GENDER BIAS IN UVEITIS: RESULTS FROM A STUDY AT ARMED FORCES INSTITUTE OF OPHTHALMOLOGY RAWALPINDI

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ABSTRACT

Objective: Current study aimed at finding the differences in etiology of uveitis among male and female genders among patients presenting to the Uveitis Clinic of AFIO, Rawalpindi.
Study Design: Cross sectional study.
Place and Duration of Study: Armed Forces Institute of Ophthalmology Rawalpindi, from Nov 2017 to Oct 2018.
Methodology: A total of 182 patients diagnosed to have uveitis were recruited through non-probability consecutive sampling. Patients with diabetic retinopathy, vitreous hemorrhage, post-surgical uveitis and tumor associated uveitis were excluded. Data including demographic and ocular history were noted. Investigations were carried out to ascertain the underlying cause.
Results: A total of 182 patients were included in the study ranging from 8 to 69 years of age with a mean age of 42 ± 8.5 years. Seventy six (41.7%) were males while 106 (58.3%) were females. Causes included idiopathic in 118 (65%), infectious causes in 31 (17%) and non-infectious causes in 33 (18%). After gender stratification, it was found that in 48 (63.2%) males and 70 (66%) females no cause could be ascertained (idiopathic). Among the 33 infectious causes 20 were males whereas 13 were females. Among 31 patients with non-infectious causes 8 were males and 23 were females. These gender differences were statistically significant; p=0.017.
Conclusion: Infectious causes were more common among males whereas non-infectious causes are more frequent among females.

Keywords: Autoimmune, Behcet's disease, Causes, Gender, Infections, Uveitis.

INTRODUCTION

Differences in incidence, presentation, and course of diseases between males and females are commonly observed and eye diseases are no exception. The burden of blindness worldwide is unequal between men and women, with women accounting for 64.5% of blindness[1]. When adjusted for age, the overall odds ratio of blind women to men is 1.43[2]. Uveitis is one of the sight threatening conditions of the eye, characterized by infectious and non-infectious inflammation in the eye. Uveitis by its name seems to be the inflammation of the uvea, the vascular portion of the eye, but it may involve retina, vitreous, optic nerve and anterior chamber. It is common usually in ages 20 to 70 years[3]. Each year around 10% people go blind due to uveitis[4]. Patients with uveitis may present with sight threatening complications, including cataract, glaucoma, macular edema, vitreous debris, while macular edema being the most common among all[5,6]. Glaucoma and cataract may be triggered either by the use of steroids, or the inflammatory blockage of the outflow of the fluid from the eye[7]. Normally the interior of the eye is immune privileged due to the presence of blood aqueous and blood retinal barriers. In various inflammatory and infectious conditions of the eye, these barriers are compromised resulting in uveitis. Broadly, its etiology can be divided into, infectious and non-infectious.

It has been observed that there is a gender difference with a greater preponderance of non-infectious uveitis in women than in men[8]. The prevalence of autoimmunity in women is higher than in men[9]. Uveitis with autoimmune

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etiologies, such as those resulting from Bechet's disease, rheumatoid arthritis, systemic lupus erythematosus (SLE) and sarcoidosis tend to be reported more frequently in women than in men[10].

Recognition of the gender difference in uveitis would allow new preventative and therapeutic strategies for patients in the future. If gender differences are found they may indicate behavioral and cultural differences in sources and hence may provide new targets for disease prevention and treatment. With the help of current study we want to highlight the gender bias, if any, in uveitis. A better understanding of etiology and demography of uveitis will help to device an effective strategy to manage this potentially blinding condition in early stages.

METHODOLOGY

It was a hospital-based cross-sectional study carried out at Armed Forces Institute of Ophthalmology, (AFIO) Rawalpindi. Sample size for study was calculated using the WHO calculator for sample size determination in health studies. The formula for estimating the difference between two population proportions was used. The study by Compton *et al*[13] showed that males comprised 31% of non-infectious uveitis while there were 69% females. Keeping the confidence interval at 95%, absolute precision at 10% and the anticipated population proportions P1 and P2 at 0.69 and 0.31 respectively; the minimum sample size was 165 patients. Patients were recruited through non-probability consecutive sampling. All patients presenting to the Uveitis Clinic from November 2017 to October 2018 were screened for entry in the study. Patients diagnosed with uveitis on slit-lamp examination were enrolled in the study after their informed consent.

A total of patients with uveitis were included in the study for fulfilling the inclusion criteria and 182 completed the work up. Diagnosis was made on the basis of slit lamp examination with 90D/triple mirror Goldman lens performed by an ophthalmologist. Patients having keratic precipitates (KPs), cells and flare in the anterior chamber, cells in the vitreous chamber and presence of snowballs and vitreous debris, snow banking at pars plana, any cystoid macular edema, any choroiditis/ retinochoroiditis lesions, presence of periphlebitis or arteritis and optic nerve involvement. Subsequently, uveitis was classified as anterior, intermediate and posterior uveitis based on the classification of International uveitis study group (IUSG)[11]. Patients with diabetic retinopathy, vitreous hemorrhage, post-surgical uveitis and tumor associated uveitis were excluded. Patients in whom work up could not be completed were also excluded from the study.

After inclusion in the study a step wise approach was adopted for evaluation of possible causes. A detailed ocular and systemic history was taken. Laboratory investigations were tailored as per the guidelines cited by Smith and Nozik[12]. Complete blood picture, erythrocyte sedimentation rate, polymerase chain reaction (PCR) for VZV, CMV & Herpes Simplex virus, Human Immunodeficiency virus (HIV), VDRL and FTA-ABS, Mantoux skin test, Enzyme linked immunosorbent assay (ELISA) for Toxoplasma, serum Angiotensin converting enzyme (ACE) levels, serology for Rubella and Human leukocyte antigen (HLA) typing. Radiological investigations were performed in case of history of joint pains or respiratory complaints. Indirect ophthalmoscopy with scleral indentation, Optical coherence tomography (OCT) and fundus fluorescein angiography (FFA) were carried out where

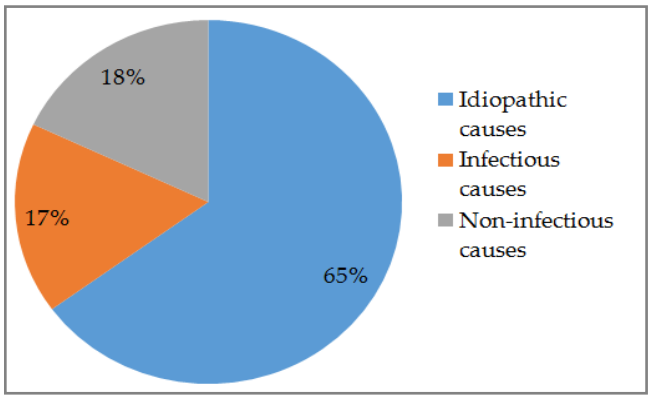

Figure-1: Causes of uveitis.

necessary. If the cause for uveitis could not be ascertained, it was termed idiopathic.

Data was entered on the proformas including the demographic and clinical details, findings of ophthalmic examination and results of investigations. Data was then analyzed using SPSS 20 version. Results were summarized as frequencies and percentages and presented as figures and tables.

Table-I: Infectious causes of uveitis.

Infectious causes					
Etiology	**n**	**Anterior uveitis**	**Posterior uveitis**	**Intermediate**	**Pan uveitis**
Tuberculosis	21	1	16	2	2
Toxoplasmosis	2		2		
Varicella zoster virus	3	1	1		1
Rubella virus	2		2		
Herpes simplex	3	1	2		

Table-II: Non-infectious causes of uveitis.

Non-Infectious Causes					
Etiology	**n**	**Anterior uveitis**	**Posterior uveitis**	**Intermediate**	**Pan uveitis**
Bechet's	9	2	5		2
Sarcoidosis	3		1	2	
Rheumatoid arthritis	3	1	2		
SPA	3	1	2		
SLE	1		1		
VKH	2		2		
FUCHS'	4	2	2		
Psoriasis	1		1		
Serpiginous choroidopathy	1		1		
Sympathetic ophthalmia	1				1
Juvenile idiopathic arthritis	1		1		
Inflammatory bowel disease	2		1	1	
Multiple Sclerosis	1			1	
Sjogren's Syndrome	1			1	

VKH Syndrome: Vogt-Koyanagi-Harada Syndrome; SpA: Spondyloarthropathies; SLE: Systemic Lupus Erythematosus.

RESULTS

A total of 182 patients were included in the study. Age of the patients ranged from 8 to 69 years with a mean age of 42 ± 8.5 years. Seventy six (41.7%) were males while 106 (58.3%) were females.

Majority had unilateral uveitis, while 69 (38%) had bilateral involvement. Anterior uveitis was present in 92 patients (50%) with 28 patients showing binocular involvement. Posterior uveitis was present in 53 patients (29%) with 20 patients showing binocular involvement. Intermediate uveitis was seen in 12 patients (7%) with 7 patients showing binocular involvement. Panuveitis was present in 25 patients (14%) with 14 patients having binocular involvement.

A cause could not be ascertained in 118 (65%) patients and were labeled as idiopathic. The causes in the remaining 64 patients were grouped into infectious and non-infectious causes. Infectious causes were found in 31 (17%) and non-infectious causes in 33 (18%) patients.

Infectious causes included tuberculosis 21 (11.5%), toxoplasmosis 2 (1.1%), varicella zoster virus 3 (1.65%), rubella virus 2 (1.1%) and herpes simplex virus 3 (1.65%). The anatomic site of involvement of these infectious agents is presented in table-I.

Among the non-infectious causes Behcet's disease was the commonest 9 (5%). Other included FUCHS 4 (2.2%), sarcoidosis, rheumatoid arthritis and ankylosing spondylitis (in each 3 (1.6%). We also had inflammatory bowel disease

and Vogt-Koyanagi-Harada syndrome 2 (1.1%). The rest included SLE, psoriasis, serpiginous choroidopathy, sympathetic ophthalmia, juvenile idiopathic arthritis, multiple sclerosis and Sjogren's syndrome (in each case 1 (0.5%).

After gender stratification, it was found that among 118 patients with idiopathic uveitis 48 were males and 70 were females. Among the 33

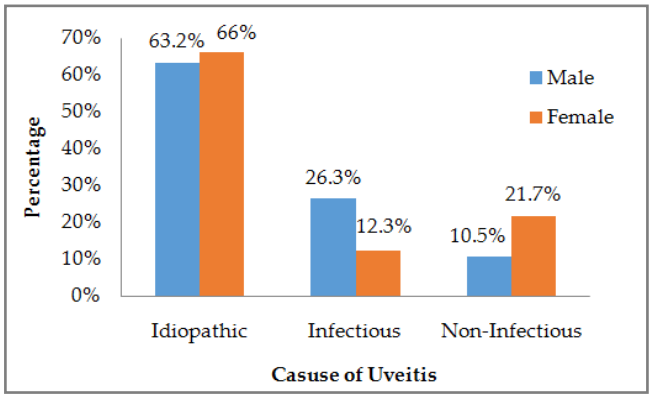

Figure-2: Gender differences in causes of uveitis.

infectious causes 20 were males whereas 13 were females. Among 31 patients with non-infectious causes 8 were males and 23 were females. These gender differences were statistically significant; p=0.017.

DISCUSSION

Uveitis is considered as inflammation of the uveal tract and adjacent structures – these include iris, ciliary body, choroid and their adjacent structures like retina, optic nerve and vitreous humor[11,12]. Apart from the vitreous and retina, the anterior chamber is often involved as well. Approximately half of the cases are idiopathic; identifiable causes include trauma, infection, and systemic diseases, many of which are autoimmune[13,14]. Symptoms include ocular pain, decreased vision, redness, floaters and photophobia. Although the presence of uveitis is detected clinically; identifying the cause usually needs laboratory testing. Treatment modalities usually include topical, locally injected long acting steroids, or systemic corticosteroids with addition of a topical cycloplegic-mydriatic agent. Steroid sparing immunosuppressive drugs may be used in cases where prolonged therapy is needed[15,16].

Uveitis is also classified by onset (sudden or insidious), duration (limited or persistent), and course (acute, recurrent, or chronic) of the disease. Patterns of uveitis usually change from region to region based on the prevalence of the infectious and non-infectious diseases in the respective country.

Our study showed a large group of idiopathic uveitis, despite manifold investiga-tions and tests. The cause remained unknown consistent with other studies conducted, where idiopathic uveitis was considerably significant[14].

More females were affected than males in our study sample. Non-infectious uveitis tends to be more prevalent in women. A similar finding was explained by Yeung *et al.* where a greater preponderance in non infectious uveitis was seen in females. The possible reasoning cited in the study was greater predilection of female gender to autoimmune diseases leading to greater presentation of the uveitides in females[15].

In a regional study conducted in India, anterior uveitis was found to be more common, followed by posterior, intermediate and pan uveitis, which was consistent with our findings[14]. The results of a Pakistani study were contrary to our results, and the possible reason explained was presence of more tuberculosis group in the sample, which presents with posterior uveitis leading to more presentation of posterior uveitis in the sample[17].

In infectious group tuberculosis remains the most common cause consistent with other regional studies conducted[12]. Incomplete treatment, microbial drug resistance and poor compliance remain the chief contributory factors in the increased prevalence of the disease and hence the eye presentations[17].

Due to the global distribution of Behcet's disease, our study sample showed considerably significant number of patients showing up with uveitis and later being diagnosed as cases of Behcet's which included 2 children of ages 8 years and 9 years respectively. It was found more

prevalent consistent with the results of Hamade *et al*. a study conducted in Saudi Arabia and few other studies[18-20].

In disease which affected females; SLE merits mention. SLE is an autoimmune disorder that causes immune complex mediated damage affecting many organs, which is associated with the production of auto-antibodies against nuclear material[7]. Among our patients, only patients affected by SLE were women[7,20,21]. While some of the gender difference can be explained by factors such as poorer access to care in females, it is not sufficient to explain the entirety of the problem[16].

While the cause for this difference among genders is largely unclear, recent evidence has pointed towards how sex hormones affect the autoimmune response; estrogen increases the response whereas androgens suppress it. However, other evidence suggests that estrogen's effect on autoimmunity may be dose dependent with lower levels being immune-stimulatory and higher levels immune-inhibitory[17]. Furthermore, women respond to injury or infection with a dominant Th2 immune response (leading to increased antibody production), while men respond with a stronger Th1 response. This may play a role in the increased prevalence of Th2-mediated autoimmune disorders in women[4]. These may include autoimmune conditions like Rheumatoid Arthritis. Moreover, estrogen has recently been shown to play a significant role in the development and function of Th17 cells, as well as the production of IL-17,[7,18]. It has also been noted that men and women may present with the same underlying cause of uveitis but with differing severity or ophthalmic manifestations. In addition, infectious uveitides do show gender differences in prevalence, primarily due to behavioral and/or cultural sources[9]. All these reports point to gender differences in clinical manifestations and pathogenesis of uveitis that may be important for disease prevention and treatment.

Some gender differences in uveitis, particularly with infectious etiology, are mediated by behavioral factors. In India, *Leptospira* infectious uveitis is more prevalent in men with up to 75% of patients being male. Exposure to this spirochete bacterium usually occurs via farming, a task usually undertaken by men. Similarly, syphilis and HIV are more common in men. This is thought to be due to an increase since 1999 of unsafe sexual practices mainly among homosexual males.

Finally, how can we make use of the gender differences to aid patient management? Firstly the above knowledge can be applied to prevent uveitis. For example, increased public education of safe sexual practices could reduce the incidence of syphilitic uveitis. Increased awareness among family medicine practitioners that women are more likely to have non-infectious uveitis and autoimmune diseases should allow for early diagnosis and adequate treatment[5]. Similarly increased awareness among pediatric rheumatologists of the increased ocular complication rate of JIA-affected boys should ensure that JIA-affected boys are referred for uveitic screening and closely follow-up[15].

One way to capitalize on the gender difference would be the use of hormonal manipulation to provide a more tailored yet efficacious therapy for future uveitis patients. Supplemental estrogen in the form of contraceptive pills has been proposed to increase the risk of SLE flares. Thus, clinicians should be judicious in their prescribing of hormonal therapy for SLE patients[5]. This contrasts with sarcoidosis, which has a second peak presentation in women over the age of 50. This increased prevalence in postmenopausal women suggests a role for sex hormone replacement. Thus hormonal therapy may be considered as a possible therapeutic adjunct for sarcoidosis patients.

CONCLUSION

Infectious causes were more common among males whereas non-infectious causes are more frequent among females. Recognition of the gender difference in etiology of uveitis should

allow for development of new preventative and therapeutic strategies for patients in the future.

CONFICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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