pISSN: 2093-940X, eISSN: 2233-4718
Journal of Rheumatic Diseases Vol. 25, No. 1, January, 2018
https://doi.org/10.4078/jrd.2018.25.1.28

Original Article

Characteristics of Uveitis in Patients with Ankylosing Spondylitis in Korea: A Single-center Survey

Bon San Koo[1,*], Jung Wook Lim[2,*], Ji Hui Shin[3], Tae-Hwan Kim[3]

[1]Department of Internal Medicine, Inje University Seoul Paik Hospital, Inje University College of Medicine, Seoul, [2]Department of Internal Medicine, Korea University Ansan Hospital, Ansan, [3]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea

Objective. Uveitis is the most common extra-articular manifestation occurring in patients with ankylosing spondylitis (AS). This study examined the characteristics of uveitis in patients with AS using a questionnaire survey.

Methods. A questionnaire-based survey was given to patients enrolled in an AS registry at a rheumatology clinic in a tertiary hospital between September 2015 and December 2015. The patients responded to several questions and sub-questions related to uveitis.

Results. A total of 750 patients participated in the survey. The number of patients diagnosed with uveitis in the ophthalmology department was 218 (29%). The most common symptoms in patients with uveitis were ocular injection (61%), eye pain (54%), and decreased visual acuity (51%). Interestingly, 91 of the 532 patients (17%) who had not been diagnosed with uveitis before also experienced similar symptoms, such as tearing, ocular injection, and eye pain. The number of patients who experienced a flare of uveitis more than once a year was 109 (50%), and 124 patients with uveitis responded that the treatment of AS had no significant effect on the prevention of uveitis recurrence.

Conclusion. The clinical characteristics of uveitis that patients experience was investigated through surveys. Because uveitis in patients with AS is not well diagnosed and treated, active screening for suspected symptoms and the prevention of a recurrence is needed. **(J Rheum Dis 2018;25:28-33)**

Key Words. Uveitis, Ankylosing spondylitis, Surveys and questionnaires

INTRODUCTION

Uveitis is a common extra-articular manifestation in patients with ankylosing spondylitis (AS) [1]. It is characterized by intraocular inflammation of the iris, ciliary body, and/or choroid. Acute anterior uveitis is the most common form seen in patients with AS, and those who are affected generally present with redness and pain of the eye, photophobia, blepharospasm, miosis, and reduced vision.

The prevalence of uveitis in patients with AS is approximately 33%, and increases with disease duration and human leukocyte antigen-B27 positivity [1]. In an observational survey of spondyloarthritis patients in France, recurrence and complications of uveitis occurred in 52.3% and 11.7% of patients, respectively [2]. Although the pathological mechanisms are unknown, uveitis is known to be closely associated with AS. Nevertheless, diagnosis of both diseases may be delayed because rheumatologists and ophthalmologists tend to focus only on the diseases of their disciplines [3,4]. For this reason, eye diseases in some patients with diagnosed AS can progress further, and may result in serious and/or permanent complications.

Although tumor necrosis factor (TNF) inhibitors have been found to be an effective treatment for controlling ex-

Received : August 9, 2017, **Revised** : October 13, 2017, **Accepted** : October 16, 2017

Corresponding to : Tae-Hwan Kim, Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, 222 Wangsimni-ro, Seongdong-gu, Seoul 04763, Korea. E-mail : thkim@hanyang.ac.kr
*These authors contributed equally to this work.

tra-articular manifestations, including uveitis [5-7], many patients still experience the discomfort and complications associated with recurrent uveitis. Recurrences can vary in severity between patients and in the same patient, with the time between recurrences also differing greatly.

We conducted a survey to better understand the presentations of uveitis as experienced by the patients. The survey was also considered helpful for investigation of the pathogenesis and progression of extra-articular manifestations in AS. Thus, the aim of this study was to investigate the characteristics of patients with eye diseases including uveitis using a questionnaire for patients with AS.

MATERIALS AND METHODS

Patients and clinical data

Patients with AS were surveyed at a rheumatology clinic in a tertiary hospital between September 2015 and December 2015. All patients were previously diagnosed with AS according to the modified New York criteria [8]. The institutional review boards of all involved institutions approved this study (HYUH 2015-05-016). Informed consent was not obtained because this study was noninvasive and questionnaire-based.

Clinical data including patient age, sex, disease duration, history of hypertension and diabetes, and the use of disease modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and/or biologics were collected using electronic medical records. The number of patients using each biologic was determined, including all agents used prior to the investigation.

Questionnaire content

The questionnaire in Korean was presented to patients who visited the hospital for rheumatology outpatient treatment. The survey included 750 patients who were asked to fill out the questionnaire. The questionnaire consisted of items for uveitis with a few minor items prepared with the approval of an ophthalmologist. The primary content of the questionnaire was about the presence of uveitis that was diagnosed in the ophthalmology department and symptoms related to uveitis. Other questions included: "How often do the uveitis symptoms occur?", "Has uveitis occurred in both eyes at the same time?", "What treatment for uveitis did you receive at the time of diagnosis?", "Have there been any changes in the frequency of uveitis after treatment of AS?", "Were you diagnosed with uveitis before you were diagnosed with AS?", "Have you been advised to undergo tests for autoimmune diseases, including AS, for your uveitis?", "Do you know that frequent recurrent uveitis can be accompanied by complications such as cataract, glaucoma, and retinal vascular inflammation?". In addition, we asked if there were any other eye diseases in patients without uveitis.

Statistics

Patients who had been diagnosed with uveitis in the

Table 1. Clinical characteristics of patients with AS (total) and differences between patients with and without uveitis

Variable	Total (n = 750)	Uveitis (n = 218)	Non-uveitis (n = 532)	p-value
Men	645 (86)	190 (87)	455 (86)	0.559
Age (y)	38.67 ± 10.80	40.93 ± 9.87	37.73 ± 11.04	< 0.001
Disease duration of AS (y)	8.23 ± 7.40	10.44 ± 7.58	7.33 ± 7.13	< 0.001
Hypertension	104 (14)	42 (19)	62 (12)	0.008
Diabetes mellitus	29 (4)	12 (6)	17 (3)	0.144
DMARDs*	354 (47)	103 (47)	281 (53)	0.987
NSAIDs*	742 (99)	215 (99)	527 (99)	0.597
Steroids*	488 (65)	64 (29)	334 (62)	0.040
Biologics*	385 (51)	133 (61)	252 (47)	0.001
Etanercept	134 (35)	63 (47)	71 (28)	< 0.001
Adalimumab	132 (34)	36 (27)	96 (38)	0.030
Infliximab	69 (18)	33 (25)	36 (14)	0.010
Infliximab biosimilar	49 (13)	16 (12)	33 (13)	0.766
Golimumab	67 (17)	21 (16)	46 (18)	0.544

Values are presented as number (%) or mean ± standard deviation. AS: ankylosing spondylitis, DMARDs: disease modifying antirheumatic drugs, NSAIDs: nonsteroidal anti-inflammatory drugs. *Medication used for AS treatment.

ophthalmology department were classified as the uveitis group and patients without uveitis were classified as the non-uveitis group. Mann-Whitney and chi-square tests were used for comparisons between groups. P-values<0.05 were considered statistically significant. All statistical analyses were performed using SPSS Statistics 17.0.1 (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical characteristics of patients with AS

A total of 750 patients were included in this study. Table 1 summarizes baseline characteristics. Of the 750 patients, 645 (86%) were men, and the mean age was 38.7±10.8 years. The mean symptom duration was 8.2±7.4 years. A total of 104 (14%) patients had hypertension and 29 (4%) had diabetes. The number of patients who received a prescription for a DMARD, an NSAID, a steroid, or a biologic was 354 (47%), 742 (99%), 488 (65%), and 385 (51%), respectively.

Difference between patients with and without uveitis

Among the 750 patients with AS, 218 (29%) had been diagnosed with uveitis in the ophthalmology department. The clinical characteristics of the patients diagnosed with uveitis are described in Table 1. The patients in the uveitis group were predominantly older and had longer disease duration than those in the non-uveitis group. Hypertension was also more prevalent in the uveitis group. Steroids were used more in the non-uveitis group, and biologics were used more in the uveitis group. Among biologics, etanercept was used significantly more in the uveitis group, whereas adalimumab and infliximab were used significantly more in the non-uveitis group.

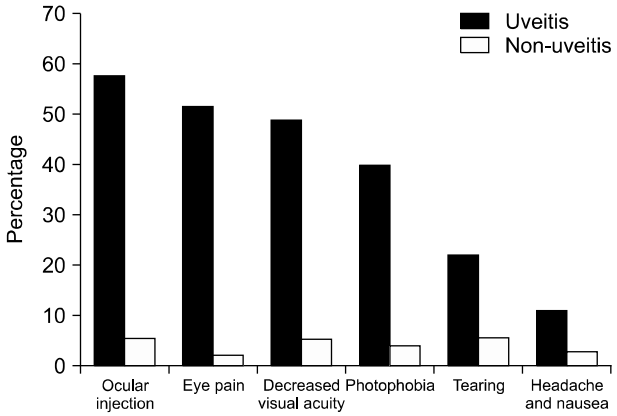

Figure 1. Eye symptoms among patients with and without uveitis.

Table 2. Questions about diagnosis and treatment asked among 218 patients with uveitis

Question	Yes	No	No answer
1. How often do the uveitis symptoms occur?	182 (83)	-	36 (17)
Once every two years or less	34 (16)	-	-
Once a year	54 (25)	-	-
Twice a year	33 (15)	-	-
More than twice a year	22 (10)	-	-
Right (%, mean frequency±standard deviation)	147 (67, 2.00±2.53)		-
Left (%, mean frequency±standard deviation)	147 (67, 1.95±2.44)		-
2. Has uveitis occurred in both eyes at the same time?	62 (28)	146 (67)	10 (5)
3. What treatment for uveitis did you receive at the time of diagnosis?	213 (98)	-	5 (2)
Eye drops	58 (27)	-	-
Steroids	3 (1)	-	-
Eye drops and steroids	144 (66)	-	-
Other medications	6 (3)	-	-
No treatment	2 (1)	-	-
4. Have there been any changes in the frequency of uveitis after treatment of AS?	65 (30)	124 (57)	29 (13)
5. Were you diagnosed with uveitis before you were diagnosed with AS?	69 (32)	132 (61)	17 (8)
6. Have you been advised to undergo tests for autoimmune diseases, including AS, for your uveitis?	53 (24)	145 (67)	20 (9)
7. Do you know that frequent recurrent uveitis can be accompanied by complications such as cataract, glaucoma, and retinal vascular inflammation?	115 (53)	103 (43)	-

Values are presented as number (%). AS: ankylosing spondylitis.

Symptoms of uveitis

Patients diagnosed with uveitis were asked about eye symptoms (Figure 1). The most common eye symptom was ocular injection (126 patients, 61%) followed by eye pain (113 patients, 54%), decreased visual acuity (107 patients, 51%), photophobia (87 patients, 42%), tearing (48 patients, 23%), and headache or nausea (24 patients, 12%). Among 532 patients without uveitis, 91 (17%) had more than one eye symptom: specifically, tearing (29 patients, 6%), ocular injection (28 patients, 5%), decreased visual acuity (27 patients, 5%), photophobia (21 patients, 4%), headache or nausea (14 patients, 3%), and eye pain (11 patients, 2%).

Patients diagnosed with uveitis were asked additional questions about development and recurrence of the condition (Table 2). The number of uveitis recurrences ranged from 1 to 12. Patients with flares of uveitis occurring more than once a year represented 50% of the total number. Fifty-four (25%), 33 (15%), and 22 (10%) patients had uveitis once a year, twice a year, and more than twice a year, respectively. The number of patients with recurrent uveitis once every 2 years or less was 34 (16%). The mean recurrence rate of uveitis was 2.00±2.53 in the right eye and 1.95±2.44 in the left. Interestingly, 62 of the patients (28%) had uveitis involving both eyes at the same time.

Most of the patients with uveitis answered that they were treated with both eye drops and steroids (144 patients, 66%). Other patients were treated with only eye drops (58 patients, 27%). Very few patients were treated with steroids alone (3 patients, 1%). Regarding the recurrence of uveitis, 146 of the patients (67%) answered that treatment for AS did not affect the incidence of uveitis.

Considering that 69 patients (32%) were diagnosed with uveitis before being diagnosed with AS, only 25 of the 69 (36%) were advised to have screening for uveitis-related diseases. During the presentation of uveitis symptoms, only 53 patients (24%) were advised to have tests or were tested for autoimmune or autoinflammatory diseases, including AS.

Of the 750 patients, 350 (47%) knew about the complications of uveitis. Among patients with uveitis, 115 of 218 (53%) answered that they knew about the complications of uveitis. These results indicate that the level of education for complications of uveitis is still deficient.

Table 3. Other eye diseases among 95 patients

Disease	Patient
Conjunctivitis	20 (21)
Dry eye	15 (16)
Iritis	12 (13)
Glaucoma	7 (7)
Floater	6 (6)
Retinopathy	5 (5)
Acute hemorrhagic conjunctivitis	4 (4)
Cataract	3 (3)
Keratitis	3 (3)
Nasolacrimal obstruction	1 (1)
Tonic pupil	1 (1)
Other diseases	18 (19)

Values are presented as number (%).

Eye diseases other than uveitis in patients with AS

Of the 750 patients with AS, 95 (13%) answered that they had an eye disease other than uveitis. We further asked those who answered that they had a disease to describe the exact name of the disease (Table 3). Conjunctivitis (21%) was the most common, followed by dry eye (16%), iritis (13%), glaucoma (7%), floater (6%), retinopathy (5%), viral conjunctivitis (4%), cataract (3%), keratitis (3%), nasolacrimal duct obstruction (1%), and tonic pupil (1%).

DISCUSSION

The most common ophthalmic manifestation is acute anterior uveitis, which occurs in 40% of patients with AS [9,10]. Men are more commonly affected, and the condition occurs typically in young adults between the ages of 20 and 40 years. Among our patients with AS, 41% answered that they had an eye disease. Uveitis, which occurred in 29% of patients, accounted for the majority of the ocular diseases observed in our study. In addition, there were various other diseases, which were not definitively identified regarding their association with AS.

We observed that age, hypertension, and use of biologics were more prevalent in the uveitis group than in the non-uveitis group. Older patients had a higher prevalence of hypertension, and associations between uveitis and hypertension in AS have been reported [11]. Considering that there was not much difference in age between the uveitis and non-uveitis groups, it seems that there is an association between uveitis and hypertension. In addition, since etanercept was used significantly more in the uveitis group, it was possible that etanercept also affected

the recurrence of uveitis [12-14].

Uveitis includes symptoms such as red, painful, and photophobic eyes and blurred vision. The symptoms in our patients with uveitis varied. Furthermore, in our study, 91 (17%) non-uveitis patients also complained of eye symptoms similar to those of uveitis patients, such as ocular injection and decreased visual acuity, although 19 patients with an eye disease other than uveitis were included. Our results indicate that there might be some patients with eye diseases including uveitis.

Interestingly, 50% of the patients reported recurrence of uveitis more than once a year. Moreover, 57% of the patients answered that there was no change in recurrence of uveitis, even after treatment of AS. Although approximately 50% patients with AS had used DMARDs or biologics, it seems that drugs targeting AS did not effectively decrease the recurrence of uveitis from the patient perspective. However, several studies have reported that TNF inhibitors reduce the frequency of uveitis [7,12-14]. In the future, new drugs for uveitis, satisfactory to both the physician and patient and more effective than drugs currently used, need to be developed.

Although uveitis including panuveitis or posterior uveitis is more likely to cause loss of vision, uveitis in patients with AS rarely leads to blindness. Verhagen et al. [15] reported that only 9% of patients became permanently visually impaired or blind in at least one eye because of uveitis. Although TNF inhibitors are effective in reducing the frequency of uveitis in patients with AS, their potential side effects and the cost of treatment should be considered when prescribing these drugs [15]. In addition, because treatment for AS is still insufficient to affect the recurrence rate and complications of uveitis, new treatment methods targeting uveitis are needed.

Our study had several limitations. First, the use of a questionnaire that depends on the patient's ability to recall information may be less reliable than other methods. However, the questionnaire was valuable in terms of understanding the patient's perception of AS-related eye disease. Second, data on the efficacy of drugs for uveitis were not available because of the limitations of the survey. Third, there may be some differences between our study and previous studies [2,5,7,14], because the medical system in Korea (including the medical insurance and medical delivery system) is different from that of other countries. In our study, eye symptoms and eye diseases might be overestimated because the patient has easy access to the hospital.

CONCLUSION

Various eye symptoms, treatment responses, and management of uveitis were investigated using a questionnaire in patients with AS. Based on these data, it is necessary to identify patients who remain undiagnosed and to be more active in managing eye diseases including uveitis.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Zeboulon N, Dougados M, Gossec L. Prevalence and characteristics of uveitis in the spondyloarthropathies: a systematic literature review. Ann Rheum Dis 2008;67:955-9.
2. Canouï-Poitrine F, Lekpa FK, Farrenq V, Boissinot V, Hacquard-Bouder C, Comet D, et al. Prevalence and factors associated with uveitis in spondylarthritis patients in France: results from an observational survey. Arthritis Care Res (Hoboken) 2012;64:919-24.
3. Feltkamp TE, Ringrose JH. Acute anterior uveitis and spondyloarthropathies. Curr Opin Rheumatol 1998;10: 314-8.
4. Haroon M, O'Rourke M, Ramasamy P, Murphy CC, FitzGerald O. A novel evidence-based detection of undiagnosed spondyloarthritis in patients presenting with acute anterior uveitis: the DUET (Dublin Uveitis Evaluation Tool). Ann Rheum Dis 2015;74:1990-5.
5. Braun J, Baraliakos X, Listing J, Sieper J. Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. Arthritis Rheum 2005;52:2447-51.
6. Coates LC, McGonagle DG, Bennett AN, Emery P, Marzo-Ortega H. Uveitis and tumour necrosis factor blockade in ankylosing spondylitis. Ann Rheum Dis 2008;67: 729-30.
7. Guignard S, Gossec L, Salliot C, Ruyssen-Witrand A, Luc M, Duclos M, et al. Efficacy of tumour necrosis factor blockers in reducing uveitis flares in patients with spondylarthropathy: a retrospective study. Ann Rheum Dis 2006;65: 1631-4.
8. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.
9. 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. Ophthalmology 2004;111:802-9.
10. Pathanapitoon K, Dodds EM, Cunningham ET Jr, Rothova A. Clinical spectrum of HLA-B27-associated ocular inflammation. Ocul Immunol Inflamm 2017;25:569-76.
11. Berg IJ, Semb AG, van der Heijde D, Kvien TK, Hisdal J,

Olsen IC, et al. Uveitis is associated with hypertension and atherosclerosis in patients with ankylosing spondylitis: a cross-sectional study. Semin Arthritis Rheum 2014;44: 309-13.
12. Gaujoux-Viala C, Giampietro C, Gaujoux T, Ea HK, Prati C, Orcel P, et al. Scleritis: a paradoxical effect of etanercept? Etanercept-associated inflammatory eye disease. J Rheumatol 2012;39:233-9.
13. Kakkassery V, Mergler S, Pleyer U. Anti-TNF-alpha treatment: a possible promoter in endogenous uveitis? observational report on six patients: occurrence of uveitis following etanercept treatment. Curr Eye Res 2010;35:751-6.
14. Lim LL, Fraunfelder FW, Rosenbaum JT. Do tumor necrosis factor inhibitors cause uveitis? A registry-based study. Arthritis Rheum 2007;56:3248-52.
15. Verhagen FH, Brouwer AH, Kuiper JJ, Ossewaarde-van Norel J, Ten Dam-van Loon NH, de Boer JH. Potential predictors of poor visual outcome in human leukocyte antigen-B27-associated uveitis. Am J Ophthalmol 2016;165: 179-87.