

HLA-B27 ASSOCIATED UVEITIS

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INTRODUCTION

The HLA-B are a group of cell surface molecules encoded for by the major histocompatibility locus on chromosome 6 of the human genome. These genes show various polymorphic forms, one of which is the B27. Seventy to 80% of people with the HLA-B27 antigen have no clinical manifestations related to the presence of this gene. However, it has been estimated that up to 20% of people carrying this antigen have at least one of several associated conditions. These include :

Isolated acute anterior uveitis

The spondyloarthropathies

Ankylosing Spondylitis

Reiter's Disease and Reactive Arthritis

Psoriatic Arthritis

Undifferentiated Spondyloarthropathies

Enteropathic Synovitis

Inflammatory Bowel Diseases

EPIDEMIOLOGY

The HLA-B27 associated uveitic syndrome is the second commonest cause of anterior uveitis, following idiopathic uveitis. It accounts for 40 to 70% of cases of acute anterior uveitis in different patient populations. Like most of the other conditions associated with the B27 gene, B27 associated acute anterior uveitis also has a higher frequency in males than in females.

CLINICAL PRESENTATION

Classically, B27 associated uveitis presents with sudden onset acute anterior uveitis in a young patient. It starts in one eye but is usually asymmetrically bilateral. The inflammation may be more severe than that found in idiopathic anterior uveitis and may be associated with a fibrinous reaction (25%), a hypopyon (14%) and the formation of posterior synechiae. Studies show that it is also associated with higher recurrence rates than the idiopathic variety.

Posterior segment involvement in HLA-B27 associated uveitis is an under recognized phenomenon but has been shown to occur in up to 17% of patients with B27 associated uveitis. This may take the form of posterior vitritis, vasculitis or papillitis.

Uveitis associated with the HLA-B27 gene may occur in the presence or absence of an associated systemic conditions; some patients may present with the ocular symptoms as the first

manifestations of a systemic condition that may declare itself later. Because of this, and because in some patients a systemic condition, even though present may not have been diagnosed, it becomes vital to take a detailed history and to conduct a focussed systemic examination of these patients.

Features associated with the spondyloarthropathies are the presence of lower back pain due to sacroiliitis, an asymmetric, pauciarticular, peripheral, inflammatory large joint arthritis, the inflammation and ultimate calcification of the tendinous insertions into bones (enthesiopathy) and extra-articular (bowel, skin, eye, vascular) manifestations in the absence of serum rheumatoid factor or the rheumatoid nodules classically seen in rheumatoid arthritis. These conditions are HLA-B27 associated, but although the presence of this gene is extremely helpful in the diagnosis, its absence does not exclude them. The spondyloarthropathies also show considerable clinical overlap, so that sometimes it may be difficult to distinguish between them.

TABLE 1: OCULAR INVOLVEMENT IN THE HLA-B27 ASSOCIATED SYSTEMIC CONDITIONS

Condition	Ocular Involvement
Ankylosing Spondylitis	Acute anterior uveitis (AAU) Conjunctivitis
Reiter's Syndrome and Reactive Arthritis	Conjunctivitis Anterior uveitis Keratitis
Undifferentiated Spondyloarthropathy	Anterior uveitis (acute or chronic) Vitritis Retinal Vasculitis
Psoriatic Arthropathy	Anterior uveitis Conjunctivitis Dry eye Keratitis
Inflammatory Bowel Disease	Conjunctivitis Episcleritis/Scleritis Anterior Uveitis

	<p>Vitritis</p> <p>Retinal vasculitis</p> <p>Peripheral ulcerative keratitis</p>
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Ankylosing Spondylitis (AS)

This condition is present in 1 in 1000 to 1 in 2000 of the white population; it shows a lower incidence in Blacks and Asians. It was traditionally considered more common in males, but it is now recognized that it may be equally common in females, although less severe. It varies from a relatively asymptomatic condition visible only on X-rays, to a crippling disease. The typical patient is a young man with lower back pain and morning stiffness, with a progressive loss of spinal movement. The main lesion is that of progressive spinal fusion with spinal ankylosis and sacroiliac joint involvement that results in a fixed, kyphotic spine and restricted respiratory excursion. It may also be associated with hip and knee involvement, amyloidosis, aortitis and apical lung fibrosis.

Sacroiliac joint X-rays must be obtained in patients with HLA-B27 positive uveitis and a suggestive history; they show sclerosis and obliteration of the joint space, with ligamentous calcification. A X-ray of the spine shows squaring of the vertebrae, and in severe cases, the characteristic ankylosed 'bamboo' spine. In patients in whom the X-ray changes are subtle, a radioisotope scan picture of the sacroiliac joint may be helpful.

HLA-B27 is found in nearly 90% of patients with ankylosing spondylitis. Ocular involvement may take the form of conjunctivitis or acute anterior uveitis(AAU), which occurs in 20 to 30% of patients with this condition. It is usually asymmetric and bilateral, involving only one eye at a time; the other symptoms and signs are as described above.

AS may be present in between 30 and 50 % of patients with acute anterior uveitis. As mentioned, recognizing AS is of vital importance in a patient with AAU, as it is a potentially crippling disease that requires referral to and long term management by an internist.

Reiter's Syndrome

This condition is diagnosed on the basis of the triad of non-specific urethritis, arthritis and conjunctivitis, often with the presence of iritis. It is commoner in males than in females and tends to occur between the age group of 15 and 40 years. It may be post-infectious, following non-gonococcal (chlamydia, ureaplasma) urethritis or infectious dysentery. Systemic conditions associated with Reiter's include the characteristic skin condition called keratoderma blenorrhagicum (brown aseptic abscesses on the palms and soles of the feet), mouth ulcers, circinate (serpiginous) balanitis, Achilles tendonitis and plantar fasciitis and aortic incompetence (rare).

Thirty to 60% of the patients have conjunctivitis, which, although non-infectious, may be associated with a mild mucoid discharge. Between 3 and 12% of the patients have iridocyclitis. A few patients may also have keratitis with multifocal, punctate subepithelial lesions and anterior stromal infiltrates.

Psoriatic Arthropathy

Psoriatic arthropathy occurs in around 20% of patients with the characteristic skin and nail lesions of psoriasis, and is a usually benign arthritis involving the small joints of the hands, although rarely, it may be a severe destructive arthritis known as arthritis mutilans. Twenty percent of patients with psoriatic arthropathy, (but not the psoriatic skin lesions alone), develop uveitis. This is usually an anterior uveitis, but is atypical in that it may start as a bilateral uveitis, unlike the other B27 associated conditions and may have a possible chronic course. In a small percentage of patients, the uveitis is also associated with keratitis, dry eye or conjunctivitis.

Inflammatory Bowel Disease

The inflammatory bowel diseases are a spectrum of similar conditions that include within them the two well-known syndromes of Crohn's disease and Ulcerative colitis (UC). These conditions are characterized by a recurrent, often bloody diarrhea associated with abdominal cramping. These patients may have a non-destructive arthritis that manifests as large joint effusions. Although associated with HLA-B27, these conditions also show an independent association with ankylosing spondylitis.

Ocular involvement in UC may take the form of conjunctivitis, episcleritis/scleritis, peripheral ulcerative keratitis or uveitis. Patients with scleritis and IBD are more likely to HLA-B27 negative and to have no associated sacroiliitis. Uveitis with IBD generally occurs in a setting of HLA-B27 positivity and sacroiliac involvement (although uveitis with UC and HLA-B27 negativity is more common than with the other conditions described above). Unlike the classic uveitis associated with the B27 gene, uveitis in IBD may occur in both eyes simultaneously and is subacute or chronic in up to 50% of cases of Crohn's associated uveitis. It may be more extensive than typically seen, with vitritis and retinal vasculitis, again more common in Crohn's than in UC.

Undifferentiated Spondyloarthropathy

This condition is diagnosed in patients with a spondyloarthropathy that does not fall clearly into one of the categories mentioned above. Uveitis may occur in both eyes simultaneously in these conditions and may be chronic. Vitritis, retinal vasculitis and exudative retinal detachment may also occur.

4. DIAGNOSTIC TESTING

Although opinions vary as to the importance of the diagnostic testing for the HLA-B27 gene, we believe that all patients with recurrent anterior uveitis and the absence of another clear etiologic agent, must be tested for HLA-B27, because of its prognostic implications and because it may help in therapeutic planning. Patients who give a history suggestive of a spondyloarthropathy should be tested for the HLA-B27 gene irrespective of the location of the uveitis and the number of episodes. We believe that patients with a suggestive history should be screened for the gene even if they present with a first episode of uveitis.

5.

Treatment

Treatment of the acute uveitis is with topical steroids and cycloplegics. Periocular steroids are indicated in severe inflammation. The inflammation associated with the B27 gene has traditionally been viewed as easy to control, but as mentioned above, and discussed in the section on complications and prognosis, recurrences may be more frequent than in idiopathic recurrent uveitis and the complication rate is higher. Therefore, many patients require something additional to prevent recurrences of the uveitis and the complications associated with repeated topical steroid use.

NSAIDs may be invaluable in these patients not only in preventing recurrences but also in controlling the joint inflammation. In patients who are not controlled on NSAIDs, other immunomodulatory agents may have to be added. We believe that chronic systemic steroid therapy is not a choice because of their side effects. Non-alkylating immunosuppressive agents are the next drugs of choice in the case of failure with NSAIDs. There is experience in the use of methotrexate and azathioprine in these patients and a recent review of our 25 year experience in the use of methotrexate at the Massachusetts Eye and Ear Infirmary shows good efficacy in these patients, although less so than in patients with idiopathic uveitis (unpublished data). Immunosuppressives are also used in patients who are unresponsive to topical steroids or are steroid dependant. They may also be indicated in posterior pole involvement. In the case of failure to control recurrence of inflammation with adequately high doses of non-alkylating immunosuppressives, a combination of non-alkylating agents or the use of alkylating agents may have to be considered. Intravenous immunoglobulin has been suggested as another option in patients with posterior pole involvement who fail to respond to or are unable to tolerate the above medications, although there is very limited experience in the use of this modality especially in this particular cohort of patients.

6. COMPLICATIONS AND

Prognosis

The prognosis in patients with HLA-B27 associated uveitis is controversial. Although some authors report no significant differences or, indeed, a better prognosis in patients with an HLA-B27 haplotype than in patients with idiopathic uveitis, others show just the opposite. A review of our data at the MEEI Uveitis Service shows that B27 positive patients had more severe inflammation, more recurrences, a higher complication rate and worse visual outcome (11% of patients with visual acuity less than 20/200 compared to 2% in B27 negative patients) than patients with idiopathic uveitis. Complications included extensive, persistent synechiae, glaucoma secondary to the inflammation itself or to the use of topical steroids, vitritis, papillitis and cystoid macular edema. The HLA-B27 patients were also more likely than the idiopathic patients to require systemic therapy for the ocular condition, and this was even more so in patients with systemic disease associated with the B27 positive uveitis.

Posterior segment involvement in HLA-B27 associated uveitis is an under recognized phenomenon, with some studies reporting a very small percentage of patients with HLA-B27 associated uveitis as having posterior segment involvement. However, posterior segment involvement in these patients has been emphasized in European data and a review of our cases showed posterior involvement in 17% of patients. Although this may be an overestimate due to the concentration of 'difficult' cases in a subspecialty referral center, it nevertheless emphasizes the point that HLA-B27 associated disease is not necessarily restricted to the anterior segment of the eye.

7.

Conclusions

HLA-B27 associated uveitis is a recurrent condition that may be more severe and persistent than idiopathic anterior uveitis. It may also have more extensive ocular involvement and therefore a worse visual prognosis than idiopathic uveitis. Testing for this gene is thus important, as it helps the ophthalmologist identify a cohort of patients who may be more difficult to control and require more aggressive therapy to prevent potential sight-threatening consequences. Testing by the ophthalmologist may also be the first step in establishing the diagnosis of an associated systemic condition. Patients with uveitis and the HLA-B27 haplotype should be informed of the recurrent nature of their disease, the probable association with systemic disease and the potential for

developing sight-threatening ocular complications. Ophthalmologists should keep a low threshold for the initiation of systemic therapy in patients with this condition. Although NSAIDs are the first line systemic drugs and often the mainstay of treatment in this group of patients, over 20% may require the addition of immunosuppressive agents to achieve control of their inflammation.

8. REFERENCES

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REVIEW QUESTIONS FOR HLA-B27 ASSOCIATED UVEITIS

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1. All are features of HLA-B27 associated uveitis EXCEPT:

Anterior uveitis

Acute onset

Iris atrophy

Posterior synechiae

2. Which one statement is true regarding HLA-B27 associated uveitis :

Ankylosing spondylitis is a disease found in men only

Scleral thinning is a relatively common feature

Reiter's syndrome always follows symptomatic urinary tract infection

Posterior segment involvement may occur

3. All the following are true EXCEPT:

A) Crohn's disease is associated with a substantial incidence of posterior involvement

B) Inflammatory diseases of the bowel can be associated with uveitis and sacroiliitis

C) Psoriasis can be associated with uveitis in the absence of arthritis

D) Post-infectious arthritis in HLA-B27 positive individuals is associated with uveitis

4. HLA-B27 associated uveitis is found in all of the following diseases EXCEPT:

A) Crohn's

B) Reiter's

C) Behcet's

D) Psoriatic Arthropathy

5. Which one of the following is true about HLA-B27 associated uveitis:

It is present in over 50% of people with the HLA-B27 gene

B) It is

6. All of the following are useful in the management of HLA-B27 associated uveitis EXCEPT:

Methotrexate

Topical steroids

Cycloplegics

Colchicine

NSAIDs

7. A 28 year old male presents to the clinic with a two day history of pain and photophobia in the left eye. On examination he has 2+cells in the anterior chamber of the left eye, with no other significant finding. Examination of the right eye is within normal limits. Review of systems is significant for allergy to penicillin and occasional headaches. What would be the next most appropriate step in the management of this patient:

A) Reassure patient and send him home with follow up in 4 weeks

B) Prescribe topical cycloplegic drops and topical steroid drops

C) Prescribe topical cycloplegic and steroids drops and investigate for the cause of uveitis, including HLA-B27

D) Prescribe oral NSAIDs

8. The same patient presents 4 months later with severe pain and blurriness of vision in the right eye, that he noted when he woke up that morning. Examination of the right eye shows 3+ cells and flare and a 2mm hypopyon. Examination of the left eye is within normal limits. On enquiry, the patient remembers noting some back stiffness for the past few months. What would be the most appropriate steps at this stage:

A) Reassure patient and send him home with follow up in 4 weeks

B) Prescribe topical cycloplegic drops and topical steroid drops

C) Prescribe topical cycloplegic and steroids drops and investigate for cause including HLA-B27 and a sacroiliac joint X-ray

D) Prescribe oral NSAIDs

9. A 35 year old male presents to the clinic with reduced vision and a red eye, OD, for the last 2 days. This is the first such episode. Review of systems discloses occasional pain on the back of his ankles. There is a history of prostatitis 3 months ago, but the patient does not remember if any causative organism was found. On examination, OD is diffusely injected, and he has 3+ cells and flare in that eye. The OS is within normal limits. The most appropriate steps at this stage would be:

A) Reassure patient and send him home with follow up in 4 weeks

B) Prescribe topical cycloplegic drops and topical steroid drops

C) Prescribe topical cycloplegic and steroids drops and investigate for cause including HLA-B27

D) Prescribe oral NSAIDs

10. A 32 year old female with a history of recurrent anterior uveitis and HLA-B27 positivity has had episodes of uveitis 4 times in the last 5 months. Her episodes have typically responded to steroids and her pressures have always been within the normal range. She wants to know what you plan to do in the case of later episodes of uveitis.

A) Reassure the patient that HLA-B27 associated uveitis is a benign condition that is typically easily treated with topical steroids

B) Discuss with the patient the need for NSAID therapy to prevent recurrences and complications due to topical steroids

C) Discuss with the patient the need for chlorambucil therapy

D) Advise a cataract extraction