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Case Report

A Newborn with Arhinia: Suspected BAM Syndrome

Burunsuz Bir Yenidoğan: BAM Sendromu

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ABSTRACT

Bosma arhinia microphthalmia (BAM) syndrome is a rare condition, characterized with eye defects, complete absence of nose, and hypogonadotropic hypogonadism. The symptoms and severity of disorder can alter from one patient to another. The etiology of the majority of the reported cases has remained unknown. The case report of a female baby, who was born through vaginal delivery with characteristic features of midface hypoplasia, nasal aplasia, hypertelorism and other anomalies related to BAM syndrome and challenges during follow-up period are shared in this article.

Keywords: Craniofacial dysmorphology, arrhinia, eye defects, hypogonadotropic hypogonadism, BOSMA, BAM

ÖZ

Bosma arhinia mikroftalmi (BAM) sendromu, burnun tamamen yokluğu, göz anomalileri ve hipogonadotropik hipogonadizmin ile karakterize nadir bir durumdur. Semptomlar ve şiddeti olgular arasında değişiklik göstermektedir. Bildirilen olguların çoğunluğunun etiyolojisi bilinmemektedir. Bu yazıda, 35. gebelik haftasında vajinal yolla doğan, orta yüz hipoplazisi, nazal aplazi, hipertelorizm ve BAM sendromuna bağlı diğer anomalileri olan bir kız bebek ve takip sürecindeki tecrübeler paylaşılmıştır.

Anahtar kelimeler: Kraniyofasiyal dismorfoloji, arini, göz anomalisi, hipogonadotropik hipogonadizm, BOSMA, BAM

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INTRODUCTION

Bosma arhinia microphthalmia (BAM) syndrome is a rare condition, characterized with eye defects, complete absence of nose, and hypogonadotropic hypogonadism. In 1981, Bosma et al.[1] described two males with severe hypoplasia of the nose, hypoplasia of the eyes, sensory abnormalities of taste and smell, and hypogonadism. Around the same time, Ruprecht and Majewski[2] described two German siblings with similar defects (Ruprecht-Majewski Syndrome). Since that time, BAM syndrome has been reported in fewer than 100 patients worldwide. Although SMCHD1[3,4], FSHD2[5] and other gene mutations were detected in a few cases, its etiology remained mostly unknown[6]. The symptoms and severity of the disorder can alter from one patient to another. Neonates, and obligatory nasal breathers with the absence of external nose, are at risk of airway collapse. There are no clear guidelines about management in the delivery room. We report a late preterm neonate with arhinia and other congenital malformations consistent with BAM syndrome.

CASE REPORT

A female baby who was born via vaginal delivery at 35th week of gestational age due to late deceleration of fetal heart rate detected during the non-stress test in a 25-year-old healthy mother during routine controls, was intubated and referred to our hospital because of dysmorphic features and lack of respiratory effort in the delivery room. Patient's family stated that regular follow-ups were realized throughout the pregnancy and there was no abnormality in the prenatal history. In addition, there was no consanguinity between the parents and they had two healthy boys aged seven and nine years. The patient's birth weight (2,180 g: 29th pctl), birth length (45 cm: 37th pctl), and head circumference (30.5 cm: 17th pctl) were as indicated[7]. In the physical examination; midface hypoplasia, nasal aplasia, hypertelorism, low-

placed left eyeball, downslanting palpebral fissures, low ear, several skin tags in front of right ear, severely malformed left external auditory canal, high-arched palate, large gap between both big toes and second toes were detected (Figure 1).

Abdominal ultrasonographic and echocardiographic examinations did not reveal any abnormal findings other than patent foramen ovale. In the ccomputed tomography examination of the skull bones; no aeration was observed in the left tympanic bone, and total osseous atresia was noted in the left external ear canal. Aeration was not observed in both mastoid bones. The external auditory canal opening to the right side was very thin. Quite hypoplastic nasal bone, and absence of the nasal cavity were noted. Bilateral Cochleas and vestibules were normal. However, semicircular canals could not be evaluated (Figure 2). In the cranial magnetic resonance imaging (MRI) of the patient whose electroencephalography examination was normal for his age, lipoma in the supracerebellar region, frontoethmoidal encephalocele, hypoplasia in the cerebellar vermis and left external auditory canal atresia were detected. No abnormal findings were found in the blood tests (Table 1). Moderate conductive hearing loss on the left and severe conductive hearing loss on the right were detected by hearing test.

Karyotyping and microarray analyzes were performed subsequently. Karyotype analysis revealed the presence of 46,XX. In microarray analysis, an 85 Kbp deletion of unknown clinical significance characterized by the presence of an *Online Mendelian Inheritance in Man* (OMIM) gene [CATION CHANNEL AMILORIDE-SENSITIVE, NEURINAL, 1; *ACCN1* (601789)] in the 17q12 region was detected. The data obtained from microarray analysis was searched in the Database of Genomic Variants, DECIPHER, OMIM and other related databases with the methods recommended in the literature. Thus, this small deletion was thought to be not related to the patient's clinical features.

The patient was followed up as intubated, and breastfeeding was started at the postnatal 48th hour. Tracheostomy was opened for airway patency on the seventh day. The patient was followed up on mechanical ventilator for fifteen days and received antibiotherapy with the diagnosis of late neonatal sepsis during this period. Due to difficulties in oral intake, the patient, whose follow-up was continued with a heat and moisture exchanger, was fed via an orogastric tube. Oral feeding was provided with the development of sucking/swallowing reflex and after being monitored with her mother for seven days, the patient was discharged on the postnatal 60th day (Figure 3). On evaluation performed after two weeks, the patient's body weight (3.185 g: 11th pctl), height (50 cm: 12th pctl), and head circumference (35 cm: 22th pctl) were masured as indicated[8]. Blood tests performed during mini-pubertal period and routine evaluations are given in Table 1.

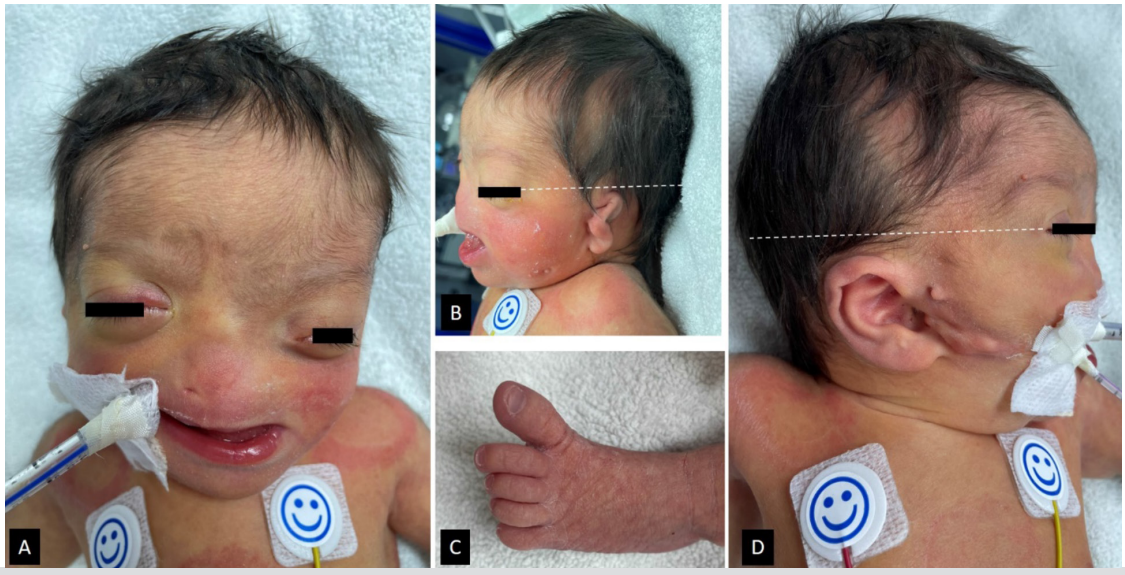

Figure 1. A) Midface hypoplasia, nasal aplasia, hypertelorism, low placed left eyeball, down slanting palpebral fissure, low ear, B) severely malformed left external auditory canal, C) large gap between both big toes and second toes, D) several skin tags in front of right ear

DISCUSSION

The frontonasal processes appear around the fourth gestational week of age and give rise to the majority of the skeletal elements of the face during the processes of proliferation, differentiation and apoptosis[9]. Malformations that may occur during this process are manifested by various craniofacial anomalies such as Apert syndrome, BAM syndrome, Crouzon syndrome and Treacher Collins syndrome etc. BAM syndrome, firstly defined in 1981, has three decisive components: arhinia, ocular malformations and hypogonadotropic hypogonadism[10]. Some of the patients were shown to have mutations in *SMCHD1*, *FSHD2* and other genes[3-6]. However, genetic mutations have not been identified in most cases or medical centers have failed to perform relevant genetic analyzes. However, any known pathogenic mutations have not been identified in most of the cases or medical centers have failed to perform further genetic analyzes Several candidate genes including *ALX4, PAX6, FGF, RAX, SOX2* and *CHX10* have been evaluated, and yet no significant associations have been found[11]. According to OMIM (603457) database, BAMS related only to *SMCHD1* gene locating on chromosome 18p11. *SMCHD1*, codes a protein regulating gene activity by altering the structure of DNA, and plays an essential role in the inactivation of X chromosome[12].

Table 1: Patient's laboratory results at specified times

	Postnatal 3rd day	2nd month
Hb (gr/dL)	16.8	9.8
MCV (fL)	118	89.9
Blood Glucose (mg/dL)	85	98
BUN (mg/dL)	5.4	7.7
Cre (mg/dL)	0.67	0.22
Albumin (g/dL)	2.9	4.09
AST/ALT (U/L)	64/17	31/18
TSH [m (IU)/mL]	6.5	3.4
fT_4 (ng/dL)	1.57	1.1
ACTH (pg/mL)	-	58
Cortisol (µg/dL)	-	32.3
FSH [m (IU)/mL]	-	<0.001
LH [m (IU)/mL]	-	<0.00
Estradiol (pg/mL)	-	<11.80

Hb: Hemoglobin, MCV: Mean corpuscular volume, BUN: Blood urea nitrogen, Cre: Plasma creatinine, AST: Aspartate aminotransferase, ALT: Alanine transaminase, TSH: Thyroid stimulating hormone, fT_4: Free thyroxine, ACTH: Adrenocorticotropic hormone, FSH: Follicle stimulating hormone, LH: Luteinizing hormone

Arhinia leads to severe airway impairment and poor feeding in neonates. Considering that neonates are requisite nasal breathers, it is very difficult, but crucial for the maintenance of airway patency in the delivery room. Mouth breathing is a learned reflex which is acquired around sixth months. Hence, an obstructed airway can drive to respiratory distress[13]. In our case, antenatal diagnosis was unknown, the patient was intubated in the delivery room, and a tracheostomy was performed on the seventh day. In the reported cases, all patients, with very few exceptions, were intubated soon after birth[10,14-16]. Detection of arhinia during the antenatal period would generally be possible by using qualified ultrasound devices and adroit ultrasonographers. There are five cases diagnosed with isolated arhinia antenatally. Two of these cases did not survive, one of them was intubated on the third day, and one of them was discharged without intubation[14,16,17]. Knowing what to expect in the delivery room has an important place

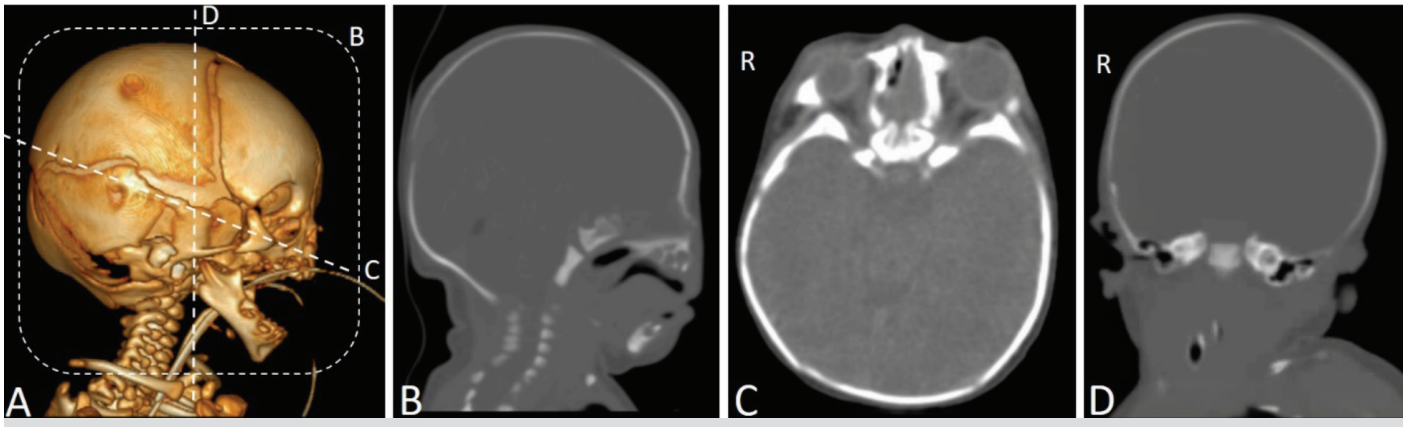

Figure 2. A) 3D model of skull bones, B, C) Sagittal and transverse section The nasal bone was observed to be quite hypoplastic, and the nasal cavity was not observed. D) Aeration was not observed in bilateral mastoids. The external auditory canal opening on the right was very thin. Bilateral cochlea and vestibule are normal

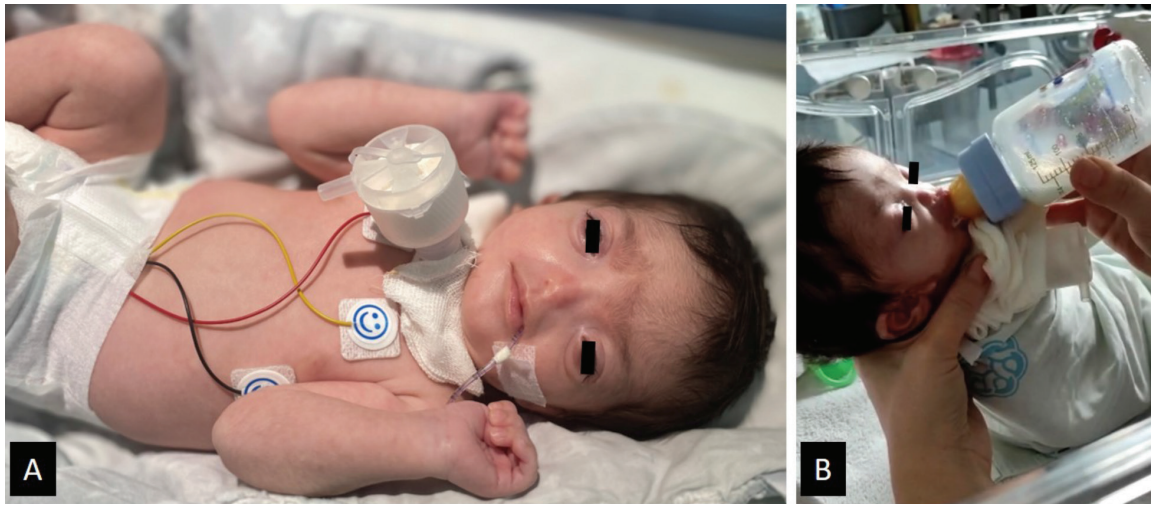

Figure 3. A) Spontan breathing, with a heat and moisture exchanger on 42nd day, B) Oral feeding started on day 51

in the future interventions to be performed. In addition, in children with nasal agenesis, disturbances in the oral food intake are expected, since simultaneous breathing is not possible when sucking. Oral food intake can be ensured with an orogastric tube taking into account the risk of cyanosis.

High-arched palate and absence of nasolacrimal ducts are the most common accompanying midfacial anomalies[10,17]. Our patient had high-arched palate and ear abnormalities described above. Ear anomalies are not well described in children with BAM syndrome. Only a few cases had hypoplasia of the auditory canals, mild conductive or sensorineural hearing loss, preauricular pits, small over-folded ears and helical crus anomalies[6,10,18,19].

Ocular malformations including coloboma, microphthalmia, anophthalmia, hypertelorism, downslanting palpebral fissures are well described[10,16]. Hypertelorism, low-placed left eyeball and downslanting palpebral fissure were observed in our patient. In addition to the described findings tigroid retinal pattern together with ectropion was observed but coloboma wasn't noted during ophthalmologic examination. The patient could make eye contact and recognize caregivers around two months of age.

Facial malformations are generally seen with central nervous (CNS) system anomalies. In the case reports and reviews, most associated CNS anomalies are absence of olfactory tracts/bulbs, frontal or frontonasal encephalocele and thin corpus callosum[10,16]. MRI scan findings in our patient have been described above. Excepting three cases (one had abnormal aortic root, one had patent ductus arteriosus, questionable aortic coarctation and pulmonary and tricuspid valve insufficiency, and one had patent ductus arteriosus), no cardiac anomalies were described in the literature[10,20,21]. In our patient's echocardiography, a patent foramen ovale was observed.

Hypogonadotropic hypogonadism, cryptorchidism, umbilical/inguinal hernia and hypospadias were also described in these patients[10,16]. Generally, case reports on exclusively neonatal cases have been published, whereas some cases have dealt with older patients[1,10,21-23]. Though cases of isolated arhinia and delayed puberty in newborns and infants have been reported[24-26], these cases had not undergone hormonal examination at the time of mini puberty. Mini puberty describes the ephemeral activation of the hypothalamic-pituitary-gonadal axis during early months of childhood. Between the 2nd and the 10th weeks of age levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) increase, make a peak, then decrease and stay at prepubertal levels until puberty[27]. In our patient around nine weeks of age, FSH, LH and estradiol levels were compatible with hypogonadotropic hypogonadism (Table 1). No shock, hypoglycemia or electrolyte abnormality were observed during the patient's follow-up period in the neonatal intensive care unit, suggesting the presence of hypothalamic-pituitary axis insufficiency.

There is no consensus about the type and timing of the reconstructive surgery to be performed. Some

authors perform reconstructive surgery in the neonatal period, while others delay it until adolesence[28]. In our case, the patient was followed up monthly with in situ tracheostomy by related departments of pediatrics, ophthalmology and ENT. Surgical correction was planned by departments of ENT and esthetic, plastic and reconstructive surgery after childhood.

Although a patient with BAM syndrome may require intensive medical support early in life due to difficulty in breathing and feeding, they usually become healthy and reproductive later on. Antenatal diagnosis is important to determine the necessary intervention to be performed in the delivery room. Owing to the rarity of BAM syndrome, there are no standardized relevant treatment protocols or guidelines. Affected individuals should be monitored by medical care team including ENT, esthetic, plastic and reconstructive surgeons, ophthalmologists, and pediatric endocrinologists.

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