

Branchio-Oculo-Facial Syndrome (BOFS) and Congenital Heart Defects

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We report the case of a 43-day-old boy with branchio-oculo-facial syndrome (BOFS) and congenital heart defect. On clinical examination, he presented growth retardation, epicanthal folds, small palpebral fissures, telecanthus, broadened nasal bridge, lip pseudocleft, micrognathia, dysplastic and posteriorly-rotated ears, branchial clefts, short and webbed neck, supernumerary nipple, hypotonia and decreased deep tendon reflexes. Echocardiography showed the presence of a type-A complete atrioventricular septal defect and patent ductus arteriosus. This description strengthens the possibility of congenital heart defects being part of the spectrum of anomalies seen in BOFS.

Introduction

Branchio-oculo-facial syndrome (BOFS) (MIM 113620)¹, first named in 1987 by Fujimoto et al², is a rare autosomal disease with a highly variable expressivity³. Mutations in genes of the *EYA-DACH-SIX-PAX* pathway, initially considered candidates for the syndrome because of their relationship with the development of some oro-facial-cervical structures and diseases overlapping with BOFS, such as the branchio-oto-renal syndrome (BOR; MIM 113650) and Townes-Brocks syndrome (TB; MIM 107480), have not been identified in BOFS patients. However, more recently, Milunsky et al⁴ studied a sample of BOFS patients and verified the presence of mutation in the *TFAP2A* gene, which is located in chromosome 6 (region 6p24) and previously related to the development of the anterior chamber of the eye^{1,4}. Despite these findings, the authors concluded that more patients should be studied to exclude possible genetic heterogeneity⁴. The syndrome is clinically characterized by the presence of branchial defects covered by a portion of normal skin, associated or not with pre-auricular or auricular pits; microphthalmia; coloboma; nasolacrimal duct obstruction; lip pseudoclefts (abnormal upper lip and filtrum resembling a poorly repaired cleft lip);

Key Words

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partial or total clefts of upper lip, and premature graying of hair^{2,3}.

Although renal malformations are frequent in patients with the syndrome, the involvement of other organs, particularly congenital heart defects (CHD) have been rarely described^{3,5}. We report a rare case of BOFS associated with CHD.

Case Report

The patient was a white boy, the first child of healthy nonconsanguineous young parents. His family history was negative for any congenital defect or genetic disease. He was born at the 36th week gestation, by cesarean section, in breech presentation. His birth weight was 2870 g (10-50th percentile), his height was 45 cm (10-50th percentile) and the 5-minute Apgar score was 9. On clinical examination at 43 days of age, his weight was 2590 g (< 3rd percentile), his height was 46 cm (< 3rd percentile), head circumference of 34 cm (< 2nd percentile), and he presented epicanthal folds, small palpebral fissures, telecanthus, broadened nasal bridge, lip pseudocleft, micrognathia, dysplastic and posteriorly-rotated ears, branchial clefts (areas of aplasia cutis) in the neck below the ears, short and webbed neck, and supernumerary nipple in right side of the chest (Figure 1).

The neurological examination revealed hypotonia and decreased deep tendon reflexes. Brain ultrasonography showed prominent lateral ventricles. Abdominal ultrasonography, eye examination and high-resolution GTG-banding karyotype were normal.

An echocardiography performed soon after birth showed the presence of an atrioventricular septal defect (AVSD) and patent ductus arteriosus (PDA).

Although cardiac surgery had been performed on the first month of life, the child progressed with hemodynamic and respiratory instability due to the heart condition, and died in the tenth month of life. Autopsy was not performed.

Discussion

The presence of some specific craniofacial anomalies in our patient, particularly telecanthus, broadened nasal bridge, lip pseudocleft, dysplastic and posteriorly-rotated ears associated with branchial clefts, which are considered possibly pathognomonic of BOFS³, supported the diagnosis. In medical databases such as *OMIM*¹ and *LMD* (London Medical Database)⁶, there is no description of the association between BOFS and congenital heart defects. However, in our review, we found four confirmed cases of BOFS presenting CHD which

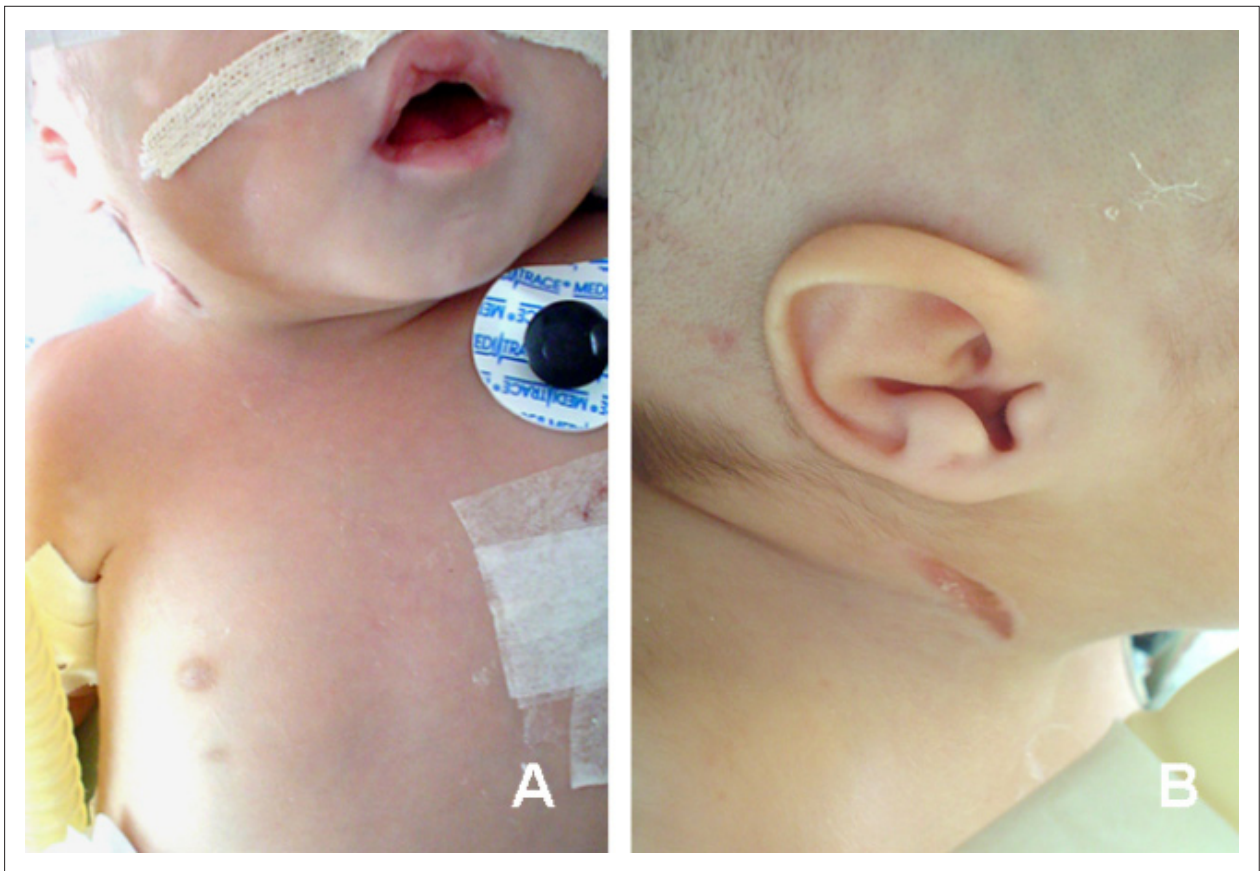


Figure 1 - A - Patient at 43 days of life presenting lip pseudocleft, branchial cleft below the right ear, short and webbed neck, and supranumerary nipple on the right side of the chest ; B - Detail of the dysplastic ear and right branchial cleft .

included: ostium secundum atrial septal defect (two cases)^{3,7}, tetralogy of Fallot (one case)⁵ and pulmonary valve stenosis (one case)⁸ (Table 1). All patients presented facial findings characteristic of BOFS associated with branchial defects^{1,3,5,8}. The present report is the first description of a patient with both BOFS and AVSD, one of the CHD more frequently associated with extracardiac anomalies, especially with Down syndrome⁹. Hing et al¹⁰ described a patient presenting multiple malformations and AVSD resembling BOFS. He presented some atypical findings such as holoprosencephaly and meningoencephalocele. The authors suggested that this patient could present a lethal variant of BOFS, or, alternatively, a syndrome not previously reported¹⁰. This case was reevaluated

by Lin et al³, who considered it atypical, probably unaffected³. Although conotruncal heart defects – malformations related to the abnormal migration of cells from the neural crest into the branchial arches, are frequently found in other syndromes with branchial arch anomalies³, Bennaceur et al⁵ were the only authors to describe a patient with BOFS presenting this type of CHD (a patient with tetralogy of Fallot)⁵. The other reports included heart defects pathogenetically classified in the group of intracardiac blood flow defects^{3,7,8} and extracellular matrix anomalies (the present case) (Table 1). Thus, this new BOFS report strengthens the possibility of congenital heart defects being part of the spectrum of anomalies observed in this syndrome.

Table 1 – Reports of BOFS associated with congenital heart defects described in the literature

Patient	Author	Year	Congenital heart disease
1	Lin et al ³	1995	Ostium secundum atrial septal defect (ASD)
2	Bennaceur et al ⁵	1998	Tetralogy of Fallot (TOF)
3	Kapoor et Kapur ⁸	2004	Pulmonary valve stenosis
4	Verret et al ⁷	2005	Ostium secundum atrial septal defect (ASD)
5	Present report		Type-A complete atrioventricular septal defect (AVSD) and patent ductus arteriosus (PDA)

Case Report

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

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