

DOI: 10.4274/mjima.2017.10

Mediterr J Infect Microb Antimicrob 2017;6:10

Erişim: <http://dx.doi.org/10.4274/mjima.2017.10>

Seroprevalence and Risk Factors for Epstein-Barr Virus Infection in Adults

Erişkinde Epstein-Barr Virüs Enfeksiyonunun Seroprevalansı ve Risk Faktörleri

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Abstract

Introduction: Epstein-Barr virus (EBV), also known as human herpesvirus 4, is the causative agent of infectious mononucleosis. Infection with EBV is associated with multiple malignancies. The aim of this study was to determine the seroprevalence and risk factors for seropositivity.

Materials and Methods: This study was conducted in Haydarpaşa Numune Training and Research Hospital in İstanbul between August 2012 and October 2012. Epstein-Barr virus viral capsid antigen IgG antibody was measured using ELISA in 500 cases. Age, gender, occupation, education level, family income, the area and type of residence, and chronic illness of the participants were also evaluated. Differences between risk groups were statistically analyzed.

Results: The mean age of the 500 study participants was 47.7 ± 19.1 (15–87) years and 289 (57.8%) were male. Mean EBV seropositivity was 96.4%, and 91% of the cases became seropositive for EBV by 15 years of age. No significant associations with age, gender, occupation, education level, family income, area and type of residence, and chronic illness were detected.

Conclusion: Epstein-Barr virus seropositivity rates were very high and about 91% of the cases become seropositive for EBV by 15 years of age. There was no significant relationship between risk factors and seroprevalence of EBV.

Keywords: Adult, Epstein-Barr virus infections, seroprevalence, socioeconomic status, risk factors

Öz

Giriş: İnsan herpes virüs 4 olarak da bilinen Epstein-Barr virüs (EBV), enfeksiyöz mononükleoz hastalığının etkenidir. Epstein-Barr virüs enfeksiyonları çok sayıda malignitelerle de ilişkilendirilmektedir. Bu çalışmanın amacı, erişkinde EBV seroprevalansını ve risk faktörlerini belirlemektir.

Gereç ve Yöntem: Bu çalışma, Haydarpaşa Numune Eğitim ve Araştırma Hastanesi'nde Ağustos 2012 ve Ekim 2012 tarihleri arasında yapıldı. Beş yüz olguda ELISA yöntemiyle EBV viral kapsid antijen IgG testi çalışıldı. Yaş, cinsiyet, meslek, eğitim durumu, gelir düzeyi, yaşanılan yer, yaşanılan ev ve kronik hastalık durumları irdelendi. Risk grupları arasındaki farklılık istatistiksel olarak araştırıldı.

Bulgular: Çalışmaya katılan 500 olgunun ortalama yaşı $47,7 \pm 19,1$ (15–87) olup, 289 (%57,8) olgu erkekti. Ortalama EBV seropozitifliği %96,4 olarak saptandı. Olguların %91'inde, 15 yaşına gelinceye kadar seropozitiflik oluşmaktaydı. Yaş, cinsiyet, meslek, eğitim durumu, gelir düzeyi, yaşanılan yer, yaşanılan ev ve kronik hastalık durumları açısından istatistiksel olarak anlamlı farklılık saptanmadı.

Sonuç: Epstein-Barr virüs seropozitifliği oldukça yüksekti ve 15 yaşına kadar olguların %91'i seropozitif hale gelmekte idi. Epstein-Barr virüs seroprevalansı ve risk faktörleri arasında anlamlı bir bağlantı saptanmadı.

Anahtar Kelimeler: Epstein-Barr virüs enfeksiyonları, erişkin, seroprevalans, sosyo-ekonomik durum, risk faktörleri



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Received/Geliş Tarihi: 21.01.2017 Accepted/Kabul Tarihi: 06.09.2017

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Mediterranean Journal of Infection, Microbes and Antimicrobials published by Galenos Yayınevi.

Introduction

Epstein-Barr virus (EBV) is a latent virus from the family *Herpesviridae* which is transmitted via the oropharyngeal secretions, blood, and contaminated belongings of infected individuals. Epstein-Barr virus is the causative agent of infectious mononucleosis, which is a generally self-limiting condition characterized by fever, sore throat, and lymphadenopathy. However, the virus is known to be associated with Burkitt lymphoma, lymphoproliferative diseases, nasopharyngeal carcinoma, Hodgkin's lymphoma, primary central nervous system lymphoma in AIDS patients, and autoimmune diseases such as multiple sclerosis^[1].

The serologic profile of EBV infection is determined using specific antibodies against the major antigens of the virus including EBV nuclear antigen, early antigen, and viral capsid antigen (VCA)^[2]. Viral capsid antigen IgM is found in the serum for 4-8 weeks during the active phase of the disease. In contrast, EBV VCA IgG appears early in acute infection and remains positive for the lifetime of the patient. Therefore EBV VCA IgG is commonly used in epidemiologic studies^[3]. Epstein-Barr virus seropositivity rates in adults in Turkey have been reported as 80-99.4%^[3,4].

Due to the oncogenic potential of EBV and its known role as an etiologic factor for many idiopathic diseases, determining EBV seropositivity is important for identifying individuals at risk^[5]. The present study was conducted with individuals over the age of 15 living in İstanbul, where receives immigrants from many regions of Turkey. The aim was to determine EBV seroprevalence and identify any significant differences in seroprevalence based on age, sex, occupation, education level, economic status, chronic diseases, and place and type of residence.

Materials and Methods

This study was performed between August and October 2012 in Haydarpaşa Numune Training and Research Hospital. A total of 500 individuals aged 15 years and over who presented to the Haydarpaşa Numune Training and Research Hospital, Infectious Diseases and Clinical Microbiology Outpatient Clinic and Blood Bank were included. Previously prepared standard questionnaires were filled in during face-to-face interviews. The study participants were asked about their age, sex, occupation, education level, economic status, chronic diseases, area and type of residence, and underlying diseases. Individuals with history of blood transfusion or surgery and immunosuppressed individuals were excluded. Ethics Committee approval was obtained from the Haydarpaşa Numune Training and Research Hospital Ethical Council (Decision number: HNEAH.KA.EK-2012/50).

A venous blood sample of about 5 cc was obtained from the participants and the serum samples were preserved at -20 °C until analysis. Micro-ELISA was used to measure EBV VCA

IgG antibody levels (NovoTec Novalisa EBV VCA IgG ELISA (Dietzenbach, Germany) as per the manufacturer's instructions. The formula $n=t^2pq/d^2$ was used to calculate the sample size required to determine the EBV VCA IgG seroprevalence in the adult Turkish population.

Statistical Analyses

Statistical analyses were done using the 'Number Cruncher Statistical System' 2007 Statistical Software package (Utah, USA). Data were analysed using descriptive statistics (mean, standard deviation) and categorical data were compared using Chi-square and Fisher's exact test. The results were evaluated at a significance level of $p<0.05$.

Results

The mean age of the 500 study participants was 47.7 ± 19.1 (15-87) years and 292 (58.4%) were male. Epstein-Barr virus VCA IgG positivity was found in 479 (96.4%) of the participants. No statistically significant differences emerged in the age and gender distribution of EBV VCA IgG-positive participants ($p>0.05$, $p=0.748$) (Tables 1, 2). There was no statistically significant difference in the gender distribution of the participants according to age groups ($p>0.05$) (Table 3).

Analysis of seropositivity rates in terms of participants' occupation, education level, and income levels revealed no statistically significant differences ($p>0.05$ for all) (Tables 4, 5, 6). There were no statistical differences in seropositivity according to the participants' place of and type of residence ($p>0.05$) (Table 7). The presence of a chronic disease was also not significantly associated with EBV VCA IgG positivity ($p>0.05$) (Table 8).

Table 1. Epstein-Barr virus viral capsid antigen IgG positivity distribution by age group

	EBV VCA IgG (+)		EBV VCA IgG (-)		p
	n=479		n=21		
Age (years)	n	%	n	%	
15-24 years	50	90.9	5	9.1	0.116*
25-64 years	310	96.9	10	3.1	-
65+ years	119	95.2	6	4.8	-

EBV: Epstein-Barr virus, VCA: Viral capsid antigen, *Chi-square test

Table 2. Epstein-Barr virus viral capsid antigen IgG positivity distribution by sex

	EBV VCA IgG (+)		EBV VCA IgG (-)		p
	n=479		n=21		
Sex	n	%	n	%	
Female	201	95.26	10	4.74	-
Male	278	96.19	11	3.81	0.748*

EBV: Epstein-Barr virus, VCA: Viral capsid antigen, *Fisher exact test

Table 3. Epstein-Barr virus viral capsid antigen IgG positivity distribution by age and sex

		EBV VCA IgG (+)		EBV VCA IgG (-)		p
		n=479		n=21		
		n	%	n	%	
15-25 years	Female	27	90.00	3	10.00	0.587*
	Male	32	91.40	3	8.60	
26-35 years	Female	34	97.10	1	2.90	0.553*
	Male	70	98.60	1	1.40	
36-45 years	Female	25	89.30	3	10.70	0.315*
	Male	53	94.60	3	5.40	
46-55 years	Female	24	100	0	0.00	-
	Male	38	100	0	0.00	
56-65 years	Female	24	96.00	1	4.00	0.584*
	Male	45	97.80	1	2.20	
66-75 years	Female	37	97.40	1	2.60	0.212*
	Male	26	89.70	3	10.00	
>75	Female	30	96.80	1	3.20	0.689*
	Male	14	100	0	0.00	

EBV: Epstein-Barr virus, VCA: Viral capsid antigen, *Fisher exact test

Table 4. Epstein-Barr virus viral capsid antigen IgG positivity distribution by occupation

		EBV VCA IgG (+)		EBV VCA IgG (-)		p
		n=479		n=21		
		n	%	n	%	
Occupation						
Unemployed		19	100	0	0	0.214*
Homemaker		126	95.5	6	4.5	-
Worker		45	93.8	3	6.2	-
Civil servant of officer		34	100	0	0	-
Retired		82	97.6	2	2.4	-
Doctor-nurse		23	100	0	0	-
Self-employed/ freelance worker		82	96.5	3	3.5	-
Other		68	90.6	7	9.4	-

EBV: Epstein-Barr virus, VCA: Viral capsid antigen, *Chi-square test

Table 5. Epstein-Barr virus viral capsid antigen IgG positivity distribution by education level

		EBV VCA IgG (+)		EBV VCA IgG (-)		p
		n=479		n=21		
		n	%	n	%	
Education level						
Illiterate + literate without formal education		88	95.7	4	4.3	0.997*
Elementary school + middle school		210	95.9	9	4.1	-
High school		97	96	4	4	-
University-graduate school		84	95.5	4	4.5	-

EBV: Epstein-Barr virus, VCA: Viral capsid antigen, *Chi-square test

Table 6. Epstein-Barr virus viral capsid antigen IgG positivity distribution by monthly income level

		EBV VCA IgG (+)		EBV VCA IgG (-)		p
		n=479		n=21		
		n	%	n	%	
<500 TL		116	96.7	4	3.3	0.546*
501-1000 TL		220	94.4	13	5.6	-
1001-2000 TL		104	97.2	3	2.8	-
>2000 TL		39	97.5	1	2.5	-

EBV: Epstein-Barr virus, VCA: Viral capsid antigen, *Chi-square test, TL: Turkish lira

Table 7. Epstein-Barr virus viral capsid antigen IgG positivity distribution by area of type of residence

		EBV VCA IgG (+)		EBV VCA IgG (-)		p
		n=479		n=21		
		n	%	n	%	
Area of residence	Rural	29	96.7	1	3.3	0.964*
	Suburban	20	95.2	1	4.8	-
	Urban	430	95.8	19	4.2	-
Type of residence	Separate house	112	94.1	7	5.9	0.113*
	Apartment	361	96.5	13	3.5	-
	Other	6	85.7	1	14.3	-

EBV: Epstein-Barr virus, VCA: Viral capsid antigen, *Chi-square test

Table 8. Epstein-Barr virus viral capsid antigen IgG positivity distribution according to chronic diseases

		EBV VCA IgG (+)		EBV VCA IgG (-)		p	p
		n=479		n=21			
		n	%	n	%		
DM*		68	97.1	2	2.9	0.775	0.753*
CKD**		37	94.9	2	5.1	0.908	0.675*
CHF‡		36	92.3	3	7.7	0.470	0.395*
COPD&		30	93.7	2	6.3	0.896	0.637*
Hypo-hyperthyroidism		10	100.0	0	0.0	0.902	0.710*
Liver disease		16	94.1	1	5.9	0.806	0.524*
Malignancy		13	100	0	0.0	0.951	1.00*
HTE		5	100	0	0.0	0.514	1.00*
Other		35	97.2	1	2.8	0.998	1.00*

EBV: Epstein-Barr virus, VCA: Viral capsid antigen, *Fisher exact test, *DM: Diabetes mellitus, **CKD: Chronic kidney disease, ‡CHF: Chronic heart failure, &COPD: Chronic obstructive pulmonary disease, &HT: Hypertension

Discussion

Epstein-Barr virus is present in the saliva of asymptomatic seropositive individuals and is easily transmitted between

people. It is known that socioeconomic level, hygiene habits, and crowded living conditions influence EBV seroprevalence, and higher seropositivity rates are seen in developing countries^[6]. In our study, the overall EBV seroprevalence was 96.4%. Our findings are consistent with those of other seroprevalence studies conducted in our country^[3,7]. Customary Turkish behaviors showing love and respect, such as hand kissing, hugging and kissing the cheeks in greeting, are believed to facilitate the transmission of EBV through saliva and may cause this high seroprevalence.

It is known that having an EBV infection at an early age has harmful effects. Burkitt lymphoma is more common among infants who have primary EBV infection at very early ages and the accompanying high EBV viremia^[8]. Many studies have shown that EBV seroprevalence increases with age^[7,9-11]. In our study, presence of EBV IgG antibodies was analysed in individuals aged 15 years and over. The EBV IgG positivity rate was 90.77% in the 15-25 years group and 97.78% in participants over 75 years old, with no statistically significant differences between age groups. This lack of significant age-related differences in seropositivity may be due to the participants having encountered a large number of viruses before the age of 15.

We also analyzed sex differences in EBV seropositivity and found that seropositivity rates were higher in males than in females. However, the difference was not statistically significant. In a study conducted with students of Edinburg University, Higgins et al.^[12] determined seropositivity rates of 68.1% in males and 78.5% in females, which was a statistically significant difference. In another study of children between 6-19 years of age, EBV seroprevalence was found to be higher in girls than in boys (68.9%, 64.2%)^[13]. A study by Özkan et al.^[3] demonstrated that women had similar rates to men.

In the present study, we investigated the relationship between EBV seropositivity and education level as well. The participants were classified as illiterate, literate without formal education, primary school graduate, secondary school graduate, high school graduate, and university graduate/postgraduate. No statistically significant association was found between educational level and seroprevalence. This result is consistent with that reported by Özkan et al.^[3]. In contrast, Balfour et al.^[9] analyzed the relationship between family education level and seropositivity and found that seropositivity was 72% for those who did not attend high school, 63% for high school graduates, and 56% for those with education beyond high school. Another study showed that EBV seropositivity in individuals with education below high school, at the high school level, and beyond high school was 83.5%, 69.5%, and 59%, respectively^[13]. As suggested by these studies, higher education level has been linked to better hygiene habits and consequently a lower risk of virus transmission. High levels of transmission in childhood indicated the importance of family education.

Being infected with EBV is known to be affected by socioeconomic status^[9]. A study analyzing the correlation between income level and EBV seropositivity reported rates of 81% in the low-income group, 75% in the mid-level income group, and 53.9% in the high-income group^[13]. In a seroprevalence study including 283 individuals in Brazil, it was reported that EBV seropositivity increases with decreasing socioeconomic level of the families^[14]. However, the findings of our study indicate that EBV seropositivity does not change significantly according to income level.

A limitation of our research is that our analysis only included adults, and did not include children. Therefore, we were unable to identify differences in seroprevalence among children, among whom EBV exposure is the highest and general manifests with subclinic infection, and we could not determine the risk factors that affect seropositivity in this age group.

Conclusion

In conclusion, this study based on the adult population of İstanbul has shown that EBV seropositivity reaches 90% by the age of 15. Due to the high seropositivity rate, there were no significant differences between groups with regard to risk factors. Because EBV infection early in life increases its oncogenicity, it is vitally important to prevent transmission to the very young. The lack of an effective vaccine against EBV infection increases the importance of protective measures. Identifying and eliminating the risk factors for virus transmission may lead to a reduction in EBV seroprevalence.

Ethics

Ethics Committee Approval: Ethics Committee approval was obtained from the Haydarpaşa Numune Training and Research Hospital Ethical Council (Decision number: HNEAH. KA.EK-2012/50).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: J.A., Concept: J.A., S.E., D.Ö.E., S.Ö., S.Ş., A.İ., Z.A.D., Design: J.A., S.E., D.Ö.E., Data Collection or Processing: S.Ö., S.Ş., A.İ., Z.A.D., Analysis or Interpretation: J.A., D.Ö.E., Literature Search: J.A., D.Ö.E., Writing: J.A., S.E., D.Ö.E., S.Ö., S.Ş., A.İ., Z.A.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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