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Review article

EPSTEIN-BARR VIRUS: CAUSES, CONSEQUENSES, DIAGNOSIS AND TREATMENT OF EPSTEIN-BARR VIRUS IN HUMAN

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Abstract: The Epstein-Barr virus (EBV) belongs to the family of herpesviruses, subfamily Gammaherpesvirinae, and genus Lymphocryptovirus. Despite this classification, there are two serotypes of the Epstein-Barr virus, namely type A and type B. Both types play significant roles in the development of viremia. Additionally, EBV infection can lead to lymphadenopathy, upper respiratory tract obstruction, spleen rupture, thrombocytopenia, and recently, there has been increased emphasis on the connection between this virus and certain malignant neoplasms. Diagnosing this virus can be challenging if clinicians rely solely on serological confirmation. In some cases, it is necessary to perform more specific methods, in addition to considering the clinical picture and history, to prove the presence of the virus in blood, nasopharyngeal swabs, and other tissue samples. The aim of this paper is to present the severity and consequences caused by the Epstein-Barr virus and to emphasize the importance of preventive measures in preventing the virus from coming into contact with susceptible individuals. Prevention plays a crucial role in reducing contact with the virus. Since the infection spreads via droplets, wearing masks in healthcare facilities and regular hand washing are hygiene priorities to prevent infection and further transmission.

Keywords: Epstein-Barr virus, carcinogenesis, transplantation, serological methods, autoimmune reactions.

INTRODUCTION

The Epstein-Barr virus (EBV) belongs to the herpesvirus family. Primarily, Epstein-Barr is a droplet virus, but it can also be transmitted through other bodily fluids (1). In addition to causing respiratory diseases, it is capable of latently infecting B lymphocytes by transcribing its own genes, leading to the genetic inversion of the immune response of B lymphocytes. This results in autoimmune reactions between B lymphocytes and other tissues, which supports the theory of the origin of multiple sclerosis (2). The primary disease caused by this virus is infectious mononucleosis, characterized by monocytosis in the blood count. This virus is linked to a wide range of diseases, including psychiatric, autoimmune, neurological, dermatological, and even malignant diseases (3). Over ninety-five percent of the population is affected by this virus, an important characteristic of which is its possession of double-stranded genetic material. The virus targets the epithelial cells of the upper respiratory tract, as well as the aforementioned lymphocytes (4). Every year, the number of patients with malignant tumors associated with EBV increases, leading to the death of over one hundred thousand individuals (5). It is estimated that over 200,000 cancer sufferers worldwide are linked to this virus (6). It has a latent presence in cells as well as strong oncogenic and epigenetic potential, and often goes unrecognized by immune factors due to its molecular mimicry, paving the way for the development of malignant tumor cells (6). The virus is also linked to epithelial and mesenchymal neoplasms (7,8). This virus possesses an envelope with a diameter ranging from 100 to 200 nm. It has DNA that is located within the nucleocapsid (9).

Symptoms, Carcinogenesis, and Epidemiological Parameters in Epstein-Barr Virus Infection

For those who manifest symptoms, they may include general weakness, enlargement of the spleen and lymph nodes, but also an increase in the number of lymphocytes in the blood. Viremia primarily occurs due to the rapid multiplication and infection of

B lymphocytes by the virus. A randomized controlled study has shown that patients suffering from chronic fatigue following infection with the virus remained in this state six months post-infection (10). Several randomized studies conducted in Chinese hospitals have shown that even after the use of sorafenib in patients undergoing tissue transplantation, the drug exhibited a protective property that prevented infection by the Epstein-Barr virus, even thirty-six months post-treatment (11). The WHO also links certain types of nasopharyngeal carcinoma (non-keratinized) to this virus (12). A meta-analysis that included 26 studies has shown a strong correlation between gingivitis and Epstein-Barr virus infection. What is particularly interesting in these studies is the fact that this correlation was not confirmed among African respondents (13). Some studies using genotyping methods revealed that over 90% of nasopharyngeal neoplasms contained high-risk Epstein-Barr virus BALF2 haplotypes. This is a clear indication of a very high correlation between the occurrence of a given cancer and the Epstein-Barr virus (14). The virus is also associated with stomach neoplasms (15). The designation "oncological virus" for the Epstein-Barr virus comes from its association with multiple malignancies, primarily those arising from B-lymphocytes (16). This virus exhibits two primary modes of infection: a latent state of infection and active viremia, the latter being attributed to the lytic potential of the virus (17). Infection with this oncogenic virus may remain asymptomatic in a certain number of individuals (18). Some studies that have been carried out so far have shown that the percentage of viruses in Reed-Sternberg cells that are pathognomonic for Hodgkin's lymphoma, and that possessed a given virus, ranges up to over 70%. More precisely, over 70% of Reed-Sternberg cells and Stennerberg's cells had Epstein-Barr virus in them (19).

Epstein-Barr Virus and Patients After Organ Transplantation

A particularly vulnerable population comprises those who have undergone tissue or organ transplantation. The Epstein-Barr virus is one of the primary concerns a few years after tissue transplantation due to its ability to remain latent in B lymphocytes and then reactivate after a few years, which confers special importance to this virus (20). In a multicenter study of individuals who were recipients of a transplanted kidney, about a quarter of the recipients developed activation of the latent Epstein-Barr virus. Such activation poses a severe problem that can lead to intense viremia and even serious consequences (21).

Diagnosing Viruses

The most commonly used methods in detecting this virus are serological tests, typically the ELISA test. However, a PCR (polymerase chain reaction) test can also be used to detect a given virus (22). PCR shows high sensitivity and specificity in detecting the viral genome, but its application requires a longer period of time than some other antigenic tests that are performed daily. Furthermore, the disadvantage of the PCR test is its considerably higher price compared to other tests (23). The PCR test detects certain types of genes within the genome of the virus, which are unique to that virus (24). The degree of probability that in the case of nasopharyngeal cancer the PCR test will detect the virus itself from the blood plasma is over 95 percent (25). Also, in the case of reactivation, more precisely reinfection of the virus from its many years of latent rest inside the cells, PCR proves to be a crucial test in proving the given, even if not an active virus. This is because PCR can multiply the virus gene up to several hundred thousand times (26).

In a case report of a 27-year-old patient with SLE (Systemic Lupus Erythematosus), who had positive serological tests for some viruses, the results were subsequently confirmed to be false positives by PCR test (27). Some studies show a very high correlation between SLE activation with the transition to latent Epstein Barr virus infection if the activation date of the chronic disease lasted more than half a year (28). Immunofluorescence assays (IFA) are considered the gold standard as a serological test for the detection of Epstein-Barr virus. However, since the performance and interpretation of IFA are complex and sometimes subjective, many laboratories use commercially available sensitivity and specific tests such as ELISA tests based on enzyme-linked immunosorbent assay or chemiluminescent methods. These tests are used as leading methods in virus detection and are simple to perform. Diagnostic approaches based on IFA, heterophile testing, immunoblot analysis, and PCR testing can be used to clarify some atypical serological results previously determined by immunoassay. This is because the PCR test can accurately detect the presence of the virus and thereby show whether ELISA and other tests were false positive or false negative (22).

The main advantage of the ELISA test compared to PCR testing is its ability to detect the virus without direct contact, relying instead on increased levels of specific antibodies. These antibodies can indicate whether the infection is acute or if the individual has developed immunity, providing protection against re-infection with the virus (29).

One method for confirming the presence of the virus is the immunofiltration method, which in a cer-

tain study showed approximately 13% false positive results (30). Additionally, exposure to and infection with multiple different viruses simultaneously can lead to a false positive finding (31). However, the Epstein-Barr virus can also trigger a strong allergic response in the body mediated by Th2-lymphocytes (32). Interestingly, over 90 percent of individuals infected with this virus do not exhibit any symptoms. There may be a latent-lytic switch in the Epstein-Barr virus. Laboratory analyses, such as the assessment of leukocyte count, procalcitonin, C-reactive protein, and interleukin levels, can be used to detect the presence of this virus (33, 34, 35). A retrospective analysis of hospitalized children in Shanghai revealed that almost 60 percent of cases were correlated with various immunological disorders (35).

Treatment of Individuals Infected with the Epstein-Barr Virus

In addition to pharmacological treatments, cellular treatments of T lymphocytes, which are specific for treating certain viruses like the Epstein-Barr virus, are possible (33). Achieving success in curing this infection has been challenging, but the drug Foscarnet has shown effectiveness in treating infections caused by the Epstein-Barr virus (34). Epstein-Barr virus infection in children, apart from sore throat, increased temperature, lymphadenopathy, and swollen eyelids, resulted in bacterial superinfection which required antibiotic application (36).

CONCLUSION

This apparently harmless virus is increasingly associated with serious chronic diseases. Serological tests, as well as the PCR test, are leading methods for the detection of this virus. An increasing number of current studies show that its role in neoplasm development is highly significant. The details are further elaborated on in the text, but the repercussions of this virus underscore the severity of Epstein-Barr infections as a public health issue.

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Sažetak

EPSTEIN-BARR VIRUS: UZROCI, POSLEDICE, DIJAGNOSTIKA I LEČENJE EPSTEIN-BARR VIRUSA KOD LJUDI

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Epstein-Barr virus (EBV) pripada porodici *Herpesviridae*, subfamiliji *Gammaherpesvirinae* i rodu *Lymphocryptovirus*. Bez obzira na to što postoje dva serotipa Epšten-bar virusa, a to su tip A i tip B, oba tipa imaju svoj značaj u nastanku viremije. Osim što može dovesti do limfadenopatije, opstrukcije gornjih respiratornih puteva, rupture slezine, trombocitopenije, poslednjih godina sve više se stavlja akcenat na povezanost ovog virusa i određenih malignih neoplazmi. Dijagnostika datog virusa može predstavljati problem ukoliko bi se kliničar oslonio samo na serološku potvrdu o ovom virusu, već pored kliničke slike i anamneze potrebno je u nekim slučajevima uraditi određene specifičnije metode da bi se dokazalo prisustvo virusa u krvi, u nazofaringejalnom brisu, ali i u uzorcima iz drugih tkiva. Cilj ovog rada je da predstavi ozbiljnost i posledice izazvane datim virusom i da naglasi preventivne mere koje zauzimaju prvo mesto u sprečavanju da virus inficira osobu, koja mu je izložena. Prevencija igra ključnu ulogu u sprečavanju kontankta sa datim virusom. Pošto se Epstein-Barr virusna infekcija prenosi kapljičnim putem, nošenje maske u zdravstvenim ustanovama, ali i redovno pranje ruku je higijenski primat da bi se sprečila zaraza i dalje širenje zaraze.

Ključne reči: Epstein-Barr virus, kancerogeneza, transplantacija, seroloske metode, autoimune reakcije.

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