WHO EMRO | Trend and seroprevalence of Epstein–Barr virus in Bahrain: 2001–2015

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الاتجاه العام والانتشار المصلي لفيروس إبتشباين - بار في البحرين : 2011-2015

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الخلاصة : تفتقر البحرين إلى المعلومات الوبائية الكافية عن معدل الإصابة بفيروس EBV ، التي من شأنها أن تساعد في إعداد تدابير للحماية من العدوى بالفيروس . ولذلك، يتمثل الهدف من هذه الدراسة في تقصّي الاتجاه العام لعدوى الفيروس في البحرين خلال فترة 15 عاماً، 2001-2015. جرى تقييم النتائج المصلية لما مجموعه 56010 مريضاً يحتمل إصابتهم بعدوى فيروس EBV. وأدرجت العينات المأخوذة في مجموع السلمانية الطبي خلال الفترة 2001-2015. وسجل وجود أو غياب الجلوبيولين المناعي G لمستضدات قُفيصات الفيروس EBV ، والجلوبيولين المناعي M لمستضدات قُفيصات الفيروس، وأضداد الجلوبيولين المناعي G للمستضدات النووية للفيروس EBV. من أصل 56010 عينة، بلغ عدد العينات القابلة للاستخدام 33310 عينة . وبلغت نسبة العينات الإيجابية للمصل 86.1 % مع اتجاه متزايد للعدوى بفيروس EBV خلال فترة الدراسة . وتبيّن وجود عدوى أولية بالفيروس في 7.4 % من العينات الإيجابية للمصل؛ منها 47.3 % في الفئة العمرية ما بين 5 و19 سنة . وتبيّن عودة الفيروس في 11 % من العينات الإيجابية للمصل؛ منها 50 % في الفئة العمرية الأصغر من 25 سنة . وبلغ عمر أصغر مريض إيجابي للمصل 11 شهراً . إن الإصابة بعدوى فيروس EBV شائعة في البحرين . وتحدث معظم حالات العدوى الأولية في الفئة العمرية ما بين سنة و 5 سنوات في حين تحدث معظم حالات عودة العدوى بعد سن 25.

ABSTRACT In Bahrain, adequate epidemiological information is lacking concerning the rate of EBV infection, which could be helpful in order to develop measures to protect against EBV infections. The aim of this study, was to investigate the trend of EBV infection in Bahrain over a 15-year period, 2001–2015. The EBV serological results of 10 560 patients with possible EBV infection were evaluated. Samples taken at the Salmaniya Medical Complex during 2001–2015 were included. The presence or absence of EBV viral capsid antigen (VCA) IgG, VCA IgM and EBV nuclear antigen (EBNA) IgG antibodies was recorded. Of the 10 560 samples, 10 333 were usable; of these, 86.1% were seropositive with an increasing trend of EBV infection over the study period. Primary EBV infection was found in 7.4% of the seropositive samples; of these, 47.3% were between 5 and 19 years. EBV reactivation was found in 11% of the seropositive samples; of these, 50% were > 25 years of age. The youngest

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seropositive patient was 11 months old. EBV is a common viral infection in Bahrain. Most primary infections occur between 1 and 5 years while most reactivation infections occur after the age of 25 years. Serial surveillance of EBV infection is needed in Bahrain. Measures to protect against EBV infections should be implemented.

Tendance et séroprévalence du virus d'Epstein Barr à Bahreïn (2001–2015)

RÉSUMÉ À Bahreïn, il n'existe aucune information épidémiologique adéquate sur le taux d'infection par le virus Epstein Barr (EBV). Or, des données dans ce domaine pourraient permettre de mettre au point des mesures de protection contre les infections par EBV. La présente étude avait ainsi pour objectif d'examiner la tendance de l'infection par EBV à Bahreïn sur une période de 15 ans (2001-2015). Les résultats sérologiques de 10 560 patients ayant une infection par EBV suspecte ont été évalués. Les échantillons prélevés au centre médical de Salmaniya entre 2001 et 2015 ont été inclus. La présence ou l'absence des anticorps IgG de l'antigène de la capside virale de l'EBV, IgM de la capside virale, et IgG dirigés contre l'antigène nucléaire de l'EBV (EBNA) a été enregistrée. Sur les 10 560 échantillons, 10 333 étaient utilisables. Sur ce nombre, 86,1 % étaient séropositifs, et montraient une tendance à la hausse des cas d'infection par EBV sur la période couverte par l'étude. Une primo-infection à EBV a été trouvée pour 7,4 % des échantillons, et sur ce chiffre, 47,3 % des sujets avaient entre 5 et 19 ans. La réactivation de l'EBV a été observée dans 11 % des échantillons séropositifs. Sur ce nombre, 50 % des sujets avaient 25 ans ou plus. Le patient séropositif le plus jeune était âgé de 11 mois. L'EBV est une infection courante à Bahreïn. La plupart des infections ont lieu entre l'âge d'un et cinq ans, tandis que les cas de réactivation de l'infection apparaissent après l'âge de 25 ans. La surveillance en série de l'infection par EBV est requise à Bahreïn. Des mesures de protection contre cet type d'iinfection devraient être mises en place.

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Introduction

Epstein-Barr virus (EBV) is a B-lymphotropic human herpesvirus which is widespread in the world. It can cause long-term immune damage and has lifelong latency in the infected host. It is

the etiologic agent for a number of autoimmune diseases and malignancies (1).

EBV is a globally prevalent virus and over 90% of the world's population is infected with the virus in adulthood. Upon infection, the individual remains a lifelong carrier of the virus and remains without serious overt consequences in most cases. However, in some individuals, the virus is implicated in the development of malignancy (2). The rate and timing of primary infections with EBV differ from one country to another. For instance, most children in the developing world are infected during childhood, in contrast to most developed countries where most primary infections occur at a later age, often in adolescence (3). The timing of primary infection is important as it affects the host differently depending on when it is acquired. For example, acquisition of primary EBV infection in preadolescents is generally mild. However, acquisition in infancy is a risk factor for later malignancy. The infection in infants and children is usually less severe than that of adults (4).

The clinical presentation of EBV infection is challenging as it may be asymptomatic or indistinguishable from other mild, short-lived infections. Therefore, it is important to use the best diagnostic tests with a high degree of confidence (5). Several serological tests can be used for diagnosing EBV infections, such as indirect fluorescent antibody, rapid monospot tests (for heterophile antibodies), and enzyme immune assay for detection of early antigens, the viral capsid antigens (VCA) and the EBV nuclear antigen (EBNA). Full automation of EBV serological diagnosis is important for routine diagnostic laboratories (6).

The use of only 3 parameters (VCA IgG, VCA IgM and EBNA IgG) can distinguish acute and past infections in immunocompetent people. The presence of VCA IgG and VCA IgM in the absence of EBNA IgG indicates acute infection, while the presence of VCA IgG and EBNA IgG in the absence of VCA IgM is typical of past infection. However, some cases may have different profiles that can create diagnostic doubts, such as the presence of VCA IgG in the absence of VCA IgM and EBNA IgG, the simultaneous presence of VCA IgG, VCA IgM and EBNA IgG, and the presence of EBNA IgG in the absence of VCA IgG and IgM. In such circumstances, in addition to following up patients to assess any changes in the antibody profile, it is also useful to perform other laboratory tests (7).

Baseline information of EBV infection in healthy populations is helpful in order to develop measures to protect against EBV infections. In Bahrain, adequate epidemiological information about the rate of EBV infection is lacking. The aim of this study, therefore, was to investigate the trend of EBV infection in Bahrain over a 15-year period, 2001-2015.

Methods

This study was a retrospective analysis of the national data of both paediatric and adult patients that had been evaluated for the presence of EBV infection for various reasons in a major tertiary care hospital in Bahrain during the 15-year period 2001-2015. The study included a total of 10 560 patients aged between 3 months and 91 years who were referred to the Salmaniya Medical Complex (SMC) Laboratory with suspected EBV infection.

On all cases and the type of EBV infections over the past 15 years were retrospectively collected from the Laboratory Information System data and entered in a Microsoft Excel database. The data were analysed separately for the trend in EBV seropositive and seronegative status. Seropositive results were further categorized into primary EBV infection, previous infection and reactivation infections according VCA IgM and VCA IgG positivity, and the presence or absence of serum EBVNA IgG. Serum EBVNA IgG and VCA IgG Figure 1). Positive VCA IgM only, or positive VCA IgM and VCA IgG with negative EBNA IgG were considered acute primary EBV infection. Positive VCA IgM and positive EBNA IgG with or without positive VCA IgG was considered EBV reactivation (8,9). Patients with haemolysed samples or with equivocal results were not included in the data analysis. Inconclusive results (could not be classified according to
Table 1
) were also excluded.

EBV VCA IgG, VCA IgM and EBNA IgG antibodies were measured by an advanced third-generation immunoassay system using an Immulite 2000 machine (Siemens Healthcare GmbH, Germany).

The sex and nationality of the patients were recorded, and they were divided into 6 age groups: 25 years. The data were analysed separately for the trend in the seroprevalence over the past 15 years using TexaSoft, WINKS SDA software 2007, 6th edition (Cedar Hill, Texas, USA). Mean differences between subgroups were tested by the Student t-test. Comparison between ratios was done using the z-score test. P **Ethical considerations**

The study was approved by the Ethics Committee of the Salmaniya Medical Center and the Secondary Health Care Research Subcommittee of the Ministry of Health, Bahrain, and was conducted in accordance with the Helsinki Declaration. No consent was obtained as it was a retrospective analysis of laboratory data which were anonymized.

Results

The study included 10 560 blood samples taken over a period of 15 years; 90 samples were rejected because of haemolysis or insufficient sample to test, and 137 samples gave equivocal results. From the remaining 10 333 valid samples, 13.9% were negative for EBV, while 6.4% showed primary EBV infection, 9.4% showed reactivation of EBV infection, and 70.3% showed previous infection with EBV. Primary EBV infection represented 40.3% and EBV reactivation occurred in 59.7% of the active infections.

Figure 2 shows the trend of EBV infection over the 15-year period. The number of screened samples increased and consequently the number of the samples with previous infections increased from the year 2010 onwards. However, the numbers of samples without infection, with primary EBV infections or with reactivation of EBV infection over the study period did not increase to the same degree.

Primary EBV infection was more common in males (M:F ratio = 1.86), while EBV infection reactivation was slightly more common in females (M:F ratio = 0.96). The majority of patients with both primary EBV infection and reactivation EBV infection were Bahraini, 87.8% and 81.6% respectively. The age trends for primary and reactivation EBV infections are shown in Tables 2 and 3 and Figures 3 and 4. Overall, primary EBV infection was most prevalent in age groups 25 years (45.3%) followed by the age group 5–10 years (15.9%). The youngest recorded case with primary infection was an 11-month-old Bahraini boy.

About 54% of cases with primary EBV infections occurred after 2008 (P

Table 4 shows a comparison of primary and reactivation EBV infections with regard to sociodemographic and clinical data. Significantly more pregnant women had reactivation of EBV infection than primary infection (P

Discussion

Primary EBV infection is often asymptomatic but may result in lifelong infection, the course of which depends on the host immune system. In some cases, primary infection can result in infectious mononucleosis (10). In our study, 86% of the tested patients were positive for EBV infection. There was a striking increase in the rate of primary infection in children between 5 and 10 years over the 15-year duration of the study together with a relative increase in the primary infection rate among males than females.

The prevalence and age distribution of this latent virus infection varies in different populations. In our study, the trend of primary EBV infection in Bahrain increased, especially during the period 2010 to 2015. This was also observed in Taiwan where the prevalence of primary EBV infection increased with a seropositive rate > 50% at the age of 2 years, > 80% at the age of 5–9 years and > 90% at age 10 years and above (11). This is in contrast with the situation in the United States of America (USA), where the EBV antibody prevalence declined in individuals aged 6-19 years from 2003/2004 to 2009/2010, mainly because of a decrease among non-Hispanic white participants (12). The increased trend of primary EBV infection in Bahrain could just be due to the increase in population numbers and hence increased the numbers of patients. In addition, the ratio of Bahraini to non-Bahraini people dropped from an average of 89% each year in the first 9 years to an average of 86% in the following 6 years, which indicates a relative increase in the number of expatriates, which could be a reason. The reasons behind the increase in primary EBV infection in Bahrain need be addressed.

A Malaysian study in 1987 showed that all the children had acquired primary infection by the age of 8 years (13). This EBV infection in early life explained the absence of infectious mononucleosis in the Malaysian population (13). A study in Espírito Santo, Brazil showed a higher prevalence of EBV antibodies in children and adolescents, with more frequent infections occurring at a younger age in children from families of low socioeconomic status (14). Another study in the Islamic Republic of Iran between 2007 and 2011 showed that 91.5% of primary EBV infections occurred by the age of 10 years compared with 72.4% in our study (15). However, a study in the USA found that about 50% of primary EBV infection in American children occurred between 6 and 8 years of age (12). The study was concerned with antibody prevalence in Americans aged 6–19 years from 2003 to 2010. It showed a decreased prevalence in the age group 6–12 years with a higher prevalence in those aged 12–19 years, which supported the need for EBV vaccination before 12 years of age (12). Our study showed a higher incidence of primary EBV infection in males than in females. A Brazilian study reported a higher incidence of EBV-associated childhood Burkitt lymphoma in male children than female children in south-eastern Brazil (16). However, in our study the number of females with EBV reactivation infection was greater than with primary infection. This increase in reactivation infection among females may be due to increased silent primary EBV infections among females. EBV tends to establish latency in the host as with other herpes viruses. Primary infection leads to transitional viraemia, followed by a strong T-cell adaptive immune response, which keeps the infection latent in immunocompetent individuals (17).

The higher rate of EBV infection among Bahrainis than non-Bahrainis could be related to the relative increase in the number of the Bahraini citizens and the easier access of Bahrainis to government medical facilities than non-Bahrainis. However, a study conducted in the USA showed different prevalence rates in different races; the prevalence of primary EBV infection was more common in non-Hispanic black children (74%), followed by Asian children (62%), then

multiracial children (54%), Hispanics (50%), and non-Hispanic white children (26%). This marked ethnicity variability of EBV prevalence could be explained by differences in demographic and socioeconomic status of families, including education and health care availability (18). However, socioeconomic position and factors related to lifestyle explain only a part of the large ethnic differences in EBV seroprevalence (19).

Unknown triggers can cause reactivation of EBV infection due to stimulation of latently infected B cells. The virus can re-infect new B cells and epithelial cells, becoming a source of viral transmission initiating reactivated EBV infection (10). In our study, reactivation was reported in 9.4% of the total sample and 11.0% of the positive samples compared with 6.4% and 7.4% respectively with primary EBV infections. Of the 1634 active infections, 40.3% were primary EBV infection and 59.7% were EBV reactivation. The most common age group for reactivation was over 25 years followed by the ages 5-10 years. In the 5-10 years age group, vitamin D deficiency was found in nearly half of the cases. Vitamin D deficiency may increase the risk of certain viral infections, while it has been shown to have some direct antiviral effects (20). Chemotherapy use was associated with EBV reactivation in 13.5% of those aged 5-10 years. Certain chemotherapeutic drugs, including gemcitabine, doxorubicin, cis-platinum and 5-fluorouracil, have been reported to induce the lytic form of EBV infection in latently infected host cells and hence EBV reactivation (21). At the same time, the use of steroids was associated with EBV reactivation in 7.7% of cases of reactivation. Steroids are a common cause of EBV reactivation from latency, possibly directly by promoting viral replication or alternatively by down-regulating the ability of the memory T-cell response to control the latent virus (22). Previous hospitalization due to respiratory tract infection was reported in 9.7% of reactivation cases. Hospitalization itself is a form of stress, which in turn could stimulate reactivation of herpesviruses including EBV (23). A strong relation was found in a study between cytomegalovirus super-infection and EBV reactivation leading the authors to suggest that cytomegalovirus might be an important co-factor in EBV pathogenesis, especially in immunocompromised patients (24). There were 3 cases of malaria infection preceding reactivation of EBV in our study. Malaria infection profoundly affects the B cell compartment, inducing polyclonal activation and hypergammaglobulinaemia. The cystein-rich inter-domain region 1alpha (CIDR1alpha) of the Plasmodium falciparum membrane protein 1 acts as a polyclonal B cell activator that preferentially activates the memory compartment, where EBV is known to persist (25).

At the same time, about 50% of the EBV reactivation occurred after the age of 25 years with nearly equal male to female ratio. In a study by Nystad and Myrmel, 42% of 43 patients with suspected primary EBV infection had late primary infection, while 49% had high-avidity IgG-antibodies, indicating an IgM response due to reactivation, which agrees with our results (4). EBV reactivation essentially occurs in clinical situations associated with chronic immunosuppression secondary to systemic disease, viral superinfection or specific treatments, as in the case of organ or bone marrow transplantation (26).

The importance of determining the epidemiological status of EBV infection in the country is to estimate the magnitude of the problem and to help to decide the need for an EBV vaccine. A vaccine against EBV would help to prevent primary EBV infection and consequently EBV-related malignancies. Such a vaccine is still in clinical trials and must be given early in life before the peak of seroconversion (as in our study) before the age of 5 years. It would also be useful in seronegative organ transplant recipients and those developing severe infectious mononucleosis, such as the male offspring of X-linked proliferative syndrome carriers (27).

Our study had some limitations. Being a retrospective study is a major limitation with inferior level of evidence compared with prospective studies. The absence of available clinical data constitutes a clear limitation when attempting to compare our results with the results of similar studies. Clinical data are important to relate the EBV infection positivity with clinical severity. At the same time, the difference between the methods used in our study compared with other studies made it difficult to compare results. We also did not correlate EBV prevalence with HLA typing and did not correlate EBV reactivation with the EBV viral DNA load. HLA typing could help to stratify the patients at risk of infection and even complications of EBV infection. High EBV viral loads are strongly associated with current or impending lymphoproliferative disorder.

Conclusion

EBV is a common viral infection in the hospital setting in Bahrain, occurring in childhood as early as 1 year of age with a high seroprevalence. The majority of primary infections occur in the age range 1-5 years while most reactivation infections occur after the age of 25 years. The effect of these epidemiological findings on the prevalence of certain diseases in Bahrain, mainly infectious mononucleosis, Burkitt lymphoma, Hodgkin disease, nasopharyngeal carcinoma and B-cell lymphoma, needs to be explored.

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