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3MC syndrome: A case report

3MC sendromu: Bir olgu sunumu

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Abstract

3MC syndrome is a rare autosomal recessive disorder associated with distinctive facial features, cleft lip/palate, short stature, developmental delay, periumbilical defects, genitourinary and sacral anomalies. Mutations in the genes which encode proteins involved in the lectin complement pathway of innate immune system; MASP1, COLEC11 and COLEC10 have been identified in patients with 3MC syndrome.

We report a 2-year-old male patient with 3MC syndrome; in whom diagnosis was confirmed by mutation analysis of the MASP1 gene.

Key words: 3MC syndrome, MASP1, COLEC11, COLEC10, blepharophytosis, epicanthus inversus.

Öz

3MC sendromu tipik yüz bulguları, yarık dudak/damak, boy kısalığı, gelişme geriliği, umblikal defekt, genitoüriner ve sakral anomaliler ile seyreden, nadir görülen, otozomal resesif geçiş gösteren bir sendromdur. 3MC sendromlu hastalarda, doğal immun sistemin lektin kompleman yolağında görev alan proteinleri kodlayan MASP1, COLEC11 ve COLEC10 genlerinde mutasyonlar saptanmıştır.

Bu yazıda, MASP1 geni mutasyon analizi ile tanısı doğrulanan 3MC sendromlu 2 yaşındaki bir erkek hasta sunulmuştur.

Anahtar Kelimeler: 3MC sendromu, MASP1, COLEC11, COLEC10, blefaroptozis, epikantus inversus.

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Introduction

3MC syndrome is a rare autosomal recessive disorder that includes different entities with overlapping features. The Carnevale, Mingarelli, Malpuech and Michels syndromes were recently redefined to be a part of 3MC syndrome [1-4]. Malpuech syndrome is characterized by caudal appendage, cleft lip and palate, hypospadias, hypertelorism, intrauterine growth restriction, micropenis, and renal anomalies [3, 5]. Michels syndrome shows anterior chamber anomalies, blepharophimosis, cleft lip and palate, craniosynostosis, and epicanthus inversus [4]. Carnevale syndrome exhibits downslanting palpebral fissures, hypertelorism, large and fleshy ears, lozenge-shaped diastasis around the umbilicus, ptosis, strabismus, and synophrys [1]. Mingarelli syndrome, with similar features of Carnevale, exhibits also humeroradial synostoses and spinal anomalies as extra features [2].

3MC syndrome is caused by mutations in the genes regulating Mannose-binding lectin (MBL) associated serine proteases (MASP) which play a role in innate immune system and embryonic development [6, 7]. Mutations in two genes, MASP1 and COLEC11 (collectin 11) were found to be responsible for 3MC syndrome [7, 8]. In 2017, Munye et al. [9] identified a new gene that was also mutated in patients with 3MC syndrome: COLEC10.

The MASP1 gene encodes three proteins, MASP-1, MASP-3 and MAp44. The three isoforms share a common trunk but differ in their C-terminal serine protease domain [6].

Here, we report a male patient with suspected 3MC syndrome, diagnosis was confirmed through molecular analysis of MASP1 gene.

Case report

A two-year-old Syrian male patient, the fifth child of a consanguineous parents, was referred for genetic analysis due to developmental delay and dysmorphisms. Family history including siblings was unremarkable. There was no known drug exposure in the prenatal period. He was born on time with a weight of 3500 gr, a neonatal tooth was noted. He was operated for cleft lip at the 11 months of age. At physical examination, his height, weight and head circumference were 82 cm (3-10 percentile),11600 g (25 percentile) and 47.5 cm (10-25 percentile), respectively. He presented with facial dysmorphism including blepharophytosis, telecanthus, epicanthus inversus, mildly down-slanting palpebral fissures, blue sclera, high arched eyebrows, wide forehead, hypoplastic ala nasi, the left sided repaired cleft lip, dental crowding and retrognathia. The anterior fontanel was extremely large (3x3cm). He also showed a skin tag at the xiphisternum, peculiar supra-umbilical depression, mongol sign and sacral dimple (Figure 1).

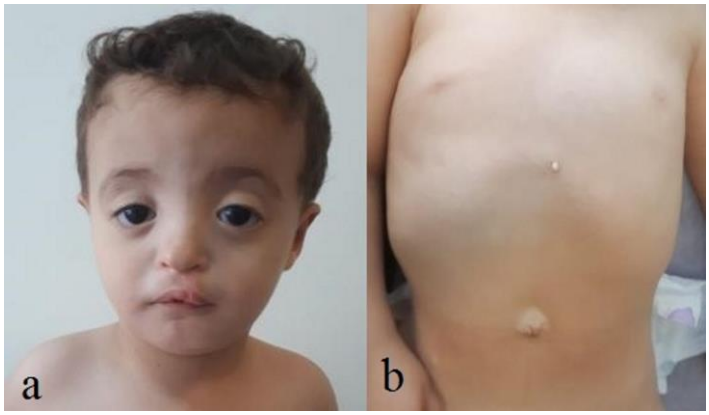

Figure 1. a ,b: Clinical pictures of the proband. (a) Photograph showing distinct craniofacial dysmorphism including a broad forehead, high arched eyebrows, blepharoptosis, hypertelorism, down-slanting palpebral fissures, blue sclera, hypoplastic ala nasi, a flat nasal tip, left sided repaired cleft lip scar. (b) Skin tag at xiphisternum and supra umbilical depression can be noted.

Routine laboratory investigations, transfontanelle ultrasonography, renal echography and bone X-ray were normal. Mild left ventricle dilation was detected on echocardiography; however, function of the left ventricle was normal. On the basis of suspected 3MC syndrome, next generation sequencing analysis (Miseq- Illumina Inc.) for all coding exons and exon-intron boundaries of the MASP1 gene was performed. Variants were named according to NM_139125. A homozygous c.1987G>T; p. Asp663Tyr mutation in the MASP1 gene was detected in the patient (Figure 2). Mutated exon was analyzed for cosegregation in unaffected parents; both parents were heterozygous carriers.

Written consent was taken from the parents of the patient.

Discussion

3MC syndrome (OMIM #257920;265050;248340) is associated with characteristic dysmorphic features (high-arched eyebrows, ptosis, blepharophimosis, hypertelorism and cleft lip/palate), short stature, developmental delay, hearing loss, umbilical hernias, urogenital and skeletal abnormalities such as craniosynostosis, radioulnar synostosis or caudal appendage [10]. We report on a two-year-old Syrian male patient with 3MC syndrome and describe his phenotype.

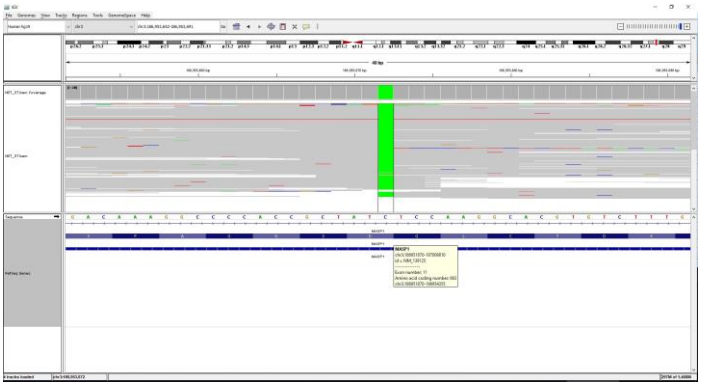

Figure 2. A screenshot from the Integrated Genomics Viewer (IGV) browser showing c.1987G>T mutation (according to NM_139125) in the MASP1 gene.

MASP1 and COLEC11 gene mutations have been held responsible for the clinical findings in 3MC syndrome. MASP1 and COLEC11 genes encode proteins related to the lectin complement pathway [7]. Mutations in another gene COLEC10, which is expressed in craniofacial tissues during development, have been identified later in 3MC patients [9]. MASP1 gene is located on chromosome 3q27-28 and encodes three protein isoforms: MASP-1, MASP-3, and MAp44, via alternative splicing [6,11]. All share the identical N-terminal amino acids. Serine protease domains in the C-terminals of MASP-1 and MASP-3 are different. MAp44 does not include a serine protease domain [8]. We identified a homozygous missense MASP1 mutation: c.1987G>T; p.D663Y (p.Asp663Tyr) (according to NM_139125) sufficient to cause 3MC syndrome in our patient. This change affects exon 11 and accordingly the C-terminal serine protease domain specific to MASP-3 [10,12]. The same domain is affected by missense mutations in previously reported patients, our findings further highlight the domain's essential role in the pathogenesis of 3MC syndrome [10,13].

Complements are an important part of innate immune defense. There are three complement activation pathways: Classical, alternative and lectin pathways. MASP1 gene is involved in lectin complement pathway [11]. We were unable to test complement function in our patient but on specific questioning, none is known to have an immunological phenotype.

We identified a homozygous missense MASP1 mutation: c.1987G>T; p.D663Y (p.Asp663Tyr) (according to NM_139125) sufficient to cause 3MC syndrome in our patient. The missense alteration, p. (Asp663Tyr), identified in the current study is the same as one reported by Atik et al. [10]. The authors reported a 6-month-old female patient presented with arched eyebrows, hypertelorism, blepharophytosis, bilateral cleft lip/palate, cliteromegaly, anterior ectopic anus, prominent coccyx with a sacral pit and a presacral capillary malformation. Echocardiography showed secundum ASD and wide PDA. Left renal agenesis and a hypoechoic solid lesion of the liver was revealed by abdominal ultrasound. The patient died 2 months after PDA ligation operation due to pneumonia [10]. Urquhart et al. [13] also described a female patient from Israel with c.1987G>T; p.D663Y mutation. The patient had typical facial features, cleft lip/palate, umbilical hernia, hearing loss, moderate intellectual disability, ventricular septal defect, hydrocephalus and tracheaesophageal fistula. Genitourinary anomaly and caudal appendage were also noted. The patient reported here was a 2-year- old Syrian male patient with a mild clinical course without any major malformations. The patient with the same mutation reported by Atik et al. [10] had poor prognosis, died 2 months after PDA ligation operation due to pneumonia. We can conclude

that expression of the phenotype in 3MC syndrome may be variable between patients even if they carry the same mutation.

Malpuech, Michels, Mingarelli and Carnevale syndromes are rare, autosomal recessively transmitted disorders. Although they are distinct entities, they share overlapping phenotypic features. Due to phenotypic similarities between Malpuech, Michels, Mingarelli and Carnevale syndromes, Titomanlio et al. [14] suggested to redefine the syndromes as the 3MC syndrome (for Malpuech-Michels-Mingarelli-Carnevale) [15]. Prevalence of 3MC syndrome is unknown; 32 affected individuals from 20 families were described in the literature until 2011 [7]. A small number of patients with mutations in COLEC11, MASP1 or COLEC10 genes have been reported until now. Sirmaci et al. [8] reported 3 Turkish patients from 2 families with MASP1 mutations. Rooryck et al. [7] reported 6 patients from 4 families with MASP1 mutations, 10 patients from 7 families with COLEC11 mutations. In 2015, Atik et al. [10] reported six patients with MASP1 mutations. More recently Urquhart et al. [13] described 2 patients with COLEC11 and 5 patients with MASP1 mutations. Gardner et al. [16] reported 2 sisters with exon 8 deletion in COLEC11. In 2017, Munye et al. [9] reported 3 patients with COLEC11, 1 patient with MASP1 and 3 patients with COLEC10 mutation. Therefore, in total, together with the isolated cases recently reported, 43 3MC patients with mutations in COLEC11, MASP1 or COLEC10 have been identified until now [17, 18]. Among 43 patients, 23 patients had mutations in MASP1 gene [9, 10, 13].

In this case report, we discussed the clinical and laboratory findings of a patient with 3MC syndrome. Diagnosis was confirmed by mutation analysis of the MASP1 gene. We found a homozygous missense mutation in MASP1. Limited number of 3MC patients have been reported in the literature, the number of patients with molecular evidence is even smaller. Thus, this report of the 3MC syndrome patient with homozygous mutation in MASP1, aims to expand the phenotype of this rare syndrome and provide insights into the genotype-phenotype correlation.

We report a 2-year-old male patient who was diagnosed with 3MC syndrome based on the phenotypic and molecular evidence. Combining empirical analysis of dysmorphology with current molecular analysis techniques can be a useful approach to understand the etiology of malformation syndromes. Further studies are required to explain the fundamental roles of lectin complement pathway genes in developmental disorders.

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