



## Branchiootic Syndrome in a Male Kid - A Rare Case Presentation with Clinical and Imaging Report

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### Abstract

Branchio-Oto-Renal (BOR) syndrome is a clinically heterogeneous autosomal dominant form of syndromic hearing loss characterized by variable hearing impairment, malformations of the pinnae, the presence of branchial arch remnants, and various renal abnormalities. BOR syndrome is caused by mutations in *EYA1* and *SIX1* which are critical to organogenesis and are expressed together in developing otic, branchial and renal tissue. Branchio-Otic (BO) syndrome comprises branchial fistulas and preauricular pits, but lacks renal anomalies. We present a rare case report of Branchio-otic syndrome in a 5 year old kid.

**Keywords:** Branchio-otic syndrome; Branchio-oto-renal syndrome; *EYA1* gene; *SIX1* gene; Chromosomal abnormality

### Introduction

Branchio-Oto-Renal (BOR) syndrome is a clinically heterogeneous autosomal dominant form of syndromic hearing loss characterized by variable hearing impairment, malformations of the pinnae, branchial arch defects, and various renal abnormalities [1,2]. BOR syndrome is caused by mutations in *EYA1* and *SIX1* which are critical to organogenesis and are expressed together in developing otic, branchial and renal tissue. Branchio-Otic (BO) syndrome comprises branchial fistulas and preauricular pits, but lacks renal anomalies [2].

The clinical course of BOR/BO syndrome shows variable expressivity with a high inter and interfamilial variability [3]. Most of the described cases results from mutations in the *EYA1* gene, which is located in 8q13.3 and encodes a member of the drosophila Eyes Absent (EYA) family of proteins [1-3]. *EYA1* was reported to act as a transcriptional coactivator, as a phosphatase and also form a complex with SIX proteins [4,5]. This complex leads to a coactivation of SIX transcription factors which are essential for normal development of several tissues and organs including the second branchial arch, ears, eyes, and kidneys [6,7].

Up to date, more than 110 different mutations in the *EYA1* gene (Molecular Otolaryngology Research Laboratory, Pendred/BOR homepage, <http://www.healthcare.uiowa.edu/labs/pendredandbor/>) have been described to be associated with BOR/BO syndrome; they are randomly scattered over the entire gene Wang et al. [8]. Few mutations have also been found in genes encoding the *SIX1* and *SIX5* proteins Krug et al. [5].

We present a rare case report of Branchio-otic syndrome in a 5 year old male kid.

### Case Presentation

A 5 year old male patient came to the department of oral medicine and radiology, with a chief complaint of decayed tooth since one week and delayed speech since childhood. Patient's mother accompanied the patient and guided throughout the examination. Further history revealed that the patient was a premature baby and had impaired speech not associated with hearing impairment, normal eating habits, normal food and sleep pattern. Patient had education from a special school at the age of 2, followed by which patient was unable to cooperate with other special students, and later on patient was shifted to normal school. History of first generation consanguineous marriage for patient's parents. Patient was initially diagnosed as bilateral congenitally absent pinna at birth by a local doctor. (Figure 1a, 1b) Audiogram at 5 months revealed progressive sensorineural hearing loss and renal ultrasound was normal.

On general examination, patient was conscious but was not responsive to verbal commands. Extraoral examination revealed, asymmetric face with frontal bossing, a bulbous nose tip, a small

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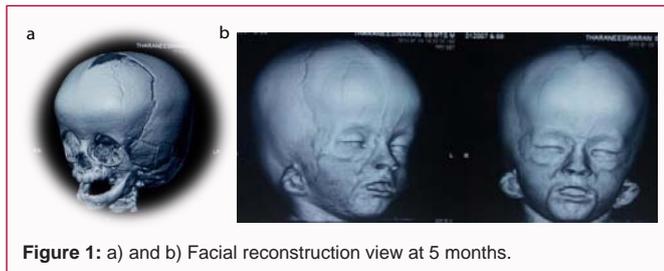


Figure 1: a) and b) Facial reconstruction view at 5 months.

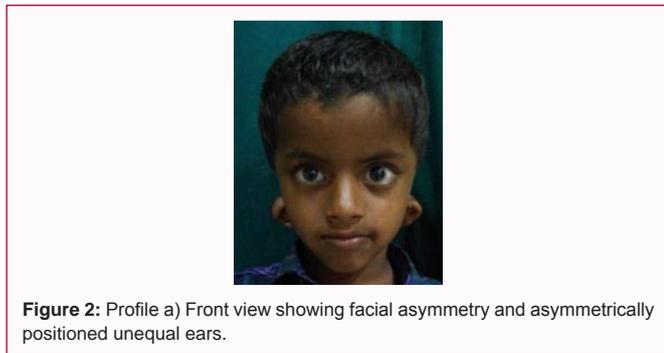


Figure 2: Profile a) Front view showing facial asymmetry and asymmetrically positioned unequal ears.

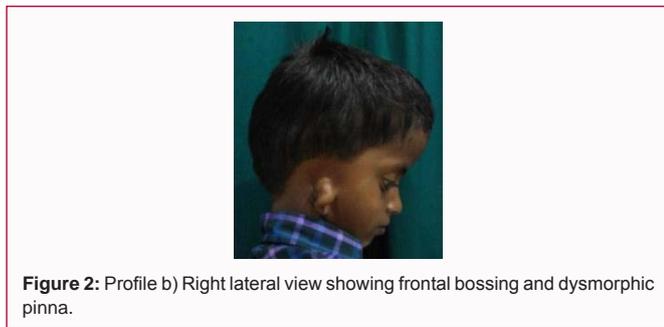


Figure 2: Profile b) Right lateral view showing frontal bossing and dysmorphic pinna.



Figure 2: Profile c) Left lateral view showing malpositioning and dysmorphic pinna.

upper lip, both the auricles appeared deformed and dysmorphic and are positioned at lower level below normal (asymmetrically positioned unequal ears). Intercanthal distance appeared to be within the normal range with broad nasal bridge. Deficient mid face region. No abnormal lump or swelling was evident on further palpation (Figure 2a-2c). Intraoral examination revealed decayed tooth 65. With all the positive findings a provisional diagnosis of congenital anacusis was made. Differential diagnosis includes branchiootic syndrome, branchiootic renal syndrome and congenital bilateral microtia. Further investigations were made under parent’s consent. Haematological investigations were under normal levels. Computed tomography revealed significantly narrowed bilateral external auditory canal (bony and membranous part) with soft tissue density within it. Both auricles appear deformed and dysmorphic. Bilateral middle ear cavity appeared smaller in size, with dysmorphic and

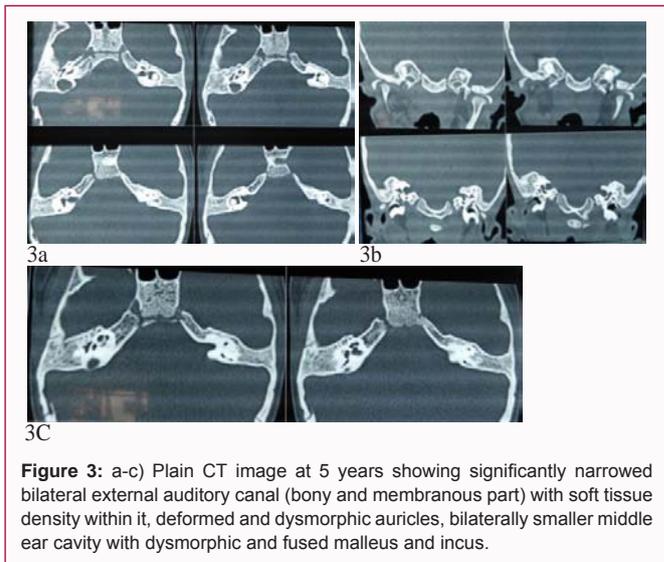


Figure 3: a-c) Plain CT image at 5 years showing significantly narrowed bilateral external auditory canal (bony and membranous part) with soft tissue density within it, deformed and dysmorphic auricles, bilaterally smaller middle ear cavity with dysmorphic and fused malleus and incus.

fused malleus and incus (Figure 3a-3c). Bilateral facial nerve showed aberrant course. Bilateral inner ear structures appear normal. Final diagnosis of branchiootic syndrome was made. Patient was further referred to a speech therapist and a pedodontist for continuous assessments and management.

**Discussion**

In this article, we present the clinical and imaging data of a male kid with signs of BO syndrome. According to the improved clinical diagnostic criteria which have been introduced by Chang et al. 2004, there are 4 major criteria to diagnose BOR syndrome, i.e. branchial anomalies, deafness/hearing loss, preauricular pits, and renal anomalies, as well as several minor criteria, such as anomalies of the external, middle or inner ear, preauricular tags, facial asymmetry, and palate abnormalities. Our patient displayed one major criterion namely deafness/hearing loss and two minor criteria namely facial asymmetry, anomalies of external and middle ear. Our patient meets the diagnostic criteria of BO syndrome due to lack of renal abnormalities. Unfortunately, we don’t have the detailed information on the molecular genetic testing.

Genetically most families with the BOR syndrome have genetic mutations on the *EYA1* gene on chromosome 8q13.3. At the same time, some BO families also show linkage to the same *EYA1* gene on chromosome 8q13.3, suggesting that the BOR and BO syndromes may be allelic phenotypes of mutations in this single gene. Some BOR families and some BO families however do not link to this gene, indicating genetic heterogeneity. A second gene locus is currently being looked for [9,10]. The *EYA1* gene is expressed very clearly between the 4<sup>th</sup> and 6<sup>th</sup> weeks of human development. Deafness relates to abnormalities in the three ossicles of the middle ear derived from the first and second branchial arches, while the branchial fistulae relate to abnormalities of the second, third and fourth arches. In the embryonic human kidney the *EYA1* gene is expressed strongly, and in the BOR syndrome there is an indicative fault between the ureteric bud branches into the renal parenchyma [11].

**Conclusion**

Branchio-otic (BO) syndrome comprises branchial fistulas and preauricular pits, but lacks renal anomalies. Hence, early diagnosis and surgical correction should be done involving a team of specialists;

geneticists, audiologists, speech pathologists, physicians, plastic surgeons, maxillofacial surgeons, pedodontist, prosthodontists and orthodontists to improve esthetics and prognosis, thus improving the quality of life.

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