Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

Complex mitochondrial disease caused by the mutation of COX10 in a toddler: a case-report study

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Introduction and importance: Cytochrome C oxidase (COX) deficiency is an uncommon inherited metabolic disorder. It is identified by a lack of the COX, also known as Complex IV. This enzyme plays a crucial role in the rate-limiting and oxygen-accepting step of the respiratory chain within the subcellular structures called mitochondria. The deficiency of COX can either be restricted to skeletal muscle tissues or can impact multiple tissues throughout the body.

Case presentation: A 3-year-old girl was admitted due to muscle weakness and a decline in developmental milestones 7 days after a significant stressor. Leukodystrophy was observed in the brain magnetic resonance imaging, and genome sequencing identified a homozygous mutation in exon 1 and 7 of chromosome 17. This mutation led to a deficiency in COX10, which is a component of mitochondrial complex IV.

Clinical discussion: In the medical field, inherited metabolic disorders can be complex to diagnose due to overlapping symptoms with other conditions. Mitochondria's oxidative phosphorylation system, including the COX enzyme complex, plays a crucial role in energy production. Mitochondrial disorders, including COX deficiency, can present at various stages of life with diverse symptoms. Treatment options focus on supportive care and potential benefits from supplements like coenzyme-Q10 and small-molecule therapies targeting mitochondrial function. Identifying genetic mutations is key for advancing treatments in this area.

Conclusion: This report presents a unique case of developmental regression and muscle weakness in a paediatric patient, which can be attributed to a rare occurrence of type 3 nuclear mitochondrial complex IV deficiency.

Keywords: case report, COX10, cytochrome c oxidase deficiency, mitochondrial complex IV, mitochondrial disorder

Introduction

Inherited mitochondrial disorders that impact oxidative phosphorylation (OXPHOS) function are prevalent with an approximate incidence rate of 1 in every 5000 individuals[1].

COX, also known as cytochrome c oxidase, is a copper-haem A terminal oxidase responsible for the rate-limiting and oxygen-accepting step of the respiratory chain, embedded within the inner membrane of mitochondria[2]. Its main function is to facilitate the transfer of electrons from reduced cytochrome c to molecular oxygen. This electron transfer process is coupled with the movement of protons across the inner membrane, which ultimately contributes to the creation of a proton gradient. This proton gradient is then utilized by adenosine triphosphate (ATP) synthase to generate ATP through the process of ATP synthesis[3].

Within the complex structure of COX, there exist several subunits that serve distinct functions. One such subunit, COX10 is a critical component involved in two significant processes: haem A biosynthesis and farnesylation of haem B. These processes are responsible for the conversion of protoheme to haem O, which serves as the immediate precursor for the production of haem A[4,5].

Malfunctioning of these complexes can result in a variety of diverse symptoms affecting muscles, liver, brain, heart, and other organs[6].

Mitochondrial deoxyribonucleic acid (mtDNA) genetics is intricate since each cell contains multiple copies of mtDNA. Mutations can be homoplasmic, affecting all mtDNA, or heteroplasmic, with a mix of mutated and wild-type mtDNA. These mutations are functionally recessive, so a biochemical phenotype

HIGHLIGHTS

- Cytochrome C oxidase (COX) deficiency is an uncommon inherited metabolic identified by a lack of the enzyme COX.
- It is crucial to take into consideration the possibility of mitochondrial disorders when there is a regression in developmental milestones following a significant stressor.
- COX deficiency rarely results in leukodystrophy of the brain.
- The variant p.Thr377Ile in the COX10 gene appears to be the main cause of the Protoheme IX farnesyltransferase protein's functional disruption.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2024) 86:3753–3756

Received 29 January 2024; Accepted 14 April 2024

Published online 29 April 2024

http://dx.doi.org/10.1097/MS9.0000000000002096

is only seen when levels of mutated mtDNA surpass a critical threshold[7].

To date, it was arduous to diagnose many patients genetically, especially those with nuclear gene mutations. However, the emergence of accessible next-generation sequencing has led to a significant increase in identifying new genetic defects that affect the OXPHOS[8]. Identifying specific genetic defects is crucial as it provides insights into the disease mechanism for the patient, personalized treatment options[9], and Predicting the prognosis for individuals, as previous studies have shown that patients with neuromuscular symptoms but without cardiomyopathy had a 95% survival rate at the same age[10].

In this study, we provide a challenging case of a 3-year-old girl who presented to the neurology department with symptoms of muscle weakness and a decline in developmental milestones.

Case presentation

A 3-year-old female patient presented to the paediatric neurology clinic with the primary concern of experiencing muscle weakness and regression in developmental milestones 9 days after an upper respiratory infection, which was diagnosed as a viral infection and managed with outpatient supportive care. Prior to this infection, the patient had an unremarkable medical history and achieved developmental milestones within the expected timeframe. However, following the viral illness, she began to exhibit a range of debilitating symptoms. Seven days after the infection, she lost the ability to walk and speak. Additionally, her mother noticed that she stopped making eye movements to observe her surroundings the day after. This particular issue persisted for a duration of 2 months.

In reference to her familial history, despite having parents who were consanguineous, there were no reported instances of noteworthy medical conditions.

During the physical examination, the patient displayed low-set ears, a high forehead, and muscular weakness, with spasticity observed in both the upper and lower extremities. The patients mother also reported experiencing food regurgitation.

Considering her developmental regression into account, the patient was admitted for investigation. Her laboratory data revealed lactic acidosis and her brain MRI manifested diffuse leukodystrophy (Fig. 1).

By the primary suspicion towards metabolic disorders, the genetic assessment using the whole-exome sequencing (WES) method was performed on DNA extracted from peripheral blood in a diagnostic laboratory. Capturing was done using the Twist Human Core Exome Kit.

A homozygous missense variant in the COX10 gene (COX10:c.1130C > T) was identified. This variant leads to the alteration of amino acid 377 from Threonine to Isoleucine in the last transmembrane domain. Most prediction software tools classify this alteration as pathogenic. This variant has not been reported in healthy populations. Based on American College of Medical Genetics (ACMG) classification, this variant is considered a variant of uncertain significance (VUS) leaning pathogenic variant. The parents of the affected individual carried this variant in a heterozygous state via Sanger sequencing.

Additionally, another homozygous missense variant with a lower pathogenicity score was found in this patient's data (COX10:c.41C > T; p.Thr14Ile). According to ACMG classification, this variant is a VUS. It has been observed in the heterozygous state in healthy populations but hasn't been reported in the homozygous state among healthy individuals. This variant was also present in the affected individual's parents in a heterozygous state via Sanger sequencing.

The variant p.Thr377Ile in the COX10 gene appears to be the main cause of the Protoheme IX farnesyltransferase protein's functional disruption. The p.Thr14Ile variant might play a role as an exacerbating factor. Functional studies might elucidate the impact of these variants on the produced protein by the COX10 gene.

By prioritizing symptom-based management, maintaining optimal health, using preventive measures to prevent symptom worsening during times of physiologic stress, and avoiding mitochondrial toxins; the patient was administered an oral mitochondrial cocktail comprising daily doses of coenzyme-Q10, biotin, thiamine, riboflavin, pyridoxine, L-Carnitine, and folinic acid.

At the 6-month follow-up after admission, the patient's food regurgitation had improved and she could swallow properly. However, her motor functions for walking, sitting, and speaking had not recovered. Additionally, she had experienced focal convulsions that were managed with 150 mg of levetiracetam and 10 mg of clobazam.

Discussion

In the field of medical practice, the consideration of inherited metabolic disorders can be complex due to the presence of signs and symptoms that can resemble other neuromuscular disorders.

The oxidative phosphorylation system, situated within the inner membrane of mitochondria, comprises five enzyme complexes (complex I–V) with multiple subunits. Among these complexes, COX (complex IV) serves as the terminal enzyme in the respiratory chain. Its primary function involves facilitating the transfer of electrons from reduced cytochrome c to molecular oxygen while simultaneously facilitating the pumping of protons across the inner mitochondrial membrane. The COX enzyme complex consists of 13 structural subunits, with three of them being encoded by mtDNA and forming the catalytic core of the enzyme. Additionally, several proteins are involved in the assembly and maintenance of this complex[11].

Previous research indicates that the prevalence of mitochondrial disorders may be as high as 1 in 5000 individuals[1], while the occurrence of COX deficiency could be as prevalent of 1 in 35 000[12].

Hence, it is crucial to consider this disorder as a potential differential diagnosis in a wide range of clinical conditions during childhood, especially when there is a sudden decline in developmental milestones following significant stressors. The disorder may manifest from prenatal stages, characterized by growth retardation, dysmorphic features, cerebellar hypoplasia (with or without optic nerve atrophy)[13,14], neonatal stages by spinal muscular atrophy-like, recurrent myoglobinuria, asphyxia-like, and respiratory distress-like[15,16], to early childhood, presenting symptoms such as myopathy, De Toni-Fanconi-Debre syndrome, renal tubular acidosis, cardiomyopathy, encephalopathy, and Leigh syndrome[17–19]. In late childhood, symptoms may include leukoencephalopathy, spinocerebellar syndrome, sensorineural hearing loss, proximal myopathy, exercise intolerance, bilateral

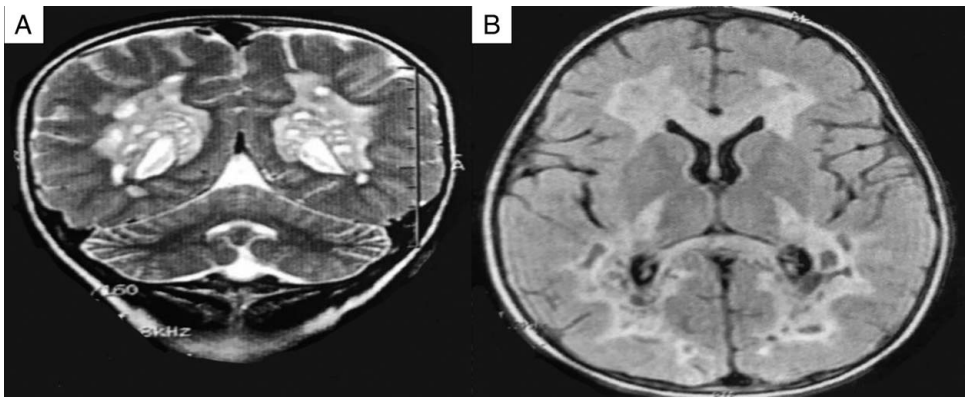

Figure 1. MRI (A) T2 and (B) T1 displaying diffuse leukodystrophy.

cataracts, and endocrinopathy. The disorder can also manifest during adolescence[20–22].

One of the main difficulties in treatment lies in the highly diverse phenotype-genotype relationship observed in individuals with mitochondrial disease. This variability is evident not just in the impact on various organs but also in the severity of the disease[23].

Currently, there is no known cure for mitochondrial disorders. However, patients afflicted with these conditions may derive some benefits from supportive treatments. These treatments include the administration of coenzyme-Q10, which plays a crucial role in various cellular processes[24]. Thiamine, essential for muscle growth and maintenance[25], riboflavin, necessary for ATP production[26], alpha lipoic acid, an antioxidant[27], vitamin E, which protects cell membranes[28], and L-Carnitine, aiding in fatty acid transport and muscle tone[29], are among the key components of a mitochondrial cocktail that these patients may find advantageous.

Moreover, new small-molecule therapies have been tested in recent years, including: (i) Manipulating cell content of mitochondria: the process of increasing mitochondrial production and decreasing mitochondrial turnover (mitophagy) can be influenced by controlling the peroxisome proliferator-activated receptor (PPAR) family of fatty acid-regulated nuclear receptor isoforms[30]. Additionally, the transcriptional co-activator PPAR-gamma co-activator 1-alpha (PGC1α), along with other nuclear receptors, are recognized as crucial regulators of mitochondrial biogenesis[31]. (ii) Restoring NAD + levels: NAD + is a crucial component for the activity of important proteins like polyADP ribose polymerase (PARP), cyclic ADP ribose synthetases, and sirtuin deacetylases[32]. Research in animals has shown that boosting NAD + levels plays a significant role in promoting mitochondrial growth, maintaining healthy mitochondrial structure, and controlling lactic acid metabolism[33,34]. (iii) Inducing mitochondrial turnover: Rapamycin, a macrolide that acts as an anti-inflammatory and anti-proliferative agent, has demonstrated potential in improving various aspects of mitochondrial dysfunction. It targets a component of the mammalian target of rapamycin (mTOR) complex, mTORC1, which plays a crucial role in maintaining cellular balance and has been associated with triggering the mitochondrial stress response in mitochondrial myopathy[35]. Studies have indicated that Rapamycin can delay symptoms and prolong lifespan in mouse models[36].

The advancement of future treatments for mitochondrial disorders depends greatly on identifying the genes and molecular pathways involved. Therefore, it is crucial to report various mutations that lead to mitochondrial defects in order to progress in this field.

In this report, we described the case of a 3-year-old girl born to parents who are closely related, exhibiting significant muscle weakness and regression in developmental milestones following an upper respiratory infection. This infection, considered a significant stressor for her age group, led to the manifestation of decompensation in her COX10 dehydrogenase deficiency.

Ethical approval

Firoozabadi Clinical Research Development Unit (FACRDU), Iran University of Medical Sciences, Tehran, Iran.

Consent

Written informed consent was obtained from the patient's parents/legal guardian for publication and any accompanying images. A copy of the written consent is available for review by the Editorin-Chief of this journal on request.

Sources of funding

There wasn't any honorarium, grant, or other form of payment to authors to produce the manuscript.

Author contribution

A.T. and M.K. admitted the patient, S.E. gathered the data and wrote the draft of the report, S.T. consulted on the genetic testing and wrote the diagnosis, all authors contributed to finalize the report.

Conflicts of interest disclosure

There is no ethical problem (approved by the research ethics committee of Iran University of Medical Sciences) or conflict of interest in our research.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Maryam Kachuei.

Data availability statement

Not applicable.

Provenance and peer review

Not applicable.

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