Observational Study

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Risk factors of uveitis in ankylosing spondylitis

An observational study

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Abstract

Background: Uveitis is the most common extra-articular manifestation in patients with ankylosing spondylitis (AS). The prevalence and characteristics of uveitis in AS have been studied in previous literatures, whereas its associated risk factors have not been clarified. Therefore, this study analyzed the risk factors of uveitis in patients with AS.

Methods: A total of 390 patients with AS who fulfilled the modified New York criteria were enrolled from January to December in 2015. The history of uveitis was accepted only if diagnosed by ophthalmologists. The medical records of the patients were retrospectively reviewed and associated information was collected, such as disease duration, HLA-B27, and the number of peripheral arthritis. Hip-joint lesion was identified by imaging examination. Meanwhile, biochemical examinations were performed to determine the patient's physical function.

Results: Of 390 patients with AS (80.5% male, mean age 33.3 years), 38 (9.7%) had experienced 1 or more episodes of uveitis. The incidence rate for hip-joint lesion was obviously higher for patients with uveitis than the nonuveitis group (44.7% vs 22.2%; $P < 0.01$). The number of peripheral arthritis was also larger for the uveitis group than nonuveitis group (2.18 ± 0.23 vs 0.55 ± 0.04; $P < 0.001$). Meanwhile, patients with uveitis had a significantly higher level of antistreptolysin O (ASO) and circulating immune complex (CIC) than those without ($P < 0.05$ and $P < 0.0001$, respectively). However, there were no significant differences in disease duration, HLA-B27, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) between the 2 groups. Binary logistic regression results showed that ASO (OR = 12.2, 95% CI:3.6–41.3, $P < 0.01$) and the number of peripheral arthritis (OR = 4.1, 95%CI:2.6–6.3, $P < 0.01$) are significantly associated with uveitis in AS.

Conclusion: This study provides some evidence that hip-joint lesion, the number of peripheral arthritis, ASO, and CIC may be associated with higher rates of uveitis in AS. The results of this comprehensive analysis suggest that the possible occurrence of uveitis in AS should not be neglected if the patients have those concomitant risk factors.

Abbreviations: AAU = acute anterior uveitis, ALT = alaninetransaminase, AS = ankylosing spondylitis, ASO = antistreptolysin O, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CI = confidence interval, CIC = circulating immune complex, CRP = C reactive protein, ESR = erythrocyte sedimentation rate, HLA-B27 = human leukocyte antigen B27, OR = odds ratio, PLT = platelet, Scr = serum creatine, SpA = spondyloarthritis, UA = urinary acid.

Keywords: ankylosing spondylitis, antistreptolysin O, circulating immune complex, hip, peripheral arthritis, risk factors, uveitis

1. Introduction

Ankylosing spondylitis (AS) is the most common inflammatory disorder that usually affects the sacroiliac joints and axial skeleton, bringing about back pain and progressive stiffness of the spine. AS occurs in 0.1% to 1.4% of the general population, and it often affects young adults with the peak age of onset between 20 and 30 years.[1] The current understanding of the pathogenesis of AS is limited in spite of the important role of human leukocyte antigen B27 (HLA-B27) having been reported over the past 30 years.

Extra-articular manifestations of AS are not rare, such as uveitis, bowel disease as well as lung, heart, skin, bone and kidney involved. Uveitis may be the most common extra-articular manifestation, occurring in 20% to 30% of the patients with AS. It is reported that about 90% of the cases involve anterior uveitis, whereas posterior uveitis occurs rarely.[2] The strong association between AS and uveitis has raised great concern among researchers and doctors.

Despite the high occurrence of uveitis in AS, knowledge on the risks factors for developing uveitis in patients with AS is limited. It is unknown that which clinical characteristics or biochemical markers can predict the possible occurrence of uveitis in AS. Thus, we may fail to early diagnose this disease if patients' ocular

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Table 1

Clinical information of patients with AS.

	Nonuveitis group (n = 352)	Uveitis group (n = 38)	*P*
Gender, male/female	283/69	31/7	>0.05
Age, y	33.3 ± 0.7	33.8 ± 0.7	>0.05
Disease duration, mo	53.1 ± 2.1	64.1 ± 9.3	>0.05
HLA-B27, positive/negative	338/14	32/6	>0.05
Hip involvement, %	22.2% (78/352)	44.7% (17/38)	<0.01*
The number of peripheral arthritis	0.55 ± 0.04	2.18 ± 0.23	<0.001*

AS = ankylosing spondylitis, HLA-B27 = human leukocyte antigen B27.

symptoms are not obvious or typical. Some doctors even misdiagnose this disease as acute hemorrhagic conjunctivitis according to painful red eye concomitant with photophobia, increased tear production, and blurred vision in patients with AS. Herein, in order to enhance the awareness of this disease and avoid missed diagnosis, we try to analyze the risk factors for uveitis in patients with AS.

2. Subjects and methods

Investigatory targets were the AS patients from Jiangsu Provincial Hospital of Integrated Traditional and Western Medicine, the First Affiliated Hospital of Soochow University and Shanghai Jiao Tong University Affiliated Sixth People's Hospital over the entire period of 2015. All patients fulfilled the 1984 modified New York criteria.[3] The diagnosis of uveitis is performed by ophthalmologists. There are no definite diagnostic criteria for uveitis, so ocular symptoms, fundus examination, and associated laboratory testing were taken into consideration to make an actual diagnosis.[4] Meanwhile, we have ruled out the patients with infectious uveitis or other systemic autoimmune rheumatic diseases (SARDs), such as psoriatic disease, inflammatory bowel disease, Reiter's syndrome, and so on. The AS patients with uveitis were enrolled in the uveitis group, whereas the remaining were included in the nonuveitis group as control.

The medical records of the patients were retrospectively reviewed and the associated information such as gender, age, disease duration, human leukocyte antigen B27 (HLA-B27) positive or negative, and the number of peripheral arthritis were collected. Hip-joint lesion was identified by imaging examination, especially the magnetic resonance imaging (MRI). Meanwhile, biochemical examinations were performed to determine the patient's physical function, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelet (PLT), IgG, IgA, IgM, antistreptolysin O (ASO), circulating immune complex (CIC), aspartate aminotransferase (AST), alaninetransaminase (ALT), albumin, blood urea nitrogen(BUN), serum creatine (Scr), urinary red blood cell (RBC), and protein.

Our study has been approved by the ethics committee of Jiangsu Provincial Hospital of Integrated Traditional and Western Medicine.

2.1. Statistical analysis

SPSS (Ver 22.0, Chicago, IL) was used to perform statistical analysis. All the data were expressed as the mean ± standard error. The difference of measurement data comparison was performed by Student's *t* test. Chi-Square Goodness-of-Fit test was used for the ratio comparison. Logistic regression analysis was used to estimate odds ratio (OR) of associated risk factors for uveitis in AS. A P value < 0.05 was considered significant.

Table 2

Biochemical characteristics in AS patients with uveitis.

	Nonuveitis group (n = 352)	Uveitis group (n = 38)	*P*
ESR, mm/h	42.0 ± 1.7	41.6 ± 5.9	>0.05
CRP, mg/L	19.8 ± 1.3	19.5 ± 2.1	>0.05
PLT, 10^9/L	252.8 ± 4.5	249.0 ± 12.4	>0.05
ALT, U/L	25.7 ± 0.8	23.4 ± 2.3	>0.05
AST, U/L	19.8 ± 0.5	24.6 ± 1.7	>0.05
Albumin, g/L	44.3 ± 0.2	45.4 ± 0.6	>0.05
BUN, mmol/L	4.8 ± 0.1	4.5 ± 0.2	>0.05
Scr, μmol/L	66.2 ± 0.8	70.0 ± 1.8	>0.05
UA, μmol/L	317.8 ± 4.2	350.6 ± 16.7	<0.05
IgG, g/L	13.9 ± 0.2	14.7 ± 0.4	>0.05
IgA, g/L	3.0 ± 0.1	2.9 ± 0.1	>0.05
IgM, g/L	1.30 ± 0.03	1.24 ± 0.06	>0.05
ASO, IU/mL	200.0 ± 13.3	308.7 ± 43.5	<0.05
CIC, mg/L	18.5 ± 0.7	27.9 ± 1.9	<0.0001
Urinary RBC	9.6 ± 0.8	10.5 ± 1.1	>0.05
Urinary protein, mg/d	74.9 ± 5.9	62.8 ± 7.6	>0.05

ALT = alaninetransaminase, AS = ankylosing spondylitis, ASO = antistreptolysin O, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CIC = circulating immune complex, CRP = C reactive protein, ESR = erythrocyte sedimentation rate, PLT = platelet, RBC = red blood cell, Scr = serum creatine, UA = urinary acid.

3. Results

We examined 390 cases of ankylosing spondylitis between the age of 12 and 60. In total 38 (9.7%) patients experiencing 1 or more episodes of uveitis were enrolled in the uveitis group with the average age of 33.8 years and a gender ratio (male/female) of 31:7 (Table 1). In the group of patients without uveitis (nonuveitis group), there were 352 individuals with the average age of 33.3 years and a gender ratio (male/female) of 283:69. Of these 38 cases in the uveitis group, 44.7% (17/38) had hip-joint lesion involvement, whereas 22.2% (78/352) of the nonuveitis group suffered from hip-joint lesion. The incidence of hip-joint lesion involvement was significantly higher in patients with uveitis in AS ($P < 0.01$). Moreover, the number of peripheral arthritis was also larger in the uveitis group than the nonuveitis group (2.18 ± 0.23 vs 0.55 ± 0.04; $P < 0.001$). However, there were no significant differences in gender, age, disease duration, and HLA-B27 between the 2 groups.

According to the results of biochemical examination (Table 2), the serum level of ASO was significantly higher in the uveitis group than the nonuveitis group (308,7 ± 43.5 IU/mL vs 200.0 ± 13.3 IU/mL, $P < 0.05$). Meanwhile, patients with uveitis in AS seemed to have higher level of CIC than the ones without uveitis (27.9 ± 1.9 mg/L vs 18.5 ± 0.7 mg/L; $P < 0.0001$). We found that the level of serum uric acid was 350.6 ± 16.7 μmol/L in the uveitis group, which was higher than that in the nonuveitis group. However, there were no significant difference in inflammatory indices (ESR, CRP, PLT), liver function indexes (albumin, AST, ALT), renal function indexes (BUN, Scr), other immunological indexes (IgA, IgG, IgM), and urine detection (urinary RBC and protein) between the 2 groups.

Binary logistic regression results showed that ASO (OR = 12.2, 95%CI:3.6–41.3, $P < 0.01$) and the number of peripheral arthritis (OR = 4.1, 95%CI:2.6–6.3, $P < 0.01$) are significantly associated with uveitis in AS (Table 3).

Table 3

Binary logistic regression analysis for the related factors for uveitis in AS.

Risk factors	*b*	*P*	OR	95%CI
ASO	2.5	<0.01	12.2	3.6–41.3
the number of peripheral arthritis	1.4	<0.01	4.1	2.6–6.3

AS = ankylosing spondylitis, ASO = antistreptolysin O, CI = confidence interval, OR = odds ratio.

4. Discussion

The present study shows that uveitis in ankylosing spondylitis is highly correlative of ASO, CIC, hip-joint lesion involvement, and the number of peripheral arthritis. However, no association between uveitis and HLA-B27 is observed.

Uveitis is defined by the inflammation of the uvea, which includes the iris, ciliary body, and choroid. Clinically, it is characterized by painful red eye, intense photophobia, increased tear production, myosis, blepharospasm, and blurred vision.[5] Uveitis associated with AS is one of the autoimmune disorders, characterized by a deviant response to the immune system, that is to say, these conditions fail to distinguish self-organs, tissues, and cells of the individual from non-self-molecules, eventually leading to the impairment of target organs due to a cross-reaction between self-proteins and bacterial peptides. Some reports proposed the theory that although immune privilege prevents large molecules and cells into and out of the normal eyes, this separation from the immune system also impedes efficient induction of peripheral tolerance to eye-specific antigens, allowing persistence in the circulation of nontolerized eye-reactive T cells, which can attack ocular cells and induce inflammation due to the breakdown of immune privilege as well as the exposure of ocular antigens such as arrestin.[6–7] This theory may roughly explain the pathogenesis of autouveitis, including uveitis in patients with AS.

In this study, we find that the level of antistreptolysin O (ASO) was significantly higher for AS patients with uveitis than those without, suggesting the infection of hemolytic streptococcus is associated with uveitis in AS. However, it is unclear whether streptococcal infection is one of the primary causes of uveitis in AS by directly or indirectly triggering ocular inflammation or the individual who is sensitive to streptococcal infection may also be predisposed to uveitis, or one uncertain factor contributes to the occurrence of uveitis together with streptococcal infection. Arise in ASO indicates the recent infection of hemolytic streptococcus or the development of streptococcal diseases. The ASO titer can be elevated within 1 week of streptococcal infection and it will reach a maximum after 3 to 6 weeks, and then return to the normal level after 6 to 12 months without reinfection.[8] Ur et al[9] reported that molecular mimicry between streptococcal M proteins and host tissue proteins, such as retinal S antigen, may stimulate brisk proliferation and activation of lymphocytes which are capable of recognizing retinal antigens. And this pathogenesis may lie at the heart of post streptococcal inflammation. In addition, many studies have focused on the association of HLA molecules with susceptibility to the development of uveitis in AS, including HLA-B27, HLA-A*02:01, HLA-DR8, HLA-DRB1*08, low-molecular-weight polypeptide (LMP2), and so on.[10–13] Interestingly, some HLA molecules are also closely associated with streptococcal infection or rheumatic heart disease (RHD) or acute rheumatic fever (ARF), such as HLA-DR4, HLA-DR7, HLA-DR5, HLA-DR6, HLA-DQ, HLA-DRB1, and so on.[14–17] Therefore, if the genetic association of uveitis in AS overlaps with the genetic susceptibility to streptococcal diseases, or individuals just have some genes associated with the 2 diseases, uveitis, and streptococcal infection with high ASO titers can simultaneously occur in patients with AS. Nevertheless, from this retrospective study, it is still difficult to draw any firm conclusions about the actual role of streptococcal infection in the pathogenesis of uveitis for patients with AS. And we cannot rule out the possibility that the infection of hemolytic streptococcus is only a coincidental event in these patients.[18]

As is well known, immune complexes (IC), produced through antigen–antibody interactions, is a physiological process, by which micro-organisms and nonself molecules can be neutralized or cleared. Under normal circumstances, IC formation can enhance complement mechanisms and mononuclear phagocyte system (MPS) to make circulating IC itself be safely eliminated. However, pathogenic IC, that fail to be cleared properly, may be induced by some factors, including the nature and quantity of the antigen, the antibody response, and the state of the systems involved in IC clearance.[19] These CIC can interact with specific sites of the body and induce local injury at their sites of deposition. In our study, AS patients with uveitis have higher level of CIC compared to the patients without, suggesting CIC is closely associated with uveitis. One recognized explanation of this phenomenon is that immune complexes participate in the pathogenesis of several types of uveitis.[20] It is reported that immune complex damage especially inclines to occur in areas with specialized vasculature, such as ciliary body, renal glomeruli, and choroid plexus. And the anatomical vasculature of these areas is similar.[21] The increase of the uveal vascular permeability and the breakdown of the immune privilege may occur following high level of CIC, which combines with basophilic leucocytes concomitant with some vasoactive amines released, such as serotonin, histamine, and platelet activating factor (PAF). Therefore, these CIC obtain access to ocular areas and in turn activate the complement system, leading to chemotaxis of leucocytes, degranulation of tissue mast cells, and amplification of inflammation.[20] The accumulation of complement components (iC3b, C1q, C3, and C4) in various parts of the eye indicates a local over-activation of the complement system.[22] However, why AS patients with uveitis had higher level of CIC still remains unknown. Unfortunately, almost all of the studies have focused on the role of immune complexes in the pathogenesis of uveitis. Very few laboratories have investigated why CIC increase in patients with uveitis or other ocular diseases. Is it due to imbalance of antigen–antibody ratio, or dysfunction of the systems involved in IC clearance? One crucial question needs to be answered. Are immune complexes the exact cause in the development of uveitis, or they are just secondary to uveitis in AS or other rheumatic disorders? Present data suggest that further studies of CIC in AS patients with uveitis are warranted.

In addition, our data show the strong correlation between uvetis in AS and the number of peripheral arthritis, suggesting that patients with severe peripheral joint involvement seem to

predispose to develop uveitis. Yilmaz et al[23] reported patients with peripheral involvement had higher disease activity, functional impairment, metrologic indices, more severe pain, night pain, and morning stiffness. And this finding was also supported by other studies.[24–26] This implicates that peripheral arthritis may be a predictor of more aggressive process in AS. Our finding is more or less similar to the evidence provided by Maksymowych et al.[27] In their study, 40.4% white individuals with AS-associated acute anterior uveitis (AAU) had peripheral arthritis, compared with only 24.8% having peripheral arthritis among the AS patients without AAU. Maksymowych et al proposed their opinion that AS patients who have developed peripheral arthritis are also susceptible to develop AAU, in spite of the possible mechanism having not been clarified. And their proposition was intensely supported by Singh et al[28] who reported that AS patients with peripheral arthritis had significantly higher prevalence of uveitis when compared with patients without peripheral arthritis. Among the peripheral joints, involvement of hips (65.79%) was the most common. Knee (31.58%), shoulder (18.42%), and ankle involvement (13.16%) followed it, respectively.[23] In our study, the prevalence of hip-joint lesion is 44.7% in the uveitis group, compared with 22.2% in the nonuveitis group. However, another study in a Chinese population reported that the prevalence of hip involvement in AS patients with AAU is just 4.4%,[29] which is obviously lower than that of hip lesion in our study. Sampaio-Barros et al[30] also reported that anterior uveitis (AU) in patients with spondyloarthritis (SpA) was statistically associated with hip involvement. Hip disease occurs in about one-third of patients with AS, leading to disability or hip replacement without effect control.[31] It has been indicated that hip arthritis seems to be associated with more severe spinal involvement, increasing the burden of AS and negatively affecting its prognosis.[31] And hip disease can be a major prognostic marker for long-term severe disease.[32] Therefore, based on our finding, 1 opinion can be proposed that AS patients concomitant with peripheral involvement or hip lesion, indicating more severe condition of patients, seem to be sensitive to develop uveitis.

Strong correlation between HLA-b27 and AAU has been widely reported and this term of HLA-B27-related uveitis has been used over a long period.[33–35] However, no difference of HLA-B27 between the uveitis group and the nonuveitis group is observed in our study. It is reported that about 30% to 50% of the cases of AAU are associated with the presence of the HLA-B27 antigen and that HLA-B27-positive individuals had a 3.8-fold greater chance of developing uveitis than the HLA-B27-negative ones.[2] Meanwhile, our data show that there is no difference between uveitis in AS and age as well as disease duration. Our results are also consistent with Chen et al[36] who reported that there was no difference of disease duration between AS patients with and without AAU. On the contrary, Essers et al[37] reported that the history of AAU in ankylosing spondylitis was invariably associated with increased age and longer symptom duration. Another evidence provided by Stolwijk et al[38] is that uveitis in patients with AS was positively associated in multivariable meta regression with disease duration. The 2 reports indicate that AS patients with greater age and longer disease duration are susceptible to develop AAU. But this association cannot be supported by our finding.

There are some limitations of our study. First, the number of enrolled AS patients is relative small, especially of the uveitis group, which may reduce the power and strength of our conclusion. Second, hitherto, there are no definite diagnostic criteria for uveitis and uveitis is diagnosed by different ophthalmologists from 3 hospitals in our study instead of only 1 specialized ophthalmologist. Third, some methods to access functional limitations and disease activity have not been used in our study, such as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Quality of Life (ASQoL). By these assessment scales, the difference of disease severity and activity between the uveitis group and the nonuveitis group can be observed, and even we can further evaluate the association between the number of peripheral involvement and the degree of disease severity.

5. Conclusions

Our study shows that hip-joint lesion involvement, the number of peripheral arthritis, ASO, and CIC may be associated with higher rates of uveitis in AS. If patients have atypical ocular symptoms concomitant with such risk factors, the possible occurrence of uveitis in AS should not be neglected. And it would be worthwhile to perform further ocular examination to diagnose definitely. Meanwhile, other factors that possibly lead to or predispose to develop uveitis should be further investigated.

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