Case Report

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Syrian child carrying multiple pathogenic variants in MBOAT7 and MT-TS1 genes: a case report on neurodevelopmental phenotypes and mitochondrial inheritance

Alyamama Kousa[a], Reem Ahmed[a,*], Pr.Diana Alasmar[b]

Introduction: The authors identify two patterns of inheritance in a Syrian child from consanguineous parents. The membrane-bound O-acyltranferase domain-containing7 (MBOAT7) gene encodes Lysophosphatidylinositol acyltranferase (LPIAT1), which is responsible for the neurodevelopment of the brain cortex. Patients with MBOAT7 variants exhibit pathogenic nervous manifestations such as global developmental delays affecting speech and motor function, intellectual disability (ID), poor coordination, and seizures, with or without MRI abnormalities. MT_TS1, the mitochondrial $tRNA^{Ser(UCN)}$ gene, is a hotspot for pathogenic mutations causing variable mitochondrial phenotypes, including hearing impairment (HI), ataxia and cognitive impairment.

Clinical presentation: The authors present a case of a 4-year-old child with motor and speech delay, truncal hypotonia, visual tic, poor coordination, autistic features and generalized seizures at 7 months of age. After normal results from lab tests and MRI imaging, along with the family's history of neurological disorders, genetic analysis was necessary to diagnose and assess the possibility of genetic counselling. Next-generation sequencing (NGS) showed two variable variants in the MBOAT7 and MT-TS1 genes. The first mutation is a homozygous variant of uncertain significance in the MBOAT7 gene, associated with the autosomal recessive Mental retardation type 57. The second variant is a heteroplasmic pathogenic variant in the MT-TS1 gene, indicative of mitochondrial disorders.

Conclusion: The presence of the MBOAT7 and MT-TS1 gene variants in the same child is noteworthy. The authors must keep genetic mutations of MBOAT7 and MT-TS1 gene in mind as a differential diagnosis for intellectual disability, seizures and autistic features in children, especially in consanguineous families.

Key words: delayed psychomotor development, MBOAT7, MT-TS1

Introduction

The Membrane-bound O-acyltranferase domain-containing7 (MBOAT7) gene encodes Lysophosphatidylinositol acyltranferase (LPIAT1), an enzyme responsible for the remodelling of membrane-bound phospholipids in LANDs cycle, producing Arachidonic acid-containing phosphatidylinositol, which involves in the natural neurodevelopment and neurometabolism in the human brain[1–3]. In 2016 Johansen *et al*.[1,2] identified for the first time MBOAT7 variants in 16 patients with global developmental delays, intellectual disability (ID), speech impairment, truncal hypotonia, early-onset seizures, and autism spectrum disorders (ASDs). MRI shows brain abnormalities, including brain atrophy and polymicrogyria, and may show normal findings[3]. The mechanism is not yet well-known[1,3]. Mitochondrial diseases are multisystem disorders that affect oxidative phosphorylation in every tissue in the body. The nervous system and skeletal muscles require high energy, so they are more affected[4,5]. Mitochondrial inheritance is maternal inheritance, meaning the mother's

HIGHLIGHTS

- The Membrane-bound O-acyltranferase domain_containing7 (MBOAT70) gene plays an important role in the inherent neurodevelopmental and neurometabolism of the human brain.
- In mitochondrial mutations such as mutations in the MT_TS1 gene, the clinical symptoms, severity, and age of onset are dependent on the degree of heteroplasmy of the mutant gene.
- Genetic counselling presents a challenge due to the apparent complexity of the genetic pattern.
- Clinicians should consider MBOAT7 and MT_TS1 defects when evaluating differential diagnoses for neurological disorders in children.

[a]Faculty of Medicine and [b]Department of Pediatrics, Faculty of Medicine, Damascus University, Damascus, Syria

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*Corresponding author. Address: Faculty of Medicine, Damascus University, Damascus, Syria. Tel.: +963 981 871 605. E-mail: reemahmed41022@gmail.com (R. Ahmed).

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mutations are transmitted to all offspring, affecting the entire genome and this is called homoplasmic, or a specific percentage called heteroplasmy[4–6]. MT_TS1, the mitochondrial $tRNA^{Ser\ (UCN)}$ gene, is a hotspot for pathogenic mutations and causes a variable mitochondrial phenotype in patients, including non-syndromic sensorineural hearing loss (SHL) and syndromic phenotype (epilepsy, ataxia, cognitive impairment, myoclonus and SHL)[4,6,7].

We report a case of a 4-year-old Syrian child born to a consanguineous family with a history of neurodevelopmental disorders, carrying two pathogenic variants in different genes: a homozygous loss-of-function MBOAT7 variant and a heteroplasmic pathogenic variant in the MT-TS1 gene.

Case presentation

Clinical history and investigations

The patient is a 4-year-old child from healthy, consanguineous parents with a family history of neurodevelopmental disorders. He was delivered full-term by caesarean section with a birth weight of 2.7 kg; because of the placenta previa. The prenatal and postnatal periods were unremarkable. At 7 months of age, he presented to the paediatric clinic with generalized seizures and delayed psychomotor development. His height was 65 cm and head circumference was 43 cm. The physical examination revealed spasticity, inability to control his head, truncal hypotonia, acceptable eye contact, and increased tendon reflexes. The MRI showed no pathological abnormalities. His 19-year-old sister also has an ID and a psychomotor delay, but she is undiagnosed (Fig. 1).

Biochemistry and blood tests

The complete blood count and urinalysis were normal. The biochemistry showed decreased levels of HCO3 and PCO2. Tandem mass spectrometry showed unremarkable results. Amino acid electrophoresis indicated that the amino acids were within the normal range.

Diagnostic strategy

There is no clinical history of infection or perinatal asphyxia. At 7 months, the baby had no reactions, did not roll over and sit, and had an onset seizure. The physical examination confirmed these delayed milestones. After normal results from lab tests and MRI imaging, along with the family's history of neurological disorders, genetic analysis was necessary to diagnose and assess the possibility of genetic counselling. Next-generation sequencing (NGS) at CENTOGENE GmbH in Germany for a peripheral blood sample revealed two variable variants following two patterns of inheritance. The first mutation is a homozygous variant of uncertain significance in the MBOAT7 gene (NM_024298.4: c.121del p.(Leu41Serfs*68)), which is associated with the autosomal recessive Mental retardation type 57. This variant creates a shift in the reading frame starting at codon 41, and the new reading frame ends in a stop codon 67 positions downstream. It is classified as a variant of uncertain significance (class 3) according to the recommendations of CENTOGENE and ACMG. The second variant is a heteroplasmic pathogenic variant in the MT-TS1 gene (NC_012920.1:m.7471dup). This finding is consistent with a diagnosis of MT-TS1 gene-associated mitochondrial disorders. This variant creates a shift in the reading frame starting at codon 11. It is classified as pathogenic (class1) according to the recommendations of CENTOGENE and ACMG. The variant is identified in 37.5% of 822 NGS reads. The genetic study helped us to diagnose and determine if we can provide genetic counselling for the following pregnancies.

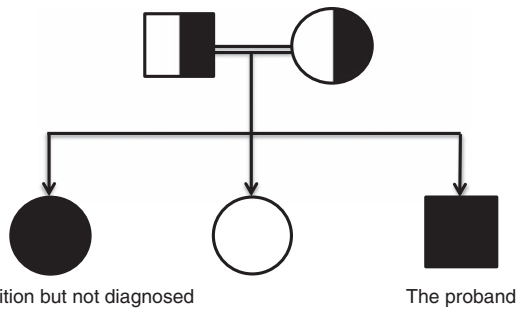

Figure 1. Pedigree of the investigated proband patient.

Treatment and follow-up

The patient received a vitamin cocktail (B1, B2, CoQ10) along with leveramax (levetiracetam 200 ml). Clinical follow-ups for 3 years showed that the child was metabolically stable, and he acquired major skills through physical therapy sessions; he gained the ability to sit at 2 years old and walk at 3 years old. At the last physical examination at 4 years of age, the height was 94 cm, head circumference was 48cm, and weight was 12.6 kg. The child no longer had spasticity and seizures, but he still has neurological symptoms, including intellectual disability (ID), poor coordination, visual tic, dysmyotonia in the left hand, and speech impairment (1–2 words). Psychologically, the child showed autistic features.

Discussion

We present a 4-year-old Syrian child with two variable variants in two different genes: the MBOAT7 and MT-TS1 genes.

The first variant identified is a homozygous variant of uncertain significance in the MBOAT7 gene. Numerous research studies have shown that this variant disturbs the remodelling of phospholipids[8,9], which explains the neurological symptoms of this mutation despite the fact that the pathomechanism is still unclear[1]. According to a study conducted in 2020, 95% (42/44) of cases diagnosed with MBOAT7 mutation until that year had a consanguineous relationship between parents[10].

A review published in 2023 reported a total of 60 diagnosed cases with mutations in the MBOAT7 gene in addition to the case discussed. As reported, those patients suffer from non-specific manifestations such as intellectual disability (94%), early-onset seizures (84%), autism spectrum disorders (ASDs) (57%), speech impairment (94%), abnormalities in head size (29%), and optic disorders (strabismus/retinal degeneration/optic atrophy) (48%). Additionally, 37% of patients present with ataxic gait, 95% with motor delay, 63% with abnormal neuroimaging (polymicrogyria, cortical atrophy, hyperintensity of globus pallidus and dentate nuclei, cerebellar dysgenesis), and metabolic profile was normal in 23 subjects; not available for the others[3]. Our

observed phenomenon displays a significant overlap with the documented characteristics in previous reports[2,11]. In particular, the child presents global developmental delay characterized by speech impairment (1–2 words), early-onset seizures (7 months of age), autistic features, visual tic, and poor coordination ending with gait imbalance with no abnormalities observed in MRI images.

The second variant identified is a heteroplasmic pathogenic variant in the MT-TS1 gene. This finding is consistent with a diagnosis of MT-TS1 gene-associated mitochondrial disorders, which leads to a wide range of mitochondrial phenotypes in affected individuals, including sensorineural hearing loss (SHL), myopathy, cognitive deficit, cerebellar ataxia, and myoclonic epilepsy, as documented in prior literature[12]. However, in the absence of sensorineural hearing loss, the clinical presentation of the child is more clearly associated with the MBOAT7 mutation than with the other gene because clinical manifestations, severity, and age of onset vary according to the level of mutant heteroplasmy, making it difficult to predict the extent of the estimated mutations' contribution[7,13].

The possibility of metabolic genetic disorders is being considered based on the aforementioned manifestations when radiological investigations and metabolic studies have yielded negative results. Furthermore, the positive family history and continuous complexity of kinship over several generations, along with the parents' desire for genetic counselling, support the need for genetic analysis to diagnose the condition and identify potential inherited diseases. Genetic counselling will be challenging due to the apparent complexity of the genetic pattern. Although it can be provided regarding the autosomal recessive mutation in the MBOAT7 gene, it will be difficult with the mitochondrial mutation in the MT-TS1 gene because we cannot predict the likelihood of passing on the mutation.

Conclusion

The co-occurrence of mutations in the MBOAT7 and MT_TS1 genes in a single child with cognitive impairment is noteworthy. To comprehensively define the clinical spectrum of these disorders, a larger cohort of individuals must be identified. Therefore, clinicians should consider MBOAT7 and other potential genetic defects, such as MT_TS1, when evaluating differential diagnosis for intellectual disability, seizures and autistic features in children, particularly those born to consanguineous families.

Ethical approval

No ethical approval was needed.

Consent

Written informed consent was obtained from the patient's parents for the publication of this case report and. A copy of the written consent is available for review by the editor-in-chief of this journal on request.

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There was no source of funding for this study.

Author contribution

A.K.: reviewed the literature, wrote and revised the manuscript, and made grammar and spelling language editing. R.A.: reviewed the literature, wrote and revised the manuscript, and made grammar and spelling language editing. D.A.: provided medical treatment, supervise the scientific and academic aspects of the manuscript, and revised it.

Conflicts of interest disclosure

There were no conflicts of interest.

Research registration unique identifying number (UIN)

No registration was needed, because it's a case report not clinical trial.

Guarantor

Alyamama Kousa and Reem Ahmed.

Data availability statement

All data are available.

Provenance and peer review

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