ORIGINAL ARTICLE

SPECTRUM OF OCULAR MANIFESTATIONS OF RHEUMATIC AUTOIMMUNE DISEASES: A TERTIARY CARE EXPERIENCE IN PAKISTAN

Zia Uddin[1], Asadullah Khan[1], Muhammad Haroon[1], Muhammad Faiq[1], Salma Rabbani[2], Naveed Aslam Lashari[1]

[1]Department of Rheumatology, Fatima Memorial Hospital, Lahore, [2]Department of Gynaecology, Rehman Medical Institute, Peshawar-Pakistan

Background: Eye involvement is a common and potentially devastating complication of various immune related rheumatic diseases. We aimed to determine the spectrum, associations and the impact of ocular manifestations among well characterised autoimmune rheumatic disease patients presenting to ophthalmology and rheumatology clinics in a tertiary care hospital in Lahore, Pakistan. **Methods:** Descriptive cross-sectional study performed in Rheumatology department of Fatima memorial hospital. Only those rheumatic disease patients were included who have been attending ophthalmology department for their ophthalmic conditions. The patients with ophthalmic symptoms who have not attended an ophthalmologist were not included in this study. Proforma was designed and the studied parameters were recorded prospectively from patient's interview and also by reviewing patient's medical and ophthalmologic medical records. Parameters assessed were demographics, symptoms and the diagnosis of eye disease, unilateral or bilateral presentation, duration of eye symptoms along with the duration of the primary rheumatologic disease, and the complications of the eye disease whether due to the eye diagnosis or its treatment. **Results:** Eighty-three consecutive patients with mean age 33±11 years, 67.5% being female were recruited. Spondyloarthritis (SpA) comprised 38.6% (n=32) of patients followed by 21.7% (n=18) of Behcet's disease. Majority of patients (68.7%) had bilateral eye symptoms. In our cohort, 70% (n=58) of the patients had uveitis and almost all of these patients had either SpA or Behcet's disease as their primary rheumatologic diagnosis. Scleritis in 15.7% (n=13) patients followed by retinal vasculitis in 9.6% (n=8) patients, while glaucoma and keratopathy were present in 2.4% (n=2) patients each comprised other manifestations. Reassuringly our uveitis patients had no long-term eye related complications either due to the disease or its treatment. **Conclusion:** Uveitis represented the most common ophthalmologic manifestation associated with underlying rheumatologic diseases in our cohort, and it was associated with underlying Behcet's disease and SpA. Uveitis associated with connective tissue diseases has good prognosis with low-risk of significant long-term complications. Moreover, uveitis associated with SpA was noted to present much earlier in its disease course.

Keywords: Uveitis; Scleritis; SpA associated Uveitis; Behcet's disease

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INTRODUCTION

Autoimmune rheumatic diseases are a heterogeneous group of conditions characterized by joint involvement along with a wide spectrum of systemic manifestations. Rheumatoid arthritis (RA) and Systemic lupus erythematosus (SLE) are the prototype diseases of this group, while spondyloarthritides, vasculitides, inflammatory myopathies and scleroderma are other important entities. Although these represent a diversity of clinical manifestation but these share a common or similar pathophysiological mechanism.[1]

Lerner A *et al* has reported the highest increase of 7.1% (annual increase) in the incidence of rheumatic disease, which is worldwide-highest among autoimmune diseases.[2] Rheumatic diseases have protean systemic presentations and organ involvement vary greatly. Eye involvement is a common and potentially devastating manifestation, which can present in a number of different ways. These diseases can involve different layers of eyes and in addition can manifest as retrobulbar or retro-orbital disease. Of equal importance is the fact that rheumatic diseases can have the ocular disease as the chief presenting symptom for considerable period of time, for example ocular sarcoidosis or HLA b27 associated uveitis.[3]

Majority of diseases have a predilection for specific eye layers or diseases, e.g, Sjogren disease specifically causes involvement of lacrimal glands causing dry eyes and keratoconjunctivitis. RA and Vasculitides like granulomatosis with polyangiitis (GPA) are usually associated with scleritis (inflammation of outer layer of eye). SLE, on the other hand, through different immune and vasculitic

mechanisms can involve different parts of the eyes and have different manifestation ranging from episcleritis, to retinal vasculitis to retinal vein thrombosis and retinal detachment.[4,5]

Eye involvement although common, differ among different diseases according to their prevalence. SLE has eye involvement in up to 1/3 of patients, with sicca syndrome being most common manifestation.[6] RA also has significant association with sicca syndrome (prevalence of up to 25%), followed by scleritis and episcleritis up to 3-4%.[7] GPA has ocular involvement in up to 30% of patients; scleritis and retrobulbar pseudotumors being common manifestation, while a very limited form of the disease confined to the eye has also been described.[8,9] Ocular involvement in sarcoidosis varies in different regions ranging from 13% in Turkish studies to up to 70% in Far eastern studies.[10] Eye involvement in Behcet's disease has a reported prevalence of above 70 %.[11]

The management of rheumatic disease related eye disorders depends on closed collaboration of ophthalmologists and rheumatologists. Little is known about ocular manifestations on autoimmune rheumatic conditions in our population. Hence, we aimed to determine the spectrum, associations and the impact of ocular manifestations among well characterised autoimmune rheumatic disease patients presenting to ophthalmology and rheumatology clinics in a tertiary care hospital in Lahore, Pakistan.

MATERIAL AND METHODS

It was a prospective cross-sectional study carried out at Rheumatology department of Fatima memorial hospital, Lahore. All patients with known autoimmune rheumatic diseases were included in this study. Patients were inquired about any ocular symptoms; however, only those patients were included in this study who have been attending ophthalmology department for their ocular symptoms, and who had an ophthalmologist diagnosed ocular disease due to underlying autoimmune rheumatic diseases. Study was approved by ethical review board and informed consent was taken from all the patients. Proforma was designed and the studied parameters were recorded prospectively from patient's interview and also by reviewing patient's medical and ophthalmologic records. Parameters assessed were demographics, symptoms and the diagnosis of eye disease, unilateral or bilateral eye presentation, duration of eye symptoms along with the duration of the primary rheumatologic disease, and the complications of the eye disease whether due to the eye diagnosis or its treatment.

The data was analysed in SPSS 23.0. Continuous variables like age were presented in form of mean±Standard deviation and categorical variables were presented in form of frequency (percentage). For association between categorical variable, we used chi square/likelihood ratio test or Fischer exact test with *p* of less than 0.05 considered significant.

RESULTS

During the study period of 6 months (from September 2018 through to March 2019), 83 patients with ophthalmologist diagnosed ocular disease were identified, attending regularly our rheumatology clinics. The mean age of patients was 33±11 years, and 67.5% of the cohort was female. Table-1 describes the demographics, the detail of primary rheumatologic diagnoses of these patients, and ophthalmological symptoms of the entire cohort. Majority of patients in our cohort (68.7%) had bilateral eye symptoms. Overall, the duration of primary rheumatologic disease at the time of assessment was 72±58 months and the duration of eye symptoms was 47±47 months. In our cohort, 38.6% (n=32) of the cohort had the diagnosis of SpA and 21.7% (n=18) of patients were suffering from Behcet's disease. Patients with other rheumatological diseases included: SLE 12% (n=10), RA and GPA 7.2% (n=6) each, and sarcoidosis 6% (n=5).

Looking at different ophthalmologic diseases in this cohort, we found that 70% (n=58) of the patients were diagnosed with uveitis and almost all of these patients had either SpA or Behcet's disease as their primary rheumatologic diagnosis. Uveitis showed significant association with male gender (p=0.04). Scleritis comprised second most common ophthalmologic symptoms in 15.7% (n=13) of patients, followed by retinal vasculitis in 9.6% (n=8) patients, while glaucoma and keratopathy each were present in 2.4% (n=2) patients. Among the cohort of SpA (n=32), the duration of SpA diagnosis was 58±55 months, and the duration of eye symptoms among patients with SpA was 54±82 month. The cohort of SpA was younger compared to the rest of the cohort - 28.8±10.8 vs. 34.5±11 years, p=0.02. Moreover, it was found that SpA patients with eye symptoms had comparable long-term visual loss and other complications (p=>0.05) compared to patients of non-SpA. Similarly, among the cohort of Behcet's disease, the duration of Behcet's disease was 92.7±55.6 months, and the duration of eye symptoms was 44.6±69 months. The age of this particular cohort and the visual complications were comparable to the rest of the cohort (p>0.05). Table-2 shows in detail the cohort of SpA and Behcet's disease compared to the rest of cohort, and Table-3 shows the characteristics of cohort of patients with uveitis. Reassuringly our uveitis patients had comparable (no worse) long-term eye related complications either due to the disease or its treatment.

Table-1: Demographic characteristics and the brief summary of result

Demographic	Percentage (n)
Total no of patients assessed	83
Mean age	32±11 years
Gender	
Female	67.5% (n=56)
Male	32.5% (n=27)
Primary Rheumatologic Diagnosis	
SpA	38.6% (n=32)
RA	7.2% (n=6)
SLE	12% (n=10)
JIA	1.2% (n=1)
GPA	7.2% (n=6)
Behcet's Disease	21.7% (n=18)
Sarcoidosis	6% (n=5)
Others	6% (n=5)
Ophthalmologic Diagnoses made	
Keratoconjunctivitis Sicca	2.4% (n=2)
Scleritis	15.7% (n=13)
Uveitis	70% (n=58)
Retinal Vasculitis	9.6% (n=8)
Glaucoma	2.4% (n=2)
Ophthalmologic complications	
Vision Loss	42% (n=35)
Keratopathy	2.4% (n=2)
Glaucoma	17% (n=14)
No Complications	38.6% (n=32)

RA=Rheumatoid Arthritis, SpA= Spondyloarthritis, SLE=Systemic lupus erythematosus, JIA=Juvenile idiopathic arthritis, GPA=Granulomatosis with polyangiitis

Table-2: Comparison of baseline demographics and ophthalmological complications of SpA and Behcet's disease subcohorts with the rest of cohort

SpA	Duration of SpA Diagnosis (months)	58±55
	Duration of Eye Symptoms (months)	54±82
	Age (years)	28.8±10.8 vs.34.5±11, *p*=0.02
	Vision Loss	37.5% (n=12) vs. 45% (n=23), *p*=0.64
	No Complications	40.6% (n=13) vs. 37 (n=19), *p*=0.81
Behcet's Disease	Duration of Behcet's Disease (months)	92.7±55.6
	Duration of Eye Symptoms (months)	44.6±69
	Age (years)	31.7±7.9 vs. 32.5±12, *p*=0.74
	Vision Loss	55.6% (n=10) vs. 38.5% (n=25), *p*=0.28
	No Complications	27.8 (n=5) vs. 41.5% (n=27), *p*=0.41

Table-3: Comparison of baseline demographics and ophthalmological complications of Uveitis sub cohort with the rest of cohort

Uveitis	Gender – Male	39.7% (n=23) vs. 16% (n=4), *p*=0.04
	Age (Years)	30.6±10.8 vs. 36.4±11.5, *p*=0.03
	Duration of SpA Diagnosis (Months)	62.6±57.5 vs. 85.6±59.5, *p*=0.14
	Duration of Eye Symptoms (Months)	41.3±41.3 vs. 62.7±56.7, *p*=0.11
	SpA – primary rheumatologic diagnosis	48.3% (n=28) vs. 16% (n=4), *p*=0.005
	Behcet's -primary diagnosis	31% (n=18) vs. 0% (n=0), *p*=0.001
	Unilateral eye disease among SpA pts	35.7% (n=10) vs. 20% (n=6), *p*=0.24
	Vision Loss	39.7% (n=23) vs. 48% (n=12), *p*=0.62
	No Complications	37.9% (n=22) vs. 40% (n=10), *p*=1.0

Gender, Age, Vision Loss and No Complications of uveitis sub cohort is compared with non uveitis cases. All cases of uveitis comprised of SpA and Behcet's disease.

DISCUSSION

Ophthalmological involvement is a common extra articular manifestation of Rheumatic diseases. This study provides a snapshot of common ocular symptoms, their complications and their underlying rheumatologic diagnoses among Pakistani patients. We noted that patients with ocular symptoms necessitating ophthalmologist follow up belonged mostly to SpA and Behcet's disease groups, followed by SLE, RA and JIA.

There are number of different clinically important findings of our study which are worth highlighting and warrant further discussion. For example, firstly, we noted that among Pakistani SpA patients, uveitis presented much earlier in the disease

course; there was approximately 4 months lag in the development of uveitis compared to the onset of SpA symptoms (54±82 vs. 58±55 months). Mostly the published literature describes the association of uveitis with longer disease duration. For example, a French study evaluated the prevalence and the factors associated with uveitis in SpA patients in a nationwide cross-sectional study in which 202 participating rheumatologists recruited 902 patients (males 61%), with a mean age of 45.3±13.4years and a mean disease duration of 10.4±9.6 years. HLA-B27 was present in 76% of the patients. Prevalence of uveitis was 32.2% (95% confidence interval (CI) 29.1–35.3%) and was recurrent in 52.3%. Uveitis was the most common extra-articular feature of SpA, and it occurred preferentially in HLA-B27-positive patients (adjusted odds ratio=2.97 [95% CI 1.83–4.81]) and with longer disease duration (≥10 years; adjusted odds ratio=1.28 [95% CI 1.16–1.41]).[12,13]

Secondly, ocular disease patients with underlying SpA and Behcet's disease had no worse long-term complications compared to other autoimmune rheumatic conditions. The same finding was noted when subpopulation of patients with uveitis were studied independently. This finding is reassuring, as uveitis comprised the main bulk of ophthalmological manifestation (70%). Moreover, it shows the overall good prognosis of patients with uveitis among Pakistani patients.

Uveitis is the most common extra-articular feature of SpA over the entire course of the disease.[14] Anterior uveitis classically presents with a red, painful eye, photophobia, and blurring of the vision. Although infectious and neoplastic causes exist, the majority of cases are presumed to be immune in origin, and this is reflected in the high prevalence of systemic disease among patients with anterior uveitis.[4,15] However, there are similarities as well as distinct differences in the patterns of uveitis in the various regions of the world because of geographical, environmental, and genetic differences.[16–20] The uveitis episodes have been reported to be unilateral in 52% of the cases, flip-flop, meaning that both eyes are involved but not simultaneously, in 42%, and bilateral in 6% in one study.[14]

Additionally, it is important to highlight that undiagnosed SpA is quite common in patients presenting with anterior uveitis. For example, one study has shown that about one quarter of 514 anterior uveitis patients had SpA, and among these SpA patients, 53% had undiagnosed SpA when they presented to their ophthalmologists. In other words, among more than half of them (53%), the diagnosis of SpA was arrived at after an episode of uveitis.[21] So, uveitis can be an important initial manifestation of underlying SpA. A novel evidence-based algorithm called Dublin Uveitis Evaluation Tool (DUET) has been recently proposed by Haroon *et al*, to guide ophthalmologists to refer appropriate anterior uveitis patients to rheumatology that will aid the early detection of undiagnosed SpA in patients presenting with anterior uveitis. In this large two-phase study, approximately 40% of patients presenting with idiopathic anterior uveitis were noted to have undiagnosed SpA, and DUET algorithm was noted to have excellent sensitivity (96%) and specificity (97%). It has a positive likelihood ratio (LR) 41.5 and negative LR 0.03.[22]

Thirdly, uveitis patients in our study had SpA (48.3% of uveitis patients) and Behcet's disease (31% of uveitis patients) as the primary rheumatologic diagnoses. There are mixed results as regards, the frequency of underlying rheumatic diseases being the cause of uveitis.[23] The National registry report of Yalcindag *et al*, reported Behcet's disease to be the most common cause of Uveitis (24.9%) followed by SpA associated uveitis (9.7%).[24] The possible cause of altered order of higher SpA than Behcet's cases in our cohort include: A higher prevalence of SpA, lower prevalence of Behcet's in our population than in Mediterranean peninsula.[25] Kim NK *et al* have also reported SpA and Behcet's disease to be the most commonly associated rheumatic causes of uveitis, (70.3% and 18.9% respectively, a finding consistent in order with ours (48.3% and 31% respectively).[26] Our study had, however, a greater percentage of Behcet's associated uveitis (31% vs 18.9%). The further classification of uveitis, or effect of treatment on the outcomes were not studied in our study and needs further studies.

Behcet's disease related uveitis in our cohort differ from the findings of Arevalo *et al*, who discovered pan uveitis to be the most common cause present in 89.4% (vs 61.1%), anterior uveitis in 7.6% (vs 27.7%) and intermediate uveitis in 3%.[27] None of the case in their study had reported posterior uveitis, a finding that was present in at least 11.2% of our cohort. In addition, bilateral uveitis was also higher in their cohort (100% vs 88.9%). The ethnic and geographical differences can be accounted for these differences.

Our study has certain limitations. The overall prevalence of ophthalmologic manifestations in rheumatic diseases could not be calculated as study population consisted only of those patients who had attended ophthalmologists for their ocular symptoms. In addition, the evaluation of different treatment regimens outcomes was not studied. We recommend prospective, longitudinal studies of primary rheumatological diseases evaluating the ophthalmological manifestations and treatment outcomes.

To conclude, uveitis is the most common ophthalmologic manifestation associated with underlying rheumatologic diseases in our cohort, mostly associated with underlying SpA and Behcet's disease and had significant association with male gender. Uveitis associated with connective tissue diseases follows a milder course with low-risk of significant long-term complications. Moreover, SpA associated uveitis presents much earlier in disease course.

AUTHORS'S CONTRIBUTION

ZU, AK: Conceptualization of the study, data collection, data analysis, data interpretation, write-up, proof reading. MH: Write-up, proof reading, data interpretation. MF, SR, NAL: Data collection, data analysis, data interpretation.

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Address for Correspondence:

Zia ud Din, Department of Rheumatology, Fatima Memorial Hospital, Lahore-Pakistan
Cell: +92 333 922 6695
Email: ziauddin239@gmail.com