Epstein-Barr Virus Behavior in Different Populations and Implications for Control of Epstein-Barr Virus-associated Tumors

Guy de-Thé
Unit of Biological Carcinogenesis, International Agency for Research on Cancer, 150 Cours Albert Thomas, 69008 Lyon, France

Summary

The epidemiology of Epstein-Barr virus (EBV) infection in populations at different risk for EBV-associated diseases indicates significant differences between the populations. EBV infection takes place much earlier in Uganda, where all children are infected before the age of 2 to 3 years, than in Southeast Asia, where nasopharyngeal carcinoma is prevalent. It is proposed that such early infection in Equatorial Africa is related to the risk for Burkitt’s lymphoma. Four possible interventions to control EBV-associated diseases are presented: (a) simple hygienic measures to delay natural primary infection by EBV; (b) EBV vaccine; (c) intervention against cofactors such as malaria in Burkitt’s lymphoma; and (d) characterization of high-risk groups to allow early detection and successful treatment.

Introduction

There is a basic difficulty in accepting the role of the herpesvirus discovered by Epstein and Barr (EBV) in the development of both BL and NPC. This virus is ubiquitous, yet these 2 tumors are relatively rare and, furthermore, have distinctive epidemiological features. The question was raised as to whether the epidemiological characteristics of EBV infection could shed light on the pathogenic role of EBV in such different diseases as BL and NPC. The epidemiology of BL suggests the intervention of a strong environmental factor relatively close in time to the clinical expression of the disease, whereas that of NPC stresses the importance of genetic factors.

Seroepidemiology served a unique role in establishing the relationship between age and rate of poxvirus infection and the inverse risk of paralytic poliomyelitis in various parts of the world. Although this example refers to an acute disease, whereas slow viral infections may be more appropriate here, the question remains: will the knowledge of epidemiological behavior of EBV in populations at different risk for EBV-associated diseases, such as IM, BL, and NPC, help in understanding the pathogenesis of and in proposing measures for controlling these diseases?

Epidemiological Behavior of EBV

Most of the seroepidemiological surveys on EBV infection in normal populations have involved small numbers of individuals not covering all age groups and not always representative of the general population. Furthermore, testing is often carried out in different laboratories, thus rendering comparison quite approximate. However, these studies were sufficient to show that EBV infection is present all over the world (for reviews see Refs. 5, 6, and 12), even in remote areas such as the North Pole or the plateau of the Matto Grosso in Brazil, where some isolated Indian tribes do not encounter infection with measles, mumps, or common respiratory viruses (2). These seroepidemiological surveys also demonstrated some basic differences in the age of primary infection with geographical area, showing that people in tropical countries suffer from earlier infection than those from a temperate climate (6). The critical role of socioeconomic status in the age of primary infection has been stressed repeatedly by Henle and Henle (8).

We have been conducting a comprehensive seroepidemiological survey in representative samples of 4 different populations at different risk for EBV-associated diseases: namely, Hong Kong and Singaporean Chinese at very high risk for NPC; Singaporean Indo-Pakistanis at very low risk for both NPC and BL; Africans from the West Nile District of Uganda at high risk for BL; and, finally, Caucasians from Nancy, France, at low risk for both EBV-associated tumors but at risk for IM. The preliminary results of this study, which involved nearly 6000 sera, were presented at the Nuremberg meeting (5) and are further discussed here.

Chart 1 gives the age-specific prevalence of antibodies against VCA in the 4 populations concerned between 0 and 19 years of age. It can be seen that up to 5 years of age the differences are remarkable. For example, in the age group 2 to 3 years, practically all Ugandan children are VCA positive, whereas in Singapore only 20% of the Chinese and 37% of the Indians showed VCA antibodies in that age group. Later on, the differences between equatorial Africa and Singapore taper off. At 10 years of age there was no great difference between the 2 areas but in Europe only 60% were infected. An unexpected phenomenon was observed in...
control of EBV-associated tumors

Uganda; although all children between 2 and 4 years of age had VCA antibodies, there was an increasing proportion of individuals with VCA antibodies less than 10 (i.e., not detectable), starting in the age group 5 to 9. This phenomenon, being much more pronounced in males than in females, raised our interest as being potentially related to a difference in immune response against the EBV infection in males and females. Furthermore, when one recalls that boys are 2.5 times more susceptible to the development of BL than are girls, this phenomenon may be relevant to BL risk.

The mode of transmission of the EBV infection is poorly known at present. The role of saliva is strongly suspected, since infectious and transforming EBV has been found in the saliva of IM patients during the clinical illness and for a long time thereafter (7), as well as in most BL patients and in a large proportion of healthy individuals in high-BL areas (P. Gerber, personal communication). This role of breast feeding should also be considered, as W. Feller (personal communication) has established EBV-carrying lymphoblastoid lines from human milk.

Mode of Immune Response to EBV Infection in Various Populations

Chart 2 gives the GMT of the VCA antibodies from seropositive individuals in the 4 ethnic groups concerned. The Ugandans showed an unexpected and very high peak of antibody response against VCA between the 1st and 2nd year of life, which reached a GMT level of 423, similar to that observed in the BL patients' group. Thereafter the VCA/GMT level progressively decreased to a GMT of 60 in the age group 10 to 14, and this level was maintained in all subsequent age groups. In contrast, the Indians (see Chart 2) sustained quite a steady immune response against EBV infection with a VCA/GMT of around 150 from 4 to 64 years of age. Humoral response to complement-fixing antibodies against soluble antigen was also found to be different in the various geographical areas and ethnic groups, and the reader is referred to de-Thé et al. (5).

Nothing is known about the mode of immune response to possible reinfection and/or reactivation of latent EBV infection. Since latency and reactivation are characteristics of herpesviral infection in man, it would be highly relevant to concentrate more effort on markers and inducing factors of reactivation. Such knowledge would certainly be of critical importance for furthering our understanding of the role of EBV in both BL and NPC.

Possible Interventions to Control the EBV-associated Diseases

Delay the Natural Primary Infection by EBV. The geographical distribution of IM in different populations can be explained by the distribution of age at which primary EBV infection occurs. When EBV infection takes place early in life, as for example in Uganda and the Far East, classical IM (with positive Paul-Bunnel reaction) is absent. Could then the high rate of EBV infection at a very early age in Uganda be linked with the risk for BL? Viral infections during the
neonatal period in infants whose reticuloendothelial system is immature may result in heavy and prolonged viral replication. That EBV infection in Uganda takes place shortly after birth is betrayed by the high level of antibodies against both VCA and complement fixing antibodies against soluble antigen in the 1- to 3-year-old children. The pathogenesis of the relationship between neonatal EBV infection and risk for BL is not known, but it may involve an EBV-specific impairment of cell-mediated immunity. If this were the case for BL, one could propose to try and delay the natural EBV infection until a later age and see if it had any effect on BL risk. This intervention could be achieved through simple measures of hygiene and may not involve a vaccine. This would mean carrying out a study of the various sociocultural habits in early age that would favor EBV transmission. The role of exchange of saliva or toys heavily contaminated with saliva, could be important.

**Would a Vaccine Help?** The 2nd possibility for control of EBV infection concerns a vaccine to which this Symposium is devoted. It may be too early to discuss the respective advantages of different types of vaccine but the time has come to discuss the advantages and disadvantages of an EBV vaccine. Several factors would favor the development of a vaccine. Marek’s disease is actually controllable to an acceptable extent with a live virus vaccine (for review see Ref. 1), and Laufs and Steinke (10) have successfully used a killed virus vaccine on lymphomas induced by oncogenic primate herpesviruses. When one considers the oncogenic potential of EBV (based on its *in vitro* transforming activity and its *in vivo* oncogenic properties in nonhuman primates), an EBV vaccine may be the ultimate stage in proving or disproving the role of EBV in the development of human tumors. The development of an EBV vaccine might be justifiable if the link between IM and Hodgkin’s disease were to become stronger. Two studies, 1 in the United States and 1 in Denmark, favor such a link (4, 13), whereas another study, carried out on U.S. veterans, does not show a positive link (11). The International Agency for Research on Cancer is coordinating a retrospective study in Scandinavia and Scotland from which it appears that IM patients have a 5-fold increased risk for developing Hodgkin’s disease, usually within 3 to 13 years (N. Munoz, personal communication). However, as discussed by Higgins *et al.* in the past (9), the use of a vaccine against a potentially oncogenic virus will pose enormous problems from the ethical and epidemiological points of view.

**Intervention against Cofactors.** This may prove to be more rewarding in the immediate future for the public health viewpoint that the development of a vaccine. The intervention of an environmental factor shortly prior to (6 to 18 months) the development of BL fits with most of the epidemiological characteristics of the disease. Holohyperendemic malaria has been claimed as a very likely cofactor in the development of BL (3). No definite study has established this point and the International Agency for Research on Cancer is contemplating a partial malaria suppression.
Detection of Highest Risk Individuals. A 4th possibility for the control of these virally associated diseases is to detect the individuals at highest risk for the tumor, permitting early diagnosis and successful treatment. If the viral markers used as criteria for selection proved to be the right ones to identify the cohort at highest risk, this could consequently reinforce the association between the viral infection and the tumor to the level of evidence. This possibility might exist for NPC, where both the immunogenetic HL-A (14) and EBV antibody profiles could represent markers for high-risk groups. If certain individuals could be shown to be at very high risk and followed, it might be possible to achieve earlier detection of the disease and also to determine the serological pattern preceding the development of the tumor, which might in turn help to determine the pathogenesis of the relationship between EBV and NPC.

Conclusion. It appears that, at the present time, intervention against cofactors may be more rewarding than direct action against the virus. In the long run, and if the link between IM and subsequent risk for lymphoma should strengthen, an EBV vaccine might become the best tool to establish and prevent the oncogenic potential of EBV in man.

References

Epstein-Barr Virus Behavior in Different Populations and Implications for Control of Epstein-Barr Virus-associated Tumors

Guy de-Thé


**Updated version**
Access the most recent version of this article at:
[http://cancerres.aacrjournals.org/content/36/2_Part_2/692](http://cancerres.aacrjournals.org/content/36/2_Part_2/692)

**E-mail alerts**
Sign up to receive free email-alerts related to this article or journal.

**Reprints and Subscriptions**
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

**Permissions**
To request permission to re-use all or part of this article, use this link [http://cancerres.aacrjournals.org/content/36/2_Part_2/692](http://cancerres.aacrjournals.org/content/36/2_Part_2/692).
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.