Epstein-Barr Virus-Malaria Interaction Models for Burkitt's Lymphoma: Implications for Preventive Trials

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Summary

Infections with both Epstein-Barr virus (EBV) and malaria have been implicated as causal factors in the pathogenesis of Burkitt's lymphoma (BL). Proposed trials of preventive measures for both infections are receiving serious consideration as possible means of establishing a causal relationship between EBV and malaria in the induction of BL. In this paper we examine certain models for the interaction of EBV and malaria in the induction of BL, and also review the aims of the longitudinal, population-based study being conducted in the West Nile District of Uganda. Given existing knowledge, the outcome of preventive trials, even for the most simple interaction models, is unpredictable and, under certain circumstances, trials of an EBV vaccine could actually increase the incidence of BL. It is suggested that trials of an EBV vaccine at this time would be premature and should be delayed at least until the results from the West Nile prospective study are clear.

Introduction

There is substantial evidence suggesting that infection with both EBV and malaria is necessary in the etiology of BL. The worldwide distribution of BL correlates closely with that of holo- and hyperendemic malaria (1) and, within Uganda, the incidence of BL varies directly with the intensity of malaria by district (6). Recently, within the Mengo districts of Uganda, the incidence of BL has decreased coincident with rapid economic development and the presumed increase in the use of antimalarial drugs (8).

Both serological (4) and nucleic acid hybridization (11) studies suggest a causal role for EBV in the induction of BL. However, no satisfactory model has been proposed that relates these 2 very common infections to a relatively rare cancer.

An acceptable model must also explain certain epidemiological features of the disease, such as the following. (a) Onset is rare before age 4 and maximal incidence occurs between 5 and 8 years of age. (b) BL rarely develops after adolescence in high incidence areas. (c) Adults that migrate from areas where BL is very uncommon to areas where it is endemic develop the disease more commonly than do nonimmigrant adults (2, 8). (d) The average age of onset varies inversely with the incidence of BL within Uganda (R. H. Morrow and M. Pike, unpublished data). (e) Clustering of dates and places of onset has been observed in some areas. (f) Seasonal variation in the dates of clinical onset has been observed (8, 10).

In this paper we (a) examine some possible models for the interaction of EBV and malaria in the induction of BL, (b) review the hypotheses that the West Nile study may test, and (c) consider the implications of a and b in relation to proposed trials of preventive measures.

Models of EBV-Malaria Interaction

If it is assumed that infection with both EBV and malaria is a sufficient condition for the development of BL (that is, no 3rd factor is involved, such as genetic susceptibility), then it may be necessary to postulate that the infections are in some way unusual. The infections may be unusual in timing, either individually or with respect to each other, or may involve atypical strains of the organisms. Since there is no evidence that atypical strains are involved (although this possibility cannot be excluded), the models developed here relate to the temporal relationships of the infections.

The evidence linking malaria to the induction of BL indicates that the relationship is not simply to infection with malarial parasites, but rather with the host response to prolonged or repeated, intense infection with malaria. In holoendemic areas, malaria imposes a continuing and intense antigenic stimulation on the population. Initial infection occurs generally in the 1st year of life, and death is most likely to occur during early attacks. With subsequent attacks, the host immune response increases and an apparent equilibrium is reached between host and parasite by age 5 or 6 (9), the age of maximal BL incidence.

There is insufficient knowledge to postulate specific mechanisms of the relation of malaria to infection with EBV in the pathogenesis of BL. It is evident that knowledge of the biology of EBV is insufficient, particularly regarding the mode of transmission and the immune response in young children. Similarly, we lack understanding of the complex immunological response to malarial infection. O’Conor (9) has reviewed various possibilities and suggested that the marked proliferation of lymphocytes resulting from the persistent antigenic stimulation of malarial infection provides the necessary milieu for transformation by an oncogenic virus and may be especially favorable for EBV, which has a...
strong affinity for lymphocytes. He further suggested that holoendemic malaria could produce a degree of immunosuppression in some persons, perhaps by blocking antibodies that shield antigenic sites. Alternatively, the repeated proliferation of immunoglobulin precursor cells might produce host tolerance to these cells following transformation. Another alternative is that intense infection with malaria overloads the immune system, leading to the breakdown of immune surveillance. Establishment of the temporal sequence of infections could be useful in determining the most likely mechanism.

The 3 temporal relationships between infection with EBV and malaria to be considered are as follows: (a) EBV infection occurs first followed by intense malarial infection; (b) EBV infection and intense malarial infection occur simultaneously; and (c) intense malarial infection is followed by EBV infection.

An underlying assumption is that primary infection with EBV is the relevant event, rather than reinfection from subsequent exposure. If the latter were involved, more cases might be expected among adults in endemic areas, since the virus is extremely common and exposure must occur repeatedly throughout life.

The epidemiological evidence is most consistent with the 1st temporal relationship proposed, i.e., primary EBV infection precedes the critical host response to malaria. In BL endemic areas, the age incidence curve of the cancer is closer to that of maximal malarial antibody levels than that of acquisition of EBV antibodies. It seems reasonable to suppose that seasonal variation in the degree of malarial exposure is more likely to occur than that of EBV transmission, giving rise to seasonal variation in onset of BL. Perhaps the best evidence favoring this proposed relationship is provided by migrants from nonmalarious areas to areas endemic for BL. Presumably, such migrants have an exposure to EBV prior to migration that is similar to that of those born locally; however, it should be stressed there is no documentation for this presumption. Yet the immigrants develop BL as adults after migration, presumably following their initial intense infection with malaria and consequent host response (2, 8). Such a relationship with malaria might also explain the inverse correlation between the average age of onset of BL and the incidence of the disease in different areas of Uganda (R. H. Morrow and M. Pike, unpublished data). In sum, although prior EBV may be a necessary factor, intense infection with malaria appears to be the precipitating event in the pathogenesis of BL.

West Nile Study

The longitudinal study being conducted in the West Nile District of Uganda (3) was designed to test a limited number of hypothetical relationships which assume that EBV infection is a necessary factor in the pathogenesis of BL. Serum samples and thick and thin malaria smears have been collected and stored from 35,000 children aged 2 to 5 years, and these children are now being followed to detect new cases of BL.

The main hypothesis the study is designed to test is that onset of BL follows primary infection with EBV in children after a fairly short latent period (less than 4 years). Since BL is rare before the age of 4 years and has a peak incidence at about age 7, the hypothesis implies that BL occurs among those children whose primary infection with EBV is later than usual for this population, i.e., after age 2 (7). This hypothesis is based on the model of infectious mononucleosis, but there are fundamental conceptual differences in terms of the latent period between infection with the virus and disease manifestation. In infectious mononucleosis, the latent period is a matter of days; in BL, this period is certainly much longer, possibly years. Thus it may require the passage of several years after the initial sera have been collected before the hypothesis can be tested. Under this model, initial sera from those children who develop BL relatively early in the follow-up period would be EBV positive, since the initial sera would have been obtained in the latent period. Those children developing the cancer later in the follow-up period would have initial sera lacking EBV antibodies. If the latent period is 2 or 3 years, then it is necessary to wait at least for this transition period before conclusions can be drawn.

If, on the other hand, we wish to test an alternative hypothesis, that BL occurs only among children who had their primary EBV infection relatively early in life, implying a latent period of more than 4 years, then we would need to demonstrate that only children who were infected with EBV early would develop BL upon being suitably infected with malaria. Unfortunately, there are far too few children in the West Nile study to test this proposition, i.e., those who are not infected, say by age 2 years, do not develop BL. The results of the study will not enable this latter “early” infection model to be distinguished from that of no causal role of EBV, or from that of a more complicated relationship involving, perhaps, reinfection or reactivation of EBV.

A further hypothetical relationship is that the age of infection with EBV is essentially irrelevant to the induction of BL, i.e., it may occur at any time prior to the onset of BL. If this is the case, then no information can be obtained from the West Nile study regarding the role of EBV.

The only other model that is directly testable in the West Nile study is that BL occurs in children with initially high EBV titers or with some other special marker of EBV infection.

Even if an independent precipitating event such as intense malarial infection is necessary to trigger the induction of BL, the interpretation of the results from the West Nile study relating the age of the EBV infection to onset of BL will not be affected.

Implications for Trials of Preventive Measures

Malaria-Control Trial. The epidemiological evidence strongly suggests that severe infection with malaria appears to be the precipitating factor in the pathogenesis of BL. Control of malarial infection may be the most effective means of interrupting the postulated causal chain leading to BL. If the purpose of a malaria-control trial is to prove the association between malaria and BL, then antimalarial chemoprophylaxis to children aged 5 and under would be
the appropriate method. To the extent that the prophylaxis controlled severe malaria but did not impair acquired immunity, BL would be eliminated. However, if the protection were complete and immunity were not acquired, then the study population would be at risk of BL when the prophylaxis was discontinued. Since the prognosis of BL becomes worse as age at diagnosis increases, the study subjects may be at increased jeopardy from BL as well as from malaria.

**EBV Vaccination Trial.** If “late” primary infection with EBV is necessary for the development of BL, then the West Nile study should provide an answer, and no vaccine trial will be necessary to prove causation. Indeed, a major consequence of the use of a killed EBV vaccine, which would probably have a limited period of protection, would be to delay the acquisition of natural infection and, thus, might actually increase the risk of BL.

If, on the other hand, EBV infection must occur early in life and BL is triggered by an independent factor, then the logistics of a vaccine trial (5) is very great. However, the effect of a successful vaccine trial under this hypothesis would be to decrease BL, and the trial would prove the relationship effectively.

If the age of EBV infection is irrelevant but must merely precede the maximal response of the host to malaria, then an EBV vaccine would be successful if infection with EBV were to be delayed until beyond this trial.

The outcome of preventive trials cannot be adequately predicted under the simplest interactive models. It would seem prudent to wait for the results of the West Nile study before embarking upon a vaccine trial. In the meantime, research should be directed to a better understanding of the biology of EBV infections and to the complex immune response in chronic malaria.

**References**

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