Egyptian Journal of Medical Human Genetics

CASE REPORT Open Access

Novel MTO1 mutations associated with an intrafamilial phenotypic variability

Catarina Maria Almeida[1,2*], Esmeralda Rodrigues[1], Teresa Almeida Campos[1], Laura Vilarinho[3] and Elisa Leão Teles[1]

Abstract

Background Mitochondrial diseases are a group of rare inborn metabolic disorders with multi-systemic manifestations. *MTO1* gene mutations are associated with MTO1 (Mitochondrial tRNA Translation Optimization 1) protein deficiency, a mitochondrial disorder, which commonly presents with lactic acidosis and hypertrophic cardiomyopathy.

Case presentation The authors describe two siblings with mitochondrial cytopathy and distinct outcomes. The index case, a female born in 1989, presented hypotonia and lactic acidosis since birth. She developed a severe myoclonic encephalopathy, movement disorder and psychomotor and growth delay. Respiratory chain enzyme complex measurement in muscle revealed a partial deficiency of complex III and IV. Throughout the years she had multiple decompensations with severe acidemia and died at age of 16, due to a respiratory infection. She never presented cardiac alterations. The younger sibling, a male born in 2002, had a less severe clinical presentation. He presented hypotonia and lactic acidosis at birth. Metabolic study performed in the first days of life revealed elevated plasma alanine and hyperlactacidemia. At 8 months of age a partial deficiency of complex IV was reported. He had a mild persistent hyperlactacidemia, psychomotor development delay, generalized hypotonia, dilated cardiomyopathy and epilepsy. In 2017, at 15 years of age, a genetic study confirmed the mitochondrial disease with identification of two MTO1 likely pathogenic variants [c.413delT (p.M138Sfs*6) / c.1450C > T (p.R484W)]. Currently, he is clinically stable, maintaining a multidisciplinary follow up. The same genotype was confirmed in his sister's stored DNA.

Conclusions With this case, report the authors emphasize mitochondrial diseases' phenotypic heterogeneity, even in the same family, and the significance of the new genetic diagnostic techniques. The authors also report a novel *MTO1* likely pathogenic variant not described to date.

Keywords Mitochondrial disease, Mitochondrial translation optimization 1, Lactic acidosis

Background

Mitochondria are the cellular organelles responsible for aerobic metabolism, among other functions. This form of energy production occurs by oxidative phosphorylation (OXPHOS) in the respiratory chain across the inner mitochondrial membrane [1]. Pathogenic variants of the mitochondrial or nuclear genome give rise to mitochondrial diseases, a group of rare inborn metabolic disorders with multi-systemic manifestations [2]. Since the mitochondria is present in virtually all cells, any organ system can be affected preferentially those relying most on aerobic metabolism. Primary mitochondrial diseases are currently defined as genetic disorders leading to

*Correspondence:
Catarina Maria Almeida
catarinalmeidalmeida@live.com.pt
[1] Inborn Errors of Metabolism Unit, Reference Center of Inherited Metabolic Diseases, Serviço de Cardiologia Pediátrica, Centro Hospitalar Universitário de São João, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
[2] Pediatric Cardiology Department, Centro Hospitalar Universitário de São João, Porto, Portugal
[3] Human Genetics Department, Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisbon, Portugal

disturbances of mitochondrial structure and function, including OXPHOS dysfunction. Estimated minimum birth prevalence of these disorders is 1 in 5000 [3]. While some well-characterized mitochondrial syndromes are recognized, many patients manifest overlapping features that don't correlate to a specific syndrome and can present an infantile, childhood or adult onset. Natural history is extremely variable, although many early-onset mitochondrial disorders lead to death in infancy and early childhood. There are many diagnostic challenges due to the complexity of the underlying disease mechanisms and heterogenous clinical presentations, hence a high index of clinical suspicion is required. After a detailed evaluation of the clinical and family history, metabolic tests and screening for multi-system involvement should be performed, including functional studies of OXPHOS enzymes in tissue biopsies. Ultimately, genomic testing, like whole exome sequencing (WES) and next generation sequencing (NGS), are required to confirm the diagnosis of a primary mitochondrial disorder through identification of pathogenic genetic variants. There are no curative treatments available for the majority of mitochondrial diseases. Supportive measures are the mainstay of treatment for most patients [1, 3].

Mutations in the *MTO1* gene that encodes the Mitochondrial tRNA Translation Optimization 1 (MTO1) protein (OMIM#614,667) are associated with a mitochondrial disease, the MTO1 deficiency. It was first described in 2012 in two Italian siblings of nonconsanguineous healthy parents, that presented lactic acidosis, hypoglycemia and hypertrophic cardiomyopathy soon after birth [4]. MTO1 protein is a subunit of an enzyme responsible for the post-transcriptional modification of the mitochondrial tRNA (mt-tRNA) that is crucial to the accuracy and efficiency of mitochondrial DNA (mtDNA) translation. These alterations result in a reduction of respiratory chain activities complexes [5].

The largest case series known to date reports 35 cases with bi-allelic mutations in *MTO1*. The revision of their clinical features corroborates the presence of lactic acidosis, global developmental delay and complex IV deficiency as hallmarks of this disease. However, there is a wide phenotypic spectrum of MTO1 deficiency and there is no typical clinical presentation [2].

Case presentation

Here we describe two siblings with a 13 year age gap and mitochondrial cytopathy with distinct outcomes. They were naturally conceived, born to non-consanguineous caucasian parents without significant family history. Informed consent for publication of the current case reports was provided by the parents.

The index case, a female, was born in 1989 at 39 weeks of gestational age by spontaneous vaginal delivery, weighing 2750 g. She was admitted to the Neonatal Intensive Care Unit (NICU) after birth due to tachypnea, hypotonia and a poor general condition. Metabolic study performed at 3 days of age revealed a severe lactic acidosis with an elevated blood lactate and elevated plasma alanine (Table 1). Additionally, respiratory chain enzyme complex measurement in muscle revealed a partial deficiency of complex III and IV (Table 1). She sat unsupported at 6 months of age and started to walk at 2 years. First, words were after 2 years of age and she presented a relevant psychomotor and growth delay, with hypotonia, ataxia and severe motor incoordination. At 4 years, she started to register myoclonic seizures and developed a severe myoclonic encephalopathy confirmed by electroencephalography. She was commenced on oral sodium valproate, clobazam, thiamine and B-complex vitamins in another center. In our center she suspend valproate treatment and maintained the other drugs. Available genetic studies were all negative (most common mutations of mitochondrial DNA: 3243A > G, 3271A > G, 8344A > G, 8993A > G, and single and multiple deletions). Later on, she started coenzyme Q10. At age 12 years, the patient presented a severe scoliosis. Seizures were controlled but throughout the years she had multiple metabolic decompensations with severe acidemia and died at age of 16, due to a respiratory infection. Cardiac evaluation was always normal.

The younger sibling, a male, presented a milder phenotype. He was born premature in 2002, at 32 weeks of gestational age by cesarean delivery, weighing 2000 g. He was admitted in the NICU in the first hour of life due to grunting with respiratory distress that needed mechanical ventilation. He also presented hypotonia and lactic acidosis. Metabolic study performed at 8 days of life

Table 1 Results of metabolic study

Laboratory parameters	Index case	Younger Sibling	Reference range
Blood lactate (mmol/L)	10.20	6.5	0.62–2.44
Respiratory chain enzyme complex III (nmol/min/mg)	15.40	54.9	35.00–65.00
Respiratory chain enzyme complex IV (nmol/min/mg)	6.10	5.7	16.00–30.00
Lactate to pyruvate ratio	NA	53	10–25
Plasma alanine (umol/L)	NA	550	236–410

Summary of metabolic study performed in the described cases. *NA* not available

revealed an elevated plasma alanine, lactic acidosis and a lactate to pyruvate elevated ratio. At 8 months of age a partial deficiency of complex IV was reported in the respiratory chain enzyme complex measurement in muscle. All values are depicted in Table 1. He sat unsupported at 12 months of age, started to cruise between 30 and 33 months and started to walk at 4 years. He maintained a psychomotor and growth delay with special educational needs. At 19 months of age, a dilated cardiomyopathy was detected. He needed to start therapy with enalapril and furosemide at the age of 6 and currently remains stable and without cardiovascular symptoms. Between 4 and 6 years of age he had simple febrile seizures. At 11-years-old afte,r a surgical correction of an acute appendicitis with peritonitis, and despite perioperative care, he had status epilepticus and started anti-epileptic drugs (levetiracetam and recently perampanel because of an increased seizure frequency). Cerebral magnetic resonance imaging in 2015 showed a small increase in the lactate/pyruvate peak in spectroscopy without any other alterations. In 2017, at 15 years of age, a Next Generation Sequencing panel of 210 nuclear genes associated with mitochondrial diseases, confirmed the mitochondrial disease with identification of two novel *MTO1* likely pathogenic heterozygous mutations [c.413delT (p.M138Sfs*6) / c.1450C > T (p.R484W)] not described to that date. Posteriorly, the mutation c.1450C > T (p.R484W) a pathogenic missense mutation, (arginine (R) is replaced by tryptofan (W), was reported by O'Byrne et al. for the first time in 2018 [2]. The c.413delT (p.M138Sfs*6) is a frameshift mutation where methionine (M) is the first amino acid changed in position 138, it makes serine (S) instead, the length of the shift frame is 6, including the stop codon (*).

The same genotype was confirmed in his sister's stored DNA. The parents refused their genetic testing. A family pedigree is represented in Fig. 1. Although he maintains a mild persistent hyperlactacidemia and generalized hypotonia to date, he is clinically stable keeping a multidisciplinary follow up. The cardiomyopathy is stable with an enlargement of the left ventricle and a slightly depressed cardiac function.

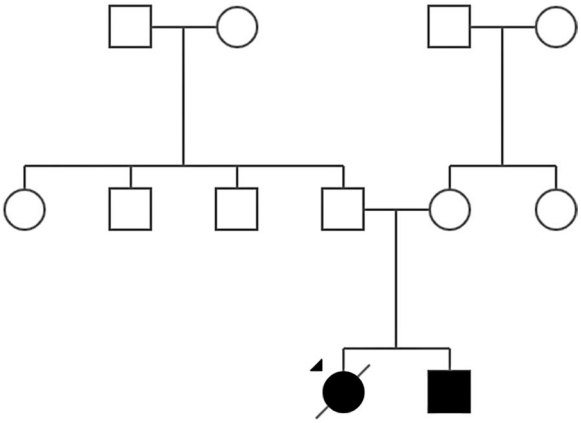

Fig. 1 Family pedigree

Discussion

The *MTO1* gene encodes a ubiquitously expressed enzyme essential to protein synthesis via optimization of mtDNA [2]. All of the *MTO1* variants are extremely rare. It is hard to estimate the population frequency of the variants found since they are either not observed in the available databases or observed at very low frequencies [2]. These variants lead to an altered MTO1 protein synthesis affecting the post-transcriptional modification of the mt-tRNA leading to a reduction of mtDNA dependent respiratory chain activities [2]. Common clinical features such as lactic acidosis, complex IV deficiency in muscle and development and cognitive impairment are described as hallmarks of this primary mitochondrial disease [2]. Our findings were consistent with the information reviewed in literature. The two patients presented illustrate the large phenotypic spectrum. There is no typical presentation for MTO1 deficiency and it should be considered in patients with distinct features. Our index case presented a relevant psychomotor and growth delay, as well as a severe myoclonic encephalopathy. On the other hand, the younger sibling presented a dilated cardiomyopathy in addition to the psychomotor and growth delay. Early reports suggested that hypertrophic cardiomyopathy (HCM) at a young age is characteristic of MTO1 deficiency, however O'Byrne et al. proved that this is not a hallmark clinical feature [2]. One of the patients described in that study developed a dilated form of cardiomyopathy, like our male case, and the authors believe this might be a progression from HCM [2]. Patients can also present hypotonia, feeding difficulties and ocular pathology, among other signs and symptoms. Both cases described had an early-onset with detection of laboratorial alterations in the first days of life. This finding is consistent with previous reports for the majority of mitochondrial diseases concerning the respiratory chain [2, 6]. A positive correlation between early neonatal presentation and unfavorable prognosis is described by some authors [7]. Common neurologic manifestations of primary mitochondrial diseases are hypotonia, muscle weakness and cognitive impairment [8]. In the presented cases, hypotonia was found at birth and throughout the years both siblings revealed an important development delay. Inclusively, the index case presented a severe myoclonic encephalopathy confirmed by electroencephalography. However, the younger sibling presented an improvement of hypotonia and muscle

control. Mitochondrial markers are not specific of MTO1 deficiency and the majority of cases were diagnosed by whole generation sequencing [2] This seems to be a pan-ethnic condition since cases have been reported in different countries [2].

Conclusions

The authors presented two patients from the same family to emphasize mitochondrial diseases' phenotypic heterogeneity. A Next Generation Sequencing Gene panel allowed to detect two pathogenic mutations in the *MTO1* gene, a novel mutation [c.413delT (p.M138fs)] and an already reported [2]. There is no typical clinical presentation for this condition, but some common features were described in this case series and also in our case report, such as hypotonia and a global developmental delay. [2] Furthermore this cases report delineates the importance of genomic testing, not only to confirm the diagnosis but also to provide genetic counselling and reproductive options to the affected family. Additionally, the authors want to draw attention to the impact of NGS technologies in inherited phenotypes which are not clarified during many years.

Abbreviations

HCM	Hypertrophic cardiomyopathy
mtDNA	Mitochondrial DNA
MTO1	Mitochondrial tRNA translation optimization 1
mt-tRNA	Mitochondrial tRNA
NGS	Next generation sequencing
NICU	Neonatal intensive care unit
OXPHOS	Oxidative phosphorylation
WES	Whole exome sequencing

Acknowledgements

The authors would like to thank the family for consenting the publication of this case report.

Author contributions

The first author wrote the case report. The other authors provided writing assistance and manuscript revision. All authors read and approved the final manuscript.

Funding

No funding.

Availability of data and material

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Declarations

Ethics approval and consent to participate

Informed consent for participation was provided by the parents. The study was approved by the ethics committee of Centro Hospitalar Universitário de São João.

Consent for publication

Consent for publication of the current case reports was provided by the parents.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Received: 20 July 2022 Accepted: 12 January 2023
Published online: 20 January 2023

References

1. Saudubray J, Baumgartner M, Walter J. Inborn metabolic diseases. 6th ed. Springer; 2016.
2. O'Byrne J, Tarailo-Graovac M, Ghani A, Champion M, Deshpande C, Dursun A et al (2018) The genotypic and phenotypic spectrum of MTO1 deficiency. Mol Genet Metab 123(1):28–42
3. Rahman S (2020) Mitochondrial disease in children. J Intern Med 287(6):609–633
4. Ghezzi D, Baruffini E, Haack T, Invernizzi F, Melchionda L, Dallabona C et al (2012) Mutations of the Mitochondrial-tRNA modifier MTO1 cause hypertrophic cardiomyopathy and lactic acidosis. Am J Human Genet 90(6):1079–1087
5. Tischner C, Hofer A, Wulff V, Stepek J, Dumitru I, Becker L et al (2014) MTO1 mediates tissue specificity of OXPHOS defects via tRNA modification and translation optimization, which can be bypassed by dietary intervention. Hum Mol Genet 24(8):2247–2266
6. Taylor R, Pyle A, Griffin H, Blakely E, Duff J, He L et al (2014) Use of Whole-exome sequencing to determine the genetic basis of multiple mitochondrial respiratory chain complex deficiencies. JAMA 312(1):68
7. Martín M, García-Silva M, Barcia G, Delmiro A, Rodríguez-García M, Blázquez A et al (2016) The homozygous R504C mutation inMTO1gene is responsible for ONCE syndrome. Clin Genet 91(1):46–53
8. Finsterer J (2012) Cognitive dysfunction in mitochondrial disorders. Acta Neurol Scand 126(1):1–11

Publisher's Note