Ocular Manifestations of Connective Tissue Diseases in Patients Attending Clinics in Aminu Kano Teaching Hospital, Northwestern Nigeria

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ABSTRACT

Purpose: The study determined the ocular manifestations of connective tissue diseases in Nigerian patients.

Methods: A single-centre cross-sectional study conducted at Aminu Kano Teaching Hospital, Kano, northwestern Nigeria. Study participants were patients aged 18years and above who had already been diagnosed with connective tissue diseases (CTDs). Participants were interviewed and examined; and data was collected using a semi-structured questionnaire. Data obtained was analysed using IBM SPSS version 22, Armonk, NY.

Results: A total of 140 patients were recruited and examined. Of these, 123 (87.9%) were females, and 17 (12.1%) were males (M:F =1:7), with mean age of 37.1±13.9 years. Majority of them (86.4%) had ocular manifestations. The commonest type of CTDs with ocular manifestation was rheumatoid arthritis (43.8%), followed by systemic lupus erythematosus (28.5%) and systemic sclerosis (6.6%). Among the patients with ocular manifestations, 70 (57.9%), presented with dry eye disease, 17 (14.0%) had cataract, 10 (8.3%) had episcleritis and 7 (5.8%) had keratitis. Dry eye syndrome (55%), cataract (13.3%) and episcleritis (5.0%) were found to be more frequent in patients with rheumatoid arthritis. There was a statistically significant association between the presence of CTD-related ocular manifestations and female gender ($p<0.001$).

Conclusion: Dry eye syndrome, episcleritis, keratitis and cataract were frequent ocular manifestations of CTDs. Periodic ophthalmic examination is important for patients with CTDs.

Keywords: Connective tissue, Diseases, Ocular manifestations, Nigeria.

INTRODUCTION

Connective tissue diseases comprise a heterogeneous group of disorders that have connective tissue of the body as the primary target of pathology. Connective tissue diseases are important structures that hold the cells of the body together and form a matrix for the body.[1] Connective tissues are composed of two main structural protein molecules, collagen and elastin, which are frequently injured by inflammation. Specific causes of connective tissue diseases are not known; however, there are genetic and environmental factors that are considered to increase the risk of developing the disease.[1] There are several interfaces between ophthalmology, rheumatology and dermatology. Ophthalmologists face the dilemma of whether ocular inflammation is due to a systemic connective tissue disease, while, on the other hand, the rheumatologists and dermatologists have to consider the possibility of ocular manifestations that are relatively common in some connective tissue diseases. Moreover, these ocular manifestations may influence therapeutic decisions of both rheumatologists and dermatologists. The role of the ophthalmologist is to manage these patients with severe active disease from the acute phase to the long-term management of complications arising from the disease or related to its treatment.[2]

There are two categories of connective tissue diseases. The first category consists of those that are inherited due to a single gene defect e.g. Ehlers-Danlos syndrome, Epidermolysis

bullosa, Marfan syndrome, Osteogenesis imperfecta, Stickler and Alport syndrome. The second category, which is commonly seen as autoimmune, consists of disorders in which antibodies directly target connective tissues, e.g. systemic lupus erythematosus, rheumatoid arthritis, scleroderma, Sjogren's syndromes, spondyloathropathies, polymyositis, dermatomyositis, sarcoidosis, systemic vasculitides, mixed and undifferentiated connective tissue diseases.[3] Patients are clinically diagnosed and labelled with connective tissue diseases by consultant rheumatologists and dermatologists who offer treatment and management in their clinics.

Some selected ocular manifestations of connective tissue diseases include: dry eye syndrome (gritty sensation, redness, burning, photophobia or blurring of vision),[4,5] scleritis,[6] episcleritis[7] and scleromalacia perforans.[8] Episcleritis presents with a painless red eye or minimal discomfort, but vision is preserved.[9] Connective tissue diseases can present with perilimbal corneal involvement known as peripheral ulcerative keratitis (PUK),[10] punctate epithelial erosions,[11] corneal scarring,[12] corneal ulceration,[13] corneal hemorrhage and retinal vasculitis.[14]

In Nigeria, connective tissue diseases are not as uncommon as once thought,[15] and the ocular manifestation of these diseases in Nigeria is grossly understudied.

According to the Sustainable Development Goals (SDG) 3- "Good Health and Wellbeing," investment in health care capacity and health care quality translates into positive health outcomes. Every individual in a society, including patients with connective tissue diseases, has the right to access quality health care services.[16]

In the Nigeria National Blindness and Visual Impairment Survey, the prevalence of ocular manifestations of connective tissue diseases was not studied,[17] thus contributing to a wide gap in the literature on connective tissue diseases that needs to be addressed.

There is poor understanding of the ocular manifestations of connective tissue diseases among physicians; many rheumatologists and dermatologists also miss the diagnosis of ocular manifestations of connective tissue diseases.[15]

There has been an increase in the number of reports of rheumatoid arthritis (RA) from West Africa in the last decade that has shed some light on the fallacy of the earlier belief that RA and other systemic autoimmune connective diseases are rare in Africa.[18] While various extra-articular manifestations of RA have been documented in patients from this region, the extent and the distribution of ophthalmic disorders due to RA and its treatment have not been reported.[18]

The aim of this study is to determine the ocular manifestations of connective tissue diseases in patients attending rheumatology and dermatology clinics in Aminu Kano Teaching Hospital (AKTH), Kano, Nigeria, in order to identify specific patterns of ocular features associated with connective tissue diseases for the purpose of early detection and prompt management of patients with connective tissue diseases. This will ultimately promote interdisciplinary practice patterns and establish a strong working link between ophthalmologists, rheumatologists and dermatologists in patient management.

METHODS

This is a hospital-based cross-sectional study carried out in the rheumatology, dermatology and ophthalmology clinics of Aminu Kano Teaching Hospital (AKTH), Kano State. The study was conducted from January 2023 to July 2023. The study population consisted of patients already diagnosed with connective tissue disease who were more than 18 years old. Patients with other systemic diseases with ocular manifestations, such as diabetes mellitus and hypertension, and those with pre-existing ocular morbidity, such as orbital tumours, glaucoma, and cataract, were excluded.

The study commenced following ethical approval by the AKTH research ethics committee, and adhered to the tenets of the Helsinki Declaration. Written informed consent was obtained from participants before recruitment into the study. A simple random sampling technique was employed in recruitment of study participants. All patients clinically diagnosed with connective tissue diseases during the period of data collection constituted the sampling frame. Clinic day appointment register was used to identify and obtain the list of patients with connective tissue disease. The total numbers of patients that met the inclusion criteria were pooled and a computer generated simple random technique was used to select the patients until the required sample size was obtained. Patients who had other systemic diseases with ocular manifestations, coexisting ocular morbidities, were too ill to allow for detailed examination or declined consent were not included.

All patients who fulfilled the eligibility criteria were interviewed using the interviewer-administered semi-structured questionnaire, to collect information on demographic characteristics, connective tissue disease history, ocular/ visual symptoms associated with the diseases and history of drug treatment. Patients then underwent eye examination aimed at assessing the following: Visual acuity, Adnexa / Anterior segment structures, Dry eye test, Intraocular pressure, Posterior segment structures, Refraction, Colour vision test and Ocular ultrasound brightness mode scan (where indicated).

The data collated was coded and entered into a spreadsheet for statistical analysis with IBM SPSS version 23, Armonk, NY. Data was expressed as mean, ratio, standard deviations, ranges and frequencies.

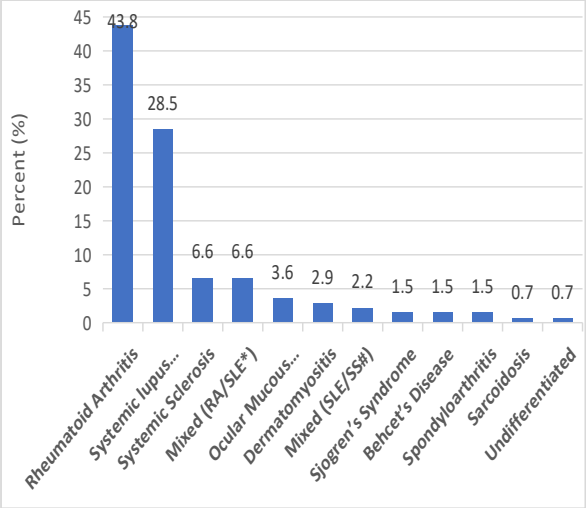
Frequency distributions of relevant variables were generated and presented in tables and charts. Bivariate analysis was conducted using cross-tabulations, and Chi-square test was used to determine associations between socio-demographic and clinical characteristics. Statistical significance was set at $p < 0.05$.

RESULTS

A total of 140 patients diagnosed with connective tissue diseases (CTDs) were included in the study. The participants' ages ranged from 18 to 85 years, with a mean age of 37.1 ± 13.9 years. There were 123 (87.9%) females and 17 (12.1%) males (M:F ratio =1:7).

Distribution of connective tissue diseases among study participants

There were 137 patients with autoimmune connective tissue diseases, while three had heritable connective tissue diseases. Out of the 137 patients with autoimmune connective tissue diseases, 60 (43.8%), had rheumatoid arthritis, 39 (28.5%) had systemic lupus erythematosus, nine (6.6%) had systemic sclerosis, while five (3.6%) had ocular mucous membrane pemphigoid (Figure 1). Among the three patients who had heritable connective



**RA/SLE – rheumatoid arthritis/ systemic lupus erythematosus*
 # SLE/SS – systemic lupus erythematosus/systemic sclerosis

Figure 1: Distribution of autoimmune connective tissue diseases in the patients

tissue diseases, 2 patients had Marfan's syndrome, and 1 had epidermolysis bullosa.

Ocular manifestations of connective tissue diseases among study participants

Among 140 patients included in the study, 121 (86.4%) had ocular manifestations, while 19 (13.6%) did not have any ocular manifestations. The frequency of ocular manifestations among patients with the various connective tissue diseases was as follows: Rheumatoid arthritis -50 (83.3%), Systemic lupus erythematosus - 34 (87.2%), Systemic sclerosis 9(100.0%), sarcoidosis -1 (100.0%), Sjogren's syndrome - 2 (100.0%), Behcet's disease -1 (50.0%), Mucous membrane pemphigoid -4 (80.0%), dermatomyositis -4 (100.0%), Marfan's syndrome -2 (100.0%) and epidermolysis bullosa -1 (100.0%) as shown in Table 1.

Majority of the patients with ocular manifestations, 70 (57.9%), had dry eye syndrome (DES), while episcleritis was observed in 10 (8.3%) patients and keratitis in 7 (5.8%), as shown in Table 2. The pattern of ocular manifestations within specific autoimmune connective tissue diseases is presented in Table 3.

With regards to the heritable connective tissue diseases, the two patients with Marfan's syndrome had dry eye syndrome, iridodonesis,

Table 1: Frequency of ocular manifestations within different connective tissue diseases

Connective tissue diseases	Frequency	Percentage
Rheumatoid Arthritis (n= 60)	50	83.3
Systemic lupus Erythematosus (n= 39)	34	87.2
Systemic Sclerosis (n= 9)	9	100.0
Mixed (RA/SLE*) (n=9)	9	100.0
Ocular Mucous Membrane Pemphigoid (n= 5)	4	80.0
Dermatomyositis(n=4)	4	100.0
Mixed (SLE/SS#) (n=3)	3	100.0
Sjogren's Syndrome (2)	2	100.0
Behcet's Disease (n=2)	1	50.0
Spondyloarthritis (n=2)	0	0.0
Marfan's Syndrome (n=2)	2	100.0
Sarcoidosis (n=1)	1	100.0
Undifferentiated (n=1)	1	100.0
Epidermolysis Bullosa (n=1)	1	100.0

Table 2: Overall pattern of ocular manifestations among the patients

Anterior segment manifestations	Right Eye Freq	%	Left Eye Freq	%
Dry eye syndrome	70	57.9	68	56.2
Cataract	17	14.0	17	14.0
Episcleritis	10	8.3	10	8.3
Low IOP	9	7.4	9	7.4
Keratitis	7	5.8	7	5.8
Anterior uveitis	4	3.3	8	6.6
Corneal ulcer	3	2.5	3	2.5
Symblepharon	3	2.5	3	2.5
Scleritis	2	1.7	2	1.7
Conjunctival granuloma	2	1.7	2	1.7
Keratic precipitates	2	1.7	2	1.7
Lens subluxation	2	1.7	2	1.7
Iris atrophy	2	1.7	2	1.7
Iridodenesis	2	1.7	2	1.7
High IOP	2	1.7	2	1.7
Keratoconjunctivits	1	0.8	1	0.8
Posterior segment manifestations				
Color vision defect	9	7.4	14	11.5
Retinal vasculitis	8	6.6	8	6.6
Macular edema	6	5.0	6	5.0
Optic disc swelling	5	4.1	5	4.1
Secondary Glaucoma	4	3.3	5	4.1
Optic neuritis	3	2.5	2	1.7
Posterior uveitis	2	1.7	1	0.8
Vitritis	1	0.8	1	0.8
Vitreous opacity	1	0.8	0	0.0
Optic atrophy	1	0.8	5	4.1
Retinal detachment	1	0.8	1	0.8
Macular Scar	1	0.8	2	1.7
Adnexal manifestations				
Eyelid stiffness	3	2.5	3	2.5
Heliotrope rash	3	2.5	3	2.5
Eyelid blister	1	0.7	1	0.7

Table 3: Pattern of ocular manifestations within autoimmune connective tissue diseases

Connective tissue disease/ ocular manifestations	Frequency	Percentage
Rheumatoid Arthritis (n=60)		
Dry eye syndrome	33	55.0
Cataract	8	13.3
Episcleritis	3	5.0
Systemic lupus erythematosus (n=39)		
Dry eye syndrome	17	43.6
Retinal vasculitis	4	10.3
Systemic sclerosis (n=9)		
Dry eye syndrome	8	88.9
Eyelid stiffness	2	22.2
Symblepharon	2	22.2
Dermatomyositis (n=4)		
Heliotrope rash	3	75.0
Dry eye syndrome	1	25.0
Eyelid stiffness	1	25.0
Behcet's disease (n=2)		
Conjunctival granuloma	2	100.0
Dry eye syndrome	1*	50.0
Keratitis	1*	50.0
Anterior uveitis	1*	50.0
Sarcoidosis (n=1)		
Conjunctival nodule	1	100.0
Posterior uveitis	1	100.0
Sjogren's syndrome (n=2)		
Dry eye syndrome	2	100.0
Ankylosing spondylitis (n=2)		
Episcleritis	1#	50.0
Dry eye syndrome	1#	50.0
Retinal vasculitis	1#	50.0
Mucous membrane pemphigoid (n=5)		
Keratitis	3	60.0
Dry eye syndrome	3	60.0
Episcleritis	2	40.0
Symblepharon	1	20.0

*"*manifestations in the same patient with Behcet's disease*
#manifestations in the same patient with Ankylosing spondylitis"

lens subluxation, lens opacity, RD, color vision defect and low intraocular pressure. While the patient with epidermolysis bullosa had dry eye syndrome and eyelid blister.

All the three patients with mixed systemic lupus erythematosus and systemic sclerosis presented with non-microbial conjunctivitis, dry eye syndrome, corneal ulcer, and anterior uveitis. Whereas, of the nine patients with mixed rheumatoid arthritis and systemic lupus erythematosus, six had dry eye syndrome, four patients had lens opacity, retinal vasculitis and color vision defect, two had optic neuritis and disc edema, and one patient had optic atrophy. The only patient who had undifferentiated CTD presented with lens opacity and low intraocular pressure.

Risk factors associated with ocular manifestations of connective tissue diseases among study patients

Female gender was statistically significantly associated with ocular manifestations of CTDs, with a p-value of <0.001. The associations

Table 4: Socio-demographic factors associated with ocular manifestations connective tissue diseases

Sociodemographic Characteristics	Ocular manifestation Yes (n=121) Freq (%)	No(n=19) Freq (%)	Test of association	P Value
Age			Fisher's exact test	0.092
18-25	19(76.0)	6(24.0)		
>25	102(88.7)	13(11.3)		
Gender			Pearson chi-square	<0.001*
Male	6(35.3)	11 (64.7)		
Female	115(93.5)	8 (6.5)		
Religion			Fisher's exact test	0.523
Islam	117(86.7)	18(13.3)		
Christian	4(80.0)	1(20.0)		
Ethnicity			Fisher's exact test	0.703
Hausa	114(86.4)	18(13.6)		
Non-Hausa	7(87.5)	1(12.5)		
Education			Fisher's exact test	0.619
Formal	101(86.3)	16(13.7)		
Informal	20(87.0)	3 (13.0)		
Occupation			Fisher's exact test	0.527
Employed	35 (87.5)	5 (12.5)		
Unemployed	86 (86.0)	14 (14.0)		

** statistically significant at p-value of <0.05*

between other sociodemographic factors and CTD-related ocular manifestations were not statistically significant, with p values > 0.05 (Table 4).

DISCUSSION

The overall prevalence of ocular manifestations among patients with CTDs in the study was 86.4%. This is much higher than the figure from a previous study which showed a global pooled prevalence of 30%.[19] The marked difference may be related to the differences in the study design and the study populations. Majority of the patients studied were females between the age of 24 to 50 years. This is in keeping with a study that showed CTDs are commonly seen in females.[20] This may also contribute to the higher prevalence seen in this study.

The prevalence and pattern of ocular manifestations in patients with RA were found to be similar to some previous studies.[18,21,22] Dry eye syndrome (DES) was the most common ocular manifestation found. Other less common manifestations include: anterior uveitis and secondary glaucoma. This slightly varies from another study, which reported DES (16%) and glaucoma (5%) to be the most common ocular presentation in patients with RA.[19] Our findngs are comparable to a study in India, which reported 77 (39%) had ocular manifestations among 196 patients, DES occurred in 28% and was similarly the most common ocular manifestation.[23] The study also showed that 3% had episcleritis, 2% had scleritis, and 1% had PUK and sclerosing keratitis.[23] This study demonstrates that ocular manifestations account for common extra-articular manifestations of patients with RA.

The prevalence and pattern of ocular manifestations in patients with SLE were found to be similar to a study[24] in which DES was the most common ocular manifestation. Other less common ocular presentations include episcleritis, scleritis, anterior uveitis and optic disc edema. This is similar to a study which reported the prevalence of ocular manifestations of SLE to be 35% and DES is the most common ocular manifestation.[24] However, this finding differs from a study which reported blepharitis (53.5%) as the most common ocular manifestation, followed by madarosis (28.2%) and stromal keratitis (5.6%), but the patients were Caucasians (32%), Africans (11%) and Indians (1%).[25] This suggests that ocular manifestation in patients with SLE is common across all geographic locations, including Africa.

The prevalence of ocular manifestations in patients with systemic sclerosis appears to be low. The most common ocular presentations are DES, eyelid stiffness and symblepharon. This varies from the findings of a previous study that reported the prevalence of ocular manifestations in systemic sclerosis to be 47% in Australia.[26] This difference can be due to the number of patients with systemic sclerosis studied being higher (n=92) than the patients in this study (n=9). The study reports DES (37-39%) to be the most common ocular manifestation, eyelid stiffness (29-65%), blepharophimosis (37-40%) and rarely lagophthalmos.[26] Although it is a rare condition worldwide, there is an increase in incidence and prevalence occurring between 30 to 50 years of age, three times more common in women than men. Patients of African descent are affected by the condition twice as often as patients of Caucasian descent.[27]

The ocular manifestations of the five patients with mucous membrane pemphigoid (MMP) were keratitis, DES, episcleritis and symblepharon. This finding is similar to a study which reported 60-70% of patients with MMP have ocular manifestations.[28] Although mostly seen in women 2 to 3 times more than in men at an average of 65 years with no ocular predilection, this study probably found few patients because the patients that were studied were younger. Another study similarly showed ocular manifestations of MMP to be 70%,[29] mean age of 60-65 years,(M:F = 1:2) and can affect any race, but more common in Caucasians.[29] Patients presented with conjunctivitis, keratitis, symblepharon, conjunctival keratinization and entropion.[27]

Risk factors for CTDs related to ocular manifestation may include sociodemographic characteristics, treatment and type of

medication. There was a statistically significant association ($p < 0.05$) between ocular manifestations of CTDs and female gender in this study. This shows that ocular manifestation occurs more commonly in females than in males. This is similar to a study on CTDs and the overall influence of gender, which reported that autoimmune diseases are more common in women than in men, and females have a higher prevalence of ocular manifestations compared to males.[20] Another study has also mentioned that female gender is a risk factor in the occurrence of ocular manifestations.[30] This is in keeping with what was obtained in this study, with ocular manifestations being more common in females. Another study also reported that age is a positive predictor of ocular manifestation.[18] This is different from the finding in this study, in which most of the female patients were found to be between 24 to 50 years of age but ocular manifestation was not found to be associated with age.

Geographic differences in patients with ocular manifestations of CTDs have been reported in another study, with a higher prevalence in East Asian populations.[30] The heterogeneity between the studies is possibly due to different patient populations, non-standardized definitions of ocular manifestations, where some studies were using manifestations or presentations, while others were using involvement or complications. Most studies did not separate the age of onset. All of these may contribute to the differences in the results seen.[31] Akintayo et al reported female gender to be associated with a higher prevalence of ocular manifestation than male gender, a mean age of presentation of 47.2 ± 12.5 years.[18] This is similar to what is obtained in this study, where the female gender with a mean age of 37.1± 13.9 years has more ocular manifestations of CTDs. Some studies reported that the black race/ethnicity is associated with a higher incidence and prevalence of ocular manifestations, with the difference being marked in women.[18,30] This is not in keeping with the findings in this study, because there was no comparison with any other race.

It is crucial for medical professionals to collaborate on the diagnosis, treatment and research of ocular manifestations of CTDs across subspecialties. The ophthalmologist may encounter these conditions and fail to recognize the background systemic disease, while a rheumatologist and dermatologist may be preoccupied with the other aspects of CTDs and miss ocular manifestations[4] and overlook the smouldering morbidity due to the disease or its treatment in the eye.[18] Early diagnosis, treatment and prompt referral of patients to these specialists is significant in reducing ocular morbidity and mortality of patients with CTDs.

CONCLUSION

Ocular involvement is commonly seen in CTDs, with dry eye syndrome, episcleritis, keratitis and cataract being the more frequent ocular manifestations. Periodic ophthalmic examination is important for patients with CTDs, as ocular changes may be observed in asymptomatic patients.

RECOMMENDATIONS

All patients with connective tissue disease should have a detailed ophthalmic assessment at diagnosis and periodically. There is a need for full collaboration among rheumatologists, dermatologists and ophthalmologists, with prompt ophthalmic assessment and treatment of patients suspected to have eye manifestations. There is a need to carry out more in-depth studies to further assess the risk factors for ophthalmic manifestations of connective tissue disease.

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