

CLINICAL SCIENCE

Prevalence of eye disease in Brazilian patients with psoriatic arthritis

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OBJECTIVES: The aim of this study was to report the type and frequency of ocular manifestations in Brazilian psoriatic arthritis patients.

METHODS: We conducted a cross-sectional study in a Brazilian tertiary hospital. The test group included 40 patients who had psoriatic arthritis according to the Classification Criteria for Psoriatic Arthritis. A control group of 40 individuals was matched for age and gender. All of the patients underwent ophthalmic evaluation, which included best-corrected visual acuity, slit lamp and fundus examinations, and dry eye diagnostic tests (Schirmer I, tear break-up time and rose bengal). Demographic parameters were also evaluated.

RESULTS: The mean age of the patients was 53.9 ± 13.1 years; the mean disease duration was 8 ± 10.5 years. Most of the patients were women (60%), and the majority had polyarticular disease (57.5%). Several ocular abnormalities were found, including punctate keratitis, pinguecula, blepharitis, pterygium, cataract, glaucoma, uveitis, and retinal microvascular abnormalities. There were no significant differences in the rates of these abnormalities compared with the control group, however. The Keratoconjunctivitis sicca and dry eye diagnostic tests were more often positive in the patients with psoriatic arthritis than in the control group.

CONCLUSIONS: In this study, keratoconjunctivitis sicca was the most common ocular finding related to psoriatic arthritis. Therefore, we recommend early ophthalmologic evaluations for all psoriatic arthritis patients who complain of eye symptoms.

KEYWORDS: Psoriatic Arthritis; Eye; Keratoconjunctivitis Sicca; Ocular Findings.

Lima FB, Abalem MF, Ruiz DG, Gomes BA, Azevedo MN, Moraes-Junior HV, et al. Prevalence of eye disease in Brazilian patients with psoriatic arthritis. Clinics. 2012;67(3):249-253.

Received for publication on November 24, 2011; First review completed on November 27, 2011; Accepted for publication on January 10, 2012

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INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis. Skin lesions are typically the first signs of the disease, followed by the articular manifestations. The articular manifestations may occur first in rare cases, however (1).

Psoriasis is a chronic, immunologically mediated disease with both genetic and environmental risk factors. It affects 1 to 3% of the world's population. Arthritis occurs in up to 30% of the patients with psoriasis, and it is diagnosed based on clinical and radiological features (2,3). The inflammatory arthritis associated with psoriasis is typically seronegative for rheumatoid factor and exhibits a variety of disease patterns, including oligoarticular disease, polyarticular disease, distal

interphalangeal disease (IFD), arthritis mutilans, and axial disease (4).

The seronegative spondyloarthropathies, including PsA, are a group of disorders that share many clinical and pathologic features (5). The HLA-B27 antigen is found in some patients with PsA, and this antigen can be used as a prognostic marker for clinical disease progression (6). HLA-B27 is associated with earlier onset of psoriatic arthritis and bilateral sacroiliitis and is more common in men.

An ocular inflammatory reaction is commonly found in many rheumatologic diseases (7), and there are various ocular disorders associated with psoriatic arthritis. These disorders include abnormalities of the conjunctiva, cornea, sclera, uvea, and lens. To date, there are no significant publications exploring the prevalence of eye disease in patients with psoriatic arthritis (8).

The aim of this study was to report the ocular manifestations of the psoriatic arthritis patients seen at a university hospital in Brazil.

METHODS

This cross-sectional study included outpatients with PsA seen at the university hospital of the Federal University of

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No potential conflict of interest was reported.

Rio de Janeiro, Brazil, from March 2010 to October 2010. This study was approved by the Medical Ethics Committee of the hospital. Before enrollment, all of the patients provided informed consent in accordance with the Helsinki Declaration.

The test group consisted of 40 patients who had been diagnosed with PsA according to the Classification Criteria for Psoriatic Arthritis (CASPAR) and who were being treated by the Rheumatology Unit (9).

The control group consisted of 40 patients without PsA who were recruited from the Primary Care Unit. To avoid clinical and statistical bias, these patients were selected and matched for age and gender.

In both groups, we excluded the patients younger than 18 years of age and those with inflammatory connective tissue diseases, nephropathy, lung and heart disease, gastroenterological disease/inflammatory bowel disease, neurological disease, neoplasia, metabolic bone disease, skin diseases (except psoriasis), infections, hematological disease, liver disease, previous ocular surgery, active eye infection, active ocular allergy, and evidence of an abnormal eyelid movement disorder.

We also recorded other patient characteristics, including age, gender, history of systemic hypertension or diabetes, and use of topical eye medications, for the cases and controls. The disease duration and use of systemic PsA medications were also recorded for the patients in the case group.

The patients were not permitted to use artificial tears within 2 hours of the screening evaluation.

One ophthalmologist performed all of the ophthalmic exams in sequential order.

First, the best-corrected visual acuity (BCVA) was measured using the Snellen chart.

Second, a slit lamp examination was used to evaluate the cornea for the presence of active inflammation and structural changes at a magnification of 10X to 16X. A cataract evaluation was performed according to the Lens Opacities Classification System III (10).

Third, the tear break-up time (TBUT), Schirmer I and rose bengal staining tests were used sequentially to detect dry eyes. To perform the TBUT, 1% fluorescein (Fludiat, Ophthalmopharma, Sao Paulo, Brazil) was applied to the eye, and the average of three consecutive breakup times (manually determined with a stopwatch) was calculated. A time of <10 seconds was considered abnormal. The Schirmer I test was performed by applying a 5x35 mm paper strip (Schirmer strips, Ophthalmos, Sao Paulo, Brazil) without anesthesia to the lower temporal lid margin; values of <10 mm in 5 minutes were considered to be abnormal. These cutoff values were based on the normal reference values described in the literature (11). The inferior bulbar conjunctiva was touched with a rose bengal strip (rose bengal strips, Ophthalmos, São Paulo, Brazil) to assess staining. The reaction was classified according to the van Bijsterveld Scoring System and values >3 were considered to be abnormal (12). For each sign, the most extreme measurement was used in the analysis.

The Japanese criteria for dry eyes, which include symptom evaluation, the Schirmer I or TBUT tests, and rose bengal staining, were applied (13). For a definitive diagnosis, the patient needed to have had symptoms and two positive tests. The patients who met only two criteria were classified as having probable dry eye.

The Ocular Surface Disease Index (OSDI) questionnaire was administered to assess the ocular dry eye symptoms (14).

Intraocular pressure was measured using Goldmann applanation tonometry. Values >21 mmHg were considered to be abnormal. A diagnosis of open-angle glaucoma was based on visual field, gonioscopic, and optic nerve abnormalities (15).

Funduscopy was performed using indirect ophthalmoscopy with a 20-diopter Volk lens.

Statistical Analysis

Due to the need for consistency, patients (rather than affected eyes) were matched when choosing the control group. The descriptive data are presented in tables and are expressed by frequency (n) and percentage (%) for categorical data and the mean ± SD (or median ± IQR) for numerical data.

To compare the numerical data, we used the Student's t-test for normally distributed data or the Mann-Whitney test for non-normally distributed data. We used the χ^2 test or Fisher's exact test for comparisons of categorical data.

The nonparametric method was used because some variables did not have a normal (Gaussian) distribution due to large dispersion (the hypothesis of normality was rejected in the Kolmogorov-Smirnov test).

The significance level was set at $p < 0.05$. Statistical analyses were performed using the SAS[®] version 6.11 statistical software (SAS Institute Inc., Cary, North Carolina).

RESULTS

In total, 40 PsA patients were evaluated. The mean age of the PsA patients was 53.9 ± 13.1 years, and 24 (60%) were female. The mean disease duration was 8 ± 10.5 years. The demographic data are shown in Table 1. Polyarticular disease was the most common disease characteristic (57.5%).

Majority of patients were taking medications for PsA: 27 patients (67.5%) were using methotrexate, 17 patients (42.5%) were using oral corticosteroids, 13 patients (32.5%) were using tumor necrosis factor alpha receptor antagonists (anti-TNF), and three patients (7.5%) were using antimalarial medications.

Of the four patients with glaucoma, three were using timolol maleate 0.5%, and one was using brimonidine tartrate 0.2%. In addition, four other patients were using artificial tears.

Table 1 - Demographic data by group.

| | Arthritis (n = 40) | | Control (n = 40) | | p-value |
|------------------------------|--------------------|------|------------------|------|---------|
| | n | % | n | % | |
| Age (y) * | 53.9 ± 13.1 | | 58.6 ± 12.5 | | 0.10 |
| Female gender | 24 | 60.0 | 24 | 60.0 | 1.0 |
| Diabetes | 7 | 17.5 | 5 | 12.5 | 0.53 |
| Systemic Hypertension | 17 | 42.5 | 12 | 30.0 | 0.24 |
| Mean duration of disease (y) | 8 ± 10.5 | | NS | | NS |

*Age was expressed as the mean ± standard deviation and data were analyzed with the Student's t-test for independent samples. The χ^2 test was used to compare proportions (categorical data).

The majority of the patients (90% in the study group and 85% the control group) presented with a BCVA of 0.66 or better. The remaining patients had BCVAs of 0.25 or worse in at least one eye. The low visual acuity was bilateral and was caused by nuclear cataracts in all of these patients.

Several ocular abnormalities were found upon biomicroscopy and fundoscopy evaluation. Using the data from our control group, we were able to correlate the large number of ocular abnormalities with PsA. With the exception of pterygium and uveitis, the frequency and type of ophthalmologic findings (glaucoma, cataract, blepharitis, pinguecula, punctate keratitis, and retinal microvascular abnormalities) did not differ significantly between the case and control groups. There were not enough cases of pterygium and uveitis to make comparisons between the groups. These findings are summarized in Table 2.

It is also important to note that all of the cataracts were age related, the glaucoma cases were all classified as primary open-angle glaucoma and all of the patients who presented with retinal microvascular abnormalities also presented with systemic hypertension.

All of the uveitis cases appeared to be anterior uveitis in which there were posterior and anterior synechias and corneal endothelium changes but no fundal involvement. Both of the uveitis cases were observed in patients with oligoarticular arthritis.

The mean intra-ocular pressures for all of the patients, including those with glaucoma, were 13.0±1.7 in the right eyes and 13.1±1.8 in the left eyes. These relatively normal values were most likely due to the patients with glaucoma taking medications.

Ocular tests were used to test for KCS. In the PsA group, we found 27 patients (67.5%) with abnormal TBUTs, 20 patients (50%) with abnormal Schirmer I tests, and 11 patients (27.5%) with abnormal rose bengal tests; all of these tests were significantly more likely to be positive in the PsA group. Nine patients (22.5%) in the PsA group were symptomatic and tested positive on the OSDI. However, these results were not significantly different from those of the control group. According to the criteria adopted in this study, 6 PsA patients (15%) had a definitive diagnosis and 9 (22.5%) had a probable diagnosis of KCS ($p < 0.05$ for both). In addition, the mean TBUT, Schirmer and rose bengal

Table 2 - Ocular findings by group.

| | Arthritis (n = 40) | | Control (n = 40) | | p-value |
|-----------------------------|--------------------|------|------------------|------|---------|
| | n | % | n | % | |
| Visual Acuity ≥ 0.66 | 36 | 90.0 | 34 | 85.0 | 0.49 |
| Glaucoma | 4 | 10.0 | 3 | 7.5 | 0.50 |
| Cataract | 4 | 10.0 | 8 | 20.0 | 0.21 |
| Blepharitis | 5 | 12.5 | 9 | 22.5 | 0.23 |
| Punctate keratitis | 9 | 22.5 | 4 | 10.0 | 0.13 |
| Pinguecula | 8 | 20.0 | 9 | 22.5 | 0.78 |
| Pterygium | 2 | 5.0 | 2 | 5.0 | fc |
| Uveitis | 2 | 5.0 | 0 | 0.0 | fc |
| Microvascular abnormalities | 6 | 15 | 4 | 10 | 0.49 |
| IOP right eye (mmHg) * | 13.0±1.7 | | 13.2±2.2 | | 0.73 |
| IOP left eye (mmHg) * | 13.1±1.8 | | 13.0±2.1 | | 0.86 |

fc: fewer than 5 cases.

*IOP was expressed as the mean ± SD and analyzed using the Student's t-test for independent samples. The χ^2 test or Fisher's exact test was used to compare proportions (categorical data).

Table 3 - KCS features by group.

| | Arthritis (n = 40) | | Control (n = 40) | | p-value |
|----------------------------------|--------------------|------|------------------|------|---------|
| | n | % | n | % | |
| OSDI | 9 | 22.5 | 5 | 12.5 | 0.23 |
| KCS | 6 | 15 | 1 | 2.5 | 0.05 |
| Probable KCS | 9 | 22.5 | 2 | 5 | 0.023 |
| TBUT | 27 | 67.5 | 11 | 27.5 | <0.0001 |
| ROSE BENGAL | 11 | 27.5 | 4 | 10 | 0.045 |
| SCHIRMER | 20 | 50 | 7 | 17.5 | 0.002 |
| TBUT right eye (s) * | 8±5 | | 11±2.5 | | 0.0001 |
| TBUT left eye (s) * | 8±5 | | 11±3 | | 0.0001 |
| ROSE BENGAL right eye (points) * | 2±2 | | 1±2 | | 0.0015 |
| ROSE BENGAL left eye (points) * | 1±2 | | 1±1.5 | | 0.002 |
| SCHIRMER right eye (mm) * | 10±9.5 | | 14±5 | | 0.004 |
| SCHIRMER left eye (mm) * | 10±11 | | 15±5 | | 0.005 |

*The numerical KCS measurements were expressed as the median ± IQR and analyzed using the Mann-Whitney (nonparametric) test.

The χ^2 test or Fisher's exact test were used to compare proportions (categorical data).

OSDI: Ocular Surface Disease Index; KCS: Keratoconjunctivitis Sicca; TBUT: Tear Break-up Time.

values were calculated and described in Table 3. Most of the patients in the definitive and probable KCS groups presented with oligoarthritis and/or polyarticular disease, and the majority were using methotrexate for disease control.

The demographic parameters are shown in Table 1.

In the control group, three patients were using timolol maleate 0.5%, and two patients were using artificial tears.

DISCUSSION

This study represents the largest group of Brazilian psoriatic arthritis patients who have been screened for associated ocular manifestations.

Polyarthritis was the most common PsA presentation in this study. Some researchers have concluded that oligoarthritis is the most common manifestation of PsA, whereas some have claimed that polyarthritis is more common (16). Overlapping PsA articular subtypes are common over time, and the distributions may vary as different definitions are applied. Similarly, patterns change over time due to increases in disease duration and changes in natural history that may lead patients to develop a polyarticular pattern (17).

According to the results presented here, PsA patients frequently develop ocular inflammatory conditions. Previous studies have shown that PsA patients may present with conjunctivitis, uveitis, and KCS (18). We did not find any patients with conjunctivitis because we specifically selected patients who visited the department of rheumatology for treatment.

Uveitis is an important ocular abnormality that is described in PsA patients (19). The frequency of uveitis associated with psoriatic arthritis ranges from 0.4 to 18% (20-22). In this study, 5% of the patients exhibited signs of uveitis, which was classified as anterior, unilateral and acute. In general, these signs are classically associated with spondyloarthropathies and are not specifically related to PsA. (23). It is important to emphasize that these patients

were not using anti-TNF-alpha medications because these agents may induce paradoxical uveitis in patients with rheumatic diseases (24,25).

In this study, we found a high number of abnormal dry eye tests in the PsA patients. Many of these patients met the European classification criteria for Sjogren's syndrome (26), and we believe that these results demonstrate the presence of important ocular SS signs in this study group. The presence of SS in patients with spondyloarthropathies has been corroborated by the literature (27).

We also found that 15% of the PsA patients met the criteria for KCS and that another 22.5% had probable KCS. This rate may be underestimated because we used rigid diagnostic criteria. Furthermore, the disease may have been misclassified, particularly in the early stages when the typical signs and symptoms are less clear. There is a poor relationship between the signs and symptoms of dry eye (28). Therefore, these data are important because KCS is well recognized in other rheumatologic diseases, such as rheumatoid arthritis (29,30).

Blepharitis, pterygium, pinguecula, and keratitis are ophthalmic conditions commonly found in the general population (31,32,33). Our study showed a high frequency of these findings in the PsA patients. However, these rates did not differ markedly from the data in the literature or from the control group.

Most of the patients in this study presented with good visual acuity. Cataracts were responsible for most of the visual impairment. All of these patients presented with the age-related nuclear cataract subtype, which differs from cataracts caused by uveitis or steroid use (34).

Our study group had a higher prevalence (10%) of primary open-angle glaucoma than that of the general population (0.8 a 3.0%) (15). We observed no signs of glaucoma secondary to uveitis or steroid use, which is the type of glaucoma more commonly found in rheumatologic diseases (35). Moreover, there were no significant differences between the two groups in the number of glaucoma diagnoses or average intraocular pressure values.

In this study, 15% of the patients had micro-vascular retinal abnormalities that were indistinguishable from those related to systemic hypertension. There were no significant differences between the two groups (36,37).

High levels of TNF-alpha are found in the joint fluid and tissue of patients with psoriatic arthritis. TNF-alpha induces the production of other pro-inflammatory cytokines that mediate multiple biological processes responsible for joint damage (38). A clinical trial of etanercept provided strong evidence that this medication is effective for psoriatic arthritis (39). The efficacy of anti-TNF agents for patients with uveitis and scleritis has been observed in a limited study, but anti-TNF treatment has caused both improvement and exacerbation of inflammatory eye disease (40). Another author has shown that Infliximab was effective for suppressing intraocular inflammation; the clinical symptoms improved significantly, and anterior chamber cells decreased rapidly (41). These findings may explain why the patients in this study who were using anti-TNF agents presented without uveitis or scleritis. The inflammatory conditions that they presented with were not severe (blepharitis and keratitis).

The retinal toxicity of antimalarial drugs, such as chloroquine and hydroxychloroquine, has been recognized

for many years (42). No retinopathy was found in any of the patients in this study.

The clinical efficacy of methotrexate for PsA is well known, and the agent has been a mainstay of treatment for many years. Methotrexate is associated severe adverse events, of which liver toxicity is the most common. The patients in our study maintained regular follow-ups with their rheumatologists; at the conclusion of the study, our patients did not experience any significant adverse events (43).

In conclusion, many ocular abnormalities were found in the PsA patients, including cataracts, glaucoma, and blepharitis. These findings were found in similar rates in the control group. However, the increased rate of Keratoconjunctivitis sicca in the PsA patients was statistically significant. This finding is important for understanding the disease and for clinical management. Although uveitis was not significantly more common in the PsA group, it must be monitored in PsA patients due to its clinical relevance.

AUTHOR CONTRIBUTIONS

Lima FB examined all patients, obtained ethics approval, wrote and submitted the manuscript. Abalem MF and Gomes BA wrote the manuscript. Ruiz DG recruited the patients. Yeskel AS translated the manuscript. Azevedo MN and Moraes-Junior HV directed and defined the research. Kara-Junior N directed the research.

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