DOI 10.25789/YMJ.2022.78.08

УДК617.723.2:616.31.002

V.A. Klavdenkova, K.E. Belozerov, A.A. Yakovlev, Z.S. Shogenova, L.I. Andaryanova, E.V. Gaidar, V.V. Masalova, T.L. Kornishina, E.A. Isupova, L.S. Snegireva, O.V. Kalashnikova, L.S. Sorokina, M.A. Kaneva, T.N. Nikitina, T.S. Likhacheva, I. A. Chikova, T.V. Gabruskaya, T.E. Burtseva, V.M. Argunova, P.A. Sleptsova, S.G. Boeskorova, L.V. Leontieva V.G. Chasnyk, M.M. Kostik

BEHCET'S DISEASE IN RUSSIA: DIAGNOSTIC AND TREATMENT EXPERIENCE OF CLINICS IN ST. PETERSBURG AND YAKUTIA

Saint-Petersburg State Pediatric Medical University: **KLAVDENKOVA Vera Alekseevna** – student at the Department of Pediatrics, e-mail: vera1klavdenkova@yandex.ru; **BELOZEROV Konstantin Evgenievich** – clinical resident of the Department of Hospital Pediatrics, e-mail: biancolago@bk.ru; **YAKOVLEV Alexander Alexandrovich** – clinical resident of the Department of Hospital Pediatrics, e-mail: alexandr.med18@gmail.com, **SHOGENOVA Zaira Sikhatgerievna** – Clinical Resident of the Department of Hospital Pediatrics, e-mail: z.shogenova98@mail.ru; AN**DARYANOVA Lyubov Ildarovna** – clinical resident of the Department of Hospital Pediatrics, andaryanova11@yandex.ru; **GAIDAR Ekaterina Vladimirovna** – rheumatologist, Ph.D. in medical sciences; e-mail: gaidare85@gmail.com; **MASALOVA Vera Vasilievna** – rheumatologist, assistant of the chair of hospital pediatrics of SPSPU, e-mail: masalova.vera@gmail.com; **KORNISHINA Tatiana Leonidovna** – Pediatric Cardiologist, Assistant of the Department of Hospital Pediatrics, e-mail: tk.06@mail.ru; **ISUPOVA Evgenia Alekseevna** – rheumatologist, Clinic SPSPMU; Ph.D. in medical sciences; e-mail: miaposta@list.ru; **SNEGIREVA Lyudmila Stepanovna** – rheumatologist, Clinic SPSPMU; phycisian of the highest category; e-mail: l.s.snegireva@mail.ru; **KALASHNIKOVA Olga Valerievna** – rheumatologist, head of pediatric department No.3 of the Clinic SPSMU; Associate Professor at the Department of Hospital Pediatrics; Ph.D. in medical sciences; e-mail: koira7@yandex.ru; **SOROKINA Lyubov Sergeevna** – rheumatologist, Clinic at SPSMU, e-mail: lubov.s.sorokina@gmail.com; **KANEVA Maria Alexandrovna** – rheumatologist of the Clinic SPSMU, e-mail: mariekan92@gmail.com; **NIKITINA Tatiana Nikolaevna** – ophthalmologist, assistant of the Department of Ophthalmology of the clinic SPSMU; **LIKHACHEVA Tatiana Serafimovna** – assistant of the Department of Hospital Pediatrics SPSPU, e -mail: tatianasl@list.ru; **CHIKOVA Irina Aleksandrovna** – Ph.D. in medical sciences, Associate Professor, Department of Hospital Pediatrics, SPSPMU; **GABRUSKAYA Tatiana Viktorovna** – Gastroenterologist, Assistant Professor of the Department of Gastroenterology, Faculty of Pediatrics and Postgraduate Education; e-mail: tatyanagabrusskaya@yandex.ru; Yakutsk Scientific Centre of Complex Medical problems, Yakutsk city: **BURTSEVA Tatiana Egorovna** – Ph.D. in medical sciences, professor of the Department of Pediatrics and Pediatric Surgery, Medical Institute, NEFU, chief of the laboratory of YSC KMP; e-mail: bourtsevat@yandex.ru; **ARGUNOVA Vera Maichnova** – head of the department of the CRC of the RH No.1 NCM, e-mail: cardiorevmatologsakha@mail.ru; **SLEPTSOVA Polina Andreyevna** – physician, CRC RH №1 NMC, e-mail: cardiorevmatologsakha@mail.ru; **BOESKOROVA Sargylana Gavrilievna** – resident of the Department of Pediatrics and Pediatric Surgery of the Medical Institute, M.K. Ammosov North-Eastern Federal University, e-mail: lanaboeskorova@gmail.com; **LEONTIEVA Lyudmila Viktorovna** – rheumatologist, YSC CMP, Yakutsk; **CHASNYK Vyacheslav Grigorievich** – Head of Hospital Pediatrics Department, St. Petersburg State Pediatric Medical University, Professor, Ph.D. in medical sciences; e-mail: chasnyk@gmail.com; **KOSTIK Mikhail Mikhailovich** – Professor, Department of Hospital Pediatrics, SPSPU, Ph.D. in medical sciences; e-mail: kost-mikhail@yandex.ru

Behcet's disease (BD) is a rare systemic vasculitis. It is rare in Russia, and the data on epidemiology are very limited. The study included 42 patients (M=19 (45.2%), W=23(54.8%)), with 26/42 (63.4%) having onset in childhood. Asians were 12/42 (28.6%), Europeans 30/42 (71.4%). Among the clinical features, the following organs and systems were affected in BB patients: oral ulcers (92.8%), genital ulcers (50%), eye lesions (42.9%), and skin lesions (45.2%). Laboratory tests showed increased non-specific inflammatory markers. The frequency of HLAB51-positivity was 50% and HLAB27-positivity 40%. Therapy: systemic corticosteroids (71.4%), colchicine (42.9%), TNF-a inhibitors (26.2%). Remission was recorded in 5/24 (20.8%) patients. Physicians in the Russian Federation are still insufficiently informed about this disease, which requires an expansion of the list of educational materials and programs for physicians of different specialties, taking into account the multiorgan nature of the lesion.

Keywords: Behcet's disease, vasculitis, golimumab, etanercept, ulcers.

Introduction: Behçet's Disease (BB, M35.2) is a systemic vasculitis of unknown etiology characterized by vascular lesions of different caliber and localization, with predominant clinical manifestations including recurrent oral and genital ulcers, uveitis, joints, gastrointestinal tract and central nervous system [2,3]. BD has a very wide geographic distribution with predominance in Asian and Middle Eastern countries; previously, BD was called the disease of the Great Silk Road, which connected China, India, Middle Eastern countries, including Turkey. The highest prevalence was reported in northern China and Iran (100 per 100,000) and Turkey (80-370.0 per 100,000). In Western Europe, IB is much less common with a prevalence of 0.1 per 100,000 in Sweden, 7.1 per 100,000 in France, and 15.9 per 100,000 in Southern Italy[2,21].An epidemiological study conducted in Paris showed that the prevalence of BD in persons of North African or Asian origin was significantly higher than in populations of European origin. Similar changes have been noted in Germany[2,21]. The disease occurs at almost any age, with a predominant debut in young adults, with a higher incidence in males. The delay in accurate diagnosis is at least three years, even in countries endemic for BD.

The etiology and pathogenesis of BD, like most systemic immune diseases, are currently not fully understood. It is assumed that immunological, genetic and infectious factors play a role in the onset of this disease. Both viral and bacterial infections, in particular streptococcus and herpes simplex viruses, have been described as trigger factors [23]. The HLA-B51 antigen, a member of the HLA-B5 gene family, is identified as a genetic marker of predisposition. HLA-B51-positive patients exhibit neutrophil hyperfunction. Cytokine production by T-lymphocytes in patients with IBD is biased toward type 1 (Th1) T-helpers, especially in the acute stage[23]. IL-1β, IL-6, and TNF-α play an important role in the induction of the immune response in IBD and, therefore, represent potential therapeutic targets for the disease. IL-1 and IL-6, together with IL-21 and IL-23, are involved in T-cell activation and TNF-α in the induction of autoimmunity[14]. As mentioned above, vasculitis in BD affects almost all types and sizes of vessels. Venous lesions are more common than arterial lesions. Vein involvement leads to both superficial thrombophlebitis and deep vein thrombosis[16]. The mechanisms of thrombosis in BD are still unclear. It is supposed that endothelial

dysfunction and neutrophil infiltration of the vascular wall are the key factors in the thrombotic process [27].Neutrophils can enhance chemotaxis and effector response with formation of reactive oxygen species, phagocytosis, formation of neutrophil extracellular traps and secretion of cytokines, capable to cause Th1-mediated immune response. Moreover, reactive oxygen species produced by neutrophils contribute to endothelial dysfunction and, through modification of fibrinogen structure, to thrombosis development. [25].

In the 1990s, the International Study Group (ISG) criteria were introduced, which are most commonly used in real medical practice and reflect the clinical picture [2,27]. Since 2014, an updated version of these criteria, International Criteria for Behçet's Disease (ICBD), was issued, where the pathergy test was not a mandatory but useful method [2,3]. In 2016, the Consensus classification criteria for paediatric Behçet's disease was developed, in which the paternity test was not included at all[20]. A comparison of diagnostic criteria is presented in Table 1 for clarity. The BDCAF (Behçet Disease Current Activity Form) index is also useful for practicing physicians to assess the overall activity of BD [3].

Objective: to describe clinical, laboratory, instrumental characteristics and outcomes of IBD in patients from different regions of the Russian Federation.

Materials and Methods: Included data from case histories of patients from 2014-2021 who were examined in the Third Pediatric and Ophthalmologic Departments of the SPbSPMU Clinic, the Rheumatology Department of the Yakutsk Republican Clinical Hospital and the Cardiorheumatology Department of the Pediatric Center of the Republican Hospital №1-National Center of Medicine, Yakutia, in a continuous, multicenter retrospective cohort study. We evaluated epidemiology, family history, clinical and laboratory features, treatment options and outcomes. Diagnosis was made according to the 2016 Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort (PEDBD). [20].

Results: In our study, we included data on 42 patients of different ages, sex, and racial backgrounds. The sex distribution was approximately equal, with a predominance of European origin. Childhood debut occurred in 63.4% of patients, but in one patient a reliable age of debut could not be established. A burdened family history of immunopathological diseases was described in 2 patients: maternal psoriasis (n=1), Crohn's disease (n=1). Maternal relatives of two patients had recurrent oral and genital ulcers, but the diagnosis of Behcet's disease was not established.

Clinical manifestations: Among the clinical manifestations, recurrent oral aphthas/ulcers were reported in the vast majority of patients (n=39, 92.8%), while genital ulcers were reported in half of patients (n=21, 50%). Oral mucosal ulcers were the most frequent debut manifestation of BD (n=29/40, 72.5%), which was the reason for referral to specialists. Eye lesions (anterior, posterior uveitis, iridocyclitis) (n=18/42, 42.9%), joint syndrome (arthritis or prolonged arthralgia) (n=24/42, 57.1%) were quite common, involvement of the nervous system (n=9/42, 21.4%) and gastrointestinal tract (n=15/42, 35.7%) were much less common, fever syndrome was recorded in 5 patients (11.9%). The fact of thrombus formation in the right ventricular cavity in one patient, as well as pulmonary embolism in a patient with hereditary thrombophilia (mutation in the RAI -4G/4G gene) is interesting. We also noted that Crohn's disease was diagnosed in 4 patients. Pathergy test was performed in 6 patients and was positive in half of them.

Laboratory changes: moderate inflammatory activity was laboratory noted: elevated CRP in 12/42 (28.6%) patients, with maximum numbers up to 65 mm/h, and CRP in 11/42 (26.2%), but it was impossible to estimate maximum values due to different laboratory reference values and methods of determination. Specific immunological tests were not examined in all cases: HLA-B51 was detected in 6/12 (50%) of the examined patients, and HLA-B27 antigen in 2/5 (40%). HLA A1, 25; B7,35 were detected in one.

Systemic glucocorticosteroids (71.4%) were the main mode of treatment for Behçet's disease. Non-biologic disease-modifying antirheumatic drugs were also used (n=29/42, 38.7%), in particular methotrexate, mycophenolic acid, azathioprine, colchicine, cyclophosphamide. Colchicine, was used in 18 patients (42.9%). In addition, therapy with genetically engineered immunobiological drugs (GIBP) of different groups was used. TNF-alpha blockers (etanercept, adalimumab, golimumab, infliximab) were used in 11 patients (26.2%), interleukin-1 inhibitor (canakinumab) in one, interleukin-6 inhibitor (tocilizumab) in two, and the Janus-kinase blocker tofacitinib was used in one patient. Due to lack of information, only 24 patients could be evaluated for long-term follow-up, of whom only 5 were able to achieve remission and no exac-

Table1

Diagnostic criteria for BB [2,3,35,20]

International StudyGroup (ISG), 1990		International Criteria for Behçet's Disease (ICBD), 2014		Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: PEDBD, 2016	
Main symptom	Recurrent oral ulcers	Aphthous stomatitis	2	Oral mucosal lesions	1
Additional signs	Recurrent genital ulcers	Genital ulcers	2		
		Eye lesion	2	Genital lesions	1
	Skin lesion	Skin lesion	1	Eye lesion	1
		Nervous system lesions	1	Nervous system lesions	1
	Positive paternity test	Vascular lesion	1	Sign of vasculitis	1
		Positive paternity test	1*		
Oral ulcers + 2 additional signs		A score of ≥4 is required. * counts only when the test is performed, not required		Three of six points are required	

erbations were recorded. Among those who were prescribed GIBP, three patients had to be switched to another drug because of insufficient efficacy and control of the disease. Detailed demographic characteristics of the patients included in the study are shown in Table 2.

Discussion: A study by Isabelle Koné-Paut et al. analyzed 86 cases of BD from Turkey, France, Iran, and Saudi Arabia. Researchers noted sex differences in the clinical presentation of BD in children. Although gender did not affect the occurrence of BD, male patients had a more malignant course because they were found to have an increased risk of necrotizing folliculitis, eye disease, and vascular complications, including arterial aneurysms and deep vein thrombosis. In girls, the course of the disease was more benign, with isolated mucosal lesions and arthritis [22]. Probably, testosterone has a role in the pathogenesis of a more malignant course of IB in male patients, since it not only affects the function of neutrophils, but also changes the expression levels of IL-10, TLR4, IL23R, CCR1, ERAP1 on mononuclear cells and neutrophils [34]. In a study including 3,382 patients with IB between October 1986 and December 2005 at the Behçet Department of Ankara University Medical School and the private clinic of Atmac, 110 children (3.3%) were found to have the disease in childhood. All patients were residents of Turkey, and the boy/girl ratio was 1.7:1. The age of manifestation was 1 to 16 years (mean: 11.63 ± 3.46) and the age of diagnosis was 6 to 16 years. (mean: 14.15 ± 2.13), indicating a delay in diagnosis of 2 to 3 years [9]. Depending on the presence of primary and secondary symptoms, several types of BD are distinguished (Table 3):

The initial manifestations of BD are most often recurrent oral ulcers and genital ulcers. Skin lesions are represented by papulopustular rashes and erythema nodosum and are quite common [9]. Among our patients, oral and genital ulcers were the most frequent symptoms, while cutaneous manifestations were less common. The most frequent abdominal complaints are abdominal pain, diarrhea, nausea, weight loss and bloating, which leads patients with BD to a gastroenterologist. According to the literature, the gastrointestinal (GI) tract is affected in 15%-50% of patients based on complaints and symptoms, and in 0.7%-30% based on instrumental findings, with GI involvement being more common in children [35, 13, 18]. A distinctive feature of gastrointestinal syndrome in BD is involvement of any gastrointestinal region,

Table2

Characteristics of patients with Behcet's disease

Parameter	Result n (%)
Demographics	
Gender, M/W, n (%)	19 (45.2) / 23 (54.7)
Debut of disease in childhood, n (%)	26/41 (63.4)
Asian/European, n (%)	12 (28.6) /30 (71.4)
Clinical manifestations	
Oral ulcers, n (%)	39 (92.8)
Genital ulcers, n (%)	21(50)
Fever, n (%)	5 (11.9)
Eye damage (uveitis), n(%)	18 (42.9)
Skin lesions (erythema nodosum, panniculitis), n (%)	19 (45.2)
Pathergy test, n (%), n (%)	3/6 (50)
Central nervous system lesions, n (%)	9 (21.4)
Gastrointestinal tract lesions, n (%)	15 (35.7)
Arthralgia/arthritis, n (%)	24 (57.1)
Thrombovaculitis (venous thrombosis), n (%)	6 (14.3)
Laboratory characteristics	
Erythrocyte sedimentation rate, Me (25%-75%)	26 (21-65)
Erythrocyte sedimentation rate acceleration, n (%)	12 (28.6)
Increased C-reactive protein (> 5 mg/L), n (%)	11 (26.2)
Anemia, n (%)	8 (19)
Rheumatoid factor seropositivity, n (%)	2/11 (18.2)
Presence of HLA-B27 antigen, n (%)	2/5 (40)
Presence of HLA-B51 antigen, n (%)	6/12 (50)
Therapy	
Systemic corticosteroids, n (%)	30 (71.4)
Methotrexate, n (%)	4 (9.5)
Mycophenolic acid, n (%)	1 (2.3)
Azathiaprine, n (%)	11 (26.2)
Colchicine, n (%)	18 (42.9)
Cyclophosphamide, n (%)	4 (9.5)
TNF-a inhibitors, n (%): Etanercept, n (%) Adalimumab, n (%) Golimumab, n (%) Infliximab, n (%)	16 (38.1) 1 (2.3) 7 (16.7) 4 (9.5) 4 (9.5)
Kanakinumab, n (%)	1 (2.3)
Tocilizumab, n (%)	2 (4.7)
Tofacitinib, n (%)	1 (2.3)
Outcomes	
Remission, n (%)	5/24 (20.8)
GIBT change, n (%)	3/11 (27.3)
Associated pathology, n (%): Crohn's disease. Bronchial asthma	 4 (9.5) 1 (2.3)

Abbreviations: TNF-a - tumor necrosis factor-a.

diffuse involvement occurs in no more than 15% of patients, more often there is local ulceration with localization in the small and large intestine [35]. The most difficult task is differential diagnosis of BD and inflammatory bowel disease (IBD). In our cohort, 15/42 (35.7%) had gastrointestinal involvement, with Crohn's disease diagnosed in 4 patients.

The following "red flags" noted on endoscopic examination of the intestine (fibrocolonoscopy) are assumed to be characteristic of BD: large (over 1 cm), round or irregularly shaped ulcers, with a perforated appearance, usually located in the deep layers; longitudinal ulcers are rare; less than six round and focal ulcers [35].

As for the much threatened complication of some rheumatologic diseases, macrophage activation syndrome (CAM), it is not such a characteristic clinical feature for BD. An Italian review of CAM in rheumatologic pathology describes one case associated with Epstein-Barr virus[10, 24]. Studies in patients with BD have traditionally shown signs of significant activation of monocytes and macrophages, as well as increased numbers and activation of circulating T cells and natural killer cells [35].

Only 12 (28.6%) patients were positive for the HLA-B51 antigen and 2/5 (40%) for the HLA-B27 antigen. Determination of HLA-B51 may be useful when a familial case of IBD is suspected. According to the literature, patients with simultaneous HLA-B27 and HLA-B51 positivity had a less severe course of uveitis (less retinal involvement, fewer complications, and fewer surgical techniques) and a more favorable long-term visual prognosis than HLA-B51-associated uveitis-Behçet's [30, 7, 5].

The following scope of examinations for suspected BD is suggested (Table 4).

A special form of hypersensitivity test for BD is the patergia test (phenomenon), which is a delayed skin reaction to a needle puncture in the dermis of the forearm. The reaction is considered positive if a papule or pustule forms at the puncture site 48 hours later. Only erythema is considered negative [6].

Interestingly, in the face of new challenges associated with COVID-19, a British study showed that patients with Behcet's syndrome were not at increased risk for worse outcomes. But at the same time, it is noted that 32.2% of patients with IB had an exacerbation of at least one symptom against a new coronavirus infection [26,12].Specific data indicating that patients with BD regardless of therapy were more susceptible to SARS-CoV-2 or the more severe forms of COVID-19 are not available. In general, the course of COVID-19 did not differ from the general population, and the severity of COVID-19 infection was predominantly mild [12,15].

In the context of modern ideas about personalized medicine, as well as the importance of psychological and social adaptation of patients, it seems important to form communities where volunteers, medics and patients learn about life with chronic diseases in close connection. Such global communities have been created for patients with bronchial asthma, diabetes, and other diseases. Interestingly, in the United States there is already a similar special community for patients of the American Behçet's Disease Association - ABDA [17].However, in the Russian Federation, currently, there is no such community. When establishing the diagnosis of Behcet's disease, differential diagnosis with other diseases is an urgent issue. The main points of differential diagnosis are presented in Table 5.

Differential diagnosis of inflammatory changes in the eye is important for practicing ophthalmologists for timely diagnosis of Behcet's disease. Peculiarities of eye lesions in BD and other diseases are presented in Table 5.

Conclusion: Behcet's disease requires study and attention from doctors and researchers. Physicians in the Russian Federation are still insufficiently informed

Table3

Types of Behcet's disease [31]

Complete BD type	Incomplete BD type	Probable
Presence of 4 major symptoms: 1. Recurrent aphthae/ulcers of the mouth 2. Genital ulcers 3. Eye involvement (anterior/ posterior uveitis, retinal vasculitis, etc.) 4. Skin involvement (erythema nodosum, pseudofolliculitis, etc.)	• Presence of 3 main symptoms, or • Presence of 2 primary and 2 secondary symptoms, or • Presence of recurrent ocular inflammation combined with one or more major symptoms.	• Presence of only 2 primary signs, or • Presence of 1 major and 2 minor signs.

Table4

Laboratory and instrumental diagnosis of BD

Laboratory data	Instrumental data
General blood count: increased sedimentation rate, mild anemia, neutrophilic leukocytosis (in the active stage of the disease).	Radiography of affected joints (to detect joint lesions) and overview radiography of the lungs (to detect pulmonary vascular lesions)
Biochemical blood tests: increase in C-reactive protein, alpha-trypsin, evaluation of blood electrolytes, liver tests, transaminases, and lipid spectrum.	Retinal fluorescence angiography (yellow spot edema or ischemia)
Immunological blood test: increased levels of circulating immune complexes, increased rheumatoid factor.	Abdominal ultrasound (to detect organic lesions of the gastrointestinal organs)
HLA typing: detection of HLA-B51	ECG (for the detection of cardiac lesions)
General urinalysis: moderate proteinuria, moderate hematuria.	EchoCG (to detect valve and myocardial damage)
	FGDS (to detect ulcerative and vascular lesions of gastrointestinal mucosa)
	Positive pathergy phenomenon

Abbreviations: GI - gastrointestinal tract, sedimentation rate – erythrocyte sedimentation rate, USG - ultrasound examination, FGDS - fibrogastroduodenoscopy, ECG - electrocardiography, EchoCG - echocardiography

Table5

Differential diagnosis of Behcet's disease [8,11]

The symptom	BD	JIA, systemic variant of debut	Periarteritis nodosa	SLE	Non-specific aortoarteritis Takayasu	Sarcoidosis	Crohn's disease
Oral/genital ulcers	+	-	-	+	-	+ (sarcoid ulcers)	+
Vasculitis	all vascular calibers	-	Necrotizing vasculitis, Aneurysms, stenoses, or occlusions of arteries	Microcirculatory blood vessels	Various vascular lesions (predominantly large caliber)	-/+	-/+
Rash	Papulopustular rash and erythema nodosum	Erythematous rash	ulcerative defects and lesser	butterfly erythema, heliotrope rash		erythema nodosum	erythema nodosum
Reference points	HLA B51, paternity test, all types of vascular lesions	Arthritis accompanied by prolonged fever	Specific histologic picture	ANF, multiorgan lesions, DNA antibodies	Differential BP in the extremities, vascular ultrasound findings, hypotrophy of the extremities, major vascular lesions	Intrathoracic lymph node study, bronchoscopy, spirography, histological study	Endoscopic findings, increased fecal calprotectin levels

Abbreviations: BP - blood pressure, ANF - antinuclear factor BD - Behcet's disease, SLE - systemic lupus erythematosus, JIA - juvenile idiopathic arthritis

Table6

Differential diagnosis of ocular lesions in IB [19, 28, 29, 32, 33, 1,4]

The symptom	BD	JIA	Sarcoidosis	HLA-B27-associated uveitis	Nephritis (TINU)-syndrome
Age of debut	More often in middle-aged people	More often in children	More often in children	More often in older individuals	More often in children and adolescents
Eye damage	Bilateral	Bilateral	Bilateral	Unilateral	Bilateral
Intraocular pressure	Normal or low at first, then increased	Increased	Increased	Normal or low	Increased
Extraocular manifestations	Oral ulceration, skin lesions, vasculitis	Fever, rash, hepatosplenomegaly, lymphadenopathy, serositi	Arthritis and skin lesions	Spondyloarthritis	Fever, weight loss, abdominal and flank pain, and arthralgia (related to renal dysfunction)
Complications	Cataracts, increased intraocular pressure, macular edema or maculopathy, and optic atrophy	Bacillary keratopathy, cataracts, posterior synechiae, glaucoma, maculopathy, hypotonia, and amblyopia	Keratopathy, cataracts, and glaucoma	Pupillary occlusion, cataracts, glaucoma, corneal dystrophy	Optic disc edema, multifocal chorioiditis, decreased visual acuity

Abbreviations: BB - Behcet's disease, JIA - juvenile idiopathic arthritis

about this disease, which requires expanding the list of educational materials and programs for physicians of different specialties, given the multiorgan nature of the lesion.

Funding: This work was supported by grant 20-45-01005 from the Russian Science Foundation.

Conflict of interest: all authors declared the absence of competing interests.

References

1. Drozdova E.A. Klinicheskaya diagnostika HLA–B27 associirovannogo uveita [Clinical diagnosis of HLA-B27 associated uveitis]. Russian Journal of Ophthalmology. Clinical Ophthalmology. 2005; 6(4): 137-139 (In Russ.).

2. Klinicheskie rekomendacii "Bolezn' Bekhcheta (BB) [Clinical guidelines "Behcet's disease (BD)]. Approved by the Ministry of Health of Russia, 2018.

3. Lisitsyna T.A., Alekberova Z.S., Goloyeva R.G. Bolezn' Bekhcheta: klinicheskie proyavleniya, sovremennye principy diagnostiki i terapii [Behcet's disease: clinical manifestations, modern principles of diagnosis and therapy]. Nauch-

no-prakticheskaya revmatologiya [Scientific and practical rheumatology]. 2019; 57(5): 553-563 (In Russ.). https://doi.org/10.14412/1995-4484-2019-553-563

4. Salugina S.O., Kapshrgina L.A., Starikova A.V. Revmaticheskie zabolevaniya i porazhenie glaz u detej [Rheumatic diseases and eye lesions in children]. Nauchno-prakticheskaya revmatologiya [Scientific-practical rheumatology]. 2004; 1: 78-81 (In Russ.).

5. Ahn JK, Park YG. Human leukocyteantigen B27 and B51 double-positive Behçet uveitis. Arch Ophthalmol. 2007 Oct;125(10):1375-80. doi: 10.1001/archopht.125.10.1375. PMID: 17923546.

6. Akman-Demir, G., Saip, S., &Siva, A. Behçet’s Disease. Current Treatment Options in Neurology, 13(3), 290–310. doi:10.1007/s11940-011-0120-2

7. Akpolat T, Koç Y, Yeniay I, Akpek G, Güllü I, Kansu E, Kiraz S, Ersoy F, Batman F, Kansu T, et al. Familial Behçet's disease. Eur J Med. 1992 Nov;1(7):391-5. PMID: 1341477.

8. Ambrose, N.L., &Haskard, D.O. (2012). Differential diagnosis and management of Behçet syndrome. Nature Reviews Rheumatology, 9(2), 79–89. doi:10.1038/nrrheum.2012.156

9. Atmaca, L., Boyvat, A., Yalçındağ, F. N., Atmaca-Sonmez, P., &Gurler, A. (2011). Behçet Disease in Children. Ocular Immunology and Inflammation, 19(2), 103–107. doi:10.3109/09273948.2011.555592

10. Atteritano M, David A, Bagnato G, Beninati C, Frisina A, Iaria C, Bagnato G, Cascio A. Haemophagocytic syndrome in rheumatic patients. A systematic review. Eur Rev Med Pharmacol Sci. 2012 Oct;16(10):1414-24. PMID: 23104659.

11. Bonfioli, A. A., & Orefice, F. (2005). Behçet’s Disease. Seminars in Ophthalmology, 20(3), 199–206. doi:10.1080/08820530500231953

12. Bünyamin Polat, Abdulsamet Erden, Serdar Can Güven, Berkan Armağan, Özlem Karakaş, Bahar Özdemir, Hakan Apaydın, Eren Usul, İhsan Ateş, Orhan Küçükşahin, Ahmet Omma, COVID-19 in patients with Behçet’s disease: Outcomes and rate of Behçet’s exacerbations in a retrospective cohort, Modern Rheumatology, 2021; roab016, https://doi.org/10.1093/mr/roab016

13. Cheon JH, Çelik AF, Kim WH. Behçet’s Disease: Gastrointestinal Involvement. 1st ed. In: Yazici Y, Yazici H, editors. Behçet’s Syndrome (NY): Springer; 2010;165–189.

14. Costagliola, G., Cappelli, S., & Consolini, R. (2020). Behçet’s Disease in Children: Diagnostic and Management Challenges. Therapeutics and Clinical Risk Management, Volume 16, 495–507. doi:10.2147/tcrm.s232660

15. Espinosa, G., Araujo, O., Amaro, S., Bodro, M., Moreno, P. J., Moreno, R. Cervera, R. (2020). COVID-19 and Behçet’s disease: clinical case series. Annals of the Rheumatic Diseases, annrheumdis–2020–217778. doi:10.1136/annrheumdis-2020-217778

16. Hindawi Publishing Corporation. Pathology Research International. Volume 2012, Article ID 690390, 9 pages. doi:10.1155/2012/690390 6

17. https://www.behcets.com. Датаобращения: 14.03.2022

18. Hung CH, Lee JH, Chen ST, Yang YH, Lin YT, Wang LC, Yu HH, Chiang BL. Young children with Behçet disease have more intestinal involvement. J PediatrGastroenterolNutr. 2013;57:225–229.

19. Kitaichi, N., & Ohno, S. (2008). Behçet Disease in Children. International Ophthalmology Clinics, 48(3), 87–91. doi:10.1097/iio.0b013e31817d8393

20. Koné-Paut I, Shahram F, Darce-Bello M, Cantarini L, Cimaz R, Gattorno M, Anton J, Hofer M, Chkirate B, Bouayed K, Tugal-Tutkun I, Kuemmerle-Deschner J, Agostini H, Federici S, Arnoux A, Piedvache C, Ozen S; PEDBD group. Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: PEDBD. Ann Rheum Dis. 2016 Jun;75(6):958-64. doi: 10.1136/annrheumdis-2015-208491. Epub 2015 Dec 23. PMID: 26698843.

21. Koné-Paut, I. Behçet’s disease in children, an overview. PediatrRheumatol 14, 10 (2016). doi:10.1186/s12969-016-0070-z

22. Koné-Paut, I., Yurdakul, S., Bahabri, S.A., Shafae, N., Ozen, S., Özdogan, H., & Bernard, J. L. (1998). Clinical features of Behçet’s disease in children: An international collaborative study of 86 cases. The Journal of Pediatrics, 132(4), 721–725. doi:10.1016/s0022-3476(98)70368-3

23. Kurokawa, M.S., Yoshikawa, H., & Suzuki, N. (2004). Behçet’s Disease. Seminars in Respiratory and Critical Care Medicine, 25(05), 557–568. doi:10.1055/s-2004-836147

24. Lee SH, Kim SD, Kim SH, Kim HR, Oh EJ, Yoon CH, Lee SH, Kim HY, Park SH. EBV-associated haemophagocytic syndrome in a patient with Behçet's disease. Scand J Rheumat

25. Mantovani A, Cassatella MA, Costantini C, Jaillon S. Neutrophils in the activation and regulation of innate and adaptive immunity. Nat Rev Immunol. 2011;11(8):519–531. doi:10.1038/nri3024

26. Pakhchanian H, Raiker R, KardeşS. COVID-19 among patients with Behçet syndrome in the United States [published online ahead of print, 2021 Sep 25]. ClinRheumatol. 2021;1-3. doi:10.1007/s10067-021-05936-9

27. Pineton de Chambrun, M., Wechsler, B., Geri, G., Cacoub, P., &Saadoun, D. (2012). New insights into the pathogenesis of Behçet’s disease. Autoimmunity Reviews, 11(10), 687–698. doi:10.1016/j.autrev.2011.11.026

28. Rathinam SR, Babu M. Algorithmic approach in the diagnosis of uveitis. Indian J Ophthalmol. 2013;61(6):255-262. doi:10.4103/0301-4738.114092 30

29. Saadoun, D., & Wechsler, B. (2012). Behçet’s disease. Orphanet Journal of Rare Diseases, 7(1), 20. doi:10.1186/1750-1172-7-20

30. Sakly N, Boumiza R, Zrour-Hassen S, Hamzaoui A, Ben Yahia S, Amara H, Khairallah M, Mahjoub S, Bergaoui N, Ghedira I. HLA-B27 and HLA-B51 determination in Tunisian healthy subjects and patients with suspected ankylosing spondylitis and Behçet's disease. Ann N Y Acad Sci. 2009 Sep;1173:564-9. doi: 10.1111/j.1749-6632.2009.04756.x. PMID: 19758200.

31. Takano, M., Miyajima, T., Kiuchi, M., Ohmori, K., Amemiya, H., Yokoyama, T., … Sato, H. (2008). Behçet Disease and the HLA System. Tissue Antigens, 8(4), 95–99. doi:10.1111/j.1399-0039.1976.tb00572.x

32. Tugal-Tutkun I. Pediatricuveitis. J OphthalmicVis Res. 2011;6(4):259-269. 32

33. Tugal-Tutkun, I., Gupta, V., & Cunningham, E. T. (2013). Differential Diagnosis of Behçet Uveitis. Ocular Immunology and Inflammation, 21(5), 337–350. doi:10.3109/09273948.2013.795228

34. Yavuz, S., Akdeniz, T., Hancer, V. et al. Dual effects of testosterone in Behcet's disease: implications for a role in disease pathogenesis. Genes Immun 17, 335–341 (2016). https://doi.org/10.1038/gene.2016.28

35. Yazısız V. Similarities and differences between Behçet's disease and Crohn's disease. World J GastrointestPathophysiol. 2014 Aug 15;5(3):228-38. doi: 10.4291/wjgp.v5.i3.228. PMID: 25133025; PMCID: PMC4133522.