Original Article

Pattern of Symptoms, Aetiologies, and Associated Risk Factors of Unilateral Acute Non-granulomatous Anterior Uveitis Cases Presenting in a Tertiary Eye Institute of Nepal

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ABSTRACT

Introduction: Unilateral cases of acute non-granulomatous anterior uveitis (ANGAU) make major portion in anterior uveitis group. It is characterised by recurrent episodes of sudden onset of redness, pain, and photophobia in one eye. It comprises of acute anterior uveitis mainly due to seronegative spondyloarthopathies and some idiopathic.

Objective: To know the pattern of symptoms of ANGAU in detail, to analyse if smoking and stress could be its risk factors, to confirm its association with human leukocyte antigen (HLA)-B27 gene, and to find out the effect of season in its relapse in Nepali patients.

Methodology: In this hospital-based observational study done from 2017 November to 2019 February at Tilganga Institute of Ophthalmology, all cases (census) of ANGAU were included after ethical approval.

Result: Of the total 70 patients, 38 (54.3%) were male and 32 (45.7%) were female. Majority of patients were between ages of 31-40 years (32.9%) with range (mean±SD) of 18-74 (40.16±13.96) years. Redness (91.4%), pain (64.3%), photophobia (64.3%), decreased vision (61.4%), and watering (20%) were major symptoms. Most presented during summer (45.7%). Majority were either smoker at present (40%) or were smokers in the past (24.3%). There was a positive history of stress factor in 24.3% patients. Of 50/70 cases who underwent HLA-B27 testing, 30 (60%) were positive. Sixteen out of 70 patients (22.8%) had features suggestive of SpA. Twelve out of 16 SpA cases (17.1%) had a positive HLA-B27 report. But, four patients (5.7%) denied an HLA-B27 testing.

Conclusion: Unilateral NGAU in Nepali population is strongly associated with present or past smoking, not strongly associated with stress factor, relapses mostly in summer season, and shows HLA-B27 gene positivity in slightly >50% population. Other than pain, redness, photophobia, and decreased vision, watering can also be one of the presenting symptoms of NGAU cases.

Key words: Ankylosing spondylitis; anterior uveitis; human leukocyte antigen-B27; Nepal; seronegative spondyloarthropathy.

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INTRODUCTION

Anterior uveitis (AU) makes around 50% or slightly more of the whole uveitis cases worldwide. Unilateral cases of acute non-granulomatous anterior uveitis (ANGAU) make a major portion in this AU group. It is characterised by recurrent episodes of sudden onset of redness, pain, and photophobia in one eye. It comprises of acute anterior uveitis (AAU) mainly due to seronegative spondyloarthopathies (SpA) and some idiopathic. The SpA includes following rheumatological diseases: Ankylosing spondylitis (AS), Reactive arthritis (ReA), Psoriatic arthritis (PsA), and Inflammatory bowel disease (IBD). The SpA as well as unilateral ANGAU cases are strongly associated with human leucocyte antigen (HLA)-B27. Although association of HLA-B27 with SpA in Nepali have been reported (Vaidya et al., 2013; Sah et al., 2020), to authors' knowledge, its association with uveitis has not been reported in indexed journal. The objectives of conducting this study were to know the pattern of symptoms of ANGAU in detail, to analyse if smoking and stress could be its risk factors, to confirm its association with HLA-B27 gene, and to find out the effect of season in its relapses in Nepali patients.

METHODOLOGY

This was a hospital-based observational study done from 2017 November to 2019 February at the Tilganga Institute of Ophthalmology (TIO), Gaushala, Kathmandu, Nepal. All cases (census method) of unilateral ANGAU were included in this study. Those with a history of penetrating eye injury to the same or fellow eye, new-onset uveitis within one year following intraocular surgery, blunt trauma to the same eye, and vitreous opacity > grade 1 according to Standardisation of Uveitis Nomenclature (SUN) classification were excluded (Jabs et al., 2005).

The AU was defined as the inflammation of iris with or without inflammation of parsplicata. Acute episode was defined as an inflammation having a sudden onset and a limited duration (≤3 months) as per SUN working group. Non-granulomatous inflammation was defined as the presence of fine and small keratic precipitates.

The diagnosis of unilateral ANGAU was made based on a detailed ocular and medical history and a thorough clinical examination. Visual acuity (VA) was taken by the standard Snellen's visual acuity chart at a distance of six metres. A detailed ocular examination was done under slit lamp. Posterior segment was evaluated after mydriasis under slit lamp using Volk 90D lens, or indirect ophthalmoscope as and when required. Intraocular pressure (IOP) was taken with Goldmann Applanation Tonometer.

History of smoking was taken. Ex-smoker was defined as those who were not smoking during enrolment in the study. A set questionnaire (on absence or presence of stress due death of a close family member, stress from ill-health of self or a close family member, stress from office work, study related stress, travel stress) was also filled up for each case to find out if stress triggered the disease.

A detailed medical history and physical examination in search of aetiological factors was done. Focus was guided towards seronegative spondyloarthropathies (HLA-B27 related diseases) which included evaluation

for musculoskeletal, dermatological, and gastrointestinal pathologies. All patients were routinely asked to perform HLA-B27 testing if they can afford and clinically suspected cases with seronegative spondyloarthopathies were referred for a consultation with a rheumatologist.

An aetiological diagnosis was made as follows: Cases were called seronegative spondyloarthropathy (SpA) either on clinical ground or based on the diagnosis of a rheumatologist. Cases who tested positive for HLA-B27, but who did not have SpA were called HLA-B27 associated. Cases who tested negative for HLA-B27 and did not have SpA were called idiopathic. Cases who did not have SpA, but who did not undergo HLA-B27 testing, were called indeterminate.

Since this was not a funded research, and since health insurance did not cover treatment cost, HLA-B27 polymerase chain reaction (PCR) test was ordered for only those cases who could afford it.

The collected data were stored in an electronic database (Microsoft Excel Sheet). Statistical analyses were performed with statistical software (IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, N.Y., USA)) to give descriptive values.

Ethical clearance was taken from the institutional review board (IRB) of the National Academy of Medical Sciences. Informed written consent was taken from all the participants. This study was done as per the Declaration of Helsinki.

RESULT

The total number of patients included in the study was 70, of whom 38 (54.3%) were male and 32 (45.7%) were female. The majority of the patients were between the ages of 31-40 years (32.9%) with a range (mean±SD) of 18-74 years (40.16±13.96 years). Redness (91.4%), pain (64.3%), difficulty in bright lights (64.3%), decreased vision (61.4%), and watering (20%) were the major symptoms. Majority of the patients (30%) presented on the third day of the onset of symptoms. By the fourth day of the onset of symptoms, 75.7% cases sought treatment. Most of the cases presented during summer (45.7%) between June and August. The majority of them were either smoker at present (40%) or were smokers in the past (24.3%). There was a positive history of stress factor in 17 (24.3%) patients (Tables 1, 2, 3).

Of 70 patients, only 50 underwent HLA-B27 testing, and 30 patients (60%) showed a positive result. On systemic evaluation (n=70), 16 patients (22.8%) had features suggestive of SpA. Of these, 14 had ankylosing spondylitis and 2 had Reactive arthritis. Twelve out of 16 SpA cases (17.1%) had a positive HLA-B27 report. But, four (5.7%) patients denied an HLA-B27 testing. HLA-B27 associated cases (with positive HLA-B27 status but without SpA) were 18 (25.7%). Idiopathic cases (with negative HLA-B27 status and absence of SpA) were 20 (28.5%). On the remaining 16 cases (22.8%) without SpA, who did not undergo HLA-B27 testing aetiology could not be determined (Table 4).

Table 1: Demographics of unilateral cases of acute non-granulomatous anterior uveitis (N = 70).

Age	**Range (years)**	**Mean±SD**
	18-74	**40.16±13.96**
Age range	**Frequency (Percentage)**	
≤20	4 (5.7)	
21-30	16 (22.9)	
31-40	23 (32.9)	
41-50	9 (12.9)	
>50	18 (25.7)	
Gender	**Frequency (Percentage)**	
Male	38 (54.3)	
Female	32 (45.7)	

Table 2 : Pattern of symptoms and duration of symptoms of unilateral cases of acute non-granulomatous anterior uveitis at presentation (N = 70).

Symptoms	**Frequency (Percentage)**
Pain	
No	25 (35.7)
Yes	45 (64.3)
Redness	
No	6 (8.6)
Yes	64 (91.4)
Photophobia	
No	25 (35.7)
Yes	45 (64.3)
Watering	
No	56 (80)
Yes	14 (20)
Decreased vision	
No	27 (38.6)
Yes	43 (61.4)
Duration of symptoms presentation (in days)	Frequency (Percentage)
1	3 (4.3)
2	14 (20)
3	21 (30)
4	15 (21.4)
5	9 (12.9)
6	4 (5.7)
7	3 (4.3)
8	1 (1.4)
Total	70 (100)

Table 3: Season at presentation, history of smoking, and stress factors.

Parameters	Frequency (Percentage)
Season at presentation	
Summer (June-August)	32 (45.7)
Winter (December-February)	10 (14.3)
Spring (March-May)	10 (14.3)
Autumn (September-November)	18 (25.7)
Smoker	
Positive	28 (40)
Negative	25 (35.7)
Ex-smoker	17 (24.3)
Total	70 (100)
Stress factor	
Yes	17 (24.3)
No	53 (75.7)
Total	70 (100)

Table 4: Diagnosis of patients on the basis of course, HLA-B27 status and systemic association

Parameters	Frequency (Percentage)
HLA-B27 status	
Positive	30 (60)
Negative	20 (40)
Total	50 (100)
Seronegative spondyloarthropathy (SpA)	Frequency (Percentage)
Yes	16 (22.8)
No	54 (77.2)
Total	70 (100)
Etiological Diagnosis	Frequency (Percentage)
SpA with HLA-B27 positive	12 (17.1)
No SpA with HL-B27positive	18 (25.7)
SpA with HLA B 27 not done	4 (5.7)
No SpA & HLA-B27negative(Idiopathic)	20 (28.5)
No SpA, HlA-B 27 not done(Indeterminate)	16 (22.8)
SpA with HLA-B27 positive	12 (17.1)
Total	70 (100)

DISCUSSION

In present study, we included 70 patients with unilateral ANGAU and conducted their descriptive analysis. Many studies on uveitis show a preponderance of males (Camilo et al., 2014; Das et al., 2009; Rodriguez et al., 1996; Singh et al., 2004). Same finding was observed in this study.

In terms of symptoms, commonest one that brought patients of ANGAU to hospital was redness (91.4%). Although authors of present study expected ocular pain to be as common as redness symptom due to the nature of the disease, it was found to be only 64.3%. Watering is not a very commonly reported symptom of ANGAU. But in this study 1/5th of the study population had this complaint. The findings of this study varied from the findings of the study done by Camilo et al., (2014) in Brazil where 76% presented with ocular pain, 59.8% with redness, and 46.2% with diminution of vision.

Many of the ANGAU patients were found to suspect that their disease had a tendency to relapses more in winter time. In a study done in Chinese patients with HLA-B27 associated acute anterior uveitis, episodes of uveitis was more common in winter (Chung et al., 2009). This was the reason the authors of current study wanted to confirm whether it would be the same in Nepal as well. But the patients in this study predominantly presented during the summer between June and August (32/70, 45.7%). Second highest number of cases (18, 25.7%) presented during the autumn (September–November). In fact it was lowest (10, 14.3%) in winter and spring each. This finding is almost comparable with that of a study done in West Africa, Sierra Leone, in which uveitis was reported to be more prevalent between May and August (Ronday et al., 1996). To find out why relapses occurred mostly in the warmer months is out of the scope of this study. However, in a study conducted in Iran, no correlation was seen between the onset of uveitis and the season (Soheilian et al., 2004).

The possibility of a smoker (present or ex) having any kind of intraocular inflammation was found to be about two folds higher than of a never smoker in the study by Lin in et al., (2010) Similar finding was reported in the paper by Yuen et al., (2015). However, in the first one relation between smoking and infectious uveitis was stronger, whereas in the second one it was with non-infectious uveitis. As expected, this research also revealed that the current and ex-smokers (41.4% and 35.7 %) are higher risk of having ANGAU than those who never smoke (22.9%).

Due to lack of funding, HLA-B27 test could not be performed on all the cases. Since patients had to self-pay for the test, only 71.4% (n = 50/70) could do it. Association of HLA-B27 with seronegative spondyloarthropathy (SpA) in Nepali population has been reported by two different research groups. In these two hospital-based studies, HLA-B27 positivity rate was seen in cases of SpA. In Vaidya et al., (2013) paper, 52.9% (n = 54/102) patients of SpA were HLA-B27 positive, where as in Sah et al., (2020) study, only 23.2% (n = 26/112) were positive for HLA-B27. But its association with ANGAU in Nepali population has not been studied so far. The positive result in cases of ANGAU in this study, which is 60% (n = 30/50), is higher than in those reported in

cases with SpA. In fact, this is one of the main highlights of this study. This result is similar to a report from North India (Gupta et al., 1978) which showed that 64.3% of AAU cases were positive for HLA-B27. However, the sample size was only 28 in that study. In another study done in a part of North India, which included 80 cases of anterior uveitis, six posterior uveitis and three panuveitis, 56.2% cases tested positive for HLA-B27, while it was positive in only 3% of controls (Mishra and Bharucha, 2008). The positive rate in that study could have been slightly higher than 56.2% if only anterior uveitis cases were included. Similar to that result, HLA-B27 allele was present in 55.4% of the anterior uveitis patients and 0.87% of the controls in a study done in Cuba (Torres et al., 2013). But in similar study done by Wakefield et al. (1986), at Sydney Eye Hospital, only 47% of anterior uveitis cases were HLA-B27 positive.

Previous research have shown that individual with positive HLA-B27 have more severe form of SpA than those with negative HLA-B27 (Chang et al., 2005). Although at presentation, only 22.8% (n = 16/70) cases (17.1%, n = 12/70 positive for HLA-B27 and 5.7%, n = 4/70 with HLA-B27 status unknown) had systemic features of SpA, the rest of the patients could develop these systemic features later in the life. In a paper from Italy, the researchers reported that HLA-B27 positive cases were more likely to have systemic disease, (50% vs 17.1%) particularly SpA with significant p-value. The AAU was diagnosed before SpA in 57% of patients who were HLA-B27 positive (Accorinti et al., 2010). So, based on the presence of HLA-B27 gene patients of ANGAU can be counselled about these possibilities and can be educated about the early symptoms of SpA.

Patients in this study population had a good visual status at presentation, and visual outcome improved in 94.3% of patients. A study done by Uy et al., (2001) in 157 eyes of patients with HLA-B27 associated uveitis showed the presence of cystoid macular oedema in 13.4% which had a significant association with the presence of vitreous cells. Although there is the scope of statistical analysis to see similar associations in non-granulomatous anterior uveitis (NGAU) with HLA-B27 status and other co-morbidities, current study was largely limited to the description of its patterns.

One limitation of this study is the inability to find out the HLA-B27 status of 20 (28.5%) of the study population, due to which the possibility of them having severe form of SpA (in those who already had the disease) or developing SpA down the road, could not be ascertained.

Nonetheless, this study has successfully demonstrated the importance of early diagnosis, management, and systemic evaluation of patients with unilateral NGAU in the Nepali population in the hospital basis.

CONCLUSION

In conclusion, unilateral NGAU in Nepali population is strongly associated with present or past smoking, not strongly associated with stress factor, relapses mostly in summer season, and shows HLA-B27 gene positivity in slightly more than fifty percent population. Other than pain, redness, photophobia and

decreased vision, watering can also be one of the presenting symptoms of NGAU cases. Patients with unilateral NGAU must be thoroughly evaluated for seronegative spondyloarthropathies, and the timely treatment of uveitis followed by adjustment of dosage of medication according to response results in the resolution of inflammation and a good visual outcome in these patients.

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