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Causes of granulomatous uveitis at a referral centre

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Abstract

Background: Granulomatous uveitis is a heterogeneous group of disorders and diverse underlying Etiologies with wide geographical variations.

The aim of the study: Is to determine the regional causes of granulomatous uveitis in a referral center in Iraq.

Method: This prospective case series observational study was undertaken at Iraq's Ibn-alhitham teaching eye hospital from March 2020 to March 2021. Patients with active granulomatous uveitis were studied. All patients had a comprehensive ophthalmological exam and normal laboratory testing. Other targeted tests were done if appropriate based on the clinical picture.

Results: A study of 94 eyes from 55 patients found the most frequent underlying cause of eye issues was VKH in 42 eyes (44.68%) across 21 patients. The second most common cause was presumed ocular TB, affecting 28 eyes (29.79%) in 15 patients, who were older on average (37.7 ± 14.4 years) and responded well to anti-tuberculous treatment. Toxoplasmosis, viral anterior uveitis, and presumed/probable ocular sarcoidosis were less common, affecting 10 eyes (10.63%), 6 eyes (6.38%), and 4 eyes (4.26%) respectively.

Conclusion: In a referral centre in Iraq, VKH (42 eyes) (44.68%) caused the most granulomatous uveitis, followed by presumed ocular TB (28 eyes) (29.79%), ocular toxoplasmosis (10 eyes) (10.63%), viral anterior uveitis (6 eyes) (6.38%), and presumed and probable ocular sarcoidosis (4 eyes) (4.26%).

Keywords: Causes, granulomatous, uveitis, a referral, centre

Introduction

Uveitis is a heterogeneous group of disorders characterized by inflammation of the uvea, which includes the iris, ciliary body, and choroid, often involving the retina and vitreous [1]. It is responsible for 25% of blindness worldwide [2]. The standard uveitis nomenclature (SUN) system classifies uveitis into anterior, intermediate, posterior, and panuveitis based on anatomical location [3]. Uveitis symptoms include decreased visual acuity, redness, and pain, and it is classified clinically into granulomatous and non-granulomatous types [4]. Granulomatous uveitis is a chronic inflammatory process affecting both the anterior and posterior segments of the eye. Clinical features include large keratic precipitates, anterior chamber cells, vitreous inflammation, iris nodules, posterior synechiae, and focal or diffuse choroidal lesions, sometimes accompanied by neuroretinitis [5]. Causes include infections (e.g., tuberculosis, syphilis, Lyme disease, toxoplasmosis, viral infections), autoimmune conditions (e.g., Vogt-Koyanagi-Harada (VKH) disease, sympathetic ophthalmia), and systemic inflammatory diseases (e.g., sarcoidosis) [6]. Pathologically, it involves lymphocyte and plasma cell infiltration, proliferation of mononuclear cells into epithelioid and giant cells, leading to nodules and fibrosis [7]. Tuberculous (TB) uveitis, caused by *Mycobacterium tuberculosis*, can present as anterior, intermediate, posterior, or panuveitis. Anterior TB uveitis typically has an insidious onset and chronic course, presenting as unilateral or bilateral granulomatous uveitis with keratic precipitates and sometimes iris nodules or granulomas, often complicated by posterior synechiae formation and cataract [8]. Intermediate uveitis may feature snowball opacities and complications like cystoid macular edema, cataract, peripheral retinal neovascularization, and vitreous hemorrhage [8, 9]. Posterior uveitis in presumed intraocular tuberculosis often presents with choroidal lesions such as focal, multifocal, serpiginous-like choroiditis, choroidal nodules, neuroretinitis, choroidal granuloma, and retinal vasculitis [10]. Diagnosis involves a history of residence or contact in TB-endemic areas, clinical features, positive tuberculin skin test (TST) or interferon-gamma releasing assay (IGRA), and a favourable response to anti-tuberculous treatment [11]. Toxoplasmosis, the most common cause of infectious chorioretinitis, is caused by the protozoan *Toxoplasma gondii*. Active ocular toxoplasmosis presents as white focal retinitis, while recurrent cases show a satellite lesion.

Spill-over anterior uveitis with granulomatous or stellate keratic precipitates is common, and severe vitritis may obscure fundus visualization ("headlight in the fog"). Diagnosis is mainly clinical, supported by serology [12]. Vogt-Koyanagi-Harada (VKH) disease is a multisystemic autoimmune condition characterized by bilateral diffuse granulomatous panuveitis with auditory, integumentary, and neurological manifestations. The autoimmune reaction targets antigens associated with melanocytes. VKH presents with bilateral granulomatous anterior uveitis, varying degrees of vitritis, choroidal thickening, optic disc edema, mutton-fat keratic precipitates, and iris nodules. Chronic VKH involves recurrent granulomatous uveitis, iris nodules, depigmentation, and stromal atrophy. Diagnosis is clinical, based on modified criteria requiring the absence of penetrating ocular trauma, bilateral uveitis, and neurological and auditory symptoms [13]. Sarcoidosis is a multisystemic granulomatous disorder with unknown etiology, often presenting as acute or chronic anterior granulomatous uveitis. The revised international workshop on ocular sarcoidosis (IWOS) criteria for diagnosis include exclusion of other causes, intraocular clinical signs, systemic investigation results, and staging based on clinical and laboratory findings [14]. Viral anterior uveitis, particularly from the herpes group, presents with granulomatous uveitis, sectoral and patchy iris atrophy, and ocular hypertension, which is diagnostic for herpetic uveitis. Posterior uveitis manifestations include acute retinal necrosis, cytomegalovirus (CMV) retinitis, and retinal vasculitis [15]. Complications of granulomatous uveitis include cataract, glaucoma, synechiae, band keratopathy, vitreous hemorrhage, maculopathy, retinal detachments, and phthisis [16]. Treatment varies by cause and may involve antimicrobial therapy for infections or anti-inflammatory and immunosuppressive drugs for autoimmune conditions like VKH and sarcoidosis [17]. The aim of the study is to determine the causes of granulomatous uveitis at a referral center in Iraq.

Method

This prospective case series observational study was conducted at Ibn-Alhaitham Teaching Eye Hospital in Iraq, involving patients with active granulomatous uveitis from March 2020 to March 2021. Patients with a history of trauma, ocular surgery, or drug-induced uveitis were excluded [18]. Demographic data such as age, gender, history of present illness, and the presence of systemic diseases were collected. Ophthalmological examinations included uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA), intraocular pressure (IOP) measurement, slit-lamp examination of the anterior segment, and posterior segment examination with a slit lamp and + 90 condensing lens. Routine tests included CBC with differential, GUE, ESR, chest X-ray, and TST and/or IGRA blood tests. Additional tests were ordered based on the clinical picture, and consultations with rheumatologists, dermatologists, neurologists, or internists were conducted as needed [18]. Presumed TB uveitis was suspected in patients with a history of contact with TB-infected individuals, suspected clinical features, and exclusion of other uveitis causes. Diagnosis was supported by positive TST and/or IGRA tests and a good response to standard anti-tuberculous treatment [19]. VKH diagnosis was clinical, following the revised diagnostic criteria, with additional OCT imaging and fundus fluorescein angiography (FFA) as needed [3]. Toxoplasmosis

diagnosis was clinical, based on the presence of toxoplasma focal retinochoroiditis, supported by serology. Positive serological tests for anti-toxoplasma IgM and IgG titers confirmed the diagnosis, while a zero IgG titer excluded it [18]. Presumed and probable ocular sarcoidosis diagnoses followed revised IWOS criteria. Patients with compatible uveitis underwent investigations, including negative TST and/or IGRA tests, positive serum lysozyme, positive serum ACE, chest X-ray showing bilateral hilar lymphadenopathy (BHL), and chest CT scans for confirmatory diagnosis. Presumed ocular sarcoidosis was defined by compatible uveitis with BHL on chest X-ray, without biopsy confirmation. Probable ocular sarcoidosis was diagnosed without biopsy or BHL, based on more than three intraocular signs and more than two systemic investigations [14]. Viral (herpetic) anterior uveitis was diagnosed clinically by granulomatous uveitis with characteristic sectoral iris atrophy, posterior synechiae, and ocular hypertension, with a complete response to antiviral treatment [15]. The study adhered to the Declaration of Helsinki, received approval from the scientific committee of the Iraqi Board of Ophthalmology, and obtained permission from the study center. Statistical analysis was performed using IBM® SPSS® Statistics Version 23. Descriptive variables were presented as frequencies, percentages, and numerical data as mean ± standard deviation (SD).

Results

During the study period (from March 2020 to March 2021), there were 55 patients enrolled, and 94 eyes since 39 patients had bilateral granulomatous uveitis while 16 patients had unilateral disease, the most frequent diagnosis was VKH with 21 patients (38.18%) (42 eyes), followed by presumed IOTB with 15 patients (27.27%) patients (28 eyes), ocular toxoplasmosis 10 patients (18.18%) (10 eyes), viral anterior uveitis 5 patients (9.09%) (6 eyes), and lastly presumed & probable ocular sarcoidosis 2 patients (3.64%) (4 eyes) for each one of them (and they will be included together as unconfirmed ocular sarcoidosis in the rest of tables).

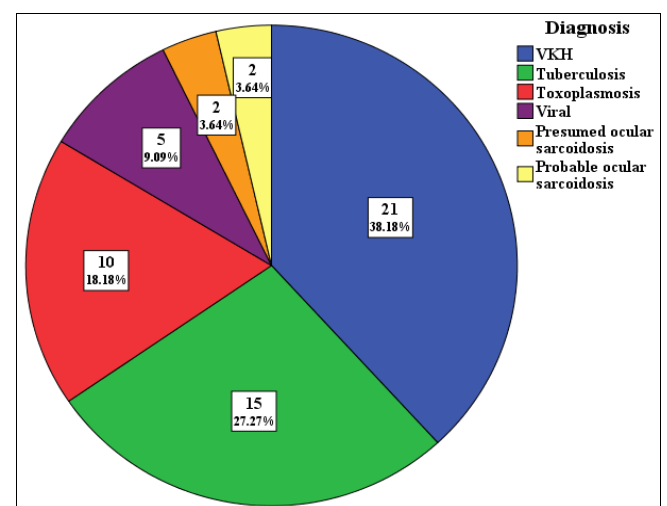


Fig 1: Distribution of the patients included in the study according to diagnosis

The mean age of the 55 patients was 29.9±14 years. The mean age of patients with VKH was 25.5±10.7 year, presumed ocular TB patients were older with mean age of 37.7±14.4 years. The mean age of patients with ocular

toxoplasmosis was 23.5±12.8 years and the mean age of patients with viral anterior uveitis was 37.4±14.7 years while The mean age of patients with unconfirmed ocular sarcoidosis was 31.8±18.5, So the youngest age was predominant in patients with ocular toxoplasmosis, while the oldest age was predominant in presumed ocular TB patients. Males formed 43.6% of cases while 56.4% were females which formed 80% of viral cases, while gender distribution was close in other diseases. Only one patient

with viral infection had bilateral disease (20%) since the number of viral anterior uveitis patients is 5, and all VKH and unconfirmed ocular sarcoidosis patients had bilateral granulomatous uveitis (100%) and all patients with toxoplasmosis had unilateral active retinochoroiditis and 6 cases (60%) of them had inactive chorioretinal scars in the other eye presumed to be due to inactive congenital toxoplasmosis. As shown in Table 1.

Table 1: Basic characteristics of the patients sample included in the study according to the diseases

Variables	VKH	TB	Toxo.	Viral	Unconfirmed ocular sarcoidosis	Total
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Age groups						
<20	7(33.3)	1(6.7)	4(40)	1(20)	1(25)	14(25.5)
20-29	3(14.3)	5(33.3)	2(20)	1(20)	1(25)	12(21.8)
30-39	9(42.9)	0(0)	3(30)	0(0)	1(25)	13(23.6)
40-49	2(9.5)	5(33.3)	1(10)	2(40)	0(0)	10(18.2)
50-59	0(0)	4(26.7)	0(0)	1(20)	1(25)	6(10.9)
Gender						
Male	11(52.4)	6(40)	5(50)	1(20)	1(25)	24(43.6)
Female	10(47.6)	9(60)	5(50)	4(80)	3(75)	31(56.4)
Laterality						
Unilateral	0(0)	2(13.3)	10(100)	4(80)	0(0)	16(29.1)
Bilateral	21(100)	13(86.7)	0(0)	1(20)	4(100)	39(70.9)
Total	21(100)	15(100)	10(100)	5(100)	4(100)	55(100)

Toxo.: Toxoplasmosis, TB: tuberculosis, VKH: Vogt-Koyanagi-Harada disease

At presentation there were 17 eyes (18.1%) with VA [from 6/6 to 6/12], 21 eyes (22.3%) with VA [from 6/18 to 6/36]. BCVA was [6/60 and less] in 27 (64.3%) of eyes with VKH, 17 (60.7%) of eyes with presumed ocular TB, 5 (50%) of

eyes with ocular toxoplasmosis, 2 (33.3%) of eyes with viral anterior uveitis, 5 (62.5%) of eyes with unconfirmed ocular sarcoidosis, As shown in Table (2).

Table 2: Best corrected visual acuity at presentation according to the diagnosis

Visual acuity	VKH	TB	Toxo.	Viral	Unconfirmed ocular sarcoidosis	Total
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
6/6- 6/12	0(0)	10(35.7)	3(30)	2(33.3)	2(25)	17(18.1)
6/18-6/36	15(35.7)	1(3.5)	2(20)	2(33.3)	1(12.5)	21(22.3)
6/60-CF	21(50)	12(42.9)	4(40)	2(33.3)	2(25)	41(43.6)
Hand movement & light perception	6(14.3)	5(17.9)	1(10)	0(0)	3(37.5)	15(16)
Total	42(100)	28(100)	10(100)	6(100)	8(100)	94(100)

Toxo.: Toxoplasmosis, TB: tuberculosis, VKH: Vogt-Koyanagi-Harada diseases

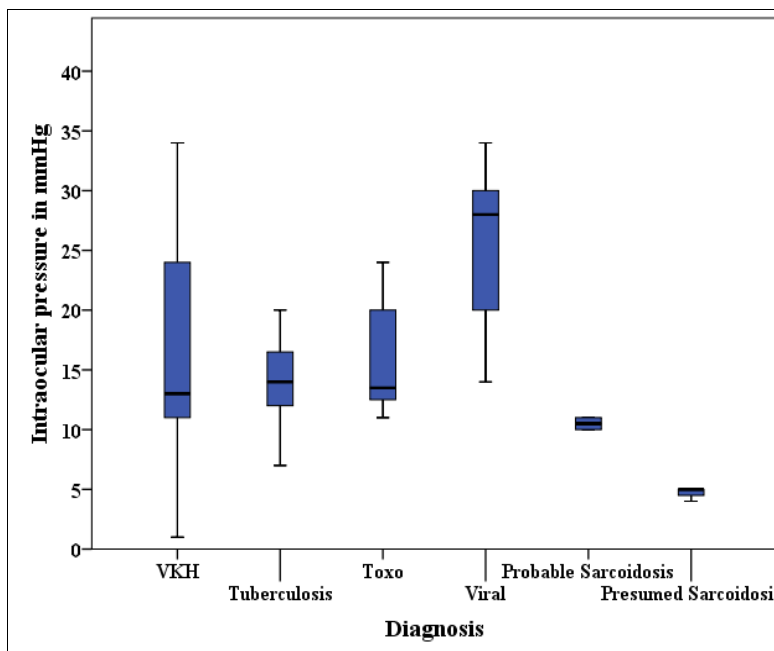


Fig 2: Distribution of IOP according to diagnosis

The mean IOP in eyes with viral anterior uveitis was 25.7 ± 7.3 mmHg, and in eyes with ocular toxoplasmosis it was 17.9 ± 8.7 mmHg, in eyes with presumed ocular TB it was 15.4 ± 6.3 mmHg, and in eyes with VKH it was 15.4 ± 8.1 mmHg, while in probable ocular sarcoidosis it was 10.5 ± 3.1 mmHg, as illustrated in Figure 2.

At presentation keratic precipitates (large in size) was found in all cases of unconfirmed ocular sarcoidosis and viral anterior uveitis. Posterior synechia was predominant in unconfirmed ocular sarcoidosis (7 eyes) (87.5%) followed by viral anterior uveitis cases (5 eyes) (83.3%). Sectoral iris atrophy was seen only in eyes with viral anterior uveitis (4

eyes) (66.7%). Iris nodules were seen only in cases with unconfirmed ocular sarcoidosis (4 eyes) (50%). Vitritis was found in all the cases except viral anterior uveitis cases. In toxoplasmosis, there were 10 eyes (100%) with unilateral active retinochoroiditis and 6 cases (60%) of them had inactive chorioretinal scars in the other eye presumed to be inactive congenital toxoplasmosis. Sunset glow fundus and exudative retinal detachments was found only in VKH (22 eyes) (52.3%) and (5 eyes) (11.9%) respectively. Cataract was predominantly seen in (32 eyes) (76.2%) of VKH. Elevated IOP was predominantly seen in viral anterior uveitis cases (4 eyes) (66.7%), As shown in Table (3).

Table 3: Distribution of study sample according to diagnosis and ocular signs & complications at presentation

Variables	VKH	TB	Toxo.	Viral	Unconfirmed ocular sarcoidosis	Total
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
KPs	34(81)	15(53.6)	4(40)	6(100)	8(100)	67(71.3)
Posterior synechia	19(45.2)	12(42.9)	1(10)	5(83.3)	7(87.5)	44(46.8)
Sectoral iris atrophy	0(0)	0(0)	0(0)	4(66.7)	0(0)	4(4.3)
Iris Nodules	0(0)	0(0)	0(0)	0(0)	4(50)	4(4.3)
Vitritis	42(100)	28(100)	10(100)	0(0)	8(100)	88(93.6)
Sunset glow	22(52.3)	0(0)	0(0)	0(0)	0(0)	22(23.4)
Chorioretinal scar	2(4.8)	4(14.3)	10(100)	0(0)	0(0)	16(17)
Active retinochoroiditis	0(0)	0(0)	10(100)	0(0)	0(0)	10(10.6)
Vasculitis	0(0)	5(17.9)	0(0)	0(0)	2(25)	7(7.4)
Optic disc swelling	4(9.5)	0(0)	0(0)	0(0)	0(0)	4(4.3)
Active choroiditis	8(19)	18(64.3)	0(0)	0(0)	0(0)	26(27.7)
Optic disc pallor	2(4.8)	2(7.1)	0(0)	0(0)	0(0)	4(4.3)
Retinal detachment	5(11.9)	0(0)	0(0)	0(0)	0(0)	5(5.3)
cataract	32(76.2)	11(39.3)	2(20)	1(16.7)	4(50)	50(53.2)
Elevated IOP	13(31)	2(7.1)	4(40)	4(66.7)	0(0)	23(24.5)
Total	42(100)	28(100)	10(100)	6(100)	8(100)	94(100)

Toxo.: Toxoplasmosis, TB: tuberculosis, VKH: Vogt-Koyanagi-Harada disease, RD: retinal detachment. KPs: keratic precipitates

Discussion

This study investigated the causes of granulomatous uveitis in a referral center in Iraq, highlighting its varied etiology and demographic factors. Granulomatous uveitis, a chronic inflammatory condition affecting the uvea, can result from systemic conditions, autoimmune reactions, and infectious diseases [20]. The most frequent diagnosis in this study was VKH (38.18%), followed by presumed ocular TB (27.27%), ocular toxoplasmosis (18.18%), viral anterior uveitis (9.09%), and unconfirmed ocular sarcoidosis (7.27%). These findings align with previous studies in Iraq and neighboring regions, which reported similar etiological distributions [18]. Patients with presumed ocular TB and viral anterior uveitis were older, in their fourth decade, compared to other causes predominantly affecting the third decade. This observation is consistent with studies from Brazil and Japan, where patients with presumed ocular TB and viral uveitis also presented in their fourth and fifth decades [15, 21]. The younger age of VKH patients in this study compared to other studies suggests a broader age range for VKH presentation, including early childhood [22]. Gender distribution in this study showed a female predominance in viral and unconfirmed ocular sarcoidosis cases, similar to other studies that reported higher female incidence in herpes simplex or varicella zoster uveitis and ocular sarcoidosis [15]. These differences may stem from hormonal, physiological, and susceptibility variations between genders [23]. In VKH patients, posterior uveitis was the most frequent presentation, with vitritis observed in 100% of cases, sunset glow fundus in 52.3%, optic disc swelling in 9.5%, and exudative retinal detachment (ERD) in 11.9%. These features differ from studies in Iran and Saudi Arabia, where

higher incidences of ERD and optic disc swelling were reported, possibly due to the different stages of VKH at presentation [24, 25]. VKH progresses through four stages, from prodromal to chronic recurrent, with varying clinical features at each stage [26]. Presumed ocular TB patients in this study exhibited bilateral disease (86.7%), active choroiditis (64.3%), keratic precipitates (KPs) (53.6%), posterior synechiae (42.9%), vitritis (100%), and vasculitis (17.9%). These findings are similar to previous studies in Iraq, but differ from reports in Nepal, where different patterns of clinical findings and presentations were noted. The variation in clinical presentation could be due to geographical differences, pathogen polymorphisms, and diagnostic criteria [10-27]. All cases of retinal toxoplasmosis in this study presented unilaterally, with 60% showing retinal scars in the other eye, anterior uveitis in 40%, posterior synechiae in 10%, and vitritis in 100%. These findings are comparable to an Iranian study, which reported similar frequencies of KPs and vitritis in ocular toxoplasmosis [28]. The mechanisms of *Toxoplasma gondii* infection and spread within the retina involve complex interactions and multiple migration routes [29]. Viral anterior uveitis cases showed higher frequencies of KPs (100%), sectoral iris atrophy (66.7%), elevated intraocular pressure (IOP) (66.7%), and no vitritis, which were higher compared to other studies [15, 30]. Elevated IOP in herpetic anterior uveitis correlates with viral load and trabeculitis severity, varying by virus type and infection stage [31]. Probable/presumed ocular sarcoidosis cases exhibited bilateral disease (100%), with panuveitis, posterior synechiae (87.5%), iris nodules (50%), and vasculitis (25%). These findings are consistent with other studies, though

presentation can differ by race, with white patients more likely to have posterior involvement^[32, 33]. Sarcoidosis often presents ocular symptoms before systemic manifestations, highlighting the need for thorough ocular examination in suspected cases^[34].

Conclusion

In a referral center in Iraq, VKH caused the most granulomatous uveitis with 42 eyes (44.68%) in 21 patients, followed by presumed ocular TB with 28 eyes (29.79%) in 15, ocular toxoplasmosis with 10 eyes (10.63%) in 10, viral anterior uveitis with 6 eyes (6.38%) in 5, and presumed and probable ocular sarcoidosis with 4 eyes (4.26%) in 2 patients.

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