

Uveitis is not just an ophthalmologists' concern

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Abstract

Objective: To find the causes and characteristics of uveitis and its subtypes among Pakistani population, and to create awareness that early diagnosis and treatment of uveitis requires a multi-disciplinary approach.

Methods: The retrospective study involved 98 diagnosed uveitis patients. Data was analysed regarding associated systemic diseases, infections, ocular syndromes, anatomical localisation, age, and gender.

Results: In 85% of the patients, a classified form of uveitis was observed: associated systemic diseases were found in 24%, the most frequent one being sarcoidosis (9.8%) and V-K-H syndrome (7.4%); ocular syndromes were present in 10%, the most frequent being birdshot retinochoroidopathy (6.1%) and pars planitis (3.7%); and infections in 48%, the most frequent being tuberculosis (50.6%) and hepatitis (4.9%). Among classified uveitis, posterior uveitis was found in 46%, intermediate uveitis in 10% and anterior uveitis in 7% of the patients. Panuveitis was diagnosed in 36% of cases. The remaining 1% showed extrauveal manifestations.

Conclusions: Causes of uveitis vary considerably by geographic location around the world. Granulomatous diseases are the most frequent cause of uveitis in Pakistan. Hence, detailed and expensive investigations in our context are not justified in all patients. The data offer guidance to rheumatologists and consultant physicians to facilitate efficient diagnostic testing.

Keywords: Uveitis, Epidemiology, Ocular syndrome, Infections (JPMA 62: 92; 2012).

Introduction

Inflammation of the uveal tract or the adjacent ocular structures is defined as uveitis. International Uveitis Study Group (IUSG) has categorised uveitis as anterior uveitis, intermediate uveitis, posterior uveitis and an additional term, panuveitis, has also been explicated.¹

Uveitis frequently conceals the diagnosis of ocular involvement related to underlying systemic disease, out of which approximately 40% are identified as immune-mediated.² A genetic predisposition may also account for the development of uveitis in some patients.³ The recognition of uveitis is important to an ophthalmologist, but the diagnosis of underlying systemic disease or infection requires multi disciplinary approach more often by an internist and a rheumatologist. The disease spectrum and its pathogenesis range from autoimmunity to neoplasia to viruses. Hence, the diagnostic process holds out a challenge and is mainly clinical. Despite improvement in diagnostic techniques and treatment methodologies, uveitis continues to be one of the major causes of visual impairment.⁴

Epidemiological knowledge of uveitis is crucial for diagnosis, without any need for unnecessary investigations, which varies widely.⁵ Age, gender, race, geographic location, travel history, social habits and occupation; all contribute to the causes.⁶ Awareness of such differences in the disease pattern is constitutive in deriving a region-specific list of differentials, which, in turn, facilitates the final diagnosis. Factors contributing to such regional variations in the causes of uveitis are complex and not understood completely, but include both host and environmental factors.

Many small and large cohort studies on the subject have been conducted in the developed and the developing countries.⁷⁻¹⁵ However, a cohort study on the subject has never been conducted and published in Pakistan, except for a few small single centre based studies.^{16,17} This study of ours presents a cohort of uveitis patients referred from all over Pakistan to the largest eye hospital of the country.

The objective was to find the causes and characteristics of uveitis and its subtypes among Pakistani population. The secondary objective was to create awareness amongst the treating physicians/ophthalmologists that early diagnosis and treatment of uveitis requires a multi-disciplinary approach.

Patients and Methods

A retrospective cohort was carried out on the basis of six months' medical records i.e. from Jan to June 2010 of all the diagnosed uveitis patients referred to Jinnah Medical College Hospital (JMCH) from Layton Rahmatullah

Benevolent Trust (LRBT) charitable eye hospital.

Founded in 1984, LRBT is the largest eye hospital group of the country, with 40 primary-eye-care clinics, 14 secondary eye-care hospitals and 2 tertiary-eye-hospitals providing free ophthalmologic treatment. Virtually, no Pakistani citizen is 200km away from an LRBT facility. A well-equipped uveitis clinic, being operated by a team of consultant ophthalmologists, has been recently established at its main hospital, which is one of the tertiary care hospitals located in Karachi. Uveitis patients are referred here from all over Pakistan. Patients requiring medical advice are referred to the nearby JMCH for systemic evaluation. JMCH is a tertiary care teaching hospital, with fully operational multi disciplinary departments affiliated with the University of Karachi and providing health facilities to the neighbouring industrial area and slums of Karachi.

Based on diagnostic and anatomic classification criteria, adopted from Standardisation of Uveitis Nomenclature (SUN) workshop¹⁸ and IUSG¹ we included and excluded uveitis and extrauveal disease as defined and classified by Jakob et al⁷ described below.

Uveal and extrauveal inflammatory eye disease is divided into two major groups (Classified and Unclassified). When no associated condition was found, in spite of the extensive examination and workup, the term Unclassified was used. Classified group was further divided into three sub-groups: ocular syndrome, infectious origin or systemic association. Clearly defined uveitis syndromes restricted to the eye¹⁹ (e.g., sympathetic ophthalmia, pars planitis, birdshot retinochoroidopathy) with no systemic involvement were included in ocular syndromes. Masquerade syndromes,¹⁹ which are non-infectious processes mistaken for inflammatory processes, and patients lost during follow-up were excluded.

Detailed ophthalmological examination was carried out by a specialist at LRBT. For systemic evaluation and diagnosing associated disease, most patients were referred to consultant physicians at JMCH. A detailed medical history, clinical examination by respective specialist and basic tests consisting of blood cell count, chemistry, serology and radiographs were performed. Subsequent tailored investigations, including HLA typing and CT scan chest, were ordered depending on suspected associations as described by Becker et al.²⁰ All findings were recorded manually and a separate file was maintained for individual patients. One final diagnosis, and management plan in each case was mutually decided by an ophthalmologist, and a consultant physician. Except for a few cases where two conditions co-existed, only one major condition was

considered as the final diagnosis.

The data was first collected on a specifically designed performa, and then analysed for frequencies of uveitis and its sub-types with regards to gender, age of onset, laterality and anatomic localisation. Analysis was done by one of the authors, using the Statistical Package for the Social Sciences (SPSS) version 16. The confidentiality of personal information was maintained throughout the study.

Results

During the study period, medical records of 98 uveitis patients (46 male, 52 female) were analysed. Male-to-female ratio was found to be 0.88:1 and mean age 35.09 ± 14.41 (range 15-72 years). Disease onset was seen most frequently among middle aged (30-50 years) males (37%) and females (58%). Females above 50 years of age formed the smallest group of patients. Although patients were referred from all over Pakistan, but were mostly from the province of Sindh (44.9%) followed by Punjab (23.5%), Kashmir (14.3%), Khyber Pakhtunkhwa (10.2%) and Balochistan (7.1%). This ethnic distribution can be explained by the fact that both the centres are located in Karachi, Sindh. Uveitis was bilateral in 65 patients, while the rest had unilateral disease.

Among the types 85% were Classified, whereas 15% had Unclassified uveitis. In the Classified group, infection was the leading cause of uveitis and 2% of the patients had masquerade syndrome. Furthermore, one patient had an infection and systemic disease concurrently (Figure-1).

In terms of age distribution and gender of patients with Classified uveitis, ocular syndrome was found

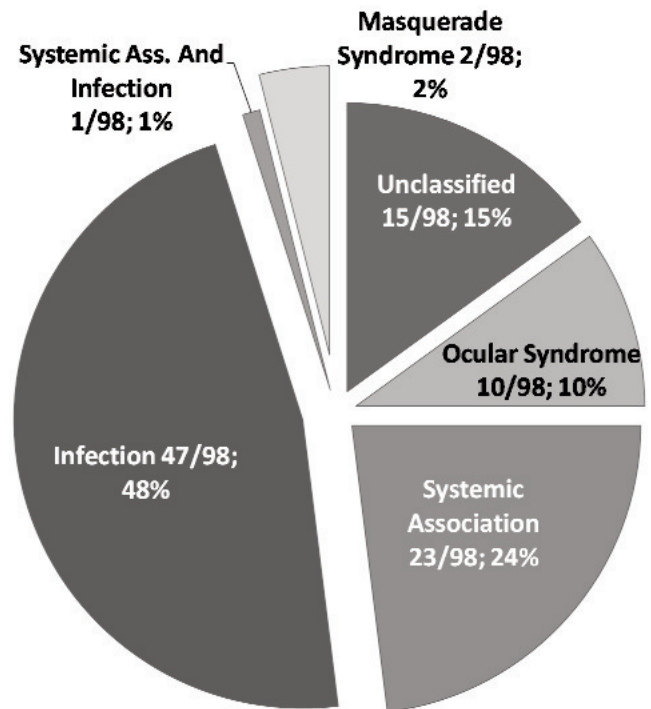


Figure-1: Categorisation of study patients. (n=98).

mainly among 25-55 years old males (60%). Among ocular syndrome, sympathetic ophthalmia was seen mostly among 25-30 years old, pars planitis in 30-40 years, and birdshot retinochoroidopathy among 45-50 years old. Uveitis of infectious origin was prevalent in females (55%). Tuberculosis was common in 30-35 years old patients, hepatitis in 25-30 years and toxoplasmosis in

Table: Anatomical localisation of uveitis and most frequently associated Classified causes of uveitis.

	Location					Total n = 81
	Anterior n = 6	Intermediate n = 8	Posterior n = 37	Panuveitis n = 29	Extrauveal n = 1	
Ocular Syndrome						
Sympathetic Ophthalmia	----	----	----	1 (3.4%)	----	1 (1.2%)
Pars Planitis	----	----	1 (2.7%)	2 (6.8%)	----	3 (3.7%)
Birdshot Retinochoroidopathy	----	----	3 (8.1%)	2 (6.8%)	----	5 (6.1%)
Infectious Condition						
Toxoplasmosis	----	----	2 (5.4%)	1 (3.4%)	----	3 (3.7%)
Tuberculosis	2 (33%)	4 (50%)	20 (54%)	15 (51.7%)	----	41 (50.6%)
Hepatitis	----	----	----	4 (13.7%)	----	4 (4.9%)
Systemic Association						
SpA	3 (50%)	----	----	----	----	3 (3.7%)
RA	----	----	1 (2.7%)	1 (3.4%)	----	2 (2.4%)
Sarcoidosis	----	3 (37.5%)	4 (10.8%)	1 (3.4%)	----	8 (9.8%)
Behcet's Syndrome	----	1 (12.5%)	----	----	----	1 (1.2%)
SLE	----	----	1 (2.7%)	1 (3.4%)	1 (100%)	3 (3.7%)
V-K-H Syndrome	----	----	5 (13.5%)	1 (3.4%)	----	6 (7.4%)
Two Co-Existent Condition						
Tuberculosis + Sarcoidosis	1 (17%)	----	----	----	----	1 (1.2%)

VKH syndrome: vogt-koyanagi-harada syndrome; SpA: spondyloarthropathies; SLE: systemic lupus erythematosus; JRA: juvenile rheumatoid arthritis; RA: rheumatoid arthritis.

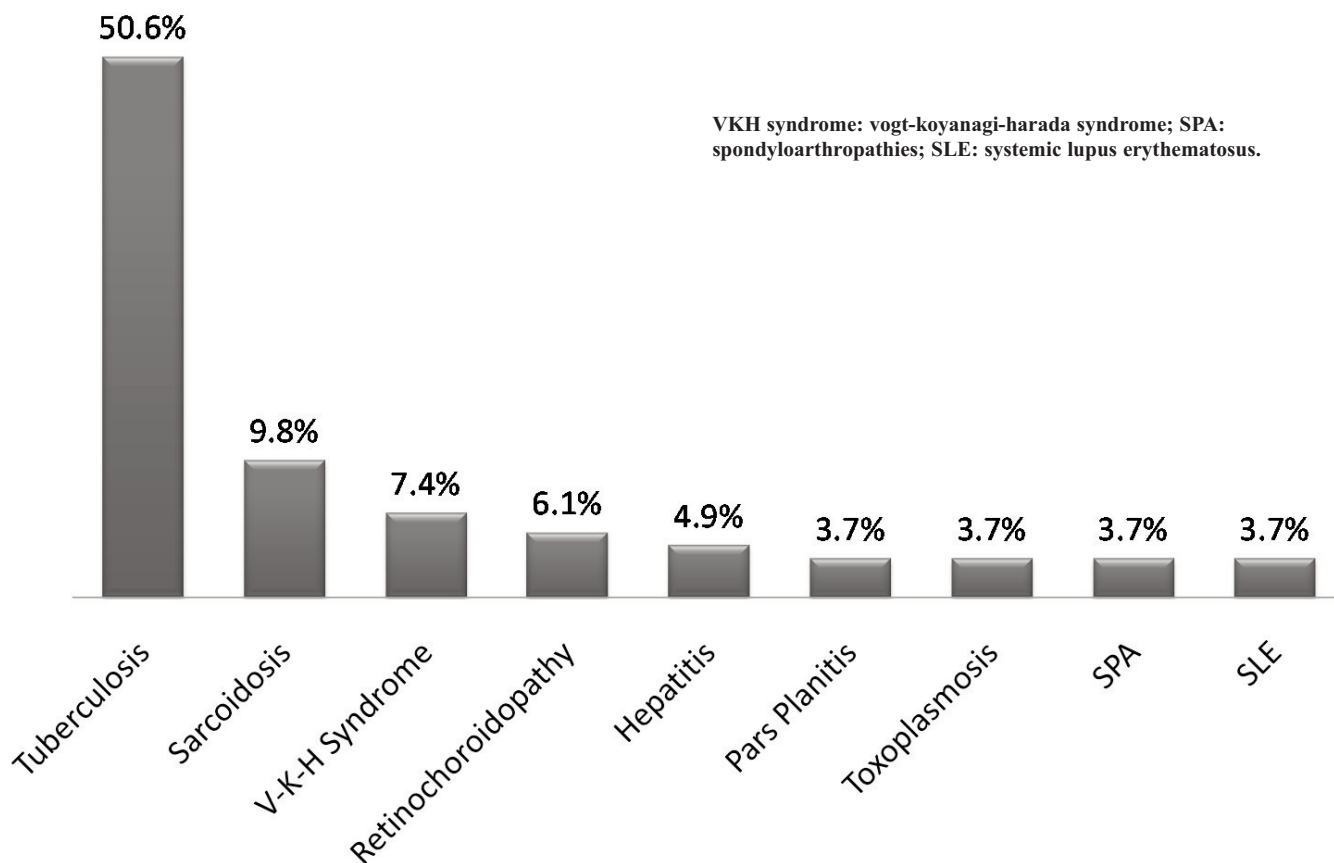


Figure-2: Most frequent form of classified uveitis (n=81).

20-30 years old patients. Of all systemic associated uveitis, 56.5% were females and mainly young adults (15-20 years old). Spondyloarthropathies were common among 20-25 years old, sarcoidosis in 15-20 years, rheumatoid arthritis in 35-40 years, Vogt-Koyanagi-Harada (VKH) syndrome in 40-45 years, Behcet's syndrome and systemic lupus erythematosus (SLE) in 20-25 years old patients (Figure-2).

Among 47 patients with uveitis due to infectious origin, 41 had tuberculosis. This includes solitary tuberculous uveitis and also systemic tuberculosis along with tuberculous uveitis. Hepatitis C was the second most common infectious cause of uveitis in the study population. Anti-HCV was found positive in 4 of 47 patients with no other significant causes. Out of 23 systemic-associated uveitis, 8 patients suffered from sarcoidosis, making it the second most common cause (Figure-2).

Among patients who had uveitis with an ocular syndrome, the most frequent cases were those of birdshot retinochoroidopathy (50%) and pars planitis (30%). Pars planitis may sometimes be associated with sarcoidosis or

occasionally show manifestation of multiple sclerosis, but is usually not associated with any other systemic disease.

As regards anatomic localization, anterior and intermediate uveitis was found in 20% of the total (20/98). Of them 57% were males with anterior uveitis and 63.6% were females with intermediate uveitis. Posterior uveitis was found in 48%, with females being the most affected (53%). Panuveitis was found in 30% of the patients with almost equal gender distribution. The remaining 2% (2/98) cases had extrauveal manifestations (Table).

Among the Classified group, posterior uveitis was the most common finding followed by panuveitis in which birdshot retinochoroidopathy, tuberculosis and sarcoidosis were mostly prevalent. Tuberculosis was seen in all anatomical locations more commonly as posterior. In this study SLE was the only extrauveal finding.

Discussion

The age distribution in the study was such that 46.1% of the patients were between 30 and 50 years and with a mean age of 35.9 years. In previous clinic-based

surveys, similar mean age of onset of uveitis was found.^{8,9,12} Our observation, that uveitis is less common among the young and the elderly, is supported by the literature.⁹ The literature offers some dispute about the male-to-female ratio in uveitis. With few exceptions^{14,17} most studies report more prevalence in women^{7-10,12,13} or an equal gender distribution. This corresponds well with our male-to-female ratio of 0.8:1. Factors contributing to such a ratio in uveitis are complex.

Anatomical localisation can give useful information to the clinician about the likely cause of uveitis. As in our cohort, with 46.9%, posterior uveitis has been described in few other cohorts to be the most common form of uveitis.¹¹ Most of the reports published to date have suggested that anterior uveitis is the most common form of uveitis.^{7,10,15} Possible reason to this pattern is frequent infectious uveitis and common tuberculous uveitis in our patients, which is posterior mainly. Posterior and panuveitis were remarkably common in reports from Africa, which could be attributed to a high incidence of infectious causes such as toxoplasmosis and onchocerciasis which affect mainly the posterior segment. Intermediate uveitis, a rare form of Classified uveitis,¹⁵ is usually due to a systemic disease, often sarcoidosis. If extrauveal inflammation such as scleritis occurs, the strategy in the search of associated disease should focus on SLE.

The study demonstrated a frequency of 85% Classified and 15% of Unclassified uveitis. Whereas Iqbal et al¹⁷ have stated 51% as Classified and 49% Unclassified uveitis in their study conducted in Peshawar. Arguments supporting our figures could be technology advancement, disease awareness and improvement in diagnosis since the year 2003. Also, our data included diagnosed uveitis patients referred from all over Pakistan, undergone thorough workup by multi-disciplinary approach. This is also different from the literature of Europe and the USA^{7,15} as they included patients lost during follow-up in their total numbers. Uveitis is mainly idiopathic in developed countries as compared to the developing countries where it is mostly associated with an infectious condition. Reports from less developed and other developing countries also show lesser frequency of Classified uveitis as compared to our study. For instance, Singh et al¹⁰ found 51.2% in India. Our study corresponds well to Khairallah et al⁸ in North Africa and Biziorek et al¹³ in Poland. They also showed high percentages of Classified as compared to Unclassified uveitis which support our findings.

Infectious conditions (48%) was found to be the largest group among the Classified forms. Their diagnosis is especially important because they require completely

different therapies. In our cohort, infections corresponded to the results found by others.^{21,22} Tuberculosis, already an endemic in this region,²³ was also most frequently associated with Classified uveitis (50.6%). The literature from a few countries agreed with our results in that infection most frequently comprised tuberculosis.¹⁰⁻¹² This is different from the rest of the world where toxoplasmosis and herpetic infections are more common. Data from other cohorts in Pakistan is approximately similar, but not comparable due to their limited sample size and smaller study universe.

Systemic diseases (24%) was the second most frequent association with uveitis after infections. Literature from the developed countries shows more systemic associated uveitis than infectious origin.^{7,15} Data from the less-developed and developing countries, however, correspond well with our results, suggesting infections are more prevalent in these regions. The infectious-to-systemic uveitis ratio in these regions are: Singh et al¹⁰ in India states 29.7% to 19.1%, Islam et al¹² in Saudi Arabia states 36% to 21% and Mercanti et al¹⁴ in Italy states 40.3% to 13.6%. High burden of infectious diseases and increasing rates of antimicrobial resistance in South Asia by Zaidi et al²¹ also supports our result.

Specific ocular syndromes affected fewer patients (10%), and this was reflected in the literature. Among the most frequent conditions overall, however, clearly belonged to the category of ocular syndromes. These were birdshot retinochoroidopathy followed by pars planitis.

Among our cases of Classified uveitis, HLA-B27-positive anterior uveitis without systemic manifestation, Fuchs uveitis syndrome (FUS), herpetic infection, multiple sclerosis and Lyme disease were rarely seen (Table). These differences in causes of uveitis reflect regional and genetic factors. For instance, Behcet's disease is rare in the USA and Europe, while it is frequent in countries along the ancient Silk Road. HLA-B27-associated diseases, in contrast, are more common among the Caucasians. Bodaghi, et al²⁵ did not report FUS, herpetic infection, or toxoplasmosis among their most common causes, but instead listed diagnoses such as Vogt-Koyanagi-Harada syndrome. We also report V-K-H syndrome as the third most frequent cause of uveitis among our patients.

Changing patterns of uveitis are seen in studies from a number of countries done at different periods of time.⁵ These pattern changes are because of a multitude of factors, including genetic, ethnic, geographic and environmental. Awareness of such regional differences in the disease pattern is essential in deriving a region-specific list of differential diagnoses and also in understanding the predictive values of diagnostic tests, which, in turn,

facilitate the final diagnosis.

Conclusion

Causes of uveitis vary considerably by geographic location around the world. The study data and comparison offer guidance for rheumatologists and consultant physicians to facilitate efficient diagnostic testing. The study, on the basis of highly sophisticated data from all over Pakistan, identify anatomic diagnosis and classification by a team of consultant physicians and ophthalmologists. This compared with the rest of the world, and recommended specific diagnostic steps in a given patient with uveitis. Detailed and expensive investigations in a developing country like Pakistan are not justified in all patients. The epidemiological data of our study will benefit doctors and patients across Pakistan as well as in the neighbouring countries on a similar development scale as ours.

Acknowledgements

Special thanks are extended to the patients who participated in the study. We would also like to acknowledge Dr. Kamran Hameed, Dr. Munira Shakir and Miss Anum Shazad for reviewing the final manuscript.

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