Jacobsen's syndrome: case report

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Liudmila Yu. Barycheva[1,2], Leila I. Bachieva[1], Natal'ja A. Koz'mova[1]

[1] *Stavropol State Medical University, 310, Mira St., Stavropol, 355017, Russia.*

[2] *Regional Children's Clinical Hospital, 3, Semashko St., Stavropol, 355029, Russia.*

Liudmila Yurievna Barycheva — Dr. Sci. (Med.), Professor, Head of the Department of Immunology with a course of continuing professional education, Stavropol State Medical University; Allergist-Immunologist, Regional Children's Clinical Hospital; ORCID ID: 0000-0002-4069-0566, e-mail: for_ludmila@inbox.ru.

Leila Ibragimovna Bachieva — 2nd year resident at the Department of Faculty Pediatrics, Stavropol State Medical University, ORCID ID: 0009-0008-7785-4676, e-mail: bachleila@mail.ru.

Natal'ja Aleksandrovna Koz'mova — assistant of the Department of Immunology with a course of continuing professional education, Stavropol State Medical University; Allergist-Immunologist, Regional Children's Clinical Hospital; ORCID ID: 0000-0003-0971-5347, e-mail: n-kozmova@mail.ru.

Annotation

Introduction. Jacobsen syndrome (JS) is a rare genetic disease associated with the deletion of chromosome 11q, characterized by multiple malformations, hematological and immune disorders. The development of immunodeficiency in JS is often underestimated, which leads to recurrent infectious complications.

Presentation of a clinical case. The article presents a clinical case of a patient with a deletion of chromosome 11q and combined immunodeficiency. Our patient had recurrent infections, cytopenic syndrome, combined immunodeficiency, as well as other clinical manifestations of Jacobsen syndrome.

In addition to a decrease in serum immunoglobulins, a deep deficiency of the T-cell link of immunity with a low content of T-lymphocytes, recent emigrants from the thymus, has been established.

Conclusions. The peculiarity of the presented clinical case is that with a relatively small amount of deletion 11q, the child realized a complete clinical phenotype of the disease and a deep combined immunodeficiency. The article was written to improve doctors' knowledge about this rare form of congenital immunodeficiency.

Keywords: Jacobsen syndrome, del 11q, combined immunodeficiency.

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Синдром Якобсена: отчет о клиническом случае

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Барычева Л. Ю.[1,2], Бачиева Л. И.[1], Козьмова Н. А.[1]

[1] *ФГБОУ ВО «Ставропольский государственный медицинский университет», 355017, г. Ставрополь, ул. Мира, д. 310, Россия*

[2] *ГБУЗ СК «Краевая детская клиническая больница», 355029, г. Ставрополь, ул. Семашко, д. 3, Россия*

Барычева Людмила Юрьевна — д. м. н., профессор, заведующий кафедрой иммунологии с курсом дополнительного профессионального образования, Ставропольский государственный медицинский университет, врач аллерголог-иммунолог, ORCID ID: 0000-0002-4069-0566, e-mail: for_ludmila@inbox.ru.

For correspondence:
Lyudmila Yurievna Barycheva, Dr. Sci. (Med.), Professor, Head of the Department of Immunology with a course of continuing professional education, Stavropol State Medical University; Allergist-Immunologist, Regional Children's Clinical Hospital.

Address: 310, Mira St., Stavropol, 355017, Russia.

E-mail: for_ludmila@inbox.ru.

Для корреспонденции:
Барычева Людмила Юрьевна, д. м. н., профессор, заведующий кафедрой иммунологии с курсом дополнительного профессионального образования, Ставропольский государственный медицинский университет, врач аллерголог-иммунолог.

Адрес: 355017, г. Ставрополь, ул. Мира, д. 310, Россия.

E-mail: for_ludmila@inbox.ru.

Бачиева Лейла Ибрагимовна — ординатор 2-го года кафедры факультетской педиатрии, Ставропольский государственный медицинский университет, ORCID ID: 0009-0008-7785-4676, e-mail: bachleila@mail.ru.

Козьмова Наталья Александровна — ассистент кафедры иммунологии с курсом дополнительного профессионального образования, ORCID ID: 0000-0003-0971-5347, e-mail: n-kozmova@mail.ru.

Аннотация

Введение. Синдром Якобсена (СЯ) — редкое генетическое заболевание, связанное с делецией хромосомы 11q, характеризующееся множественными пороками развития, гематологическими и иммунными расстройствами. Развитие иммунодефицита при СЯ часто является недооцененным, что приводит к рецидивирующим инфекционным осложнениям.

Изложение клинического случая. В статье приведено клиническое наблюдение пациента с делецией хромосомы 11q и комбинированным иммунодефицитом.

У нашего пациента отмечались рецидивирующие инфекции, цитопенический синдром, комбинированный иммунодефицит, а также другие клинические проявления синдрома Якобсена. Кроме снижения сывороточных иммуноглобулинов, установлен глубокий дефицит Т-клеточного звена иммунитета с низким содержанием Т-лимфоцитов — недавних эмигрантов из тимуса.

Заключение. Особенностью представленного клинического случая является то, что при сравнительно небольшом объеме делеции 11q у ребенка реализовался полный клинический фенотип заболевания и глубокий комбинированный иммунодефицит. Статья написана для улучшения знаний врачей об этой редкой форме врожденного иммунодефицита.

Ключевые слова: синдром Якобсена, синдром делеции 11q, комбинированный иммунодефицит.

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INTRODUCTION. Jacobsen syndrome (JBS; MIM 147791), also known as the syndrome of terminal deletion 11q, is a rare genetic disease, caused by the loss of continuous set of genes in the long arm of chromosome 11 [1, 2, 3]. The disease occurs in 1 per 100 000, with a ratio of women to men 2:1 [4, 5]. 85 % of recorded cases arise by mutation de novo [4].

Since the first description of Jacobsen syndrome in 1973 there have been more than 200 recorded cases, characterized by deletions and affecting telomeric regions of chromosome 11. The size of the deletion is 7–20 Mb and the proximal breaking point is inside or closer to the telomeric end of the sub-band 11q23.3 [6, 7, 8]. This terminal haploinsufficiency might affect the function of more than 100 different genes. The diagnosis of complete syndrome is established when BSX, NRGN, ETS-1, FLI-1 and RICS (ARHGAP32) genes are involved in the deletion. Patients with smaller deletions have a partial phenotype [2, 6]. Variability of phenotype-genotype might be associated with incomplete penetrance as well as with other genes of interest, located on 11q, such as TIRAP, FLI-1, NFRKB, THYN1 and SNX19 [9].

The disease covers a wide range of clinical manifestations. Studies show that 97 % of patients have from mild to severe mental retardation. The degree of neurocognitive disorder is closely associated with the size of the deletion [5, 10].

Platelet abnormalities occur in 88,5–94% of cases. There is noted neonatal thrombocytopenia that may resolve with time, and platelet dysfunction of long-lasting nature [11]. There is an increased number of small megakaryocytes (micromegakaryocytes) and their delayed maturation in the bone marrow [12].

Congenital heart defects, most often, defects of the interventricular septum and left-side obstructive lesions, are found in 56 % of patients, and they are the most common cause of death [5, 7]. Hypoplastic left heart syndrome, one of the most severe congenital heart diseases, is described in 5–10 % of patients with Jacobsen syndrome (compared to 0,02 % in the general population) [13]. Studies in humans and mice showed that ETS-1 gene, located in a “cardiac critical area” on the terminal part of chromosome 11, is the cause of congenital heart disease [2, 13].

Craniofacial dysmorphism (> 40 %) is often manifested in the form of trigonocephaly, ocular hypertelorism, strabismus, eyelid ptosis, coloboma of the iris and wide nose bridge. There is skin syndactyly on the hands, abnormal palmar crease and hypoplastic thenar space. Feet are short, flat with syndactyly of the 2nd and 3rd toes [5, 7].

In 2004 P. D. Grossfeld and colleagues conducted the prospective analysis of 110 patients with the syndrome of terminal deletion 11q. There were no clear signs of immunodeficiency, no recorded life-threaten-

List of abbreviations/список сокращений:

BSX:	brain specific homeobox
ETS-1:	proto-oncogene 1, transcription factor
FLI-1:	proto-oncogene, ETS transcription factor
JAM3:	junctional adhesion molecule 3
KREC:	kappa-deleting recombination excision circle
NFRKB:	nuclear factor related to kappaB binding protein
NRGN:	neurogranin
RICS:	Rho GTPase activating protein 32
SNX19:	sorting nexin 19
THYN1:	thymocyte nuclear protein 1
TIRAP:	TIR domain containing adaptor protein
TREC:	T-cell receptor excision circle
ADP:	adenosine diphosphate
IVIG:	intravenous immunoglobulin
CHD:	congenital heart disease
DIVS:	defect of the interventricular septum
DISS:	defect of the interstitial septum
IUGR:	intrauterine growth retardation
DC:	disturbed circulation
AS:	Apgar score
SCIG:	subcutaneous immunoglobulin
JS:	Jacobsen syndrome
FC:	functional class
CKD:	chronic kidney disease

ing and (or) opportunistic infections in the studied cohort. However, recurrent episodes of otitis media and (or) sinusitis were frequent and observed in 42 out of 78 patients (54 %) [5].

The first immune defect, recorded in this syndrome, was antibody deficiency [14]. A number of studies have noted a decrease in all classes of immunoglobulins (IgA, IgM, IgG) and disorder of specific antibody formation in response to vaccination with pneumococcal polysaccharide vaccine, which is typical for patients with common variable immunodeficiency [15]. The mechanism by which the terminal deletion of chromosome 11 contributes to the development of immunodeficiency is not fully understood. It is assumed that immunodeficiency occurs mainly due to ETS (ETS-1) or FLI-1 gene loss. ETS-1 is highly expressed in NK-cells, B- and T-lymphocytes and involved in the development of NK-cells, differentiation of T- and B-lymphocytes [16, 17, 18].

Only in 2020 the disease was considered as congenital immune system defect and included in the classification of primary immunodeficiencies, namely in the group of combined primary immunodeficiency states with syndromic manifestations [19].

DESCRIPTION OF THE CLINICAL CASE

Here we present a clinical case of a patient aged 7 with diagnosed Jacobsen syndrome. The patient's parents gave consent to the use of information, including the child's photo, in research and publication.

The boy K. Was born from the second pregnancy, second birth, in the 37th week of gestation. Heart disease was recorded parenterally at 18 weeks. Birth weight is 2030 g, length — 46 cm, AS (Apgar score) — 7/8 points. Tetralogy of Fallot is diagnosed in the neonatal period (aortic dextroposition, membranous ventricular septal defect up to 6,9 mm, secondary defect of interatrial septum up to 5,0 mm, interventricular septum hypertrophy). Circulatory failure – 1B. FC 2 (NYHA). There is intrauterine growth retardation of grade III, abnormalities of the facial skeleton. Radical correction of double-outlet right ventricle was carried out at the age of 10 months.

Due to congenital anomaly, the child has been examined by a geneticist, inherited metabolic diseases are excluded, the normal male karyotype is established (46 XY), dysplastic phenotype has been ascertained: facial dysmorphism, trigonocephaly, hypertelorism, antimongoloid slant, ptosis, highly arched palate, anomaly of the external auditory canal on the left, sparrow chest (fig. 1).

Psychomotor retardation, restless behaviour, sleep disruption and autoaggression were observed from the first month of life. The patient was observed by the neurologist with the diagnosis "Symptomatic epilepsy". Mental retardation. Behavioral disorders. Alalia. At the age of 7 the patient has sign language, says single words, does not fix attention; there is motor awkwardness and a significantly limited scope of actions.

Polycystic left kidney, 1-2 degree of chronic kidney disease, is diagnosed at the age of 5. At an early

Рис. 1. **Признаки лицевого дисморфизма: тригоноцефалия, широкая переносица, гипертелоризм глаз, птоз, низко посаженные ушные раковины, тонкая верхняя губа**
Fig. 1. **Signs of facial dysmorphic disorder: trigonocephaly, wide bridge of the nose, hypertelorism of the eyes, ptosis, low-set auricles, thin upper lip**

age the by experienced frequent respiratory infections — ARVI (up to 9 times per year), pleural and purulent otitis media, bronchitis, poor weight gain. Till the age of 3 there were 4 reported episodes of purulent otitis; he was hospitalized twice with bronchopneumonia, got repeated antibiotic therapy (at least 4 per year). From 1 year 4 months complete blood count has revealed thrombocytopenia in the range of 78–88*10^9/l, leukopenia — 3,3–1,6*10^9/l. At the age of 3 the boy came to the attention of the allergist-immunologist of the Regional Children's Clinical Hospital in Stavropol, there was a significant reduction in TREC (T-cell receptor excision circle) rates, all populations of T-lymphocytes, hypoimmnoglobulinemia (Table 1). Given a distinctive phenotype, primary immunodeficiency, DiGeorge syndrome, was suspected. However, parathyroid hormone and ionized calcium were within reference values. Substitution therapy with intravenous immunoglobulins (IVIG) was initiated, followed by subcutaneous immunoglobulin (SCIG); preventive antimicrobial therapy (cotrimoxazole, fluconazole, azithromycin) was prescribed.

To clarify the diagnosis in FSBI Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, fluorescence in situ hybridization FISH on chromosome 22 was conducted, however, 22q11.2 deletion was not found. The child's blood was sent for NGS-sequencing (next generation sequencing), "immunological panel". There was a two-fold reduction in reads of all FLI-1 gene exons, localized on chromosome 11 that pointed to deletion of one of the two gene copies. When specifying the size of the defect by molecular genetic microarray, there was identified terminal deletion on the region of chromosome 11 11q24.2q25 at a size of 10084933 base pairs with coverage of 44 genes in the imbalance region as well as microduplication of chromosome 16 16p13.11 at a size of 14435773 base pairs (31 genes) and chromosome 22 22q13.31q13.33 with a length of 6730554 base pairs (52 genes) that indicated an unbalanced translocation between *11q* and *22q* with high probability. The child got the confirmed rare syndromal immunodeficiency: Jacobsen syndrome. Paris-Trousseau thrombocytopenia. The number of genes in the imbalanced region included the genes, responsible for the development of immune responses (TIRAP, FLI-1, JAM3).

In order to estimate our patient's immune dysfunction, we have analyzed levels of immunophenotyping and serum immunoglobulins during the 4-year follow-up (Table 1). There is a critical decrease in TREC and KREC ("BT test" ("Generium", Russia)), persistent T-cell immunodeficiency with a decrease in the level of total T-lymphocytes, T-helper cells, T-cytotoxic lymphocytes. A reduction in naive T-helper

Table 1. **Investigation of subpopulations T-, B-lymphocytes, immunoglobulins and platelets in a patient with Jacobsen syndrome**
Таблица 1. **Исследование субпопуляций Т- и В-лимфоцитов, иммуноглобулинов и тромбоцитов у пациента с синдромом Якобсена**

Indicators	3 years	5 years	6 years	7 years	Norm
Leukocytes*10^9/l	3,8	2,23		3,5	6,1–9,9
Lymphocytes/μl	1216	820	590	1,2	1,5–7,0
T-cell $CD3^+$/μl	510	500	650	420	900–4500
Helper T-cell $CD3^+CD4^+$/μl	310	300	460	290	500–2400
Naive helper T-cell $CD3^+CD4^+CD45^+CD197^-$/μl		46,5	53		200–2500
Memory helper T-cell TEMRA $CD3^+CD4^+CD45^+CD197^-$/μl		15,3	66,6		0,025–25
Cytotoxic T-cell $CD3^+CD8^+$/μl	150	140	160	110	300–1600
Naive cytotoxic T-cell $CD3^+CD8^+CD45^+CD197^+$/μl		34,1	40,3		42–1300
Memory cytotoxic T-cell TEMRA $CD3^+CD8^+CD45^+CD197^-$/μl		58,7	37,9		57–340
B-cell $CD19^+$/μl	280	100	120	120	200–2100
Naive B-cell $IgD^+IgM^+CD27^-$/μl		75	91		147–431
Switched memory B-cell $IgD^-IgM^-CD27^+$/μl		5	5,2		31–94
NK-cell $CD16^+CD56^+$/μl	360	250		160	100–1000
TREC/μl	1,9	2,9	0		30–327
KREC/μl	48,1	36	20,9		75–541
IgA (g/l)	0,31	0,27	0,28	0,41	0,9–1,9
IgM (g/l)	0,34	0,17	0,12	0,2	0,8–1,9
IgG (g/l)	2,9	5,52	8,79	9,0	8,7–11,7
Platelets*10^9/l	60	80	78	95	204–356

cells and T-cytotoxic T-lymphocytes as well as naive B-lymphocytes and switched memory B-lymphocytes (Switched memory B-cell) was shown. The reduction of these indicators was combined with hypoimmunoglobulinemia.

Levels of B-lymphocytes, serum IgA and IgM remained low throughout the follow-up period. IgG levels were normalized due to regular replacement IVIG/SCIG therapy.

Given the presence of FLI-1 gene deletion, causing the development of thrombocytopenia with dense platelet granule defect, there was functional platelet study — a decrease in platelet aggregation with ristocetin up to 29 % and adrenaline to 38% was noted, aggregation with ADP (adenosine diphosphate) was within normal limits — 36 %.

Serious systemic infectious diseases were not revealed against the background of preventive therapy.

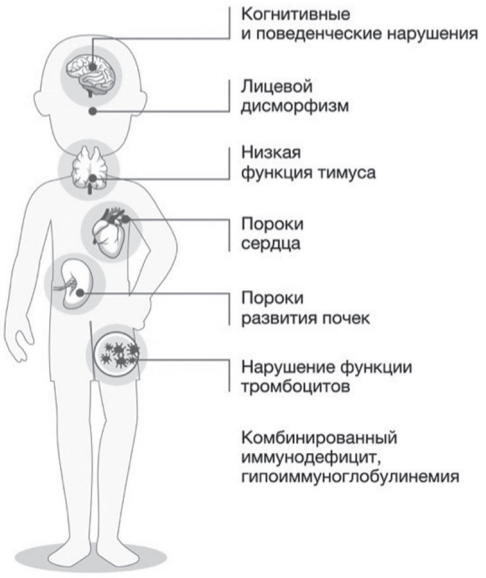

Fig. 2. **Clinical features of Jacobsen syndrome**
Рис. 2. **Клинические особенности синдрома Якобсена**

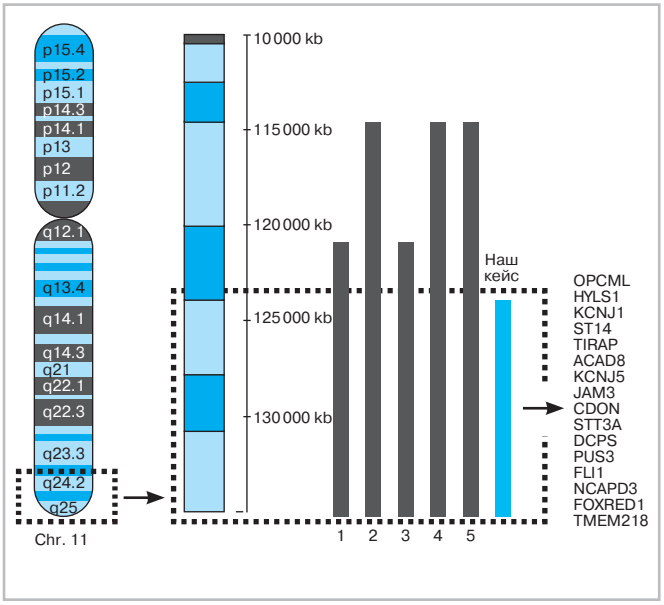

Fig. 3. **Deletion *11q24.2q25* in a patient with partial Jacobsen syndrome. On the left is chromosome 11 with a critical region of deleted genes in comparison with deletions described in available sources [5, 20, 21, 22, 24]. On the right are the deleted genes**
Рис. 3. **Делеция *11q24.2q25* у пациента с частичным синдромом Якобсена. Слева — хромосома 11 с критической областью удаленных генов в сравнении с делециями, описанными в доступных источниках [5, 20, 21, 22, 24]. Справа — удаленные у пациента гены**

DISCUSSION

Jacobsen syndrome is a rare form of a genetic disease that has recently been classified as primary combined immunodeficiency [15, 19].

The presented case corresponded to the complete clinical phenotype of the disease, despite the genetic traits of partial Jacobsen syndrome. Our patient experienced typical dysmorphic features such as low growth, microcephaly, facial skeleton anomaly, congenital heart disease, chronic kidney disease, mental retardation, cytopenic syndrome (fig. 2).

In recent years, researchers have focused on genotype-phenotype correlations as well as candidate gene reading, responsible not only for cognitive impairment and multiple malformations in patients with Jacobsen syndrome, but also for immune defects [20, 33]. The deletion level in Jacobsen syndrome may vary (fig. 2). Its level in our clinical case is much lower, in comparison with the deletions, described in other sources (fig. 3).

Three genes in the deleted region 11q24.2q25 were associated with the defect in immune regulation (FLI-1, TIRAP, JAM3).

It is known that FLI-1 encodes a transcription factor, specific to erythroblast transformation. However, FLI-1 heterozygous deletion might cause dysmegakaryopoiesis, functional disorders of T-lymphocytes, deficiency of T-helper cells and a low level of serum IgM [23, 24, 25] that is confirmed in experimental models [26]. It was found that FLI-1 gene modulates a marginal zone follicular B-cell development in mice [27]. Previously it was shown that patients with Jacobsen syndrome are quite often the holders of FLI-1 gene deletion [2, 28, 29, 30]. FLI-1 gene haploinsufficiency was has been suggested as a genetic change, responsible for immune system defects in Jacobsen syndrome.

The number of gene in the imbalance area also included TIRAP genes (607948, 611162, 614382),

encoding signaling protein of Toll-like receptors — TLR2 и TLR4. For the past two decades, their key role in reactions of the innate immune response on bacterial lipopolysaccharides has been determined and their relevance in antitumor immunity has been confirmed [31].

JAM3 gene is part of the family of connective-tissue adhesion molecules with high expression on the cell surface of T-cytotoxic lymphocytes and activated cells. Besides, there is a large number of JAM3 molecule, presented on megakaryocytes and platelets that implies its part in the inflammatory process, mediated by monocytes [2].

Immunological data on patients with Jacobsen syndrome in the world is significantly limited, however, there are accumulated reports on serious disorders in the process of maturation and differentiation of all compartments of T- и B-lymphocytes in the syndrome of terminal deletion 11q [32].

Our patient has experienced persistent impairment of the T-cell component of immunity and antibody formation for 4 years of observation.

Previous studies have showed that T-lymphocyte reduction and [28, 32] their functional defects [15, 20] are observed in the majority of patients with 11q disorder that is often accompanied by hypersensitivity to persistent herpes viruses CMV, HSV1, VZV, human papilloma virus [34].

In the work of Baronio M. and colleagues (2022) 66,7 % of patients with JS had a defined reduction in $CD3^+$-cells, 58,3 % — T-helpers. Naive T-helpers were low in 45,4% of patients, TREC rates — in 88,9 % [32].

Data on a decrease in the total number of B-lymphocytes as well as immunoglobulins in patients with JS were first published back in 1998 [33]. Several studies have shown hypoimmunoglobulinemia with reduced IgG, IgA, IgM and disorder of specific antibody formation in response to pneumococcal polysaccharide vaccine that is compatible with the phenotype of common variable immunodeficiency [15]. The literature describes clinical cases of adult patients with humoral immunodeficiency manifestations, which exacerbated over time [23, 34]. For example, a girl with JS has suffered from recurrent sinopulmonary infections since the age of 18, she experienced a decreased IgG level, a low number of switched memory B-cells as well as disorder of specific antibody formation [34]. A low number of B-lymphocytes with $IgD^-IgM^-CD27^+$ phenotype is also noted in other studies [15] which has coincided with the obtained data.

Depending on eliminated genes, various immunological phenotypes can be observed, however, their correlation with deletions of particular genes, situated in 11q region, are not well understood. Trachsel T. And colleagues (2022 г.) described a patient with JS and severe primary immunodeficiency, who had decreasев antibody titers against *Haemophilus influenza*, content of B-lymphocytes and switched memory B-cells. Another patient with heterozygous deletion of TIRAP, FLI-1, NFRKB, THYN1 and SNX19 suffered a severe bacterial infection, had predominantly a low number of switched memory B-cells [30]. There is an opinion that clinical manifestations of immunodeficiency in patients with JS can have varying degrees of severity, however, they increase with age in the absence of treatment [23, 28, 34, 35].

CONCLUSION

Patients with partial 11q deletion have a high risk of inborn immunity errors due to loss the genes, responsible for immune responses, which function is only being studied. The presented clinical case in conjunction with literature data demonstrates the importance of immunological observation of patients with JS. We have shown that even quite small 11q deletion might cause the formation of severe combined immunodeficiency, that's why patients with JS require a regular immunological screening by lymphocyte immunophenotyping as well as defining serum immunoglobulins. It should be noted that immunological disorders might develop over time and require to be re-tested. In case of quantitative and qualitative defect of T- and B-lymphocytes as well as serious infectious complications, it is necessary to consider preventive administration of antibacterial agents and replacement therapy with immunoglobulin preparations.

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THE AUTHORS' CONTRIBUTION TO THE WORK

Liudmila Yu. Barycheva — concept of the article, text development, literature review, editing.
Leila I. Bachieva — literature review, text development, translation into English.
Natal'ja A. Koz'mova — patient monitoring, laboratory examination.

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Барычева Л. Ю. — концепция публикации, написание текста, обзор литературы, редактирование.
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