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REVIEW ARTICLE

Epstein-Barr virus infection of infants: implications of early age of infection on viral control and risk for Burkitt lymphoma

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Abstract Since its first description by Denis Burkitt, endemic Burkitt's lymphoma (BL), the most common childhood cancer in sub-Saharan Africa, has led scientists to search for clues to the origins of this malignancy. The discovery of Epstein-Barr virus (EBV) in BL cells over 50 years ago led to extensive sero-epidemiology studies and revealed that rather than being a virus restricted to areas where BL is endemic, EBV is ubiquitous in the world's population with an estimated greater than 90% of adults worldwide infected. A second pathogen, *Plasmodium falciparum* (*P. falciparum*) malaria is also linked to BL. In this review, we will discuss recent studies that indicate a role for *P. falciparum* malaria in dysregulating EBV infection, and increasing the risk for BL in children living where *P. falciparum* malaria transmission is high.

PALABRAS CLAVE
Virus de Epstein-Barr;
Linfoma de Burkitt;
Plasmodium falciparum;
Malaria;
Citidina desaminasa inducida por activación

Infección en lactantes por virus de Epstein-Barr: implicaciones de la infección a temprana edad sobre el control viral y el riesgo de linfoma de Burkitt

Resumen Desde la primera descripción por Denis Burkitt, el linfoma de Burkitt (LB) endémico —el tipo de cáncer pediátrico más común en el África subsahariana— ha guiado a los científicos a investigar este padecimiento en la búsqueda de claves para entender sus orígenes. El descubrimiento desde hace 50 años del virus de Epstein-Barr (VEB) en el LB ha conducido a extensos estudios sero-epidemiológicos y ha revelado que, más que ser un virus restringido a áreas donde el LB es endémico, el VEB es ubicuo en la población mundial, con un estimado mayor del 90% de adultos infectados a escala global. Un segundo agente patógeno se ha

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ligado al LB, el *Plasmodium falciparum (P. falciparum*) malaria. En esta revisión se discuten los estudios recientes que indican el papel de *P. falciparum* malaria en la desregulación de la infección por VEB y en el aumento del riego del LB en niños que viven en regiones con alta transmisión de *P. falciparum* malaria.

1. Introduction

Burkitt's lymphoma (BL) is a monoclonal B cell non-Hodgkin's lymphoma with a high proliferative index[1]. Endemic BL is extranodal and tumors are frequently found in the jaw or abdominal region[2]. The peak age of onset is 6 years[3] indicating that there is a very short time frame between exposure to cancer promoting events and the emergence of malignancy. There are three forms of BL found worldwide: endemic, sporadic, and AIDS-associated and all carry a t8;14 chromosomal translocation resulting in the deregulation of the c-myc oncogene[4,5]. It is likely however, that different pathogenic mechanisms drive the emergence of these BL subtypes[6,7]. The focus of this review is on the endemic form of BL (herein referred to simply as BL).

Both molecular and epidemiologic studies have indicated that there is an etiologic link between EBV and the endemic form of BL[8–11]. At the molecular level, the viral genome is present in all cells[12], exists as a clonal population within the tumors[9] and the viral protein EBNA-1[13] along with viral non-coding BART microRNAs[14,15] are consistently expressed within the tumors. In addition, the capacity of EBV to transform B cells also highlights the virus' oncogenic potential. A large-scale prospective study conducted in Uganda in the 1970s provided evidence that EBV infection was a risk factor for BL. In this study, greater than 40,000 children were prebled, serum was stored and when tumors appeared, very high antibody titers against the EBV viral capsid antigen (VCA) were found in children who subsequently developed BL. The elevated VCA titers, and the stability of the elevated VCA antibodies over time, led de-Thé et al.[16] to suggest that infection of infants with EBV early in life could result in an infection that was poorly controlled by the host and thus increased the risk for BL. *Plasmodium falciparum*, is also connected to BL both based on the overlapping regions of high malaria transmission with areas of high BL incidence[17–20] as well as case control studies[21,22].

2. Epstein-Barr virus transmission

EBV is an enveloped gamma herpes virus that is transmitted primarily through contact with saliva[23]. In developed countries, there is a biomodal distribution of the age of EBV infection with 30-50% of children infected before 5 years of age and then a later transmission occurring in young adulthood. For example, in a recent study by Condon et al., they evaluated the seroprevalence of EBV infection in a cross-sectional study of children in the U.S. aged 18 months-20 years of age. They found that 31% of the children were EBV seropositive by 5 years of age, whereas 71% were seropositive by 19 years of age[24]. Infection in childhood is thought to be primarily asymptomatic while the later age of infection can cause infectious mononucleosis (IM), a self-limiting disease[25]. IM is characterized by expansion of both EBV-specific and non-specific CD8+ T cells. In a study of Gambian infants infected with EBV by 14 months of age, although there was EBV-specific CD8 T cells detected, there was no concurrent over expansion of the CD8+ T cell pool[26] perhaps explaining why EBV infection in infants is asymptomatic.

There are a limited number of published longitudinal studies on primary EBV infection in infants[27–32] and most have utilized only serologic markers as indicators of infection. In a more recent study following an infant cohort born in rural areas in Kenya, significantly higher levels of EBV infection at less than 1 year of age were observed as compared to other studies[31]. Of note, in the malaria high transmission area, 35% of infants were infected with EBV by 6 months of age suggesting that malaria infection modulated the age of EBV infection[31]. Early age of EBV infection was also observed in Kenyan infants born to HIV infected mothers[32]. Both of these studies found that early age of acquisition of EBV was associated with a poor control of EBV infection as indicated by high viral loads that were maintained over time. The neonatal immune system is not as effective as the adult immune system for reasons that include lack of immunologic memory, immaturity and skewing towards a Th2 phenotype[33–35]. Early transmission of EBV could induce tolerance of the viral antigen and consequently limit the specific immune response, as seen for early age of hepatitis B virus infection[36]. Alternatively, infants lack a fully functional cytotoxic T cell response before 12 months of age[34], so infection early in life could lead to ineffective or minimal control of the virus. Early age of infection with subsequent high viral loads could increase the risk for subsequent EBV-associated malignancies.

An alternative source of EBV transmission has been hypothesized to be breast milk[37–39] but in most studies to date, only viral DNA was measured. More recently, infectious virus, not just viral DNA, was found in breast milk providing support to the hypothesis that breast milk could be a source for EBV transmission[40]. Pregnant women with malaria have high viral loads[41], and the loss of control of EBV latency following *P. falciparum* infection during pregnancy and subsequent increase in EBV load in circulation possibly contribute to enhanced shedding of EBV in maternal breast milk post-partum[40] and drives early age of transmission of EBV. EBV DNA was detected in breast milk of HIV infected mothers[38,39] and this could contribute to early age of EBV infection in infants born to HIV infected women. Why there is higher prevalence of EBV in breast milk of mothers in developing[40] as compared to developed countries[42]