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IS IT POSSIBLE TO CUT DOWN THE NUMBER OF UNKNOWN ETIOLOGY IN UVEITIS?

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✧ ***Background.*** According to the data in national literature, uveitis comprises 5–15% among all eye diseases. The etiological data on uveitis are still under discussion. Our ***aim*** was to decrease the percent of undefined uveitis. ***Methods.*** The first part was to collect the retrospective data on uveitis etiology (2008–2012). The second one consisted of examining all new patients seen in our uveitis center at the Department of Ophthalmology of the Academician I.P. Pavlov First State Medical University (2014–2016) with up to date methods, like laser photometry, dual angiography and other laboratory and instrumental investigational tests. ***Results.*** The percent of unknown etiology was decreased from 61,9 % to 17 %. ***Conclusion.*** The complex of modern investigational ophthalmological, laboratory and instrumental methods give the opportunity not only to diminish the proportion of undefined uveitis, but also to treat patients with more specific entities.

✧ ***Keywords:*** uveitis; etiology; work-up; indocyanine green angiography.

МОЖНО ЛИ СОКРАТИТЬ ДОЛЮ УВЕИТОВ НЕЯСНОЙ ЭТИОЛОГИИ?

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✧ ***Введение.*** Увеиты — это гетерогенная группа относительно редких и сложно диагностируемых заболеваний. Она составляет 5–15 % от всей офтальмологической патологии. Высокая социальная и экономическая значимость заболевания обусловлена длительным и, в большинстве случаев, хроническим течением и частым развитием осложнений. В то же время эффективность лечения зависит от правильной и своевременной диагностики. ***Цель.*** Совершенствование диагностики увеитов при системных заболеваниях. ***Материалы и методы.*** Исследование состояло из двух частей: ретроспективный анализ 205 архивных историй болезни (2008–2012 гг.) и проспективное обследование 210 пациентов с диагнозом «увеит», обратившихся впервые для уточнения этиологии воспалительного процесса (2014–2016 гг.). Второй группе пациентов общепризнанное обследование было дополнено лазерной фотометрией, ангиографией с индоцианином зеленым и уточняющим комплексом лабораторно-инструментальных методов. ***Результаты.*** В результате полученных данных была предложена новая система комплексного обследования пациентов с диагнозом «увеит», которая позволила установить этиологию или сопутствующее увеиту заболевание в 83 % случаев, в отличие от 38,1 % при использовании общепризнанных методик. ***Заключение.*** По данным исследования, наиболее распространенными заболеваниями являются HLA-B27 ассоциированный передний увеит и задний увеит, ассоциированный с саркоидозом. Разработанная система клинико-инструментальной диагностики помогла сократить долю увеита неясной этиологии в 3,6 раза и провести более специфическую терапию пациентам.

✧ ***Ключевые слова:*** увеит; этиология; ангиография с индоцианином зеленым.

INTRODUCTION

Uveitis accounts for 5%–15% of all ocular pathologies and occurs in 5%–7% of hospitalized patients [1, 2]. According to authors from the Helmholtz Moscow Research Institute of Eye Diseases, uveitis accounts for 7%–30% of all eye diseases, and the incidence is 0.3–0.5 cases per 1,000 population [3]. The number of patients with uveitis hospitalized in the city inpatient facilities is gradually decreasing; in 2008, only 3.2%–2.7% of the patients were admitted because of uveitis [T.I. Kuznetsova, International Ophthalmological Congress "White Nights," 2015]; in 2010, the proportion of patients hospitalized because of uveitis increased to 2.7%–2.0%. Thus, a majority of patients were treated as outpatients.

According to V.T. Tran et al. (Switzerland), the prevalence of uveitis is 17.5 cases per 100,000 population [4]. In the United States, it varies from 15 to 52 per 100,000 population [5, 6].

Epidemiological data on uveitis differ significantly worldwide depending on the geographic, genetic, nutritional, and demographic factors [7].

In India, uveitis of infectious etiology predominates; in particular, tuberculous uveitis accounts for 10% of all uveitis cases reported in India. In Saudi Arabia, an infectious etiology has already been established in a smaller percentage of cases (20.3%); uveitis of a presumably tuberculous etiology was detected in 52% of the patients, herpetic etiology was diagnosed in 26%, and toxoplasmosis was reported in 16% [9].

European data on uveitis epidemiology also vary, but to a lesser extent. In 1994, V.T. Tran et al. published the results of a retrospective analysis of case histories of 558 patients (740 eyes), conducted in a uveitis clinic at the Jules Gonin Hospital (Lausanne, Switzerland). In 69% of patients, the cause of uveitis was identified. The most common diseases were HLA-B27-associated acute anterior uveitis (15.9%), uveitis associated with herpes zoster ophthalmicus (9.7%), toxoplasmosis (9.5%), sarcoidosis (5.9%), and pars planitis (5.6%), Fuchs uveitis (5.4%), anterior uveitis caused by herpes viruses (4.1%), and acute retinal necrosis (2.3%) [4]. According to N.P. Jones (Manchester, UK, 2015), who examined 3,000 new patients, Fuchs uveitis (11.5%), sarcoidosis (9.7%), pars planitis (7.9%), idiopathic acute anterior uveitis (7.0%), and toxoplasmosis (6.9%) predominated [10].

In 2011, E.M. Nashtaei et al. conducted a meta-analysis of published epidemiological data [11]. The study included six articles from the Middle East (a total of 2,693 cases) and seven articles published in Europe (a total of 4,379 cases). The authors identified general trends in this geographical area, namely, the prevalence of anterior localization uveitis. Most of the anterior and intermediate uveitis cases were idiopathic; among the posterior ones, toxoplasmosis became the most common etiological factor, and Behcet's disease and idiopathic uveitis were the second most common etiological factors.

According to the American data, in particular, C.S. Foster, idiopathic uveitis (37.8%) prevailed among anterior uveitis, which is in contrast with the European results [12]. The association between uveitis and *HLA-B27* antigen has not been described; however, its relationship with seronegative (RF negative) HLA-B27 positive arthropathy was revealed in 21.6% of patients, with juvenile idiopathic arthritis in 10.8%, and herpes etiology (herpes simplex and varicella-zoster) in 9.7% of patients. Fuchs uveitis was noted in 5% of patients. Among the subtypes of intermediate uveitis, idiopathic uveitis (69.1%), sarcoidosis (7.5%), and multiple sclerosis (8.0%) were most common. Among the subtypes of posterior uveitis, toxoplasmosis was the most common (24.6%), idiopathic uveitis was diagnosed in 12.3% of patients, cytomegalovirus retinitis was detected in 11.6%, and its association with systemic lupus erythematosus as well as with chorioretinitis *Birdshot* (as "fine shot") was reported in 7.9%. The more rare causes of posterior uveitis were sarcoidosis (7.5%) and acute retinal necrosis (5.5%). In a smaller percentage of cases, Epstein–Barr virus-associated chorioretinitis (2.9%), toxocariasis (2.5%), Behcet's disease and syphilis (2.0% each), acute posterior multifocal placoid pigment epitheliopathy (2.0%), and serpiginous choroidopathy (1.65%) were reported. The most common causes of panuveitis were sarcoidosis (14.1%), multifocal choroiditis with panuveitis (12.1%), Behcet's disease (11.6%), systemic lupus erythematosus (9.1%), syphilis, Vogt–Koyanagi–Harada syndrome (5.5% each), *HLA-B27* antigen (4.5%), sympathetic ophthalmia (4.0%), tuberculosis (2.0%), and fungal retinitis (2.0%).

In Russian literature, published data on the uveitis etiology also vary. The studies described below were conducted not only at different times but also with differing diagnostic capabilities. The ophthalmological centers where the studies were performed were located in different geographical areas with different social and economic levels and had different specializations in the provision of ophthalmological care. Due to

these factors, the data below are difficult to compare with each other, and larger studies could contribute to obtaining the overall picture of the epidemiological data for the country.

In 1984, research was performed in the Helmholtz Moscow Research Institute of Eye Diseases. According to N.S. Zaitseva and L.A. Katznelson, among all uveitis cases, viral etiology accounted for 8.6%; focal infection, 8.6%; tuberculosis, 20.5%; toxoplasmosis, 4.3%; mixed infection, 1.5% [3]. Sarcoidosis-associated uveitis was reported in 1.3%–7.6% of patients; uveitis associated with rheumatic diseases was found in 9.4%, while Behcet's disease and Vogt–Koyanagi–Harada disease was detected in 18%. Unspecified uveitis accounted for 27.2% of the cases. According to the anatomical classification, infectious factors prevailed among the subtypes of posterior uveitis only, namely, tuberculosis and toxoplasmosis, as well as in unspecified uveitis, possibly idiopathic (28.5%), and rheumatic posterior uveitis was less common (6.4%).

The study conducted by E.I. Ustinova (1995, a total of 114 patients) in the eye tuberculosis department of the Research Institute of Phthisiopulmonology showed that among chronic endogenous uveitis cases, that of tuberculous etiology was 34%, that of herpes virus was 31%, that of systemic and syndromic diseases was 8%, that of toxoplasmosis was 4%, that of focal infection was 3%, and that with unspecified etiology was 20% [13].

According to L.A. Katargina and L.T. Arkhipova (2004), in the etiological structure of anterior uveitis, idiopathic iridocyclitis and HLA-B27-associated acute anterior uveitis are the most common, as well as rheumatoid anterior uveitis, enteroviral uveitis in children, herpetic iridocyclitis, and some others [1]. With regard to the characteristics of patients with posterior uveitis, a significant proportion presented with infectious lesions, among which toxoplasmosis (up to 30% of all posterior uveitis), tuberculosis, histoplasmosis, and toxocariasis were the most frequent. The results of the study revealed that idiopathic chorioretinitis and retinovasculitis were much more common compared with other etiological factors, and the incidence of various infectious lesions increased in immunocompromised patients (with AIDS and other conditions).

In 2011, in the city of Novosibirsk, a study on uveitis etiology was conducted (n = 226). In 50% of the cases, an infectious etiology was established; in 41%, its association with systemic diseases was revealed; and in 9%, its association with an eye injury was reported [14]. According to localization, the incidence of anterior uveitis was 61%; intermediate, 2%; posterior, 34%; generalized, 3%. In 2011–2013, a study was performed in Tyumen (n = 616) [15]. Approximately 42% of the cases were associated with systemic diseases, 29.9% with infections, and 12.7% with trauma, while the etiology in 12.7% of the patients was not established. In most cases, anterior uveitis was diagnosed (86% of patients); meanwhile, intermediate uveitis was reported in 1.1% of the cases, posterior uveitis in 11.1%, and panuveitis in 1.8%.

In 2015, in the Helmholtz Moscow Research Institute of Eye Diseases, 85 patients with a chronic course of generalized uveitis were examined [16]. In 10.6% of the patients, focal infection was detected as the cause of uveitis, tuberculosis in 4.7%, and systemic autoimmune diseases (Bekhterev's disease, Behcet's disease, and rheumatoid arthritis) in 18.8%. In 65.9% of patients, intraocular inflammation was not established as a specific cause. Most patients were infected with herpes simplex virus (97.2%), cytomegalovirus (89.3%), Epstein–Barr virus (96.2%), toxoplasmosis (58.9%), chlamydia (28.5%), and mycoplasma (33.9%), including mixed infection in 62%, according to the results of blood serum testing. Signs of infection reactivation during uveitis exacerbation were detected in 66.1% of patients.

Most of the studies listed lack data on eye sarcoidosis and HLA-B27-associated uveitis; however, according to international data, the latter is the leading cause of uveitis. There is also a significant predominance of infectious etiology compared with non-infectious etiology. To determine the underlying mechanism of why inflammation can cause uveitis, further larger studies are required, which will be based on contemporary research methods and classifications.

The study aimed to improve the uveitis diagnostics that address the recognition of their unclear forms and identification of the course aspects. Using ophthalmic methods such as laser photometry and indocyanine green and fluorescein angiography, a complete picture of the inflammatory process localization will be created, and its degree of activity will be determined. Using modern laboratory and instrumental examination methods, we aimed to identify the etiology or diseases associated with the development of uveitis.

MATERIALS AND METHODS

The study consisted of two parts: a retrospective analysis of 205 archival case histories of the Department and the Clinic of Ophthalmology of the Academician I.P. Pavlov First State Medical University reported between 2008 and 2012 and a prospective examination of 210 patients diagnosed with uveitis who first contacted on outpatient basis the Department and the Clinic of Ophthalmology of the Academician I.P. Pavlov First State Medical University, to clarify the association between inflammatory process and development of uveitis from January 2014 to December 2016. In group 1, the average age was 51 ± 19.5 years, men and women were represented in almost equal amounts, with a slight prevalence of men (53%). Group 2 included 81 men (38.6%) and 129 women (61.4%), and the average age was 43 ± 16 years.

All patients underwent standard ophthalmological examinations (visometry, perimetry, tonometry, biomicroscopy, and ophthalmoscopy). In group 1, the examination was supplemented with optical coherence tomography and/or fluorescent angiography, as well as B-scanning. In group 2, the examination for all patients was supplemented with laser photometry of the aqueous humor (KOWA FM-600, Japan), optical coherence tomography (SPECTRALIS® Heidelberg Engineering, Germany), and fluorescent angiography (HRA2 Heidelberg Engineering, Germany). If necessary, the study was supplemented with indocyanine green angiography (HRA2 Heidelberg Engineering, Germany).

To clarify the etiology and uveitis associated diagnosis, group 1 underwent clinical blood test with determination of the erythrocyte sedimentation rate and white cell count, biochemical blood test (alanine aminotransferase, aspartate transaminase, total bilirubin, creatinine, glomerular filtration rate, and glucose), C-reactive protein, rheumatoid factor, syphilis blood test (Wasserman reaction), HIV test (form 50), hepatitis B test, and hepatitis C test. Some patients were examined by appropriate specialists to rule out the foci of chronic infection in the ENT organs, oral cavity, and/or urogenital tract, including additional instrumental methods according to their recommendations. The patients were examined in the outpatient department of the St. Petersburg Research Institute of Phthisiopulmonology to confirm if the disease was caused by tuberculosis bacteria. The patients also underwent blood tests to measure the level of *M* and *G* immunoglobulins, *Herpes simplex* 1 and 2, varicella-zoster virus, cytomegalovirus, Epstein–Barr virus, toxoplasma, and/or toxocariasis.

Clinical and instrumental examination of group 2 patients was supplemented with laboratory tests such as *HLA-B27* antigen blood tests and tests that measure the levels of angiotensin-converting enzyme (ACE), antinuclear factor and antistreptolysin O, cyclic citrullinated peptide antibodies (CCPA), nucleosomes, double-stranded DNA, cardiolipin, anti-neutrophil cytoplasmic antibodies (ANCA), and instrumental procedures such as magnetic resonance imaging (MRI) of the sacroiliac joint (STIR T1 mode) and brain and computed tomography (CT) of the lungs. If the examinations revealed positive results or if the patient showed symptoms of systemic disease, the patients were referred to the appropriate specialists (rheumatologist, pulmonologist of the sarcoidosis center, gastroenterologist, oncologist, neurologist, etc.).

In diagnostically complex cases, the aqueous humor was studied using the polymerase chain reaction method to detect the presence of herpes virus DNA and to detect blast cells using the cytofluorimetrical method. Humor was collected at a rate of 200 μl after the insulin needle was inserted into the anterior chamber of the eye under aseptic conditions. Patients had to undergo an examination to assess for the presence of "masquerade syndrome," which was based on a full-fledged ophthalmological examination using angiography with two stains (fluorescein and indocyanine green) in combination with clinical, laboratory, and instrumental examinations.

RESULTS

Based on a retrospective analysis of archival case histories, the effectiveness of conventional ophthalmological, laboratory, and instrumental examinations was evaluated. The etiologic factors or concomitant diseases were detected in 38.1% of the patients in group 1. The most common concomitant diseases reported in this study were post-traumatic uveitis (6.8%) and chronic infection (odontogenic or rhinosinusogenic), which was detected in 6.3% of the cases (Fig. 1). The most common infectious etiological factor was herpes infection (5.9%). Other infectious causes were tuberculosis (1.5%), cytomegalovirus (1.5%), and a combination of HIV and cytomegalovirus infection (0.5%). The association of uveitis with systemic and syndromic diseases was established in

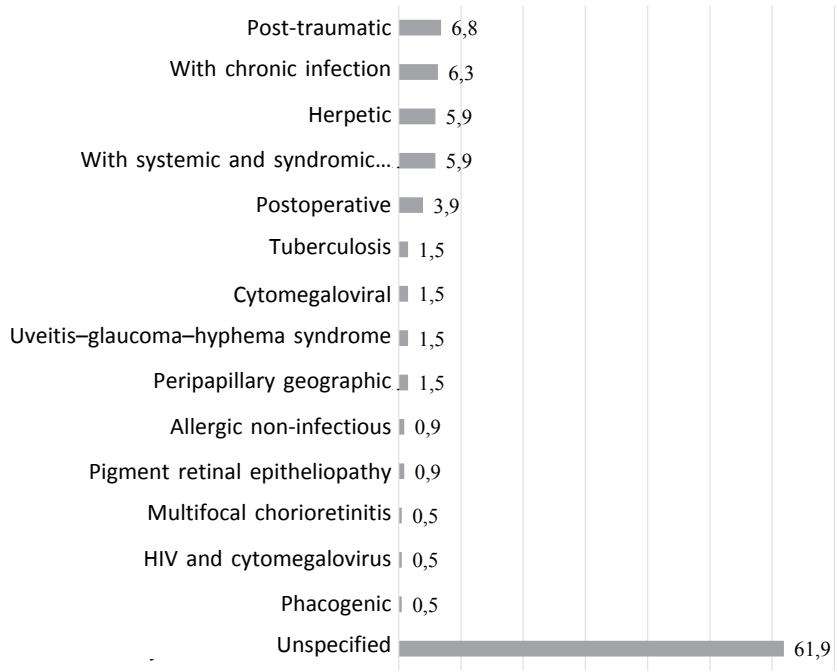

Fig. 1. Distribution of all uveitis according to the etiology and specific diagnosis

Рис. 1. Распределение увеитов по этиологии и сопутствующему заболеванию в первой группе (% от общего количества, $n = 205$)

5.9% of the cases (12 patients). The most common condition associated with uveitis was Bekhterev's disease (7 patients). In some cases, an association has been established between uveitis and rheumatoid arthritis, juvenile idiopathic arthritis, chronic nonspecific polyarthritis, Behcet's disease, and sarcoidosis.

Thus, in 61.9% of the cases, the conventional ophthalmologic, clinical, and instrumental examinations did not reveal the etiology or concomitant disease.

In group 2, statistically analyzing the data obtained, it was found that in order to determine the etiology and uveitis associated disease, the first clinical and instrumental examination should include blood tests to determine the presence of *HLA-B27* antigen and measure the levels of ACE, antinuclear factor, antistreptolysin O, ANCA, CT of the lungs, MRI of the sacroiliac joint (*STIR T1* mode), and MRI of the brain.

In particular, a statistically significant difference was observed in the level of serum ACE between clinically granulomatous uveitis and non-granulomatous uveitis ($n = 87$, $p = 0.000073$, Fig. 2, Table 1).

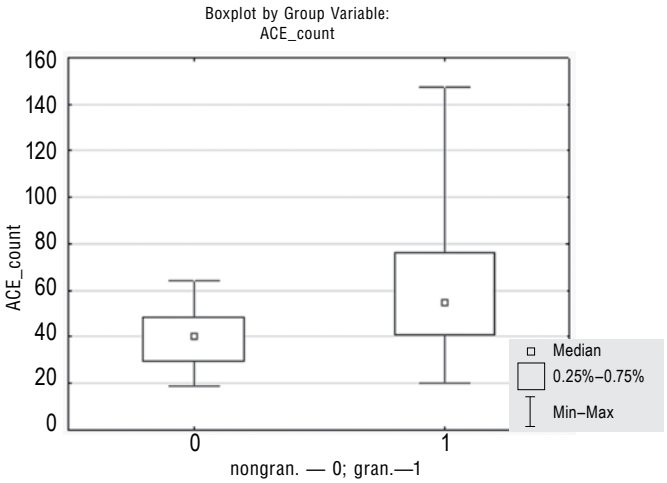

Fig. 2. The difference of ACE amount in blood between granulomatous (1) and nongranulomatous (0) uveitis

Рис. 2. Различие негранулематозного (0, $n = 31$) и гранулематозного (1, $n = 56$) увеитов по количеству АПФ в крови

Table 1 / Таблица 1

Mean and median ACE in granulomatous (1) and nongranulomatous (0) uveitis
Среднее и срединное значение АПФ при негранулематозном (0) и гранулематозном (1) увеитах ($n = 87$)

Uveitis type	ACE value (*ACE count*)				
	M (mean)	Amount	Q25	Me (median)	Q75
0	39.5	31	29.6	40.3	48.7
1	61.28	56	41.15	54.75	76.3

Table 2 / Таблица 2

***P* value in comparing sarcoidosis with other uveitis entities according to the ACE in blood**
Значения вероятности (*p*) при сравнении увеита, ассоциированного с саркоидозом, с другими этиологическими факторами и сопутствующими заболеваниями по уровню АПФ (*n* = 95)

Diagnosis	Idiopathic	Herpetic	Seronegative spondyloarthritis	Fuchs uveitis	Multifocal choroiditis
Sarcoidosis	0.000005	0.091	0.045	0.003	0.04

Considering that the results of the ACE tests depend on the established etiology of uveitis, a statistically significant increase in the enzyme amount was observed in patients with sarcoidosis compared with those with other etiological factors or concomitant diseases (Table 2), except for herpetic etiology and *Birdshot* chorioretinitis.

Among patients diagnosed with sarcoidosis uveitis, ACE exceeded the norm in only 75% of the patients. In 12.5% of the patients, the value was borderline (from 50 to 70 ACE unit); meanwhile, 12.5% of the patients tested negative for sarcoidosis uveitis. Among the latter, half of the patients were treated with ACE inhibitors.

Thus, the ACE level is an important diagnostic factor to confirm the granulomatous type of inflammation and identify sarcoidosis as a concomitant disease.

A blood test to confirm the presence of *HLA-B27* antigen is extremely useful in patients with unilateral (or alternating) non-granulomatous uveitis; it was used to confirm the diagnosis of 95.2% of the patients with anterior clinically non-granulomatous uveitis ($n = 36$). However, if the patients with unilateral non-granulomatous uveitis did not present any typical clinical manifestations, they were considered as carriers of the antigen. For example, 13.3% of the patients with chronic bilateral idiopathic posterior uveitis tested positive for *HLA-B27* antigen.

To clarify the association between uveitis and seronegative spondylitis, a sacroiliac joint MRI should be performed (*STIR T1* mode) in addition to the blood tests to confirm the presence of the *HLA-B27* antigen, since in 4.76% of the patients, the antigen was not detected, and MRI showed signs of sacroiliac disease ($n = 21$).

In patients with HLA-B27-associated uveitis and uveitis associated with seronegative spondylitis or Bekhterev's disease, dusty precipitates were visible in 84.2% of the cases; in 15.8% of cases, they were noted in very large amounts, so some gathered at points for 33.6 ± 11.7 years (from 23 to 40).

In the study, 95 patients were examined for rheumatoid arthritis (rheumatoid factor, CCPA, and consultation with a rheumatologist), but the association of uveitis was detected in only 1.4% of all patients with uveitis. One of the three patients with a verified diagnosis of rheumatoid arthritis tested positive for rheumatoid factors, but all three patients tested negative for CCPA. The association between uveitis and rheumatoid arthritis was confirmed by ruling out other concomitant diseases. Rheumatoid arthritis was initially diagnosed in all three patients by a rheumatologist several years before uveitis onset. Taking these circumstances into consideration, the need to perform the tests to determine the presence of rheumatoid factors and CCPA are necessary, but not paramount.

According to our data, the antistreptolysin O blood test was positive in only 8.3% of the 24 patients. However, the post-streptococcal uveitis diagnosis was confirmed in all 24 patients; therefore, it should be recommended to rule out or confirm post-streptococcal uveitis.

In 16% of patients (out of 50 patients), the level of the antinuclear factor was found to be higher than normal (more than 1 : 160); in one patient, the titer was significantly increased (1 : 2560). In one patient, Behcet's disease was verified after consultation with a rheumatologist, taking into account the clinical course of the disease (vasculitis and herpetiform stomatitis). Blood tests performed to determine the presence of anti-double-stranded DNA antibodies, anti-nucleosome antibodies, ANCA, and anti-cardiolipin antibodies did not reveal any systemic disease.

Based on our results, the antinuclear antibody test is recommended as a screening method for identifying systemic pathologies; aside from undergoing this test, the patient should also consult a rheumatologist to clarify the diagnosis. Since ANCA-associated vasculitis is a life-threatening pathology, this study must be prescribed to patients with signs and symptoms of vasculitis.

Table 3 / Таблица 3

The system of work up in patients with uveitis after the exclusion of infectious etiology
Система обследования пациента с предположительным диагнозом «увеит» после исключения инфекционной этиологии

Primary ophthalmic techniques	Primary laboratory and instrumental methods
1. Standard ophthalmologic examination	1. Blood test for *HLA-B27* antigen, ACE, ASL-O, ANF, ANCA
2. Laser photometry of aqueous humor	2. MRI of the sacroiliac joint (*STIR T1*)
3. OCT	3. CT scan of the lungs
4. PAG with involvement of the posterior segment	4. MRI of the brain
5. Indocyanine green and fluorescein angiography in cases of suspected tuberculosis, syphilis, toxoplasmosis, sarcoidosis, Vogt–Koyanagi–Harada syndrome, chorioretinitis *Birdshot*, sympathetic ophthalmia, and all choriocapillaritis, including peripapillary geographical choroidopathy	

Based on the results of the brain MRI ($n = 107$), five patients showed signs of demyelination, while one patient had brain damage associated with HIV infection. Three of the five patients with uveitis associated with multiple sclerosis, verified by a neurologist, had symptoms of peripheral uveitis. Thus, a brain MRI should be performed in patients with peripheral uveitis as well as for the detection of multiple sclerosis, especially in patients aged 23–40 years.

In patients with sarcoidosis-associated uveitis ($n = 34$), the diagnosis was confirmed in 40.9% of the patients using a chest X-ray; in 59.1% of the patients, intrathoracic lymphadenopathy was detected by a chest CT. Thus, CT is preferable to detect sarcoidosis. Using an abdominal ultrasound, which was prescribed in patients with sarcoidosis, liver damage was diagnosed in one of seventeen patients.

Due to the invasiveness of the technique, spinal puncture was only performed in two patients to confirm Vogt–Koyanagi–Harada disease. In both cases, using the said technique, the diagnosis was confirmed. Notably, the two patients had a history of exudative retinal detachment. Since spinal puncture is an invasive method, it can only be recommended in patients with suspected Vogt–Koyanagi–Harada disease or exudative retinal detachment.

Based on the results, a new clinical instrumental method was proposed for patients diagnosed with uveitis (Table 3). The developed method revealed the etiology or uveitis associated disease in 83% of patients from group 2 and 38.1% of those from group 1.

Among patients in group 2, 174 had non-infectious uveitis (82.86%), 34 had infectious uveitis (16.19%), and 2 had "masquerade" neoplastic syndrome (0.95%). Most cases had chronic uveitis (68.5%), 11% had an acute course, while 20.5% had a recurrence. Posterior uveitis was more common in the group under study (58.6%), while anterior uveitis (33.3%) was less common; panuveitis was reported in 6.2%, while intermediate uveitis was noted in 1.9%.

Figure 3 presents the distribution of all patients by etiology and concomitant disease. HLA-B27-

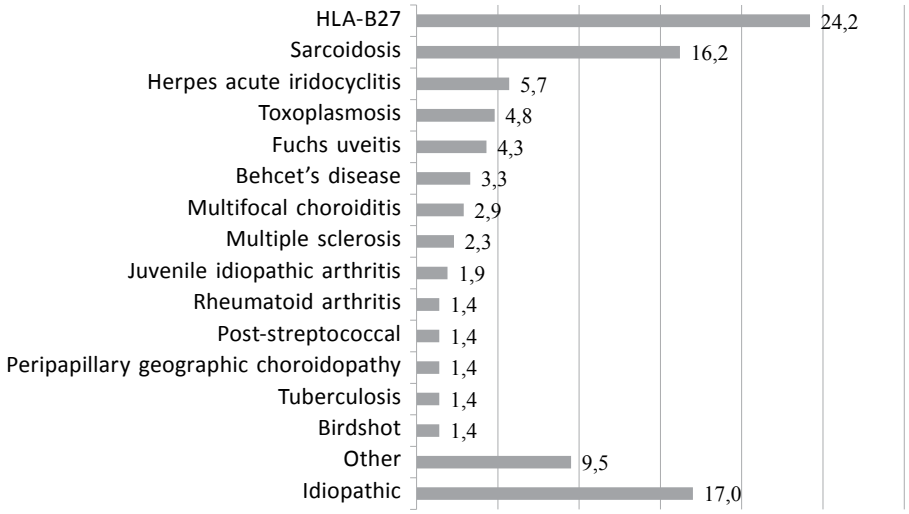

Рис. 3. Распределение этиологических факторов и сопутствующих увеиту заболеваний среди всех 210 случаев

Fig. 3. Distribution of etiology and specific diagnosis in all uveitis cases (210)

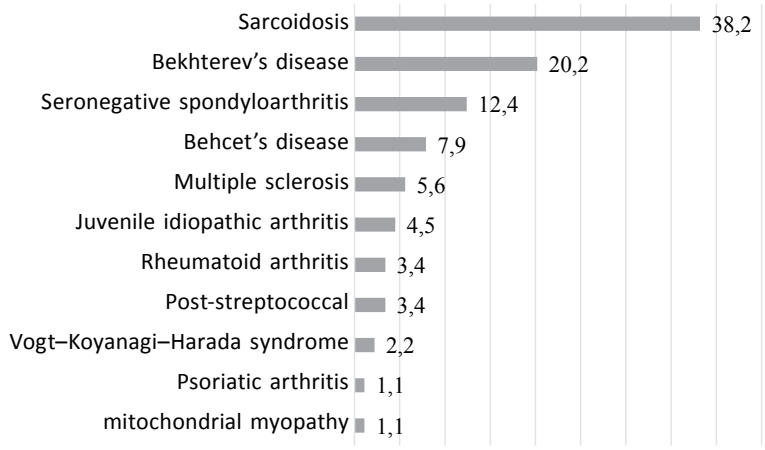

Fig. 4. Distribution of uveitis, associated with systemic syndromes and diseases (n = 89)

Рис. 4. Распределение пациентов с увеитом при системных и синдромных заболеваниях (n = 89)

associated anterior uveitis (24.2%) and sarcoidosis-associated posterior uveitis (16.2%) were the most common types of uveitis. Moreover, herpes virus (5.7%) and *Toxoplasma gondii* (4.8%) were the most common infectious etiological factors. Fuchs uveitis was diagnosed in 4.3% of cases, and Behcet's disease was noted in 3.3%. Among those with choriocapillaritis, multifocal choroiditis was the most common (2.9%). The association between uveitis and multiple sclerosis was reported in 2.3% of cases, 1.9% between uveitis and juvenile idiopathic arthritis, and 1.4% between uveitis with rheumatoid arthritis. In 1.4% of the cases, uveitis of post-streptococcal etiology was established. Meanwhile, inflammation was not established as the cause of uveitis in 17% of the patients.

The concept of "other" causes of uveitis (Fig. 3) included isolated cases of acute retinal necrosis (2), "masquerade" neoplastic syndrome, pars planitis (2), Vogt–Koyanagi–Harada disease (2), endophthalmitis (2), syphilitic (2) and cytomegalovirus (1) uveitis, progressive external retinal necrosis (1), sympathetic ophthalmia (1), syndrome of multiple rapidly disappearing white spots (1), acute posterior multifocal placoid pigmented epitheliopathy (1), mitochondrial myopathy (1), psoriatic arthritis (1), and uveitis caused by a *Candida* fungus (1).

The association between uveitis and systemic and syndromic diseases (Fig. 4) was established using the new system; the most common were sarcoidosis (30.7%), Bekhterev's disease (16.2%), and seronegative spondyloarthritis (9.9%). In more rare cases, uveitis has been associated with Behcet's disease (6.3%), multiple sclerosis (4.5%), and juvenile idiopathic arthritis (3.6%).

Depending on the associated concomitant disease revealed and etiology of uveitis, patients received therapy in various institutions of the city or, in most cases, in the Department of Ophthalmology of the Academician I.P. Pavlov First State Medical University in close collaboration with other specialists (rheumatologist, neurologist, etc.). By identifying the concomitant disease or etiology, the patients received a more specific therapy and were handled by an appropriate specialist. For example, with uveitis associated with an autoimmune disease (n = 82), 75% of the patients received systemic treatment, and only 25% required exclusively local therapy: most cases were associated with sarcoidosis. Among patients with non-infectious uveitis where a systemic disease was not detected (n = 80), 67% of patients underwent local therapy, 27% received local and systemic treatment, while 6% were still under observation.

DISCUSSION

The resulting etiological structure of uveitis corresponds largely to world literature data. The differences are due to the fact that patients were referred for consultation to clarify the diagnosis from other medical institutions where they were initially examined. In connection with this circumstance, most of the patients in group 2 had posterior uveitis (and not anterior, according to the world literature). The group 2 also has several patients with sarcoidosis-associated uveitis, which is partly due to the referral of several uveitis patients to our center, including those from the sarcoidosis office of the city hospital no. 2. There are specialized institutions in St. Petersburg that can treat patients with eye tuberculosis and HIV

infection; therefore, the category of these patients is less represented in the group under study.

In our opinion, when examining a patient diagnosed with uveitis, it is important to detect all full-fledged clinical presentations of uveitis using laser photometry of the aqueous humor, and in the case of posterior panuveitis, with dual angiography (sodium fluorescein and green indocyanine). It is worth noting that indocyanine green angiography has become one of the most important ophthalmological examination methods. First, it clearly demonstrated the localization of the inflammatory process: 51 patients (91 eyes, 77.1%) had stromal lesions, 4 patients (6 eyes, 5.1%) had lesions of a choriocapillary layer, and a combination thereof was noted in 3 patients (4 eyes, 3.4%). Second, the technique revealed signs of granulomatous inflammation in 27.5% of patients. Third, indocyanine green angiography suggested diagnosis in 80%–80.2% of patients, which was subsequently confirmed during a general clinical examination. It must be emphasized that such signs as hyperfluorescence of the optic nerve head, choroidal vasculitis, dark spots, or dark foci indicated the inflammatory process and thus influenced the patient management.

After an ophthalmological examination, a comprehensive general clinical examination with additional instrumental techniques and consultations with specialists from various fields (rheumatologist, pulmonologist, oncologist, etc.) is required. All of these aspects were formulated in the form of a clinical instrumental diagnostics system presented in Table 3.

CONCLUSION

According to the study, the most common diseases were HLA-B27-associated anterior uveitis and sarcoidosis-associated posterior uveitis. Among the infectious etiological factors, *T. gondii* and *Herpes* family viruses were the most common. The developed system of clinical instrumental diagnostics contributed to the reduction in the proportion of uveitis of unclear etiology by 3.6 times and more specific therapy for patients. To obtain a more complete epidemiological data, multicenter studies using contemporary examination methods are required. Our study showed that for the examination of patients diagnosed with uveitis, a multidisciplinary approach and the joint work of many specialists is required; therefore, it is necessary to establish specialized centers that provide a combination of these services.

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