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CASE REPORT

Prenatal Counseling and Diagnosis of COX20 Gene-Related Mitochondrial Complex IV Deficiency: A Case Report and Literature Review

Junyou Su[1,*], Lingdong Zeng[2,*], Hongfei Chen[1], Junru Tong[1], Yan Chen[1], Lingling Huang[1], Li Deng[1], Yan Huang[1]

[1]Department of Obstetrics, The Second Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, 530007, People's Republic of China; [2]Department of Pediatrics, The Second Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, 530007, People's Republic of China

*These authors contributed equally to this work

Correspondence: Li Deng; Yan Huang, Email dengli@gxmu.edu.cn; huangyanHY2020@163.com

Background: COX20-related mitochondrial complex IV deficiency is a rare autosomal recessive metabolic disorder that arises from biallelic loss-of-function mutations. Given the lack of specific treatments, affected children are at a heightened risk of disability. Consequently, prenatal counseling and prenatal diagnosis should be conducted to reduce the birth rate of children with such mitochondrial diseases. We report a case of COX20 gene associated mitochondrial complex IV deficiency in a child, and describe the prenatal counseling and prenatal diagnosis of the mother in subsequent pregnancies to provide reference for prenatal counseling and prenatal diagnosis of this disease.

Case Presentation: In this study, we presented a case of a pediatric patient who displayed symptoms such as gait instability, ataxia, cognitive impairment, dysarthria, muscle weakness, and absent reflexes. Through the application of whole-exome sequencing (WES), compound heterozygous COX20 mutations (c.41A>G and c.259C>T) were detected, leading to the confirmation of a diagnosis of mitochondrial complex IV deficiency. A thorough review of the existing literature revealed seven additional cases carrying the same mutations. Moreover, this report delineated the process of prenatal counseling and diagnostic testing that was undertaken for the subsequent pregnancy of the patient's mother.

Conclusion: The presence of ataxia, cognitive impairment, and peripheral neuropathy in children should prompt consideration of COX20-related mitochondrial disease. Utilizing WES is beneficial for identifying COX20 mutations, and offering prenatal counseling and diagnostic testing to mothers of affected children can reduce the birth rate of children with such mitochondrial diseases.

Keywords: COX20, complex IV deficiency, prenatal counseling, prenatal diagnosis

Introduction

Mitochondrial diseases, arising from mutations in genes of either the nuclear or mitochondrial genomes, represent the most prevalent form of inherited metabolic disorders, affecting approximately 1 in 5000 individuals.[1] The proper assembly of Cytochrome C oxidase (COX) or Complex IV (CIV), a crucial terminal oxidase in the mitochondrial respiratory chain, relies on the intricate coordination between mitochondrial and nuclear genes. Dysregulation in Complex IV assembly results in mitochondrial complex IV deficiency, a severe early-onset neuro-muscular disorder (OMIM:220110) characterized by multi-systemic manifestations.[3,4]

In 2013, Radek Szklarczyk first documented that the mutations in the COX20 gene, also known as FAM36A, lead to reduced levels and impaired function of mitochondrial complex IV, resulting in symptoms like ataxia and hypotonia in affected individuals.[5] Human COX20 is a chap-erone that stabilizes COX2 and interacts with the COX2-specific metallochaperones SCO1 and SCO2 to promote CuA site matur-ation, thereby facilitating COX2 insertion into the assembling CIV holoenzyme.[6] When COX20 gene mutation affects its stability, it will lead to CIV function defect. To date, there have been 33 confirmed cases

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of mitochondrial complex IV deficiency worldwide due to COX20 mutations, involving 11 distinct mutations. Notably, seven cases have exhibited compound heterozygous variants of c.41A>G and c.259C>T.[5,7–10,12–14] This deficiency predominantly affects children, with symptoms typically emerging between 1 and 2 years of age. Common clinical presentations include axonal peripheral neuropathy, ataxia, dystonia, dysarthria, and cognitive impairment. Given the absence of effective therapeutic interventions, this disorder imposes a substantial burden on families, emphasizing the critical role of genetic counseling in averting its recurrence in subsequent generations.

Previous research has primarily focused on exploring the genetic phenotypes and mutation profiles of complex IV deficiency, neglecting the crucial aspect of genetic counseling for women planning to conceive after having a child affected by this condition. This study conducted a literature review of five cases characterized by COX20-related mitochondrial complex IV deficiency, with particular emphasis on the compound heterozygous mutations c.41A>G and c.259C>T. One of these cases was managed at the Second Affiliated Hospital of Guangxi Medical University. Moreover, we delineated the genetic counseling process implemented for the mother's subsequent pregnancy to improve counseling strategies in similar contexts. The details of this case are reported with the written informed consent of the patient's mother (guardian). This case report has been approved by the Medical Ethics Committee of the Second Affiliated Hospital of Guangxi Medical University [Approval number: 2024-KY (0802)].

Case Presentation

The patient was an 11-year-old male born full-term in 2013 without a history of birth asphyxia or resuscitation. Initially meeting developmental milestones such as head control at three months, independent sitting at seven months, and unaided walking at two years, he later experienced regression starting at age three. This regression manifested as challenges in maintaining an upright sitting posture, an unsteady gait, slurred speech, and delayed responses. Upon assessment at our outpatient clinic in 2018 at age five, he displayed an unsteady gait and delayed language development. Physical examination revealed adequate mental alertness but poor comprehension, unclear articulation, absence of cranial nerve abnormalities, poor trunk extension control, low muscle tone in the limbs, and absent bilateral knee reflexes. Metabolic screening via blood tandem mass spectrometry and urine gas chromatography showed no anomalies. Furthermore, MRI scans of the head, cervical, thoracic, lumbar, and sacral spine yielded normal results. Electromyography (EMG) revealed significantly reduced compound muscle action potential (CMAP) amplitude in lower limb motor nerves, with no response in the distal right peroneal nerve. Absence of sensory nerve action potential (SNAP) was noted in all sensory nerves, along with abnormalities in the right tibial F-wave, and prolonged motor unit potential (MUP) in the left deltoid and right anterior tibial muscle, indicating peripheral neuron damage. Previous high-throughput sequencing (HTS) at a different medical facility showed no abnormalities. Despite intermittent treatment with L-carnitine and rehabilitation training, the patient's symptoms progressed. By the age of nine in 2022, he had lost the ability to sit, stand, or walk independently, and exhibited impairments in language, cognition, and limb strength.

In 2022, whole-exome sequencing (WES) revealed compound heterozygous mutations in the COX20 gene (c.41A>G, p.Lys14Arg and c.259C>T, p.Gln87Ter), resulting in a diagnosis of mitochondrial complex IV deficiency. Subsequent genetic testing indicated that the patient's mother carried the c.41A>G (p.Lys14Arg) heterozygous mutation in COX20, while his father carried the c.259C>T (p.Gln87Ter) heterozygous mutation. Notably, both parents were asymptomatic.

In 2022, after a previous case of mitochondrial complex IV deficiency in their child, the mother of the patient underwent amniocentesis during a subsequent pregnancy. The procedure confirmed that the fetus carried identical mutations in the COX20 gene as the proband. Consequently, the parents chose to terminate the pregnancy during the mid-trimester. In 2024, the mother conceived again with the intention of ensuring the birth of a healthy offspring. Early in the pregnancy, chorionic villus sampling was performed to promptly assess the fetal health status. Karyotype analysis and HTS of the chorionic villi revealed no anomalies. WES detected only the heterozygous mutation c.41A>G (p.Lys14Arg), consistent with the maternal genotype. On August 30, 2024, the mother delivered a healthy daughter.

Review of Literature on Patients with Compound Heterozygous Variants in the COX20 Gene: c.41A>G (p.Lys14Arg) and c.259C>T (p.Gln87Ter)

We summarized the clinical features observed in individuals with mitochondrial complex IV deficiency resulting from compound heterozygous variants c.41A>G (p.Lys14Arg) and c.259C>T (p.Gln87Ter) in the COX20 gene. This summary

Table 1 Clinical Characteristics of Patients with Compound Heterozygous Variants in the COX20 Gene: c.41A>G (p.Lys14Arg) and c.259C>T (p.Gln87Ter)

Case	Gender	Age of Onset (Years)	Gait Instability	Ataxia	CI	Dysarthria	Muscle Weakness	Absent Reflexes	Cranial MRI	PN	Reference
1	Female	5	+	+	+	+	+	+	—	S+M	Hu CP et al[7]
2	Male	4	+	+	+	+	+	+	—	S+M	Hu CP et al[7]
3	Male	1.5	+	+	+	+	+	+	—	S+M	Dong HL et Al[10]
4	Female	1.5	+	+	+	—	—	+	Thalamus-T2 high single	S	Ban R et al[8]
5	Male	2	+	+	+	+	+	+	—	S+M	Ban R et al[8]
6	Male	1	+	+	+	+	+	+	—	S+M	Ban R et al[8]
7	Male	1.4	+	+	+	+	—	+	—	S	Chen L et al[9]
8	Male	3	+	+	+	+	+	+	—	S+M	Case reported in this study

Notes: CI, Cognitive impairment; PN, Peripheral neuropathy; +, Presence; —, Absence; S, Sensory axonal damage; M, Motor axonal damage.

was based on our cases and seven cases documented in prior literature (Table 1). All patients from China presented symptoms during childhood, such as gait instability, ataxia, cognitive impairment, dysarthria, muscle weakness, and absent reflexes. Electromyography indicated sensory and motor axonal involvement in 5 patients and isolated sensory axonal involvement in 2 cases. While MRI findings were unremarkable in 6 cases, 1 case exhibited Thalamus-T2 high signal intensity, correlated with strabismus and visual impairment.

Discussion

The COX20 gene encodes a crucial transmembrane protein necessary for the formation and maintenance of mitochondrial complex IV, the terminal enzyme of the mitochondrial respiratory chain. Mutations in COX20 lead to decreased levels of the COX20 protein, disrupting the assembly of complex IV and mitochondrial oxidative phosphorylation (OXPHOS). Consequently, this impairs the respiratory reserve capacity of neuronal cells and diminishes cell proliferation during metabolic stress.[5,10] To date, 34 cases of mitochondrial complex IV deficiency resulting from COX20 gene mutations have been documented. Among these cases, eight (23.53%) involved compound heterozygous COX20 mutations: c.41A>G (p.Lys14Arg) and c.259C>T (p.Gln87Ter). Notably, 30 out of the 34 patients carried the c.41A>G mutation, either in a homozygous or heterozygous state, with six cases originating from the US and 24 from China.[7–9] Dong et al (2019) suggested a potentially higher prevalence of COX20 mutations in the Chinese population, particularly the c.41A>G mutation.[10] However, further investigations with larger cohorts are warranted to validate this observation.

Patients with compound heterozygous COX20 mutations (c.41A>G and c.259C>T) typically manifest symptoms in childhood, including difficulty walking, ataxia, cognitive impairment, dysarthria, muscle weakness, and absent reflexes. The predominant presentation involves axonal peripheral neuropathy with a sensory nerve predominance, often accompanied by motor nerve involvement. Peripheral neuropathy is common in mitochondrial disorders, such as those associated with POLG mutations.[15] In COX20-related neuropathy, sensory nerve involvement is prominent, potentially attributed to its preferential expression in proprioceptive neurons.[10] Therefore, in cases of unexplained polyneuropathy, clinicians should contemplate the prospect of mitochondrial disease linked to COX20 mutations, emphasizing the utility of early exome sequencing for prompt diagnosis.

In this study, the proband and chorionic villi samples from the mother's subsequent pregnancies to HTS and WES. While WES successfully pinpointed the mutations in the COX20 gene, HTS did not, owing to its focus on analyzing chromosomal copy number variants larger than 100 kb.[16] Hence, for individuals suspected of harboring COX20 mutations, it is advised to undergo WES to ensure precise detection.

In prenatal counseling it is necessary to emphasize to patients and families that mitochondrial complex IV deficiency caused by COX20 mutations currently lacks a specific treatment, and management primarily relies on supportive therapies and nutritional supplementation. However, these approaches offer limited symptom relief, particularly for gait instability and

cognitive decline and there is no effective way to detect and prevent this disease by common tests. Due to the high disability rate and progressive nature of the disease, it is essential for families with a history of the condition to receive prenatal counseling and diagnostic testing. Because the COX20 variant is a biallelic variant, the mutant gene in children with mitochondrial disease comes from both parents, so it is necessary to screen the parents of children with mitochondrial disease. Being an autosomal recessive disorder, mitochondrial complex IV deficiency carries a 25% risk of transmission to offspring if both parents are carriers. Therefore, parents may opt for preimplantation genetic diagnosis (PGD) during in vitro fertilization (IVF) to ensure the transfer of unaffected embryos or choose prenatal diagnosis during a natural pregnancy. Although PGD is costly, it allows for genetic testing before embryo implantation, thereby enhancing the selection process in IVF.[17,18] In the present case, the mother opted for prenatal diagnosis for her second and third pregnancies. During the second pregnancy, testing identified the same compound heterozygous mutations, leading to termination. In the third pregnancy, WES revealed only the c.41A>G mutation, consistent with the mother's carrier status, ruling out mitochondrial disease associated with COX20 mutations. This outcome enabled the mother to proceed with a successful pregnancy and the birth of a healthy child.

Conclusion

In conclusion, individuals presenting with peripheral neuropathy, ataxia, and cognitive decline should be evaluated for COX20 mutations. WES stands out as a dependable approach for identifying such mutations while offering prenatal counseling to parents of affected children is imperative in mitigating the occurrence of mitochondrial disorders. Moreover, given the lack of specific treatments, affected children are at a heightened risk of disability. How to provide effective treatment for children with such diseases, which is also an important issue to be solved in the future.

Data Sharing Statement

All data have been submitted along with the case report.

Ethics Approval and Informed Consent

This case report has been approved by the Medical Ethics Committee of the Second Affiliated Hospital of Guangxi Medical University [Approval number: 2024-KY (0802)].

Consent for Publication

Written informed consent was obtained from the patient's guardians to publish the case details.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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