Johanson-Blizzard Syndrome: A Rare Case Report

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ABSTRACT

Several of the anatomic malformations are difficult to diagnose. A group of population has characteristic anatomic changes but even in this group the diagnosis may not be considered, if one or more of the major features are present. The Johanson-Blizzard syndrome has distinctive craniofacial changes that should be easily recognized. It is an autosomal recessive condition characterized by typical facies, exocrine pancreatic insufficiency, hypothyroidism and group of other features like oligodontia, growth retardation, bilateral hearing loss and midline scalp defects. A 9-year-old boy with Johanson-Blizzard syndrome is described in this article along with oral manifestation and less emphasized feature café-au-lait spots.

Keywords: Hypothyroidism, Johanson-Blizzard syndrome, Midline scalp defects, Oligodontia, Pancreatic insufficiency.

INTRODUCTION

In 1971, Johanson and Blizzard reported a new syndrome in three unrelated girls characterized by congenital aplasia of the alae nasi, deafness, hypothyroidism, dwarfism, absent permanent teeth, and malabsorption. Children with this syndrome had been described earlier by Morris and Fisher in 1967 and Townes in 1969, as examples of trypsinogen deficiency disease. Townes and White subsequently reviewed the patient reported in 1969 and described the presence of additional features which confirmed the diagnosis of the Johanson-Blizzard syndrome.

It is a rare autosomal recessive condition with the most apparent feature being bilateral absence of the nasal alae which gives distinctive appearance. Other anomalies include ectodermal scalp defects, microcephaly, wide and open fontanelles, sensorineural deafness due to abnormal development of cochlea and petrous temporal bone, developmental delay, pancreatic insufficiency, hypothyroidism, and defects of the anorectal and genitourinary system.

CASE REPORT

A 9-year-old boy with his parents, giving history of non-consanguineous marriage came for evaluation of missing lower front teeth. He had attained developmental milestones as per age according to his parents. His prenatal and natal histories were not significant. His mental status was average accounting for an IQ assessment of 90 in Wechsler scale. The height of the patient was 120 cm (132.2 cm, ICMR) and weight was 15 kg (28.1 kg, ICMR). Café-au-lait spots were present on the chest and back, 3 in number, varying in size from 2 to 3 mm measured from the longest axis (Fig. 1). On examination they were flat, light brown and uniformly hyperpigmented with distinct border. Similar kind of lesion was present in his father in the right lumbar region of almost similar size, color and border. There was aplasia of skin and subcutaneous tissue in the region of posterior fontanelle. Microcephaly with patchy loss of hair, mild facial asymmetry, esotropia, malformed pinna, low set ears, hypoplastic ala nasi, flat nasal tip were also present (Fig. 2). Oral manifestations included thin upper lip, angular cheilitis, missing maxillary right upper first molar and lower permanent central and lateral incisors, patchy loss of papillae on the anterior two-third of the tongue (Fig. 3).

The panoramic radiograph showed mixed dentition stage of the child, and it also depicted missing lower permanent central incisors, lateral incisors and maxillary second molar follicles (Fig. 4). The skull radiographs revealed midline scalp defects (open anterior and posterior fontanelle) (Figs 5 and 6). On further investigation, the patient had exocrine pancreatic insufficiency,
hypothyroidism and had moderate sensorineural hearing impairment (Table 1).

Patient is put on pancreatin for a month to improve his malabsorption related problems. With respect to the dental treatment of the patient, the carious lesions were excavated and restored. The patient is under regular follow-up.

**DISCUSSION**

Indeed the ‘gestalt’ of the Johanson-Blizzard syndrome is so distinct that seen once, it should not be missed. The picture is determined by the unusual nasal configuration. The severe aplasia of the alae nasi leads to the appearance of a thin, torpedo shaped nose with large nostrils. In addition, the hair is swept-up, especially frontally, and has a patchy distribution over the scalp. Closer inspection shows areas of alopecia with underlying aplasia cutis congenita, which are characteristically in the midline and in the occipital region. They heal to form atrophic scars.1

Autosomal recessive mode of inheritance was inferred by the equal sex ratio and the consanguinity noted in a number of instances. However, the exact nature of the genetic defect remained elusive until 2005, when mutations in the ubiquitin E3 ligase UBR1 gene were found to be causative and absence of the UBR1 protein was confirmed when pancreatic tissues from affected patients were analyzed (Zenker et al, 2005). Since then, no further reports of UBR1 mutations appeared in the literature, which could possibly be attributed to the rarity of this syndrome whose frequency is estimated at 1 in 250,000 births.5

The most prominent effect of JBS is pancreatic exocrine insufficiency. Varying degrees of decreased secretion of lipases, pancreatic juices, such as trypsin, trypsinogen and others, as well as malabsorption of fats, and disruptions of glucagon secretion and its response to hypoglycemia caused by insulin activity are major concerns when JBS is diagnosed. Associated with developmental errors, impaired apoptosis, and both prenatal and chronic inflammatory damage, necrosis and fibrosis of the pancreatic acini and even evidence of absent pancreatic acini, with intact pancreatic ducts and islet cells surrounded by connective tissue has been reported. Pancreatic exocrine insufficiency in JBS can additionally stem from congenital replacement of the acini with fatty tissue. Near total replacement of the entire pancreas with fatty tissue has also been reported. This is a progressive, sometimes fatal consequence of the disorder.6,7

About one-third of patients have hypothyroidism that contributes further to the physical and psychomotor retardation. The cause of hypothyroidism has been debated, whether primary or acquired. Growth hormone deficiency has also been noted in a few cases. Nearly 60% of the patients have moderate mental retardation. Kristjansson suggested hypopituitarism is a part of the spectrum of the Johanson-Blizzard syndrome.8,9

Findings with the inner ear in JBS, give explanation to the presence of bilateral sensorineural hearing loss in the most patients affected by the disorder. The formation of cystic tissue in both the cochlea and vestibule, with resulting dilation (widening) and malformation of these delicate structures has been implicated. Congenital deformations of the temporal bone and associated adverse anatomical effects on innervation and development of the inner ear also contribute to this type of hearing loss.7
The association of café-au-lait spots with JBS has not been stressed in literature. Though, originally reported in the second case by Johanson and Blizzard, other authors have not consistently reported this. The association of café-au-lait spots with this syndrome is uncommon and a less sized association. Whether this association is coincidental or Johanson-Blizzard syndrome is associated with neurofibromatosis or some other neurocutaneous syndrome, is an enigma.8

One of the typical features of Johanson-Blizzard syndrome is absent tooth buds along with high arched palate, and retardation of dental and maxillary growth have been reported. The roots of the deciduous teeth are short, irregular and deformed. The crown of the few secondary teeth are frequently reduced in form, incisors being conical, maxillary molars having only three cusps. The tooth pulp horns are large. Permanent first molars are somewhat taurodont.9,10

### Table 1: An array of investigations was carried out and the results of the investigation are as tabulated

<table>
<thead>
<tr>
<th><strong>Complete blood count</strong></th>
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<tbody>
<tr>
<td>• Hemoglobin: 11.4 gm/dl (11-16.5)</td>
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<tr>
<td>• Red blood cells: 3.88 x 10⁶/mm³ (3.80-5.80)</td>
</tr>
<tr>
<td>• White blood cells: 7.5 x 10³/mm³ (3.5-10.0)</td>
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<tr>
<td>• Platelet count: 290 x 10³/mm³ (150-390)</td>
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<th><strong>Metabolic panel</strong></th>
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<tr>
<td>• Serum total proteins: 7.8 GMS% (6-8)</td>
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<tr>
<td>• Serum albumin: 4.6 GMS% (3.5-5.0)</td>
</tr>
<tr>
<td>• Serum alkaline phosphatase level: 313 IU/L (upto 125 IU/L)</td>
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<tr>
<td>• Random blood sugar: 136 MGS%</td>
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<tr>
<td>• Blood urea: 25 MGS% (10-40)</td>
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<tr>
<td>• Creatinine: 0.6 MGS% (0.5-2.0)</td>
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<th><strong>Thyroid function test (chemiluminiscence)</strong></th>
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<tr>
<td>• Thyroxine (T4): 6.18 mcg/dl (6.4-13.3) (indicating hypothyroidism)</td>
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<tr>
<td>• Triiodothyronine (T3): 1.34 ng/ml (0.9-2.4)</td>
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<tr>
<td>• Thyroid stimulating hormone: 1.97 mclU/ml (0.7-6.4)</td>
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**BERA test: (Brain-stem Evoked Response Audiometry)**

40 dB to 110 dB rare click stimuli were delivered to right and left ears separately and monaural responses recorded. Wave ‘V’ was recordable at 40 dB on right side and 60 dB on left side. Wave one was formed at 110 dB on either side. No other waves were recordable. The finding suggested bilateral sensorineural hearing impairment.

**Stool microscopy for steatorrhea (Fig. 7):** Microscopy was performed and interpreted along the lines outlined by Drummey and colleagues (1961) with slight modification. In each microscopic field (a) the number of fat particles is counted, and (b) the size of the particles is noted in comparison with that of an average red blood cell. Neutral fat appears as yellow or pale orange refractile fat globules. Two ++ corresponded to a significant excess of fat and the sample showed material with 20-100 fatty clumps or globules in the range 10-50 μm in diameter.
Johanson-Blizzard syndrome shares proteolytic deficiency features with other disorders like cystic fibrosis, Schwachman syndrome, cartilage hair hypoplasia, trypsinogen deficiency disease, Donlan syndrome and intestinal enterokinase deficiency. Their differentiation and the use of electrophoretic studies of pancreatic enzymes have been discussed at length by Townes. Several other syndromes are characterized by varying degrees of hypoplasia of nasal alae: Trichinophalangeal syndrome, occulodento-osseous dysplasia, craniocarpotarsal dysplasia and Roberts syndrome. Aplasia cutis congenita usually occurs as an isolated finding but may be seen with trisomy 13, focal dermal hypoplasia, Sakati syndrome, etc. Aplasia cutis congenita of scalp is associated with a plethora of disorders (Adams-Oliver syndrome).\(^1\),\(^{11}\)

While there is no cure for JBS, treatment and management of specific symptoms and features of the disorder are applied and can often be successful. Pancreatic insufficiency and malabsorption can be managed with pancreatic enzyme replacement therapy, such as pancrelipase supplementation and other related methods. Nasal deformity is one of the initial presenting features of the Johanson-Blizzard syndrome, a plastic surgery consultation is sought early in child’s life, although other medical and surgical interventions may take precedence. Sensorineural hearing loss can be managed with the use of hearing aids and educational services designated for the hearing impaired. Special education, specialized counseling methods and occupational therapy designed for those with mental retardation have proven to be effective for both the patient and their families.\(^2\),\(^{2,3}\)

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