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A STUDY OF OCULAR MANIFESTATIONS IN AUTOIMMUNE CONNECTIVE TISSUE DISEASES IN ADULTS

Ophthalmology

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ABSTRACT

Purpose: To study the prevalence of ophthalmic manifestations in connective tissue diseases, to monitor the progression.
Methods: Prospective, non comparative, observational cohort study in tertiary care hospital, from June 2014 to September 2015, in 50 adult patients, with autoimmune connective tissue disease .
The demographic data, history regarding the disease, were recorded.
Ophthalmic examination included visual acuity, slit lamp examination, dry eye tests, dilated fundus examination ,intraocular pressure.
Results: Maximum patients (44%) were in the age group of 31-40 years. Rheumatoid arthritis was most common(52%).The prevalence of ocular manifestations was 74%. 81.08% patients had anterior segment manifestations. 18.92% patients had posterior segment manifestations. Only 4 patients had worsened at the end of the study.
Conclusions: In connective tissue diseases, prevalence of ocular manifestations in our study was 74%. Females were more commonly and aggressively affected . It is necessary to screen patients for ocular manifestations .

KEYWORDS

Ocular manifestations, connective tissue diseases, rheumatoid arthritis

Introduction

Connective tissue diseases are inflammatory diseases with immune mediated systemic damage against body's own tissue antigens (Autoimmunity).

Inflammation may involve the ocular adnexa (lids, lashes, orbit), the ocular surface like tear film, sclera, cornea, the uveal tract, lens, vitreous cavity or the retina.

Sometimes eyes may be the first presenting feature of a systemic disease. And patients with known systemic disease should have periodic ophthalmic examination to monitor for ocular involvement as well as to diagnose any treatment related complications.

These systemic inflammatory diseases include Rheumatoid arthritis (RA), Systemic lupus Erythematosus (SLE), Wegener's granulomatosis, Ankylosing spondylitis, Sarcoidosis, Polyarteritis Nodosa (PAN), Behcet's Disease, Systemic sclerosis (SSc), Primary Sjogren's syndrome etc. The ocular involvement in these conditions correlate with the disease severity and duration.

AIMS AND OBJECTIVES OF THE STUDY

1. To study the prevalence of ophthalmic manifestations in known cases of connective tissue diseases.
2. To analyse sex–wise distribution of ocular manifestations in connective tissue diseases.
3. To analyse the involvement of anterior and posterior segment of the eye in these diseases.
4. To monitor the progression of the ocular manifestations.

MATERIALS AND METHODOLOGY

It was a prospective, non comparative , observational cohort study carried out in a tertiary care hospital, from June 2014 to September 2015.

Sample size was 50 patients (100 eyes).

Inclusion Criteria :

1. All Patients in age group of 18 -60 years with diagnosed connective tissue disease by Medicine department , based on antibody titres and clinical criteria for diagnosis of connective tissue diseases.
2. Patients with ocular symptoms who presented to Ophthalmology OPD , suspicious of connective tissue disease based on history and clinical examination, whose diagnosis was confirmed by Medicine department.

Exclusion criteria:

Ocular symptoms due to some other cause, pre-existing ocular disease, comorbid illness like diabetes.

The study was approved by the Institutional Ethics Committee for research on human subjects.

Written informed valid consent was taken from the patients.

Data Collection:

Demographic data of patients were recorded.

The patients were asked history regarding the disease diagnosed; symptoms , duration of the disease , personal history and history of any systemic disease.

Ocular symptoms were asked for like blurring of vision, redness, pain and photophobia, foreign body sensation. Past history of ocular symptoms, use of medications or surgery was asked.

Ophthalmic examination included visual acuity, slit lamp examinati on, dry eye tests [Schirmer's test, Tear Film Break Up time (TBUT)], Rose Bengal staining, dilated fundus examination (Fundus fluoroscein angiography wherever indicated)

Visual Acuity was examined using Snellen's chart . Undilated slit lamp examination was done to look for keratoconjunctivitis sicca (KCS), episcleritis, scleritis , anterior uveitis and complicated cataract.

Intraocular pressure was measured on applanation tonometry.

Tests for Dry eye were performed:

Schirmer's test ,Tear film break up time (TBUT). TBUT <10 seconds was considered abnormal.

Ocular surface staining with Rose Bengal stain was done. Positive corneal and conjunctival staining was considered abnormal.

Dry eye was graded as follows and accordingly treated:

Grade	Schirmer's test value(mm)	Severity
0	>10	No dry eye
1	6-10	Mild
2	3-5	Moderate
3	<3	Severe

In relevant cases with posterior segment involvement, Fundus Fluoroscein Angiography was performed in patients with normal basic renal function tests. Fluoroscein dye (3 ml of 20% concentration) was injected intravenously in the antecubital vein and serial photographs were taken on the fundus camera with dilated pupils, until the dye was washed off.

Patients were treated with the following for specific conditions:

Dry eye : Carboxy-methyl cellulose(CMC) eye drops (0.5%- in mild to moderate dry eye 6-8 times in a day and 1% in severe dry eye 2 hourly). Temporary punctal plugs were given in both puncta of one eye in a case of severe dry eye in a case of Sjogren's Syndrome. After consent, the silicon plugs were inserted in both the upper and lower puncta of right eye under slit lamp with a Mac Pherson forceps followed by tapering course of low potency steroid, Loteprednol (0.5%) eye drops.

For filamentary keratitis, N acetyl cysteine (10%) eye drops were added to CMC eye drops 6 times in a day. Short course of steroid Loteprednol(0.5%) was added four times in a day in tapering doses over 4 weeks.

Peripheral Ulcerative Keratitis was treated with a 6 weeks tapering dose course of eye drops Prednisolone(1%) over 6 weeks.

Acute anterior uveitis was treated with 4 week course of Eye drops Prednisolone(1%) or Loteprednol (0.5%) 6 times in a day based on severity of inflammation along with Eyedrops Homatropine (2%).

One case of corneal perforation was managed on emergency basis with a tectonic keratoplasty with post operative steroid Eyedrops Prednisolone (1%) 6 times in a day , Eyedrops Moxifloxacin (0.5%) 6 times in a day, Eyedrops Carboxy methyl cellulose (1%) 6 times a day and Eyedrops atropine(1%) 2 times a day for 6 months .

Secondary glaucoma was managed by three topical medications Eyedrops Timolol(0.5%) twice a day, Eyedrops Dorzolamide (2%) twice a day and Eyedrops Brimonidine(0.2%) twice a day.

No surgical treatment was needed for any complications .

For posterior uveitis and intermediate uveitis, posterior subtenon injection triamcinolone acetonide (0.5 cc = 20mg) was given along with systemic steroids (Tablet Prednisolone 1mg/kg tapered over 6 weeks.)

Vitreous haemorrhage was conservatively treated with Tablet Vitamin C (500mg) three times in a day for 3 months. No surgical treatment was indicated.

Cystoid macular edema was treated with a single injection of preservative free intravitreal Triamcinolone acetonide (0.1 ml = 4 mg)

At follow up visits , patients evaluation with respect to best corrected visual acuity, the dry eye tests, slit lamp examination and fundus imaging wherever relevant was done. Patient's symptomatic improvement was asked. Symptomatic patients were evaluated on day 3, day 7 and then weekly for a month and then 3 monthly and as and when required. Asymptomatic patients were evaluated at 3, 6 and 9 months.

Table 1: Age-wise distribution of patients

Sr. No.	Age distribution(Years)	No.of patients	Percentage of patients
1	21-30	12	24%
2	31-40	22	44%
3	41-50	12	24%
4	51-60	4	8%
	Total	50	100%

Table 2 : Sex-wise distribution of patients

Sr. No	Sex	No. of patients	Percentage of patients(%)
1	Male	15	30%
2	Female	35	70%
	Total	50	100%

Table 3 : Distribution of Connective tissue diseases in the study population

Sr. No	Disease	No. of	Patients	Total no. of patients of the disease	% of patients of study population
		Males	Females		
1	RA	7	19	26	52
2	SS	0	2	2	4
3	Sarcoidosis	1	3	4	8
4	AS	5	2	7	14
5	Sjogren's Sydrome	1	1	2	4
6	SLE	1	4	5	10
7	Behcet's Disease	0	2	2	4
8	Seronegative spondyloarthropathy	0	2	2	4
	Total	15(30%)	35(70%)	**50**	**100%**

Table 4 : Prevalence of ocular manifestations in Connective tissue diseases

Sr. No	Disease	No. of patients with no ocular manifestations	No. of patients with ocular manifestations			Total no. of patients with the disease	% of affected patients
			(Males)	females)	Total		
1	RA	8	6	12	18	26	69.23
2	SS	0	0	2	2	2	100
3	Sarcoidosis	0	1	3	4	4	100
4	AS	3	3	1	4	7	57.14
5	Sjogrens Syndrome	0	1	1	2	2	100
6	SLE	1	0	4	4	5	80
7	Behcet's Disease	0	0	2	2	2	100
8	Seronegative Spondyoarthropathy	1	0	1	1	2	50
	Total	13	11	26	37	50	
		Total patients with ocular manifestations= 11+26 = 37 (74% of the total patients)					

Table 5 : Prevalence of anterior segment involvement in Connective tissue diseases

Sr.No	A	B			C	D
		Males	Females	Total		
1	RA	6 (33.33%)	12 (66.66%)	18	18	100
2	SS	0	2 (100%)	2	2	100
3	Sarcoidosis	0	1 (100%)	1	4	25
4	AS	3 (75%)	1 (25%)	4	4	100
5	Sjogren's Sydrome	1 (50%)	1 (50%)	2	2	100
6	SLE	0	1 (100%)	1	4	25
7	Behcet's Disease	0	1 (100%)	1	2	50
8	Seronegative spondyloarthropathy	0	1 (100%)	1	1	100
	Total	10(33.33 %)	20(66.67%)	30(100%)	37	81.08

A: Disease
B : No. of patients with Anterior segment manifestations
C: Total no. of patients with ocular manifestations in the disease
D : % of patients with anterior segment manifestations

Table 6 : Different types of anterior segment manifestations noted in the study.

Manifestation	No. of patients(%)
Dry eye	10
Filamentary keratitis	3
PUK	1
Episcleritis	3
Scleritis	5
Anterior uveitis	8
Corneal perforation	1
Complicated cataract	2
Secondary glaucoma	1

Table 7 : Prevalence of posterior segment manifestations in connective tissue diseases

Sr.No	A	B			C	D
		Males	Females	Total		
1	RA	0	0	0	18	0
2	SS	0	0	0	2	0
3	Sarcoidosis	1 (33.33%)	2 (66.67%)	3	4	75
4	AS	0	0	0	4	0
5	Sjogren's Sydrome	0	0	0	2	0
6	SLE	0	3 (100%)	3	4	75
7	Behcet's Disease	0	1 (100%)	1	2	50
8	Seronegative spondyloarthropathy	0		0	1	0
	Total	1 (14.29%)	6 (85.71%)	7 (100%)	37	18.92

A: Disease
B: No . of patients with posterior segment involvement
C: Total no. of patients with ocular manifestations in the disease
D : % of patients with posterior segment manifestations

Table 8 :Different types of posterior segment manifestations

Type of Manifestation	No. of patients
Vasculitis/Posterior uveitis	4
CME	2
Vitreous haemorrhage	1
Intermediate uveitis	1

Table 9 : Best corrected Visual acuity in the study population at the initial presentation

Visual acuity	No. of eyes(%)
PL+,projection of rays present, HMCF	2
1/60 -5/60	3
6/60-6/24	25
6/18-6/6	70

None of the patients were bilaterally blind. 2 patients had vision of Perception of light with normal projection of rays. One of the patients had long standing corneal opacity in one eye. The other patient had a corneal perforation secondary to severe dry eye. Visual acuity was low in most of the elderly population due to lenticular sclerosis.

Table 10 : Progression of ocular manifestations over the study period

Follow up over	3 months	6 months	9 months
Worsened	7	9	4
Improved	20	9	11
Status quo	20	27	30

Table 11: Patients who lost to follow up

Months of follow up	At <3months	3-6 months	6- 9 months	Total
No. of patients lost to follow up	2	3	0	5

DISCUSSION

Worldwide the prevalence of Rheumatoid arthritis is about 1% affecting middle aged females; female to male ratio being 3:1(1)

The prevalence of SLE was found to be 15 to 50 per lakh population with female to male ratio being 6-10:1 and the peak age of onset being 15-40 years (2)

Prevalence of Sjogren's syndrome is 0.5- 3%, female to male ratio being 24:1 and the frequency increases with increasing age , most commonly affects females in age group of 30- 50 years. (3)

The prevalence of systemic sclerosis in the studies done in different population ranges from 280 cases per million(in US) to 13-48 cases per million in UK. Female to male ratio is 3:1 .(2)

The global prevalence for Ankylosing spondylitis was calculated and was estimated to be 16.7 cases per 10000 population in Asian population . Young adult males are commonly affected ; Male to female ratio is 3:1 (4)

Behcet's disease is very rare in India. Few major studies from North India have documented 58 cases over a period of 16 years. Male to female ratio is 3:2.(5)

In our study, of the 50 patients with connective tissue diseases 52% (26patients) had Rheumatoid arthritis , 14% (7 patients) had Ankylosing spondylitis, 10% (5 patients) suffered from Systemic Lupus Erythematosus ,8% (4 patients) were of Sarcoidosis , 4% (2patients) each of Systemic Sclerosis, Sjogren's Syndrome, Behcet's Disease and Seronegative Spondyloarthropathy. (Psoriatic arthritis and Inflammatory bowel disease) .

The patients were maximum in the age group of 31-40 years (44%) followed by 24 % patients each in age group of 21-30 years and 41-50 years. Only 8 % patients were in the elderly age group of 51years and above. The mean age of population in the study was 38.9 years .

All the connective tissue diseases in our study affected the middle age group predominantly.

Females were more prone to be affected than males in all diseases except Ankylosing spondylitis which showed male preponderance in our study.

Out of the 50 patients in the study, 13 patients (26%) were unaffected while the remaining 37 patients (74%) were affected .Out of the affected patients, females constituted 70.27 % and the rest were males (29.73%).

Thus it showed that in our study females were more prone to ocular manifestations.

81.08% of the affected patients had anterior segment manifestations in our study.

In cases of RA, all 18 affected patients (i.e. 69% patients of RA) had anterior segment manifestations .Dry eye was most common i.e. in 5 patients (27.7%) followed by filamentary keratitis in 3 patients (16.6%) and Peripheral Ulcerative keratitits in1 patient (5.5%). 3 patients(16.6%) manifested with episcleritis , and 4 patients(22.2%) with nodular scleritis with 1 patient having scleromalacia . 2 patients presented with anterior uveitis , one of which had associated secondary glaucoma.

A study by Reddy et al, concluded that ocular manifestations are present in 39% of the population.(6) This was much less compared to our study.

A study by M. Cojocaru et al, revealed that the most frequent manifestation in RA is secondary Sjogren's syndrome i.e. in about 10% patients.(7)

In the present study scleritis was found in 2% (four patients) of the study population out of which one case was nodular scleritis and the rest were diffuse scleritis which was comparable to the previous studies.

No patients in our study had posterior subcapsular cataract due to lesser duration of disease and lower dosage of steroids.

Among the 2 affected patients of Systemic sclerosis, both had severe dry eye. 1 patient of Sarcoidosis had chronic granulomatous uveitis.

According to a study by Waszczykowska et al incidence of keratoconjunctivitis sicca in systemic sclerosis was 22%.(8) No posterior segment manifestation was found in our study. A study by Hassenstein et al, showed patients in Germany with systemic sarcoidosis had anterior uveitis (35%) ,posterior uveitis (25%) and late complications like posterior synechiae, secondary glaucoma, complicated cataract , optic atrophy and intraocular calcification.(9)

Out of the 4 affected patients of Ankylosing spondylitis , 3 had acute episode of anterior uveitis while 1 of them had chronic anterior uveitis at the first presentation.

Both patients of Sjogren's syndrome had severe dry eye .One female patient had LE corneal thinning followed by corneal perforation for which tectonic keratoplasty had to be done. But the graft failed due to poor ocular surface.

1 patient of SLE had dry eye . In SLE, sicca syndrome 56 patients (15 - 30%), episcleritis, conjunctivitis, retinal vasculitis(5%) have been reported by Frith P. et al.(10)

1 patient of Behcet's disease had anterior uveitis with associated complicated cataract.

1 patient of Psoriatic arthritis had scleritis of both eyes.

Thus the most common anterior segment manifestation in connective tissue disease was dry eye (10 patients) and filamentary keratitis mainly attributed to Rheumatoid arthritis followed by SLE and Sjogren's Syndrome.

Of which 8 females and 2 males had dry eye, while 2 females and 1 male had filamentary keratitis. Episcleritis was present in 2 females and 1 male. Scleritis was present in 4 females and 1 male , the severe form of scleromalacia being present in female. Anterior uveitis was equally distributed in both sexes attributable mainly to higher prevalence of Ankylosing spondylitis in males. Anterior segment complications like complicated cataract, corneal perforation and secondary glaucoma were all present in females.

Posterior segment manifestations were found in 7 patients(18.92%) in the study. Of which posterior uveitis in the form of perivascular sheathing and cotton wool spots were present in 2 patients of Sarcoidosis, along with CME in 1 of them, 1 patient of Behcet's Disease and 1 patient of SLE.

1 patient of SLE had only RE Cystoid macular edema confirmed on OCT.

One patient of SLE presented with RE Vitreous haemorrhage.

One male patient of Sarcoidosis presented with only LE intermediate uveitis with no systemic features . He was then diagnosed as ocular sarcoidosis.

All the posterior segment manifestations were present in females.

Visual acuity in most patients was better than 6/18 . 70 eyes had vision between 6/18 -6/6 . 25 eyes had vision between 6/60 to 6/24. 3 eyes had vision between 1/60 to 5/60 due to vitreous haemorrhage , intermediate uveitis and PUK.

Only 2 eyes had vision limited to perception of Light with accurate projection of rays. One patient had failed keratoplasty graft done for perforated cornea and the other patient had a pre-existing corneal opacity since childhood.

A study by Akpek EK et al , has concluded that patients of Sjogren's syndrome with vision threatening ocular findings are 3.19 times more likely to have systemic manifestations like peripheral neuropathy , interstitial nephritis and vasculitis .(11)

The progression of the patients in the study was monitored. 5 patients were lost to follow up over 15 months. Of the 45 patients , maximum patients (30 patients) maintained the status quo as the presentation or had improved (11 patients). Few patients worsened which was attributable to long duration of the disease, severity of disease at presentation, Behcet's disease which shows fast progression, development of complications like secondary glaucoma and complicated cataract .

Of the patients who had no ocular manifestations, only 4 developed new signs. 2 patients of Ankylosing spondylitis had an episode of acute anterior uveitis. 1 patients of RA had abnormal dry eye test and 1 patient of SLE developed signs of vasculitis with cystoid macular oedema on optical coherence tomography.

Conclusions

We studied 50 adults diagnosed as connective tissue disease referred form Medicine OPD .Maximum patients (44%) were in the age group of 31-40 years. Female to male ratio was 2.3:1. Most common disease in the study was Rheumatoid arthritis which constituted 52% of the total study population. The prevalence of ocular manifestations was 74%. Females were more commonly and aggressively affected than males.70.27 % of the affected were females while 29.72% were males. 81.08% patients had anterior segment manifestations .Of which the most common presentation was Dry eye and its sequelae. 18.92% patients had posterior segment manifestation. 1 male (14.29%) and 6 females.(85.71%). Most patients had a visual acuity of better than 6/18 .Only 5 eyes had visual acuity less than 1/60. Only 4 patients had worsened at the end of the study. Rest of them remained the same or had improved on treatment.

The manifestations may be vision threatening if not attended to at an appropriate time. Hence it is necessary to screen patients for ocular manifestations with or without symptoms to institute early management in these cases.

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