Bohring Opitz Syndrome: A case of a rare genetic disorder

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ABSTRACT

Bohring-Opitz syndrome (BOS) is a rare genetic disorder, characterized by feeding difficulties, developmental delay, microcephaly, micrognathia, limb anomalies, and typical phenotypic facial features. The cause of the syndrome is identified as *de novo* heterogeneous mutations in the ASXL1 gene, but other mutations have been described in some patients. Most patients die in early childhood due to infections and comorbidities. As molecular confirmation by genetic studies is not always possible, this syndrome is diagnosed on the basis of distinctive clinical features. We report a case of the 6-month-old male child having gastroesophageal reflux and physical features of microcephaly, sloping forehead, sparse hair, craniosynostosis, telecanthus**,** hypertelorism**,** prominent eyes, posteriorly rotated ears, high-arched palate, micrognathia, pes planus, and typical BOS posture. A multidisciplinary approach is required for managing these patients.

Key words: *Bohring-Opitz syndrome, Dysmorphism, Genetic mutation*

Bohring-Opitz syndrome (BOS) is a rare congenital disorder of unknown etiology which was first described in 1999 by Bohring *et al*. and described 4 cases with characteristic features [1]. Diagnostic criteria were defined later based on the phenotypic manifestations. The characteristic features of this condition are typical facial appearance, microcephaly, palatal abnormalities, facial nevus flammeus, short stature, joint abnormalities, abnormal tone, failure to thrive, and severe to profound developmental delay. The patients present with repeated respiratory infections, feeding difficulties, and failure to thrive. These patients require repeated hospitalization and infant mortality is high. Approximately 32 cases have been reported worldwide. Molecular analysis, done in some patients, has demonstrated mutations in ASXL1 gene while mutations of ASXL3 gene were identified in few patients. We report a case of the 6-month-old male child having gastroesophageal reflux (GER) and clinical features of BOS.

CASE REPORT

A 6-month-old male child presented to the department with a chief complaint of failure to thrive and a history of recurrent vomiting since the age of 1 month. He was born of a third degree consanguineous marriage to a 24-year-old primigravida mother by full-term normal delivery. His birth weight was 2.8 kg. He was admitted to neonatal intensive care unit on day 3 of life for neonatal hyperbilirubinemia and hypocalcemic convulsions. At 1 month of age, he was treated with a splint for a foot deformity. He had severe feeding intolerance and recurrent episodes of non-bilious vomiting due to GER disease. The baby was repeatedly hospitalized for these complaints. Written informed consent was obtained from the parents for taking the photographs.

On clinical examination, his length was 56 cm and weight was 2.9 kg. The weight for length z score was <−3 standard deviation (SD) suggestive of severe failure to thrive. Head circumference was 38.5 cm with a Z-score <−3 SD suggestive of microcephaly. On head to toe examination, dysmorphism was noted. His craniofacial features included microcephaly, sloping forehead, sparse hair, craniosynostosis, telecanthus, prominent eyes, posteriorly rotated ears, high-arched palate, micrognathia, and pes planus (Fig. 1). He had a characteristic BOS posture, i.e., shoulder being held externally rotated and adducted, elbows flexed, and wrists flexed [2]. Neurological examination revealed truncal hypotonia with hypertonic limbs. Ophthalmological examination was normal. His developmental quotient assessed by Developmental Assessment Scales for Indian Infants showed a motor score of 23±7 and a mental score of 39±2, suggestive of profound developmental delay.

On investigation, magnetic resonance imaging (MRI) brain showed thinned out corpus callosum and periventricular white matter changes. Barium swallow showed Grade 2 GER (Fig. 2). Hemogram revealed nutritional anemia. Serum cholesterol was normal, i.e., 115 mg/dl. Chromosomal analysis showed 46 XY which was normal. TORCH titers and metabolic screening were negative. Ultrasonography of the abdomen was normal. Confirmatory genetic mutation testing (ASXL1 gene mutation) was not done due to financial constraints.

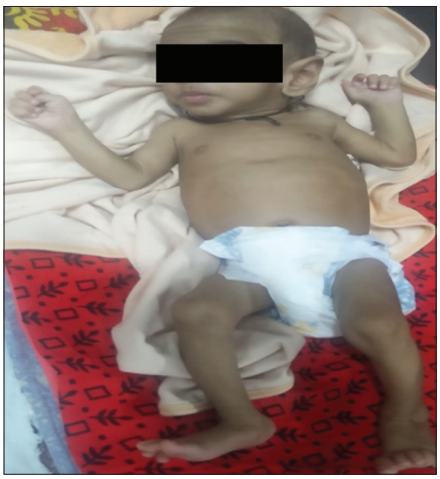

Figure 1: Patient with typical Bohring-Opitz syndrome posture

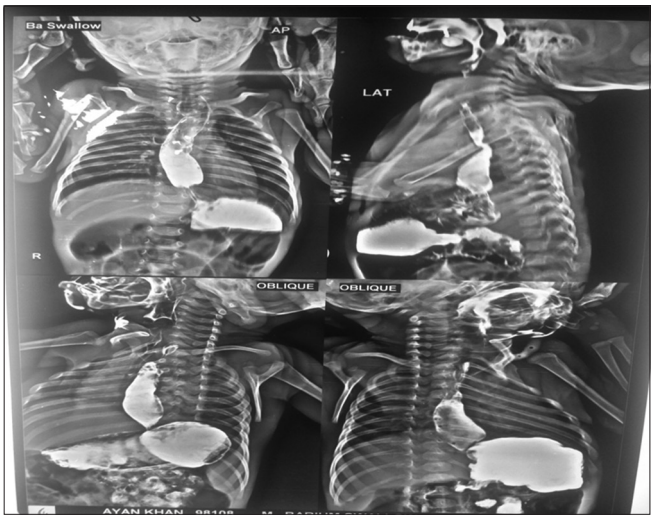

Figure 2: Barium swallow showing Grade II gastroesophageal reflux

This patient was treated with antibiotics for infections. For GER, thickening of feeds, positioning, and proton-pump inhibitors were started. Vitamin supplementations were also given. Patients with this disorder need a multidisciplinary approach as it affects the individuals physically, medically, cognitively, behaviorally, and psychologically. Occupational therapy and physiotherapy were started to improve the activity of daily living and range of motion and to prevent contractures. The child is on regular follow-up and now, he is 23-month and has started gaining weight. His present weight is 7.61 kg and length is 75 cm (weight for length z score is at −3 SD). His head circumference is 40 cm (z score <−3 SD). TThe child had a flexion deformity with limitation of movements which is improving with physiotherapy. Now, he is able to sit with support and has also started recognising parents. He is tolerating feeds well and the frequency of vomiting has decreased significantly.

DISCUSSION

There are approximately 32 cases of BOS reported worldwide [3]. Our patient has characteristic features of this syndrome and associated comorbidities. Molecular diagnosis, i.e., ASXL1 gene mutation is a confirmatory test, but it is not available at most of the centers, so diagnosis is mainly based on phenotypic characters [4]. The clinical features of this syndrome are similar to Smith–Lemli–Opitz syndrome, desmosterolosis, and lathosterolosis which are disorders of cholesterol synthesis.

All the cases (100%) present with feeding difficulties, severe to a profound learning disability, prominent eyes, microcephaly, and the typical BOS posture. Our patient had all these features. Low hairline with thick hairs is present in around 90% of BOS cases and 10% of cases can have a normal hairline. In the present case, the patient had a normal hairline. Majority of the patients described in literature required gastrostomy for feeding. Our patient was managed with medications and appropriate feeding advice. Around 80–90% of cases present with intrauterine growth restriction, trigonocephaly, low set ears, hypotonia, and brain abnormalities [2]. Around 70% of patients have structural brain abnormalities such as ventriculomegaly, generalized atrophy involving the corpus callosum and brainstem, and delayed myelination. MRI brain of our patient showed thinned out corpus callosum. This was consistent with MRI brain findings in other patients studied by Magini *et al*. [2] and Visayaragawan *et al*. [5]. Contractures are common and congenital dislocations may be present. Cardiac and ophthalmologic manifestations are present in 50% of cases. Ophthalmic features include strabismus, retinal, and anterior chamber abnormalities and myopia.

The molecular basis of BOS was recently identified, making molecular diagnosis possible [3]. For almost 50% of cases that meet the clinical criteria for BOS, *de novo* frameshift and nonsense mutations in the ASXL1 gene have been detected. Bainbridge *et al*. identified four individuals with *de novo* truncation mutations in a related gene, ASXL3 (chromosome 18) [6]. Of note, ASXL3 is in the same gene family as ASXL1 and mutations in ASXL3 are known to be associated with a disorder that is similar to BOS. Majority of the reported cases are inherited sporadically, although Greenhalgh *et al*. described a brother and sister with BOS, suggesting the possibility of autosomal recessive inheritance or germline mosaicism [7]. Only 11 cases of clinically diagnosed BOS have been confirmed by molecular analysis of the ASXL1 gene [5,8].

The mortality in this syndrome is usually high, due to the presence of various infections. If the child survives the early childhood period, then the chance of mortality is decreased due to the improvement of feeding difficulties. Parental education and training regarding feeding and care of the child are important in management and outcome of a child diagnosed with BOS.

CONCLUSION

BOS is a rare and difficult to diagnose disorder. Its diagnosis is mainly based on the phenotypic characters. A multidisciplinary approach can improve the outcome of the patient as in our case.

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