. The other structural subunits are encoded by nuclear genes and contribute to the regulation and assembly of COX complex.

The COX10 is one of the nuclear genes responsible for encoding a protein essential for cytochrome c oxidase synthesis. This gene encodes for the enzyme heme A: farnesyltransferase. While this enzyme is not a structural component of COX, it plays a crucial role in ensuring the proper assembly pathway of COX, therefore essential for the proper function of the mitochondrial respiratory chain [11].

Heme A: farnesyltransferase assists in the conversion of protoheme (also known as heme B) into heme O. This transformation is accomplished through the farnesylation of a vinyl group at position C2[12] of the protoheme. Heme O subsequently undergoes conversion into heme A, which is one of the crucial prosthetic groups necessary for the proper functioning of COX. This conversion process involves the participation of Cox15p, ferredoxin, and ferredoxin reductase [13]. Heme A: farnesyltransferase is anticipated to have between 7 to 9 transmembrane domains and is situated within the inner mitochondrial membrane, with hydrophilic loops between transmembrane domains II/III and VI/VII [14]. A highly conserved motif is responsible for transferring a farnesyl group to the pyrrol ring A of ferrous protoheme IX. Once attached to the heme, this farnesyl chain serves as a hydrophobic anchor to position the heme within the complex IV [15].

Here we report a Lebanese female, with a specific gene mutation in the nuclear COX10 gene resulting in the substitution of a threonine (Thr) amino acid at position 172 by a hydrophobic alanine (Ala) amino acid. This variant was also detected in both parents of the patient in a heterozygous state therefore the homozygous state of the variant is confirmed in the patient. This shift from a hydrophilic to a hydrophobic amino acid seems a critical aspect of the mutation's impact on the structure and function of the protein encoded by the COX10 gene. The substitution in the gene region may induce a structural change, potentially affecting the synthesized protein's properties. What makes this case particularly significant is that, to our knowledge, this is the first instance where such a substitution in the COX10 gene has been described, and it is shown to have substantial implications for mitochondrial function. Specifically, it leads to a severe impairment of the electron transport chain, which is a fundamental process in mitochondrial energy production. This ensuing mitochondrial dysfunction can be considered as causative of the global failure to thrive, microcephaly and global developmental delay. And since the mitochondrial oxidative phosphorylation is essential for cellular energy production that is necessary for lens to maintain transparency [16], cataracts can be expected to be seen in patients affected with COX10 mutation.

In summary, the nuclear gene COX10 encoding heme A: farnesyltransferase is crucial for the proper functioning of COX. While it may not be a structural subunit of the complex, its role in heme A maturation is indispensable for the expression of a fully functional COX complex. Mutations in this gene may lead to cytochrome c oxidase deficiency and are also implicated in other genetic disorders.

These findings underscore the significance of the COX10 gene in maintaining mitochondrial function and the potential consequences of genetic mutations in this context.

Conclusion

Here we report the case of a Lebanese female patient with a novel COX10 mutation, presenting with microcephaly, failure to thrive, global developmental delay, congenital cataracts, and a muscle biopsy showing red ragged fibers and absent COX from muscular walls of perimysial arterioles. To our knowledge this is the first reported case of a patient with COX10 gene mutation presenting with congenital cataracts. This finding adds to the reported clinical spectrum of the disease and suggests the possibility of other overlooked signs in rare disorders especially in highly consanguineous societies.

Conflict of Interest

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

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