

# A Rare Case Report - Bohring Opitz Syndrome

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**Abstract:** *Bohring- Opitz syndrome (BOS) first described by Bohring et al in 1999, is a rare congenital disorder of unknown etiology. He described 4 cases with characteristic features (1). This syndrome is characterized by distinctive facial features and posture, growth failure, variable intellectual disability, and variable anomalies (2). The diagnosis of BOS is established in a proband with suggestive clinical features and/or identification of constitutional heterozygous pathogenic variant in ACXL1 by molecular genetic testing. We hereby present a case which phenotypically matches the findings of this syndrome.*

**Keywords:** BOS-Bohring opitz syndrome

## 1. Introduction

Bohring- Opitz syndrome (BOS) first described by Bohring et al in 1999, is a rare congenital disorder of unknown etiology. He described 4 cases with characteristic features(1). This syndrome is characterized by distinctive facial features and posture, growth failure, variable intellectual disability, and variable anomalies(2). The diagnosis of BOS is established in a proband with suggestive clinical features and/or identification of constitutional heterozygous pathogenic variant in ACXL1 by molecular genetic testing. We hereby present a case which phenotypically matches the findings of this syndrome.

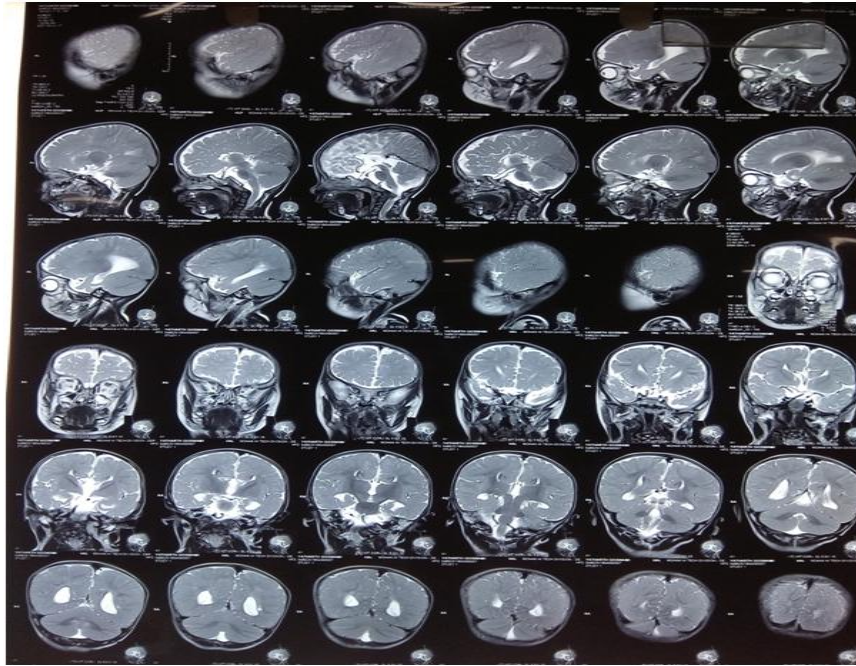
## 2. Case Report

A 12-month-old male child presented to our department with chief complaints of not achieving developmental milestones as per age, feeding difficulties since birth. He was post-term, appropriate for gestational age male child born to a 24-year-old primigravida mother out of non-consanguineous marriage via vaginal route with a significant history of polyhydramnios detected in last USG scan. Birth weight was 2kg. Since birth the baby had feeding difficulties and was diagnosed with cleft-palate. Also child had recurrent history of lower respiratory tract infections every 2-3 months for which child had to be admitted and receive nebulisations. Mother noticed neck is tilted towards right side since 9 months of age. Development wise child was delayed in all 4

milestones motor > mental, with DQ of ~90% in social/mental milestones and ~65% in gross-motor, fine-motor and language milestones. Also, history of early hand preference of right side with reduced activity of left upper and lower limb noted since 4-5 months of age.

**Significant findings on general examination were(1) hypertelorism, (2)Depressed nasal bridge, (3) bullous nose, (4) long philtrum, (5) inverted m slope of upper lip, (6) cleft palate, (7) retrognathia, (8) malformed ears, (9)plagiocephaly, (10) triangular face, (11)Clinodactyly, syndactyly in both feet and (12) neuro-cutaneous marker present at back (Café-au-lait spots and Nevus flammeus). On genital examination hypospadias was present. BERA was suggestive of (13) moderate hearing loss in right ear and moderate to severe hearing loss in left ear. MRI brain reveals (14) complete agenesis of corpus callosum with colpocephaly. X ray cervical spine showed altered cervical curvature. 2D-echo was done to rule out cardiac abnormality. Confirmatory genetic mutation testing (ASXL 1 gene mutation) could not be done due to financial constraints.**

Patient with this disorder need a multidisciplinary approach. Occupational therapy and physiotherapy was started to improve activity of daily living and to prevent contractures. Paediatric surgery opinion for cleft palate and hypospadias was taken and surgery was advised. Child is on regular follow-up now.



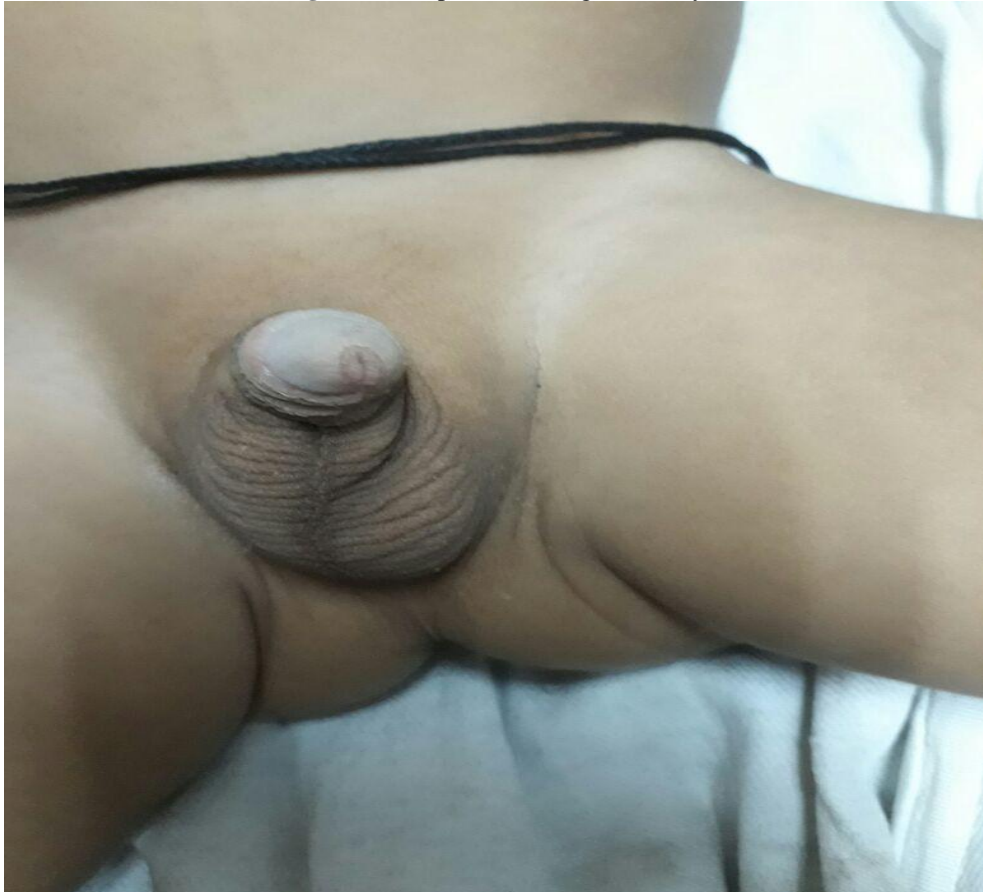
**Figure 1:** MRI brain showing colpocephaly with complete agenesis of corpus callosum



**Figure 2:** Altered spinal curvature with atlantoaxial dislocation



**Figure 3:** Ear pinna showing deformity



**Figure 4:** Genitalia showing hypospadias



**Figure 5:** Syndactyly

Facial features suggestive of (1) hypertelorism, (2) depressed nasal bridge, (3) bullous nose, (4) long philtrum, (5) inverted m slope of upper lip, (6) cleft palate, (7) retrognathia, (8) malformed ears, (9) plagiocephaly, (10) triangular face.

### Discussion

BOS has a 40% infant mortality rate and many patients die before 5 years of age<sup>(3)</sup>. Mortality is usually due to recurrent infections, bradycardia or respiratory distress /failure<sup>(3-4)</sup>

Hastings, et al<sup>(3)</sup> proposed a set of diagnostic criteria in which 7 out of 10 features must be present: typical facial appearance (trigonocephaly/prominent metopic ridge, retrognathia, prominent eyes with hypoplastic supraorbital ridges, up-slanting palpebral fissures, depressed nasal bridge, anteverted nares, low-set and posteriorly rotated ears, palatal abnormalities and broad alveolar ridges, flammeus

nevus, low anterior hairline), microcephaly, IUGR and short stature, joint abnormalities, abnormal tone, severe/profound developmental delay, susceptibility to infections, feeding difficulties, and high infant mortality. Other characteristics described in other reports include hirsutism, exophthalmos, and low frontal and temporal hairline. Systemic manifestations have also been described, including gastrointestinal, ophthalmologic, cerebral and cardiac anomalies. Of the latter, the cardiac defects specifically described in the literature include: pulmonary hypertension, biventricular hypertrophy, patent ductus arteriosus (PDA), patent foramen ovale (PFO), dysplastic pulmonary valve with mild stenosis, atrial septal defect (ASD), and perimembranous ventricular septal defect (VSD<sup>(3-6)</sup>). Given the small number of reported cases of BOS, it is difficult to establish the significance of other abnormalities as unique to BOS or as manifestations of concomitant conditions.

The mechanism and inheritance pattern of BOS remain unclear, however de novo heterozygous frame shift or nonsense mutations in ASXL1 gene have been identified in ten of cases of BOS by different authors<sup>(4, 7, 8)</sup>. The ASXL1 gene has been associated with both activation and silencing of HOX genes, which are involved in body segment formation, chromatin remodelling, as well as having oncogene properties<sup>(9, 10)</sup>. Interestingly, not all patients with BOS have abnormalities in their ASXL1 gene, suggesting the possibility of multiple etiologies<sup>(3, 4)</sup>. Mutations of the ASXL3 gene, which is part of the same gene family as ASXL1, have been described in five distinct cases<sup>(11, 12)</sup>. While these patients had similar characteristics as those found in patients with BOS, they did not fully exhibit the specific characteristics defined for BOS<sup>(5)</sup>.

Treatment of BOS is supportive and often includes a gastrostomy tube (G-tube) for feedings and mechanical ventilation in the neonatal period. As patients survive through early childhood, problems such as feeding difficulties and recurrent infections become less significant. Despite early intervention, profound intellectual delay tends to persist, although there is case by case variability in severity<sup>(3)</sup>. Children who survive into their teenage years and adulthood still face significant morbidity despite decreased mortality.

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