HLA antigen typing in patient with chronic uveitis & in patients with Behcet's disease presenting with chronic uveitis

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الخلاصة:
التهاب عنبية العين المزمن يعتبر من الاسباب المهمة لتضرر وتلف حاسة الابصار ويعتقد ان هنالك اسباب مناعية قد تقف خلف هذا الالتهاب.ان الهدف من هذا البحث هو دراسة وجود علاقة بين مستضد الكريات - البيضاء البشرية في المرضى المصابين بالتهاب عنبية العين المزمن في مرضى بهجت المصابين بهذا الالتهاب .لقد تم ادخال ٤٤ مريضا عراقيا من المصابين بالتهاب عنبية العين المزمن ممن راجعو مركز العيون في مستشفى الحكيم العام للفترة من ٢٠٠٩ ولغاية ٢٠١١ حيث تم فحص مستضد الكريات - البيضاء البشرية في كل هؤلاء المرضى والذين من ضمنهم فقط ٦ مرضى لديهم مرض بهجت حيث لوحظ عدم وجود اية علاقة احصائية مهمة بين نمط مستضد الكريات - البيضاء البشرية وبين التهاب عنبية العين المزمن في حين ان نمط مستضد الكريات - البيضاء البشرية من النوع B51 كان موجودا في كل المرضى المصابين بمرض بهجت ويشكون من التهاب عنبية العين المزمن.

Abstract:
Background: Uveitis is a significant cause of visual impairment and immune mechanisms are thought to be involved in the pathogenesis of disease. The main aim of this study is to find a relationship between specific HLA antigen pattern in patients with chronic uveitis and in patients with Behçet's disease presenting with chronic uveitis in Iraqi patients.
Patients and methods: A total number of 44 Iraqi patients (male=18 & female=26) with mean age 31,4 years that had been referred and examined at the ophthalmology center from January 2009 to march 2011 were enrolled in our study. Only 6 patients enrolled in the study (13,6%) fulfilled the criteria of Behçet's disease according to international classifications**.**
Results: There was no significant statistical association between HLA antigen and chronic uveitis in our study (p value = 0.98) and anterior uveitis occurred in about 24 patients (54.5%) and pan uveitis in 20 patients (45.5%) while intermediate uveitis was not diagnosed in our patients enrolled in this study. The 6 patients (13,6%) that fulfilled criteria for Behcet's disease (3 with anterior uveitis and 3 with panuveitis) and all the patients showed strong association with HLA B51 which is the more prevalent antigen in the patients enrolled in this study (27%)**.**

Introduction

Uveitis is a group of disorders that lead to inflammation of the iris, ciliary body, choroid, and adjacent Structures [1]and it may be induced in genetically susceptible individuals by different aetiological factors including infection, autoimmune, traumatic, or neoplastic events.[2]

The distribution of the types, clinical associations, and causes of uveitis in a given population is strongly influenced by various genetic, geographic, and environmental factors and the uveitis is a significant cause of visual impairment accounting for 10% of blindness in the Western world.[3]

Idiopathic uveitis is the most common form of chronic uveitis seen different parts of world and it is a heterogeneous entity in its clinical severity and immune mechanisms are thought to be involved.[4]

The role of the human leukocyte antigens (HLA) in the immune response is well established especially class I (*HLA*) that is closely associated with disease susceptibility in patients with uveitis and HLA genes have been shown to be associated with a number of uveitis entities, including Behcet disease, birdshot retinochoroidopathy, Vogt-Koyanagi- Harada (VKH) syndrome, sarcoidosis, sympatheticophthalmia and juvenile idiopathic arthritis.[5,6]

The strong association of HLA-A29 with birdshot chorioretinopathy was first reported almost 40 years ago [7] and patients with HLA-B27–associated uveitis typically have a recurrent, acute, unilateral or unilateral alternating, anterior uveitis[8].

Comparison of uveitis statistics from various countries is usually biased due to different patient selection, diagnostic work-up and criteria. However, when comparing different surveys on uveitis around the world, it may be seen that the anterior form of uveitis is the most common [9, 10] whereas intermediate uveitis has the lowest incidence [11].

On the other hand, idiopathic uveitis is the leading type in the turkey where the most frequently observed systemic disease was Behcet's disease [12]

Behcet's disease is a multisystem disorder and is common among people over the old Silk Road extending from China to Turkey with the highest numbers in Istanbul and Turkey and the lowest in the United States of America *and HLA-B51* is the primary gene involved in the pathogenesis of Behcet's disease [5, 13]

The main aim of this study was to find a relationship between HLA antigen pattern in patients with chronic uveitis and in patients with Behçet's disease presenting with chronic uveitis in Iraqi patients

Patients and methods

A total number of 44 Iraqi patients (male=18 & female=26) age range 31,4 years that had been referred and examined at the ophthalmology center in AL-Hakeem general hospital in AL-Najaf city from January 2009 to march 2011 were enrolled in our study.

All patients had a comprehensive ocular and systemic history, including an extensive review of medical systems with special emphasis regarding the rheumatologcal signs & symptoms, history of tuberculosis and toxoplasmosis, diagnostic criteria for Behcet's disease [14], ankylosing spodylitis [15] & family history of any rheumatological disorders or uveitis. Complete ophthalmic examination was performed in all cases, including best-corrected Snellen visual acuity, slit-lamp examination and dilated fundus examination with three-mirror lens.

Chronic uveitis has been defined as inflammation characterized by prompt relapse (in less than 3 months) after discontinuation of therapy according to criteria proposed by the International Uveitis Study Group (IUSG) [16].

The primary site of inflammation determines if the uveitis is anterior, intermediate, posterior, or panuveitis. If the primary structure is the anterior chamber, then the diagnosis is anterior uveitis. Likewise, an intermediate uveitis is an inflammatory

response located in the vitreous. Retinal or choroidal inflammation is designated as posterior uveitis, and inflammation at all sites is diagnosed as panuveitis.

Routine investigations done for the patients were included the erythrocyte sedimentation rate, antinuclear antibody, complete blood count, tuberculin test, anti tuberculus antibody, toxoplasmosis antibody and C-reactive protein.

HLA typing was done by two stage lymphocytoxicity micromethod, using a battery of 80 well defined HLA antisera. Several HLA antigen may be demonstrated in the same patient. Informed consent was obtained for each patient who was tested for *HLA* typing.

48 patients were enrolled as a healthy control group matched to age and sex to the group of uveitis and all of them had no features or evidence by history and examination for uveitis, ankylosing spondylitid and Behçet's disease.

Only 6 patients enrolled in the study (13, 6%) fulfilled the criteria of Behçet's disease according to international classifications [14] while on the other hand no patients meet the criteria for ankylosing spondylatis in this study.

Chi-square had been applied for categorized variables at level of significance $\alpha=0.05$ (p value <0.05) by using SPSS program version 17.

Results

There was no significant statistical association between HLA antigen and chronic uveitis in our study (p value = 0.98) (table 1).

Regarding the clinical type of uveitis, anterior uveitis was occurred in about 24 patients (54.5%) and pan uveitis in 20 patients (45.5%) while intermediate uveitis was not diagnosed in our patients enrolled in this study (table 2).

There were only 6 patients (13, 6%) that enrolled in this study that fulfilled criteria for Behcet's disease (3 with anterior uveitis and 3 with panuveitis) and all the patients showed strong association with HLA B51 which is the most prevalent antigen in the patients enrolled in this study (27%) (Table 2) and (table 3).

Table 1 comparison between patients with chronic uveitis with healthy control in distribution of HLA typing.

HLA antigen	Patients with chronic uveitis(n=44)	Healthy control(n=48)
A1	6 (13.6%)	8
A2	2 (4.5%)	8
A3	2(4.5%)	4
B45	6 (14 %)	5
B51	12 (27 %)	8
B6	8(18 %)	6
B8	4 (9 %)	4
CW1	2 (4.5 %)	2
CW3	2 (4.5 %)	3

Table 2 distribution of HLA antigen between the clinical types of uveitis and Behcet's disease

HLA antigen	Patients with Anterior uveitis(n=24)	Patients with Pan uveitis(*n*=20)	Patients with Behcet's disease(*n*=6)
A1	4	2	1
A2	1	1	null
A3	1	1	1
B45	3	3	null
B51	6	6	6
B6	5	3	null
B8	2	2	null
CW1	1	1	null
CW3	1	1	null

Table 3 characteristics of patients with Behçet disease with uveitis

variables		Number of patients
sex	male	2
	female	4
Pan-uveitis		3
Anterior uveitis		3
HLA B51		6
HLA A1		1
HLA A3		1

DISCUSSION

There is little studies that cover the subject of the HLA typing or the causes of uveitis in Iraq and surrounding Arabian countries despite the fact that Uveitis is a significant cause of visual impairment and its association with other systemic inflammatory disease.

The main finding of this study showed no significant association between HLA antigen and chronic uveitis.

The mechanisms by which most HLA molecules influence uveitis are unknown, and even in conditions with the strongest association; HLA cannot be the only genetic susceptibility.[17, 18]

Susceptibility to uveitis may be associated with HLA, but little is known about susceptible class II alleles or the potentially pathogenic epitopes that they present and there is evidence that an autoimmune response to retina may causally involved in pathogenesis of human uveitis and leading to identifying and isolating retinal Ag-specific T cells from uveitis patients and may facilitate their development as biomarkers for the disease.[19]

Recent evidence have shown that polymorphisms of a number of immune response genes including HLA and non-HLA genes (such as TNF and some chemokines), may contribute to the susceptibility to some uveitis entities.[2]

Furthermore, HLA-B27-negative anterior uveitis tends to be a more heterogeneous entity that demonstrates a tendency toward being more likely to be bilateral, chronic uveitis, which is infrequently associated with systemic diseases. [20]

Other finding of our study showed a very strong association of Behçet disease causing uveitis (all the 6 patients) with HLA B51.

Several studies have confirmed this association in Japanese, Isreli, Turkish, and Saudi patients and demonstrate that the HLA-B5 is the primary gene involved in the pathogenesis of Behc¸et disease that can aid in the diagnosis [21, 22]

HLA status in Behçet's disease has supported the idea of an immunogenetic predisposition ever since a strong association with HLA-B5 was first described by Ohno *et al* in Japanese patients in 1973 [21] and Ocular involvement occurs in 67 to 95% of patients with Behcet's disease and is usually late in the course of the disease[23].

In this study, the main limitations encountered include the followings:

first, the small number of patients, second it may subject to bias as it based on specialized ophthalmology center not on multicenter based study and the population sample of this study may not represent a random sample of the population in Iraq and third the accuracy and sensitivity of serological method for HLA typing used in this study may reach to 90% for class I HLA antigen.

Despite these limitations, this study provide a valuable knowledge and information regarding chronic uveitis and Behcet's disease in Iraq and open the way for further studies in these topics.

Conclusion: there was no significant association between specific HLA antigen and chronic uveitis and HLAB51 antigen appeared in all patients with Behcet's disease presenting with chronic uveitis

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