

Etiology and Clinical Patterns of Uveitis at Three Ophthalmic Clinics in Tajikistan

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Abstract: A prospective observational study was conducted at three ophthalmic clinics to assess the clinical patterns and etiology of uveitis in the Central Asia Republic of Tajikistan. All patients underwent physical and ophthalmologic examinations. Extensive efforts were made to determine the etiology of uveitis, including workups for Behçet's Disease (BD) and Vogt-Koyanagi-Harada (VKH) syndrome. All patients were tested for the presence of HLA-B27. Presence and/or history of tuberculosis and syphilis were ruled out. HSV, CMV, Chlamydia trachomatis and HIV antibody titers were determined by ELISA. Uveitis was diagnosed in 51 patient ages 14 to 60 were with women accounted for 60.8%. Bilateral uveitis was presented in 74.5% cases and dominated in all age groups. Seven HLA-B27-positive patients had isolated uveitis without systemic manifestations and five had uveitis associated with spondyloarthritis (SpA). In total, uveitis was associated most commonly with SpA (23.5%), BD (9.8%), and VKH syndrome (5.9%). In 41.2% of uveitis cases, etiology was unknown. Conclusions: The overall clinical patterns and etiology of uveitis in Tajikistan are comparable to those reported from outside the Central Asia region. Bilateral uveitis dominated in all age groups with HLA-B27-positive uveitis present in 23.5% of patients and more common in men.

Keyword: Uveitis, HLA-B27 Antigen, Spondylitis, Behcet Syndrome, Vogt Koyanagi Harada Syndrome

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I. Introduction

A broad group of ocular diseases and conditions linked to intraocular inflammation is commonly referred to as uveitis. The term uveitis covers inflammation of the uvea, which includes the iris, ciliary body, and choroid. It also often includes inflammation of adjacent intraocular structures, such as the retina (retinitis), optic disc (papillitis), and vitreous (vitritis)[1]. Uveitis is a complex disease with environmental influences[2], some genetic predispositions[3], involvement of immune T and B cells, and cytokine and chemokine signatures and signaling[4]. It is a potential cause of visual morbidity in the working age group[5, 6]. Prolonged visual loss occurred in two-thirds of uveitis patients, with many patients meeting the criteria for legal blindness at some point in their follow-up. Older patients with bilateral inflammation and increasing duration of reduced vision are at the greatest risk of severe visual loss[7]. Poorly controlled inflammation is often associated with the development of ocular complications[6]. Uveitis is associated closely with a variety of systemic diseases and may be the first sign of those diseases, hence being a vital warning sign that allows early diagnosis and medical intervention[8]. Inflammatory eye diseases often occur in conjunction with systemic inflammatory disorders, such as Behçet's Disease (BD), sarcoidosis, human leukocyte antigen (HLA)-B27-associated disorders, and Vogt-Koyanagi-Harada (VKH) syndrome, often with different clinical phenotypes. Infectious uveitis was recently extensively reviewed[9, 10]. Also, uveitis's potential association with Zikavirus infection[11, 12] was added to a large group of infectious uveitis[13].

The combination of effects on sight, ocular discomfort, systemic disease, and treatment-related side effects often has a significant impact on the subject's quality of life and deserves considerable attention. The worldwide prevalence of uveitis is estimated at 100-150/100,000 persons[8] and varies significantly by geographical region and country[7, 14]. In the United States, the rate of noninfectious uveitis among adults was 121 cases per 100,000 persons[15]. In a recent nationwide cohort study in South Korea, the annual incidence of uveitis ranged from 91 to 123/100,000[16]. The socioeconomic impact of uveitis can be as significant as that of diabetic retinopathy and, in most cases, those affected are individuals of working age. Information on uveitis in the Central Asia region is notably absent from

recent reviews[14].The Republic of Tajikistan is a Central Asia country with a diverse landscape and climatic conditions ranging from desert to high-altitude mountains. The dominating ethnic group is Tajik (84.3%) with a large minority of Uzbek (12.2%), while other groups are Kyrgyz, Russian, Turkmen, and Tatar. In this article, we provide the initial analysis of uveitis in the Republic of Tajikistan.

II. Material and Methods

The current observational study was conducted at the Ophthalmic Department of the National Medical Center of the Republic of Tajikistan; the Department of Ophthalmology, Avicenna Tajik State Medical University; the ophthalmic patient care unit of Sogdiysk Oblast tertiary hospital named after Kutliddinov, and the Eye Microsurgery Regional Center in the city of Khujand. All procedures followed the tenets of the Declaration of Helsinki, and informed consent was obtained from all patients and the control group subjects. All patients underwent an ophthalmologic examination, as well as a general clinical examination.

The ophthalmologic evaluation included visometry, biomicroscopy, ophthalmoscopy, tonometry, and autorefractometry, and was used to diagnose uveitis. The Standardization of Uveitis Nomenclature (SUN) Working Group recommendations[17, 18] were used in uveitis classification. During the period of 2011–2014, 51 subjects were diagnosed with uveitis (Fig. 1).

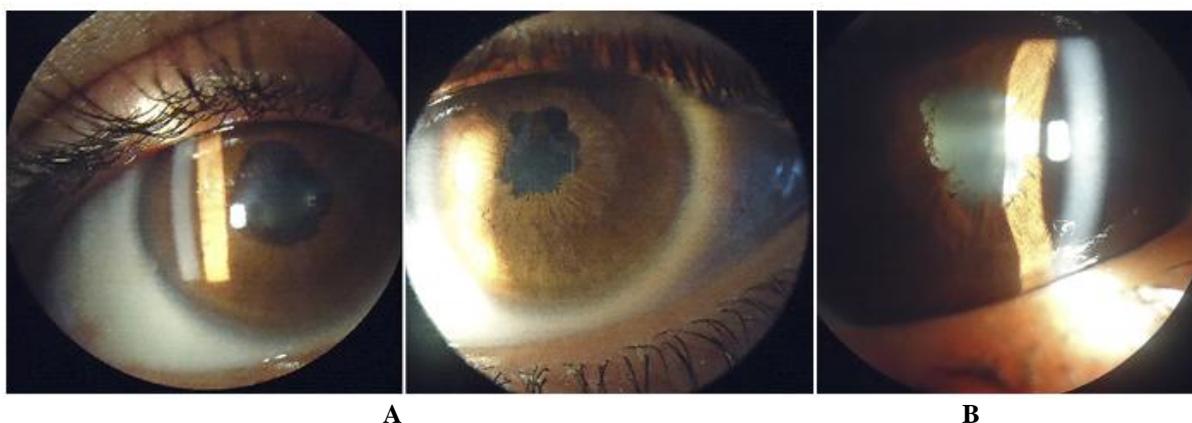


Figure no 1: A. HLA-B27-negative bilateral chronic panuveitis associated with rheumatoid arthritis. Circular posterior synechiae, pigment on the anterior lens capsule. B. HLA-B27-positive acute anterior uveitis, not associated with SpA. Circular posterior synechiae, fibrin in the field of a pupil.

Extensive efforts have been made to identify etiology of the disease[1].The general clinical examination of the patient included: a general examination by a therapist and a rheumatologist, a chest x-ray, an x-ray of the sinuses, according to indications, and computed tomography of the sacroiliac and peripheral joints. Updated International Criteria for Behçet's Disease were followed in diagnosing BD[19, 20]. The multisystem nature of VKH syndrome was taken into account during diagnosis based on the revised international criteria[21].The control group included 50 subjects (20 men and 30 women) who did not have laboratory and clinical signs of uveitis or articular syndrome at the time of the survey. All patients were tested for the presence of serum HLA-B27. Presence and/or history of tuberculosis and syphilis were ruled out. To exclude other specific infections that cause inflammation of the choroid, all patients undertook the determination serum antibody titer by ELISA to the herpes simplex virus (HSV) and cytomegalovirus (CMV), Chlamydia trachomatis, and HIV. At the same time, all patients underwent laboratory tests: a comprehensive metabolic panel, complete blood count with erythrocyte sedimentation rate determination, urinalysis, determination of C-reactive protein, and serum rheumatoid factor.

Statistical data processing was performed using the software package STATISTICA 6.0 (StatSoft, Inc., USA). For absolute values, the mean values and the standard deviation ($M \pm m$) were calculated; for quality indicators, the relative value (p, %). Differences were considered statistically significant when $p < 0.05$.

III. Results

Fifty-one patients were diagnosed with uveitis during 2011–2014 at three leading ophthalmology centers in the Republic of Tajikistan. Women dominated among the uveitis patients (60.8%) while men constituted 39.2%. The subjects' ages were between 14 and 60 years, with a narrower range in men, between 15 and 49 years old, and a broader range in women, between 14 and 60 years old. Most patients (94.12%) with uveitis of various etiologies were under 50 years of age. More than 84% of patients with uveitis were people of working age from 19 to 60 years. Bilateral uveitis was identified in 38 subjects (74.5%) and unilateral uveitis was presented in 13 cases (25.5%). In men, unilateral uveitis was diagnosed in eight cases with the remaining 12

subjects having bilateral uveitis. In women, the difference was more dramatic, with 26 subjects showing bilateral uveitis and only five women having unilateral uveitis. Bilateral uveitis dominated all age groups (Table 1).

All subjects in the control group were HLA-B27-negative. Out of 51 patients, only 12 (23.5%) had HLA-B27-positive uveitis (Table 2). From this group, seven patients (13.7% of total) had isolated uveitis without systemic manifestations and five (9.8%) HLA-B27-positive patients had uveitis associated with spondyloarthritis(SpA) (Table 2). The HLA-B27-positive uveitis was more common in men (seven) compared to

Table no 1:Ocular manifestation of uveitis in different age groups.

Age	Ocular manifestation				Total	
	Unilateral		Bilateral			
	Number	%	Number	%	Number	%
Under 18	0	0.0	5	9.8	5	9.8
19 - 30	6	11.8	13	25.5	19	37.3
31 - 40	6	11.8	9	17.6	15	29.4
41 - 50	1	1.9	8	15.7	9	17.6
51 - 60	0	0.0	3	5.9	3	5.9
Total	13	25.5	38	74.5	51	100

women (five). In the remaining group of 39, the HLA-B27-negative patients, five patients were diagnosed with BD, three had VKH syndrome, two had viral uveitis, one had rheumatoid arthritis (RA), and 21 patients had uveitis origin undetermined. The HLA-B27-negative uveitis was present in 26 women and 13 men. The most common was uveitis associated with SpA (12 subjects) and with BD (5 subjects). Bilateral uveitis was identified in nine (75%) out of 12 patients with SpA and in 28 (58.9%) of 39 patients with different etiology.

Table no 2:Etiology of uveitis.

Diagnosis		Age					Total	%
		Under 18	19- 30	31- 40	41- 50	51- 60		
HLA-B27-positive uveitis	Isolated	1	3	2	1	0	7	13.7
	Associated with SpA	0	2	2	1	0	5	9.8
HLA-B27-negative uveitis	Associated with SpA	1	1	4	0	1	7	13.7
	Associated with HSV or CMV	0	1	1	0	0	2	3.9
	BD	0	5	0	0	0	5	9.8
	Associated with VKH syndrome	0	1	2	0	0	3	5.9
	Associated with RA	0	1	0	0	0	1	2.0
	Unknown etiology	3	5	4	7	2	21	41.2

Table no 3:The SUN Working Group Grading Scheme for Anterior Chamber Cells.

Cells in anterior chamber	HLA-B27 (+) uveitis n=12	HLA-B27 (-) uveitis n=39	Total N=51
0	0	0	0
0.5+	0	0	0
1+	5	27	32
2+	4	7	11
3+	2	4	6
4+	1	1	1

Table 3 describes the inflammation level based on the Working Group Grading Scheme for Anterior Chamber Cells [17, 18]. Overall, in both HLA-B27-positive and HLA-B27-negative patients, grades 1+ and 2+ dominated. Grade 3+ was present in 17% and 10% of cases for HLA-B27-positive and HLA-B27-negative patients, respectively. Only one patient in each HLA-B27 group reached a grade 4+ anterior chamber cells level.

Table no 4: The SUN Working Group Anatomic Classification of Uveitis.

Uveitis Type	Pathology	Number of cases
Anterior	Iridocyclitis	36
Intermediate	Posterior cyclitis	2
	Hyalitis	1
Posterior	Chorioretinitis	1
Panuveitis	Anterior chamber, vitreous and retina	10
	Anterior chamber, vitreous and choroid	1

Anatomically anterior uveitis dominated in the observed group, with 36 cases (71%) diagnosed as iridocyclitis. Eleven cases (22%) of panuveitis constituted the second largest group (Table 4). In the current study, we observed the duration of uveitis almost equally distributed between sudden onset, recurrent, and chronic (Table 5). Sudden onset was observed in 75% of HLA-B27-positive uveitis cases and in all cases of HSV- or CMV-associated uveitis. Noticeably, all the cases of BD-associated uveitis had chronic manifestation (Table 5). All patients with VKH syndrome (100%) and patients with HLA-B27-negative uveitis associated with SpA in 85.7% of cases were women who had bilateral intraocular inflammation.

Table no 5: Uveitis onset categories.

Category	Uveitis type and association								
	HLA-B27-positive		HLA-B27- negative						
	Isolated	SpA	SpA	HSV and CMV	BD	VKH	RA	Etiology Unknown	Total
Sudden	5	4	2	2	0	1	0	5	19
Recurrent	2	1	2	0	0	2	0	9	16
Chronic	0	0	3	0	5	0	1	7	16
Total	7	5	7	2	5	3	1	21	51

IV. Discussion

Our results provide the first glimpse of uveitis in the geographically and ethnically diverse population of Tajikistan. This is a limited observational study confined to three centers and could be further limited by the attendance at centers by different population groups, especially in rural areas. Nevertheless, we were able to identify a variety of uveitis patients with different disease etiology.

Age. Mean age for uveitis diagnoses was 31.6 ± 1.6 , with more than 84% of patients in the 19- to 60-year age range. This agrees well with the published data showing a very wide range of uveitis onset from ages 7 to 74. The average age based on the 42 reported cases in the recent review [14] was 36.8, with a minimum average reported at 24.9 for Hawaii and a maximum of 50.6 for Finland. Hence, similar to our study in Tajikistan, uveitis was most common in middle-aged patients. In a comparable Turkish population study, the mean age at uveitis presentation was 36.6 ± 15.7 years, with the majority of patients (83.3%) in the 17- to 60-year age group [22]. Guney and co-authors [23] reported for the Turkish population the mean age at the presentation at 39.1 ± 12.6 .

Gender. In our study, uveitis more often occurred in women (60.8%) compared to men (39.2%). In the U.S. population-based study, it was found that female gender is a positive risk factor for uveitis [2]. However, in Turkish population studies, uveitis was reported to be more common in men, 54% (1M:0.83F) [22]. Several studies indicate that acute anterior uveitis is more prevalent in male patients [24]. In a global analysis of uveitis epidemiology [14], out of 52 reported observations in 20 (38.4%) cases, women had a high prevalence of uveitis. However, in the majority of cases (63.46%), the difference between male and female subjects was within the 10% range.

Unilateral and Bilateral Entities. Unilateral uveitis is reported to be either equally frequent or even more common compared with bilateral [14]. In Tajikistan, bilateral uveitis was identified in 38 subjects (74.5%) and unilateral uveitis was presented in only 13 cases (25.5%). In men, unilateral uveitis was diagnosed in eight cases, with the remaining 12 subjects having bilateral uveitis. In women, the difference was more dramatic, with 26 subjects showing bilateral uveitis and only five women having unilateral uveitis. In our case, bilateral uveitis was dominating all age groups.

HLA-B27. HLA-B27-positive anterior uveitis is the most commonly diagnosed form of anterior uveitis and represents the largest entity of noninfectious uveitis around the world, with HLA-B27-positive anterior uveitis diagnosed in approximately 2–14% in large surveys, which included all patients with uveitis [25]. A link between HLA-B27 and uveitis was initially described in 1973 [26]. Loh and Acharya [6] found that in HLA-B27-positive uveitis, poorly controlled inflammation was associated with the development of ocular complications, including vision loss. In a retrospective longitudinal cohort study with HLA-B27-positive uveitis seen at a tertiary care center, researchers found that ocular hypertension (0.10/eye/year) and posterior subcapsular cataracts (0.09/eye/year) were the most common complications. Patients with chronic inflammation were also at greater risk of complications [6]. Simultaneously, the prognosis for the visual outcome and complications of HLA-B27-positive uveitis is rather favorable compared with HLA B27-negative patients, as <2% developed legal blindness and <5% visual impairment [25]. Overall, about 50–75% of HLA-B27-positive patients with acute anterior uveitis have an associated spondyloarthropathy, with ankylosing spondylitis, reactive arthritis, and undifferentiated spondyloarthropathy the most common diagnoses [27]. It was estimated that over a lifetime, a patient with ankylosing spondylitis has about a 50% chance of having at least one episode of uveitis, and HLA-B27-positive patients who have uveitis usually have spondyloarthritis and frequently are unaware of this diagnosis [3]. In Iran, out of 44 ankylosing spondylitis patients with acute anterior uveitis, 34 (77.27%) were HLA-B27-positive [28]. In Tajikistan, the frequency of systemic disease associated with HLA-B27-positive

uveitis seems to be comparable to the frequency reported in Cuba (59%)[29], Korea (53 %)[30], and Italy (50%)[31].

In Tajikistan, 41.67% of patients with HLA-B27-positive uveitis were associated with SpA. The exact mechanism by which HLA-B27 predisposes to systemic inflammatory conditions has been the subject of intensive research[32, 33]. HLA-B27 has a high degree of genetic polymorphism, with more than 220 alleles determined at DNA sequencing[34]. Some HLA-B27 subtypes have been associated with increased SpA risk[35], although for the majority of subtypes, the physiological and biochemical significance and a role in the etiopathogenesis of the disease needs to be clarified. The prevalence of HLA-B27 varies widely between ethnic populations. HLA-B27 positivity is virtually absent among sub-Saharan Africans, South American Indians, and Australian Aborigines. The highest prevalence—over 50%—is observed in the Pawaia tribe in Papua New Guinea and Haida natives of western Canada. The prevalence of HLA-B27 is around 10% for many populations[27]. Determined as part of the 2009 U.S. National Health and Nutrition Examination Survey data, the weighted, age-adjusted U.S. HLA-B27 prevalence was estimated at 6.1%, with a 1:1.12 male-to-female ratio[36]. Tsiroukiet al.[14] summarized 38 studies with HLA-B27 results and reported a minimum of 0.2% in Japan and a maximum of 47% prevalence in Australia. An average relevance of HLA-B27-positive uveitis was 8.6%. In our sample of the Tajik population, HLA-B27 was found in 12 out of 101 examined subjects (prevalence 11.88%), with the male-to-female ratio 1:0.71. This male-to-female ratio is very similar to 1M:0.78F reported by Agnani et al.[37]. However, Tripathi et al. report in their study in Indore, India, an HLA-B27-positive uveitis ratio of 1M:0.33F[38]. In an analysis of a decade of clinical records of 177 HLA-B27-positive patients at the University Medical Center Utrecht, The Netherlands, Braakenburg and co-authors[39] also concluded that at the onset of acute anterior uveitis, the prevalence of HLA-B27-associated systemic disease was more frequent in males.

VKH syndrome. VKH syndrome is a multisystemic disorder characterized by bilateral granulomatous panuveitis with exudative retinal detachments from inflammation of the choroid. T-cell-mediated autoimmune responses against antigenic components of melanocytes and melanocyte-associated antigens are thought to be the main driving forces of the disease[40]. In Tajikistan, VKH syndrome was diagnosed in 5.88% patients with uveitis. In a global analysis of publications from 1976 to 2015, an average of 5.74% was reported in 34 publications that provided data for VKH and uveitis[14]. The low frequency of 0.4% was reported for Turkey[41] and the high frequency of 22.4% for Thailand[42]. However, at Siriraj Hospital, Mahidol University, Bangkok, Thailand, VKH was diagnosed in only 8.7% of cases. In Bangladesh, diagnoses of VKH were reported as 8.4%[43]. VKH disease is more common as a cause of uveitis in Japan (frequency 7.0%) compared to the United States (frequency 1.5%)[44].

BD. BD is closely associated with uveitis and is characterized by a variety of treatment options and mixed outcome for visual impairment[45]. BD is a multisystemic complex disorder with unknown etiology and a distinct geographical distribution. The course of disease is characterized by exacerbations and spontaneous remissions, and tends to be more active and severe during the first years[20]. BD is a variable vessel vasculitis that follows a relapsing and remitting course. The heterogeneity in clinical manifestations that can include oral and genital ulcers, nodular and papulopustular lesions, peripheral arthritis, uveitis, arterial aneurysms, venous and arterial thrombosis, central nervous system involvement, and intestinal ulcers, can cause challenges in the diagnosis, management, and disease assessment of BD[45]. BD is a major cause of noninfectious uveitis in many Asia-Pacific countries, ranging from 4% to 28% of uveitis cases[40]. With a frequency of 3.9%, BD is more common as a cause of uveitis in Japan than in the United States (frequency 0.9%)[44]. BD is one of the most common noninfectious etiologies in Turkish uveitis patients (24.9%)[22] and (6.6%)[23] as reported in separate studies. In a global epidemiology review, BD-associated uveitis was reported in 42 out of 56 reviewed publications[14] with an average of 8.24%. The maximum percentage was reported for Turkey (32.2%) and a minimum of 0.3% for India. In our observational study, five patients were diagnosed with BD, representing 9.8% of all cases, constituting one of the major uveitis associations with known etiology.

HSV and CMV. Only two cases of infection-associated uveitis were registered in our study. Toxoplasmosis with 7.1% uveitis was common in Turkey[22], as well as HSV uveitis (6.0%)[22] and (13.3%)[23] as reported in separate studies. The association of uveitis with a variety of infections was recently extensively reviewed[9-13].

Unknown etiology. We report that 41.2% of cases of uveitis were of unknown etiology. Based on extensive analysis of publications from 1962 to 2009 in Medline database, Chamset al.[46] concluded that despite progress in laboratory techniques, imaging technology, and finding new causes for uveitis such as HTLV-1- and HLA-dependent diseases, the frequency of uveitis with unknown etiology (idiopathic) is increasing.

V. Conclusions

Fifty-one subjects aged 14-60 were diagnosed with predominantly bilateral uveitis in a prospective observational study at three leading ophthalmic clinics in Tajikistan. The overall clinical patterns and etiology of uveitis in Tajikistan are comparable to those reported from outside the Central Asia region. Women accounted

for 60.8% of uveitis patients. Bilateral uveitis dominated in all age groups with HLA-B27-positive uveitis present in 23.5% of patients and more common in men. In total, uveitis was associated most commonly with SpA(23.5%), BD (9.8%), and VKH syndrome (5.9%). In 41.2% of uveitis cases, etiology was unknown.

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