HHS Public Access

Author manuscript

Ocul Immunol Inflamm. Author manuscript; available in PMC 2024 July 01.

Published in final edited form as:

Ocul Immunol Inflamm. 2023 July ; 31(5): 978–980. doi:10.1080/09273948.2022.2075760.

Prevalence of Epstein-Barr Virus in Patients with Intraocular Inflammation

Kareem Moussa, MD[1,2,3], **John A. Gonzales, MD**[2,3], **Jessica Shantha, MD**[2,3], **Nisha R. Acharya, MD, MS**[2,3], **Thuy Doan, MD, PhD**[2,3]

[1]Department of Ophthalmology and Vision Science, University of California, Davis, Sacramento, CA

[2]F.I. Proctor Foundation, San Francisco, San Francisco, CA

[3]Department of Ophthalmology, University of California, San Francisco, San Francisco, CA

Abstract

The relationship between Epstein-Barr Virus (EBV) infection and uveitis is unclear. We conducted an observational cross-sectional study to determine the prevalence of EBV in uveitis and to describe the clinical features of EBV positive uveitis cases. This study was carried out at the F.I. Proctor Foundation at University of California, San Francisco. All patients with suspected infectious uveitis who underwent unbiased metagenomic deep sequencing (MDS) were included. Demographics, testing information, and clinical features were documented. 11 out of 288 patients with suspected infectious uveitis had EBV detected by RNA-seq in intraocular fluid. The prevalence of EBV in uveitis in our study sample is 4%. 3 out of 11 EBV-positive eyes (27%) were found to have biopsy-proven vitreoretinal lymphoma. Future studies are needed to determine if EBV may drive the development of vitreoretinal lymphoma and if its presence should heighten the suspicion for vitreoretinal lymphoma.

Keywords

uveitis; intraocular lymphoma; ocular inflammation; ocular inflammation; molecular diagnostics

Introduction

Epstein-Barr Virus (EBV), also known as human herpesvirus 4, is one of the most common human viruses. A double-stranded DNA virus, it is perhaps best known as the cause of infectious mononucleosis and has also been associated with various lymphoproliferative disorders. The role, if any, that EBV may play in the pathogenesis of intraocular infection and inflammation remains elusive. Several case reports and small case series have suggested a possible link between EBV and uveitis[1–5]. Large polymerase chain reaction (PCR)-based observational studies have not identified a pathogenic role for EBV in the development of

Corresponding author: Kareem Moussa, MD, Assistant Professor of Ophthalmology, University of California, Davis, 4860 Y Street, Suite 2400, Sacramento, CA 95817, Phone: (916) 734-6074, kamoussa@ucdavis.edu.

Disclosure statement: The authors report there are no competing interests to declare.

uveitis, relegating EBV's role in uveitis to that of an innocent bystander rather than a direct pathogen[6–9].

Determining if EBV may play a pathogenic role in uveitis will help guide diagnostic and treatment considerations in patients with uveitis. Metagenomic deep sequencing (MDS) is a diagnostic tool capable of detecting any pathogen in minute amounts of fluid[10]. In this study, we sought to determine the prevalence of EBV in ocular fluid specimens in patients with uveitis presenting to a tertiary care referral center, and to describe the clinical features of eyes with EBV and uveitis.

Methods

Study Design

This is a descriptive observational cross-sectional study in which we sought to determine the prevalence of EBV in ocular fluid specimens obtained in patients with presumed infectious uveitis. This study adheres to the Declaration of Helsinki. It was approved by the Institutional Review Board at the University of California, San Francisco.

Study Population and Time Frame

All patients who presented for evaluation at the F.I. Proctor Foundation at University of California, San Francisco, were suspected of having infectious uveitis, and had RNA-seq MDS performed, as previously described, on an ocular fluid specimen (aqueous or vitreous fluid) between September 1, 2016 and December 1, 2019 were included in the study[10]. Demographic information, clinical features, and final diagnosis were collected for patients in whom EBV was detected.

Results

A total of 288 samples from 288 patients were included in the study. In patients in whom bilateral disease was present, the eye with the greater degree of inflammation underwent ocular fluid sampling and MDS. A total of 11 eyes (63.6% female), mean age 55.6 years (median age 56 years, range 27–78 years) had EBV RNA detected by MDS, all of whom did not have a known immunodeficiency including Human Immunodeficiency Virus (HIV). No other viruses were detected by MDS. The prevalence of EBV in our study population was 11/288 = 4%. Three of the 11 eyes with EBV (27%) were found to have biopsy-proven vitreoretinal lymphoma. A summary of the demographic and clinical features of the patients in our study population with EBV detected in ocular fluid can be found in Table 1.

Discussion

EBV infection is ubiquitous. Over 90% of adults in the United States and worldwide are antibody seropositive. Spread by intimate contact, most infections are asymptomatic. In humans, the virus establishes latency in B lymphocytes, T lymphocytes, epithelial cells, and myocytes, and is capable of transforming lymphocytes. EBV infection has a well-known association with lymphoproliferative disorders and a variety of lymphomas[11].

A wide body of evidence supports a central role for EBV in the pathogenesis of HIV-related primary central nervous system lymphoma (PCNSL), likely due to muted EBV-specific CD4+ T cell effector function in patients with HIV[12]. The most common histology in PCNSL is diffuse large B cell lymphoma (DLBCL). In recent years, EBV has been associated with DLBCL in patients over 50 years old without any known immunodeficiency, which has been termed EBV positive DLBCL of the elderly. This clinical entity is more prevalent in Asian countries, and has worse outcomes compared to EBV negative DLBCL[13,14].

Vitreoretinal lymphoma is a subtype of CNS lymphoma in which the intraocular structures are infiltrated by lymphoma cells. The impact of EBV on the development of vitreoretinal lymphoma is an unexplored topic. In our series of 11 EBV positive eyes, 3 (27%) were found to have biopsy-proven vitreoretinal lymphoma. This finding raises the question of a possible association between EBV and the genesis of vitreoretinal lymphoma. Given the known associations between EBV and various lymphomas in HIV-positive individuals, and EBV and DLBCL in the elderly, it may not be surprising to discover that EBV in ocular fluid may drive the development of vitreoretinal lymphoma. Identifying a pathogenic role for EBV in vitreoretinal lymphoma may provide diagnostic and prognostic information for this life-threatening disease.

Given that the majority of adults have detectable EBV antibodies in the plasma, one may predict that the detection of EBV genomic material in ocular fluid is to be expected, as lymphocytes serve as host cells for EBV, and the breakdown of the blood ocular barrier in uveitis leads to infiltration of these lymphocytes into the eye. In this study, RNA-seq was used to comprehensively detect pathogens. The presence of RNA copies of a DNA virus, such as EBV, suggests active replication of the virus. Further, in a separate study of 11 HIV-negative immunocompromised patients with uveitis, out of which 6 had EBV DNA detected in ocular fluid by PCR, only 1 patient had EBV DNA detected in serum by PCR, arguing against the possibility that EBV DNA detected in the eye is due to “overflow” from the peripheral circulation[6]. The use of EBV-directed PCR on intraocular fluid is rarely done for patients with intraocular inflammation as its utility is unclear. However, our results suggest that EBV RNA testing may serve an adjunctive role when the suspicion for vitreoretinal lymphoma is high on the differential.

The patients included in our study are, on average, older than those found to be EBV positive by PCR in a similar study by Smit et al, in which the mean age was 37 years, and a majority of the patients in our study were of either Asian or Latinx descent[7]. Most of the patients in the study by Smit et al were of “mixed” ethnicity. While these findings likely represent the demographics of the geographic regions served by the clinic, the study is too small to imply an association between race/ethnicity and the findings observed.

Limitations

While we found EBV to be present in the ocular fluid specimens of all patients with vitreoretinal lymphoma in this study, we cannot make any inferences about causality as such an inference cannot be supported in a cross-sectional study. The study is also limited by the small sample size and the single center setting.

Conclusions

The prevalence of EBV in ocular fluid from patients with uveitis presenting to a tertiary care referral center is relatively low. Almost one-third of patients with EBV detected in ocular fluid were found to have biopsy-proven vitreoretinal lymphoma.

Funding Source:

This work was made possible, in part, by NIH-NEI EY002162 - Core Grant for Vision Research, Research to Prevent Blindness Unrestricted Grant, and K08EY026986 to Thuy Doan, MD, PhD.

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Table 1.

Demographic and clinical features of EBV positive uveitis cases. Note: Latinx is a gender-neutral term used to refer to individuals of Latin American descent.

Patient	Age at onset of uveitis	Sex	Race/Ethnicity	Granulomatous?	Anatomic location	Laterality	Final Diagnosis
1	56	Male	Other	No	Anterior/ intermediate	Unilateral	Lymphoma
2	45	Female	East Asian	No	Panuveitis	Unilateral	Lymphoma
3	75	Male	East Asian	No	Intermediate	Unilateral	Lymphoma
4	69	Female	Southeast Asian	Yes	Panuveitis	Bilateral	Possible Eales disease
5	63	Female	Latinx	No	Anterior	Bilateral	Undifferentiated
6	78	Female	Latinx	No	Panuveitis	Unilateral	Undifferentiated
7	56	Female	East Asian	No	Anterior	Unilateral	Undifferentiated
8	58	Male	South Asian	No	Anterior	Bilateral	Undifferentiated
9	31	Female	Latinx	No	Anterior	Unilateral	Undifferentiated
10	54	Male	Southeast Asian	No	Anterior/ intermediate	Unilateral	Undifferentiated
11	27	Female	East Asian	No	Anterior	Unilateral	Undifferentiated