GENE EBNA3C: TYPES OF INFECTION BY EBV (EBV1 and EBV2), CORRELATION WITH CLINICAL AND BIOCHEMICAL PARAMETERS (AST, ALT and GGT) IN INDIVIDUALS WITH INFECTIOUS MONONUCLEOSIS OF THE METROPOLITAN AREA OF BELÉM, PARÁ, IN THE PERIOD OF 2005-2016

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Abstract

Two types of EBV (EBV1 and 2) have been shown to infect humans. Detect the types of EBV that cause infectious mononucleosis and correlate these viral types with biochemical parameters (AST, ALT and GGT) on in the metropolitan region of Belém, 2005 to 2016. A total 76 cases of infectious mononucleosis, processed the Instituto Evandro Chagas, Ananindeua, Brazil. Evaluated by PCR used primers the region EBNA 3C. EBV1 infection was observed in 71.1% (54/76) of individuals, among whom those > 14 years constituted 66.7% (36/54), the average age was 23 years, and the number of women infected was higher (61.1% [33/54]) than that of men (38.9%[21/54]). The symptoms/clinical signs observed in infection by EBV1 were cervical lymphadenopathy in 64.8% (35/54), fever in 63% (34/54), headache and arthralgia in 20.3% (11/54), and exanthema in 18.5% (10/54). Infection by EBV2 was observed in only 17.1% (13/76) of cases. Co-infection by EBV1 and EBV2, most frequently showing symptoms of fever and cervical lymphadenopathy, occurred in 66.7 (6/9) and 55.6% (5/9) of individuals. EBV1 was predominant in 71% of clinical cases of infectious mononucleosis. Correlation of biochemical parameters in infection by EBV1, EBV2, and co-infection by EBV1/2 revealed a statistically significant difference in mean changes of EBV1 in individuals older than 14 years.

Background

Epstein-Barr virus (EBV) belongs to the order *Herpesvirales*, family *Herpesviridae*, subfamily *Gammaherpesvirinae*, genus *Lymphocryptovirus* and species *Human gammaherpesvirus 4* 1. EBV was the first oncogenic virus found to infect humans 2,3. The hexagonal nucleocapsid viral particles were formed with linear, double filament, enveloped DNA, with a diameter of 180 to 200 nm 4.

Although symptomatic infections with these viruses occur in benign form, EBV has been implicated in the genesis of a variety of lymphoproliferative disorders and severe epithelial neoplasms such as African Burkitt's Lymphoma 5, carcinoma and nasopharyngeal 6.

In Brazil, several studies have recorded the high frequency of antibodies in the studied populations. Studies conducted by Monteiro et al. (1998), found that at least 70% of the serum samples analyzed in the city of Belém, state of Pará, contain IgG antibodies to EBV, at the outpatient clinic level ranging from 53.8% to 95.6%, or in the community (81.1% to 100%) 7.

Positive indexes were expressive, even in the lowest age groups. These results suggest that active and recent infection (infectious mononucleosis) was detected in 10.6% (25/234) of children and adolescents researched in northern Brazil 8.

Data from Young and Murray (2003) demonstrated that EBV is present in about 90% of individuals and is controlled by the immune system, mainly by cellular immunity; which may make the subject more susceptible to virus proliferation and may trigger lymphoproliferative disorders 9,10.

It is increasingly important to identify in the populations the epidemiological characteristics associated with the risk of EBV infection in order to reduce the clinical conditions associated with possible morbidity and mortality 11.

Reported that the difference between the sequences encoding for EBV Nuclear Antigens (EBNA2, 3A, 3B, and 3C) allows the identification of different genotypes with distinct epidemiological characteristics 12.

According to Young et al. (2000), how human and geographic assemblages can influence the distribution of EBV genotypes 1 and 2, changing as rates of detection of these viral genotypes in diseases associated with EBV 13. Type 1 EBV has been more present in western regions and type 2 is more frequently found in sub-Saharan Africa and New Guinea than in other parts of the world 14.

Reported that the phenotypic difference between EBV1 and 2 is more efficient during immortalization of B cells in EBV1 lymphoblastoid cell lines (LCLs) compared to EBV2. This fact reinforces the biological and functional difference between the two viral types where B cell immortalization in vitro was shown to be more effective by type 1 EBV 15. According to Mandell et al. (2001) differentiations of genotypes can clarify the different immune responses during viral persistence 16.

The metropolitan area of Belém still lacks studies to characterize the different types of circulating EBV (EBV1 and EBV2) associated with clinical, demographic (gender, age and origin) and molecular findings that describe the epidemiology of the infection caused by these viral agents due to its characteristics of viral persistence that can induce chronic infections and reactivations in human populations with genetic competence to possible oncogenic events.

The objective of this study was to detect the types of Epstein Barr virus (EBV1 and EBV2) that cause infectious mononucleosis (IgMVCA / EBV +) and to relate biochemical parameters (ASL, ALT and GGT) from the metropolitan area of Belém between 2005 and 2016.

Methods

Type of Study

The current study was descriptive and retrospective. Samples from 76 clinical cases of infectious mononucleosis that were reactive to EBV/VCA IgM, tested by the RIDASCREEN® (R-Biopharm, Darmstadt, Germany) enzyme immunoassay kit, processed in the Virology section and the biochemical dosages (AST, ALT and GGT) in the pathology section of the Evandro Chagas Institute, Ananindeua, Brazil, from the metropolitan area of Belém, collected between 2005 and 2016 and later evaluated by PCR for the EBNA3C gene for recognition of EBV types.

Identification of the EBNA 3C gene through PCR

Nucleic acid extraction

They were extracted using QIAamp DNA Mini (Qiagen, Germantown, MD) according to the manufacturer's protocol.

Identification of the EBV EBNA3C gene

For the identification of EBV type we used EBNA-3C primer 17. Due to the flanking regions of the type-specific variation primary sites, the resulting PCR products were of two different sizes derived from EBV1 (153pb) and EBV2 (246pb). Five microliters of the eluted ADN were used for PCR amplification with a primer concentration of 0.05 μM (5' GCCAGAGGTAAGTGGACTTT 3' and 5' TGGAGAGGTCAGGTTACTTA 3', respectively). PCR was performed in 0.5 mL microcentrifuge tubes in a final 25 μL mixture containing 0.125 μL (5U / μL) Platinum Taq DNA Polymerase (Invitrogen, Brazil), 1.5 mM MgCl_2 (Invitrogen™, Brazil), 0.2 mM dNTPs (Invitrogen™, Brazil), 5 μL of 10X buffer (Invitrogen™, Brazil) and 2 μL (20 μM / μL) of the abovementioned primers. After denaturation of the DNA mold at 94°C / 1 min, PCR cycle conditions (PTC 100 / Peltier Effect Cycle, Thermostable Controller) included 40 cycles of denaturation at 94°C / 30 sec, annealing at 58°C / 30 sec, extension at 72°C / 1 min, after 1 final extension cycle at 72°C / 7 min. Water (negative control) and B958 and P3HR1 cell lines (positive controls) were used for the amplification of EBV1 and EBV2 in each amplification series.

Ethical Considerations

The research was approved by the research ethics committees of the Evandro Chagas Institute (CAAE nº 65332717.2.0000.0019, with legal opinion nº 2098453, dated June 4, 2017).

DATA ANALYSIS

The results were organized and stored composing a database in Microsoft Office Access 2016, *Statistical Package for Social Science* - SPSS 17.0 and "GraphPadPrism 7.0 for Windows" (GraphPad software, San Diego, CA, USA) 18.

Results

DETECTION OF EBV 3C GENE OF THE EBV

EBV DNA was detected in 76 cases of infectious mononucleosis to identify the type of EBV by PCR for the EBNA3C gene, 55.3% (42/76) belonged to the female gender and 44.7% (34/76) to the male gender. The cases came from the cities of Belém with rates of 76.3% (58/76), Ananindeua with 22.4% (17/76) and Marituba with 1.3% (1/76).

As to the clinical picture, a multiplicity of signs and symptoms were noticed, such as: fever in 65.8% (50/76), cervical lymphadenomegaly in 60.5% (46/76), pharyngitis (15/76) in 19.7 %, arthralgia in 17.0% (13/76), headache in 9.2% (7/76) of the patients. With fever days, 22% (11/50) reported their permanence for up to 5 days, 16% (8/50) for 10 days, 20% (10/50) for 15 days, 16% (8/50) for 20 days, 16% (8/50) for more than 20 days, and 10% (5/50) had no information in the epidemiological record.

The EBV1 infection was observed in 71.1% (54/76); the most frequent age group was > 14 years old, with 66.7% (36/54) of the individuals, since the age range was of 23 years, the number of women was higher 61.1% (33/54) was higher than in men with 38.9% (21/54).

As for the origin of the individuals with EBV genotype 1, the frequencies were: city of Belém with rates of 76.0% (41/54), Ananindeua with 22.2% (12/54) and 1.8% (1/54) of Marituba.

The symptoms/clinical signs observed in infection by EBV1 were cervical lymphadenopathy in 64.8% (35/54), fever in 63% (34/54), headache and arthralgia in 20.3% (11/54), and exanthema in 18.5% (10/54) (Fig. 1).

In EBV2 infection, 17.1% (13/76) cases were observed, where the most frequent symptom was fever in 76.9% (10/13), the individuals were distributed in only two ranges, being > 14 years old, slightly higher, with 53.8% (7/13) individuals, compared to 6 to 14 years old, in 46.2% (6/13) individuals; the average age was 24 years, with the males being more frequent 76.9% (10/13) than females 23.1% (3/13).

Co-infection with EBV1 and EBV2 is more frequent in children and cervical lymphadenopathy in 66.7% (6/9) and 55.6% (5/9), respectively. The most frequent age group was > 14 years, with 44.4% (4/9) of the individuals, since the age group of 2 to 5 years presented 22.2% (2/9) individuals and 6 to 14 years 33.3% (3/9) individuals, an average age of 21 years, the number of women of 66.7% (6/9) was higher than that of men with 33.3% (3/9).

In the assessment of hepatic function, alterations to AST in EBV1 infection were confirmed in 14,8% (8/54) with results above the reference values (5-40 U/L) and 7.7% (1/13) for EBV2. It is worth mentioning that the reference values are the same in the three age groups (Fig 2). When analyzing the mean values by age group, the range of >14 years was outside the normality limits with more frequency of alterations, thus presenting statistical difference (p-value < 0.05).

Values above the reference values (2-41 U/L) were also observed for ALT (Fig 3). The mean value was outside the limits of normality in the age groups of 6 to 14 years and >14 years, presenting a statistical difference (p-value < 0.05) by the *Wilcoxon* test.

For the evaluation of GGT, some altered results were observed, but no changes were found in the age group of 2 to 5 years, given the reference values: (5 - 55 U/L), changes in the age group from 6 to 14 years were all values above normal, given the same reference range of the previous age group, and in the range of >14 years the greatest number of alterations were perceived, above or below, given reference values:

(12 - 43 U/L) (Fig 4). The mean value was outside the limits of normality in the age group of > 14 years, and the mean values presented a statistical difference (p-value <0.05) by the *Wilcoxon* test.

Discussion

Primary EBV infection is usually asymptomatic and may progress to benign lymphoproliferative disease called infectious mononucleosis (IM), especially in late childhood or early adulthood in developing countries 4.

Infectious mononucleosis is characterized by significant clinical polymorphism where factors such as age, immune status and comorbidities have been described as parameters in clinical evolution from asymptomatic infections to more severe conditions evidenced by acute complications such as multiple organ failure, disseminated intravascular coagulation, ulcer/perforation of digestive tract, coronary artery aneurysm, lymphomas and lymphohistiocytes and EBV-associated hemophagocytic 19, 20.

Mendoza et al. (2008) confirm that EBV infection has an incubation period ranging from 4-6 weeks with prodromal symptoms of asthenia, anorexia, headache and chills, often precede the signs and symptoms of mononucleosis: fever (that can reach 39-40° C) accompanied by pharyngotonsillitis and lymphadenopathy 21, 22, 23. In agreement, in our study, fever was the clinical finding in 65.8% (50/76) cervical lymphadenomegaly in 60.5% (46/76), pharyngitis in 19.7% (15/76), arthralgia in 17.0% (13/76), headache in 9.2% (7/76) in the 76 patients analyzed.

Regarding the types of EBV infection cite that there are two different types of EBV 24. Describe that EBV types are related to variation in the EBNA2 and EBNA3 gene sequence; commonly known as types 1 and 2 17, 25.

Studies conducted in other countries have demonstrated the predominance of EBV1 infection in China with rates of 76.3%, Argentina in 75.9%, Sweden in 67% and Hong Kong 57% 26, 27, 28, 29.

Our findings revealed that EBV1 was frequent in 71.1% (54/76) cases of infectious mononucleosis from the metropolitan area of Belém, Brazil. A total of 68 samples of Chinese individuals with the aim of identifying circulating types according to the EBNA 3C gene by PCR obtained the following results: 76.3% (45/59) detectable for EBV-1, 20.3% (12/59) were EBV-2 and 3.4% (2/59) EBV-1 and EBV-2 (Coinfected) and 13.2% (9/68) of the samples did not amplify.

A study conducted by Deng et al. (2014) with samples of 209 Japanese patients obtained the following results: 146/209 (69.9%) was detected for EBV, and 107/146 (73.3%) was for EBV- 1, 27/146 (18.5%) for EBV-2 and 12/146 (8.2%) for coinfecting (EBV-1 and EBV-2) and 63/209 (30.1%) were not amplified for the EBNA3C gene 30.

A study conducted in Qatar revealed similar frequencies with predominance of EBV1 (72.5%, 37/51) compared to genotype 2 (3.5%), and mixed infections were detected in 4% of the samples 31. The

determination of the types of EBV in the present study made it possible to distinguish the molecular epidemiology and circulation of these viral agents.

Hepatic Evaluation

The most clinically relevant transferases are aminotransferase (aspartate amino transferase - AST, alanine amino transferase -ALT) and γ -glutamyl transferase (GGT) which express the main indexes of liver function 32, where in normal individuals small changes may occur (less than twice the reference value). In patients with infectious mononucleosis caused by EBV, values up to 5 to 10 times higher than the reference values have been reported and may even progress to fulminant hepatitis; which is not present with bilirubin abnormalities 33, 34,.

Analyzed 95 patients with infectious mononucleosis and 95 healthy controls for AST, ALT and GGT they report that alterations were elevated in patients with infectious mononucleosis compared to the controls researched 34.

Our results when compared to the EBV types (EBV1, EBV2 and EBV1/2) correlated with the age group and values of AST and ALT were statistically significant ($p < 0.005$); Similar data were cited by Zhang et al. (2018) reported in this study ALT, AST and GGT levels were significantly increased in cases of infectious mononucleosis compared to controls, indicating that transferase levels can be used to diagnose and treat as a risk alert for the infection caused by MI34.

Conclusion

This a pioneering studies with identification of EBV1 in 71.1% of clinical cases of infectious mononucleosis in the metropolitan area of Belém, Pará, from 2005 to 2016. In 11.8% of the cases, co-infection by types EBV1 and EBV2 occurred. Cervical lymphadenopathy and fever were the most relevant clinical findings and signs in the EBV types circulating in the metropolitan area of Belém. Correlation of biochemical parameters (AST, ALT and GGT) with type of infection by EBV1, EBV2, and co-infection by EBV1/2 revealed a statistically significant difference in mean changes of EBV1 in individuals older than 14 years.

Abbreviations

EBV: Epstein-Barr virus; LCLs: lymphoblastic cell lines; AST: aspartate amino transferase; ALT: alanine amino transferase; GGT: γ -glutamyl transferase; MI: infectious mononucleosis.

Declarations

Competing interests

There authors declare that there are no competing interests.

Authors' contributions

The work presented here was carried out as a collaboration between all authors. TAFM, IBC, IBC, TLSC, BMRC, AAP, AESS, FLPR, AJMF, carried out most experiments. TAFM and JLFM made contributions to design, analyze data and interpret data. TAFM and RCMS have been involved in drafting the manuscript. JLFM and TAFM gave most financial support. TAFM, AAP and AESS collected and assembled the data. All the authors have given final approval to publish the manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published. No any other data available for supplementary materials.

Ethics approval and consent to participate

All participants provided informed written consent for all study procedures and for the use of their data for scientific evaluation and publication in a blinded form. This study was conducted in accordance with the Declaration of Helsinki, and it was approved by of the Evandro Chagas Institute with legal opinion nº 2098453, dated June 4, 2017).

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Figures

Figure 1

Signs and symptoms of infectious mononucleosis in patients infected with EBV-1, 2005 to 2016.

Figure 2

Evaluation of ALS of individuals with EBV 1, EBV 2 and EBV 1 and 2 infection.

Figure 3

Evaluation of AST of individuals with EBV 1, EBV 2 and EBV 1 and 2 infection.

Figure 4

Evaluation of GGT activity in individuals with EBV 1, EBV 2 and EBV 1 and 2 infection.