

HLA-B27-related uveitis and seasonal variation—an Indian perspective

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Purpose: To study seasonal variation and systemic associations in HLA-B27 related uveitis (HBU). **Methods:** This was a retrospective, observational chart review conducted in a single, tertiary eye care hospital, from January 2015 to December 2019. New cases presented from January 2017 to December 2019 were studied for incidence patterns (Group X). Cases with ≥ 1 -year follow-up were studied for systemic association (Group Y) and cases with ≥ 4 episodes of active uveitis were studied for recurrence pattern (Group Z). A year was divided into 3 segments of the year (SoY): 1. November–February, 2. March–June, 3. July–October. **Results:** We found 157 cases of HBU from January 2015 to December 2019. The incidence in Group X ($n = 105$) was found to be least in SoY 2 in all 3 years (2017–2019). In Group Y ($n = 85$), 39 cases (45.88%) were diagnosed as spondyloarthropathies, among which 20 were of ankylosing spondylitis (23.52%). More than 1/2 the total number of episodes occurring in the same SoY (SoY Max), in Group Z ($n = 25$), was seen in 14 (56%) cases. SoY Max was the first segment (SoY 1) for most of these cases ($n = 7$). In Group Z, 8 (32%) patients were on immunomodulatory therapy at presentation. **Conclusion:** Our study confirms seasonal variation in HBU patients by documenting the least incidence from March to June and identifies 56% of patients that can have a maximum number of recurrences in a specific season of the year. Outcomes of surgical interventions planned accordingly, and responsible environmental factors for HBU should be studied further.

Key words: HLA-B27 uveitis, recurrence, seasonal variation, systemic associations

Human leucocyte antigen (HLA) B27 related uveitis (HBU) is the second most common form of anterior uveitis (after idiopathic anterior uveitis) in India and worldwide.^[1,2] Acute nongranulomatous anterior uveitis, alternating in both the eyes is typical of HBU. The recurrent course of the disease may develop sight-threatening complications in poorly managed eyes. Surgical interventions such as cataract surgery can be challenging. It may yield unpredictable results due to immediate postoperative inflammatory sequelae, especially when operated without adequate and prolonged control of the inflammation.

Various studies have reported seasonal variations in uveitis.^[3–6] Few authors reported an increased incidence of HBU and ankylosing spondylitis related uveitis in the transitional and cold season of the year.^[4,5,7] This may prompt ophthalmologists not to plan surgical interventions (primarily cataract surgery) during this season in HBU cases.

On this background, we aimed to study seasonal variation, pattern of incidence, pattern of recurrence, and systemic association in clinically diagnosed cases of HBU in our set up.

Methods

This was a retrospective, observational chart review conducted in a single tertiary eye care hospital located in Southern India. The study was approved by the ethics committee and

adhered to the declaration of Helsinki. Case records of patients diagnosed with HBU in the uveitis department from January 2015 to December 2019 were reviewed. The clinical diagnosis of HBU was made based on acute presentation: sudden onset of pain, redness, photophobia with or without blurring of vision; the presence of circumcilliary congestion, nongranulomatous keratic precipitates (KPs), moderate–severe anterior chamber reaction with or without fibrin or hypopyon, posterior synechiae with or without vitritis.^[8] [Fig. 1]. The diagnosis was further supported or confirmed with a systemic history of spondyloarthropathies (diagnosed by a rheumatologist) and/or positive HLA-B27 test. New cases presented in the last 3 years (between January 2017 and December 2019) were studied for incidence patterns (Group X). Cases with ≥ 1 year of follow-up were studied for systemic association (Group Y) and cases with ≥ 4 episodes of active uveitis (episode at presentation + number of recurrences) were studied for recurrence pattern (Group Z). Cases in which HLA-B27 test was not done were excluded. Patients with multiple intraocular surgical interventions (≥ 2 /year) were excluded. Episode immediately after the surgical intervention was not counted as recurrence. Non-resident Indians (NRI) were also excluded from the study to avoid regional environmental bias. Patient's demographics, diagnosis, systemic association, month of

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presentation, month of recurrence, and the total duration of follow-up were studied.

A year was divided into three segments [Segment of the Year (SoY)] based on the normal weather statistics for Bangalore, Karnataka (India) (<https://www.yr.no/place/India/Karnataka/Bangalore/statistics.html>): 1. November–February (21.1°C–23.6°C), 2. March–June (24.6°C–28.0°C), 3. July–October (23.5°C–23.9°C). March–April and September–October were considered a transition period.^[5]

SoY and month of the presentation were noted for each patient in Group X and the incidence pattern was studied for the year 2017, 2018, and 2019. In group Z, a total number of episodes of active uveitis for each individual during their entire follow-up period were counted. Those episodes were categorized into SoY 1, SoY 2, and SoY 3. Individuals with more than half of the total episodes occurring in the same SoY (SoY Max) in Group Z were noted. A number of episodes in transition months, total number of episodes, and total duration of follow-up period per individual was studied for Group Z. Patients in Group Y were studied for their systemic ailments. Rheumatologist's opinion was sought when necessary and their diagnosis and treatment [immunomodulatory therapy (IMT)] was noted.

Results

Our series included 157 cases of HLA-B27 related uveitis from January 2015 to December 2019. Hundred and nine (69.42%) were males and 48 were females. The mean age of presentation was 43 years (range: 11–86 years). Sixty (38.21%) had bilateral alternating disease. Hundred and thirty-six (86.62%) cases were HLA-B27 positive. Nongranulomatous anterior uveitis was the anatomical diagnosis made in all cases. Cystoid macular edema was observed only in two cases in this series. Ten cases also had moderate to severe vitritis and three mimicked presentation of endogenous endophthalmitis characterized by grade 3–4 vitreous haze along with fibrinous hypopyon uveitis but no choroiditis or retinitis lesions. All 3 cases tested positive for HLA-B27 and 2 of them had multiple but less severe recurrences, while the third case was lost to follow-up after successful management of the first attack.

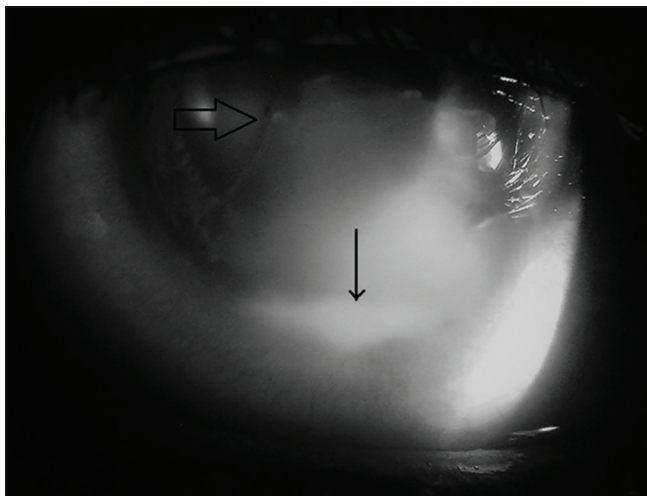


Figure 1: Anterior segment photograph showing fibrinous reaction in the anterior chamber (thick arrow) and hypopyon (thin arrow) in an HLA-B 27 positive 34-year-old man without any systemic ailment

Hundred and five cases (Group X) presented between January 2017 and December 2019 ($n = 38$ in 2017, $n = 33$ in 2018, and $n = 34$ in 2019) were studied for incidence pattern. The least number of patients were seen in SoY 2 in all 3 years [Fig. 2]. In SoY 1 maximum number of cases were seen in 2017, followed by 2019 and followed by 2018 whereas in SoY 3 mild reversal of the pattern was seen [Fig. 2]. Upon studying individual months of SoY 1 and 3 (July – February), no specific pattern in the incidence was observed [Fig. 3]. Only 22.85% of patient presented in the transition season.

In Group Z, 25 patients were studied for the recurrence pattern. The mean total number of episodes per patient was 5.64 (range 4–10). More than half of the total number of episodes per patient occurring in same SoY (SoY Max) was seen in 14 (56%) cases. SoY Max was first segment for 7 cases, second segment for 4 cases, and third segment for 3 cases [Fig. 4]. One case in Group Z had all ($n = 4$) relapses in the same SoY (first). The mean follow-up in Group Z was 6.5 years. (range: 2–17 years). Twenty-one patients received IMT in this group and 8 of them were on IMT at the presentation.

In Group Y, 85 cases with ≥ 1 year follow-up were studied for systemic associations. Thirty-nine (45.88%) cases were diagnosed as spondyloarthropathies by their rheumatologists, among which 20 (23.52%) were of ankylosing spondylitis. Fourteen (16.47%) cases were diagnosed as nonspecific arthritis. Rest 32 (37.64%) cases out of 85 had no systemic ailments, which could be attributed to HBU. Out of the 53 (39 + 14) patients, 27 (51%) had a diagnosed systemic disease before presentation to us while others were diagnosed during follow-up with us. The mean follow-up was 3.76 years (range: 1–17). Seventy-two (84.7%) were HLA-B27 positive. In total, 56 patients received IMT in this group and 13 of them were on IMT at the presentation.

Discussion

Our study has shown that the incidence of HBU is least in SoY 2 in our set up. More than 50% of cases can have a predilection for the specific season for their recurrences, commonly SoY 1, and most of the HBU cases have a systemic association, particularly spondyloarthritis.

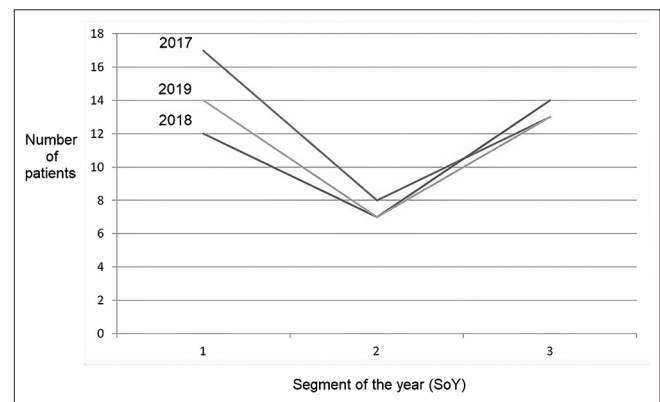


Figure 2: The graph of incidence pattern (Group X) for the year 2017, 2018, and 2019 with number of patients along Y-axis and SoY along X-axis shows least number of patients were presented in SoY 2 in all 3 years

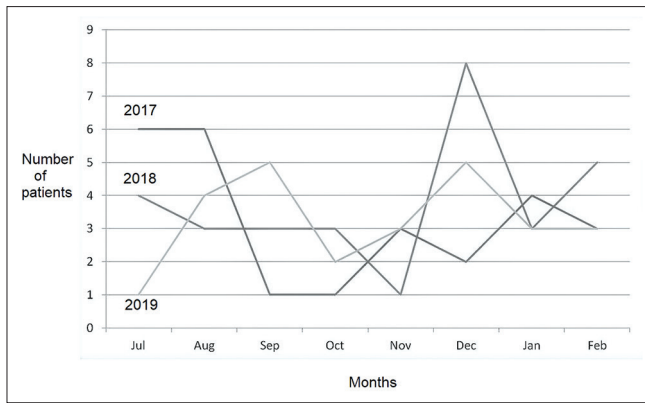


Figure 3: The individual month-based graph of incidence for SoY 1 and SoY 3 (July–February) for the year 2017, 2018, 2019, with number of patients along Y-axis and months along X-axis, shows a 'crisscross' pattern

It is known that ankylosing spondylitis is common in males. We also found a similar gender correlation with HBU cases, most of our cases were young males. Most of our cases (86%) were HLA-B27 positive, rest 14% fell into the same category of HBU-uveitis based on their clinical presentation, course of the disease and systemic association like ankylosing spondylitis or spondyloarthritis diagnosed by their rheumatologists. It is also known that 26% of clinically diagnosed cases of ankylosing spondylitis may have a negative HLA-B27 test,^[9] and so can be true for other HLA-B27 related diseases including HBU. Correlation of spondyloarthropathy and HBU was strong in our study. In 49% of cases, uveitis was the presenting feature of systemic HLA B 27 related disease, while 37% had only ocular disease. Ophthalmologists should be aware of clinical features of HBU in the absence of systemic complaints and should confirm the diagnosis by advising HLA-B 27 test to prognosticate the patient's systemic disease. Clinical manifestations of HBU are well described in the literature. A recent study on HBU emphasized on posterior segment manifestations in the form of vitritis,^[8] we also had three patients who presented with severe vitritis, confusing clinical picture with endogenous endophthalmitis [Fig. 5].

In our study SoY 2 (March–June) was found to be the least common season for the detection of new cases of HBU. This segment of the year is considered to be warmer in our region compared to SoY 1 and SoY 3. This observation was in accordance with previous studies done elsewhere, which noted an increased incidence in the winter season.^[4,7] But upon analyzing individual months of SoY 1 and SoY 2, no specific pattern in the incidence was observed in our study [Fig. 3]. Also, in contrast to previous studies,^[5] no obvious peak in incidence during transition season (March–April and September–October) was observed. Our study has seen more number of cases in SoY 1 of 2017 whereas in SoY 3 of 2018 and 2019, there was a relative increase in numbers compared to 2017 [Fig. 2]. We presume this shift may have a relation with the global climate change seen over the past few years. This was one of the reasons that we studied the incidence in the last 3 years.

To study the pattern of recurrence and its seasonal variation, we analyzed cases who had at least three recurrences (total 4 episodes including the first attack of uveitis - Group Z). It was found that 56% of patients had a particular season (SoY Max) when they had a maximum number of recurrences. Upon

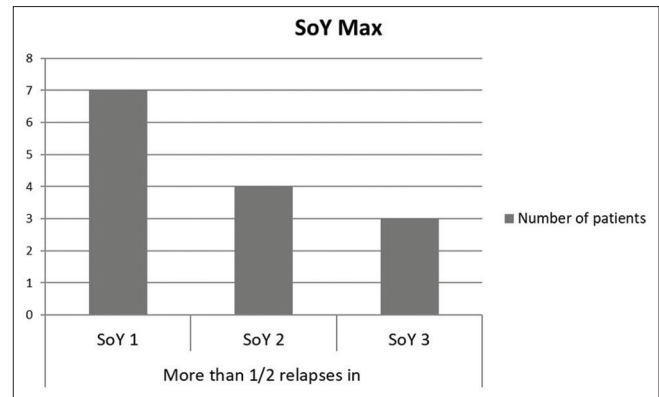


Figure 4: Graph of SoY Max (Group Z) with the number of patients along Y-axis and SoY along X-axis shows patients with more than half of the total number of recurrences were seen predominantly in SoY 1

studying the patients with SoY Max, we observed that those attacks were mainly seen in SoY 1 [Fig. 4]. One patient even had all four episodes in a single SoY (first). The above observations make us certain that the incidence and recurrence rate for HBU is higher between November and February in our region but the pattern may change in the coming few years due to global climate change.

The role of environmental factors in HLA-B27 related diseases have been studied in the past and remains under investigation. An experimental study on HLA-B27 positive rats, raised in a germ-free environment were noted disease-free whereas those raised in non-germ-free environment and exposed to bacteria manifested of spondyloarthropathy.^[10,11] The human gut microbiome can also show seasonal variation due to seasonal dietary changes.^[12] It is known that the HLA-B27 gene can be modified by environmental factors and a triggering environmental factor, such as bacterial infection, may initiate HLA-B27 related diseases like ankylosing spondylitis in susceptible individuals.^[13] Variation in thrombocytes and platelet-lymphocyte rate and their correlation with ankylosing spondylitis and rheumatoid arthritis in spring and winter has been recently reported.^[14] One can speculate a similar environmental mechanism in the pathogenesis of HBU patients to explain the seasonal variation.

The literature on the pattern of uveitis and seasonal variation is scarce. A recently published Indian study on uveitis (88% anterior uveitis) and seasonal variation noted a distinctly higher number of cases in winters followed by transitional season,^[5] while a study from Wills Eye Hospital, Philadelphia, noted the increased occurrence of nongranulomatous anterior uveitis during the summer months.^[6] Similarly, a Finnish study also noted an increased incidence of all uveitis cases in the warm and transitional seasons.^[4] Regional temperature variation may not be similar in different seasons in different places over the planet. Due to this reason, we excluded NRIs from our study. All the above studies were not particularly focused on HBU and did not study the pattern of recurrence during a long term follow up as in our study. In contrast to Kausar *et al.*,^[5] we did not observe increased recurrences in a transition season. Mercanti *et al.* also noted significantly more recurrences in the cold and in transitional months in endogenous uveitis, but their study included only 58% anterior uveitis and HLA-B 27 association was not studied.^[3] An Australian study that looked into acute anterior uveitis, its seasonal variation, and HLA B 27 relation, found increased incidence from August to December mainly due to HLA-B27 negative cases, but

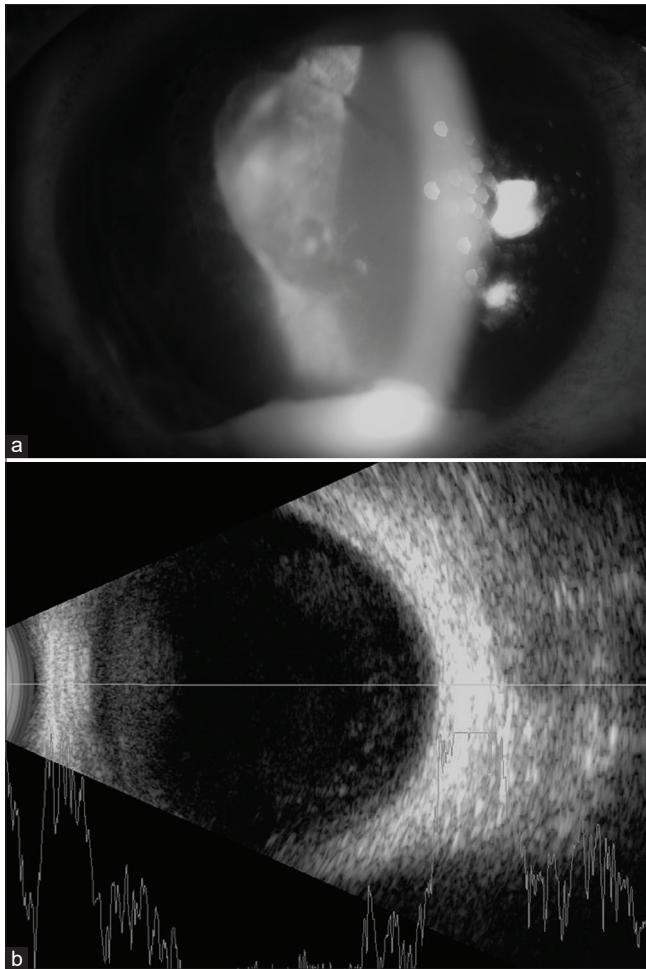


Figure 5: Anterior segment photograph showing heaped hypopyon, severe fibrinous reaction obscuring the view of the lens (a), B scan shows a moderate amount of vitritis in the affected eye prompting endogenous endophthalmitis (b), but broken posterior synechiae in other asymptomatic eye gave clue towards HLA-B 27 related uveitis in a 38-year-old systemically healthy male

they also noted a slight increase in the incidence of HLA-B 27 positive cases from August to November.^[7] Again, in this study, the pattern of recurrence was not studied. Our study is different from all the above studies in that, it was focused on one particular uveitic entity, “HLA-B 27 related uveitis” and not uveitis as a whole. We not only studied the incidence pattern but also the pattern of recurrence for each individual. Findings from our study confirmed the previous observation that HBU incidence is more in the winter season in our subcontinent. Our study also added that more than 50% of HBU cases can have a recurrence pattern with relatively common attacks between November and February. Moreover, it was also evident that each patient can have a predilection for different segments of the year for recurrences. Identifying such cases may help surgeons to choose a safe period for surgical interventions as well as for immunologists to consider tapering of IMT in the appropriate season.

Limitations of our study were relatively smaller numbers in Group Z but were explainable as we included cases with four or more attacks of uveitis. Lack of control group was another drawback of our study. Merits of our study were large cohort available to study incidence pattern, systemic association, and a long-term follow-up of Group Y and Z patients.

Conclusion

In conclusion, our study confirms the seasonal variation in HBU patients by documenting the least incidence from March to June and identifies 56% of patients that can have a maximum number of recurrences in a specific season of the year. Evaluation of surgical outcomes by avoiding surgical interventions in SoY Max in selected HBU cases needs to be studied further. Environmental factors that are responsible for the onset or recurrences of HBU also need to be investigated further.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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