Primary Epstein–Barr Virus Infection: Impact of Age at Acquisition, Coinfection, and Viral Load

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(See the major article by Slyker et al on pages 1798–806.)

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Primary Epstein–Barr virus (EBV) infection acquired at an early age or in concert with another pathogen can result in poor control of EBV replication and may be a risk factor for subsequent chronic illnesses including malignancy. Slyker and colleagues report in this issue of the Journal that primary EBV infection was more frequent and more severe in infants coinfected with human immunodeficiency virus type 1 (HIV-1) than in those who were HIV-negative [1]. Their clinical research study, which used repository samples and archival data from an investigation of Kenyan infants born to HIV-infected mothers [2, 3], makes several important observations. First, HIV-infected infants acquired primary EBV infection sooner than their HIV-uninfected counterparts. Second, infants coinfected with EBV and HIV had higher EBV plasma loads that were slow to clear. Finally, primary EBV infection caused more pneumonia, hepatosplenomegaly, and hospitalization in coinfected infants than in HIV-negative infants.

Moorman et al previously reported another example of coinfection damaging the host's ability to contain EBV [4]. Kenyan children aged 1–4 years from a district of intense perennial malaria transmission (Kisumu) had a higher percentage of parasitemia and higher EBV blood viral loads than children of the same age from a low malaria transmission district (Nandi). In this case, the coinfecting pathogen was *Plasmodium falciparum* instead of HIV. Piriou and colleagues [5] recently extended these results by showing that infants in Kisumu, the holoendemic malaria district, acquired primary EBV sooner and had higher viral loads throughout the first 2 years of life than infants in Nandi, the low malaria transmission district. Both parasitemia and EBV loads were higher among children living in the Kisumu district and among those infected with EBV at a younger age.

What are the implications of these findings? Guy de-Thé hypothesized decades ago that "long and heavy exposure to EBV" was an important risk factor for endemic Burkitt lymphoma [6]. His evidence was that EBV-specific antibody titers (presumably reflective of chronic viral replication) were elevated in children years before they developed endemic Burkitt lymphoma [7]. The recent studies mentioned above [1, 4, 5] used quantitative molecular techniques to support his hypothesis. They clearly documented that early age at primary infection results in higher and more sustained levels of EBV viremia. However, these studies were too short to observe an effect of age at acquisition or EBV load on subsequent malignancy.

The mechanism by which infection with 1 pathogen weakens host defenses against another has not been elucidated. One possibility is that in coinfections specific T-cell surveillance to 1 or both pathogens is impaired. In support of this, Moorman et al reported that EBV-specific T-cell surveillance was suppressed by intense prolonged malaria exposure, as evidenced by fewer EBV-specific interferon γ responders to latent and lytic EBV peptides and fewer interleukin 10 responders to lytic EBV peptides among Kenyan children from a holoendemic malaria district vs those from an area of a low malaria transmission [8].

The report by Slyker and colleagues raises an intriguing question: How does HIV-1 infection in the infant lead to earlier acquisition of EBV? We suggest that because mothers of HIV-positive infants had lower percentages of $CD4^+$ T cells and higher HIV loads, they were more immunocompromised than the mothers of HIV-negative infants and likely had higher EBV loads in saliva,

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blood, and other body fluids. If so, their infants would have had a greater probability of contracting the minimum infectious dose of EBV at any time after birth.

Is it better to acquire primary EBV infection earlier or later in life? Some would say earlier because preadolescent children do not commonly experience infectious mononucleosis, whereas adolescents and young adults do. However, data in addition to those from Africa suggest that early acquisition of primary EBV infection is harmful. In areas where nasopharyngeal carcinoma is endemic, such as southern China, EBV infection is presumed to occur at an early age. Environmental agents acting in conjunction with the host's genetic background are thought to impair immune control of EBV infection, eventually leading to nasopharyngeal carcinoma [9]. Multiple sclerosis is another disease that may be triggered by early acquisition of primary EBV infection. A significantly higher percentage of children with multiple sclerosis have been infected with EBV than matched controls, and their antibody profiles indicate that they acquired EBV sometime before the diagnosis of multiple sclerosis [10, 11].

The pathogenic potential of EBV is enhanced by coinfection. Besides EBV/HIV and EBV/malaria coinfections, active cytomegalovirus infections posttransplant increase the probability that an allograft recipient will develop posttransplant lymphoproliferative disorder due to EBV [12, 13]. Posttransplant lymphoproliferative disorder is serious and may be fatal.

We found that the maximum blood viral load was significantly related to development of posttransplant lymphoproliferative disorder among our transplant recipients [14] and also to the severity of infectious mononucleosis in undergraduate students [15]. The study by Slyker et al provides additional evidence that the magnitude of EBV viremia correlates with the severity of EBV infection.

The majority (62%) of EBV/HIV–coinfected infants in the Slyker study were classified as poor controllers because they had EBV DNA in at least 2 plasma samples collected ≥3 months apart. However, 38% of them were categorized as good controllers because EBV was not detected in their plasma or found only once. As the authors state, "defining the genetic, immunologic and viral factors discriminating good from poor EBV controllers may have high relevance for both the development of an efficacious EBV vaccine and for understanding the early risk factors for EBV-associated malignancies."

A limitation of the study is that EBV loads were only measured in infants' plasma. The data would have been more comprehensive and probably more informative if viral loads had also been done on oral swabs, whole blood, and peripheral blood mononuclear cells from the babies and on the maternal samples collected at 32 weeks of gestation. Monthly pediatric examinations were done in this study, which adds a direct clinical perspective to the findings. However, these physical evaluations may not have been done frequently enough because the clinical findings in primary EBV infection can be short lived. Therefore, it is possible that some acute manifestations of primary EBV infection were missed, thus underestimating the true burden of EBV disease.

Despite these limitations, the study by Slyker et al provides additional impetus for designing trials to prevent EBV infection in African infants, especially HIV-infected offspring of HIV-infected mothers. Immunization could be a successful approach. An EBV vaccine was safe, immunogenic, and reduced the incidence of infectious mononucleosis in a Belgian phase 2 trial [16, 17]. We advocate a clinical trial of an EBV vaccine to prevent or reduce the severity of primary EBV infection in African infants born to HIV-infected mothers or those living in areas of holoendemic malaria. Such a vaccine trial is long overdue.

In summary, early age at acquisition, active coinfection, and high blood viral load impact the host's ability to control primary EBV infection. When EBV is acquired early in life or is part of an active coinfection, conditions are ripe for "long and heavy exposure" to EBV, which is a likely risk factor for endemic Burkitt lymphoma, nasopharyngeal carcinoma, and possibly multiple sclerosis. Identifying and ameliorating the conditions responsible for EBV infection before adolescence may be an important public health step in relieving the worldwide burden of EBV-associated diseases.

Notes

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