

Johanson Blizzard Syndrome



Medical Science

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Dr Sunil Kumar B M	Associate Professor of Pediatrics, M. S. Ramaiah Medical College MSRIT Bangalore- 560054, INDIA
Dr Vishwas S N	Associate Professor of Pediatrics, M. S. Ramaiah Medical College MSRIT Bangalore- 560054, INDIA
Dr Sathish Kumar K M	Associate Professor of Pediatrics, M. S. Ramaiah Medical College MSRIT Bangalore- 560054, INDIA
Dr Aftab Ahmed	Associate Professor of Pediatric surgery, M. S. Ramaiah Medical College MSRIT Bangalore- 560054, INDIA

ABSTRACT

Johanson Blizzard syndrome is a rare syndrome with distinctive facial features, exocrine pancreatic insufficiency, deafness, hypothyroidism and failure to thrive. Congenital heart defects, moderate to severe mental retardation have been described with Johanson Blizzard syndrome; other features associated with Johanson Blizzard syndrome include oligodontia of permanent teeth, scalp defects, imperforate anus, lacrimal duct fistula, cardiac and CNS anomalies. We describe a 5 month old male infant with classical clinical features with an uncommon association of renal pelvicalyctesia.

Introduction

Johanson Blizzard syndrome (JBS) is a rare hereditary disorder with an estimated frequency of 1 in 2, 50,000 births (1). First described in 1971 by Johanson and Blizzard (2), it is associated with distinctive dysmorphic facial features, exocrine pancreatic insufficiency, deafness, hypothyroidism and failure to thrive. Congenital heart defects, moderate to severe mental retardation have been described with JBS, other features associated with JBS include oligodontia, scalp defects, imperforate anus, lacrimal duct fistula, cardiac and CNS anomalies (3,4,5). Diabetes is seen in older children suggesting a progressive nature of the pancreatic disease. It has also been associated with severe hepatic impairment (6). Unusually high number of café-au-lait spots has been reported in a female infant with JBS (8). The genetic basis for JBS has been mapped to chromosome 15q15-q21, with mutation in UBR1 gene (7). We describe a 5 month old male infant with JBS with an uncommon association of renal pelvicalyctesia. The importance of this association is uncertain.

Case report:

A 5 month old male infant, a first child of a non-consanguineous parentage presented to us with history of recurrent attacks of loose greasy stools, failure to thrive, developmental delay and abnormal facial features. On examination he had a weight of 2600 gms (<3rd percentile), length of 52 cms (<3rd percentile), and a head circumference of 36.5 cms (< 3 SD below normal for age and sex). His head to toe examination showed microcephaly with a wide anterior fontanelle of 5x4 cms, he had pallor, his nose had bilateral aplasia of alae nasi giving rise to a beak like nose, the scalp hair was sparse with an up sweeping of hairs, low set ears, and long philtrum with small down turned upper lip (Figure 1 and 2). His CNS examination showed wasting of muscles with hypotonia. His per abdomen examination showed hepatomegaly 3 cms below right costal margin with a span of 7 cms, the margins were round and consistency was soft. Cardiovascular and respiratory system examination was normal.

His routine laboratory evaluation done showed (Table 1) hemoglobin of 8.6 gm/dl, normal leukocyte count and a normocytic normochromic anemia on peripheral smear examination. Liver function tests, renal function tests, serum electrolytes and blood sugar were normal. Pancreatic amylase and pancreatic lipase levels were low. Thyroid function tests showed low T4 and increased TSH levels suggestive of Hypothyroidism. His chest X-Ray and echo cardiograph were normal, ultra sound examination of abdomen showed left renal pelvicalyctesia.

The patient was managed with oral thyroxine, pancreatic enzymes, and other supportive measures. During subsequent fol-

low ups patient was noticed to have motor developmental delay and mild anemia. After the age of 9 months he was lost to the follow ups.

Discussion:

Johanson Blizzard syndrome is a multisystem disorder first described in 1971 by Johanson and Blizzard (2). The most important and constant features necessary to make a diagnosis are hypoplasia or aplasia of alae nasi, and an exocrine pancreatic defect, other features occur at varying frequencies and are shown in Table 2. The patient presented here had typical facial dysmorphic features, exocrine pancreatic insufficiency, which is pathognomic of JBS. He also had other feature as shown in the Table 2.



Figure1. Five month boy with Aplasia of alae nasi, beaking of nose.



Figure 2. Note the up sweeping of hair, small down turned upper lip, long philtrum.

Table 1. Laboratory results.

	Values	Normal range
Hemoglobin	8.6gm/dl	10.5-13.5 gms/dl
Total leukocyte count	11,340 cells/mm ³	6000-17500 cells/mm ³
Platelets	2.3 lakhs/mm ³	1.5-4 lakhs/mm ³
Total bilirubin	0.6 mg/dl	0.1-1.0 mg/dl
Direct bilirubin	0.2 mg/dl	0.1-0.4mg/dl
ALT	38 IU/l	0-41 IU/l
AST	24 IU/l	0-35 IU/l
ALP	390 U/L	180-1200 U/L
Total proteins	6.6 gm/dl	6-8.4 gm/dl
Albumin	3.1 gm/dl	3.4-4.8 gm/dl
Globulin	2.8 gm/dl	2.6-4.6 gm/dl
TSH	10.86 microIU/ml	0.7-8.4 microIU/ml
T3	1.6 nmol/l	1.6-4.1 nmol/l
T4	70.6 nmol/l	73-206 nmol/l
Pancreatic amylase	7.2 U/L	13-53 U/L
Pancreatic lipase	9 U/L	13-60 U/L

Table 2. Features in Johanson Blizzard syndrome

Aplasia of alae nasi *
 Exocrine pancreatic insufficiency*
 Scalp defect/aplasia cutis*
 Bilateral cystic dilatation of cochlea,
 low set ears *
 Temporal bone defects
 Short stature/growth retardation*
 Dental anomalies
 Microcephaly*, Hypotonia*
 Lacrimal duct anomalies,
 coloboma of lids, fistula,
 Congenital cataract
 Cholestatic liver disease
 Café au lait spots
 Growth hormone deficiency
 Hypothyroidism*
 Hypopituitarism
 Mental retardation
 Developmental delay*
 Anorectal anomalies
 Deafness
 CVS anomalies
 Renal, Vesicoureteric reflux,
 Hypospadias*,
 duplex of vagina and uterus
 Hair abnormalities*
 Diabetes mellitus

*** Features seen in our case.****The clinical features of JBS include,**

The face: The facial features are secondary to unusual nasal configuration. The hypoplasia or aplasia of alae nasi leads to a thin nasal tip with large nostrils giving rise to a beak like nose, the upper lips are long and narrow with a small pointed chin. Lacrimal duct fistulas are also seen.

Hair: Hair is developmentally abnormal with coarse texture, are sparse. Characteristic upsweeping of hair, especially frontal hair is seen.

Tooth: JBS patient have distinctive abnormalities of the teeth. The deciduous teeth may have microdontia, are cone-shaped, and are widely spaced, with short, malformed, irregular roots. The permanent teeth may be abnormal with small size and malformed roots.

Skin: Aplasia cutis congenital with atrophic scars is seen characteristically along midline and occipital areas. Kulkarni M.L *et al* have described a unusually high number of café-au-lait spots in a female infant with JBS (8). The significance of this association was uncertain.

Malabsorption: Exocrine pancreatic defect is one of the most important feature of JBS. In these patients the destruction of pancreatic acinar cells may begin in utero with subsequent replacement of pancreas by fatty tissues. Diabetes has been seen in older children suggesting a progressive pancreatic disease. All the exocrine enzymes and their pro-enzymes are low or absent in JBS. The severe malabsorption caused by enzyme deficiency leads to hypoproteinemia, edema, anemia and failure to thrive. This could be a cause for mortality in these patients in spite of enzyme replacement therapy.

CVS: Congenital heart diseases including Atrial septal defects, ventricular septal defects, dextrocardia with transposition of great vessels and rhabdomyoma has been described.

Mental retardation: The exact cause for mental retardation is not known. The degree of mental retardation cannot be predicted as there are reports of severe mental retardation to mild developmental delay. Daentl *et al* (5) had shown focal migrational defects in brain necropsy. Moeschler *et al* (6) found a small structurally normal brain.

Hearing: Moderate to severe sensorineural hearing loss has been documented in these patients.

Short stature: Has been seen in > 80% of patients, it has been postulated to be secondary to hypothyroidism, malabsorption, growth hormone deficiency, and hypopituitarism.

Hypothyroidism: In the original reports of JBS, hypothyroidism was present. It was reported that condition was acquired rather than congenital. True etiology of hypothyroidism was not established in those cases and there are reports of central hypothyroidism in subsequent reports. Growth failure, deafness have also been attributed to hypothyroidism.

Anorectal anomalies: Hurst and Baraitser (10) have reported that 11 of 22 children with JBS had anorectal abnormalities, most often imperforate anus. Vanlieferinghen *et al*. (11) in an autopsy of an aborted JBS patient had described anorectal atresia with sigmoidovesical fistula. Bilateral ureteral dilatation with hydronephrosis and polycystic dysplasia of the kidneys were also present. Renal pelvicalyectesia seen in our case was not reported in the cases reviewed.

Genetic basis: Molecular basis of JBS has been mapped to chromosome 15q15-q21 with identified mutation in UBR-1 gene. UBR-1 gene is highest in skeletal muscle and pancreatic acinar cells. UBR-1 encodes one of the several ubiquitin ligases of N – end rule pathway, an ubiquitin dependent proteolytic pathway. UBR-1 is considered to play a critical role in development and maintenance of acinar cells. In patients with JBS, destruction of acinar cells which may begin in-utero, results in development of exocrine pancreatic insufficiency.

Prognosis: Children with JBS can die in infancy because of malabsorption, infection and failure to thrive as noted by Mardini *et al* (12). They can survive into adolescence with short stature, absent permanent teeth, and sigmoidostomy. With medications for pancreatic insufficiency and hypothyroidism they require prolonged medical supervision.

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