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Article

Compound Heterozygous Mutations Presented with Quadriparesis and Menopause. A Case Report

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Abstract

Mitochondrion regulates cellular metabolism with the aid of its respiratory complexes; any defect within these complexes can result in mitochondrial malfunction and various conditions. One such mutation can occur in *SLC25A10*, resulting in mitochondrial DNA depletion syndrome. It should be noted that the pattern of inheritance of this syndrome is autosomal recessive. However, we present a case with compound heterozygous mutations within this gene resulting in disease. An 18-year-old female was referred to our clinic due to menopause with a medical history of hearing loss, spasticity, hypotonia and quadriparesis. The child's birth and development were uneventful until the initiation of movement reduction and hypotonia when she was 12 months old. Afterward, the hypotonia progressed to quadriparesis and spasticity throughout the years. Our patient became completely quadriplegic up to the age of 3 and became completely deaf at 10. Her puberty onset was at the age of 9, and no significant event took place until she was 17 years old when suddenly her periods, which were regular until that time, became irregular and ceased after a year; hence, a thorough evaluation began, but similar to her previous evaluations all tests were insignificant. Nonetheless, we suspected an underlying metabolic or genetic defect; thus, we ordered a whole-exome sequencing (WES) workup and found simultaneous heterozygous mutations within *SLC25A10*, *HFE* and *TTN* genes that could explain her condition. When all other tests fail, and we suspect an underlying genetic or metabolic cause, WES can be of great value.

Keywords: *SLC25A10*; mitochondrial DNA depletion syndrome; compound mutations; case report

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Through respiration, the mitochondrion regulates cellular metabolism. This function arises from the mitochondrial respiratory complexes, resulting in electron transfer and oxidative phosphorylation. (Osellame et al., 2012) However, any disruption within these respiratory complexes may result in various conditions based on the nature of the interruption. Genetic mutations, even some nuclear mutations, can affect the mitochondrial function by disrupting coding proteins' structural and assembly factors essential for mitochondrial function. (Osellame et al., 2012; Pieczenik & Neustadt, 2007) One such gene is *SLC25A10*, which encodes a mitochondrial integral membrane protein with the same name, functioning as a catalyzer for dicarboxylate transport. Various studies have reported mutations within this gene. Dysfunction within the coded protein can impair the activity of one of these respiratory complexes, called mitochondrial respiratory complex I, resulting in various conditions ranging from fatal diseases in neonates to neurodegenerative disorders in adults (Lash, 2015; Pieczenik & Neustadt, 2007; Punzi et al., 2017). To our knowledge, only one autosomal recessive *SLC25A10* compound mutation resulting in neurological conditions was reported in a 9-year-old boy (Punzi et al., 2017). Here, we discuss the second case that resulted from simultaneous mutations in the aforementioned gene resulting in hearing loss, spasticity, hypotonia and quadriparesis in an 18-year-old female referred to us due to menopause.

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Case Presentation

An 18-year-old female was referred to our clinic due to menopause with a background of hearing loss, spasticity, hypotonia and quadriparesis. She was the only child of a census (cousins) parents with no history of familial and metabolic diseases, abortions or child deaths. The child's birth, development and status were uneventful until the initiation of her first symptoms when she was 12 months old when the parents noticed that her movement had decreased and she was slowly losing the ability to hold her head up; the child was referred to a pediatrician due to suspecting developmental regression and metabolic conditions. However, at that time, based on numerous insignificant lab test results (e.g. acidosis, accumulation of metabolites), she was diagnosed with cerebral palsy (CP), which explained some of the symptoms that she already had and some that had yet to come. The hypotonia, which began when she was about one year, progressed to quadriparesis and spasticity throughout the years. Our patient became completely quadriplegic by the age of 3, began losing her hearing, and became completely deaf (bilateral) at the age of 10. It should be noted that

quadriparesis and hearing loss, and mild mental retardation were the only findings throughout the years. Her puberty onset was at the age of 9, and no significant event took place until she was 17 years old when suddenly her periods, which were regular until that time, became irregular and ceased after a year; thus, an endocrinologist consult was sought, and she was referred to us. We started a complete assessment of the patient; our only clinical findings were bilateral hearing loss, hypotonia and weak spontaneous movements consistent with her previous diagnosis (CP).

No other abnormalities within the systems were detected. Upon assessment, it was found that she had two episodes of brief generalized tonic–clonic convulsions exacerbated by fever at the ages of 16 and 21 months; no other episode of seizures was reported. Nonetheless, after the second seizure, preventive therapy with phenytoin 5mg/kg divided into three doses per day was initiated and continued till her puberty with dose adjustments. Furthermore, we assessed her growth parameters which were within the normal range for her sex and age throughout the years. Moreover, to rule out any underlying condition and metabolic abnormalities, complete laboratory analyses were ordered, including complete blood count liver function tests, including aspartate aminotransferase, also known as serum glutamic oxaloacetic transaminase, alanine aminotransferase, also known as serum glutamic pyruvic transaminase, prothrombin time, partial thromboplastin time and international normalized ratio, renal function tests (urine analysis, serum creatinine, urine sodium and potassium levels, and 24-hour urine protein levels), arterial blood gas, alongside anion gap, serum glucose, triglyceride, cholesterols, lactate, iron, ammonia, plasma amino acid profile, and electrolytes (calcium, potassium, sodium, phosphorus, chlorine) as well as cerebrospinal fluid glucose, amino acid and ammonia levels. However, all tests were insignificant, and no abnormalities were detected. Nonetheless, we suspected an underlying metabolic or genetic defect. Hence, we ordered a whole-exome sequencing (WES) workup for our patient. The method of WES, as well as the material used, is the same as described by Khonsari, Nami et al. (2020) and Noorian et al. (2021). WES results indicated the presence of two heterozygous variants within the *SLC25A10* gene as follows: gene/transcript (RefSeq): SLC25A10/NM_001270888.1, variant location chromosome 17 exome 9, variant c.684C>T p.Pro228Pro (synonymous variant) and SLC25A10/NM_001270888.1 variant location chromosome 17 exome 10 variant c.790-37G>A (intronic variant, ClinVar Accession: VCV000446176.2). Other findings included a heterozygous mutation in TTN/NM_001256850.1 variant location chromosome 2 exome 14 variant c.2371-1G>A (splice acceptor variant, ClinVar Accession: VCV000582625.4) and heterozygous mutations in HFE/ NM_000410.4 variant location chromosome 6 exomes 4 and 2 variants p.Cys282Tyr (missense variant, ClinVar Accession: VCV000000009.42) and c.187C>G (p.His63Asp) (missense variant, ClinVar Accession: VCV000000010.42), respectively. The WES result was confirmed with Sanger PCR.

Mutations within the *HFE* gene can result in conditions such as hemochromatosis, diabetes and even hearing loss due to iron metabolism dysregulation in the body (Barton et al., 2015; Castiglione et al., 2015).

Mutations within the *TTN* gene can cause myopathies with vast clinical presentations as they can disrupt titin synthesis in muscles (Savarese et al., 2018; Spinazzola et al., 2009).

Mutations within the *SLC25A10* gene can result in mitochondrial DNA depletion syndrome, resulting in mitochondrial respiratory complex I malfunction. This condition can present itself in various forms, such as metabolic abnormalities, muscle weakness, neuropathy, hearing loss, encephalopathy and pubertal abnormalities (El-Hattab & Scaglia, 2013).

We also sequenced parental genes as well and confirmed the results with Sanger PCR. The parental test results indicated that the variants NM_001270888.1(SLC25A10):c.684C>T p.Pro228Pro, NM_000410.4(HFE):c.187C>G (p.His63Asp) and NM_001267550.2(TTN):c.2371-1G>A were paternally inherited, and variant NM_001270888.1(SLC25A10):c.(790-37G>A) was maternally inherited. NM_000410.4(HFE):c.845G>A (p.Cys282Tyr) was not detected in the parents. Upon proper medical evaluations, no signs or symptoms within the parents were detected. Hence, with the proper diagnosis, possible outcomes and disabilities were detected, and thus, proper preventive steps were taken.

Discussion

Although this article reports the second case of compound heterozygous autosomal recessive mitochondrial mutations that resulted in disease manifestation (Punzi et al., 2017), the aim of this report was not to evaluate the function of the gene, nor molecular evaluations, but to discuss the possibility of the hypothesis that regardless of the recessive pattern of inheritance of some genes, compound mutations with similar outcomes and affected organs may have a synergic effect on one another. As seen in some cases, despite the mutations having no known relativity, their compound synergic effect was similar to that of a homozygous case. (Khonsari, Nami et al., 2020) Moreover, it should be noted that this case is different from the case reported by Punzi et al. (2017). As we reported, one of the *SLC25A10* mutations was synonymous; thus, it might seem that this mutation is of no clinical significance; however, recent studies indicate that synonymous mutations can result in diseases by affecting mRNA splicing and disrupting protein expression, function and conformation (Brule & Grayhack, 2017; Cartegni et al., 2002; Corrado et al., 2016; Macaya et al., 2009; Sauna & Kimchi-Sarfaty, 2011). Hence, similar to another case, the presence of some mutations in each parent did not result in a detectable condition; the simultaneous occurrence of the mutations, however, resulted in disease (Khonsari, Nami et al., 2020).

The excess severity of neurological condition reported by Punzi et al. (2017) could be due to the presence of an extra mutation (NM_001270888.1: c.304A > T, p.Lys102) within the *SLC25A10* gene, strengthening the hypothesis that compound heterozygous mutations can have a synergic effect despite their recessive pattern of inheritance.

In our patient, the compound effect of both *SLC25A10* mutations could explain her menstrual abnormalities. The severe muscle weakness could be due to the synergic effect of *SLC25A10* and *TTN* mutations. Moreover, her hearing loss could be due to the compound effects of *HF*E and *SLC25A10* mutations, as both of them can, in fact, cause hearing loss, as mentioned before.

It is interesting that the father did not have any signs and symptoms despite having various mutations as well. This could be due to the synonymous nature of his *SLC25A10* mutation and lacking the compound effects of NM_001270888.1(SLC25A10):c.(790–37G > A) mutation.

Another discussable matter is the usage of WES to detect the underlying cause of some conditions. Some genetic disorders are easily detected due to their particular phenotype. (Buske et al.,

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2015; Khonsari, Hakak-Zargar et al., 2020; Pontikos et al., 2020) However, some conditions cannot easily be detected as they may seem benign or present, similar to another condition (Noorian et al., 2021) or such as with this case be the result of compound mutations resembling the disease rising from homozygous mutations but lesser in severity and symptoms. Despite WES being an expensive test, when genetic defects are highly suspected, it can be beneficial (Noorian et al., 2021) since proper diagnosis of genetic defects is of great value, since if diagnosed properly, preventive measures can be taken, proper treatment will be possible, and the prognosis of the patient can be determined.

Conclusion

At first, our patient was diagnosed with CP without finding any metabolic or genetic defects. However, due to suspicion of an underlying genetic defect, WES was performed for our patient and the proper diagnosis was made; hence, when all other tests fail, and we suspect an underlying genetic or metabolic condition, WES can be very helpful.

Data. The data presented in this study can be obtained from the corresponding author upon reasonable request.

Authors' contributions. All authors participated in preparing the manuscript equally.

Financial support. Not applicable.

Conflict of interest. None.

Ethical standards. The Ethics Committee of Alborz University of Medical Sciences approved this case report. Informed consent was obtained from the participants and written informed consent was obtained from her parents regarding the usage of their data for research and publication purposes. All methods were performed in accordance with the relevant guidelines and regulations.

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