Johanson - Blizzard Syndrome

Sangeetha S[1], Gangavaram Kavya[2], G. Roopashri[3], Maria Priscilla David[4]

ABSTRACT

Introduction: Johanson-Blizzard syndrome (JBS) is a rare autosomal recessive disease characterized by exocrine pancreatic insufficiency, hypoplastic or aplastic nasal alae, cutis aplasia on the scalp, and other features including developmental delay, failure to thrive, hearing loss, mental retardation, hypothyroidism, dental abnormalities, and anomalies in cardiac and genitourinary systems.

Case report: This paper presents a case of a 7 year old patient with Johanson-Blizzard syndrome and emphasizes the importance of diagnosing this syndrome for providing appropriate treatment for these patients.

Conclusion: This report highlights the need for a multidisciplinary approach and management of specific symptoms and features of the disorder.

Keywords: Johanson-Blizzard Syndrome, Alae Nasi Aplasia, Anemia, Cutis Aplasia, Exocrine Pancreatic Insufficiency.

INTRODUCTION

In 1971 Johanson and Blizzard reported a new syndrome in three unrelated girls called Johanson Blizzard syndrome (JBS). It is a rare autosomal recessive disorder characterized by exocrine pancreatic insufficiency, hypo plastic or absent alae nasi, ectodermal scalp defect, microcephaly, congenital deafness and growth retardation. Since then approximately only 60 cases were related in the literature across the world[1] and 2 cases in India till date[2]. Morris and Fisher in 1967 and Townes in 1969 explained children with this syndrome as examples of trypsinogen deficiency disease. Townes and White further reviewed the patient reported in 1969 and described the presence of additional features which confirmed the diagnosis of the Johanson-Blizzard syndrome[6]. We report a male patient with this rare syndrome.

CASE REPORT

A 7-year-old male patient reported with his parents to the Department of Oral Medicine and Radiology with the complaint of missing teeth in the upper and lower front teeth region since 2 years. A thorough review of the family history revealed that he is the 4th child of second degree consanguineous married parents. On further investigation, the parents reported that their 1st child is 10 year old female healthy and alive, the 2nd conception resulted in intra uterine death at 8 months, the 3rd child was born in good clinical condition, weighed 2.4kg and cried immediately after birth but had distinct facies that included a small beak-like nose with hypo plastic alae nasi, imperforate anus and was suspected/diagnosed of JBS. Reconstruction of imperforate anus was done on the 3rd day but he had persistent /prolonged diarrhoea with recurrent hospital admissions and succumbed to the disease at 3 months of age due to overwhelming sepsis. The birth history of the present patient was uneventful. He weighed 2.8 kg, had head circumference of 31 cm and length of 44 cm. Baby was also found to have imperforate anus and transverse colostomy was done on the 2nd day of life. Persistence of loose stools for which serum amylase and lipase pancreatic enzyme levels were evaluated and found to be low. The patient was put on fat soluble vitamins, pancreatic enzyme replacement therapy for pancreatic exocrine insufficiency. There was poor weight gain, severe anaemia, anasarca secondary to hypoprotenimea, failure to thrive, sensorineural hearing loss and not able to speak secondary to hearing loss. However his MRI of brain and thyroid profile was normal and karyotyping to 46XY. He had global developmental delay and delayed skeletal maturation. He was prescribed bilateral hearing aids and regular physiotherapy with early intervention program for his developmental delay.

On General physical examination the patient is hypotonic and pale, weighs 7.8kgs and 80cms in height. On Extra oral examination the occipito frontal circumference is 46 cm which is suggestive of microcephaly. He has striking dysmorphic facies with a small beak-like nose, hypo plastic alae nasi, low set ears, thin upturned upper lip, prominent eyes with long eyelashes (figure 1), frontal upsweep of hair (figure 2), midline aplasia cutis, sparse coarse scalp hair with areas of patchy alopecia and irregular coarse hair over scalp (figure 3).

Intraoral examination revealed presence of 55,53,63,65,73,75,83,85 and missing teeth w.r.t 52,54 62,64 72,74,82,84,11,21,31,41.The deciduous canine (53,63,73,83) are conical in shape and the deciduous 2nd molars (55,65,75,85) are grossly decayed.(figure 4, 5). A provisional diagnosis of anodontia due to Johanson Blizzard syndrome was arrived at. Differential diagnosis of Shwachman-Diamond syndrome, Pearson Marrow-Pancreas syndrome was considered. The panoramic radiograph showed mixed dentition stage of the

[1]Senior Lecturer, Department of Oral Medicine and Radiology, [2]Postgraduate Student, Department of Oral Medicine and Radiology, [3]Reader, Department of Oral Medicine and Radiology, [4]HOD, Department of Oral Medicine and Radiology, M. R. Ambedkar Dental College and Hospital, India

Corresponding author: Dr. Sangeetha. S, M. R. Ambedkar Dental College and Hospital, Department of Oral Medicine and Radiology, 1/36, Cline Road, Cooke Town, Bangalore- 560005, India

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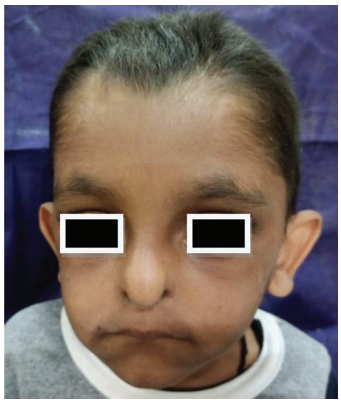

Figure-1: Typical Clinical Appearance of Johanson–Blizzard Syndrome Showing Hypoplastic Alae Nasi

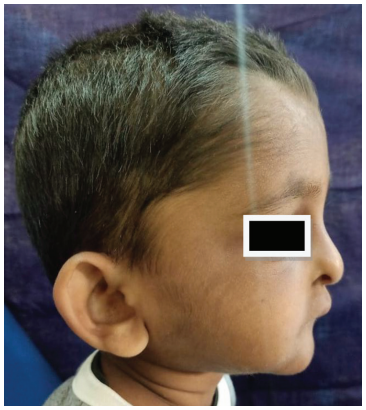

Figure-2: Clinical Appearance of Profile

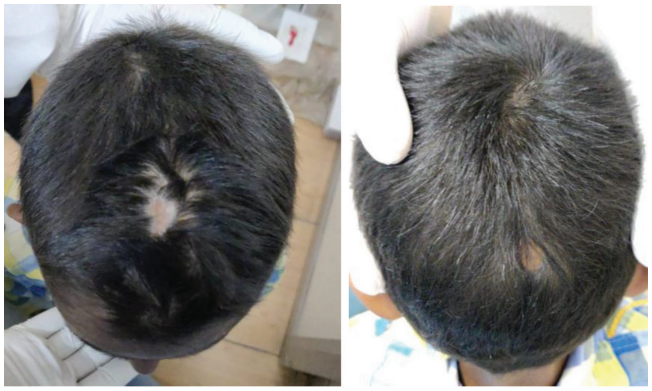

Figure-3: Patchy Alopecia with Irregular Coarse Hair over Scalp

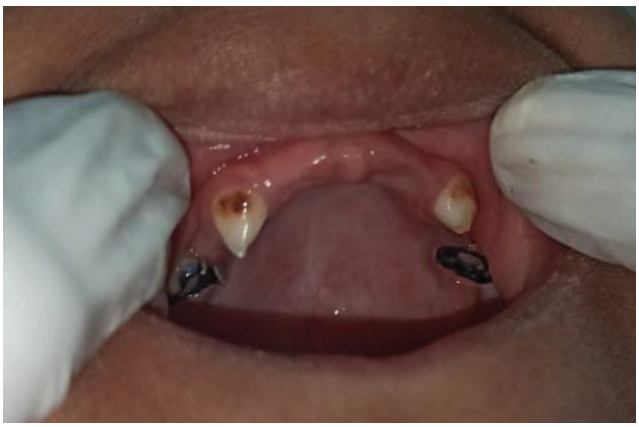

Figure-4: Intra Oral Clinical Examination Showing Absence of Teeth in the Maxilla

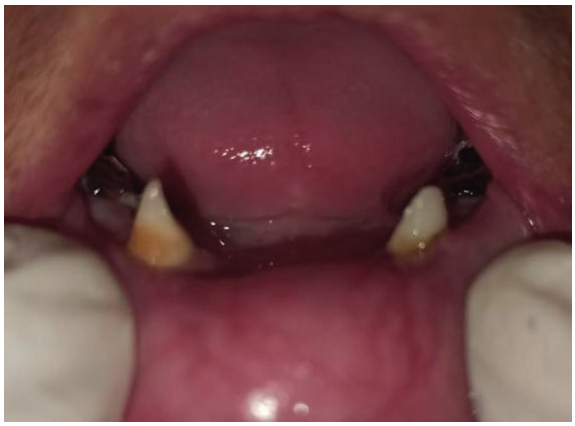

Figure-5: Intraoral Clinical Examination Showing Absence of Some Teeth and Microdontia of 34, 43 (Conical)

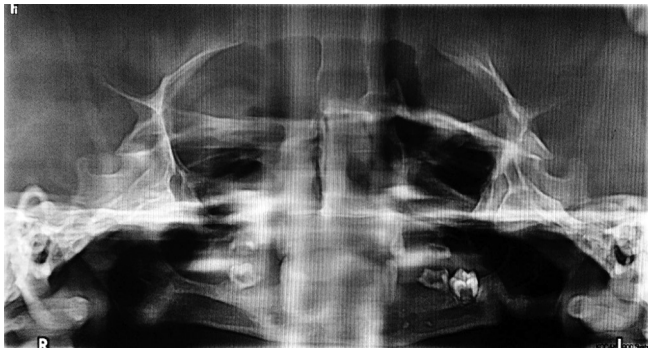

Figure-6: Panoramic Radiograph

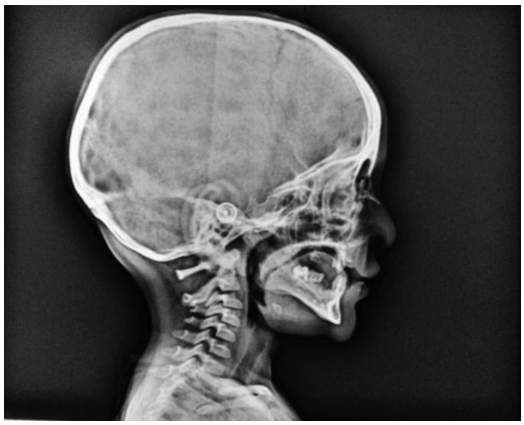

Figure-7: Lateral View depicting mild open anterior fontanelle

child and it also depicted absence of all the teeth except left lower permanent first molar, also reveals the absence of maxillary and mandibular second molar follicles (figure 6).The skull radiograph revealed midline scalp defects(open anterior fontanelle) (figure 7)

Treatment of extraction of the grossly decayed teeth and a removable denture is advised.

DISCUSSION

JBS is a rare disorder exhibiting various genetic abnormalities with an incidence of around 1 per 2,50,000. The exact genetic cause is obscure. Transmission is thought to be autosomal recessive and showed no difference in gender but demonstrate prevalence to consanguinity and familial pedigree data[1]. The genetic defect causing the disease was

Exocrine pancreatic insufficiency
Hypoplasia/aplasia of alae nasi
Scalp defect /aplasia cutis
Sensory neural hearing loss
Bilateral cystic dilation of cochlea, low set ears, and temporal bone defect
Growth retardation, short stature
Dental anomalies: Oligodontia and absence of permanent teeth
Anorectal anomalies: imperforate anus
Hypotonia, microcephaly, and mental retardation sometimes normal intelligence
Lacrimal duct anomalies, coloboma of the lids, superior puncta absence, lacrimal cutaneous fistula, and congenital cataract
Abnormal frontal hair pattern (upsweep)
Vesicoureteric reflux, hypospadia, and duplex of uterine and vagina
Congenital heart diseases such as myxomatous mitral valve, PDA, VSD, ASD, dextrocardia, complex congenital heart disease, and cardiomyopathy
Cholestatic liver disease (one case)
Café au lait spots
Hypothyroidism
Growth hormone deficiency
Hypopituitarism
Impaired glucagon secretion response to insulin induced hypoglycemia
Diabetes mellitus

Table-1: Clinical Features of Johanson-Blizzard Syndrome 3

Sl no	Clinical features	This case
1.	Hypo plastic alae nasi	+
2.	Pancreatic insufficiency/failure to thrive	+
3.	Aplasia cutis congenital	+
4.	Mental retardation	_
5.	Dental anomalies	+
6.	Deafness	+
7.	Anorectal anomalies	+
8	Microcephaly	+
9.	Genitourinary abnormalities	+
10.	Hypothyroidism	_
11.	Cardiac malformation	_

Table-2: Comparison of general clinical features and the features in this case

unclear until 2005. It was later mapped to disease-associated mutation of UBR1 gene located on chromosome 15q15–21 and identified UBR1 gene in 12 unrelated families with Johanson–Blizzard syndrome. UBR1 encodes one of at least four functionally overlapping E3 ubiquitin ligases of the N-end rule pathway, a conserved proteolytic system whose substrates include proteins with destabilizing N-terminal residues[3].

Johanson-Blizzard syndrome affects multiple organ systems of the body. Most of the symptoms are present at birth (congenital) or early childhood. However, characteristic features include insufficient intestinal absorption (malabsorption) of fats and other nutrients due to abnormal development of the pancreas (exocrine pancreatic insufficiency); hypoplasia or aplasia of the alae nasi, growth retardation, failure to thrive during the first years of life. In addition, there are number of variable abnormalities present in a high proportion of patients, detailed report is given in Table 1.

The constant signs necessary to make a diagnosis of JBS is easy and distinct that cannot be missed in the neonatal period those with unusual nasal configuration, aplasia of alae nasi which gives the appearance of the torpedo shaped nose with large nostrils[4]. In addition the unusual hair growth pattern that is upward sweep of hair frontally[5], areas of alopecia with underlying aplasia cutis congenital which form atrophic scars are characteristically seen in midline and in the occipital regions [3, 6]. In the absence of major structural abnormalities medical attention is sought out because of failure to thrive.

The present patient's parents had a consanguineous marriage. Consanguinity is seen in a number of reported cases where mutations in the ubiquitin E3 ligase UBR1 gene were found to be causative and absence of the UBR1 protein was confirmed from the analysis of pancreatic tissue of the affected patients [6].

Pancreatic insufficiency leading to malabsorption is common feature in JBS as described by Towens. Towens and White reported absence of trypsin, chymotrypsin, carboxytrypsin and lipase where the parenchyma of the pancreatic gland is replaced by fatty tissue causing severe malabsorption leading to hypoproteinaemia, odema, anaemia and failure to thrive[3]. In this patient there is pancreatic insufficiency which is being replaced by the external pancreatic enzyme (CREON).

Physical and psychomotor retardation has been attributed to malabsorption, poor nutritional state and hypothyroidism where the child will not grow unless the pancreatic insufficiency is treated with pancreatic enzyme replacement therapy. There have been sufficient cases of short children with normal thyroid function[4]. This patient has normal thyroid function.

However the short stature should be linked to the growth hormone deficiency that might cause retardation in this syndrome rather than hypothyroidism. Some cases are reported with hypothyroidism. This can be due to severe malnourishment causing depression of the thyroid binding globulin[4]. However this patient had a normal thyroid function at the age of 7 years and there are children with normal thyroid function.

Mental Retardation/Development delay: The cause is obscure. The degree of retardation cannot be predicted 13 out of the 22 children reported have development delay[4].

Anorectal Anomalies: Imperforate anus is seen in majority of the cases. These children are treated with initial surgical management like transverse colostomy[4]. This patient had imperforate anus and was treated with transverse colostomy

on day one, which is consistent with the other reported cases. Hearing loss has been attributed to severe sensorineural hearing loss with associated absence of vestibular function[4], This patient had moderately severe sensorineural hearing loss and hearing aids was given at the age of 3 years.

Difficulty to speak can however be related secondary to hearing loss in some patients. In this patient this feature is present secondary to loss of hearing.

Comparison of general clinical features and the features in this case is given in Table 2.

CONCLUSION

Johanson-Blizzard Syndrome is a rare autosomal recessive disorder exhibiting various genetic abnormalities affecting multiple organ systems of the body. This highlights the need for a multidisciplinary approach and management of specific symptoms and features of the disorder. It is of utmost importance to identify the oral manifestations and provide oral rehabilitation to these patients.

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