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ARTICLE

The association of uveitis with hepatitis B and hepatitis C viruses: a large-scale population-based study

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PURPOSE: To examine the association of uveitis with hepatitis B (HBV) and hepatitis C (HCV) chronic infections
METHOD: This is a population-based cross-sectional study. The study encompassed 13,183 consecutive patients with uveitis and 65,331control subjects. The prevalence of chronic HBV and HCV infections was compared between patients diagnosed with uveitis and age-, sex-, and ethnicity-matched controls. Lifetime prevalence rates of HBV and HCV were calculated for patients with uveitis and control individuals. Odds ratio (OR) for HBV and HCV was evaluated across different strata.
RESULTS: The lifetime prevalence rate of chronic HBV infection was greater in patients with uveitis than in controls (1.2% vs. 0.8%, respectively; $P < 0.001$). The association of HBV with uveitis was statistically significant among individuals older than 40 years of age, both sexes, and individuals of Jewish ethnicity. The lifetime prevalence of HCV was comparable between patients with uveitis and controls (0.8% vs. 0.7%, respectively; $P = 0.189$). Thus, no independently significant association was found between uveitis and HCV (fully-adjusted OR, 1.15; 95% CI, 0.93–1.42; $P = 0.211$).
CONCLUSIONS: Uveitis is associated with HBV. The association was more prominent among older and Jewish patients. Patients with uveitis may benefit from screening for HBV. An association between uveitis and HCV has not been found.

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INTRODUCTION

Uveitis is an umbrella term that includes a wide spectrum of intraocular inflammatory conditions in which the various parts of the eye may be attacked by the immune system [1]. More than two million patients worldwide have uveitis. Approximately 35% of these individuals experience severe visual loss and legal blindness [2].

Uveitis can be classified across several categories, including disease course, laterality, primary anatomic location of inflammation and morphologic features [3]. Some uveitis are associated with infection or systemic disease while others are immune-mediated and limited to the eyes [4]. The diagnosis of uveitis involves clinical findings (ocular and systemic), ocular imaging, laboratory tests, and imaging [3]. Treatment of the non-infectious uveitis includes corticosteroids and immunosuppressive drug therapy while treatment of infectious uveitis includes anti-infective drugs [5].

Hepatitis is defined as inflammation of the liver [6]. It can result from a variety of causes such as viruses, heavy alcohol use, autoimmune, drugs, or toxins [6]. Viral hepatitis from hepatitis B (HBV) hepatitis C (HCV) is considered the most common cause of hepatitis, worldwide. While viral hepatitis was found to elicit several immune-mediated conditions [7–9], its association with uveitis was poorly investigated. In the current study, we sought to evaluate the association of uveitis with HBV and HCV chronic infections using a large-scale study.

METHODS

Design and database

This population-based cross-sectional study was based on the ground of Clalit Health Services (CHS) database. CHS is the biggest healthcare maintenance organization in Israel, providing healthcare services for roughly 4,500,000 enrolees. CHS possesses an inclusive database with consistent input from pharmacies, clinical consultations, and administrative frameworks. Data retrieved from the CHS database consisted of demographic variables as well as diagnoses of chronic diseases.

The study was authorized by the institutional review board (IRB) of Ben-Gurion University in compliance with the declaration of Helsinki (approval code: 0212-17-COM).

Study population and variables

Patients were defined as having uveitis when a diagnosis of uveitis was documented (with ICD-9 code) by a board-certified ophthalmologist or in the discharge letters of patients admitted to inpatient ophthalmologic wards. All patients fulfilling these eligibility criteria between the years 1999 and 2020 were subject to inclusion. Viral Hepatitis were diagnosed with a blood test and positive results were documented with ICD- 9 code.

Five control patients were chosen for each case patient. Control individuals were arbitrarily selected from the list of CHS enrolees who lack a diagnosis of uveitis, and were matched to cases by age, sex, and ethnicity. Outcome measures were adjusted for demographic variables as well as for alcoholism and drug abuse. The latter diagnoses were extracted from the chronic disease registry of CHS.

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Table 1. Descriptive characteristics of the study population.

Characteristic	Patients with uveitis (*N* = 13,183)	Controls (*N* = 65,331)	*P* value
Age, years			
Mean (SD)	48.5 (20.0)	48.4 (19.9)	1.000
Median (range)	50.0 (0.1-93.0)	50.0 (0.1-93.0)	
Sex, N (%)			
Male	6,010 (45.6%)	29,784 (45.6%)	0.999
Female	7,173 (54.4%)	35,547 (54.4%)	
Ethnicity, N (%)			
Jews	10,103 (76.6%)	50,025 (76.6%)	0.872
Arabs	3,080 (23.4%)	15,306 (23.4%)	
BMI, kg/m^2; Mean (SD)	27.2 (8.0)	27.2 (6.2)	0.499
Smoking, N (%)	5,039 (38.2%)	23,435 (35.9%)	**<0.001**
SES, N (%)			
Low	5,363 (40.8%)	26,644 (40.9%)	0.976
Intermediate	5,158 (39.2%)	25,510 (39.1%)	
High	2,639 (20.0%)	13,065 (20.0%)	

N, Number; *SD*, standard deviation; *BMI*, body mass index; *SES*, socioeconomic status.

Table 2. The association between uveitis and HBV stratified by age, gender, and ethnicity and adjusted for putative confounders.

Subgroup	HBV in patients with uveitis (*N* = 13,183) N (%)	HBV in controls (*N* = 65,331) *N* (%)	OR (95%CI)	*P* value
All	164 (1.2%)	554 (0.8%)	1.47 (1.24–1.76)	<0.001
Age, years				
<40	34 (0.8%)	136 (0.6%)	1.25 (0.86–1.82)	0.250
40-59	73 (1.7%)	233 (1.1%)	1.57 (1.20–2.04)	0.001
≥60	57 (1.3%)	185 (0.8%)	1.52 (1.13–2.05)	0.005
Gender				
Male	93 (1.5%)	312 (1.0%)	1.51 (1.12–1.91)	0.001
Female	71 (1.0%)	242 (0.7%)	1.45 (1.11–1.89)	0.005
Ethnicity				
Jews	123 (1.2%)	409 (0.8%)	1.52 (1.24–1.86)	<0.001
Arabs	41 (1.3%)	145 (0.9%)	1.39 (0.97–1.97)	0.069
Multivariate analyses				
Age- and sex-adjusted OR (95% CI)			1.47 (1.24-1.75)	<0.001
Fully adjusted OR (95% CI)[a]			1.47 (1.23-1.75)	<0.001

N, Number; *OR*, odds ratio; *CI*, confidence interval.
Adjusted for age, sex, ethnicity, drug abuse, and alcoholism.

Statistical analysis

Distribution of demographic and clinical variables was compared between patients with and without uveitis utilizing t-test and Chi-square test, as indicated. The prevalence rates of HBV and HCV were estimated across the general study groups, as well as within age, sex, and ethnic subgroups. Crude and adjusted odds ratio (OR) and confidence intervals (CI) were demonstrated. Logistic regression was employed to investigate the independent association between uveitis and hepatitis viruses in a multivariate analysis. All statistical analyses were carried out by SPSS software, version 25 (SPSS, Chicago, IL, USA).

RESULTS

Our study consisted of 13,138 patients with a new diagnosis of uveitis and 56,331 age-, sex-, and ethnicity- matched control subjects. The mean (SD) age at presentation of uveitis and enrollment of controls was 48.5 (20). In all, 45.6% of study participants were males and 76.6% were of Jewish ethnic background. The prevalence of smoking was greater in patients with uveitis than in their control individuals (38.2% vs. 35.9%, respectively; $P < 0.001$). Characteristics of study population are further detailed in Table 1.

Hepatitis B chronic infection

The prevalence rate of chronic HBV infection was greater in patients with uveitis than in controls (1.2% vs. 0.8%, respectively). Therefore, a statistically significant association emerged between uveitis and HBV infection (OR 1.47; 95% CI, 1.24–1.76; P < 0.001). Table 2 demonstrates ORs for HBV in patients with uveitis as stratified by age, sex, and ethnicity. The association of HBV with uveitis was statistically significant among individuals older than 40 years of age, both sexes, and individuals of Jewish ethnicity (Table 2). The association fell short of significance in those aged

younger than 40 years and those belonging to an Arab ancestry (Table 2).

The association retained its statistical significance also following the adjustment for age and sex (age- and sex-adjusted OR, 1.47; 95% CI, 1.24–1.75; $P < 0.001$) as well as for age, sex, ethnicity, drug abuse, and alcoholism (fully-adjusted OR, 1.47; 95% CI, 1.23–1.75; $P < 0.001$; Table 2).

Hepatitis C chronic infection

The prevalence of HCV chronic infection was comparable between cases and controls (0.8% vs. 0.7%, respectively) lacking statistical significance (OR, 1.15; 95% CI, 0.93–1.41; $P = 0.189$). In a stratified analysis, uveitis failed to demonstrate a significant association with HCV in any of the age, sex, and ethnicity investigated strata (Table 3). Similarly, a multivariate logistic regression analysis did not reveal a significant association between uveitis and HCV infection (Table 3).

DISCUSSION

The current large-scale population-based study disclosed a significant association between HBV and uveitis. This association held true in both sex and was more prominent among older patients. The lifetime prevalence of HCV, on the other hand, was not increased among patients with uveitis.

The association between uveitis and different infections was examined in the past. [10–12] However, there are only few studies that examined the association between uveitis and hepatitis. Most of those studies, described the association between uveitis and autoimmune hepatitis, [13, 14] uveitis and drugs for hepatitis [15, 16], and uveitis and hepatitis B vaccine [17, 18]. There is only one study that examined the risk for uveitis among patients with HBV and HCV [19]. Tien et al. examined weather patients with viral hepatitis and cirrhosis are at risk of uveitis in the years following hepatitis [19]. They found that viral hepatitis may increase the risk of subsequent uveitis and that patients with HBV and HCV coinfection had the highest risk for subsequent uveitis [19].

We found that the lifetime prevalence of HCV among patients with uveitis is the same as for patients without uveitis. The underlying of mechanism of this observation is yet to be delineated. However, one putative explanation refers to the fact that the immune reaction of uveitis includes: cytotoxic antibodies, cell-mediated reactions and complement-mediated immune response [20]. These immune responses also work against HCV infection [21] so maybe when the immune system is working against the uveitis, it also working against the HCV. Therefore, uveitis does not associated with HCV. This hypothesis need to be examined in further studies.

HBV is a different type of virus. It is a 42-nanometer, partially double-stranded DNA virus classified in the Hepadnaviridae family while HCV is a 55-nanometer, positive-strand RNA virus classified in the Flaviviridae family [22]. HBV is approximately 5-10 times more infectious than HCV, and far more stable [21]. Moreover, nowadays, HCV is a curable disease while the treatment for HBV can delay or limit liver damage [22]. It was reported in the past, that patients with different inflammatory diseases are at increased risk for HBV [23–26]. Therefore, it was not surprising to find that also patients with uveitis are at increased risk for HBV. This association between uveitis with HBV is probably not casual in the current big population study.

The association of uveitis with HBV was most prominent among those above 40 years of age. It is known that in older ages individuals do not respond to immune challenge as robustly as the young [27]. Therefore, maybe when there are two factors that hint about weak immune system as old age and uveitis, it increase the risk for infectious disease like HBV.

Patients with intermediate uveitis, posterior uveitis, and pan-uveitis undergo different blood tests in order to find the trigger for uveitis [1]. HBV antigen and antibodies are not usually taken [1]. Nowadays HBV is a disease that can be prevented, by the HBV vaccine [28]. Therefore, according to the results of this study, asking about other risk factors for HBV should be included in the anamnesis of patients with uveitis, and in case of suspicion screening for HBV antibodies should be done. This may decrease the risk for HBV among patients with uveitis.

This study is not without limitations. One of the limitations is that there was no differentiation between the patients with anterior uveitis to intermediate, posterior and panuvitis. The latter are considered more severe [29] than the first and required more systemic treatment [29]. Moreover, there is no differentiation according to the aetiologies of uveitis. This is due to the fact that the data was collected primarily for the purposes of running a health system rather than for research. However, we do not think there is likely to be systematic bias in the way data were collected

Table 3. The association between uveitis and HCV stratified by age, gender, and ethnicity and adjusted for putative confounders.

Subgroup	HCV in patients with uveitis ($N = 13,183$) N (%)	HCV in controls ($N = 65,331$) N (%)	OR (95%CI)	P value
All	112 (0.8%)	484 (07%)	1.15 (0.93–1.41)	0.189
Age, years				
<40	16 (0.4%)	91 (0.4%)	0.88 (0.51–1.49)	0.623
40-59	54 (1.3%)	210 (1.0%)	1.28 (0.95–1.73)	0.106
≥60	42 (0.9%)	183 (0.8%)	1.13 (0.81–1.58)	0.475
Gender				
Male	66 (1.1%)	273 (0.9%)	1.20 (0.92–1.57)	0.185
Female	46 (0.6%)	211 (0.6%)	1.08 (0.79–1.49)	0.634
Ethnicity				
Jews	101 (1.0%)	443 (0.9%)	1.15 (0.92–1.43)	0.212
Arabs	11 (0.4%)	41 (0.3%)	1.37 (0.70–2.67)	0.356
Multivariate analyses				
Age- and sex-adjusted OR (95% CI)			1.14 (0.93–1.41)	0.196
Fully adjusted OR (95% CI)[a]			1.15 (0.93–1.42)	0.211

N, Number; *OR*, odds ratio; *CI*, confidence interval.
[a]Adjusted for age, sex, ethnicity, drug abuse, and alcoholism.

in relation to exposure and outcome that might lead to a spurious association. Another limitation is the ethnicity of the population in this study which included only Jewish and Arab subjects, reflecting the ethnic composition of the Israeli population. African and Asian [30], who are known for their increased risk of HBV were not represented in this study. Further prospective studies are needed to evaluate this epidemiological relationship in other ethnic groups as well as the differences between different types of uveitis. Moreover, owing to the cross-sectional design, the temporal relationship in which uveitis and hepatitis appeared was unknown. This interferes with drawing firm conclusions about causality.

In conclusion, we demonstrate a significant association of uveitis with HBV, but not HCV, chronic infection. The association was more prominent among older and Jewish patients. The current study should increase the awareness of clinicians about the need for HBV screening for patients with uveitis. Further research is required to investigate the effect of HBV on the phenotype of uveitis.

Summary

What was known before

- Uveitis is an umbrella term that includes a wide spectrum of intraocular inflammatory conditions in which the various parts of the eye may be attacked by the immune system.
- Viral hepatitis from hepatitis B (HBV) hepatitis C (HCV) is considered the most common cause of hepatitis, worldwide.
- While viral hepatitis was found to elicit several immune-mediated conditions, its association with uveitis was poorly investigated.

What this study adds

- There is a significant association between HBV and uveitis. This association held true in both sex and was more prominent among older patients.
- The lifetime prevalence of HCV was not increased among patients with uveitis.

DATA AVAILABILITY

Due to the nature of this research, the data cannot be shared publicly, so supporting data is not available.

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AUTHOR CONTRIBUTIONS

MK- Conception or design of the work, Data analysis, and interpretation, Drafting the article, Final approval of the version to be published. OZ—Conception or design of the work, Data analysis, and interpretation, Drafting the article, Final approval of the version to be published. KK—Conception or design of the work, Data analysis, and interpretation, Drafting the article, Final approval of the version to be published. ADC—Conception or design of the work, Data collection, Critical revision of the article, Final approval of the version to be published. OM—Critical revision of the article, Final approval of the version to be published. OW- Conception or design of the work, Critical revision of the article, Final approval of the version to be published.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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