Jornal de Pediatria 2022;98(2): 115—116

Jornal de Pediatria
www.jped.com.br

EDITORIAL

The burden of Epstein-Barr virus infections in children*

Henry H. Balfour, Jr. [a,b]

[a] University of Minnesota Medical School, Department of Laboratory Medicine and Pathology, Minneapolis, United States
[b] University of Minnesota Medical School, Department of Pediatrics, Minneapolis, United States

Epstein-Barr virus (EBV) arguably is the cause of the most common infection on the planet. By the time we reach adulthood, nearly 90% of us have been infected.[1] Some of us will get infectious mononucleosis and some of us will develop chronic EBV-driven diseases such as lymphoma or multiple sclerosis. While we know something about EBV infections in adolescents and young adults, and something about EBV infections in immunocompromised hosts, there is surprisingly little known about EBV infections in preadolescent children.

The article by Shi et al. in this issue provides some information to fill that gap.[2]

Their article is almost as important for what it does not say than for what it says. What the article says is that 7.3% of 38,175 children from eastern China tested as inpatients or outpatients had EBV DNA in their plasma. The sample size is large and the relatively high prevalence of plasma EBV DNA is noteworthy, especially considering that EBV DNA is found more often in whole blood rather than plasma during primary EBV infection,[3] and plasma EBV DNA correlates with the clinical outcome of Hodgkin lymphoma whereas whole blood EBV DNA does not.[4]

What this article does not say, or more correctly cannot say, is that EBV caused the illnesses that brought the children to medical attention. Because of its notorious proclivity to reactivate after primary infection, finding EBV DNA in plasma may simply reflect a prior EBV infection unrelated to the cause of the present illness.

Had the authors tested the children's plasma for EBV-specific antibodies, the stage of EBV infection could have been characterized as primary (acute), convalescent, or past.[5] The point is that primary (acute) EBV infection is much more likely to be responsible for the present illness than reactivation or reinfection.

The diagnosis of infectious mononucleosis, which is the most common clinical expression of primary EBV infection, can be confirmed in children with EBV-specific antibody tests. At the University of Minnesota, we use enzyme immunoassays to measure IgG and IgM antibodies against EBV viral capsid antigen (VCA) and IgG antibodies against EBV nuclear antigen-1 (EBNA-1).[6] The patterns of VCA IgM positive only, or VCA IgM and IgG positive but EBNA-1 IgG negative, signify acute primary EBV infection. In contrast, the non-specific heterophile antibody tests may be falsely negative in children, especially those 4 years of age and younger.[7]

At the University of Minnesota, we do not test body fluids by polymerase chain reaction (PCR) to diagnose EBV diseases because such tests do not distinguish primary infection from reactivation or reinfection. The major value of quantitative PCR testing is to monitor the clinical course of chronic EBV infections in the immunocompromised host.[8]

The prevalence of plasma EBV DNA differed by age in this study. The highest prevalence occurred in Chinese children between 2 and 6 years old, which is consistent with their age at acquisition of EBV antibodies,[1,9] and recently acquired EBV infections are more often accompanied by viremia.

Plasma EBV DNA was statistically significantly more prevalent in outpatients than in inpatients. The reason for this is not immediately evident. Because the study was retrospective, the indications for obtaining a plasma PCR test were not uniform. An explanation could be that outpatient clinicians were more selective in ordering the assay, reserving it for infectious mononucleosis-like illnesses that have a higher probability of being EBV-positive. In that regard, when the authors looked at the association of plasma viral load with the clinical syndromes, they reported higher quantities of plasma EBV DNA in children with the diagnoses of infectious

DOI of original article:
http://dx.doi.org/10.1016/j.jped.2021.05.006
E-mail: balfo001@umn.edu
* See paper by Shi et al. in pages 142—6.

https://doi.org/10.1016/j.jped.2021.06.001

mononucleosis, "atypical EBV infection," or hemophagocytic lymphohistiocytosis—the three diseases studied that were probably caused by EBV.

This paper encourages us as pediatricians to consider EBV in the\differential diagnosis of acute infections Recognition that an illness is due to EBV helps us avoid unnecessary prescription of antibacterial drugs and to give some consideration to the use of valacyclovir.[10] A caveat is that causality for any of the six reported clinical entities could not be established by this study. Also, genetics and the environment play a major role in disease expression and its severity. Therefore, the data by Shi et al.[2] are not necessarily applicable to patients of different races/ethnicities or who live in geographical locations other than eastern China.

EBV has two "EBNA types," which differ from each other in their EBNA-3A, EBNA-3B, and EBNa-3C genes.[11] A recent study from northern Brazil reported that of 76 patients with infectious mononucleosis, 54 (71%) had type 1, 13 (17%) had type 2, and 9 (12%) had mixtures of the two EBNA serotypes.[12] The authors suggested that patients were sicker if they harbored EBNA type 2. Of 79 Minneapolis-St. Paul students with infectious mononucleosis, 69 (87%) had type 1, 8 (10%) had type 2, and 2 (2.5%) had mixtures.[6] The distribution pattern in Minneapolis-St. Paul was somewhat similar to that found in Belém, but the proportion of patients with EBNA type 1 genotypes was higher in Minnesota. Also, in Minnesota, there was no difference in the severity of illness according to the EBNA genotype.

A prophylactic EBV vaccine could prevent EBV diseases from ever happening in the first place.[13] A rationale to give it early in life would be that early acquisition of EBV is a risk factor for developing chronic EBV-driven malignancy or autoimmune diseases. There is some evidence to support this. A multinational study reported that children with multiple sclerosis were statistically significantly more likely to be EBV-infected than EBV-naïve.[14] Younger age at the time of primary EBV infection among Kenyan infants was accompanied by a higher level of EBV viremia, suggesting that those children were at a higher risk for Burkitt lymphoma.[15]

The other and perhaps more compelling reason to give EBV vaccine as early in life as possible would be to demonstrate that EBV can permanently scar the immune system even if it causes few if any symptoms. Thus, the burning question yet to be answered: what is the burden of EBV disease in young children? Will the risk-benefit equation be favorable? Shi et al. have told us that finding a part of the virus in children's plasma is relatively common. It doesn't belong there but is it causing harm and if so how much? We need to find out.

Funding

Supported by grants from the University of Minnesota International Center for Antiviral Research and Epidemiology, the Richard M. Schulze Family Foundation, the Randy Shaver Cancer Research and Community Fund, the Matt Cwiertny Memorial Foundation, and the University of Minnesota Foundation.

Conflicts of interest

The author declares no conflicts of interest.

References

1. de-Thè G, Day NE, Geser A, Lavoue MF, Ho JH, Simons MJ, et al. Sero-epidemiology of the Epstein-Barr virus: preliminary analysis of an international study—a review. IARC Sci Publ. 1975: 13—6.
2. Shi T, Huang L, Tian J. Prevalence of Epstein-Barr viral DNA among children at a single hospital in Suzhou, China. J Pediatr (Rio J). 2022;98:143—7.
3. Balfour Jr HH, Holman CJ, Hokanson KM, Lelonek MM, Giesbrecht JE, White DR, et al. A prospective clinical study of Epstein-Barr virus and host interactions during acute infectious mononucleosis. J Infect Dis. 2005;192:1505—12.
4. Kanakry JA, Li H, Gellert LL, Lemas MV, Hsieh WS, Hong F, et al. Plasma Epstein-Barr virus DNA predicts outcome in advanced Hodgkin lymphoma: correlative analysis from a large North American cooperative group trial. Blood. 2013;121:3547—53.
5. Hess RD. Routine Epstein-Barr virus diagnostics from the laboratory perspective: still challenging after 35 years. J Clin Microbiol. 2004;42:3381—7.
6. Balfour Jr HH, Dunmire SK, Hogquist KA. Infectious mononucleosis. Clin Transl Immunology. 2015;4:e33.
7. Horwitz CA, Henle W, Henle G, Goldfarb M, Kubic P, Gehrz RC, et al. Clinical and laboratory evaluation of infants and children with Epstein-Barr virus-induced infectious mononucleosis: report of 32 patients (aged 10-48 months). Blood. 1981;57:933—8.
8. Holman CJ, Karger AB, Mullan BD, Brundage RC, Balfour Jr. HH. Quantitative Epstein-Barr virus shedding and its correlation with the risk of post-transplant lymphoproliferative disorder. Clin Transplant. 2012;26:741—7.
9. Kangro HO, Osman HK, Lau YL, Heath RB, Yeung CY, Ng MH. Seroprevalence of antibodies to human herpesviruses in England and Hong Kong. J Med Virol. 1994;43:91—6.
10. Balfour Jr HH, Hokanson KM, Schacherer RM, Fietzer CM, Schmeling DO, Holman CJ, et al. A virologic pilot study of valacyclovir in infectious mononucleosis. J Clin Virol. 2007;39:16—21.
11. Sample J, Young L, Martin B, Chatman T, Kieff E, Rickinson A, et al. Epstein-Barr virus types 1 and 2 differ in their EBNA-3A, EBNA-3B, and EBNA-3C genes. J Virol. 1990;64:4084—92.
12. Monteiro TA, Costa IB, Costa IB, Corrêa TL, Coelho BM, Silva AE, et al. Genotypes of Epstein-Barr virus (EBV1/EBV2) in individuals with infectious mononucleosis in the metropolitan area of Belém, Brazil, between 2005 and 2016. Braz J Infect Dis. 2020;24:322—9.
13. Balfour Jr HH, Schmeling DO, Grimm-Geris JM. The promise of a prophylactic Epstein-Barr virus vaccine. Pediatr Res. 2020;87:345—52.
14. Banwell B, Krupp L, Kennedy J, Tellier R, Tenembaum S, Ness J, et al. Clinical features and viral serologies in children with multiple sclerosis: a multinational observational study. Lancet Neurol. 2007;6:773—81.
15. Piriou E, Asito AS, Sumba PO, Fiore N, Middeldorp JM, Moormann AM, et al. Early age at time of primary Epstein-Barr virus infection results in poorly controlled viral infection in infants from Western Kenya: clues to the etiology of endemic Burkitt lymphoma. J Infect Dis. 2012; 205:906—13.