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REVIEW ARTICLE

Clinical Spectrum of HLA-B27-associated Ocular Inflammation

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ABSTRACT

Human leukocyte antigen (HLA)-B27-associated anterior uveitis (AU) is the most commonly diagnosed form of AU and represents the largest entity of non-infectious uveitis around the world. The most typical ocular manifestation associated with HLA-B27 consists of unilateral AU of acute onset. The HLA-B27-associated acute AU represents a distinct clinical entity occurring typically in young adults between the ages of 20 and 40 years. HLA-B27-associated acute AU is typically unilateral and lasts usually several weeks and diminishes within 3 months in the majority of patients. The anterior chamber shows typically severe cellular reaction and flare, as well as a fibrinous exudate. Frequently, posterior synechiae are formed and occasionally hypopyon is present. The pattern of the disease is recurrent with a full remission between the attacks. Intraocular pressure during active periods is typically low due to inflammation of ciliary body and decreased aqueous production. Less typical presentations are also recognized and include the development of chronic inflammation, posterior segment involvement, episcleritis, and scleritis. An isolated retinal vasculitis in HLA-B27-positive patients may develop, mostly in those with inflammatory bowel disease. Chronic AU, which may be either unilateral or bilateral affects up to 20% of patients. Ocular complications of HLA-B27-associated AU are diverse and include commonly posterior synechiae, cataract, glaucoma and/or hypotony. The visual outcome and complications of HLA-B27-associated AAU are frequently being compared with HLA B27-negative patients with AU and show that the prognosis of HLA-B27-associated uveitis is rather favorable, as <2% developed legal blindness and <5% visual impairment. A novel algorithm called the "Dublin Uveitis Evaluation Tool (DUET)" has been proposed to guide ophthalmologists to refer appropriate HLA-B27-positive patients with uveitis to rheumatologists.

Keywords: HLA B27-associated uveitis, clinical manifestations, anterior uveitis, acute anterior uveitis

Uveitis represents an important ocular manifestation in patients with human leucocyte antigen (HLA)-B27-associated systemic disorders such as ankylosing spondylitis (AS), reactive arthritis, inflammatory bowel disease (IBD), and psoriatic arthritis, but HLA-B27-associated uveitis regularly manifests as an isolated ocular disorder without other systems being involved. HLA-B27-associated acute anterior uveitis (AAU) represents the most frequent ocular disorder associated with HLA-B27.

Anterior uveitis (AU) is the most common form of uveitis encountered by ophthalmologists in the majority of populations.[1–3] AU reaches prevalence of 80% in the total uveitis population in general ophthalmological practice, but the prevalence of AU from tertiary centers, which are a subject to referral bias towards posterior and

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panuveitis, tends to be much lower (~25%).[1–3] The prevalence of HLA-B27 varies among different population groups. In most Caucasian populations, the prevalence of HLA-B27 is approximately 8%, while in African, Arab, and Asian populations, the prevalence is lower (~1–5%), which also reflects the lower prevalence of HLA-B27-associated AU in these regions (0.3–14% vs 13–32% in Caucasian populations).[4–6]

EPIDEMIOLOGY AND FREQUENCY OF HLA-B27-ASSOCIATED UVEITIS

The frequencies of HLA-B27-associated AU in large surveys of uveitis are illustrated in Table 1, in which the studies from the last decade are summarized.[2,6–29] The HLA-B27-associated AU was diagnosed in approximately 2–14% in large surveys, which included all patients with uveitis. This variation can be explained by the variable percentage of patients with anterior uveitis in a given series and moreover, depends on HLA-B27 frequency in a specific population and probably on yet unidentified environmental factors. Studies which include AU or AAU patients solely, usually indicate a higher frequency of HLA-B27-associated uveitis of approximately 33–67% across different racial groups, except in one study from Saudi Arabia, in which HLA-B27-associated uveitis was only 0.6% (Table 2) .[5,30–37] In addition to genuine differences, these distinctions might be a consequence of

TABLE 1. Human leukocyte antigen (HLA)-B27-associated uveitis in uveitis surveys from the last decade.

							HLA-B27-associated AU in all	
First author, year	Country[a]	Patients (*n*)	AU (%)	IU (%)	Post-U (%)	Pan-U (%)	With uveitis (%)	With AU (%)
Grajewski et al. (2015)[7]	Germany	474	53	19	21	7	10	19
Llorenç et al. (2015)[8]	Spain	1022	52	9	23	15	13	24
Abdulaal et al. (2014)[9]	Lebanon	209	26	12	25	38	2.8	7.5
Rahimi et al. (2014)[10]	Iran	475	40	11	28	21	2	5
Al-Shakarchi (2014)[11]	Iraq	318	24	6	40	30	–	–
Al Dhahri et al. (2014)[12]	Saudi Arabia	642	37	5	11	47	4.8	7
Liberman et al. (2014)[13]	Chile	611	40	8	18	33	4	10
Nakahara et al. (2014)[14]	Japan	468	41	1	17	41	3	7
Silpa-Archa et al. (2014)[15]	Thailand	446	45	1	14	40	2	4.5
Sittivarakul et al. (2013)[16]	Thailand	254	35	10	20	35	8	22
Nizamuddin et al. (2013)[17]	Saudi Arabia	587	57	8	9	26	0.3	5
Barisani-Asenbauer et al. (2012)[18]	Austria	2619	60	15	18	7	10	17
Cimino et al.[19] (2010)	Italy	1064	51	6	23	20	5	–
Jakob et al. (2009)[2]	Germany	1598	52	26	16	7	7	15
De-la-Torre et al. (2009)[20]	Colombia	693	29	4	36	31	–	–
Kitamei et al. (2009)[6]	Japan	1240	45	-	5	50	4	9
Keino et al. (2009)[21]	Japan	834	27	1	22	50	2	7
Das et al. (2009)[22]	India	308	47	13	30	10	11	23
Hamade et al. (2009)[23]	Saudi Arabia	488	60	6	11	24	2	17
Kazokoglu et al. (2008)[24]	Turkey	761	53	7	13	28	2.4	7
Pathanapitoon et al. (2008)[25]	Thailand	200	25	9	46	21	6	24
Rathinam et al. (2007)[26]	South India	8759	57	10	11	22	–	–
Khairallah et al (2007)[27]	North Africa	472	35	16	28	21	4.4	13
Sengun et al. (2005)[28]	Turkey	300	44	9	27	21	2	3
Yang et al. (2005)[29]	China	1752	46	6	7	42	14	31

[a]All tertiary centers except in the study of Rathinam SR, et al.,[26] which was community-based.
AU, anterior uveitis; IU, intermediate uveitis; Post-U, posterior uveitis; Pan-U, panuveitis.

TABLE 2. Human leukocyte antigen (HLA)-B27-associated uveitis among patients with acute anterior uveitis.

First author, year	Country	Patients with AU (*n*)	Positivity of HLA-B27 in patients with AAU (%)	Associated HLA-B27 systemic diseases (%)
Karaconji et al. (2013)[30]	Australia	241	39	11
Torres et al. (2013)[31]	Cuba	83	55	59
Bawazeer et al. (2013)[5]	Saudi Arabia	335	0.6	Not determined
Mathur et al. (2012)[32]	India	42	33	14
Mishra et al. (2011)[33]	India	89	56	4.5
Park et al. (2009)[34]	Korea	82	67	53
Accorinti et al. (2010)[35]	Italy	165	36	50
Pathanapitoon et al. (2006)[36]	Thailand	121	44	15
Tuncer et al. (2005)[37]	Turkey	109	40	Not determined

AAU, acute anterior uveitis.

variable referral to tertiary centers and might be also influenced by an inconsistent work-up for uveitis, including the testing for HLA-B27. Similarly, the frequency of systemic disease associated with HLA-B27-associated uveitis seems to be lower in Japan (1.3%), India (15%), and Thailand (15%) when compared with Western countries (~50%).[14,32,35,36,38] The association of AS with HLA-B27 is about 90%. The male preponderance in HLA-B27-associated AU is usually emphasized (up to 3 times more frequently than in females), though some studies showed no difference between the genders.[30,34,35,39] Males suffer commonly from AS, while females had later onset of systemic disease characterized by undifferentiated spondyloarthropathy and peripheral arthritis.[40–42]

Types of Ocular Inflammation Associated with HLA-B27

The most typical ocular manifestation associated with HLA-B27 consists of unilateral AU of acute onset. The HLA-B27-associated AAU represents a distinct clinical entity occurring typically in young adults between the ages of 20 and 40, and has a frequent association with seronegative arthritic syndromes, of which the most prevalent is AS.[43] Less common forms of ocular involvement include chronic AU, which is more common in females, and non-AS systemic disorders, such as IBD and psoriatic arthritis. Involvement of the posterior segment (including complications of AU or genuine posterior uveitis) was also observed as well as scleritis.[44] The activity of uveitis is not necessarily correlated with the activity of systemic HLA-B27-associated disease.[45]

The HLA-B27-associated AAU is typically unilateral and the intraocular inflammation usually lasts several weeks and diminishes within 3 months in the majority of patients. Occasionally, in severe cases, the time to remission may take longer than the 3 months, which is usually considered as a division border between acute and chronic forms of uveitis. The pattern of the disease is recurrent and HLA-B27-associated AAU is characterized by a full remission between the attacks.[46] The course of HLA-B27-associated AAU has a tendency to occur in the first affected eye, may alternate between the eyes, but both eyes are almost never affected at the same time.[47] The first episode of HLA-B27-associated AAU commonly occurs in young adult patients and the frequency of attacks decreases with the age of the patients. The cause of the AAU recurrences is not entirely known; the possible provoking triggers include infections with Gram-negative bacteria, stress, specific season, and trauma.[48]

Intraocular pressure (IOP) during active periods is typically low due to inflammation of ciliary body and decreased aqueous production. Sometimes, IOP may be high due to trabeculitis, accumulation of inflammatory cells, and debris in the trabecular meshwork, or the high IOP steroid response. In hypotonic eyes, the circulation of the cells in the anterior chamber diminishes and the trabecular meshwork might easily become damaged, which leads to persistent high IOP even after the inflammation subsides. The lower capacity of outflow in patients with iridocyclitis might result in a situation when IOP is low during the attacks (due to decreased aqueous production) and becomes elevated after the inflammation becomes quiet and the aqueous production is restored. In such cases, the quick change from high to low IOP is typical. Posterior segment involvement during AAU is relatively rare, but cystoid macular edema (CME) and disc edema may develop.

Less Common Forms of HLA-B27-associated Uveitis

While acute or recurrent, unilateral AU is the most typical presentation for HLA-B27-associated ocular inflammation, less typical presentations are also recognized, and include the development of posterior segment inflammation; chronic or persistent anterior uveitis; as well as episcleritis and scleritis. Of these less typical presentations, posterior segment involvement in a patient with HLA-B27-associated uveitis is perhaps most common, and can include vitritis with or without pars plana exudates, optic disc swelling or papillitis, and CME.[46,49–51] Hypotony maculopathy has also been reported in association with severe HLA-B27-associated AU, but is rare.[52,53] It is important to separate genuine inflammatory involvement located in the posterior segment from what can be considered complication of AU, such as CME. Such posterior segment complications occur most often in the setting of moderate to severe AU and, as such, are perhaps more appropriately considered spillover or secondary complications of co-existing anterior segment inflammation.[54] A noteworthy exception appears to be the occurrence of isolated retinal vasculitis in a patient with IBD, most often due to Crohn's disease.[55–57] Chronic AU, which may be either unilateral or bilateral, is also well recognized in HLA-B27-positive patients, affecting up to 20% of patients in some clinic-based cohorts.[39,58–60] By definition, patients with chronic HLA-B27-associated uveitis require longer-term treatment, often including systemic immunosuppression. Both bilateral involvement and a chronic disease course appear to be more common in women and children. HLA-B27-associated episcleritis and scleritis are uncommon, but can occur.[61–63] HLA-B27-associated posterior scleritis, while reported, appears to be uncommon.[44]

Complaints and Ocular Clinical Examination

HLA-B27-associated uveitis is generally a benign non-granulomatous unilateral disease presenting with a sudden onset of a classic triad of pain, redness, and photophobia. A 1- or 2-day stage of ocular discomfort may precede the typical manifestations. Blurred vision can also be present due to intense exudation into the anterior chamber and anterior vitreous. This decrease in visual acuity is greater than in those patients who are HLA-B27-negative.[46] During AAU, patients typically complain of pain and photophobia; ocular pain during near distance activities, as reading is also typical and points out to the presence of cyclitis. Patients with recurrences commonly recognize this pattern and consult their ophthalmologist at an early stage, sometimes even before cells in anterior chamber become detectable. On the other hand, if a patient during an active attack of HLA-B27-associated AAU reports less pain and photophobia, usually this indicates that activity of uveitis is decreasing. This pattern of subjective complaints preceding the objective signs might be useful when adjusting the treatment.

The main external signs are conjunctival and limbal hyperemia. Corneal edema may develop due to a combination of endothelial decompensation and low intraocular pressure. Anterior segment involvement may include fine whitish-gray keratic precipitates and fibrin on the endothelium. Typically, there are no mutton-fat keratic precipitates.[64] The anterior chamber shows cells and flare, due to the breakdown of the blood-aqueous barrier, and in severe inflammation, a fibrinous exudate in the anterior chamber may occlude the pupil, ending up with an iris bombé.

Fibrinous membrane formation in the absence of granulomatous keratic precipitates is a classic presentation of HLA-B27-positive anterior uveitis.[64] Sanghvi et al. reported four patients that could not be distinguished from endogenous endophthalmitis. These patients occupied a position at the margin of the spectrum of severity; their symptoms were hyperacute, with very severe fibrinous uveitis, including vitritis, which gave rise to suspicion of infectious endophthalmitis.[65] Most patients present with an intense cellular reaction, 3+ cells in >60% of them. Iris vessels may be dilated and rarely, spontaneous hyphema can occur. Due to severe inflammation, posterior synechiae can occur in about 13% of the patients in the acute phase of the disease.[58,59] Typically, the intraocular pressure in the affected eye is lower than in the contralateral eye as a result of diminished aqueous humor production by the inflamed ciliary body. More severe cases with hypotony defined as intraocular pressure <6 mmHg have been reported. van der Veer et al. reported five patients who developed severe anterior uveitis with nearly identical symptoms, and were specifically associated with hypotony and a serous retinal detachment.[53] The incidence of hypopyon among HLA-B27-positive patients with AAU was 14.5% compared with 2.2% in HLA-B27-negative patients. In those patients with more severe presentations and posterior segment involvement, the incidence of hypopyon was 25% compared with 4.4% of patients without posterior segment involvement.[66] Cells are commonly found in the anterior vitreous and more rarely, patients can develop diffuse vitritis.[50]

Additional Examinations

Referral to Rheumatologist or Other Specialist

An HLA-B27 test should be performed on all patients with recurrent non-granulomatous AU because both the natural history and the outcomes will be different from HLA B27-negative patients. On the other hand, seronegative spondyloarthropathies are strongly associated with both AU and HLA-B27 positivity.[67] HLA-B27-positive AAU may have posterior segment complications that may need additional testing. CME, papillitis, and retinal vasculitis have been reported as posterior segment manifestations. Braakenburg et al. reported nine HLA-B27-positive patients with uveitis and retinal vasculitis. Ocular coherence tomography (OCT) and fluorescein angiography may be indicated to detect these complications.[49,50,58,68]

Patients with HLA-B27-associated AU are highly likely to develop several (presumably autoimmune) diseases known as "seronegative spondyloarthropathies" since their rheumatoid factor is negative. The likelihood of HLA-B27-positive patients with uveitis to develop a rheumatic disease varies from 33% to 90% according to several studies.[43] Although the rheumatologic symptoms preceded the first attack of uveitis in >80% of the cases, there are still a number of patients in whom uveitis is going to be the first sign. The ophthalmologist may be the first physician to suspect spondylitis or sacroiliitis. The prevalence of a rheumatic disease increases with the duration of the disease, and since rheumatologic symptoms may be overlooked as nonspecific, the ophthalmologists may play a central role in diagnosing ankylosing spondylitis.[69] The novel evidence-based algorithm called the "Dublin Uveitis Evaluation Tool (DUET)" has been proposed to guide ophthalmologists and primary care physicians to refer appropriate AAU patients to rheumatologists.[70]

Visual Outcomes and Complications

Ocular complications in HLA-B27-associated AU are diverse, and include commonly posterior synechiae, cataract, ocular hypertension, or glaucoma and hypotony (Table 3) .[25,30,31,34,35,39,60] Epiretinal membrane and

TABLE 3. Ocular complications of human leukocyte antigen (HLA)-B27-positive anterior uveitis and HLA-B27-negative anterior uveitis.

First author, year Country	Patients with AU (*n*)		Follow-up duration	Follow-up at time of complications	Posterior synechiae (%)		OHT/Glaucoma (%)		Cataract (%)		CME (%)		Special comments
	HLA-B27+	HLA-B27–			B27+	B27–	B27+	B27–	B27+	B27–	B27+	B27–	
Torres et al. (2013)[31]	46	37	At least 6 months	End of follow-up per patient	69	56	NA/16	NA/30	45	26	30	10	All chronic cases were excluded.
Cuba													No difference in complications between HLA-B27-positive and -negative AU
Karaconji et al. (2013)[30]	95	146	At least12 months	At 3 months, per patient	9	2	0/0	3/3	1	3	0	2	All chronic cases were excluded.
Australia													HLA-B27-negative AAU tended to have moreassociated complications and poor visual outcome
Park et al.[34] (2009)	55	27[a]	Median 36.5 months	End of follow-up, per affected eye	23	12	27/2	40/10	6	15	9	2.5	No difference in complications between HLA-B27- positive and -negative AU
Korea													
Accorinti et al. (2010)[35]	60	105	Mean 33.41 ± 30.31 months (range 4–99 months)	End of follow-up, per patient	26	22	5/5	3/3	10	9	2.4	2.5	No difference in complications between HLA-B27-positive and -negative AU
Italy													
Pathanapitoon et al. (2006)[25]	53	68	Mean 20 months	End of follow-up, per patient	9	7	21/19	40/31	13	18	5	3	All chronic cases were excluded. Ocular hypertension was more common in HLA-B27-negative AU
Thailand													
Loh et al.[60] (2010)[b]	99		Mean 2.1 years	At presentation, per affected eye[a]	17	NA	NA/NA	NA/NA	14	NA	NA	NA	Risk of complications higher in chronic AU, male gender, and poorly-controlled and chronic inflammation
USA													
Braakenburg et al. (2008)[39]	177		At least 12 months, 80 patients >10 years	At 12 months, per patient	44	NA	11/2	NA/NA	11	NA	13	NA	Long-term visual prognosis in HLA-B27-positive AAU is favorable. Males suffer earlier from systemic disorder, but over time the prevalence is similar to females
The Netherlands				At 10 years, per patient	48	NA	10/5	NA/NA	11	NA	9	NA	

[a]Only idiopathic HLA-B27-negative AU included.

[b]During the follow-up, the incidence of new complications per eye-year was for ocular hypertension 0.10, for cataracts 0.09, posterior synechiae 0.05, cystoid macular edema 0.016, hypotony 0.006, and visual loss (to ≤20/200) 0.023.

AAU, acute anterior uveitis; OHT, ocular hypertension; CME, cystoid macular edema; NA, not available.

band keratopathy can occur, but are less frequent. The incidence rate of any ocular complication was 0.22/eye-year, which is lower than in other uveitis entities, such as juvenile idiopathic arthritis-associated uveitis or uveitis associated with Behcet disease.[60] The most common complications consisted of elevated IOP, followed by the development of cataract and synechiae, but the incidence of secondary glaucoma is not known. Chronic inflammation occurred in approximately 20% of patients and was associated with a higher rate of ocular complications.[60] CME occurred in 10–30% of HLA-B27-associated AU and prolonged subclinical macular edema was documented by OCT, even despite full clinical and functional recovery.[71,72]

The visual outcome and complications of HLA-B27-associated AAU are frequently being compared with HLA-B27-negative patients with AU or AAU and therefore, the results of such studies slightly vary according to the etiology of HLA-B27-negative counterparts. The comparisons of HLA-B27-positive and -negative AU outcomes are obviously related to the causes of HLA-B27-negative AU in a given population, which might be very different in different areas of the world. Moreover, the comparison with only idiopathic cases depends also on their previous work-up (e.g., exclusion of viral causes based on clinical findings solely, or substantiated by intraocular fluid assessment).

The visual prognosis of HLA-B27-associated uveitis is rather favorable as <2% developed legal blindness and <5% visual impairment. Despite the potential for moderate-to-severe vision loss in up to 10% of patients with HLA-B27-associated uveitis, individual episodes of anterior uveitis tend to resolve within 4–6 weeks when adequately treated, and the overall prognosis is generally good.[58,73,74] Loh and Acharya estimated the risk of complications and vision loss to be ≤20/50 at some stage during the course of disease, and to be 10-fold greater in patients with moderate-to-severe inflammation and nearly three times greater in patients with chronic HLA-B27-associated uveitis. They added, however, that vision improved to ≥20/40 with treatment in nearly 75% of these patients.[60] The risk factors for developing visual loss included the presence of posterior synechiae at presentation, corticosteroid-sparing therapy, corticosteroid periocular injections, poorly-controlled inflammation, chronic development, and male gender.[60] Intraocular surgery in patients with HLA-B27-associated uveitis has to be taken seriously and a preventive treatment around the surgery with systemic and local steroids should be given even in a quiet eye with previous HLA-B27-associated uveitis.[75–78]

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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