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Review for Disease of the Year: Epidemiology of HLA-B27 Associated Ocular Disorders

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Abstract

Acute anterior uveitis is generally recognized as the most common form of uveitis. An association with HLA-B27 is seen in approximately half of cases of acute anterior uveitis. The prevalence of HLA-B27 varies widely between ethnic populations, with an approximate 8-10% prevalence in non-Hispanic whites and lower prevalence in Mexican- (4%) and African- (2-4%) Americans. A group of systemic inflammatory diseases, the spondyloarthropathies, likewise demonstrates a strong association with HLA-B27. The strength of association varies depending on the specific spondyloarthropathy, with the strongest association found in patients with ankylosing spondylitis. The majority of patients with HLA-B27 associated uveitis will have an underlying spondyloarthropathy. Suspicion for HLA-B27 associated uveitis should prompt a careful clinical history to assess for features of a spondyloarthropathy as the characteristics of any associated uveitis may vary.

Keywords

Epidemiology; HLA-B27; Acute anterior uveitis; Iritis; Spondyloarthropathy

Uveitis, defined as intraocular inflammation, often affects working-age populations between the ages of 20 and 50.¹ Uveitis and its sequelae remain an important cause of blindness in the Western world, with estimates suggesting uveitis causes 3 to 15% of all cases of total blindness.^{2,3} In the United States, recent population-based studies suggest between 2 and 2.5 million people with prevalent uveitis, with up to 10% of all cases of blindness due to these diseases.⁴⁻⁶ The socioeconomic burden imposed by uveitis is therefore large, especially given that uveitis disproportionately affects a younger, and likely more productive, sector of society.

Various population-based studies have suggested an annual incidence of uveitis of 17 to 52.4 per 100,000 person-years, with prevalence between 38 and 370 per 100,000 population.⁷⁻¹¹ The wide range in incidence and prevalence in part reflect geographic variations, differences

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in nomenclature, analytic methods, and the various study populations analyzed. As an example, a review of the causes of uveitis in predominantly tropical countries identified a higher incidence of infectious uveitis.¹² Despite these variations, anterior uveitis is generally recognized as the most common form of uveitis, although differences in incidence and prevalence vary according to the study population analyzed. In studies derived from general ophthalmology practices, anterior uveitis accounts for approximately 80–90% of uveitis cases, whereas the reported percentage is generally lower in tertiary care centers.^{13–15}

Historical overview

The identification of a link between HLA-B27 and inflammatory disease was first described in 1973, with reports of association with uveitis, ankylosing spondylitis, reactive arthritis, ulcerative colitis and psoriasis.^{16–19} Subsequent work has further defined the association of HLA-B27 with systemic disease and characterized the features of accompanying ocular inflammation. The mechanism by which HLA-B27 predisposes to these systemic conditions remains incompletely understood; however, efforts have begun to elucidate molecular changes that may contribute to pathogenesis.

The HLA-B locus is part of the major histocompatibility complex (MHC) located on chromosome 6 and encodes for a class I MHC surface antigen. These membrane bound proteins are expressed on somatic cells and act to present antigen to CD8+ T-cells. HLA-B27 encodes a number of alleles with polymorphic differences that primarily change amino acids in the antigen-binding cleft. Differences in antigen presentation secondary to changes in the binding pocket are thought to contribute to the development of HLA-B27 associated disease, possibly by presentation of an ‘arthritogenic’ (or ‘uveitogenic’) peptide. An etiologic role for exposure to intracellular bacteria such as *Yersinia*, *Shigella*, *Salmonella* and *Chlamydia* has also been proposed based on the known role these bacteria play in triggering reactive arthritis.²⁰

HLA-B27 Seropositivity in the General Population

The prevalence of HLA-B27 varies widely between ethnic populations. The highest prevalence is observed in the Pawaia tribe in Papua New Guinea (53%)²¹, the Haida natives of western Canada (50%)²² and the Chukotka Eskimos of eastern Russia (40%).²³ HLA-B27 prevalence is also relatively common in northern Scandinavia (14–16%).^{24,25} Amongst Caucasians, 8–10% are thought to be HLA-B27 positive. Rates are lower in Chinese (2–9%)^{26,27} and Arab (2–5%)²⁸ populations. HLA-B27 positivity is rare in the Japanese (<1%)²⁹ and virtually absent amongst sub-Saharan Africans, South American Indians and Australian Aborigines.³⁰ A population-based survey in the United States found a prevalence of 7.5% in non-Hispanic whites and of 4.6% in Mexican Americans. In this study, prevalence rates could not be reliably estimated in other ethnic groups, including African Americans due to the low numbers of HLA-B27 individuals in these groups³¹; however, others have found a prevalence of 2–4% in African Americans.^{32,33}

The HLA-B27 locus is highly polymorphic with 105 known subtypes and 132 genetic alleles.³⁴ The most common HLA-B27 subtypes vary with ethnicity.³⁵ The HLA-B27*05

allele is present in almost 90% of HLA-B27 positive individuals of Northern European descent, the HLA-B27*04 allele is most common in the Japanese and Chinese and HLA-B27*02 is present in >30% of several Mediterranean populations.³⁶ It is thought the HLA-B27*05 allele may be the ancestral subtype based on its widespread distribution.³⁷ The HLA-B27*05, HLA-B27*02 and HLA-B27*04 subtypes are commonly associated with disease, whereas other subtypes, such as HLA-B27*06 and HLA-B27*09, are thought to be disease-neutral. Alterations in the antigen-binding cleft between subtypes are thought to change the specificity of antigen binding and contribute to the differences in disease association.³⁴ The mechanisms by which these allelic differences contribute to disease pathology and the extent to which differences in subtype frequencies between populations influence the disease burden amongst ethnicities remains to be fully elucidated.

HLA-B27 and Seronegative Spondyloarthropathies

Several systemic inflammatory diseases demonstrate a strong association with HLA-B27. As a group, these disorders are known as the seronegative spondyloarthropathies, with seronegativity referencing a negative test for rheumatoid factor. The prevalence of seronegative spondyloarthropathy varies by ethnic group and is thought to be approximately 0.5–1% in the United States³⁸, 0.5–0.8% in an ethnically diverse Chinese population^{39,40} and 0.01% in the Japanese.²⁹ These differences partly reflect the variations in prevalence of HLA-B27 observed in these populations.

The strongest association with HLA-B27 exists in ankylosing spondylitis, where HLA-B27 is present in greater than 90% of Caucasian patients with this disease.⁴¹ Indeed, HLA-B27 positivity increases one's relative risk for developing ankylosing spondylitis 50 to 100 fold.⁴² Additional seronegative spondyloarthropathies associated with HLA-B27 include reactive arthritis, psoriatic arthritis, enteropathic arthropathy, and a less well-defined group of disorders collectively labeled as undifferentiated spondyloarthropathy. Reactive arthritis is a sterile, inflammatory arthritis typically preceded by infection with a gastrointestinal or genitourinary pathogen. Estimates regarding the presence of HLA-B27 in reactive arthritis vary greatly. In general, it is estimated that HLA-B27 is present in 30–80% of patients.^{43,44} HLA-B27 positivity correlates with more severe and prolonged arthritis as well as a higher incidence of sacroiliitis.^{45–47} Additionally, extra-articular manifestations such as uveitis are seen more commonly in HLA-B27 positive reactive arthritis patients.⁴⁸ Evidence suggests that between 4 and 30% of all patients with psoriasis will develop an associated inflammatory arthropathy or psoriatic arthritis.^{49,50} HLA-B27 is associated with the development of sacroiliitis in such patients, although with a weaker association than that seen in ankylosing spondylitis or reactive arthritis.^{51,52} Nonetheless, the prevalence of HLA-B27 in patients with psoriatic arthritis is estimated to be between 40–50%.⁵¹ Patients with inflammatory bowel disease, especially those with significant colonic involvement, are also prone to developing an inflammatory arthropathy.⁵³ The presence of HLA-B27 in a patient with inflammatory bowel disease often is associated with the development of sacroiliitis, spondylitis, enthesitis, and peripheral arthritis.⁵⁴

HLA-B27 Acute Anterior Uveitis

Acute anterior segment ocular inflammation can occur in association with the HLA-B27 allele either alone or in the context of a systemic inflammatory disease. The prevalence of HLA-B27 in patients with acute anterior uveitis is thought to be approximately 50%.¹⁶ The strong association of HLA-B27 with anterior uveitis makes it one of the most common etiologies for anterior uveitis, underlying between 18–32% of cases in Western countries.⁴⁴ Despite this high incidence, indiscriminate testing for HLA-B27 is not recommended in all patients with acute anterior uveitis due to the high population prevalence of B27 in some ethnic groups.⁴⁴ This is similar to recommendations made for B27 testing in the spondyloarthropathies.⁵⁵ Testing is best directed by a careful and thorough patient history and physical exam and the identification of certain key clinical features should direct testing for HLA-B27.

HLA-B27 associated uveitis classically presents as a symptomatic, unilateral, sudden onset, and limited duration anterior segment inflammation, and is typically characterized as acute anterior uveitis. The first episode of uveitis typically presents between the ages of 20–40 years. There is a male preponderance, with men affected 1.5–2.5 times more frequently than females.^{56,57} The degree of inflammation can often be severe, including presentation with hypopyon and anterior chamber fibrin. Symptoms frequently include photophobia, ocular pain, eye redness and blurred vision. The inflammation frequently responds well to topical therapy, with disease-free intervals off therapy. Recurrence can occur in either eye and it is common to see inflammatory episodes ‘flip-flop’ between eyes.⁵⁶ A longitudinal study of HLA-B27 positive patients found a median of three attacks in patients followed for more than one year (range 1–26 attacks) with a median interval of 14 months (range 1–420 months).⁵⁷ Another study found the average frequency of recurrence was 1.1 ± 0.8 per year in patients less than 5 years from their initial attack and 0.8 ± 0.6 per year in patients more than 5 years from their first attack, suggesting recurrence may become less frequent with longer duration of disease.⁵⁸ Recurrence may be more common in HLA-B27 positive patients with systemic disease than those without systemic manifestations.^{58,59}

Even with treatment, ocular complications can develop. The most common complications include development of posterior synechiae, ocular hypertension or glaucoma, posterior subcapsular cataract, and epiretinal membrane. Less commonly, cystoid macular edema, band keratopathy and ocular hypotony may occur.⁶⁰ If recurrences are frequent or topical therapy cannot be discontinued without recurrence, some patients are advanced to immunosuppressive therapy in an effort to minimize inflammatory complications and the side effects of topical treatment.

Evidence is mixed whether visual outcomes and complication rates differ between HLA-B27 associated anterior uveitis compared with other anterior uveitis etiologies. Several studies have found no difference in vision^{56,61} and ocular complications⁵⁶ between patients with and without B27 as an underlying etiology. Other studies found greater number of ocular complications^{59,61} and higher percentage of legally blind eyes⁵⁹ in HLA-B27 positive patients. The differences in outcome measures likely reflect the etiologic heterogeneity of HLA-B27 negative anterior uveitis and the potential bias reflected in more severely affected

HLA-B27 uveitis patients being referred to the tertiary centers conducting the majority of these studies.

Acute Anterior Uveitis and Association with Spondyloarthropathies

Approximately 50–75% of patients with HLA-B27 acute anterior uveitis have an associated spondyloarthropathy,^{57,58,62} with ankylosing spondylitis, reactive arthritis and undifferentiated spondyloarthropathy the most common diagnoses. Uveitis develops less commonly in patients with inflammatory bowel disease (2–5%) or psoriatic arthritis (7%).⁶³ Gender differences exist in the development of uveitis in patients with spondyloarthropathy, with uveitis in the setting of ankylosing spondylitis more likely to develop in men, whereas uveitis in the setting of inflammatory bowel disease is more likely to develop in women.^{64,65} Although supported by less evidence, it is suggested that gender differences in the development of uveitis in patients with psoriatic arthritis reflect the type of arthropathy involved, with men developing uveitis more commonly in the setting of axial arthritis and women more commonly in the setting of peripheral arthritis.⁶⁶

The clinical features of uveitis may vary depending on the underlying systemic inflammatory illness. Uveitis associated with ankylosing spondylitis and reactive arthritis is most likely to present with the classic acute, unilateral and alternating features described above. The inflammation can be severe, resulting in anterior chamber fibrin or hypopyon.⁶⁷ The uveitis in inflammatory bowel disease and psoriatic arthritis is more variable in presentation.⁶³ About half of patients with these conditions will exhibit the classic acute, unilateral presentation, with the majority of these individuals demonstrating HLA-B27 positivity. Alternatively, patients can present with an atypical, bilateral uveitis, which may be insidious in onset, chronic in duration, and involve the posterior segment.^{65,66} HLA-B27 positivity is more variable in this subset of patients. The uveitis associated with inflammatory bowel disease also can present with episcleritis or scleritis.⁶⁵ In psoriatic arthritis, uveitis is more commonly observed with axial arthropathy than with peripheral arthritis.⁶⁶

The risk for development of acute anterior uveitis correlates with the duration of the underlying spondyloarthropathy. Supporting evidence is seen in a French study of 902 patients with a mean duration of spondyloarthropathy of 10.4 years. In this patient population, uveitis was the most common extra-articular feature, occurring preferentially in HLA-B27 positive patients (adjusted odds ratio=2.97, 95% confidence interval 1.83–4.81) and in those with longer disease duration (greater or equal to 10 years, adjusted odds ratio=1.28, 95% confidence interval 1.16–1.41).⁶⁸

Uveitis may precede development of spondyloarthropathy, although more commonly, rheumatic symptoms such as back pain are present prior to the development of uveitis. Frequently, these symptoms are not identified as inflammatory until presentation with uveitis brings the patient to the attention of the medical provider. A study of 175 HLA-B27 positive patients presenting with acute anterior uveitis revealed 136 patients (77%) with an HLA-B27 associated extraocular disease, the majority of which involved either diagnosed or presumed ankylosing spondylitis. Indeed, the diagnosis of extraocular disease was made in 88 of these

136 patients only after presentation with ocular involvement.⁵⁸ Therefore, a thorough history assessing for features such as inflammatory back pain, peripheral arthritis, gastrointestinal or urinary tract abnormalities and dermatologic manifestations can aid in early detection of a spondyloarthropathy and appropriate rheumatologic referral. The ocular inflammation often responds well to topical therapy; however, extraocular manifestations may require systemic therapy. Similarly, the presence of uveitis in patients with HLA-B27 associated spondyloarthropathy may portend a poorer prognosis. Such patients may demonstrate higher disease activity, more radiographic progression, and decreased functional capacity.^{69,70}

Conclusion

HLA-B27 is unique in being one of only a few MHC class I molecules associated with disease, and is one of the strongest of all such discovered associations. It is a common etiologic factor for acute anterior uveitis, which frequently presents with a characteristic clinical course. Suspicion for HLA-B27 associated uveitis should prompt a careful clinical history to assess for features of a concomitant spondyloarthropathy, since a significant number of patients will have a related systemic disease which often may have been undiagnosed at the time of presentation to an ophthalmologist. In patients with a suggestive clinical history or with an ocular presentation of symptomatic, severe, unilateral or alternating uveitis, HLA-B27 testing should be considered. Ophthalmologists are frequently the first to identify an HLA-B27 associated process; this provides ophthalmologists the opportunity to spare patients both ocular and systemic morbidity from these inflammatory diseases.

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