

A rare cause of pancreatic insufficiency; Johanson Blizzard Syndrome

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Abstract

Johanson-Blizzard Syndrome (JBS) was first described by Johanson and Blizzard. It exhibits autosomal recessive inheritance and is characterized by mutation in the UBR1 gene on the long arm of Chromosome 15. The phenotypic features as well as diarrhoea that occurs due to the exocrine pancreatic insufficiency constitute the main clinical symptoms. This article discusses Johanson-Blizzard Syndrome due to the case followed-up by us with the symptoms of deafness and diarrhoea as well as typical facial appearance.

Keywords: Johanson-Blizzard Syndrome, Pancreatic insufficiency, Child.

Introduction

Johanson-Blizzard Syndrome (JBS) first described by Johanson and Blizzard in 1971, exhibits autosomal recessive inheritance and is characterized by mutation in the UBR1 (Ubiquitin Protein Ligase E3 Component N-Recognin 1) gene on the long arm of Chromosome 15.¹ Its incidence is approximately 1 in 250,000.^{1,2} It is commonly seen in families with consanguineous marriages and no gender difference has been observed.³

Although the severity of clinical symptoms vary from case to case,⁴ the characteristic manifestations include aplastic alae nasi, midline ectodermal scalp defects, deafness, dental abnormalities and malabsorption related to pancreatic exocrine deficiency.⁵ Cardiac anomalies have also been described.⁶

Such patients generally die during the early stages of life from malnutrition associated with digestion or absorption disorders that develop due to pancreatic enzyme deficiency or frequent infections, but a patient diagnosed at the age of 15 was also reported in the literature.^{2,4,7,8}

In this article, a patient diagnosed as JBS in the neonatal period and who was followed with pancreatic enzymes, vitamin and nutrition supplements as well as

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rehabilitation therapy without any problems, is presented. Ethical approval was obtained from legal guardians of the patient.

Case Report

A two-month old boy was brought to the paediatric gastroenterology outpatient clinic in February 2012 at Sisli Hamidiye Etfal Training and Research Hospital in Istanbul. The patient, whose parents were reported to be first degree cousins, had retarded development during the regular follow-up of pregnancy was ended. The mother's second pregnancy at term by normal vaginal delivery of a neonate with (weight: 2980 grams (10th percentile), height: 47 cm (3-10th p), head circumference: 34.5 cm (25th). He had been born with meconium stain, cried soon after birth and had a skin defect of 3X3 cm at the occipital region, hypoplasia of alae nasi (Figure-1), sacral dimple, nipple anomaly and hypospadias. He was diagnosed as JBS because the genetic examination at the neonatal clinic had revealed mutation in the UBR1 gene. The molecular analysis identified homozygosity for a sequence alteration affecting the acceptor splice site of exon 22 (Intron 21:c.2380-1G), both parents were heterozygous for the same genetic aberration.

The patient, who was breastfed, was referred to our clinic because after the 1st month the frequency of defecation had increased from 5-6 times/day to 10-15 times/day, and he had substantially watery stools and vomiting.

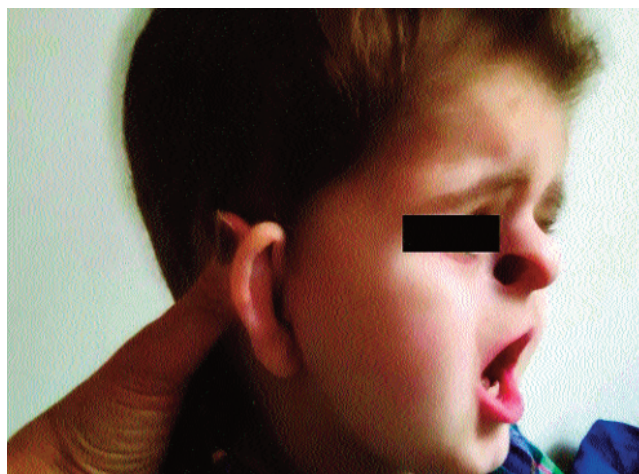


Figure-1: Hypoplasia of alae nasi.



Figure-2: Sparse teeth.

The physical examination revealed height of 51cm (3-10th p), weight of 4250 (3-10th p), the phenotypic features of JBS, normal respiration and cardiovascular system, and no organomegaly. The results of the laboratory examination were: Hgb: 9.5 g/dl, Hct: 30%, MCV: 72 fL, RBCs: 3 500.000 mm³, WBCs: 7120 /mm³, PLT: 368 000 /mm³, sodium: 135 mEq/L, potassium: 3.4 mEq/L, chloride: 101 mEq/L, total protein: 6.6g/dl, albumin: 4.7g/dl, IgA: 38 mg/dl, IgG: 590 mg/dl, IgM: 52mg/dl, TSH: 7.4 uIU/ml (0.7-5.9 uIU/ml), T3: 2 pg/ml (2.5-5.5 pg/ml), T4: 0.7 pg/ml (0.96-1.77 pg/ml), and blood gases and hepatic and renal function tests were normal. The gait analysis was normal. The faecal elastase level was below 50µg/g. The ophthalmic and neurologic examinations were normal and the ear-nose examination revealed bilateral sensorineural hearing loss. The ECHO (echocardiography) examination was normal. Anti-reflux therapy with levothyroxine 50 µg/day as well as pancreatic enzyme replacement 3000 lipase unit, lipase/120 ml, multivitamin and medium-chain fatty acid-containing formula were initiated. On the 3rd day of the therapy, it was seen that the number of defecations decreased to 5-6 times/day, number of vomitings decreased and his bodyweight started to increase. The patient, who was followed-up firstly at 15 day intervals and then monthly intervals, cut his first tooth at the age of 8 months. His number of defecations was 3-4 times/day, semi-formed, and he started to walk at the age of 14 months. He is five years old now, has totally 18 abnormally developed sharp, sparse teeth (Figure-2), watering in the eyes due to lacrimal duct obstruction, and inability speak due to bilateral sensorineural hearing loss for which cochlear implantation was recommended.

Currently, he is interested in his surroundings, able to

walk and eat, his height is 99 cm (3-10th percentile), weight is 13 kg (3rd percentile), and the number of defecations is 3-4 times/day, semi-formed.

Discussion

JBS is quite a rare syndrome seen in families with consanguineous marriages characterized with facial malformations, aplasia or hypoplasia of alae nasi, rough and dry hair with hairline extending to the forehead, structural dental anomalies, microcephaly, congenital deafness, mental retardation of various degrees, hypothyroidism, congenital cardiac diseases and exocrine pancreatic insufficiency.^{1,7,8} Our patient had the phenotypic features of JBS.

Exocrine pancreatic insufficiency is one of the main manifestations of JBS.⁵ Hypoproteinaemia, oedema, anaemia and growth retardation are observed in cases associated with severe absorption disorder. Some patients die during the early stages of life despite oral pancreatic enzyme supplementation.⁶

His faecal elastase level was below 50. No tryptic activity was detected. He did not have hypoproteinaemia despite diarrhoea and vomiting. He had anaemia and growth retardation.

Patients may have hypothyroidism or euthyroidism. No association could be established between short stature and thyroid functions, but it has been reported that hypothyroidism should be treated when diagnosed.⁶ Our patient had hypothyroidism and a thyroid extract was initiated. Currently his thyroid function tests have been normalized with therapy but he still has growth and development retardation. Cause of mental retardation is unclear since majority of the patients die during the neonatal period. Although it was reported that autopsies revealed disturbances in the regional neuronal migration in the brain, some studies reported that the brain is structurally normal with slightly smaller size.⁹ Our patient is interested in his surroundings, and the MR examination of his brain and Denver II development test revealed no moderate disorders.

One thirds of the patients show anorectal malformations however no anorectal malformations except for hypospadias were observed in our patient.⁶

Congenital cardiac anomalies reported to accompany JBS,^{6,7} but the echocardiographic examination of our patient revealed normal.

Severe deafness, mainly of nervous type, is seen in JBS.^{4,7} The ear-nose-throat examination of our patient revealed

bilateral sensorineural deafness.

The ophthalmic disorders that accompany this syndrome are lacrimal-cutaneous fistula, flat palpebral fissure, eyelid colobome, strabismus, eyelid ptosis and epicanthal folds.¹⁰ Our patient's ophthalmic examination was normal and revealed aplasia of nasolacrimal ducts and no other anomalies.

Abnormal dental development is frequently seen in the patients.^{4,8} Our patient, who is 5 years old now, cut his first tooth at the age of 8 months, but his teeth are sparse and sharp (some of them are triangular-shaped) and do not appear strong.

Conclusion

JBS is a rare syndrome which is difficult to diagnose before delivery. Aplasia of alae nasi and large sigmoid colon revealed by prenatal ultrasonography may help to diagnose this syndrome. Postnatal signs and symptoms lead to the diagnosis of JBS. The length and quality of life of the patients can be improved by administering supportive treatment for symptoms such as pancreatic enzyme deficiency, hypothyroidism, hypoalbuminaemia and cardiac anomalies.

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Conflict of Interest: None to declare

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