

Original Research Article

Uveitis of spondyloarthritis in Indian subcontinent: a cross sectional study

Finin Ninan¹, John Mathew^{2*}, Swetha Sara Philip¹, Deepa John¹, Debashish Danda²,
Sheeja Susan John¹

¹Department of Ophthalmology, Christian Medical College, Vellore, Tamil Nadu, India

²Department of Clinical Immunology and Rheumatology, Christian Medical College, Vellore, Tamil Nadu, India

Received: 25 July 2017

Accepted: 20 August 2017

*Correspondence:

Dr. John Mathew,

E-mail: johnmathew@cmcvellore.ac.in

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: The seronegative spondyloarthritis (SpA) are known to have intimate association with ocular inflammatory disease. While anterior uveitis accounts for 50-92% of all cases of uveitis in the West, it ranges between 28 and 50% in the Asian countries. The aim of this study was to document the clinical profile of uveitis in patients with spondyloarthritis in the Indian subcontinent.

Methods: In our hospital based cross sectional study, 166 patients fulfilling Assessment of SpondyloArthritis international Society' (ASAS) criteria for spondyloarthritis (SpA) were evaluated for evidence and nature of uveitis, including by a slit lamp bio microscope. The characteristics of Uveitis were defined as per the SUN (Standardization of Uveitis Nomenclature) Working Group criteria. 84.3% (140) of the patients were male.

Results: Ankylosing spondylitis was the commonest type of spondyloarthritis accounting for 69.3% patients. Evidence of past or present uveitis was found in 16.3% patients. Of the patients with uveitis 96.3% had anterior uveitis. 88.9% of the patients had redness of the eye, and 85.2% reported pain in the eye during an episode of uveitis. Mean duration of musculoskeletal symptoms prior to the diagnosis of SpA was 4.36 years. Of the 24 patients who could recall the course of uveitis 70.8% (17) had recurrent episodes. As a complication of uveitis 18.5% had cataract, and 14.8% had posterior synechiae. 78.3% patients were HLA-B27 positive. 19.2% of HLA-B27 positive patients had uveitis, whereas only 5.6% out of the 36 HLA-B27 negative patients had uveitis.

Conclusions: The proportion of patients with uveitis in our study (16.3%) was considerably less than in other studies. The characteristics and profile of uveitis in our cohort of SpA patients from the Indian subcontinent were similar to those previously reported in literature.

Keywords: HLA B27, Spondyloarthritis, Uveitis

INTRODUCTION

The seronegative spondyloarthritis (SpA) are known to have intimate association with ocular inflammatory disease.

While anterior uveitis accounts for 50-92% of all cases of uveitis in the West, it ranges between 28 and 50% in the

Asian countries.¹ 23-37% of anterior uveitis is associated with different forms of SpA.^{1,2} Uveitis in SpA may precede, accompany or follow other systemic or musculoskeletal symptoms.

The aim of this study was to document the clinical profile of uveitis in patients with spondyloarthritis in the Indian subcontinent.

METHODS

This was a hospital-based, cross-sectional study. The study was conducted over a thirteen-month-period, from April 2013 to April 2014, after receiving approval of the Institutional Review Board (IRB Min No. 8210).

Patients with a definitive diagnosis of SpA, attending the Outpatient clinics of the Department of Clinical Immunology and Rheumatology, Christian Medical College, Vellore, were screened for eligibility for enrolment in the study. Children (less than 18 years of age), patients with previous ocular trauma, surgery or laser procedure in the eye, patients with any other known uveitic entities like Fuchs heterochromic iridocyclitis, Posner-Schlossman syndrome, patients with any other ocular or systemic disease (other than SpA) which may be associated with, or masquerade as uveitis were excluded from the study.

The diagnosis of SpA, in each case, was made as per 'Assessment of SpondyloArthritis international Society' (ASAS) criteria for spondyloarthritis³ by a physician in the department, with more than one year of experience in the specialty. All patients in the study were typed for HLA-B27.

The patients were enrolled in the study after obtaining informed consent. All patients had a detailed history and ophthalmological evaluation to look for evidence of past or present uveitis. They were examined using a single Haag-Streit slit lamp bio microscope, which was standardized for the study.

The types of uveitis and their characteristics were defined as per the SUN (Standardization of Uveitis Nomenclature) Working Group criteria⁴. Diagnosis of active uveitis was made if Grade 0.5+ or more cells in the anterior chamber and fresh keratic precipitates were present, along with one or more of the following signs: circumcorneal congestion, hypopyon, posterior synechiae, peripheral anterior synechiae on gonioscopy, vitreous haze and cells, active inflammatory lesions in the retina or choroid.

A diagnosis of inactive uveitis (past episode of uveitis) was made if Grade 0 cells in the anterior chamber, pigmented keratic precipitates and/ or pigments on the corneal endothelium, and pigments on the anterior lens capsule were present, along with one or more of the following: posterior synechiae, peripheral anterior synechiae on gonioscopy, chorioretinal scars suggestive of old inflammatory lesions in the retina or choroid, history of previous episode of pain in the eye with redness, photophobia and blurring of vision.

The diagnosis of uveitis in each case was made by one of two consultant ophthalmologists in the department, with more than five years of experience in the specialty. The ophthalmologist making the diagnosis of uveitis was

masked towards the HLA-B27 status of the patient. A pre-test agreement was calculated between the two ophthalmologists, which showed excellent agreement on kappa analysis ($k=1$). In patients who were diagnosed to have uveitis, the characteristic features and complications of uveitis were recorded.

RESULTS

In this study, 203 patients with SpA were screened for eligibility for enrolment. After excluding 37 patients who did not satisfy the eligibility criteria, 166 patients were included in the study. Patients from all over the Indian subcontinent participated in the study.

The age of the patients in the study ranged from 19 to 63 years. The study had 140 male (84.3%) and 26 female (15.7%) patients.

Ankylosing spondylitis was the most common type of spondyloarthropathy, seen in 115 patients (69.3%), followed by undifferentiated spondyloarthropathy (37 patients, 22.3%) Table 1.

Table 1: Type of spondyloarthritis.

Type of spondyloarthritis	No. of patients (total 166)
Ankylosing spondylitis	115 (69.3%)
Undifferentiated spondyloarthropathy	37 (22.3%)
Psoriatic arthritis	11 (6.6%)
Inflammatory bowel disease	2 (1.2%)
Reactive arthritis	1 (0.6%)

Table 2: Age at onset of arthritic symptoms.

Age group (years)	No. of patients (%)
16-25	79 (47.6)
26-35	52 (31.3)
36-45	35 (21.1)

Evidence of past or present uveitis was found in 27 of the 166 patients (16.3%). Twenty-two (15.7%) of the 140 male patients and five (19.2%) of the 26 female patients had uveitis. Twenty-six (96.3%) of the 27 patients with uveitis had anterior uveitis. One patient had combined anterior and intermediate uveitis. All uveitis cases were acute, non-granulomatous and of limited duration. Only four (14.8%) among the 27 patients with uveitis had active uveitis.

Pain and redness of the eye were found to be the most common symptoms in patients diagnosed to have uveitis. 88.9% of the patients had redness of the eye, and 85.2% reported that they had pain in the eye during an episode of uveitis.

Arthritic symptoms started at a young age in the majority of the patients. The age of onset of joint symptoms is given in Table 2.

The mean duration of musculoskeletal symptoms prior to the diagnosis of SpA was 4.36 years. The largest group (71 patients, 42.8%) had the diagnosis of SpA made between 6 months to 5 years after the onset of systemic symptoms. The duration of joint symptoms before diagnosis of SpA is shown in Table 3.

Table 3: Duration of joint symptoms before diagnosis of SpA.

Time to diagnosis of SpA from onset of symptoms	No. of patients (%)
<6 months	44 (26.5)
6 months - 5 years	71 (42.8)
5-10 years	34 (20.5)
10-15 years	7 (4.2)
>15years	10 (6.0)

SpA: Spondylorthritis

Ocular symptoms and diagnosis

Twenty one of the 27 patients with uveitis could recall the age at onset of ocular symptoms and diagnosis of ocular disease. Out of these 21 patients, the largest group (10 patients, 47.6%) had the onset of ocular symptoms between 26-35 years of age. The age of onset of ocular symptoms is shown in Table 4.

Table 4: Age at onset of ocular symptoms (n=21).

Age group (years)	No. of patients (%)
16-25	4 (19.0)
26-35	10 (47.6)
36-45	6 (28.6)
46-55	1 (4.8)

Diagnosis of the ocular disease was made at presentation in 19 (90.5%) out of the 21 patients. Only two patients (9.5%) had a delay in diagnosis of uveitis.

Of the 21 patients who could recall the age at onset and diagnosis of ocular disease, 19 (90.5%) had onset of musculoskeletal symptoms before the symptoms of uveitis. However, ocular diagnosis was made earlier than systemic diagnosis of SpA in 10 of these 19 patients (52.6%).

Twenty four of the 27 patients with uveitis could recall the course of uveitis. 17 of these 24 patients (70.8%) had recurrent episodes of uveitis. Out of the 17 patients who had recurrent episodes of uveitis, 14 patients (82.4%) had unilateral, alternating episodes (affecting one eye first, followed by the other eye after several months), and three patients (17.6%) had recurrent episodes in the same eye.

Out of the 27 patients with uveitis in the study, five patients (18.5%) had cataract, and four patients (14.8%) had posterior synechiae. One patient had steroid-induced raised intra ocular pressure, and one patient had cystoid macular edema with epiretinal membrane.

HLA-B27 status and uveitis

Of the 166 patients recruited, 130 (78.3%) were HLA-B27 positive and 36 (21.7%) were HLA-B27 negative. Twenty five out of the 130 HLA-B27 positive patients (19.2%) had uveitis, whereas only two out of the 36 HLA-B27 negative patients (5.6%) had uveitis (OR 4.05, CI 0.91 to 17.98). This is shown in Table 5.

Table 5: Uveitis in spondyloarthropathy based on HLA B27 status.

Uveitis	HLA-B27 positive n (%)	HLA-B27 negative n (%)
Present	25 (19.2)	2 (5.6)
Absent	105 (80.8)	34 (94.4)

HLA: Human Leucocyte Antigen

Characteristics of uveitis in HLA-B27 positive and negative spondyloarthropathy patients (Figure 1).

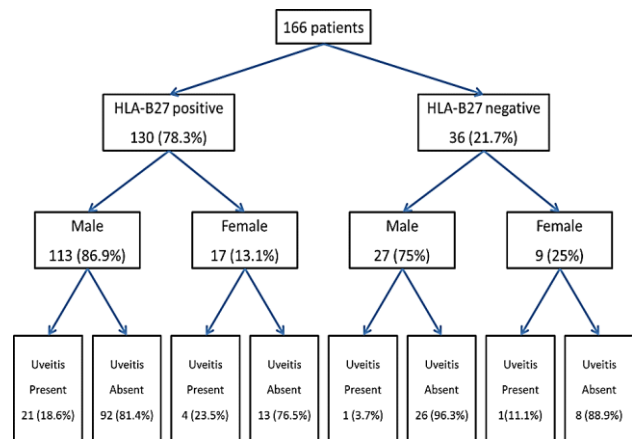


Figure 1: Prevalence of Uveitis in Spondyloarthritis patients based on gender and HLA-B27 status.

There was male predominance noted among both HLA-B27 positive (86.9%) and HLA-B27 negative patients (75%) with SpA. However, uveitis was found to be more common among female patients in both HLA-B27 positive and negative categories (23.5% and 11.1% respectively compared to the number in males; OR 1.35, (CI 0.40 - 4.55)

All the uveitis cases were anterior, except for one HLA-B27 positive patient, who had combined anterior and intermediate uveitis. Out of the 24 patients who could recall the course of the ocular disease, 22 were HLA-B27 positive. It was found that 15 patients (68.2%) out of the 22 had recurrent episodes. Both HLA- B27 negative patients with uveitis had recurrent episodes.

Among the 25 HLA-B27 positive patients with uveitis, four patients (16%) had cataract, four patients (16%) had posterior synechiae and one patient (4%) had epiretinal membrane and cystoid macular edema. One of the two

HLA-B27 negative patients had cataract and steroid-induced raised intra ocular pressure.

DISCUSSION

Uveitis is a common extra-articular manifestation of seronegative spondyloarthritis.

Systemic and ocular symptoms and diagnosis

The onset of ocular symptoms of SpA may occur before, concurrently or after the onset of systemic symptoms. Most studies report that the systemic symptoms precede ocular symptoms by months to years as in our case.^{5,6} In our study, musculoskeletal symptoms started most commonly in the second and third decades (79 patients, 47.6%). In these patients, there was a delay ranging from 1 to 11 years between the onset of systemic and ocular symptoms.

In our study, we found that there was a substantial delay, as much as 15 years or more, in the diagnosis of systemic disease in many patients with SpA, the majority of patients (71, 42.8%) had a delay of 6 months to 5 years after the onset of their arthritic symptoms for their systemic diagnosis to be made. The mean duration of symptoms prior to the diagnosis of SpA was 4.36 years. Feldtkeller, et al. has also reported a similar delay in systemic diagnosis (mean - 8.8 years).⁷ Aggarwal, et al. found a mean (\pm SD) delay of 6.9 (\pm 5.2) years prior to diagnosis of systemic disease in their study.⁸

Most of the patients with uveitis in our study had their ocular disease diagnosed at the time of onset of ocular symptoms, except for two patients (9.5%) who had a diagnostic delay of up to 5 years. Similar observations were made by many authors and the diagnosis of previously undiagnosed spondyloarthritis was made in more than half the patients as a result of ophthalmic consultation for an episode of anterior uveitis.^{2,5,9,10}

In marked contrast to this scenario, since the ocular symptoms of SpA are usually acute, painful, and associated with a sudden decrease in vision, patients usually seek urgent medical help for this complication unlike the nonspecific and mild musculoskeletal symptoms in early disease. Most of our patients, therefore, could recollect the dramatic eye events, although recollect bias in patients with milder eye disease is possible.

Prevalence of uveitis

Our study showed a much lower prevalence of uveitis among the SpA patients (27 out of 166 patients - 16.3%) in contrast to the figures of 32.7% reported in the systematic review of uveitis in SpA by Zeboulon, et al.¹¹

Methodology followed by different studies to diagnose uveitis may explain this. In the study by Zeboulon, et al.

prevalence of uveitis was primarily obtained through history in their systematic review and it was the limitation of that study.¹¹ History suggestive of past uveitis elicited from a patient, may be very subjective, as ocular pain, discomfort and redness may be present in many ocular conditions other than uveitis. There is also a high chance of recall bias. Therefore, it is very important to correlate the history suggestive of uveitis with findings on clinical examination, which corroborate this history. Moreover, many studies have not stated the criteria that have been used to diagnose uveitis.^{6,8} Since this is a diagnosis based solely on clinical examination, defining criteria for the diagnosis of uveitis, the expertise of dedicated ophthalmologist in making the diagnosis and the standardization of the slit lamp bio microscope used for examining patients are all extremely important determinants of the accuracy of the diagnosis made.

In our study, we employed stringent diagnostic criteria, which included both history and clinical findings. Examination techniques and instruments were standardized, and pre-test agreement was calculated between the two ophthalmologists conducting the clinical examination and making the diagnosis, which showed excellent agreement on kappa analysis ($k=1$). However, it is possible that, while the accuracy of diagnosis would have been high, we may have underestimated the prevalence of uveitis, by missing out on mild cases of past anterior uveitis without significant sequelae in the eye. On the other hand, many previous studies had used less stringent criteria for the diagnosis of uveitis and may have overestimated the prevalence of uveitis in spondyloarthritis patients.^{6,8,11}

Characteristics of uveitis

Although SpA is a disease with a male preponderance, the extra-articular manifestations of the disease including uveitis, have been found to be more in women.^{8,11} In our study also, the majority of patients (140, 84.3%) were men. However, uveitis was found more commonly in women in our study. Uveitis was found in 5 out of 26 women with spondyloarthritis (19.2%), compared to 22 out of 140 men (15.7%).

The uveitis in SpA is typically described as anterior, acute, recurrent, unilateral / alternating and non-granulomatous.¹¹⁻¹⁴ Anterior uveitis accounted for 96.29% of uveitis in our study, similar to other international studies.¹¹ All patients in our study had acute, non-granulomatous uveitis.

Majority of cases of uveitis were recurrent (70.8%), of these most had unilateral alternating episodes while some had recurrent episodes in the same eye. Zeboulon, et al. have also reported the anterior uveitis in patients with spondyloarthritis in their review to be recurrent in 50.6% and unilateral in 87.3% cases.¹¹ Cataract and posterior synechiae were the more common complications of uveitis seen in our study. Less common

complications included steroid-induced raised intra ocular pressure, and cystoid macular edema with epiretinal membrane. This is similar to reports of complications of uveitis associated with SpA in existing literature.^{12,15,16}

HLA-B27 status

The prevalence of HLA B27 positivity (78.3%) in our cohort of patients was similar to that reported in other studies.¹¹ We also found that the prevalence of HLA B27 positivity was higher among patients with Ankylosing spondylitis (84.34%), compared to patients with other types of SpA (64.7%). Different studies have consistently shown that the prevalence of uveitis is higher in HLA B27 positive SpA compared to HLA B27 negative SpA1, our study shows that this is true for the Indian subcontinent population also.^{7,11,17}

Limitations of the study was the diagnosis of uveitis in the study was made based on a pre-defined set of criteria, which included both history and findings on clinical examination. Since this was a cross-sectional study of spondyloarthritis patients to screen for evidence of past or present uveitis, most of the patients in the study did not have active uveitis. While there was no ambiguity in diagnosis of active uveitis, diagnosis of inactive or past uveitis on the basis of history and findings on clinical examination is not so easy. Recall bias is a major pitfall while eliciting history regarding symptoms of past uveitis especially in those with mild uveitis who may have a negative recall bias. Moreover, even the most meticulous clinical examination may not aid in diagnosing mild cases of past anterior uveitis without significant sequelae in the eye.

Overall, the accuracy of our diagnosis of uveitis is likely to be high in view of our adoption of stringent criteria for the diagnosis of uveitis. However, this approach may be less sensitive for screening uveitis due to underestimation of the occurrence of uveitis as we may have missed out on mild cases with minimum sequelae. In contrast, earlier studies using less stringent criteria, may have overestimated the prevalence of uveitis in spondyloarthritis patients.

CONCLUSION

The proportion of patients with uveitis in our study (16.3%) was considerably less than in other studies. The characteristics and profile of uveitis in our cohort of SpA patients from the Indian subcontinent were similar to those previously reported in literature.

The mean duration of musculoskeletal symptoms prior to diagnosis of SpA was 4.36 years. More than half of the patients with uveitis had the onset of systemic symptoms before ocular symptoms. Uveitis was diagnosed at the time of onset of ocular symptoms in the majority of patients. Most cases of uveitis occurred between 6

months to 5 years of the onset of musculoskeletal symptoms.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. Chang JH, McCluskey PJ, Wakefield D. Acute anterior uveitis and HLA-B27. *Surv Ophthalmol.* 2005;50(4):364-88.
2. Pato E, Bañares A, Jover JA, Fernández-Gutiérrez B, Godoy F, Morado C, et al. Undiagnosed spondyloarthritis in patients presenting with anterior uveitis. *J Rheumatol.* 2000;27(9):2198-202.
3. Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis.* 2009;68 Suppl 2:ii1-44.
4. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol.* 2005;140(3):509-16.
5. Monnet D, Breban M, Hudry C, Dougados M, Brézin AP. Ophthalmic findings and frequency of extraocular manifestations in patients with HLA-B27 uveitis: a study of 175 cases. *Ophthalmol.* 2004;111(4):802-9.
6. Prakash S, Mehra NK, Bhargava S, Vaidya MC, Malaviya AN. Ankylosing spondylitis in North India: a clinical and immunogenetic study. *Ann Rheum Dis* 1984;43(3):381-5.
7. Feldtkeller E, Khan MA, van der Heijde D, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol Int.* 2003;23(2):61-6.
8. Aggarwal R, Malaviya AN. Clinical characteristics of patients with ankylosing spondylitis in India. *Clin Rheumatol.* 2009;28(10):1199-205.
9. Tay-Kearney ML, Schwam BL, Lowder C, Dunn JP, Meisler DM, Vitale S, et al. Clinical features and associated systemic diseases of HLA-B27 uveitis. *Am J Ophthalmol.* 1996;121(1):47-56.
10. Linssen A, Meenken C. Outcomes of HLA-B27-positive and HLA-B27-negative acute anterior uveitis. *Am J Ophthalmol.* 1995;120(3):351-61.
11. Zeboulon N, Dougados M, Gossec L. Prevalence and characteristics of uveitis in the spondyloarthropathies: a systematic literature review. *Ann Rheum Dis.* 2008;67(7):955-9.
12. Maza MS. Seronegative Spondyloarthropathies. In: Foster CS, Vitale AT. *Diagnosis and treatment of uveitis.* Philadelphia: W B Saunders; 2002:581-600.

13. Whitcup SM. Anterior Uveitis. In: Nussenblatt RB, Whitcup SM, editors. *Uveitis Fundamentals and Clinical Practice*. 4th ed. China: Elsevier; 2010:251-64.
14. Lyons JL, Rosenbaum JT. Uveitis associated with inflammatory bowel disease compared with uveitis associated with spondyloarthropathy. *Arch Ophthalmol.* 1997;115(1):61-4.
15. Rosenbaum JT. Characterization of uveitis associated with spondyloarthritis. *J Rheumatol.* 1989;16(6):792-6.
16. Rodriguez A, Akova YA, Pedroza-Seres M, Foster CS. Posterior segment ocular manifestations in patients with HLA-B27-associated uveitis. *Ophthalmol.* 1994;101(7):1267-74.
17. Khan MA, Kushner I, Braun WE. Association of HLA-A2 with uveitis in HLA-B27 positive patients with ankylosing spondylitis. *J Rheumatol.* 1981;8(2):295-8.

Cite this article as: Ninan F, Mathew J, Philip SS, John D, Danda D, John SS. Uveitis of spondyloarthritis in Indian subcontinent: a cross sectional study. *Int J Adv Med* 2017;4:1441-6.