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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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### KEYWORDS

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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.

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### 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 riesgo del LB en niños que viven en regiones con alta transmisión de *P. falciparum* malaria.

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## 1. Introduction

Burkitt's lymphoma (BL) is a monoclonal B cell non-Hodgkin's lymphoma with a high proliferative index<sup>1</sup>. Endemic BL is extranodal and tumors are frequently found in the jaw or abdominal region<sup>2</sup>. The peak age of onset is 6 years<sup>3</sup> 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<sup>4,5</sup>. It is likely however, that different pathogenic mechanisms drive the emergence of these BL subtypes<sup>6,7</sup>. 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<sup>8-11</sup>. At the molecular level, the viral genome is present in all cells<sup>12</sup>, exists as a clonal population within the tumors<sup>9</sup> and the viral protein EBNA-1<sup>13</sup> along with viral non-coding BART microRNAs<sup>14,15</sup> 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.<sup>16</sup> 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<sup>17-20</sup> as well as case control studies<sup>21,22</sup>.

## 2. Epstein-Barr virus transmission

EBV is an enveloped gamma herpes virus that is transmitted primarily through contact with saliva<sup>23</sup>. In developed countries, there is a bimodal 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<sup>24</sup>. Infection in childhood is thought to be primarily asymptomatic while the later age of infection can cause infectious mononucleosis (IM), a self-limiting disease<sup>25</sup>. 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<sup>26</sup> perhaps explaining why EBV infection in infants is asymptomatic.

There are a limited number of published longitudinal studies on primary EBV infection in infants<sup>27-32</sup> 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<sup>31</sup>. 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<sup>31</sup>. Early age of EBV infection was also observed in Kenyan infants born to HIV infected mothers<sup>32</sup>. 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<sup>33-35</sup>. 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<sup>36</sup>. Alternatively, infants lack a fully functional cytotoxic T cell response before 12 months of age<sup>34</sup>, 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<sup>37-39</sup> 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<sup>40</sup>. Pregnant women with malaria have high viral loads<sup>41</sup>, 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<sup>40</sup> and drives early age of transmission of EBV. EBV DNA was detected in breast milk of HIV infected mothers<sup>38,39</sup> 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<sup>40</sup> as compared to developed countries<sup>42</sup>

could also reflect the higher burden of EBV in the general population.

### 3. EBV persistence

A model for EBV persistence proposed by Thorley-Lawson, the Germinal Center (GC) Model, is an elegant model based on years of study of healthy U.S. adults<sup>43</sup>. In this model, EBV exploits the differentiation of B cells in the lymphoid tissue to set up a lifelong persistent latent infection in memory B cells in equilibrium with the host. In healthy, EBV-seropositive adults, there is a stable, low frequency of latently infected cells estimated at 1-200 EBV positive B cells in 10<sup>5</sup> total B cells<sup>44</sup>. Without enrichment for B cells from peripheral blood, it is difficult to detect EBV infected cells in healthy EBV seropositive adults by PCR amplification using real-time quantitative PCR<sup>45,46</sup> or quantitative competitive PCR<sup>47</sup>. However, unaccounted for in this model is how other systemic infections can influence EBV persistence.

#### 3.1. Malaria and EBV persistence

In the last decade, several studies have pointed to a profound dysregulation of EBV persistence and immunity in children due to malaria<sup>31,46,48-57</sup>. Repeated malaria infections during infancy expand the viral load<sup>54</sup> and an expansion of EBV infected cells during acute malaria has also been found<sup>49,58</sup>. The cysteine rich interdomain 1 $\alpha$  (CIDR1 $\alpha$ ) of the *P. falciparum* erythrocyte membrane protein, which is expressed in infected red blood cells, binds to non-immune immunoglobulins, and acts as a T-cell independent B-cell activator<sup>59</sup> and induces EBV reactivation from B cells<sup>60</sup>. EBV is more frequently reactivated in children living in a malaria endemic region<sup>48</sup> and more directly, elevated viral DNA in plasma is found during acute malaria<sup>51,52</sup>. A decline in EBV DNA in the plasma following anti-malaria treatment<sup>53</sup> is also indicative of viral reactivation driven by Plasmodium infection.

In children living in a malaria endemic region, EBV viral loads are more readily detected as compared to western controls<sup>46,49</sup> suggestive of a long-term consequence of repeated malaria infections. More recently, in regions of the Gambia where malaria transmission has been reduced, the dysregulation of EBV immunity by malaria appears to have also been minimized<sup>61</sup>.

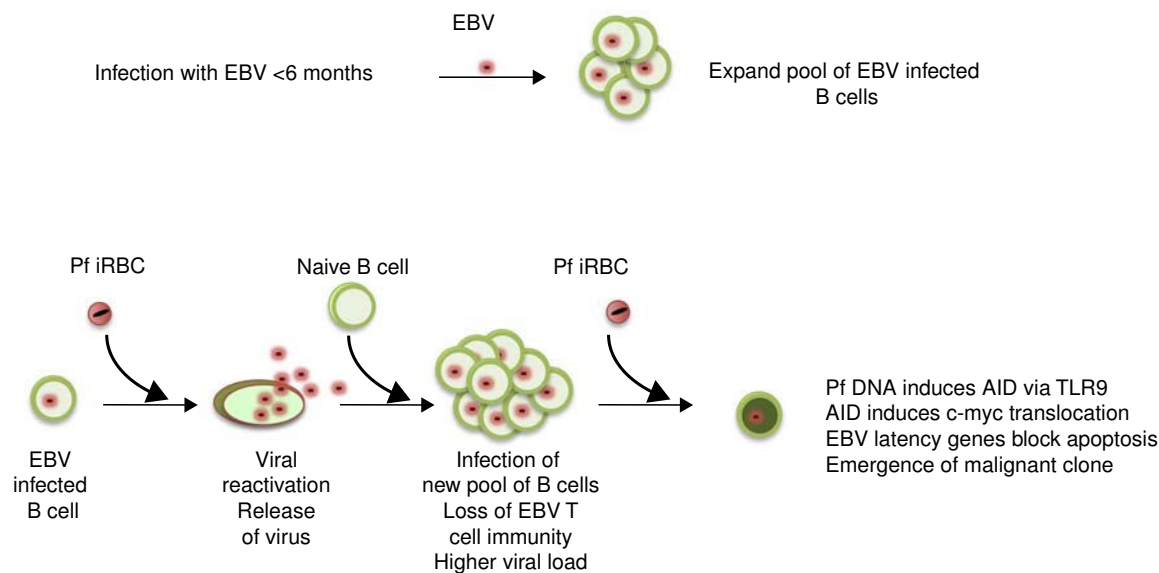
### 4. Activation induced cytidine deaminase (AID) and BL

While it is likely that elevated EBV load increases the risk for BL, the mechanistic link is unknown. In transplant patients, EBV viral load is monitored closely and elevated viral load is associated with increased risk for post-transplant lymphoproliferative disease<sup>62</sup> yet these patients do not go on to develop BL. So, elevated viral load alone is not sufficient for the emergence of a malignant clone. Recent clues point to a model where chronic antigenic activation of EBV-infected B cells within the context of repeated *P. falciparum* infections may lead to cytogenetic abnormalities induced by the enzyme activation induced cytidine deaminase (AID)<sup>63-65</sup>.

AID is required for class switch recombination and somatic hypermutation in germinal center B cells<sup>66</sup>. But AID over-expression in AID deficient B cells was sufficient to induce IgH-c-myc translocations<sup>67</sup> characteristic of BL. AID also induces lesions on the c-myc gene<sup>68</sup>. In addition, when E $\mu$ -c-myc transgenic mice were crossed with AID deficient mice, only AID+/+ mice developed predominantly mature B cell lymphomas<sup>69</sup>. The strongest evidence for a role of aberrant AID activation by Plasmodium infection comes from a recent study by Robbiani et al.<sup>70</sup> In this study, the authors found that repeated infections of p53-deficient mice with *Plasmodium chabaudi* resulted in development of B-cell lymphomas that had the characteristic c-myc translocation. Moreover, development of the lymphomas was dependent on AID. Although these studies were done in mouse models, these data argue for a critical role of AID in the c-myc:IgH translocation characteristic of BL and suggest that aberrant AID expression could be a risk factor for lymphomagenesis. In support of this hypothesis, a strong correlation between AID expression in peripheral blood lymphocytes and increased risk for non-Hodgkin's lymphoma was observed<sup>71,72</sup> and children who were EBV viral load positive from a malaria endemic region were found to have elevated AID expression<sup>63</sup>. Cell culture studies showed that *P. falciparum* could induce AID activation and class switch recombination in B cells<sup>64,73</sup>. If overexpression of c-myc occurred following an AID-mediated translocation, normal B cells would die by apoptosis. However, EBV latent proteins are anti-apoptotic and could thus allow a B cell to tolerate the c-myc translocation<sup>74</sup>.

### 5. BL and EBV association

Although EBV can be readily detected in the endemic pediatric form of BL found in sub-Saharan Africa, there is a variable association of EBV with the sporadic form of BL. Sporadic BL that occurs in adults in developed countries rarely has EBV detected in the tumor. However, in South America, there is an intermediate level of EBV detected in sporadic BL tumors<sup>75</sup>. A larger series of cases of BL from Brazil found a predominance of EBV detection in the pediatric form of BL as compared to adults and a higher prevalence of pediatric EBV+ BL in the northern part of Brazil where there is also a higher prevalence of malaria and other infectious diseases<sup>76</sup>. The intermediate incidence of EBV association with sporadic BL in South America raises the question of whether malaria infection in other parts of the world outside sub-Saharan Africa could also drive lymphomagenesis. A key difference of malaria transmission in Africa is the perennial and intense nature vs. the epidemic and seasonal transmission found in South and Central America. However, it is possible that there could exist a concurrence of early age of EBV infection and malaria infection that could increase the risk for lymphomagenesis in other parts of the world. Studies on the age of EBV infection in Latin America remain few. A recent report from a pediatric hospital case series in Mexico found symptomatic EBV infection occurring in children characteristic of infectious mononucleosis with a mean age of 5 years<sup>77</sup> much younger than seen in U.S.-based series<sup>23</sup>. However, a limitation of the Mexico study is that it was based on hospitalized cases rather



**Figure 1** Model for interaction between EBV and *P. falciparum* malaria. *P. falciparum* (Pf) malaria results in EBV transmission in infants <6 months of age. These infants have poor control of EBV infection and a higher number of latently infected cells. Repeated infection with *P. falciparum* throughout infancy and early childhood expands the number of infected cells by inducing EBV reactivation and reinfection of new pool of B cells as well as suppression of EBV T cell immunity. *P. falciparum* can also act on the EBV infected B cells to induce AID via TLR9 ligation and subsequent c-myc translocation. Because EBV induces epigenetic changes in the infected B cells, the c-myc translocation is tolerated and there is emergence of a malignant B cells.

than a population-based study so true incidence cannot be determined. Nonetheless, this study does suggest that EBV infection is occurring in very young children in Mexico.

## Summary

Cumulative evidence suggests that EBV persistence is in dysequilibrium when primary infection occurs in very young infants and co-infection with *P. falciparum* malaria is common. The prevailing model for EBV persistence, the Germinal center model, was based on studies of healthy U.S. adults and as such does not take into account the disruption to B cell homeostasis<sup>78,79</sup> and germinal center architecture that occurs during acute *P. falciparum* malaria infection<sup>80</sup> or the ability of Plasmodium to directly interact with B cells through either TLR9 ligation<sup>81</sup> or binding of the *P. falciparum*-infected red blood cell to B cells<sup>60</sup>. This dysequilibrium of EBV persistence results in high numbers of latently infected cells, which are at risk for AID activation induced by *P. falciparum* and subsequent c-myc translocation (Fig. 1). Not discussed in this review is a potential role for EBV to suppress apoptotic pathways in latently infected cells,<sup>82</sup> which would allow B cells with a c-myc translocation to emerge. It remains to be seen whether other pathogens can also lead to dysequilibrium of EBV infection and higher viral loads and account for some of the diverse burden of EBV-associated malignancies worldwide.

## Conflict of interest

The author declares no conflict of interest of any nature.

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