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Branchio-oculo-facial Syndrome: A Rare Condition with Unusual Clefts – A Case Report

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Abstract

Branchio-oculo-facial syndrome (BOFS) is a rare autosomal dominant disorder characterized by diverse clinical phenotype attributed to mutations in the Transcription Factor AP-2 alpha (TFAP2A gene). The defining characteristics of BOFS encompass branchial cleft anomalies, ocular anomalies, and unique craniofacial dysmorphisms. The diagnosis is mainly clinical. Management involves various disciplines. Genetic counselling plays a crucial role. BOFS represents a complex syndrome that requires a high index of suspicion for diagnosis. Early intervention and coordinated care among specialists are crucial for improving outcomes. Genetic counselling plays a crucial role.

Keywords: Branchio-oculo-facial syndrome, branchial clefts, cleft lip and cleft palate, dysmorphic face, nasolacrimal duct stenosis or atresia, Transcription Factor AP-2 alpha mutation.

Introduction

Branchio-oculo-facial syndrome (BOFS) is a rare autosomal dominant disorder which has a wide range of clinical manifestations. It may manifest with branchial skin defects, ocular abnormalities, distinctive facial anomalies, and additional features such as ectopic

thymus, subscale cysts, as well as renal and dental abnormalities.[1]

The primary cause of BOFS is thought to be mutations in the Transcription Factor AP-2 alpha (TFAP2A) gene, which codes for the transcription factor AP-2 alpha.[1,2] Throughout the development of the embryo, this gene is crucial for the formation of facial structures. Although occasional cases resulting from de novo mutations have been reported, autosomal dominant inheritance accounts for the majority of cases.[2]

The defining characteristics of BOFS encompass branchial cleft anomalies (like cysts, sinuses, and fistulae), ocular anomalies (such as microphthalmia, coloboma, and lacrimal duct stenosis), and unique craniofacial dysmorphisms. Facial features can encompass a wide nasal bridge, cleft lip and/or palate, irregular ear shapes, and hypertelorism.[3]

Skin tags, hemangiomas, and the presence of ectopic thymic tissue within branchial cysts are the cutaneous characteristics that have been noted. Dental anomalies, such as absent or malformed teeth, are frequently observed, and a minority of cases have reported associated intellectual disabilities.[4]

The diagnosis is mainly clinical, with genetic testing used to confirm TFAP2A mutations. Consideration of differential diagnoses include branchiootorenal syndrome, CHARGE syndrome, and various craniofacial dysmorphisms. Diagnostic imaging, such as CT or MRI, along with audiologic assessments, is frequently required when hearing loss or structural ear defects are present.

Management encompasses various disciplines, necessitating precise correction of defects and effective symptomatic treatment. Genetic counselling plays a crucial role due to the heritable nature of the disorder.[2,5]

We report a clinically diagnosed case of BOFS – a term female baby with bilateral complete cleft lip and palate, branchial arch anomaly and nasolacrimal duct stenosis.

Case description

A term female baby with a birth weight of 2.096kg was delivered vaginally delivery to a 24 year old G2A1 mother and 30 year old father in a non-consanguineous marriage after an uneventful antenatal period. Mother had repair for cleft lip and palate and history of a spontaneous abortion 01 year prior, at 12 weeks of gestation. She also had Varicella zoster infection at 5 weeks of gestation which was managed with Acyclovir, with no history of any unsupervised drug intake or radiation exposure. Anomaly scan done at 18 weeks showed bilateral cleft lip and cleft palate.

Clinical examination at birth: Baby did not need any resuscitation but was noticed to have dysmorphic face, with bilateral complete cleft lip and palate, micrognathia, telecanthus, uplslanting palpebral fissures and a broad nasal tip as seen in Figure 1 and 2. Ears were low set, posteriorly rotated and overfolded. Epithelial defect of size 4x2cm was noted on the lateral aspect of neck bilaterally over the sternocleidomastoid muscle with mucosal lining as seen in Figure 3. Serosanguinous discharge was subsequently noticed over the defect. The possibility of branchial arch anomaly (branchial cleft) was considered. Baby also had widely spaced nipples and systemic examination was normal.

Figure 1: Baby with dysmorphic face, micrognathia, telecanthus, upslanting palpebral fissures, broad nasal tip, low set ears, bilateral complete cleft lip and palate and epithelial defect over neck and widely spaced nipples.

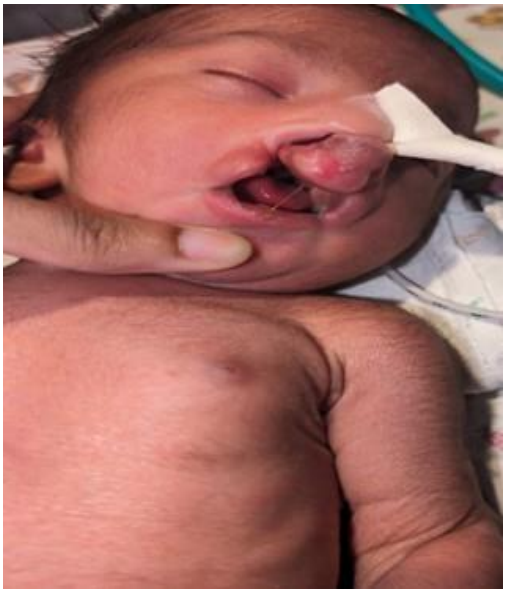

Figure 2: A closer view of the bilateral cleft lip and palate.

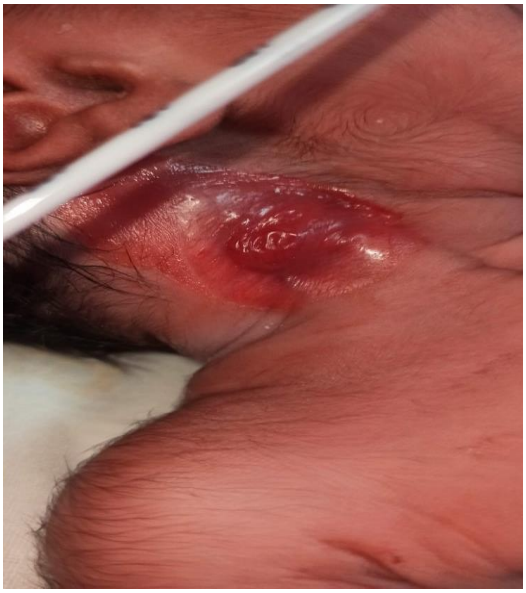

Figure 3: Epithelial defect of size 4x2cm on the lateral aspect of neck over the sternocleidomastoid muscle with mucosal lining.

Paraclinical examination: Ultrasound soft tissue of neck taken showed two fairly well defined, ovoid hypoechogenic area involving the skin and subcutaneous plane of the lateral aspect of neck bilaterally measuring 1.0 x 0.26cm on right side and 0.87x 0.19cm on left side. There was no evidence of deeper extension into the muscular plane, sinus tract or collection. Echocardiographic evaluation revealed an Ostium secundum Atrial Septal Defect with left to right shunt. Ultrasound abdomen, kidneys and urinary bladder done were normal. Blood investigations done were also normal.

Management and outcome: Baby had no respiratory distress, nasogastric feeds were initiated on Day 01 of life and subsequently changed to paladai feeds. Over the course of hospital stay, a small papular lesion developed over the epithelial defect which ruptured releasing more profuse serosanguinous discharge as seen in Figure 4. Otoacoustic emission (OAE) of both ears was inconclusive and further testing was advised. The

possibility of Branchio-oculo-facial syndrome was considered and genetic testing was advised, but was deferred due to financial constraints. Genetic counselling was given to the parents regarding future pregnancies. Baby was discharged on paladai feeds. The epithelial defect appeared to shrink over weeks with crusting on the surface. Baby presented on Day 66 of life with acute dacryocystitis of left eye due to nasolacrimal duct stenosis which was medically managed. Baby had been on paladai and breast feeds during the interim period. At 03 months of age, the baby needed readmission for severe pneumonia with sepsis. The baby succumbed to severe pneumonia despite ventillation.

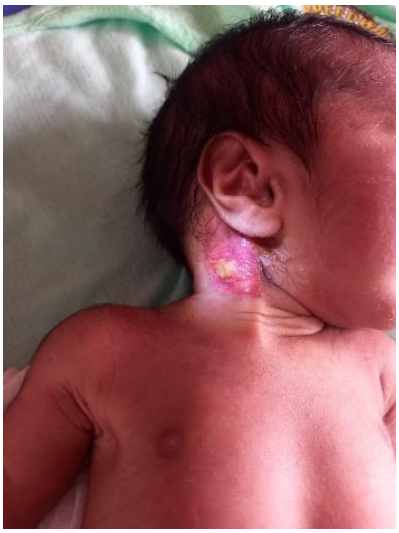

Figure 4: A small papular lesion over the epithelial defect which ruptured releasing more profuse serosanguinous discharge.

Discussion

In the early 1980s, Lee described a mother and son with bilateral branchial cleft sinuses, intrauterine and postnatal growth retardation, an odd appearance, and the mother's premature aging. Since no other family members showed the same symptoms, he proposed that the mother was the original mutant and that the syndrome was passed down as a dominant trait, most likely autosomal.[6] Subsequently, Hall reported 2 cases with hemangiomatous branchial clefts, lip pseudo clefts and an unusual facial appearance as a "novel gill slit syndrome".[7] Then, In 1987, Fujimoto described an apparently new syndrome that combined branchial sinus, ocular, and craniofacial anomalies and named it branchio-oculo-facial syndrome (BOFS OMIM 113620).[8] Though the prevalence of BOFS is not known, it is possibly a very rare condition with less than 150 individuals having a good clinical description with or without a molecular diagnosis.[2]

In individuals with BOFS, the improper development of the first and second branchial arches results in abnormal skin patches, commonly located on the neck or near the ears.[9] Cervical or infra- or supra-auricular skin defects can present in various forms, ranging from thin skin or hair patches to erythematous "hemangiomatous" lesions, and even to large weeping erosions.[10,11] Ocular anomalies noted are microphthalmia, anophthalmia, ptosis, strabismus, coloboma, cataract, and nasolacrimal duct stenosis or atresia.[12] Facial anomalies include cleft lip, pseudo labial cleft with or without cleft palate, upper lip pits, wide nasal bridge, flattened nasal tip, high palatal arch, ocular hypertelorism, low posteriorly rotated ears, and abnormalities in teeth.[3,12]

BOFS may also have an impact on other tissues and structures.[13] Most individuals with BOFS exhibit otologic abnormalities, including various forms of hearing loss, such as conductive, sensorineural, and mixed types.[14,15] Certain patients exhibit partial weakness of cranial nerve VII.[10,16] Abnormalities of the pinnae leading to malformed or prominent ears, as well as middle ear or inner ear irregularities were also observed.[14,15] Some exhibit renal malformations in the form of dysplastic, absent or multicystic kidneys, and

various other structural anomalies, along with vesicoureteral reflux.[17] Ectodermal abnormalities include premature hair graying, also known as poliosis; dysplastic nails and hypoplastic teeth.[18] Few individuals exhibit an abnormal location of thymus gland tissue on the skin of the neck, a condition referred to as dermal thymus.[19]

Significant differences exist in BOFS expression between families and even between members of the same family. After studying 41 BOFS cases from 30 families, Milunsky suggested that certain conditions must be satisfied in order to confirm the diagnosis.[3] But in 2011, formal proposals were made by a multidisciplinary group of specialists as the clinical diagnostic criteria for BOFS.[3] Without a family history of the disease, a clinical diagnosis of BOFS necessitates that an individual fulfils either all of the major criteria or two major criteria along with one minor criterion. The major diagnostic criteria for BOFS include branchial or cutaneous skin defects, ocular anomalies, and facial anomalies. The minor criteria consist presence of an affected first-degree relative who was independently diagnosed, and the presence of ectopic thymus.

Our baby presented with bilateral, cervical erythematous erosive skin defects, which were identified as one of the key diagnostic criteria for BOFS. She also had a distinct facial appearance in the form of bilateral complete cleft lip and palate, wide nasal bridge, telecanthus along with a low set posteriorly rotated, overfolded ears. Baby had nasolacrimal duct stenosis. Otoacoustic emission (OAE) of both ears was inconclusive. Thus she satisfied all the three major criteria and was clinically diagnosed as BOFS.

The TFAP2A gene, which is associated with BOFS, is located in the P24.3 region of chromosome 6. It has 437 amino acids and encodes the protein transcription factor AP-2-α, which regulates genes to contribute to the development of the eye, ear, face, trunk, and neural tube during embryonic life.[20] Abnormal development of these organs result due to mutations in the TFAP2A gene.[1] BOFS shows almost complete penetrance.[21] Forty to fifty percent of BOFS cases are inherited from the parents, while 50-60% are caused by entirely new causative variants. A thorough examination of individuals within a family exhibiting BOFS is essential to uncover subtle indicators such as early graying, fine hair on the neck, or heterochromia irides.[22]

The common differential diagnosis of BOFS include Branchiootorenal (BOR) syndrome; Coloboma, Heart defects, Choanal atresia, Retardation of growth and development, Genital and Ear abnormalities (CHARGE) syndrome; oral-facial-digital syndrome; cerebro-costo-mandibular syndrome; and cerebro-oculo-facio-skeletal syndrome.[17] Both BOFS and BOR may present with hearing loss, renal anomalies, and nasolacrimal duct stenosis; however, the unique craniofacial anomalies as well as ocular anomalies are exclusively documented in BOFS; and punctuate sinus tracts in neck, kidney and urinary tract abnormalities are associated with branchiootorenal (BOR) syndrome.[12,17] Our baby did not have renal anomalies and sinus tracts in neck, therefore the possibility of BOR syndrome was excluded. It is essential to differentiate BOFS from CHARGE syndrome and 22q11.2 deletion syndrome. All these conditions may manifest with eye, ear, and orofacial clefts; however, CHARGE syndrome is characterized by the absence of skin defects and BOFS facial features, while 22q11.2 deletion syndrome frequently presents with heart defects, but lacks BOFS facial features. Our

baby had branchial skin defects along with a peculiar face. Therefore CHARGE syndrome was not considered. Children with BOFS receive treatment through a multidisciplinary team that includes craniofacial specialists, plastic surgeons, otolaryngologists, and speech therapists. The overall prognosis of BOFS is favorable. However, there have been instances of multiple fetal deaths occurring in affected families.[16] Genetic testing enables a molecular diagnosis in cases where children exhibiting clinical signs of BOFS do not fulfill the established clinical diagnostic criteria. Families must have access to genetic counselling and prenatal diagnostics for the discovery of genetic mutations.

Conclusion

Since BOFS shares characteristics with other branchial arch syndromes, it is a complex syndrome that necessitates a high index of suspicion for diagnosis. Our understanding of its etiology and pathogenesis has improved due to developments in molecular genetics, which has made family planning and diagnosis more precise. For impacted individuals to have better results, early intervention and interdisciplinary care coordination are essential. Genetic counselling plays a crucial role for families impacted by the heritable nature of the disorder.

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