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ORIGINAL RESEARCH

Ocular Manifestations in Colombian Patients with Systemic Rheumatologic Diseases

Pilar Uribe-Reina[1,2]
Juliana Muñoz-Ortiz[1,2]
Carlos Cifuentes-González[1]
Juliana Reyes-Guanes[2]
Juan Pablo Terreros-Dorado[1]
William Zambrano-Romero[1,3]
Carolina López-Rojas[2]
Fabien Mantilla-Sylvain[3]
Rubén Darío Mantilla-Hernández[3]
Alejandra de-la-Torre[1]

[1]Neuroscience Research Group "NeURos", Escuela de Medicina y Ciencias de la Salud, Universidad del Rosario, Bogotá, Colombia; [2]Escuela Barraquer, Research Group, Escuela Superior de Oftalmología del Instituto Barraquer de América, Bogotá, Colombia; [3]Fundación Para la Investigación en Dermatología y Reumatología (FUNINDERMA), Bogotá, Colombia

Purpose: To establish the prevalence of ocular involvement in a Colombian population with rheumatologic diseases.

Design: Observational cross-sectional study.

Methods: We included a probabilistic sample size of 797 patients who attended a rheumatologic disease center in Bogotá, Colombia. Statistical analysis with descriptive measures and Chi-square independence test between rheumatologic diseases and ophthalmological symptoms and diseases was performed.

Results: Eighty-four percent of the population were women, and the mean age was 54.61± 15.64 years. The most common condition was rheumatoid arthritis (33.37%), followed by fibromyalgia (22.71%), Sjögren Syndrome (19.72%), and systemic lupus erythematosus (9.91%). Almost 7% of the patients presented polyautoimmunity. Thirty-five percent of the patients reported one or more ophthalmological symptoms, being dry eye sensation the most common (30.86%), followed by ocular pain (2.76%), red-eye, and decreased visual acuity (both 2.63%). Similarly, 21.45% of the patients presented one or more ophthalmological diagnoses, being keratoconjunctivitis sicca the most common (15.93%), followed by cataract, uveitis (1.38% each), and scleritis (1.25%).

Conclusion: Almost a third of the patients reported any ocular involvement. It is crucial to be aware of the most common ophthalmic manifestations among the different rheumatologic diseases in our population, to offer early specialist referral and timely treatment.

Keywords: rheumatology, ophthalmology, ophthalmic findings, keratoconjunctivitis sicca, prevalence

Introduction

Autoimmune diseases (ADs) are a heterogeneous group of disorders that can affect specific target organs or even organ systems due to the loss of tolerance to self-antigens.[1] Many of these diseases share clinical signs, symptoms, physiopathological mechanisms, and genetic factors.[2] The prevalence of ADs varies from study to study. Some studies calculate that ADs affects 5% of the American population,[3] especially the female gender. They can compromise several systems such as the musculoskeletal, cardiovascular, pulmonary, hematopoietic, gastrointestinal, endocrine, central nervous system, and eyes.[4,5]

Within the extra-articular manifestations of rheumatologic diseases, different ocular pathologies have been described. These types of disease may affect the eye in different presentations during the natural course of the pathology, and frequently involve the eye as the first manifestation.[6,7] An example can be rheumatoid arthritis (RA), which may debut with episcleritis.[6] On the other hand, eye manifestations

Correspondence: Alejandra de-la-Torre
Neuroscience Research Group - NeURos, Escuela de Medicina y Ciencias de la Salud, Universidad del Rosario, Carrera 24 # 63C - 69, Bogotá, Colombia
Tel +57 3102482196
Email alejadelatorre@yahoo.com

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can reflect the inflammatory activity of an entity. For example, in inflammatory bowel disease, an episode of episcleritis is directly related to the pathology control.[8] In addition, the eye is a sensitive indicator for potentially lethal occult systemic vasculitis in patients with RA who develop peripheral ulcerative keratitis or necrotizing scleritis.[9]

Many ADs have been related to specific ocular manifestations, such as systemic lupus erythematosus (SLE), Sjögren syndrome (SS), Spondyloarthropathies, and Vasculitis associated with ANCAS, among others.[10,11] The main structures affected in the eyes by systemic inflammatory diseases are the cornea, sclera, uvea, and retina, thus compromising vision.[4,6]

There is a significant impact on the life quality of patients with ADs. Besides, ocular manifestations in these patients can lead to important morbidity and worsen life quality, due to its symptoms and consequences. They can cause visual impairment and even blindness,[12,13] so it is important to establish its epidemiology and characteristics to give them the attention they need.[14]

The present study aims to estimate the prevalence of ophthalmological compromise and the different clinical presentations in a group of patients with ADs from a rheumatology health center in Bogotá, Colombia.

Methods

Design

We conducted an observational descriptive cross-sectional study in patients who attended a rheumatologic disease center in Bogotá, Colombia, to document the presence of ophthalmic diseases and manifestations, from 2013 to 2019.

Study Population

Patients older than 18 years old, who attended the center were included. The exclusion criteria consisted of patients with ophthalmologic conditions not related to rheumatologic diseases.

To estimate the true proportion of adult patients with ocular manifestations in rheumatological disease, a simple random sampling for finite populations was used. Taking as reference what is reported in the literature, an expected proportion of 27%, a population of 13.763 patients treated at the rheumatologic center, a confidence interval of 95% (taking a normal distribution critical point of 1.96), and an estimation error of 3%, a sample size of 793 medical records was obtained. Based on the information available, 4 additional cases were considered for a total of 797 medical records. The sample size calculation was done using R Software 4.0.4 samplingbook-package[15] (https://www.R-for the estimation project.org/). All patients' diagnoses included in this study were classified according to the International Classification of Disease, tenth edition (ICD-10).

Data Collection

The evaluation and extraction of the medical records were performed by our trained personnel, for 4 months. We elaborated and validated a database in Microsoft Excel Microsoft (Microsoft Corp., Redmond, WA, USA) to record the information. Variables included were demographic, rheumatologic diseases, ocular symptoms, and ocular diagnosis.

Statistical Analysis

Following the data registration, the database was submitted for statistical analysis. The results were reported as means and standard deviation for continuous variables and frequency distribution tables for categorical variables. Associations between categorical variables were assessed using the Chi-square independence test between rheumatologic diseases and ophthalmological symptoms and diseases, with 95% and 99% confidence levels. All analyses were done in software R version 4.0.4.

Bias Control

Confounding bias may be considered because it is possible that the ocular diseases found during our review, were not necessarily related to rheumatologic diseases. Control of this type of bias was achieved through the design of a temporality variable, which indicated the appearance of ocular diseases concerning rheumatologic disease diagnosis. Although it is well known that some ADs may debut with ophthalmologic manifestations even before systemic affection, patients with ocular manifestations before ADs diagnosis were excluded.

Results

Most of the patients were female (84.06%), and the mean age was 55 years. Most of the population was between 40 and 65 years of age. Analyzing some of the risk factors associated with autoimmune disease, family history of autoimmune disease and history of smoking were the most frequent. The least frequent risk factors were active smoking, silicon prosthesis, and tattoos, with percentual fractions below 7%. Sociodemographic data are shown in Table 1.

Table 1 Sociodemographic Data

Variable	Data n (%)
Female	670 (84.06%)
Age (mean, SD)	54.61 ± 15.64 years
Active smokers	49 (6.14%)
Past smokers	178 (22.33%)
Tattoos	16 (2%)
Silicon prosthesis	22 (2.76%)
Family history of autoimmune disease	211 (26.47%)
Mean age of autoimmune disease diagnosis	Female: 45.88 years Male: 50.656 years

Abbreviation: SD, Standard deviation.

A total of 45 different rheumatologic pathologies were found in the 797 patients, and in them, 1112 rheumatological diagnoses were registered (taking into account that a patient may present more than one diagnosis). Figure 1A shows that the most common diagnoses were RA, followed by fibromyalgia (FM), SS, and SLE. It is important to highlight that almost 7% of the patients presented polyautoimmunity. Only those pathologies with 10 or more cases are graphically displayed. On the other hand, 21 different ophthalmological pathologies were found in the 797 patients, and 208 ophthalmological diagnoses were recorded in them. Figure 1B shows that the most common ophthalmological diagnosis was keratoconjunctivitis sicca. Those pathologies with less than 2 cases were graphically omitted.

All patients with Reiter syndrome (RS), Type 1 Diabetes, Large size vasculitis, Pernicious anemia, Celiac disease, Neuromyelitis optica (NMO), Pemphigoid, and Sclerosing cholangitis presented at least one ophthalmological symptom. Besides, almost 75% of patients with SS reported ophthalmological symptoms, followed by patients with Vasculitis associated with systemic disease (66.67%), Autoimmune hepatitis (62.5%), Multiple sclerosis (MS) (60%), Hashimoto Thyroiditis (HT) (55%), Myasthenia Gravis (50%), polyautoimmunity (43.63%) and SLE (43.03%).

Regarding ophthalmological diagnosis, all the patients with celiac disease and NMO presented an ophthalmological diagnosis, followed by SS (78.34%), vasculitis associated with systemic disease (66.67%), small size

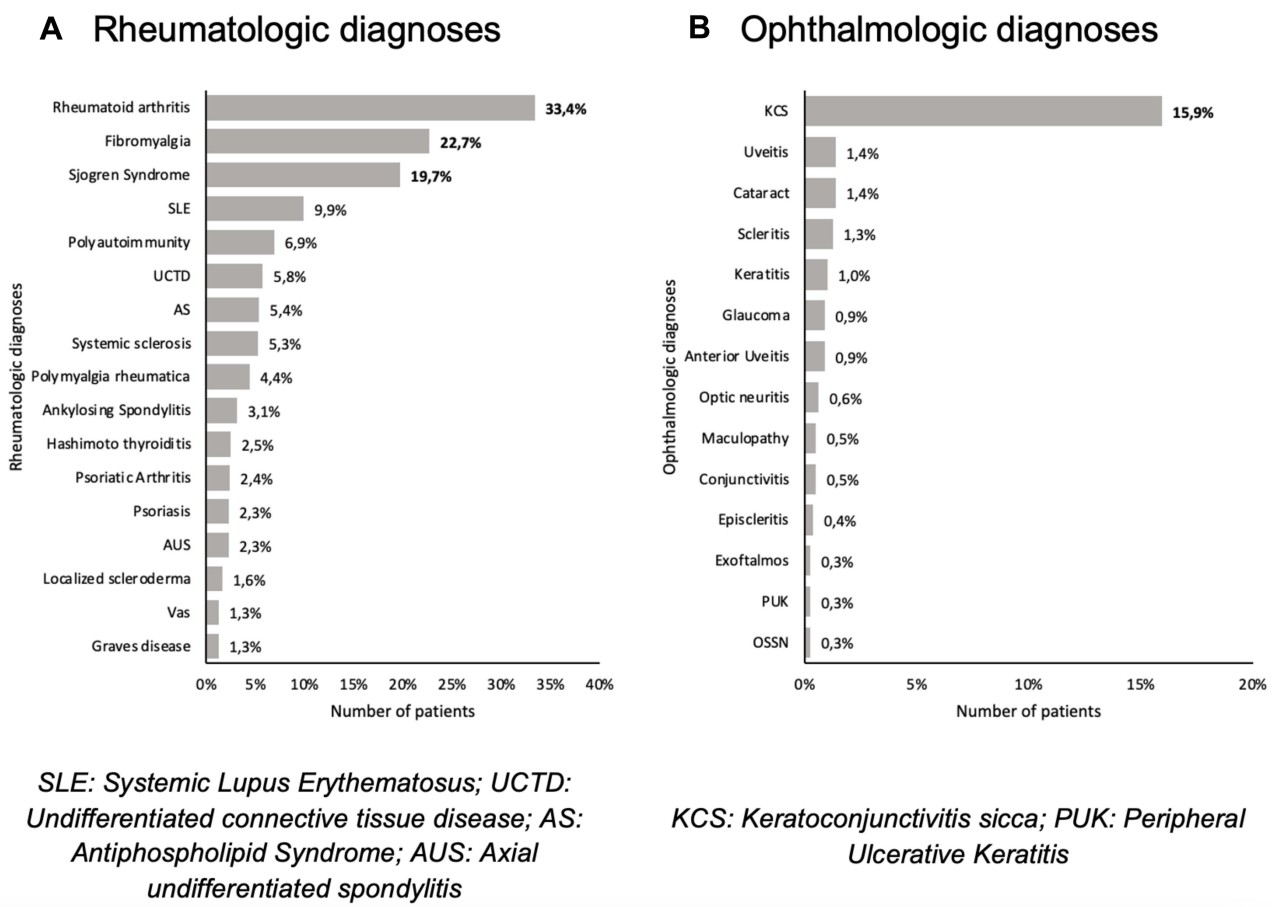

Figure 1 Most common rheumatologic and ophthalmologic diagnoses.

vasculitis associated with ANCA (66.67%), MS (60%), Large size vessel vasculitis, Polymyositis (PM), and RS (50% each). Additionally, 24.05% of the patients with SLE and 18.42% of the patients with RA had some form of ophthalmic manifestation.

It is important to mention that RA, SS, psoriatic arthritis, and psoriasis were statistically associated with the presence of ocular symptoms. In the same way, SS and polyautoimmunity had a statistically significant association with the presence of ophthalmological diagnosis. All rheumatologic diseases with their ophthalmological symptoms and diagnosis proportions are shown in Table 2.

From the total sample, 21.45% presented one or more ophthalmologic diagnoses, being KCS the most prevalent and the single common pathology among the 4 most prevalent rheumatologic diseases. KCS and keratitis were found to be statistically associated with SS. The ophthalmological diagnoses vs rheumatologic diseases data are shown in Table 3.

Thirty-five percent of the patients reported one or more ophthalmological symptoms, being dry eye (DE) sensation the most common (30.9%), followed by ocular pain (2.8%), red-eye (2.6%), and decreased visual acuity (VA) (2.6%). Considering the 4 most prevalent rheumatologic pathologies, we observe how dry eye, ocular pain, red eye, decreased VA, and photophobia were common in patients with these diagnoses. In particular, dry eye had a statistically significant association with SS, photophobia with SLE, and pruritus with FM. The ophthalmological symptoms vs rheumatologic diseases data are shown in Table 4.

An extension of Tables 3 and 4 are presented in Appendix 1 and Appendix 2.1 and 2.2, which show specific ocular symptoms and ophthalmologic diagnoses for each rheumatologic disease. Rheumatologic diseases with no ocular symptoms and/or ophthalmologic diagnoses were omitted.

Discussion

To the best of our knowledge, we present the fourth cross-sectional study addressing ocular manifestations in rheumatologic diseases worldwide[16–18] and the first in Latin America. We report an extended number of rheumatologic diseases, without excluding any reported previously.

As is well known, women tend to be more likely to have ADs. Even though we included both sex population, the female prevalence was 84.06%. This agrees with the results of similar studies, which have reported a female prevalence of 71.2 to 91.96%.[17,19]

The mean age of our population was 54.61 ± 15.64 years. Similarly, the mean ages of 44.3 ± 13.7 and 48.9 ± 19.3 have been reported in comparable studies.[19,20] Contrarily, one study reported a mean age of 67.6 ± 14.5.[16]

The most prevalent rheumatologic diseases found in our study were RA, FM, SS, and SLE. Similarly, data reported by Levitt et al coincides that RA is the most prevalent AD.[16] Remarkably, polyautoimmunity represented 6.9% of our studied population. To the best of our knowledge, there is no available data to compare this result.

Our study reported one or more ophthalmological diagnoses in 21.45% of the population. Interestingly, 35% of the population reported at least one ophthalmologic symptom. Similar studies have reported ophthalmological manifestations in 2–7.7% of their studied population.[16,17,20] Recently, a systematic review with meta-analysis by Turk et al[21] corroborates our data, as it shows that the ocular involvement in ADs is between 20–33%. These differences may be attributed to the inclusion of a greater number of rheumatologic diseases and ophthalmological diagnoses and symptoms compared to the mentioned similar studies. In the same way, the difference between the proportion of patients with ophthalmological symptoms and ophthalmological diagnosis could be attributed to ophthalmological disease sub-diagnosis.

In terms of ocular symptoms, we observed that the most frequent was DE in 30.86% of the patients. Similarly, Ausayakhun et al[18] reported DE as the most prevalent manifestation, in 19.9% of the studied population.

Regarding ocular diagnosis, the most frequent was KCS (15.93%), followed by cataract and uveitis. Contrarily, Ciurtin et al[17] and Levitt et al[16] reported anterior uveitis as the most frequent manifestation associated with HLA-B27 and Sarcoidosis, respectively. Our study reported a uveitis prevalence of 1.38%, anterior uveitis prevalence of 0.88%, posterior uveitis prevalence of 0.13%, and panuveitis of 0.13%.

Interestingly, we found that 6.9% of our population presented polyautoimmunity, which is defined as the concurrence of two ADs in the same patient.[2] From them, almost 44% reported ocular symptoms, being DE the most common, and 42% presented an ophthalmological diagnosis. KCS was the most common diagnosis, found in 33.36% of the sample. Information is scarce regarding

Table 2 Ocular Symptoms and Ophthalmological Diagnosis for Each Rheumatologic Disease

		Sample n (%)	Ocular Symptoms	Ophthalmological Diagnosis
Connective tissue disease				
Rheumatoid arthritis		266 (33.37%)	80 (30.08%) *	49 (18.42%)
Sjögren syndrome		157 (19.72%)	117 (74.72%) **	123 (78.34%) **
Systemic Lupus Erythematosus		79 (9.91%)	34 (43.03%)	19 (24.05%)
Polyautoimmunity		55 (6.9%)	24 (43.63%)	23 (41.82%) **
Systemic sclerosis		42 (5.27%)	19 (45.23%)	9 (21.43%)
Localized Scleroderma		13 (1.63%)	3 (23%)	1 (7.7%)
Undifferentiated Connective Tissue Disease		46 (5.78%)	17 (37%)	6 (13%)
Juvenile Idiopathic Arthritis		5 (0.62%)	0	0
Mixed Connective Tissue Disease		4 (0.5%)	1 (25%)	0
Sarcoidosis		3 (0.38%)	1 (33.33%)	0
Spondyloarthropathies				
Ankylosing Spondylitis		25 (3.14%)	4 (16%)	3 (12%)
Psoriatic Arthritis		19 (2.38%)	1 (5.26%) *	1 (5.2%)
Axial undifferentiated spondylitis		18 (2.26%)	5 (27.78%)	3 (16.66%)
Undifferentiated peripheral spondylitis		5 (0.63%)	0	0
Reactive Arthritis		5 (0.63%)	1 (20%)	0
Reiter syndrome		2 (0.25%)	2 (100%)	1 (50%)
Enteropathic arthritis	Chron Disease	3 (0.38%)	1 (33.3%)	0
	Ulcerative Colitis	1 (0.125%)	0	0
	Celiac disease	1 (0.125%)	1 (100%)	1 (100%)
Myositis				
Polymyalgia rheumatica		35 (4.39%)	10 (28.57%)	5 (14.29%)
Dermatomyositis		7 (0.88%)	3 (42.85%)	3 (42.86%)
Polymyositis		2 (0.25%)	0	1 (50%)
Autoimmune glandular disease				
Hashimoto thyroiditis		20 (2.51%)	11 (55%)	6 (30%)
Graves' disease		10 (1.25%)	1 (10%)	1 (10%)
Type 1 Diabetes		1 (0.13%)	1 (100%)	0
Autoimmune hematologic diseases				
Antiphospholipid Syndrome		43 (5.4%)	14 (32.55%)	8 (18.6%)
Autoimmune thrombocytopenic purpura		4 (0.50%)	0	0
Pernicious anemia		2 (0.25%)	2 (100%)	0
Autoimmune hemolytic anemia		1 (0.13%)	0	0
Vasculitis				
Vasculitis associated with probable etiology		10 (1.25%)	3 (30%)	2 (20%)
Vasculitis associated with a systemic disease		3 (0.38%)	2 (66.67%)	2 (66.67%)
Medium size vessel vasculitis		3 (0.38%)	1 (33.33%)	1 (33.33%)
Small size vessel vasculitis associated with ANCA		3 (0.38%)	1 (33.33%)	2 (66.67%)
Behcet Disease		3 (0.38%)	1 (33.33%)	1 (33.33%)
Large size vessel vasculitis		2 (0.25%)	2 (100%)	1 (50%)
Henoch-Schönlein purpura		1 (0.13%)	0	0

(*Continued*)

Table 2 (Continued).

	Sample n (%)	Ocular Symptoms	Ophthalmological Diagnosis
Autoimmune dermatologic diseases			
Psoriasis	18 (2.26%)	1 (5.55%) **	2 (11.1%)
Vitiligo	3 (0.38%)	1 (33.3%)	1 (33.3%)
Pemphigoid	1 (0.13%)	1 (100%)	0
Autoimmune liver diseases			
Primary biliary cholangitis	1 (0.25%)	0	1 (50%)
Autoimmune hepatitis	8 (1%)	5 (62.5%)	2 (25%)
Sclerosing cholangitis	1 (0.13%)	1 (100%)	0
Autoimmune neurological diseases			
Multiple Sclerosis	5 (0.63%)	3 (60%)	3 (60%)
Neuromyelitis Optica	2 (0.25%)	2 (100%)	2 (100%)
Myasthenia gravis	2 (0.25%)	1 (50%)	0
Other rheumatologic diseases			
Fibromyalgia	181 (22.71%)	63 (34.8%)	36 (19.88%)

Notes: p-value is based in Chi-square proof with a 95% (*) and 99% (**) confidence level.

Table 3 Ophthalmological Diagnoses Associated to the Main Rheumatologic Diseases

Rheumatologic/ Ophthalmological Diagnoses	Rheumatoid Arthritis		Sjögren Syndrome		SLE		Fibromyalgia		Total Per Symptom	
	Ocurrence	p-value	Ocurrence	p-value	Ocurrence	p-value	Ocurrence	p-value	Ocurrence	%
Keratoconjunctivitis sicca	34 (12.78%)	0.1	121 (77.07%)	0.0001**	16 (20.25%)	0.34	28 (15.46%)	0.93	127	15.93%
Uveitis	3 (1.13%)	0.91	2 (1.27%)	1	0		1 (0.55%)	0.93	11	1.38%
Cataract	4 (1.5%)	1	1 (0.63%)	0.6	1 (1.26%)		1 (0.55%)	0.46	11	1.38%
Scleritis	6 (2.25%)	0.14	3 (1.91%)	0.67	0		0	0.17	10	1.25%
Keratitis	2 (0.75%)	0.89	6 (3.82%)	0.0004**	2 (2.5%)	0.4	2 (1.1%)	1	8	1.0%
Glaucoma	2 (0.75%)	1	2 (1.27%)	0.9	0	0.8	2 (1.1%)	1	7	0.88%
Anterior uveitis	1 (0.37%)	0.49	2 (1.27%)	0.9	0		0		7	0.88%
Optic neuritis	0		2 (1.27%)	0.56	2 (2.5%)	0.13	1 (0.55%)	1	5	0.63%
Maculopathy	3 (1.13%)	0.21	1 (0.63%)	1	0		2 (1.1%)	0.47	4	0.5%
Conjunctivitis	1 (0.37%)	1	1 (0.63%)	1	1 (1.26%)	0.86	0		4	0.5%
Episcleritis	1 (0.37%)	1	1 (0.63%)	1	0		0		3	0.38%
Exoftalmos	0		0		0		0		2	0.25%
Peripheral ulcerative keratitis	1 (0.37%)	1	1 (0.63%)	0.85	0		0		2	0.25%
Ocular Surface Squamous Neoplasia	2 (0.75%)	0.21	0		0		0		2	0.25%
Retinal vasculitis	0		0		0		0		1	0.13%
Panuveitis	0		0		0		0		1	0.13%
Posterior uveitis	0		0		0		0		1	0.13%
Corneal perforation	1 (0.37%)	0.72	1 (0.63%)	0.44	0		0		1	0.13%
Macular edema	1 (0.37%)	0.72	0		0		0		1	0.13%
Central retinal artery ocussion	0		1 (0.63%)	0.44	0		1 (0.63%)	0.44	1	0.13%
Blind eye	0		0		0		0		1	0.13%
Retinal detachment	1 (0.37%)	0.72	1 (0.63%)	0.44	0		1 (0.63%)	0.44	1	0.13%

Notes: **p-value is based in chi squared proof with a 99% confidence level.

Table 4 Ophthalmological Symptoms Associated to the Main Rheumatologic Diseases

Disease/Symptom	Rheumatoid Arthritis		Sjögren Syndrome		SLE		Fibromyalgia		Total Per Symptom	
	Ocurrence	p-value	Ocurrence	p-value	Ocurrence	p-value	Ocurrence	p-value	Ocurrence	%
Dry eye	72 (27%)	0.106	113 (72.43%)	0.000**	28 (35.9%)	0.385	57 (31.49%)	0.928	246	30.86%
Ocular pain	9 (3.4%)	0.595	4 (2.56%)	1,00	1 (1.27%)	0.616	3 (1.67%)	0.446	22	2.76%
Red eye	10 (3.77%)	0.244	6 (3.82%)	0.456	2 (2.5%)	1,00	3 (1.66%)	0.497	21	2.63%
Decreased VA	4 (1.5%)	0.236	6 (3.82%)	0.452	2 (2.5%)	1,00	2 (1.10%)	0.229	21	2.63%
Photophobia	2 (0.75%)	0. 213	3 (1.91%)	1,00	6 (7.6%)	0.000**	1 (0.55%)	0.276	14	1.76%
Floaters	3 (1.13%)	1,00	1 (0.63%)	0.815	0		3 (1.66%)	0.716	9	1.13%
Burning	3 (1.12%)	0.668	2 (1.27%)	0.745	0				6	0.75%
Foreign body sensation	1 (0.37%)	0.872	2 (1.27%)	0.564	0		0		5	0.63%
Tearing	3 (1.12%)	0.431	2 (1.27%)	0.563	0		2 (1.10%)	0.697	5	0.63%
Pruritus	2 (0.75%)	0.863	1 (0.63%)	1,00	0		3 (1.66%)	0.057*	4	0.5%
Diplopia	0		0		1 (1.27%)	0.475	0		2	0.25%

Notes: ** p-value is based in chi squared proof with a 95% confidence level. * p-value asymptotically significant for a 95% confidence level.

ocular manifestations in polyautoimmunity. We hypothesize that this could be attributed to genetic and epigenetic factors. To the best of our knowledge, we present the first ocular involvement prevalence for this condition.

Ocular Manifestations in the Most Prevalent Diseases

RA was the most common diagnosis in our sample, with 266 (33.37%) patients. Regarding ocular symptoms, 30.08% reported at least one, being DE the most common (27%), followed by red eye, ocular pain, decreased VA, floaters, burning, and tearing. The most common diagnoses were KCS (12.78%) and scleritis (2.25%), followed by cataract, uveitis, and maculopathy. Among extra-articular RA manifestations, ophthalmologic involvement is often significant and causes diverse degrees of ocular morbidity. Its prevalence varies between studies, ranging from 10–58%.[22–25] A systematic review and meta-analysis by Turk et al[21] reported a prevalence of 18%. DE and KCS have been reported as the most common ocular manifestation (10–58%), followed by scleritis (1–5%),[21–30] which is very similar to our results. Other associated ocular manifestations are anterior uveitis (4%),[31] keratitis (3%),[23] and PUK (<1%).[24]

SS was found in 19.72% of our sample. Almost 75% presented at least one ocular symptom and nearly 79% had an ophthalmologic diagnosis. The most common symptom was DE, followed by red-eye, decreased VA, and ocular pain. The most common diagnosis was KCS (77.07%), followed by keratitis, and scleritis. Ocular compromise in SS is well described in the literature. The characteristic phenotype of SS includes ocular and oral dryness due to autoimmune inflammation of lacrimal and salivary glands.[32] The prevalence of ocular involvement in SS was reported to be 89% in a recent systematic review,[21] which is slightly higher than the one we found. Other studies report even higher prevalence, ranging from 93–96%.[33,34] As expected, the most common diagnosis was KCS, as it has been reported.[32,35–37] Similarly, other ophthalmologic diagnoses had been described. Akpek et al reported the following ocular involvement in a group of SS patients: corneal perforation (3.1%), corneal ulcer (0.6%), corneal scarring (4.3%), papillary conjunctivitis (7.4%), follicular conjunctivitis (2.5%), uveitis (1.2%), scleritis/episcleritis (0.6%), optic neuropathy (1.8%), and orbital inflammation (1.8%).[14]

SLE diagnosis was found in 79 patients (9.91%) of our sample. Thirty-four patients reported ocular symptoms, being DE the most common, followed by photophobia, red-eye, and decreased VA. Similarly, 20.25% of the patients had KCS diagnosis, 2.5% keratitis and ON, and 1.26% conjunctivitis and cataract. It is well known that ocular manifestations can be found in nearly one-third of SLE patients,[21,38–42] which is similar to our results. SLE can affect any part of the eye and its severity can range from mild manifestations to severe, being a sight-threatening disease.[39] As our results, it is reported that the most common ocular manifestation in SLE is KCS,[41,43] which can affect from one-quarter to one-third of SLE patients.[44] Another common ocular manifestation is retinal vasculitis; in a study by Stafford-Brady et al, 7% of patients with SLE developed retinal vasculitis.[45] Interestingly, none of our patients had this diagnosis. On the other hand, neuro-ophthalmic manifestations of lupus

Table 5 Literature Reported Ophthalmological Symptoms and Diseases Associated to Rheumatologic Diseases

Rheumatologic Disease	Literature	
Connective tissue disease		
Rheumatoid arthritis	Ocular involvement 10–58%,[21–25] Dry eye 10–58%,[21–25] Scleritis 1–5%,[21–30] Anterior uveitis 4%,[31] Keratitis 3%,[23] PUK <1%[24]	
Sjögren syndrome	Ocular involvement 89–96%,[21,33,34] Dry eye and KCS the most common 90–97%,[21,32,34–37] Corneal scarring 4.3%,[14] Corneal perforation 3.1%,[14] ON 1.8%,[14] Uveitis 1.2%,[14] Corneal ulcer 0.6%,[14] Scleritis/episcleritis 0.6%[14]	
Systemic Lupus Erythematosus	Ocular involvement in one third of the patients,[21,38–42] KCS most common ocular manifestation 25%,[41,43,44] Retinal Vasculitis 7%,[45] ON 1%,[45] Uncommon, PUK,[39] Scleritis,[39] Epiescleritis,[39] Choroidopathy with serous detachments,[39] Orbit myositis,[39] Internuclear Ophthalmoplegia,[39] Blepharospasm,[39] Retinal Necrosis,[39] Uveitis[40]	
Polyautoimmunity	Dry eye Secondary Sjögren Syndrome and rheumatoid arthritis 4–18%,[51,52] Dry eye Secondary Sjögren Syndrome and Systemic Lupus Erythematosus 11%,[51] Thyroid-associated orbitopathy Celiac disease and HT or GD,[53] Dry eye Secondary Sjögren Syndrome and Primary Biliary Cirrhosis[54]	
Systemic sclerosis	Pinguecula 82.2%,[55] KCS 14.2–79%,[17,56,57] Eyelid stiffness 29–65%,[57–59] Astigmatism 55%,[60] Glaucoma 23%,[55] Loss of sackcloth 15.6%,[55] Uveitis 3%[60]	
Localized Scleroderma	Ocular manifestations 2.1–6,7%,[61,62] Glaucoma,[63] Uveitis,[61,62] Eyelid/eyelash involvement,[62] Epiescleritis,[61,62] Dry eye,[61] Keratitis,[61] Papiledema[61]	
Undifferentiated Connective Tissue Disease	Scleritis,[64] ON,[65] Corneal thinning[66]	
Juvenile Idiopathic Arthritis	Uveitis 17%-12%,[67,68] Band keratopathy 7–70%,[69,70] Ocular hypotony 19%,[70] KCS 8.5%[70]	
Mixed Connective Tissue Disease	KCS (48%),[71] Maculopathy (5%),[72] Retinal vasculitis,[73,74] NO[75]	
Sarcoidosis	Ocular involvement 13–79%,[21,76–78] Uveitis,[79] Scleritis,[80] Dry eye,[79,80] Conjunctival nodules[79]	
Spondyloarthropathies		
Ankylosing Spondylitis	Uveitis 10–50%,[17,81–83] Dry eye[84]	
Psoriatic Arthritis	Ocular involvement 22.5–31.25%,[85,86] KCS 15%,[86] Glaucoma 10%,[86] Cataract 10%,[86] Pinguecula 20.0%,[86] Pterygium 5%,[86] Uveitis 5%[85,86]	
Axial undifferentiated spondylitis	Uveitis 17%,[87] Dry eye,[84]	
Undifferentiated peripheral spondylitis	Uveitis 8%[88]	
Reactive Arthritis	Conjunctivitis 10.52%,[17] Uveitis 5.26%[17]	
Reiter syndrome		
Enteropathic arthritis	Chron Disease	Ocular involvement 10–43%,[89,90] Ocular inflammatory disorders 0.3–13%,[8] Episcleritis (2–5%),[8] Uveitis(0.5%-3.5%),[8] Scleritis;[8] KCS[8]
	Ulcerative Colitis	
	Celiac disease	Dry eye,[53] Cataract,[53] Uveitis,[53] NO,[53] Orbital myositis,[53] CRVO,[53] nyctalopia[53]
Myositis		
Polymyalgia rheumatica	Uveitis,[11,91] Scleritis and necrotizing scleritis,[11,91,92] Episcleritis[11,92,93]	

(*Continued*)

Table 5 (Continued).

Rheumatologic Disease	Literature
Dermatomyositis	Dry eye,[94] Macular edema,[94] Retinitis,[94] CRAO[94]
Polymyositis	Dry eye[18]
Autoimmune glandular disease	
Hashimoto thyroiditis	Thyroid-associated ophthalmopathy 22%,[95–97] Dry eye,[96,97] Proptosis,[95–97] Ocular myopathy[95–97]
Graves' disease	Ocular involvement 67%,[98] Thyroid-associated ophthalmopathy 25%,[99] Dry eye 11%,[98] Proptosis,[98] Lid lag[98]
Type 1 Diabetes	Macular edema,[100] Glaucoma,[100] RD;[100] Cataract,[100] Dry eye[101,102]
Autoimmune hematologic diseases	
Antiphospholipid Syndrome	Ocular involvement 8–88%,[21,103–106] CRVO,[104,107–109] CRAO,[104,107–109] Branch retinal vein occlusion,[104,107–109] Branch retinal artery occlusion,[104,107–109] KCS,[104] Anterior uveitis,[110] Retinal vasculitis,[110] Scleritis and necrotizing scleritis[106,111]
Autoimmune thrombocytopenic purpura	Spontaneous bilateral peripapillary,[112] subhyaloid and vitreous hemorrhage,[112] Massive subretinal hemorrhage,[113] Purtscher's retinopathy;[114] Progressive retinopathy,[115] Valsalva retinopathy,[116] Suprachoroidal hemorrhage simulating melanoma[117]
Pernicious anemia	ON,[118,119] Delayed visual evoked potential,[120] Retrobulbar neuritis[121,122]
Autoimmune hemolytic anemia	Retinal phlebitis,[123] Bilateral macular hemorrhage[124]
Vasculitis	
Vasculitis associated with probable etiology	No prevalence data
Vasculitis associated with a systemic disease	Episcleritis,[125] Scleritis,[125] PUK,[125] Uveitis,[125] Retinopathy[125]
Medium size vessel vasculitis	CRAO,[126,127] ON,[126] Scleritis,[127] Non granulomatous uveitis,[127] Retinal vasculitis,[127] PUK,[127] Pseudotumor of the orbit[127]
Small size vessel vasculitis associated with ANCA	Ocular involvement 12.5–15.62%,[16,128] ON 50%,[128] Scleritis 28%,[128] Iritis 28%,[128] Retinal vasculitis 17%,[128] Oculomotor disorder 17%,[128] PUK 11%[128]
Behcet Disease	Cataract 30.3%,[129] Panuveitis 20%,[129] Posterir uveitis 15.1%,[129] Anterior uveitis 63.2%,[130] Periphebitis 65%,[130] Optic atrophy,[129] RD,[129] Macular edemar,[129] Papillary edema,[129] Ocular hypertonia,[129] retinal ischemia[129]
Large size vessel vasculitis	Anterior ischemic optic neuropathy 81%,[131] Ocular involvement 40–80%,[132] Amaurosis fugax 25.6–30.6%,[131,133] Cilioretinal artery occlusion 22%,[131] CRAO 14%,[131] Posterior ischemic optic neuropathy 7%[131]
Henoch-Schönlein purpura	Anterior uveitis,[134] Anterior ischemic neuroptthy,[135] Cystoid macular edema,[136] Retinal hemorrhages,[136] Cotton wool spots,[136] Episcleritis[137]
Autoimmune dermatologic diseases	
Psoriasis	Ocular involvement 10–67%,[138–140] Anterior uveitis 82%,[85] Bilateral uveitis 64%,[85] Cataract 28–30.2%,[85,141] KCS 16.28%,[141] Posterior uveitis 9.9%,[85] Macular edema 7.2%,[85] Intermediate uveitis 3.3%,[85] Central serous chorioretinopathy 2.4%,[85] Episcleritis 2.4%,[85] Glaucoma 2.3%,[141] Retinal vasculitis 1.6%[85]
Vitiligo	Ocular involvement 22.2–66.6%,[142,143] Pigmentation on anterior chamber 18%,[143] Retinal pigment epithelium hypopigmentation 9%,[143] Uveitis 5%,[143] Hypopigmented spots on the iris 3%,[143] KCS[143,144]

(*Continued*)

Table 5 (Continued).

Rheumatologic Disease	Literature
Pemphigoid	Conjunctival erosions 33.3%,[145,146] Epiphora 23.9%,[145] Eyelid and medial epicanthus erosion 20.8–41.6%,[145,146] Dry eye;[146] Conjunctival fibrosis,[145,146] Symblepharon,[146] Ankyloblepharon,[146] Frozen eye[146]
Autoimmune liver diseases	
Primary biliary cholangitis	Refractive issues 27.8%,[147] Cataract 12.5%,[147] Dry eye and KCS,[54,147] Panuveitis,[148] Persistent subretinal, Fluid due to central serous chorioretinopathy[147,148]
Autoimmune hepatitis	
Sclerosing cholangitis	
Autoimmune neurological diseases	
Multiple Sclerosis	Ocular pain 92%,[149] Dyschromatopsia 88%,[149] ON 25–75%,[150–152] Intranuclear ophthalmoplegia 30%,[153] Intermediate uveitis 28.3%,[154] Marcus Gunn pupil,[155] Retinal periphlebitis[154]
Neuromyelitis Optica	Decreased VA 80%,[156,157] Anterior ON 40%,[156] Retrobulbar ON 36%,[156] Oculomotor abnormalities,[158] Intranuclear ophthalmoplegia[158]
Myasthenia gravis	Ophthalmoparesis in eyelid elevators and extraocular muscles,[159,160] Decreased VA,[161] Dry eye.[162]
Other rheumatologic diseases	
Fibromyalgia	Dry eye,[49] Scleritis,[163–165] Decreased retinal nerve fiber layer[166]

are not common. ON is the most common diagnosis and can be present in 1% of SLE patients,[45] which is similar to our results. Other uncommon diagnoses are PUK, scleritis, episcleritis, choroidopathy with serous detachments, orbit myositis, internuclear ophthalmoplegia, blepharospasm, and retinal necrosis.[39] None of our patients presented these diagnoses.

FM is a disease characterized by chronic and generalized musculoskeletal pain. The etiology of this disease is still unknown. Although it is not classified as an autoimmune disease, it is considered a rheumatologic disease.[46,47] In our population FM was one of the most prevalent diseases, present in 22.71% of our patients. Ocular manifestations were present in 34.8%, being DE the most frequent (31.49%). In the same way, KCS was present in a significant proportion of these patients (15.46%). There is a debate in the literature about the association of FM with DE. Aykut et al[48] found that FM patients had increased corneal sensitivity and secondary eye discomfort related to dry eye disease, but there were no positive tests for dry eye disease. Contrarily, Vehof et al[49] found that FM has an OR of 2.2 for DE. This does not help to make a clear statement in the face of this debate, so we think that larger case-control studies should be done to support some of these data. Additionally, some of our patients with FM presented uveitis, maculopathy, and ON as ocular manifestations. To the best of our knowledge, these ocular manifestations have not been previously reported. Although no statistically significant data relating to ocular manifestations and FM were found, novel related manifestations were described. These manifestations are an input to study a possible relationship between these variables in further research.

Ophthalmological symptoms and diseases related to other rheumatologic diseases that have been reported in the literature are shown in Table 5.

Limitations

It is well known that some drugs used for the treatment of rheumatological diseases can cause adverse effects or ocular toxicity, as in the case of chloroquine and corticosteroids.[50] However, to control this confounding bias, this investigation included a temporality variable in its analysis, to ensure the relationship between ocular manifestations and diseases and the rheumatological disease.

One of the most important limitations was the lack of ophthalmologists in the rheumatology center. General practitioners and a rheumatologist were the ones that documented the main symptomatology and evident ophthalmological signs at the physical examination.

When symptoms and/or signs were noted in the rheumatology consultation, patients usually assisted to an ophthalmological examination, and descriptions and findings were consigned in the patients' record. Nevertheless, this issue may generate an underestimation, resulting in a slight variation of the results.

Due to the medical records heterogeneity and the follow-up loss, diseases were newly classified according to the International Guidelines and the Tenth Edition of the International Classification of Diseases (ICD-10). The limitation lies in the difficulty of comparing some of the included diagnoses with other studies that used the ICD-9 classification.

Conclusion

In our population, almost a third of patients reported ocular involvement. It is crucial to know its prevalence and the most common manifestations among the different rheumatologic diseases to offer early specialist referral and timely treatment. Dry eye corresponded to the main ocular manifestation, which requires strict monitoring to prevent severe complications. A multidisciplinary approach allows the monitoring of the disease and shared decisions on adequate therapy, enriching the knowledge of both parts and achieving the main objective, helping the patient.

Abbreviations

ADLT, Alejandra de-la-Torre; AS, Ankylosing spondylitis; ANCA, Antineutrophil Cytoplasmic Antibodies; APS, Antiphospholipid Syndrome; AD, Autoimmune Disease; Ads, Autoimmune Diseases; CCG, Carlos Cifuentes-González; CLR, Carolina López-Rojas; CRAO, Central Retinal Artery Occlusion; CRVO, Central Retinal Vein Occlusion; DM, Dermatomyositis; DE, Dry Eye; EA, Enteropathic Arthritis; FMS, Fabien Mantilla-Sylvain; FM, Fibromyalgia; GCA, Giant Cell Arteritis; GD, Grave's disease; HT, Hashimoto Thyroiditis; HR, Hazard Ratio; HSP, Henoch-Schonlein purpura; HLA-B27, Human leukocyte antigen B27; IgA, Immunoglobulin A; IBD, Inflammatory Bowel Disease; JPTD, Juan Pablo Terreros-Dorado; JMO, Juliana Muñoz-Ortiz; JRG, Juliana Reyes-Guanes; JIA, Juvenile Idiopathic Arthritis; KCS, Keratoconjunctivitis Sicca; SL, Localized Scleroderma; LES, lupus erythematosus systemic; MCTD, Mixed Connective Tissue Disease; MS, Multiple Sclerosis; NMO, Neuromyelitis Optica; OR, Odds Ratio; ON, Optic Neuritis; PUK, Peripheral Ulcerative Keratitis; PUR, Pilar Uribe-Reina; PMR, Polymyalgia Rheumatica; PM, Polymyositis; PsA, Psoriatic Arthritis; ReA, Reactive Arthritis; RS, Reiter Syndrome; AR, rheumatoid arthritis; RDMH, Rubén Darío Mantilla-Hernández; SS, Sjörgen Syndrome; SSc, Systemic Sclerosis; TA, Takayasu Arteritis; TAO, Thyroid Associated Ophthalmopathy; AV, Visual Acuity; WZ, William Zambrano.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available by the corresponding author on reasonable request.

Ethics Approval

This study adheres to the ethical principles for human research established by the Helsinki Declaration, the Belmont Report, and Colombian Resolution 008430 of 1993. The confidentiality of the information has been preserved based on the Habeas data law (Organic Law 1581 of 2012). This investigation was presented to the research ethics committee of the Escuela Superior de Oftalmología del Instituto Barraquer de América, Bogotá, Colombia. However, as it is a retrospective study and according to the policies of the institution, it did require a registration process but did not require an ethics committee approval process.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests in this work.

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