Bol Med Hosp Infant Mex. 2016;73(1):47–54

Boletín Médico del
Hospital Infantil de México (English Edition)

www.elsevier.es/bmhim

PUBLIC HEALTH

Epidemiology of Epstein-Barr virus-associated pediatric lymphomas from Argentina

Paola Chabay[a,b,*], **María Victoria Preciado**[a,b]

[a] *Laboratorio de Biología Molecular, División Patología, Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina*
[b] *Instituto Multidisciplinario de Investigación en Patologías Pediátricas (IMIPP), Consejo Nacional de Investigaciones Científicas y Técnicas-Gobierno de la Ciudad de Buenos Aires (CONICET-GCBA), Buenos Aires, Argentina*

Received 3 December 2015; accepted 3 December 2015
Available online 9 January 2016

KEYWORDS
Epstein-Barr virus;
Hodgkin lymphoma;
Burkitt lymphoma;
Diffuse large B-cell lymphoma;
Pediatric lymphoma

Abstract More than 90% of the population is infected by Epstein-Barr virus (EBV), which has sophisticatedly evolved to survive silently in B cells for the life of infected individuals. However, if the virus-host balance is disturbed, latent EBV infection could be associated with several lymphomas. The age at primary infection varies substantially worldwide, and exposure to EBV is likely to be due to socioeconomic factors. In Argentina, EBV infection is mostly subclinical and 90% of patients are seropositive by the age of 3 years; therefore, its epidemiological characteristics resemble those of an underdeveloped or developing population. EBV-positive Hodgkin lymphoma (HL) in young adults from developed populations has been attributed to delayed primary EBV infection as suggested by the association with recent mononucleosis development. EBV-associated Burkitt lymphoma and Hodgkin lymphoma in children from Argentina display frequencies similar to those observed in developed countries, whereas EBV presence in pediatric diffuse large B-cell lymphoma is slightly increased compared to those populations. However, EBV presence is statistically associated particularly with patients < 10 years of age in all three entities. Therefore, a relationship between low age of EBV seroconversion and B-cell lymphoma development risk could be suggested in children from Argentina.

PALABRAS CLAVE
Virus de Epstein-Barr;
Linfoma de Hodgkin;
Linfoma de Burkitt;
Linfoma difuso de células B;
Linfoma pediátrico

Epidemiología de linfomas pediátricos asociados con el virus de Epstein-Barr en Argentina

Resumen Más del 90% de la población se encuentra infectada con el virus de Epstein-Barr (VEB), que ha evolucionado sofisticadamente para sobrevivir de por vida de manera silenciosa en las células B de individuos infectados. Sin embargo, si el balance entre el virus y el huésped se altera, la infección latente por VEB se podría asociar con linfomas severos. La edad de la

* Corresponding author.
E-mail address: paola_chabay@yahoo.com.ar (P. Chabay).

infección primaria varía sustancialmente a escala global, y la exposición al VEB al parecer se relaciona con factores socioeconómicos. En Argentina, la infección por VEB es mayormente subclínica, y el 90% de los pacientes son seropositivos a la edad de 3 años. Por lo tanto, las características epidemiológicas se asemejan a aquellas de una población subdesarrollada o en vías de desarrollo. El linfoma de Hodgkin (LH) positivo para VEB en adultos jóvenes se ha atribuido a una infección por VEB tardía en economías desarrolladas, como lo sugiere la asociación con el desarrollo de mononucleosis. En Argentina, el linfoma de Burkitt y el linfoma de Hodgkin asociados con VEB en niños presentan frecuencias similares a las observadas en países desarrollados, mientras que la presencia de VEB en el linfoma difuso de células B pediátrico se encuentra con un ligero aumento comparado con estas poblaciones. Sin embargo, la presencia de VEB en los tres padecimientos se asocia estadísticamente, en particular, con pacientes menores de 10 años. Por ello, se podría sugerir una la relación entre la menor edad de seroconversión y el riesgo de desarrollo de linfoma de células B en niños de Argentina.

1. Introduction

Epstein–Barr virus (EBV) is a ubiquitous double-stranded DNA virus that belongs to the Herpesviridae family and Gammaherpesvirinae subfamily. EBV is characterized by a tropism for B-lymphocytes displaying latent infection in the host and the capacity for transforming B-lymphocytes. More than 90% of the population worldwide carries the virus,[1] which has sophisticatedly evolved to survive in B cells for the life of infected individuals. The result is a finely balanced relationship that allows the virus to be acquired silently early in life and carried thereafter as a lifelong asymptomatic infection in the B lymphoid system. However, the virus-host balance can be disturbed in various ways, and one of a range of virus-associated diseases may then ensue.[2] Latent EBV infection is linked to many human malignancies. In immunocompetent persons, EBV is associated with ~20% of Burkitt lymphoma (BL) in the developed world, almost all African BL, 50% of Hodgkin lymphoma (HL), 10% gastric carcinomas, almost all endemic nasopharyngeal carcinoma (NPC), certain fractions of diffuse large B-cell lymphoma and T-cell lymphoma. In the absence of normal T-cell immune responses, EBV-infected B-lymphocyte proliferations can cause lymphoproliferative disease (LPD), similar to post-transplant LPD. The persistence of EBV genomes in cells of these malignancies, even in subjects with otherwise normal immune response, is consistent with the notion that EBV genomes are important for malignant cell growth.[3]

The age at primary infection varies substantially worldwide, and exposure to EBV is likely to be due to socioeconomic factors. Young children most likely acquire primary EBV infection due to close contact that involves exchange of oral secretions via shared items such as toys, bottles, and utensils. Before the age of 10 years, primary infection is usually asymptomatic. In adolescents and young adults, however, primary EBV infection frequently presents as infectious mononucleosis (IM). Seroprevalence of EBV varies widely by geographic location. Data indicate that primary EBV infection occurs at a younger age among persons from lower vs. higher socioeconomic backgrounds, which has been attributed to crowded living conditions.[4] A delay in acquiring a primary EBV infection at an older age in childhood or adolescence, which usually occurs in more developed countries, can manifest itself as infectious mononucleosis, occurring in ~25–75% of EBV-infected persons.[5] The severity of primary EBV infection in adults increases with age, and patients > 40 years of age are especially prone to serious illness. EBV infections in children < 10 years are often overlooked, either because they are entirely asymptomatic or because they do not present with a typical IM syndrome.[4]

There is a hypothesis that proposes that the clinical presentation variability related to the age of EBV primary infection is linked to the different magnitude of the viral dose received by a child or a young adult through salivary contact.[6] Another possibility is that IM in adolescents may reflect the global CD8+ T-cell lymphocytosis, with a great proportion of activated EBV-specific CD8+ T-cells.[7] In contrast, it was recently described in children from Africa that asymptomatic EBV infection elicits a virus-specific CD8+ T-cell response that can control the infection, without CD8+ T-cells overexpansion.[8] Moreover, it was suggested that preexisting NK cell populations in children may provide an explanation for why IM occurs more frequently in adolescents and adults than in children.[9] In Argentina, EBV infection is mostly subclinical and 90% of patients are seropositive by the age of 3 years; therefore, its epidemiological characteristics resemble those of an underdeveloped or developing population.[10]

2. EBV infection in relation to lymphoma development

As previously mentioned, EBV is among the infectious agents whose clinical manifestations vary according to age at primary infection. Moreover, its epidemiological behavior is similar to that of HL. The relatively few cases of EBV-positive HL in younger adults may be attributed to delayed primary EBV infection as suggested by the association with mononucleosis.[11] In fact, IM was associated with an increased risk of EBV-positive HL, along with the particularly pronounced risk in younger adults. Furthermore, IM-associated lymphomas occurred with a median of 2.9 years after infection in patients from a developed