CASE REPORT

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Clinical manifestations of Johanson-Blizzard syndrome in a patient with nucleotide variants in the *UBR1* gene

Kliničke manifestacije Johanson-Blizzard-ovog sindroma kod bolesnika sa nukleotidnim varijantama *UBR1* gena

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Abstract

Introduction. Johanson-Blizzard syndrome (JBS) is a very rare genetic disorder caused by a mutation of the ubiquitin protein ligase E3 component N-recognin 1 (*UBR1*) gene. Clinical diagnosis is based on the pathognomonic combination of congenital exocrine pancreatic insufficiency and characteristic signs of facial dysmorphology (nasal wing hypoplasia/aplasia and oligodontia of permanent teeth). Diagnosis is confirmed by genetic screening of the *UBR1* gene. The aim of this case report was to emphasize that nucleotide variants in the *UBR1* gene, described as benign or unclassified, should still be considered a genetic cause of the clinical characteristics in patients with JBS. **Case report.** We present an 8-month-old child, with clinical features of JBS, who was admitted to our hospital due to poor weight gain and loose stools. Upon admission, signs of protein-energy malnutrition, facial dysmorphology, and other anomalies were observed. The child had hypotonia and convergent strabismus. A laboratory examination confirmed exocrine pancreatic insufficiency and hypothyroidism. Genetic testing confirmed two single nucleotide variants in the *UBR1* gene – chromosome 15q15.2: NM_174916.3:c.4700+12A>G (intron 42) and NM_174916.3 *UBR1*:c.862-18C>T (intron 07). A pancreatic enzyme replacement therapy with liposoluble vitamin supplementation and adequate nutrition was conducted. **Conclusion.** Recognizing the clinical features of JBS and confirming it with genetic analysis is essential, especially in patients with idiopathic pancreatic insufficiency. Even when genetic confirmation is not possible, adequate treatment is necessary for normal growth and development of the child.

Key words:
exocrine pancreatic insufficiency; genes; hypothyroidism; johanson-blizzard syndrome; mutation; ubr1 protein, human.

Apstrakt

Uvod. Johanson-Blizzard-ov sindrom (JBS) je veoma redak genetički poremećaj uzrokovan mutacijom gena *ubiquitin protein ligase E3 component N-recognin 1* (*UBR1*). Klinička dijagnoza se zasniva na prepoznavanju patognomonične kombinacije kongenitalne egzokrine insuficijencije pankreasa i karakterističnih znakova facijalne dismorfologije (hipoplazija/aplazija nosnih školjki i oligodoncija stalnih zuba). Dijagnoza se potvrđuje genetičkim skriningom *UBR1* gena. Cilj rada bio je da se ukaže na to da nukleotidne varijante *UBR1* gena, koje se opisuju kao benigne ili neklasifikovane, ipak treba razmotriti kao genetički uzrok kod bolesnika sa kliničkim karakteristikama JBS-a. **Prikaz bolesnika.** Prikazano je dete uzrasta osam meseci, sa kliničkim karakteristikama JBS-a, koje je primljeno u bolnicu zbog nenapredovanja u telesnoj masi i neformiranih stolica. Na prijemu su bili prisutni znakovi proteinsko-energetske malnutricije, facijalne dismorfologije i druge anomalije. Dete je imalo hipotoniju i konvergentni strabizam. Laboratorijskim ispitivanjem potvrđena je egzokrina insuficijencija pankreasa i hipotireoidizam. Genetičkom analizom potvrđene su dve nukleotidne varijante *UBR1* gena – hromozom 15q15.2: NM_174916.3:c.4700+12A>G (intron 42) i NM_174916.3 *UBR1*:c.862-18C>T (intron 07). Sprovedena je supstituciona terapija pankreasnim enzimom uz suplementaciju liposolubilnim vitaminima i uz adekvatnu ishranu. **Zaključak.** Prepoznavanje kliničkih karakteristika JBS-a i potvrda sindroma primenom genetičkih analiza, posebno je važna kod bolesnika sa idiopatskom insuficijencijom pankreasa. Čak i kada genetička potvrda nije moguća, za normalan rast i razvoj deteta neophodna je adekvatna terapija.

Ključne reči:
pankreas, egzokrini, insuficijencija; geni; hipotireoidizam; johanson-blizzardov sindrom; mutacija; ubr1 protein, humani.

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Introduction

Johanson-Blizzard syndrome (JBS) is a very rare genetic multisystem disorder with an autosomal recessive inheritance pattern. The incidence of JBS in Europe is approximately 1 in 250,000 live births. JBS is caused by mutations in the *UBR1* gene [1, 2]. Typical clinical features predominantly affect skeletal muscles and pancreatic acinar cells. It is considered that the *UBR1* gene plays a critical role in the development and maintenance of acinar cells of the pancreas [1–5].

Destruction of acinar tissue, which may begin *in utero* in patients who suffer from JBS, results in the development of exocrine pancreatic insufficiency and fatty infiltration of the pancreas [3–7]. Clinical diagnosis is suspected according to the identification of the pathognomonic combination of congenital or infantile exocrine pancreatic insufficiency with facial dysmorphology (nasal wing hypoplasia/aplasia and oligodontia of permanent teeth) and additional features such as intrauterine growth restriction, short stature, microcephaly, scalp defects, hearing impairment, cognitive impairment of variable degree, hypothyroidism, congenital heart defects, urogenital and anorectal malformations, renal anomalies, and diabetes with onset during adolescence. The diagnosis is confirmed by the detection of a *UBR1* gene mutation [1–7]. Early diagnosis, as well as symptomatic and supportive therapy, contribute to the survival of these patients until adulthood; otherwise, pancreatic insufficiency and complications of severe malnutrition can lead to death in infancy or early childhood [4–8].

Case report

In the report, we present a boy, born as a second child from a second pregnancy (the first child from the first pregnancy was healthy) at 37 weeks of gestation by Cesarean section. The boy's birth weight was 3,180 g (57th percentile), his birth length was 52 cm (77th percentile), and his head circumference was 34 cm (55th percentile). The family history was unremarkable. When the child was four months old, his mother noticed poor weight gain and loose stools. When the boy was eight months old, he was hospitalized for diagnostic evaluation at the Department of Pediatric Gastroenterology, Hepatology, and Nutrition at the Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia. Upon admission to our hospital, the signs of protein-energy malnutrition were observed: body weight 5,500 g (< 3rd percentile); body length 63 cm (< 3rd percentile); head circumference 42 cm (< 3rd percentile). Furthermore, facial dysmorphological signs (prominent forehead, long eyelashes, otapostasis, malformed ears) and anomalies (micropenis, bell-shaped thorax, umbilical hernia, irregular dentition, and poor tooth quality) were present. The child had hypotonia and convergent strabismus. The major clinical hallmarks in the case of our patient include severe pancreatic insufficiency, irregular dentition, and poor dental quality (the primary dentition), with additional features of the JBS but without nasal wing anomaly. The varying frequencies of features in JBS [1] are shown together with the features of our patient in Table 1.

Table 1

Typical clinical characteristics of Johanson-Blizzard syndrome (JBS) [1] and the presence of features in the case of our patient

Clinical characteristics of JBS (frequency)	Presence / Type of presence
Pancreatic exocrine insufficiency (100%)	yes
Hypoplasia/aplasia *alae nasi* (> 95%)	no
Dental anomalies, oligodontia/hypodontia of permanent teeth (> 90%)	irregular dentition, poor tooth quality
Sensorineural hearing loss (75%)	no
Scalp defects/aplasia cutis congenital (65%)	no
Short stature, developmental and intellectual delays, hypotonia (60%)	yes
Hypothyroidism (40%)	yes
Microcephaly (35%)	yes
Anorectal malformations (20%)	no
Eye anomalies (lacrimal duct anomalies, coloboma, congenital cataract) (#)	no
Other minor signs* (#)	long eyelashes, eyes slanting downwards, otapostasis, malformed ears, prominent forehead, bell-shaped thorax, liver disease
Impaired glucagon secretion, abnormal response of insulin ** (#)	yes
Diabetes mellitus ** (#)	no
Congenital heart defects (25%)	no
Intrauterine growth restriction (30%)	no
Genitourinary malformations (30%)	micropenis

 # – the frequency varies widely; * Other minor signs described in JBS: abnormal frontal hair pattern (upsweep), severe facial clefting (cleft lip/palate), natal teeth, poly-/syndactyly, prostate aplasia, gastroesophageal reflux, cholestatic liver disease, café au-lait spots, growth hormone deficiency, hypopituitarism, brain and osseous malformations; ** – older children are at high risk, suggesting the progressive nature of pancreatic disease.

A laboratory examination was conducted, and exocrine pancreatic insufficiency was confirmed with elevated values of transaminases and gamma-glutamyl transferase (all laboratory results are shown in Table 2). Abdominal ultrasound showed normal pancreatic structure, but magnetic resonance cholangiopancreatography revealed severe pancreatic atrophy with fatty infiltration. Genetic testing confirmed two single nucleotide variants in the *UBR1* gene, chromosome 15q15.2 – NM_174916.3:c.4700+12A>G (intron 42) and NM_174916.3 *UBR1*:c.862-18C>T (intron 07). As the examination showed exocrine pancreatic insufficiency, pancreatic enzyme replacement therapy (pancrelipase) was started with liposoluble vitamin (A, D, E, K) supplementation. Adequate nutrition with high-fat content was introduced. The child had normal levels of free triiodothyronine (T3) [2 nmol/L; reference range (RR) 1.34–2.73 nmol/L] and thyroxine (T4) (100 nmol/L; RR 78.38–157.4 nmol/L) and an increased thyroid-stimulating hormone (TSH) level (9 mU/L; RR 0.34–5.60 mU/L), after which levothyroxine was introduced to treatment. The level of postprandial insulinemia was 3 pmol/L (RR 3.5–41 pmol/L), and it revealed a subnormal insulin response. Other analyses showed adrenocorticotropic hormone, cortisol, and prolactin levels in the RR, prepubertal levels of testosterone, luteinizing, and the follicle-stimulating hormone (2 U/L, RR 0–5 U/L), and a low normal insulin-like growth factor 1 level. An endocrinologist achieved normal genital size after three turns of testosterone depot. The electrocardiogram and echocardiogram were normal. Ophthalmic examination and hearing test were normal.

Table 2

Patient's laboratory test results

Parameter	Result	Reference range
Leukocytes ($x10^9$/L)	8.9	4–10
Red blood cells ($x10^{12}$/L)	3.8	4.1–6.0
Platelets ($x10^9$/L)	307	150–450
AST (U/L)	194.4	16.2–52.2
ALT (U/L)	193.2	12–58.8
GGT (U/L)	42	1.2–39
Amylase (U/L)	< 12	27.6–99.6
Lipase (U/L)	< 3	4.2–39
Albumin (mmol/L)	0.54	0.57–0.81
Components of complement (C) system		
C3 (g/L)	0.35	0.8–1.6
C4 (g/L)	1.3	0.15–0.45
Ammonia (μmol/L)	16	10–30
Serum lactate (mmol/L)	0.8	0.5–1
Fecal calprotectin (μg/g)	< 100	< 100
Pancreatic elastase (μg/g)	< 15	> 200
Antiviral antibodies, ratio		
HCV	< 1 s/c	< 1 s/c (negative); ≥ 1 s/c (positive)*
HBsAg	< 1 s/c	< 1 s/c (negative); ≥ 1 s/c (positive)*
CMV (IgM and IgG)	< 0.8	< 0.8 (negative); ≥ 0.8 to < 1.1 (cut-off); ≥ 1.1 (positive)**
HSV (IgM and IgG)	< 0.8	< 0.8 (negative); ≥ 0.8 to < 1.1 (cut-off); ≥ 1.1 (positive)**
Adenovirus (IgM and IgG)	< 0.8	< 0.8 (negative); ≥ 0.8 to < 1.1 (cut-off); ≥ 1.1 (positive)**
EBV (IgM and IgG)	< 0.8	< 0.8 (negative); ≥ 0.8 to < 1.1 (cut-off); ≥ 1.1 (positive)**
Coxsackie B (IgM and IgG)	< 0.8	< 0.8 (negative); ≥ 0.8 to < 1.1 (cut-off); ≥ 1.1 (positive)**
Toxoplasma gondii (IgM and IgG)	< 0.8	< 0.8 (negative); ≥ 0.8 to < 1.1 (cut-off); ≥ 1.1 (positive)**
Parvovirus B19 (IgM and IgG)	< 0.8	< 0.8 (negative); ≥ 0.8 to < 1.1 (cut-off); ≥ 1.1 (positive)**
Autoantibodies, titers		
ANA (on HEp-2 cells/primate liver tissue)	< 1:100	< 1:100 (negative); ≥ 1:320 (positive)¤
APA	< 1:100	< 1:100 (negative); > 1:100 (positive)¤
AMA	< 1:100	< 1:100 (negative); > 1:100 (positive)¤
ANCA	< 1:10	< 1:10 (negative); > 1:10 (positive)¤
LKM1	< 1:100	< 1:100 (negative); > 1:100 (positive)¤
ASMA	< 1:100	< 1:100 (negative); > 1:100 (positive)¤
Iron (μmol/L)	6.2	7.2–17.9
Transglutaminase antibody IgA (U/mL)	< 2	< 20
IgA (g/L)	0.33	0.19–2.2
IgM (g/L)	0.55	0.4–1.4
IgG (g/L)	6.79	3.5–10.0

AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase; HCV – Hepatitis C virus; HbsAg – Hepatitis B surface antigen; CMV – cytomegalovirus; HSV – Herpes Simplex virus; EBV – Epstein Barr virus; Ig – immunoglobulin; ANA – anti-nuclear antibodies; APA – anti-parietal antibodies; AMA – anti-mitochondrial antibodies; ANCA – anti-neutrophil cytoplasmic antibodies; LKM1 – liver kidney microsome antibodies type 1; ASMA – anti-smooth muscle antibodies; ratio – extinction of the control or patient sample/extinction of calibrator; s/c – signal detected on sample/cut-off value ratio; *chemoluminescent immunoassay; **enzyme-linked immunosorbent assay; HEp – human epithelial; ¤ indirect immunofluorescence.

The electroencephalogram was orderly. The child had a mild developmental delay (Brunet Lezine scale). The global development quotient range (QR) was 85. The main characteristics of the psychological aspect of the child were hyperactivity, short-term attention, and short-term interests.

Discussion

JBS is a very rare autosomal recessive disorder that affects many organ systems. The molecular basis of JBS has been mapped to chromosome 15q15-q21 with identified mutations in the *UBR1* gene. The *UBR1* gene contains 47 exons that encode one of several E3 ubiquitin ligases of the N-end rule pathway (ubiquitin-dependent proteolytic pathway) [1–5]. The spectrum of dysmorphological and clinical manifestations in JBS is variable and heterogeneous, but nasal wing hypoplasia/aplasia and exocrine pancreatic insufficiency are considered the most consistent manifestations [3–8]. Severe pancreatic insufficiency, irregular dentition, and poor dental quality (the primary dentition), with some additional features of the syndrome, were present in our patient (nasal wing hypoplasia/aplasia absent).

Exocrine pancreatic insufficiency could be a manifestation of many childhood diseases, so in the differential diagnosis, apart from JBS, the following conditions should be considered: cystic fibrosis, Shwachman-Diamond syndrome, Pearson syndrome, Jeune syndrome, pancreatic aplasia and hypoplasia, isolated enzyme deficiencies, and chronic pancreatitis (hereditary and autoimmune) [9, 10]. In patients with cystic fibrosis, the pancreatic juice is abnormally thick, causing its retention in the pancreatic canalicular system. The primary disorder in the Shwachman-Diamond syndrome is hypoplasia of the exocrine tissue of the pancreas (similar to JBS). Pearson syndrome is a very rare mitochondrial cytopathy characterized by poor fluid and electrolyte secretion in addition to reduced acinar function. Although Jeune syndrome is characterized by skeletal abnormalities of the thorax and extremities, its association with pancreatic fibrosis has been confirmed. Chronic pancreatitis is a progressive inflammatory disorder that leads to irreversible destruction of pancreas tissue. The causes of chronic pancreatitis, except ductal obstruction by stones or cystic fibrosis, are hereditary pancreatitis and autoimmune pancreatitis. In hereditary pancreatitis, gene mutations such as *PRSS1*, *SPINK1*, *CASR*, and *CTRC* increase the risk of developing pancreatitis. These mutations could impair trypsin autolysis and promote the auto-activation of trypsinogen. Autoimmune mechanisms contributing to pancreatitis can lead to multifocal fibrosclerosis. In type I autoimmune pancreatitis (IgG_4-related disease), other organs can be affected besides the pancreas, such as the intrahepatic bile ducts, salivary glands, kidneys, and lymph nodes. Recent studies have found that the hypothyroidism detected in patients with this type of pancreatitis was mild and infrequent; therefore, further studies are necessary to clarify whether hypothyroidism is another manifestation of IgG_4-related disease. In autoimmune pancreatitis type II, only the pancreas is affected, but inflammatory bowel disease can develop [9, 10]. In the case of our patient, anti-nuclear antibodies (ANA), anti-parietal antibodies (APA), anti-mitochondrial antibodies (AMA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-smooth muscle antibodies (ASMA) and anti liver kidney microsome antibodies type 1 (LKM1) autoantibodies were negative. IgG_4 analysis was not performed for technical reasons.

Recent research indicates that new *UBR1* gene mutations are being discovered at an increasing rate, as well as the impact of gene mutations on phenotypic characteristics in children with JBS. On the other hand, it is very difficult to identify all *UBR1* gene mutations and their variants [8, 11, 12]. In the case of our patient, genetic testing confirmed two single nucleotide variants in the *UBR1* gene, chromosome 15q15.2: NM_174916.3:c.4700+12A>G (intron 42) and NM_174916.3 *UBR1*:c.862-18C>T (intron 07). The *UBR1* was covered 100% in the whole exome sequencing (BioExome). Because those two unclassified intronic variants of the *UBR1* gene in a patient are considered benign, we assume that this connection is not a coincidence; because of that, we present this case. Further investigations are needed to confirm this connection. Early treatment with pancreatic enzyme and nutrition, as was done in the case of our patient, improves the patient's normal growth and development and has a normal global development quotient [7, 8, 11–13].

Prenatal diagnosis of JBS is possible. The ultrasound-verified dysmorphological signs such as hypoplasia or aplasia of the *alae nasi*, dilated sigmoid colon, or imperforated anus can be seen at 21 weeks of gestation. The molecular testing of gene *UBR1* and searching for the same mutation in a fetus as the proband using invasive procedures such as chorionic villi sampling, amniocentesis, or cordocentesis could confirm the diagnosis of JBS [1, 8, 11–13].

Conclusion

Recognition of features of JBS and genetic confirmation is very important, especially in patients with idiopathic pancreatic insufficiency. Even when genetic confirmation of the diagnosis of JBS is not possible, adequate treatment is necessary for normal growth and development of the child.

Conflict of interest

The authors declare no conflict of interest.

R E F E R E N C E S

1. *Orphanet*. Johanson-Blizzard syndrome [Internet]. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=2315 [accessed on: 2023 October 19]
2. *Sukalo M, Fiedler A, Guzmán C, Spranger S, Addor MC, McHeik JN,* et al. Mutations in the human UBR1 gene and the associated phenotypic spectrum. Hum Mutat 2014; 35(5): 521–31.
3. *Almashraki N, Abdulnabee MZ, Sukalo M, Alrajoudi A, Sharafadeen I, Zenker M*. Johanson-Blizzard syndrome. World J Gastroenterol 2011; 17(37): 4247–50.
4. *Atik T, Karakoyun M, Sukalo M, Zenker M, Ozkinay F, Aydoğdu S*. Two novel UBR1 gene mutations ın a patient with Johanson Blizzard Syndrome: A mild phenotype without mental retardation. Gene 2015; 570(1): 153–5.
5. *Alkhouri N, Kaplan B, Kay M, Shealy A, Crowe C, Bauhuber S,* et al. Johanson-Blizzard syndrome with mild phenotypic features confirmed by UBR1 gene testing. World J Gastroenterol 2008; 14(44): 6863–6.
6. *Rezaei N, Sabbaghian M, Liu Z, Zenker M*. Eponym: Johanson-Blizzard syndrome. Eur J Pediatr 2011; 170(2): 179–83.
7. *Demir D, Kendir Demirkol Y, Gerenli N, Aktaş Karabay E*. Johanson-Blizzard's Syndrome with a Novel UBR1 Mutation. J Pediatr Genet 2020; 11(2): 147–50.
8. *Liu S, Wang Z, Jiang J, Luo X, Hong Q, Zhang Y*, et al. Severe forms of Johanson-Blizzard syndrome caused by two novel compound heterozygous variants in UBR1: Clinical manifestations, imaging findings and molecular genetics. Pancreatology 2020; 20(3): 562–8.
9. *Lee JK, Enns R*. Review of idiopathic pancreatitis. World J Gastroenterol 2007; 13(47): 6296–313.
10. *Kunovský L, Dítě P, Jabandžiev P, Eid M, Poredská K, Vaculová J,* et al. Causes of Exocrine Pancreatic Insufficiency Other Than Chronic Pancreatitis. J Clin Med 2021; 10(24): 5779.
11. *Zenker M, Mayerle J, Lerch MM, Tagariello A, Zerres K, Durie PR,* et al. Deficiency of UBR1, a ubiquitin ligase of the N-end rule pathway, causes pancreatic dysfunction, malformations and mental retardation (Johanson-Blizzard syndrome). Nat Genet 2005; 37(12): 1345–50.
12. *Ellery KM, Erdman SH*. Johanson-Blizzard syndrome: expanding the phenotype of exocrine pancreatic insufficiency. JOP 2014; 15(4): 388–90.
13. *Sukalo M, Schäflein E, Schanze I, Everman DB, Rezaei N, Argente J,* et al. Expanding the mutational spectrum in Johanson-Blizzard syndrome: identification of whole exon deletions and duplications in the UBR1 gene by multiplex ligation-dependent probe amplification analysis. Mol Genet Genomic Med 2017; 5(6): 774–80.

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