CASE REPORT

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A Novel Mutation in the TBC1D20 Gene with Associated Warburg Micro Syndrome

Warburg Mikro Sendromu ile İlişkili TBC1D20 Geninde Yeni Bir Mutasyon

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ABSTRACT

Aim: Warburg micro syndrome (WARBM) is a rare autosomal recessive disorder due to mutations in the RAB3GAP1, RAB3GAP2, RAB18, and TBC1D20 genes. The syndrome is characterized by microcephaly, ocular findings such as congenital cataract, microcornea, severe intellectual disability, and hypogonadism.

Case: We present a 3-year-old boy who was diagnosed with WARBM during follow-up.The genetic analysis of the patient revealed a pathogenic mutation (c.259 260delinsCAC (p. Lys87HisfsTer42) in exon 3 of the TBC1D20 gene, which correlates with WARBM 4. Their parents were shown to carry the mutation heterozygously.

Conclusion: The WES analysis of a consanguineous Turkish family with WARBM showed a novel mutation (c.259_260delinsCAC) in TBC1D20 gene that is most likely pathogenic and allowed us to make the diagnosis of WARBM.

Keywords: Congenital cataract, Homozygous, TBC1D20, Warburg micro syndrome, Whole exome sequencing.

ÖZ

Amaç: Warburg mikro sendromu (WARBM) RAB3GAP1, RAB3GAP2, RAB18 ve TBC1D20 genlerindeki mutasyonlara bağlı olarak nadir görülen otozomal resesif bir hastalıktır. Sendrom mikrosefali, konjenital katarakt ve mikrokornea gibi oküler bulgular, ağır entellektüel gerilik ve hipogonadizm ile karakterizedir.

Olgu: Takipleri sırasında WARBM tanısı konulan 3 yaşında bir erkek çocuğu sunuyoruz. Hastanın genetik analiz sonuçları, TBC1D20 geninde ekzon 3'te patojenik ve WARBM 4 fenotipi ile korele olan bir homozigot mutasyonu (c.259_260delinsCAC; p. Lys87HisfsTer42) ortaya çıkardı. Ebeveynlerin mutasyonu heterozigot olarak taşıdığı gösterildi.

Sonuç: WES analizi WARBM'li akraba bir Türk ailesinde TBC1D20 geninde muhtemel patojenik yeni bir mutasyon (c.259_260delinsCAC) gösterdi ve WARBM tanısını koymamızı sağladı.

Anahtar Sözcükler: Konjenital katarakt, Homozigot, TBC1D20, Warburg mikro sendromu, Tüm ekzom dizileme

INTRODUCTION

Warburg micro syndrome (WARBM) is a rare autosomal recessive genetic disorder characterized by postnatal growth retardation, microcephaly, microphthalmia, microcornea, congenital cataract, optic atrophy, delayed motor development, intellectual disability, and hypogonadism (1). This syndrome is caused by mutations in four genes: *RAB3GAP1, RAB3GAP2, RAB18*, and *TBC1D20*. The *TBC1D20* gene mutations are rarely causative. Both Warburg Micro syndrome and Martsolf syndrome are autosomal recessive conditions that are similar in how they look and affect the eyes, nervous system, and endocrine system (2, 3). Loss of function mutations in *RAB3GAP1*, *RAB3GAP2, RAB18*, and *TBC1D20* genes cause Warburg Micro syndrome, which is the more serious of the two conditions. Martsolf syndrome is caused by mutations in *RAB3GAP1* and *RAB3GAP2* genes that are not as bad. (4). These genes encode Ras-associated binding (RAB) proteins and regulators, which are involved in vesicle trafficking, axonal transport, synaptic transmission, and autophagy (5). In the literature, only five mutations, including nonsense, missense, and frameshift mutations in *TBC1D20,* have been associated with Warburg micro syndrome type 4. (Clinvar, https://www.ncbi.nlm.nih.gov/clinvar/).Here, we report a novel *TBC1D20* mutation in a boy with WARBM type 4.

CASE REPORT

Due to jerking and eye twitching in his arms while sleeping, a 2-month-old boy was taken to pediatric neurology.He was born with a spontaneous vaginal delivery at 38 weeks of gestational age with a 2200 gr birth weight, 47 cm length, and a 33 cm occipital-frontal circumference. His parents were first cousins (Figure 1A). Oligohydramnios was presented prenatally. There was an abnormality in the prenatal double screening test. On physical examination, the weight was 3780 gr <3 p, the head circumference was 35 cm <3 p, the height was 48.5 cm <3p, anterior fontanel was 3x3 cm. Physical examination showed a seeking gaze, nystagmus, high palate, and micrognathia (Figure 1B). The liver was 2 cm palpable under the ribs. Furthermore, deep tendon reflexes were hypoactive. The Babinski sign was negative. The creatinine kinase (CK) value was 101 IU/L and the results of liver and kidney function tests were normal. The EEG revealed irregularity in the ground rhythm with slow wave discharges. The patient was operated for bilateral congenital cataract when he was 6-month-old. Despite the cataract operation, the eyesightwas poor. Therefore, the patient was wearing glasses. Furthermore, he had motor milestones and language delays. He could not sit without support; he could not walk or speak any single word.

Brain magnetic resonance imaging (MRI) showed thin appearance in the corpus callosum splenium, mild atrophy of the proximal cerebellum and mega cisterna magna (Figure 1C,D). Scoliosis was found ontheanteroposterior X-ray (Figure 1E). He had limitation of abduction in both hips and contractures in the ankles. The karyotype analysis was 46, XY. Copy number and single-nucleotide polymorphism analyses revealed that the patient did not have a variation in copy number. Sequencing of the complete mitochondrial genome of the patient and her mother did not identify any changes potentially associated with the patient's condition. The WES analysis showed a novel homozygous mutation in *TBC1D20* compared to the reference sequence: NM_144628.8, the splice site mutation c.259_260delinsCAC (p.Lys87HisfsTer42) in exon 3. Both parents were heterozygous for this mutation. Various software packages predict that the c.259_260delinsCAC mutation affects splicing, which could lead to a truncated, catalytically inactive protein. Based on the guidelines of the American College of Medical Genetics, this mutation classified as pathogenic (4). This mutation was predicted as disease-causing according to the protein prediction tools such as MutationTaster and SIFT. This mutation has not been reported in the Human Gene Mutation Database (HGMD).

DISCUSSION

We report a 3-year-old boy who has developmental delay, severe intellectual disability, bilateral congenital cataract, microphthalmia, thin corpus callosum, mild atrophy of the proximal cerebellum and mega cisterna magna with a novel *TBC1D20* homozygous mutation. Pathogenic variants in the *TBC1D20* gene are associated with WARBM type 4, an autosomal recessive disease, characterized by microcephaly, ocular findings (congenital cataract, microphthalmia, microcornea, and optic atrophy), cortical dysplasia, in particular corpus callosum hypoplasia, intellectual disability, and microgenitalia (2, 3). Most of the WARBM cases have been observed in males and in consanguineously married parents (4). Our case is the only son of the relative parents. Cranial MRI in four patients with WARBM type 4 showed predominantly frontal polymicrogyria, hypogenesis of the corpus callosum, enlarged lateral ventricles, and mega cisterna magna due to cerebellar hypoplasia (4-6). The brain MRI of our case demonstrated a thin corpus callosum splenium, mild atrophy of the proximal cerebellum and mega cisterna magna. He had congenital bilateral cataracts which were surgically removed at 6 months of age.

Martsolf syndrome (MS) is very similar to WARBM but it has less severe neurological and ocular phenotypes. Patients with WARBM have severe to profound intellectual disabilities. Truncal hypotonia and progressive limb spasticity can be develop in the patients with WARBM

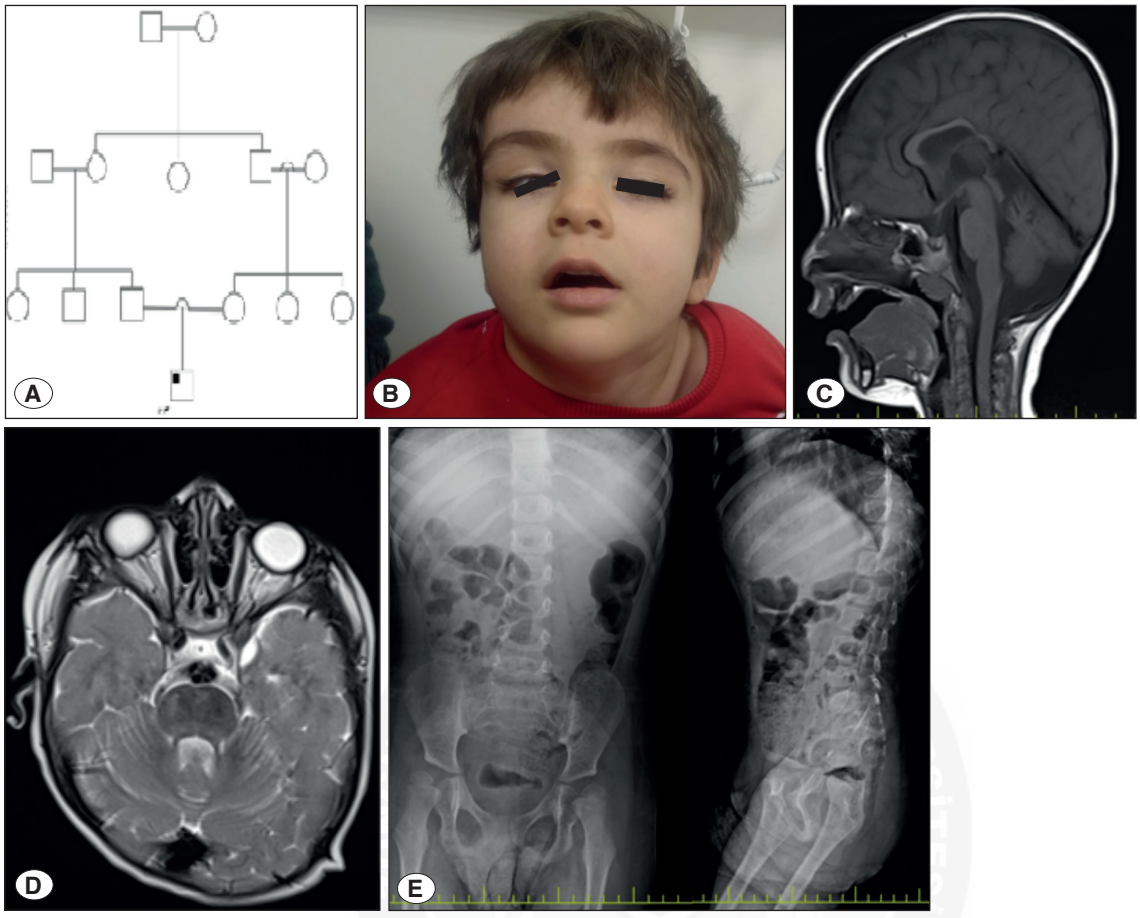

Figure 1: A) The family pedigree of the patient mega cisterna magna. **B)** Facial view of the patient from the frontal side. **C)** Brain MRI of the patient showed thin appearance in the corpus callosum splenium and mild proximal atrophy of the cerebellum. **D)** Brain MRI of the patient showed mega cisterna magna. **E)** Kyphoscoliosis appearance on A-P and lateral X-ray.

(7–10). WARBM is also associated with severe cerebral anomalies, predominantly hypoplasia of the corpus callosum and atrophy of the brain. Most MS patients do not have postnatal growth retardation, microcephaly, or severe intellectual disability (11-13). In addition to WARBM, this syndrome is linked to the loss of function of the TBC1D20 complex. Liegel et al. discovered five different *TBC1D20* loss-of-function mutations as being responsible for WARBM. Only one homozygous *TBC1D20* mutation was identified in two siblings with a moderate Martsolf phenotype (6). Hozhabri et al. reported two siblings from an Iranian family with Martsolf syndrome with a *TBC1D20* mutation (4). Furthermore, Abdel-Hamid et al. reported a patient with a nonsense (c.199C>T;p.Arg67*) *TBC1D20* mutation who was diagnosed with WARBM.Except for an Iranian family with MS associated with *TBC1D20* mutations, all previously reported individuals with *TBC1D20* mutations showed the classical WARBM phenotype (4, 14).

Our patient had a phenotype more compatible with WARBM than Martsolf syndrome.Genotype-phenotype correlation studies suggest that clinical variation in WARBM and MS may be related to the effect of gene mutations on protein function. *TBC1D20* gene mutations identified in WARBM are nonsense, frameshift or deletion mutations (7, 9). Also, the novel (c.259_260delinsCAC; p.Lys87HisfsTer42) mutation described here is a frame-shift (splice site) mutation.

The pathogenicity of the *TBC1D20* gene mutation and clinical findings of the patient are consistent with WARBM. According to the hypothesis that the phenotypic distinction in WARBM and MS might depend on the severity of the mutation, we suggested that the c.259_260delinsCAC mutation could cause WARBM. The studies may determine the effect of *TBC1D20* gene mutation on protein function in vivo or in vitro.

In conclusion, we describe a novel pathogenic mutation (c.259_260delinsCAC) in the *TBC1D20* gene in a Turkish patient with a WARBM phenotype.The identification of such mutations is essential for accurate genetic counseling. More research needs to be done to find out why patients with different *TBC1D20* mutations have different clinical signs.

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None.

Author Contributions

The idea of presenting the case to the literature and collecting the data of the case: **Ayça Kocaağa, Sevgi Yimenicioğlu.** Analysis of patient datas, writing of article and preparation of images: **Ayça Kocaağa, Sevgi Yimenicioğlu.**

Conflicts of Interest

There is no conflict of interest.

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Ethical Approval

There is no need the ethical approval because the article is case report.

Review Process

Extremely peer-reviewed and accepted.

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