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Case Report

Paediatrics Section

A Case with Complete Pancreatic Aplasia Suggestive of Johanson-Blizzard Syndrome

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ABSTRACT

Johanson-Blizzard Syndrome (JBS) is a very rare autosomal recessive multisystem disorder. We report the case of a two-month-old male with pancreatic insufficiency and severe phenotypic features. His diagnosis of JBS was established using clinical symptoms and abdominal computed tomography scan that showed pancreas aplasia. According to the best of our knowledge, no case with this syndrome has presented with complete pancreatic aplasia in the literature.

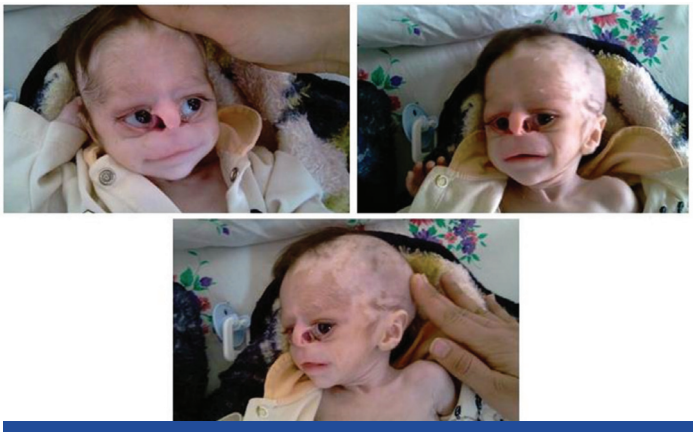
Keywords: Cyclophpsphamide, Hemorrhagic cystitis, Treatment

CASE REPORT

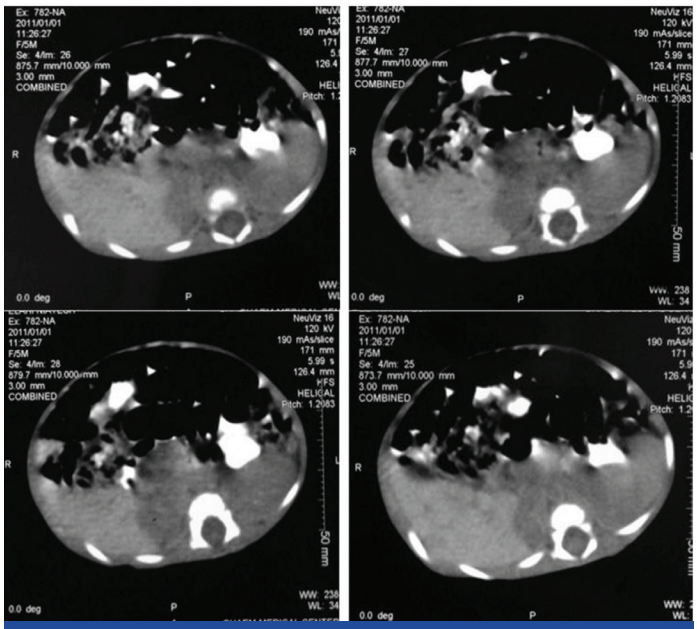
The patient was a two-month-old infant boy who was abandoned in the nursery by his parents in Feb 2013 for his specific looks. He was referred to the emergency ward suffering from severe diarrhea, dyspnea, severe FTT and suspected with pneumonia, aspiration and gastroenteritis. We became suspicious of fat malabsorption due to the acute steatorrhea, particular face look [Table/Fig-1], acute FTT and laboratory stool evaluations that found fat drops in patient's stool exam. Fat malabsorption is the result of exocrine pancreatic dysfunction. His initial laboratory evaluation is shown in [Table/Fig-2]. The only syndrome that matched the perceived symptoms in both clinical and laboratory terms was JBS. We made our diagnosis by ruling out three of four conventional differential diagnoses in the order of prevalence (cystic fibrosis, Shwachman–Diamond, Pearson and JBS). Genetic evaluation was not feasible due to high cost and the infant being in nursery. The only affordable diagnostic procedure for this patient was computed tomography (CT) scan of his abdomen. CT demonstrated complete aplasia of the pancreas with no visualized gland residing in the pancreatic bed and its bed was occupied by fatty deposits. Dilation of small bowel loops was distinctive, which were suggestive of gastroenteritis. Also, the posterior vertebral arch was formed imperfectly [Table/Fig-3]. To understand the above descriptions more clearly a number of normal CT images of upper abdominal sections are shown in [Table/Fig-4]. The following signs and symptoms led us to suggest the diagnosis: severe bilateral asymmetric sensorineural hearing loss, Pyramidal nephrocalcinosis in both kidneys (diagnosed

WBC	11.7/µL (normal: 5.5-15.5)	PT	12.6 sec
Hemoglobin	10.7g/dL (normal: 10.5-13.5)	PTT	43 sec
PLT	203 10^3/µL	TSH	3.1 µ units/mL
Total protein	4.1 g/dL (normal, 6-8)	T4	6.5
Albumin	2.9 g/dL (normal, 3.5-5)	Fecal fat drop:	2+
ANC	6786/µL	ESR	10
CRP	4+	PBS	Acantocytosis
Ca	9.2 mg/dl	K	4.9 mEq/L
Na	139mEq/L	BUN	51 mg/dl
Cr	0.6 mg/dl (0.2 - 0.4)	TG	67
Cholestrol	55mg/dL	BS	50
LDH	918U/L	B/C	Negative
U/C	*E.coli* (50000)	Stool ova and parasites	Negative

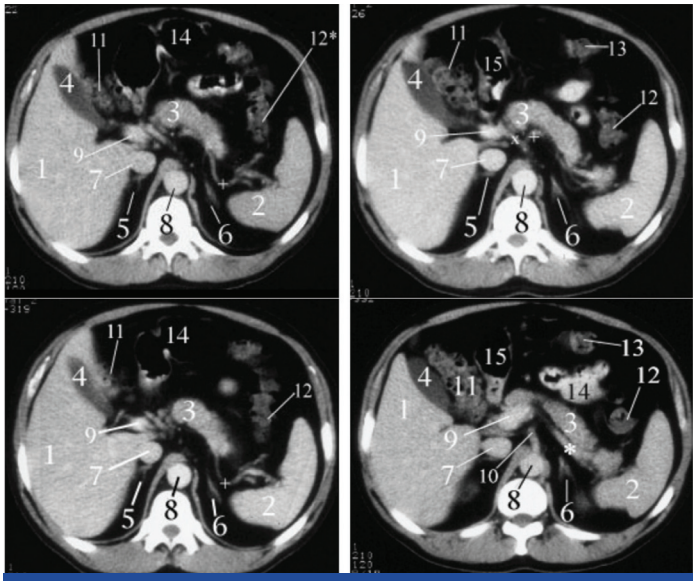
[Table/Fig-2]: Laboratory evaluation.



[Table/Fig-1]: Phenotypic feature of JBS in our patient: abnormal hair pattern, nasal alae aplasia, narrow upper lip.



[Table/Fig-3]: CT scan of the abdomen demonstrating aplasia of the pancreas. In the axial section of the abdomen with oral contrast, no image was seen in favor of the pancreas gland and its bed was occupied by fatty deposits. Dilation of small bowel loops was distinctive, which can be suggestive of gastroenteritis. Also, the posterior vertebral arch was formed imperfectly.



[Table/Fig-4]: These are axial views of the normal upper abdomen as seen by Computed Tomography. [1]Liver, [2]Spleen, [3]Pancreas, [4]Gallbladder, [5]Right Adrenal Gland, [6]Left Adrenal Gland, [7]Inferior Vena Cava, [8]Aorta, [9]Portal Vein, [10]Superior Mesenteric Artery, [10']Superior Mesenteric Vein, [11]Ascending Colon, [12]Descending Colon, [13]Transverse Colon, [14]Stomach, [15]Distal Stomach.

by prenatal ultrasound), mild dilation in the pelvis of kidneys and clinical symptoms (hair growth pattern and complete nasal alae and nostrils aplasia) [Table/Fig-1]. The patient underwent pancreatic enzyme replacement therapy and fat soluble vitamins but unfortunately died on the third day of hospitalization.

DISCUSSION

Johanson-Blizzard syndrome (JBS) is a rare multisystem disorder of which about 100 cases have been reported so far according to existing literature. The association between symptoms were first recognized by Morris and Fisher in 1967 [1] with the release of pictures of a child with atypical nose. Johanson and Blizzard first described 3 patients with aplastic nasal alae, congenital deafness, hypothyroidism, absent permanent teeth, dwarfism, intellectual disability and malabsorption in 1971. However, some early reports like Townes [1] were focused on pancreatic failure, the definition of the disease was modified after 10 years.

One of the most noticeable features of the disease is congenital hypoplasia or aplasia of the nasal alae which is seen in almost all cases (100%) and in hypoplastic forms it resembles a beak-like nose. Moreover, aplasia and nasolacrimo-cutaneous fistulae in the eyes has been reported. In addition, nearly two thirds of the patients suffer from sensorineural hearing loss since birth. They suffer multiple abnormalities in dental root and pulp and are likely to never grow teeth. They exhibit sparse inconspicuous hair and scalp alopecia. Hairline is upsweep. Hypoplasia of nipple and areola, pitting oedema and Café au lait spots has also been observed [2]. Microcephaly is reported in one third of patients and cranioectodermal dysplasia particularly in the cranial base center and fontanelle is seen in more than 80% of cases [1]. Seventy percent of patients are affected with various degrees of intellectual disability and learning disorders.

Congenital heart disease and urogenital abnormalities are amongst other manifestations observed in these patients [3]. In the urogenital system, multiple abnormalities such as hydro-nephrosis, microphallus, cryptorchidism, hypospadias and vaginal anomalies such as vaginal septum, duplication of vagina and uterus, rectovaginal fistula and hydrometrocolpos have been reported. Rectal atresia and stenosis have also been found. Fat malabsorption, steatorrhea and chronic diarrhea are present in all patients due to exocrine pancreatic insufficiency. Fat malabsorption is caused by exocrine pancreatic insufficiency in producing lipase and trypsinogen [1]. As a result of malabsorption, these patients are faced with failure to thrive (FTT) and short stature [1]. One third of the patients have congenital hypothyroidism and in some cases diabetes and growth hormone deficiency have also been reported. These children have various degrees of generalized hypotonia at birth in addition to hyper-extensibility in their joints. Delayed bone age is observed in most patients, which is probably due to digestive and endocrine disorders [1]. These patients may experience growth retardation after birth [4] which seems to be due to hypothyroidism, malabsorption and growth hormone deficiency [5].

JBS is a rare syndrome inherited with an autosomal recessive prototype. Zekner et al., indicated that mutations of either homozygous or compound heterozygous on gene *UBR1*are the cause of JBS. The synthesis of *ubiquitin ligase* can be affected by mutations in the *UBR1* gene. The most expression of *UBR1* occurs in the pancreatic acinar cells. Impairment of the ubiquitin-proteasome system is directly related to insufficient activity of *ubiquitin ligase.* Constitutive malpresence of proteins and absence of normal apoptotic destruction of damaged cells can cause both congenital and progressive inflammatory damage, fatty tissue replacement, connective tissue proliferation and errors in innervation of the acini and islets. Other areas such as craniofacial area, musculoskeletal and nervous system, dentition and organs can be affected by Mutations in the *UBR1*. This gene is located on chromosomes 15q15–q21.1 [4]. Although, JBS is primarily diagnosed through clinical manifestations, identification of *UBR1* mutation in molecular studies is suitable for suspicious cases [4] particularly for spotting carriers in patient's family or prenatal diagnosis during pregnancy. In this case severe bilateral sensorineural hearing loss, nephrocalcinosis in kidneys, aplasia of the nasal alae, abnormal hair growth pattern and complete aplasia of pancreas helped us in arriving at a suggestive diagnosis of JBS. Due to high cost of genetic tests, we only made use of clinical manifestations and CT.

In JBS, Endocrine pancreatic disorders are less common and less pronounced than the more prominent effects on exocrine function. It can be associated with either an accumulation of connective tissue islets of Langerhans, improper nerve signaling to the islets, or congenital replacement of the islets with fatty tissue [6]. Lipomatous hyperplasia of the exocrine pancreas can be detected by CT, MRI or autopsy in JBS patients. Children are able to live on least endocrine pancreatic function whereas in adolescents or adults endocrine deficiency is presented as diabetes and loss of glucagon response to hypoglycaemia [5,7]. Diabetes Mellitus is another JBS complication occurring as a result of pancreas Functional impairment. Both insulin and non-insulin dependent diabetes have been observed in these patients [8].

For treatment, main signs and symptoms of the disease must be relieved. Pancreatic exocrine insufficiency is the most important disorder of the JBS that must be treated as it is done to treat Cystic Fibrosis and SDS patients [1]. The main treatment in patients with this syndrome is pancreatic enzyme replacement, administrating fat-soluble vitamins, providing enough calorie, fluid and electrolyte therapy in case of diarrhea and adjusting blood sugar with insulin in case of hyperglycaemia. Thus we started our patient with pancreatic enzyme replacement and fat-soluble vitamin therapy but unfortunately died after 3 days of treatment.

CONCLUSION

The aim of the case report was to describe a rare manifestation of JBS and highlight the importance of organ involvement in patients with syndromic face and performing comprehensive evaluations.

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