

## CASE REPORT: Occurrence of the Rare Syndrome of Johanson-Blizzard in a Child – Longitudinal Observations

[Editor's note: For definitions of medical terms in this paper, please use Dictionary.com at <http://dictionary.reference.com/medical>]

### Abstract

*The authors review the data available in the literature on a rare genetic disorder – Johanson-Blizzard syndrome – and present their clinical observations on one patient after longitudinal follow-up. Particular emphasis is on multiple malformations which are the clinical hallmark manifestations of the disorder: congenital exocrine insufficiency, and abnormalities of the maxillofacial region, hearing and sight. Homozygous or compound heterozygous mutations in the UBR1 gene typically result in Johanson-Blizzard syndrome. A molecular genetic study detected two mutations at different sites in the UBR1 gene. These have not been previously described in the syndrome, but likely result in the patient's disorder. One of the mutations was maternally inherited. The differential diagnosis of this syndrome and multifaceted therapy, including clinical nutrition and enzyme therapy are presented. Follow-up from age 8 to 16 years of age showed a positive trend overall in the patient's condition.*

Johanson-Blizzard syndrome (JBS; OMIM 243800) is characterized by exocrine pancreatic insufficiency with multiple congenital anomalies, short stature, and variable developmental delay (Online Mendelian Inheritance in Man (OMIM, n.d.). This syndrome is a rare autosomal recessive disease (estimated prevalence 1:250,000), and it was first described by Johanson and Blizzard in 1971. According to literature data, there are fewer than 50 cases of children with such a syndrome (see the Appendix in the reference list). No follow-up data about individual patients are found in the literature.

Diagnosis of JBS causes great difficulties both due to its extremely rare occurrence and possible multiple manifestations which have been described in different combinations by various authors. However, the association of exocrine pancreatic insufficiency manifesting in the first year of life and typical facial anomalies characterized by nasal wing hypoplasia or aplasia is unique to this syndrome and allows a clinical diagnosis in almost all cases (Sucalo et al., 2014). The disease is caused by homozygous or compound heterozygous mutations in the *UBR1* gene which is located on the long arm of chromosome 15 (band15q14-21.1) (Zenker et al., 2005). The gene encodes a ubiquitin ligase of the N-end rule pathway, but currently the pathophysiological mechanisms that are responsible for the various organ manifestations in JBS are unknown.

### Authors

Larissa S. Baleva,<sup>1</sup>  
Alla E. Sipyagina,<sup>1</sup>  
Martin Zenker,<sup>2</sup>  
Julia M. Kagan,<sup>1</sup>  
Lubov I. Danilycheva,<sup>1</sup>  
Maja Sucalo<sup>2</sup>

<sup>1</sup> Research and Clinical  
Institute of Pediatrics,  
Pirogov Russian National  
Medical University RF  
Ministry of Health,  
Russia

<sup>2</sup> Institute of Human  
Genetics,  
University Hospital  
Magdeburg, Magdeburg,  
Germany

### Correspondence

lbaleva@pedklin.ru

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The list of symptoms observed in patients with JBS by different researchers is a long one. Besides malabsorption due to pancreatic exocrine insufficiency and nasal wing hypoplasia, it also includes congenital hypothyroidism due to thyroid gland hypoplasia, short stature, microcephaly, scalp defects, sparse hair, cleft lip and palate, hypodontia and abnormal or small teeth, congenital abnormality of lacrimal ducts, muscular hypotonia, mental retardation, sensorineural deafness, various heart defects (defects of interatrial or interventricular septum, dextrocardia, pulmonary trunk stenosis, transposition of great vessels), absence or hypoplasia of spleen, polysplenia, hydronephrosis, atresia or stenosis of the anus, rectovaginal fistula, vaginal septum or hydrometrocolpos, small penis, cryptorchidism, thrombocytopenia, anemia, and diabetes mellitus.

One of the leading and consistent symptoms is pancreatic exocrine insufficiency. The morphological basis of this pathology is the replacement of pancreatic acinar tissue by fat and connective tissue with relative integrity of structure and insular apparatus function. Intestinal absorption occurs due to decreased production of all pancreatic enzymes (lipase, amylase, trypsin). Large follicles with colloid content are found in the biopsy material of the thyroid gland.

In the current report we provide clinical data from the follow-up of a patient with JBS until the age of 16 years.

## Case Report

The child was first admitted to the Children's Applied Research Centre of the Antiradiation Protection Unit of the Federal State Budgetary Institution, Moscow Research Institute of Pediatrics and Pediatric Surgery, at the age of 8 years. From the family history there is no hint at parental consanguinity. The mother has gastric ulcer disease, cardiovascular and endocrinological problems. The father left the family from the moment of the child's birth; there is no information about his health.

The patient was the product of the fourth pregnancy, second delivery. The mother's first pregnancy from her first marriage resulted in a son

who was 27 years old at the patient's last visit. This half-brother suffers from bronchial asthma and congenital sensory hearing loss, but is otherwise healthy and has no dysmorphological anomalies. The mother's second and third pregnancies from the second marriage ended with miscarriage in early pregnancy. No cause was identified. The fourth pregnancy was complicated by maternal anemia and nephropathy in the first and second trimesters. Delivery of the male patient was at term and uncomplicated. The newborn's body weight at birth was 3,220 g, his body length was 51 cm, and Apgar scores of 7 and 8 after 5 and 10 minutes were recorded, respectively. At birth severe facial anomalies were evident: a cleft of the soft and hard palate, alveolar ridge, and upper lip, as well as aplasia of nasal wings with lateral facial clefting extending from the nose to the lower eyelid. Failure to thrive and delayed growth were observed from the first months of life. At the age of 3 months the patient's body weight was 3,740 g and his length was 54 cm; at the age of one year his body weight was 7,150 g and his length was 66 cm (so during the first year of life the boy grew only by 15 cm). Moreover, a delay in motor development was also noted: The boy began to hold his head at the age of 7 months, to sit unaided at the age of 11 months, and to walk when he was 2.5 years old.

Lacrimation and recurrent purulent discharge from the eyes were noted in the boy from the first days of life. Congenital abnormality of the lacrimal ducts was diagnosed.

Bulky watery and undigested stools with visible fat and mucus were noted in the child while on breast feeding plus soy and other formula from the moment of birth. Stool analysis confirmed steatorrhea of the first and second type. At the age of 4.5 months the child was examined in the Republic Children's Clinical Hospital in Tatarstan where Shwachman-Diamond syndrome was initially suspected. Major manifestations of this latter syndrome are congenital pancreatic insufficiency and hematologic disorders (more often anemia and thrombocytopenia, than the rarer pancytopenia). From the age of 7 months, the child was followed up in the Republic Children's Clinical Hospital in Moscow where Shwachman-Diamond syndrome was excluded due to the absence of bone and hematologic disorders that are characteristic of this syndrome. Also mucoviscidosis for

which congenital pancreatic exocrine insufficiency is typical was excluded by the absence of any bronchopulmonary symptoms and normal chloride concentrations in sweat. Further on, the child was followed up with the diagnosis: of congenital pancreatic insufficiency and malabsorption syndrome.

The diagnosis of JBS was first suspected by a geneticist in Scientific Advisory Department of Moscow Medical Genetic Centre of the Russian Academy of Sciences when the patient was 13 years old. From that age, therapeutic nutrition with Nutrison (a high-caloric formula produced by Nutricia, NL) and enzyme substitution with Kreon (a digestive enzyme replacement produced by Abbott Products GmbH, Hannover, DE) in small doses of 25,000 U per day were prescribed. Gastrointestinal symptoms and nutritional state improved on this regimen: abdominal pains and vomiting became rarer, formed stool appeared, the child began to gain weight.

The boy was admitted to the Radiation Risk Clinic of the Children's Applied Research Centre of Antiradiation Protection for the first time at the age of 8. At admission there were complaints of abdominal pains, nausea, undigested stool, insufficient gain in the body weight, choking and food and water entrance in the nasal cavity, lacrimation, and increased fatigue. At this time the boy's body weight was only 19 kg (below the 1<sup>st</sup> centile or -2.7 SD) and his height was 118 cm (below 2<sup>nd</sup> centile or -2.1 SD). His intelligence was normal; the child attended a regular school. At examination multiple dysmorphic stigmata were noted: frontal upsweep of hair, sparse hair, small areas of alopecia in the parietal region with scarred skin, and a pinched nose with nasal wing aplasia. Skin was clear and pale. Multiple scars were present in the area of the upper lip caused by corrective maxillofacial surgery. Deciduous teeth were small and maldeveloped and no permanent teeth were present. The tongue was covered with white plaque. Lymph nodes in the anterior cervical group were up to 0.7 x 0.5 cm; in other groups there were small, single ones. In the lungs, respiration was vesicular and conducted in all parts; rales were absent. Heart tones were clear; rhythm was regular; heart rate was 80 beats per min. Blood pressure was 110/70 mmHg. The abdomen was soft, but painful during palpation in the epigastric area,

Mayo-Robson point and gall bladder projection point. The liver was near the costal arch edge; the spleen was not palpable. Stool was light brown, loose, two times a day. Urination was painless. Male sexual development was normal.

Hematological investigations showed mild thrombocytopenia:  $113 \times 10^9/l$  (normal 150–500) on two occasions in the blood count; other parameters were within normal ranges for age. Urine analysis was normal. Increased alkaline phosphatase and lactate dehydrogenase levels were noted in the biochemical blood assay. Blood amylase was within the normal range. Increased f urine diastase was not found.

Undigested fibre and extracellular starch were found in small quantity in the series of coprology tests.

On abdominal ultrasound investigation, the pancreas was increased, parenchyma was heterogeneous due to the areas of different echogenicity. No changes of other internal abdominal organs and kidneys were found. No pathology in pancreas was found by magnetic resonance imaging conducted at this time.

An audiogram indicated right-sided neurosensory hearing loss of Stage 4.

To further evaluate the gastrointestinal complaints, esophago-gastro-duodeno-jejunoscopy was performed and revealed reflux-esophagitis, gastric cardia incompetence, pangastritis, granular bulbitis, duodenogastral reflux and duodenojejunitis with elements of mucosal atrophy. Hypolactasia of moderate severity was noted using the Biohit Lactose Intolerance Quick Test (Biohitoyi, FI). (This test identifies lactase deficiency from duodenal biopsies taken during gastroscopy.) At morphological examination of the jejunum signs of nonspecific atrophic jejunitis were noted.

No pathologic changes were found by ultrasound investigation of the thyroid gland. Thyroid hormones were within the normal range. No signs of cardiac disease were found at electrocardiogram and echocardiographic investigation.

Orthopantomography was performed and revealed the absence of all permanent teeth.

The clinical diagnosis of JBS was established on the basis of the child's craniofacial phenotype (nasal wing aplasia, abnormality of lacrimal ducts, scalp defects, sparse hair, frontal hair upsweep), presence of muscular hypotonia, congenital right-sided neurosensory hearing loss, small deciduous teeth, absence of immature permanent teeth, and significant congenital pancreatic exocrine failure.

Taking into account the mother's and father's contact with radioactive fuel, cytogenetic examination was performed in the family. Only the patient and his mother were available for analysis. Cytogenetic examination of the child revealed increased level of single and paired fragments, dicentrics, and translocations which is suggestive of genomic instability. No similar changes were found in mother.

At last examination, the boy was 15 years old. He had constantly been followed up in the Radiation Risk Rehabilitation Department. A complete clinical and laboratory investigation has been performed annually since 2006. At the age of 15 his body weight was 45 kg (5<sup>th</sup> centile or -1.6 SD), and his height was 158.5 cm (4<sup>th</sup> centile or -1.8 SD). During the previous three years the boy grew by 7 cm, and his weight gain was 14 kg.

Between 13 and 15 years of age he underwent multiple surgeries in the Maxillo-Facial Surgery Department of Russian Children's Clinical Hospital due to the congenital penetrating cleft of the upper lip and palate on the left side. Multistage surgical treatment consisted of: left-sided cheiloplasty, soft palate push-back, correction of the nasal passage fundus; and in 2011 – nasolacrimal duct catheterization from the right side, correction of velopharyngeal insufficiency, nasal septum plasty with resection of cartilaginous part.

Progressive changes of the pancreas were noted by ultrasound and computed tomography (CT). While ultrasound investigation at the age of 8 years had revealed only heterogeneous parenchyma echogenicity, MRI at the age of 12 revealed signs of fatty dystrophy of the pancreas. CT of the abdominal cavity performed in March 2013 revealed the absence of pancreatic tissue and its subtotal replacement by fat tissue.

At the age of 12 years the child had a consultation with Martin Zenker, Professor at the Institute of Human Genetics of the University Hospital in Magdeburg. At that time molecular genetic testing of the *UBR1* gene was performed in the patient, his mother and brother from the first mother's marriage. Earlier, a group of researchers managed by Professor Zenker proved that JBS results from homozygotic or heterozygotic mutations of *UBR1* gene which causes the loss of ability of the UBR1 protein to fulfil its functions (Sucalo et al., 2014).

All 47 coding exons including the flanking intron regions of the *UBR1* gene were amplified by PCR. PCR amplicons were purified and subjected to direct sequencing using an automated sequencer. Sequences were compared to the reference sequences deposited in the public database (NM\_174916) (National Center for Biotechnology Information, n.d.). In the index patient, two heterozygous sequence changes in exon 10 {c.1166\_1177del (p.A389\_F392del)} and exon 21 {c.2260C>T (p.R754C)} were identified. Both variations have not been found in other patients with JBS so far; as well, they are not known as polymorphisms. The fact that both of them predict deletion or exchange of highly conserved amino acids in the UBR1 protein, strongly suggest that these represent the mutations that are causative for the syndrome in this patient.

The same exons – 10 and 21 – were investigated in the patient's mother and only the change in the exon 21 was found in her, thus suggesting that the in frame deletion in exon 10 was inherited from the father who was not available for genetic testing, or arose as a new mutation. The elder half-brother also carried the maternally inherited *UBR1* mutation.

Currently the child consistently receives pancreatic enzyme replacement therapy by Kreon (175,000 U/day), high-caloric nutrition with Nutrison (2,000 ml/day) with the addition of courses of rice and oat porridge with Liquigen (a milk-free beverage produced by Nutricia, NL; 20 ml/day).

Taking into account the fact that last ultrasound and CT of abdominal organs revealed subtotal pancreatic tissue replacement by fatty tissue, we decided to raise the question about



possible transplantation of the pancreas. Due to this, the patient had a consultation in the Federal Scientific Shumakov Transplantology Center. Transplantation was recommended in case of irreversible pancreatic beta-cell dysfunction (i.e., Stage 5 decompensation characterized in part by severe loss of beta-cell mass) (Weir & Bonner-Weir, 2004). Meanwhile it was recommended to support the child by replacement therapy with Kreon and specialized nutrition. After transplantation the child would receive immunosuppressive therapy and a new transplant would be required after 7 to 8 years. According to an agreement with the Transplantology Centre, in the case of beta-cell failure the surgery will be performed.

This disorder can be referred to as a “rare orphan disease.” On the basis of continued clinical follow-up of the child, we suggest that correctly adjusted therapy has improved the child’s quality of life and may contribute to an increased life expectancy.

## Key Messages From This Article

**People with disabilities:** Disabilities of any kind present challenges, but this does not mean that life with a disability cannot be fulfilling. You deserve to enjoy full participation in all aspects of life, and lead an independent life, but make sure you are supported by people around you. You have the same rights to protection as any other person.

**Professionals:** An individual approach needs to be applied to each person with disabilities because they face different challenges and health conditions. People who care for disabled people sometimes are challenged by disability as well.

**Policymakers:** Policies are needed to prevent the exclusion of disabled people from any aspects of life, to improve employment outcomes, and to increase awareness and understanding of the challenges faced by people with disabilities.

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- ### Appendix: Chronological Listing of References About Johanson-Blizzard Syndrome
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