Indian Journal of Genetics and Molecular Research
Volume 1 Number 2, July - December 2012

Brachio-Otic Syndrome

Sunil Mhaske*, MD; Ramesh B. Kothari, Sandip Deokate***, MD; Ram Sethi****, DCH; Pavan Suryawanshi*****, DCH; NIshad Patil******, MD; Rahul Maski*******, DCH; Suraj Nair********

Abstract

Branchio-Otic syndrome is a rare autosomal dominant disorder characterized by syndromic association of branchial cysts or fistulae along with external, middle & inner ear malformations.

Keywords: Brachio-Otic Syndrome; BOS1; BOS2; BOS3; EYA1; Hearing loss; SIX1.

Introduction

Branchio-otic syndrome (BOS) is an autosomal dominant disorder clinically diagnosed by (1) at least three major criteria including branchial anomalies, deafness, preauricular pits, (2) two major criteria, and at least two minor criteria including external ear anomalies, middle ear anomalies, inner ear anomalies, preauricular tags, facial asymmetry, and palate abnormalities, or (3) one major criterion and an affected first-degree relative who meets the criteria for BOS syndrome. A similar syndrome associated with renal anomalies is called as Brachio-Otic-Renal syndrome.

Case Summary

An eight year old girl was admitted in our hospital with complaints of multiple swellings in both pre-auricular regions since birth and hearing loss since last 6 months. The swellings were small in size as like wheat grains initially, which then gradually increased over period to present size of almonds. The swellings were painless and without any signs of inflammation. Parents also noticed her hearing loss about 6 months back which was gradually progressing. Parents gave history of repeated attacks of upper respiratory tract infection. There was no any history of earache, ear discharge, fever, etc. Also parents didn't give any history of trauma or operative procedure over external ears. She was operated for cleft lip four years back. Her parents had family history of consanguineous marriage. She was a full term normal hospital delivery with good cry and adequate weight at birth. Our case was first issue of parents out of their four siblings (3 females and a male); none of them having any congenital anomaly.

On examination she was an average built girl with mild pallor. All vital parameters were within normal limits as per her age. On head to toe examination, she was having a pre-auricular pit on left side. Also she was having bilateral multiple pre-auricular tags. On left side, there were three pre-auricular tags of sizes 1.5*0.75 cm, 1*0.5 cm and 0.5*0.5 cm on right side; a single pre-auricular tag of size 1.5*0.75 cm was present. No any other externally detectable anomaly was present over body. Systemic examination also was

Author's Affiliation: *Prof. and Head, Dept. Of Paediatrics, P.D.V.V.P.F's Medical College, Ahmednagar (M.S.), **Asst. Professor, Dept. Of Paediatrics, P.D.V.V.P.F's Medical College, Ahmednagar (M.S.), ***Student, Dept. Of Paediatrics, P.D.V.V.P.F's Medical College, Ahmednagar (M.S.), ****Student, Dept. Of Paediatrics, P.D.V.V.P.F's Medical College, Ahmednagar (M.S.), *****Student, Dept. Of Paediatrics, P.D.V.V.P.F's Medical College, Ahmednagar (M.S.), ******Student, Dept. Of Paediatrics, P.D.V.V.P.F's Medical College, Ahmednagar (M.S.), *******Student, Dept. Of Paediatrics, P.D.V.V.P.F's Medical College, Ahmednagar (M.S.), ********Intern, Dept. Of Paediatrics, P.D.V.V.P.F's Medical College, Ahmednagar (M.S.)

Corresponding Author: Dr. Sunil N. Mhaske,MD Paediatrics, Professor and Head, Dept. Of Paediatrics, P.D.V.V.P.F. Medical College, Ahmednagar(M.S.).

E-mail: sunilmhaske@rocketmail.com

Table: Clinical features

Clinical features	BOR syndrome	BOS	Our patient
Branchial cleft fistulas	+	+	-
Renal anomalies	+	-	-
Lacrimal duct stenosis	+	+	-
Hearing impairment	+	+	+
Ear defect	+	+	-
Preauricular pits	+	+	+
Preauricular tag	+	+	+
Facial asymmetry	+	+	+
Development delay	+	+	+
Microsomia	+	+	-
Impaired speech	+	+	+
Cleft lip/palate	+	+	+
Tracheoesophageal fistula	+	+	-
Heart defect	+	+	-
Genito-urinary anomalies	+	-	-
Irregular skull shape	+	+	+
Mandibular hypoplasia	+	+	+
Micrognathia	+	+	+
Recessed jaw	+	+	+
Facial nerve paralysis	+	-	-
Central nervous system defects	+	-	-

within normal limits. Opinion from ENT department was taken which, after audiometric test, stated sensory neural hearing loss from left ear.

Following investigations were done.

Hb – 10.7 gm%; Total leukocyte count – 7500/cmm; (N-49, L-41, E-08, M-02, B-00); Platelet count – 2.34 lacs/cmm; ESR (Westergren) – 10 mm at the end of one hour; Blood urea – 19 mg%; Sr. Creatinine – 0.8 mg/dl; Sr. Sodium – 136 mmol/L; Sr. Potassium – 3.8 mmol/L.

Fig 1: Pre-auricular pit

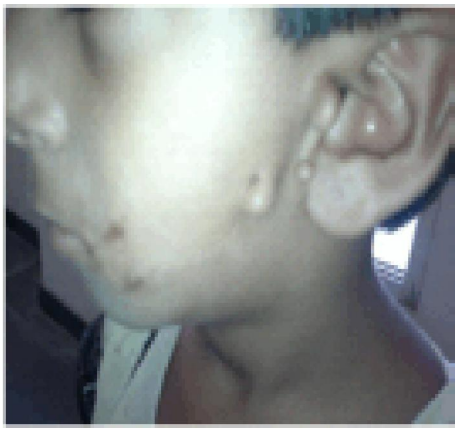
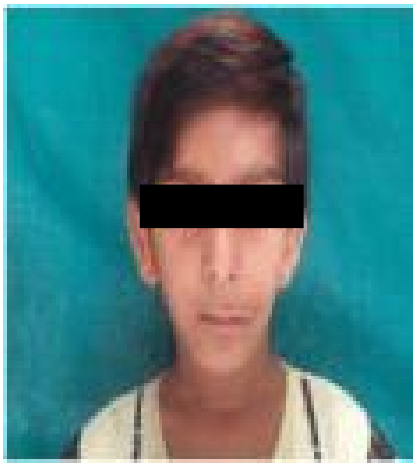


Fig 2: Facial asymmetry



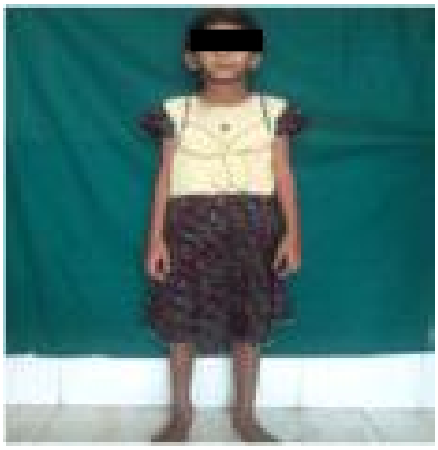
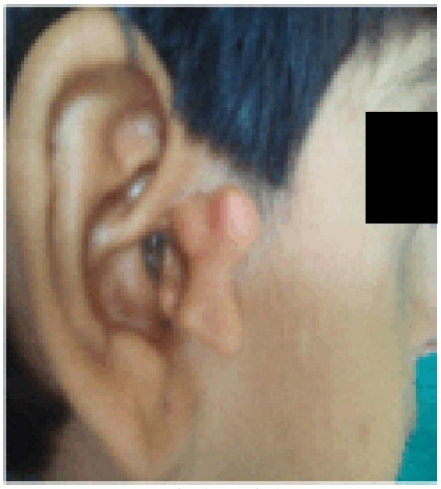
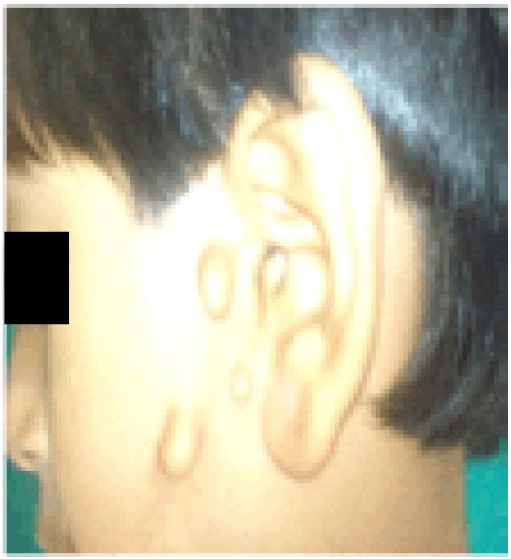


Figure 3: Pre-auricular tags

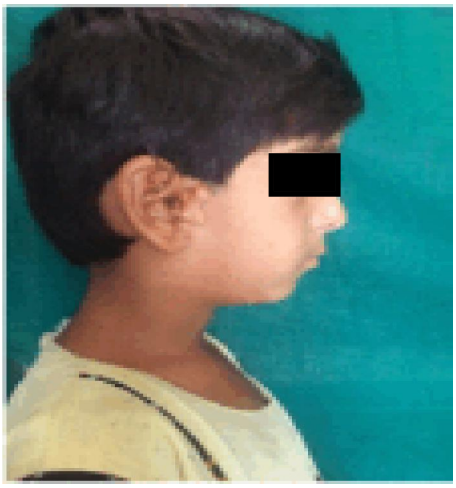


Right side

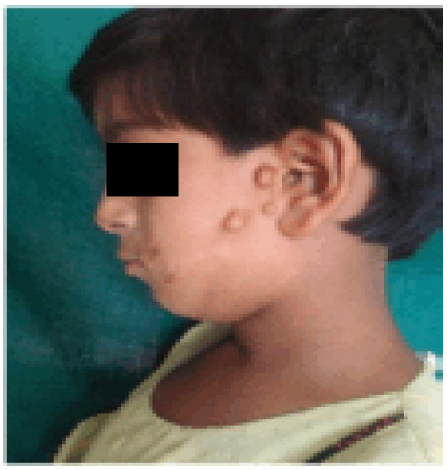


Left side

Figure 4: Recessed Jaw



Right lateral



Left lateral

Ultrasonography of abdomen and pelvis shows findings within normal limits.

X-ray chest (PA view) didn't show any abnormality.

CT Brain (Plain) was also within normal limits.

Patient was discharged and was advised follow up after 05 days as per surgery appointment.

Discussion

Branchio-otic syndrome (BOS) is a genetic condition that typically disrupts the development of tissues in the neck and causes malformations of the ears. The signs and symptoms of this condition can vary, however.

"Branchio-" refers to the second branchial arch, which is a structure in the developing embryo that gives rise to tissues in the front and side of the neck. In people with branchio-otic syndrome, abnormal development of the second branchial arch can result in the formation of masses in the neck called branchial cleft cysts. In some people, abnormal connections called fistulae form passages between these cysts and the surface of the neck. Fistulae can also develop between the skin of the neck and the throat, near the tonsils. Branchial cleft cysts and fistulae can cause medical problems if they become infected.

"Otic-" refers to the ear; most people with

branchio-otic syndrome have hearing loss and other ear abnormalities. The hearing loss is known as sensorineural deafness if it is caused by changes in the inner ear, and conductive deafness if it is caused by changes in the middle ear. Branchio-otic syndrome can also involve hearing loss that results from changes in both the inner ear and the middle ear, which is called mixed hearing loss. Other ear abnormalities associated with branchio-otic syndrome include malformations of the inner ear or middle ear and abnormally shaped outer ears (pinnae). Some affected people also have tiny holes in the skin (preauricular pits) or small flaps of skin (preauricular tags) just in front of the ear.

When the above clinical features are associated with renal anomalies is called as Brachiootorenal (BOR) syndrome. In that, "Renal" refers to the abnormalities of kidney structure and function. These abnormalities range from mild to severe and can affect one or both kidneys. In some cases, end-stage renal disease (ESRD) develops later in life. This serious condition occurs when the kidneys become unable to filter fluids and waste products from the body effectively.

Branchiootorenal syndrome (also called as Melnick-Fraser syndrome) affects about 1 in 40,000 people.

Pre-auricular tags are also found in oculo-auriculovertebral syndrome (OAVS) , also known as Goldenhar's syndrome. As ocular and vertebral components are not present in this case, so it is ruled out.

Molecular Biology

Branchio-otic syndrome (BOS) is an autosomal dominant disorder caused by mutations in the EYA1 gene, a human homolog of the Drosophila eyes absent gene (Eya). A second locus for BOS was localized to chromosome 1q31. Recently, a third gene locus for BOS to 14q21.3–q24.3 by linkage study is mapped and designated it as branchiootic syndrome 3 (BOS3). This chromosomal region contains the SIX1, SIX4, SIX6 gene cluster, the products of which are known to act in a developmental pathway of the EYA genes and OTX2. Mutations in SIX1 have been reported in patients with BOS, thus identifying SIX1 as a gene causing BOS.

References

1. Schwartz CE, Smith RJ. Branchio-oto-renal syndrome: The mutation spectrum in EYA1 and its phenotypic consequences. *Hum Mutat*. 2004; 23:582–589.
2. Fraser FC, Ling D, Clogg D, Nogrady B. Genetic aspects of the BOR syndrome—Branchial fistulas, ear pits, hearing loss,and renal anomalies. *Am J Med Genet*. 1978; 2: 241–252.
3. Hone SW, Smith RJ. Genetics of hearing impairment. *Semin Neonatol*. 2001; 6: 531–541.
4. Melnick M, Bixler D, Silk K, Yune H, Nance WE. Autosomal dominant branchio-oto-renal dysplasia. *Birth Defects Orig Artic Ser*. 1975; 11: 121–128.
5. Ruf RG, Xu PX, Silvius D, Otto EA, Beekmann F, Muerb UT, Kumar S, Neuhaus TJ, Kemper MJ, Raymond RM Jr, Brophy PD, Berkman J, GattasM, Hyland V, Ruf EM, Schwartz C, Chang EH, Smith RJ, Stratakis CA, WeilD, Petit C, Hildebrandt F. SIX1 mutations cause branchio-oto-renal syndrome by disruption of EYA1-SIX1-DNA complexes. *ProcNatlAcad Sci.* 2004; 101: 8090–8095.
6. Sensi A, Cocchi G, Martini A, Garani G, Trevisi P, Calzolari E. Branchio-oto (BO) syndrome and oculo-auriculo-vertebral phenotype: Overlapping clinical findings in a child from a BO family. *Clin Genet.* 1996; 49:300–302.
7. Verloes A, Seret N, Bernier V, Gonzales M, Herens C, Koulischer L. Branchial arch anomalies in trisomy 18. *Ann Genet.* 1991; 34: 22–24.
8. Vincent C, Kalatzis V, Abdelhak S, Chaib H, Compain S, Helias J, Vaneecloo FM, Petit C. BOR and BO syndromes are allelic defects of EYA1. *Eur J Hum Genet.* 1997; 5:242–246.