Journal of
Microbial & Biochemical Technology

Caetano et al., J Microb Biochem Technol 2016, 8:5
DOI: 10.4172/1948-5948.1000323

Review Article Open Access

Physiological Changes in Salivary Gland and Kidney that help the Diagnosis caused of Epstein-Barr virus: A Brief Review

Caetano LP[2], Costa KCT[1], Moraes ABA[2] and Alves-Balvedi RP[1]*

[1]*Institute of Biomedical Science, Federal University of Uberlândia, Brazil*
[2]*Institute of Genetics and Biochemistry, Federal University of Uberlândia, Brazil*

Abstract

Epstein-Barr virus (EBV) also called human herpes virus 4 (HHV-4) is a member of the Herpesviridae family. It is estimated that about 90% of the world population is infected, asymptomatically, with at least one subtype of this family. The primary EBV infection is characterized by infectious mononucleosis, popularly known as kissing disease. A few years ago the virus has been linked to several diseases among which stands out the autoimmune diseases and several types of cancer and agent of severe tissue injury and it is a kidney and saliva physiology modulator. The diagnosis of EBV described in literature basically occurs by techniques of *in situ* hybridization and polymerase chain reaction (PCR) of viral DNA present in collected venous blood. But this review propose demonstrate that the use of other physiological fluid, such as saliva and urine, was done a survey of less invasive detection tests. These tests are used in dynamic and emerging nanotechnology because they help in the diagnosis of diseases based on the detection of biomarkers and broaden perspectives in clinical diagnosis, prognostic and monitoring of diseases, contributing to patient care. The use of such fluids in addition to relative ease of collection is an alternative for the diagnosis is very attractive especially by the less invasive nature of the venipuncture or biopsy.

Keywords: Epstein-barr virus; Physiology; Diagnosis; Physiological fluid

Introduction

Already described in the literature, Epstein-Barr virus (EBV) also called human herpes virus 4 (HHV-4) is a member of the family Herpesviridae; subfamily ɣ-herpes widely distributed in the world and may be asymptomatic throughout the life of the host. This virus comprises DNA double linear tape, surrounded by an icosahedral capsid, covered by a glycoprotein envelope and tegument [1-3]. Discovered more than 50 years in a very common lymphoma in sub-Saharan Africa the association between EBV and this lymphoma became the first of an unexpectedly wide variety of associations found between virus and several other tumors related to serological evidence as oral and gastric carcinoma, Hodgkin's disease, immuno-compromised individuals proliferative disorders such as post-transplantation lympho-proliferative disease and a subset of lymphocytes T- and NK-cell lymphomas. Recent studies also show the association of EBV to autoimmune diseases such as rheumatoid arthritis and lupus erythematosus [4,5].

The prospects for the analysis of pathologies in saliva and urine samples are increasing since the literature describes how the pathologies result in changes in the urinary tract and salivary physiology, making detection of specific markers possible with sensitivity, selectivity, specificity, speed and low cost.

As EBV is transmitted through saliva and other body fluids such as cervical secretions, milk, semen, tears and urethral secretions in contact with the mucosal and epithelial cells of the oropharynx, nasopharynx and salivary glands and these regions occurs replication (lytic cycle) and establishes a latency [6]. This review, it was done a survey of less invasive detection tests such as urine or saliva and also analyzes commonly executed in remote periods such as renal and saliva biopsy could be prevented in the diagnosis.

Development

Physiological changes in salivary

Saliva is a fluid hypotonic in relation to plasma and contains compounds locally produced in the salivary glands (immunoglobulin A [IgA] and α-amylase), and the plasma diffused compounds (water, electrolytes, proteins, metabolites and hormones). Production and composition are dependent on the activity of the autonomic sympathetic and parasympathetic nervous system whose complementary action could result in different saliva volumes with protein and ionic distinct profiles [7].

Tests of diagnostics from saliva (oral fluid) are used in dynamic and emerging nanotechnology because they help in the diagnosis of diseases based on the detection of biomarkers and broaden perspectives in clinical diagnosis, prognostic and monitoring of diseases, contributing to patient care [8]. The use of saliva as an alternative for the diagnosis is very attractive due to ease of obtaining the sample and especially by the less invasive nature of the collected venous blood.

Salivary gland biopsy

The salivary gland biopsy is a procedure that can be done anywhere salivary glands are present as parotid, submandibular, sublingual, lip and palate. It is carried out for the diagnosis of Sjogren's syndrome, sarcoidosis, amyloidosis and lymphoma. When performing this procedure the operator should minimize discomfort to the patient and obtain an adequate sample [9].

The researches described the sublingual salivary gland biopsy

***Corresponding author:** Alves-Balvedi RP, Av Pará sn Bloco 2A sala 130, Campus Umuarama, Bairoo Umuarama, Uberlândia, MG, Brazil, Tel: +55 34 32258472; E-mail: renataalvesbalvedi@hotmail.com

Received August 26, 2016; **Accepted** September 07, 2016; **Published** September 14, 2016

Citation: Caetano LP, Costa KCT, Moraes ABA, Alves-Balvedi RP (2016) Physiological Changes in Salivary Gland and Kidney that help the Diagnosis caused of Epstein-Barr virus: A Brief Review. J Microb Biochem Technol 8: 444-448. doi: 10.4172/1948-5948.1000323

technique that makes an incision in the mucosa, starting 1 cm from anterolaterally of Wharton's duct and prolonged ante-posteriorly per 1 cm. In parotid biopsy technique is made an incision 1-2 cm below the ear lobe near the posterior mandible angle [10-12].

The palate biopsy technique was described which makes a circular incision procedure on bone. Another technique, a biopsy of the minor salivary gland was reported, which describes a linear incision of mucosa 1.5-2 cm edge parallel to red and lateral to midline. Scars, bleeding lack of sensitivity in the area of the incision are some of the complications biopsies reported by some authors [13-15].

Many studies have suggested that Epstein-Barr virus can be an agent Sjogren's syndrome (SS). SS is an autoimmune disease affecting the salivary and lacrimal glands. The histological features are lymphocyte proliferation, atrophy of the acinus and destruction of the lobes [16-18]. A comparative study between sialometry techniques and minor salivary gland biopsy in patients with Sjogren's syndrome showed no difference in sensitivity between both procedures and the authors concluded that the positivity of both tests increases the specificity for Sjögren's syndrome (95%) than when they are considered in isolation. In recent years research has focused on less invasive diagnostic methods in order to cause a minor annoyance in patients [19-21].

Saliva tests

The traditional method for diagnosis of EBV is biopsy, however, because of its invasiveness, surgical injury and risk of infection-contamination other forms are evaluated seeking less invasive, cheaper, effective and efficient. In the serum titers of antibodies against various antigens, present studies confirm that since the secretion of saliva or virus transmission step, this could also be a means of diagnosis of EBV-DNA.

Understanding the dynamics of transmission is studied from the progressive increase in associated research between EBV and HIV to date and expands the possibilities for diagnosis of viral loads and correlation between such. Analyses of the *in situ* hybridization to assess the presence of EBV in HIV-infected patients in the saliva, was determined by PCR, whereas the amount of DNA in EBV-positive samples was estimated by titration repeated. The results showed that all patients with hairy leukoplakia EBV-DNA contained saliva [22-25].

In Africa, EBV was associated with Burkitt's lymphoma as has historically been quoted. Thus, the researchers quantified EBV-DNA levels in saliva and leukocyte levels of Ugandan children with asymptomatic sickle cell disease and their mothers in RT-PCR. The results showed EBV-DNA detected in saliva in 90% of children and 79% of mothers, such as EBV-DNA was also detected in leukocytes of 86% of children and 72% of mothers. The detection of EBV-DNA in saliva was positively correlated and the results indicate that persistent infection of EBV allows it to be readily detectable in saliva [26-30].

With technological innovations, new results corroborate previous studies to better understand the EBV cycle. In 2009, sought to develop more detailed models on the persistence of EBV, the study of the dynamics of spread of the virus in healthy carriers. The study confirms that the release of saliva EBV is continuous and fast so that the virus level is replaced at intervals of time ≤ 2 min. Thus, the mouth is not a reservoir of virus, but the conduct of continuous flow of virus in saliva makes it a reliable source of study and analysis. The results showed that the virus being released at a much higher rate than previously thought too much for a high level be explained by replication in B cells in the Waldeyer's ring alone. Particular analysis needs to be enhanced by the high and low release of EBV in saliva that is not so much a function of the variation between individuals, but within individuals over time. The dynamic release describes a process that regulates the production of viruses and this increase exponentially, and is then terminated at random which can be regulated by the structural complexity of the tissue, ultimately, but is limited by the immune response [31-34].

In 2010, it was presented to the EBV and cytomegalovirus (CMV) and a broad distribution in the population and is responsible for the development of various diseases. Saliva can contain a lot of these herpes viruses and is a common vehicle horizontal transmission among close individuals. The aim of this study was to determine the DNA detection of EBV and CMV in saliva of individuals infected with HIV or not and their families, assessing the role played by immunodeficiency salivary transmission. Unstimulated saliva was collected from each participant and the DNA was extracted using the Geneclean® II Kit (BIO 101, La Jolla, CA, USA). DNA amplification of EBV and CMV was performed using a nested PCR protocol and based on the results of this study, the DNA of EBV and CMV virus is frequently amplified in saliva. The HIV-infected individuals and healthy controls showed a similar viral DNA detection frequency. Relatives of individuals HIV/EBV co-infected have a higher risk of developing EBV through non-sexual contact. For determine the frequency of EBV- DNA and CMV-DNA, in the saliva of individuals with HIV and his brothers. The experiments started from unstimulated saliva collected, extraction DNA and PCR amplification. HIV-infected individuals and healthy controls showed a similar frequency of detection of viral DNA. EBV DNA was significantly amplified in the saliva of family members of HIV/EBV co-infected individuals, from here the possibilities for comparative analysis of salivary diagnostics [25,29,35-37].

The use of cytology as a less invasive alternative in the diagnosis of hairy leukoplakia has been postulated by some authors. The use of PCR material obtained through mucosal scrapings can detect EBV viral particles present in saliva and not within the epithelial cells. To validate the cytology as a complementary exam, for diagnosis of Hairy leukoplakia using *in situ* techniques (hybridization) for the detection in oral mucosa. Thus, diagnostic studies involving hairy leukoplakia orally in situ hybridization for EBV detection based cytology via ThinPrep test Pap shown that cytology EBV-associated hybridization is simple, efficient and non-invasive tool as efficient as biopsies [19].

Physiological changes in kidney

The acute infection caused by the Epstein-Barr virus (EBV) causes fever, fatigue, pharyngitis, and renal involvement in systemic infections caused by EBV usually manifest as acute tubular necrosis and tubule-interstitial nephritis. Rarely does EBV infection causes nephritic syndrome due to minimal change disease and treatment with methyl prednisone leads to rapid and complete clinical remission.

The minimal change nephropathy is a very rare manifestation in patients with EBV infection and should be considered in patients with Infectious mononucleosis (IM) and proteinuria [38].

Renal biopsy

Infectious mononucleosis, disease caused directly by EBV, is disclosed certain serious renal complications and demonstrates studies [39,40]. Nephrotic syndrome in acute infectious mononucleosis was first published in 1963 in a case where renal biopsy was inconclusive. The most commonly described kidney injury is acute interstitial nephritis tubule [41].

Epstein-Barr virus has been associated with various renal syndromes. About 16% of patients with acute infectious mononucleosis show some evidence of renal involvement [42]. Among the various forms of diagnosis of the Epstein-Barr virus as the causative agent of a particular disease, some articles [43,44] suggest that one of the most effective is the biopsy tissue followed by in situ hybridization.

Mayer et al. found that patients diagnosed with infectious mononucleosis showed a frame and oliguric renal failure [39]. In particular cases, the patient can recover quickly with hemodialysis treatment and combined with corticosteroids, acyclovir. In renal biopsy was interstitial nephritis and immune-peroxidase studies have demonstrated a predominance of suppressor T cytotoxic cells. However, in situ hybridization in renal tissue biopsy revealed no evidence of RNA encoded by EBV-1. The results indicated that acute renal failure in infectious mononucleosis although rare and often self-limiting, may be caused by interstitial nephritis, which is probably the elapsed immune-pathological damage due to EBV infection.

Injuries in renal tubule-interstitial can occur through a primary process or as a secondary process that accompanies a variety of glomerulo-pathies, renal vascular disease, systemic disorders, among others. With respect to the primary interstitial nephritis, injury may be predominantly inflammatory or fibrotic and consequently may result in kidney failure [45]. The viral infection of the kidney tissue behaves as a pro-inflammatory potential factor that induces tissue damage. Thus proposed interrelate the primary interstitial nephritis infection caused by EBV and concluded that the viral infection of the kidney proximal tubule cells played an important role in the initiation and/or progression of injury and inflammation nephritis [46,47].

In addition, studies Becker reported chronic interstitial nephritis, as a consequence of the presence of EBV in cells of the renal proximal tubule. By in situ hybridization and PCR was possible to detect EBV DNA- in renal tissue of patients with idiopathic variety of chronic interstitial nephritis. The EBV genome was detected mainly in cells of the renal proximal tubules. Moreover, the CD21 antigen, which serves as the receptor for EBV in B lymphocytes, was detected by immunocytochemistry, particularly in the proximal tubule cells [48].

According to Iwama et al., by Southern blot technique then PCR detected the presence of EBV in renal biopsies. In 30 of the 33 samples analyzed, the β-globin gene was successfully amplified. Among the 30 patients, EBV has been detected in patients with: nephropathy IgAN A- immunoglobulin (58%), membranous nephropathy (50%), minor glomerular abnormalities (0%), and focal and/or segmental lesions (100%). In addition, the EBV detection ratio of mesangial glomerular lesions (64%) with glomerular lesions (60%), with deposition fibrinogen (73%) and immunoglobulins deposits (57%) were all larger than substantially those patients who did not obtain any effect of these variants studied (controls). Thus, these data suggest that EBV can cause damage to the glomerular mesangium and be mediated by immunoglobulin in patients with various chronic glomerulonephritis [49].

In reports of acute renal failure of unknown cause, some studies seek possible relationships that tissue inability to infectious agents. In the case study, the association was to EBV in previously healthy children hospitalized with primary infection and serologically EBV carriers. Among these, eight had acute renal failure, of which 5 (group A) were not associated with hemophagocytic syndrome virus (VAHS), while 3 (group B) had VAHS. Two patients in group A contained renal biopsies showing acute tubulointerstitial nephritis, as all individuals in the group B were consistent with this type of nephritis. These data show that EBV can be considered a causative agent [50]. What confirms evaluation performed that on renal biopsy of previously healthy children revealed deep interstitial nephritis and acute tubular necrosis, suggesting that the development of acute renal failure report with atypical lymphocytosis, leading EBV, again, as the etiologic agent [51].

EBV together with other agents in the group of herpes human virus is studied as possible agents for years in the development of urinary tract malignancies such as bladder cancer. In the study by Gazzaniga et al., bladder biopsies were evaluated by PCR. Genomic sequences of Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus type 2 (HSV-2) and human papillomavirus type 16 and 18 (HPV16, HPV18) were detected in 34%, 11%, 9% and 31%, respectively of the tissue samples. These analyzes have raised the possibility that a viral infection may contribute to the development and progression of some types of urological neoplasms in humans, so this work was considered pioneering in EBV-pool, CMV and HSV-2 with cancer bladder [52].

While there are still few studies on the etiology of renal cell carcinoma, studies have correlated the involvement of Epstein-Barr virus in this disease enlargement Including one study were evaluated nine-cell renal cell carcinoma (RCC) and two nephroblastoma (Wilm's tumor). The mRNA of these cells, in situ hybridization, longed with EBV-specific probe used, revealing immunofluorescence signals in all samples examined. These results suggest that the expression of Epstein-Barr virus antigens demonstrates its possible involvement in the pathogenesis of RCC and nephroblastoma [53].

Urine tests

The presence of EBV in the urine of patients with infectious mononucleosis (IM) was first investigated in 1994, along with blood tests for comparison purposes. Samples were analyzed by PCR and the results showed that the EBV-DNA can be detected in blood and urine, demonstrating for the first time the presence of infectious EBV in urine during the clinical course of disease and even months after clinical recovery full patients [54].

Analysis of patients with carcinomas nasopharyngeal showed that EBV-DNA was detected in the urine of 56% of patients which favors the EBV-DNA analysis in urine as a potentially applicable as a noninvasive test for the monitoring and prognosis of cancer patients [27].

Symptoms observed by infection due to the presence of EBV much of the time characteristic are somewhat unspecific and may therefore be associated with other diseases. This difficulty of diagnosis reflects in the search for a range of additional tests to medical clinical evaluation [55-57].

The urine test may be useful in further diagnosis of different pathogens, and eventually becomes a good option when compared to other methods because it is a painless examination, simple collection and usually with rapid results, which makes it more advantageous than analysis blood and biopsies, which are invasive and uncomfortable to the patient [58].

Patient urine samples may be useful for leukocyte culture research, since excess indicates inflammation, including urinary tract. As inflammation may be related to a secondary disorder caused by EBV urine culture examination was classified as specific just for a conclusive assessment [59].

When this is the most sensitive method for confirmation of EBV

presence in the body using urine as a sample, the polymerase chain reaction method (PCR) can be used effectively for the virus in the acute phase infection and even months. This technique can be used in addition to the blood and cerebrospinal fluid also [60,61].

The PCR technique is a technique with high specificity, and reproducibility is to duplicate the DNA strands involving nucleotides, primers (primer sequence), and the polymerase enzyme may use little material (sample). After a few amplification cycles are obtained multiple copies of DNA from a template strand, the end result is visualized by gel electrophoresis [62,63].

Conclusion

In the case of EBV, wen the physiological changes in salivary and kidney are presents, the PCR technique commonly used is the RT-PCR laboratories engaging the basic principles of PCR detection of a fluorescent signal system combining detection. Quantification and amplification of DNA in a single step, thus allowing greater flexibility results and this technique as well as all applications cited quantification of gene expression and also the characterization of agents. It is a rapid, sensitive and highly specific when compared to other methods [64-66].

Several researchers have sought to validate the use of RT-PCR to monitor the replication of EBV in high-risk patients for reactivation of the virus, and also as a criterion for therapeutic intervention. But use only samples of urine and only one type of diagnostic methodology can limit protocols and interfere with the results of treatment. Therefore, each case must be evaluated separately and individualized patient's condition [67-69].

The use of cytology as a less invasive alternative in the diagnosis of hairy leukoplakia has been postulated by some authors. However, the cytological characteristics of the lesion, stained with Papanicolau alone are not sufficient to establish the definitive diagnosis and the use of PCR material obtained through mucosal scrapings can detect EBV viral particles present in saliva and not within the epithelial cells. To validate the cytology as a complementary exam for diagnosis of

The simultaneous detection of different viruses in oral fluids or urine using different trials with multiple applications is an emerging field. Many of these are capable of multiplexing and nanotechnological approaches producing automated diagnostic apparatus, reliable and sensitive. However, these new detection systems require optimization and validation prior to implementation in clinical practice for diagnostic tests [8].

The purpose of diagnostic permeate characteristics of being highly sensitive, specific, selective, relatively easy in terms of development, as well as affordable, fast and accurate. Thus, the scientific attention in recent decades, implements important analytical tools used for the pathophysiology clinical diagnosis not only in serum samples as well as in saliva and urine. It is worth mentioning the relative ease of sample collection and the actual detection capability, in real time and using little sample volume are the important additional features in the implementation process.

Acknowledgement

The authors would like to thank the English teacher Hamilton Garcia Jr. for reviewing the English manuscript.

Author Contribution

All authors contributed equally to this work.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Amon F, Farrell PJ (2005) Reactivation of Epstein–Barr virus from latency. Rev Med Virol 15: 149–156.
2. Lima MAP, Rabenhorst SHB (2006) Associação do vírus Epstein-Barr (EBV) com tumores sólidos. Rev Bras Cancerol 52: 87-96.
3. Young LS, Rickinson AB (2004) Epstein-Barr virus: 40 years. Nat Rev Cancer 4: 757–768.
4. Epstein MA, Achong BG, Barr YM (1964) Virus particles in cultured lymphoblasts from Burkitt's lymphoma. The Lancet 1: 702–703.
5. Burkitt DA (1958) Sarcoma involving the jaws in African children. Br J Surg 46: 218-223.
6. Perera RA, Samaranayake LP, Tsang CS (2010) Shedding dynamics of Epstein-Barr virus: A type 1 carcinogen. Arch Oral Biol 55: 639-647.
7. Nunes LAS, Macedo DV (2013) Saliva as a diagnostic fluid in sports medicine: Potential and limitations. J Bras Patol Med Lab 49: 247-255.
8. Malamud D, Rodriguez-Chavez IR (2011) Saliva as a diagnostic fluid. Dent Clin North Am 55: 159–178.
9. Colella G, Cannavale R, Vicidomini A, Itro A (2010) Salivary gland biopsy: A comprehensive review of techniques and related complications. Rheumatology 49: 2117–2121.
10. Marx RE, Hartman KS, Rethman KV (1988) A prospective study comparing incisional labial to incisional parotid biopsies in the detection and confirmation of sarcoidosis, Sjogren's disease, sialosis and lymphoma. J Rheumatol 15: 621–629.
11. Berquin K, Mahy P, Weynand B, Reychler H (2005) Accessory or sublingual salivary gland biopsy to assess systemic disease: A comparative retrospective study. Eur Arch Otorhinolaryngol 263: 233–236.
12. Adam P, Haroun A, Billet J, Mercier J (1992) Biopsy of the salivary glands. The importance and technic of biopsy of the sublingual gland on its anterio-lateral side. Rev Stomatol Chir Maxillofac 93: 337–340.
13. Eisenbud L, Platt N, Stern M, D'Angelo W (1973) Palatal biopsy as a diagnostic aid in the study of connective tissue diseases. Oral Surg Oral Med Oral Pathol 35: 642–648.
14. Greenspan JS, Daniels TE, Talal N, Sylvester RA (1974) The histopathology of Sjogren's syndrome in labial salivary gland biopsies. Oral Surg Oral Med Oral Pathol 37: 217–229.
15. Pennec YL, Leroy JP, Jouquan J, Lelong A (1990) Comparison of labial and sublingual salivary gland biopsies in the diagnosis of Sjogren's syndrome. Ann Rheum Dis Brest 49: 37–39.
16. Draborg AH, Duus K, Houen G (2013) Epstein-Barr virus in systemic autoimmune diseases. Clin Dev Immunol 1: 1-9.
17. Saito I, Servenius B, Compton T, Fox RI (1989) Detection of Epstein-Barr virus DNA by polymerase chain reaction in blood and tissue biopsies from patients with Sjogren's syndrome. J Exp Med 169: 2191–2198.
18. Wen S, Shimizu N, Yoshiyama H, Mizugaki Y (1996) Association of Epstein-Barr virus (EBV) with Sjogren's syndrome: Differential EBV expression between epithelial cells and lymphocytes in salivary glands. Am J Pathol 149: 1511-1517.
19. Braz-Silva PH, de Rezende NP, Ortega KL, de Macedo Santos RT (2008) Detection of Epstein–Barr virus (EBV) by *in situ* hybridization as definitive diagnosis of hairy leukoplakia. Head Neck Pathol 2: 19–24.
20. Liquidato BM, Filho IM (2005) Evaluation of sialometry and minor salivary gland biopsy in classification of Sjögren's syndrome patients. Rev Bras Otorrinolaringol 71: 346-354.
21. Kalk W, Vissink A, Spijkervet FK, Bootsma H (2001) Sialometry and sialochemistry: Diagnostic tools for Sjögren's syndrome. Ann Rheum Dis 60: 1110–1116.
22. Lucht E, Biberfeld P, Linde A (1995) Epstein-Barr virus (EBV) DNA in saliva and EBV serology of HIV-1-infected persons with and without hairy leukoplakia. J Infect 31: 189-194.
23. Chan KH, Ng MH, Seto WH, Peiris JS (2001) Epstein-Barr virus (EBV) DNA in sera of patients with primary EBV infection. J Clin Microbiol 39: 4152-4154.

24. Gartzonika C (2012) Utility of real-time PCR in the diagnosis of primary Epstein-Barr virus infection. J Med Microb Diagn 2: 1-4.

25. Fellnera MD, Durand K, Rodriguez M, Irazu L (2014) Duplex real-time PCR method for Epstein–Barr virus and human DNA quantification: Its application for post-transplant lympho-proliferative disorders detection. Braz J Infect Dis 18: 271–280.

26. Mbulaiteye SM, Walters M, Engels EA, Bakaki PM (2006) High levels of Epstein-Barr virus DNA in saliva and peripheral blood from Ugandan mother-child pairs. JID 193: 422-426.

27. Chan KCA, Leung SF, Yeung SW, Chan AT (2008) Quantitative analysis of the trans renal excretion of circulating EBV DNA in nasopharyngeal carcinoma patients. Clin Cancer Res 14: 4809-4813.

28. Idesawa M, Sugano N, Ikeda K, Oshikawa M (2004) Detection of Epstein-Barr virus in saliva by real-time PCR. Oral Microbiol Immunol 19: 230-232.

29. Carvalho KSS, Silvestre Ede A, Maciel Sda S, Lira HI (2010) PCR detection of multiple human herpes virus DNA in saliva from HIV-infected individuals in Teresina, State of Piauí, Brazil. Rev Soc Bras Med Trop 43: 620-623.

30. Mollbrink A, Falk KI, Linde A, Barkholt L (2009) Monitoring EBV DNA in saliva for early diagnosis of EBV reactivation in solid tumour patients after allogeneic haematopoietic SCT. Bone Marrow Transplant 44: 259–261.

31. Hadinoto V, Shapiro M, Sun CC, Thorley-Lawson DA (2009) The dynamics of EBV shedding implicate a central role for epithelial cells in amplifying viral output. PLoS Pathogens 5: e1000496.

32. Swaminathan S, Kenney S (2009) The Epstein-Barr virus lytic life cycle. DNA Tumor Viruses 1: 285-315.

33. Hong GK, Gulley ML, Feng WH, Delecluse HJ (2005) Epstein-Barr virus lytic infection contributes to lympho-proliferative disease in a SCID mouse model. J Virol 79: 13993–14003.

34. Kumar P, Saha A, Robertson ES (2010) Epstein-Barr virus hijacks cell-cycle machinery. Microbe Magazine 5: 251- 257.

35. De França, TR, de Albuquerque Tavares Carvalho A, Gomes VB, Gueiros LA (2012) Salivary shedding of Epstein-Barr virus and cytomegalovirus in people infected or not by human immunodeficiency virus. Clin Oral Investig 16: 659-664.

36. Bibas M, Antinori A (2009) EBV and HIV-related lymphoma. Mediterr J Hematol Infect Dis 1: 1-13.

37. Mailankody S, Landgren O (2013) HIV, EBV and monoclonal gammopathy. Blood 122: 2924-2925.

38. Mikhalkova D, Khanna S, Vaidya R, Sethi S (2012) Epstein–Barr virus-associated nephrotic syndrome. Clin Kidney J 1: 50–52.

39. Mayer HB, Wanke CA, Williams M, Crosson AW (1996) Epstein-Barr virus – Induced infectious mononucleosis complicated by acute renal failure: Case report and review. Clin Infections Dis 22: 1009-1018.

40. Ozgurhan G, Ozcentin M, Vehapoglu A, Karakaya Z (2015) Acute kidney injury complicated Epstein-Barr virus infection in infancy. Case Rep. Pediatr Hindawi Corporation 1:13-16.

41. Greenspan G (1963) The nephrotic syndrome complicating infectious mononucleosis. Report of a case. Calif Med 9: 162-169.

42. Joshi A, Arora A, Cimbaluk D, Dunea G (2012) Acute Epstein-Barr virus infection-associated collapsing glomerulopathy. Clin Kidney J 5: 320-322.

43. Okano M, Gross TG (2012) Acute or chronic life-threatening diseases associated with Epstein-Barr virus infection. Am J Med Sci 343: 483-489.

44. Oliveira JL, Freitas RT, Arcuri LJ, Gomes AP (2012) O vírus Epstein-Barr e a mononucleose infecciosa. Rev Clin Med 10: 535-543.

45. Lee S, Kjellstrand CM (1978) Renal disease in infectious mononucleosis. Clin. Nephrol 9: 236-240.

46. Muso E, Fujiwara H, Yoshida H, Hosokawa R (1993) Epstein-Barr virus genome-positive tubule-interstitial nephritis associated with Kawasaki disease-like coronary aneurysms. Clin Nephrol 40: 7-15.

47. L´opez-Navida A, Domingo P, López-Talavera JC, Rabella N. Epstein-Barr virus infection associated with interstitial nephritis and chronic fatigue. Scand J Infection Dis 28: 185-187.

48. Becker JL, Miller F, Nuovo GJ, Josepovitz C (1999) Epstein-Barr virus infection of renal proximal tubule cells: Possible role in chronic interstitial nephritis. J Clin Invest 104: 1673-1681.

49. Iwama H, Horikoshi S, Shirato I, Tomino Y (1998) Epstein-Barr virus detection in kidney biopsy specimens correlates with glomerular mesangial injury. Am J Kidney Dis 32: 785-793.

50. Tsai JD, Lee HC, Lin CC, Liang DC (2003) Epstein-Barr virus-associated acute renal failure: Diagnosis, treatment and follow-up. Pediatr Nephrol 18: 667-674.

51. Norwood VF, Stargill BC (2002) Unexplained acute renal failure in a toddler: A rare complication of Epstein-Barr virus. Clinical Nephrology 17: 628-632.

52. Gazzaniga P, Vercillo R, Gradilone A, Silvestri I (1998) Prevalence of papilloma virus, Epstein-Barr virus, cytomegalo virus and herpes simplex virus type 2 in urinary bladder cancer. J Med Virol 55: 262-267.

53. Shimakage M, Kawahara K, Harada S, Sasagawa T (2007) Expression of Epstein-Barr virus in renal cell carcinoma. Oncology Reports 18: 41-46.

54. Landau Z, Gross R, Sanilevich A, Friedmann A (1994) Presence of infective Epstein-Barr virus in the urine of patients with infectious mononucleosis. J Med Virol 44: 229-233.

55. Balfour HH, Dunmire SK, Hogquist KA (2015) Infectious mononucleosis. Clinical & Translational Immunology 4: 33-45.

56. BOrysiewicz LK, Haworth SJ, Cohen J, Mundin J (1986) Epstein Barr virus-specific immune defects in patients with persistent symptoms following infectious mononucleosis. QJM 58: 111-121.

57. Cohen J (2000) Epstein–Barr virus infection. New England Journal of Medicine 343: 481-492.

58. Licht MR (2001) Urologic history physical examination and urinalysis. Office Urology Humana Press 1: 77-87.

59. Goldberg GN, Fulginiti VA, Ray CG, Ferry P (1981) In utero Epstein-Barr virus (infectious mononucleosis) infection. JAMA 246: 1579-1581.

60. Mouritsen CL, Wittwer CT, Reed G, Khan TM(1997) Detection of Epstein-Barr viral DNA in serum using rapid-cycle PCR. Biochem Mol Med 60: 161-168.

61. Lam KMC, Syed N, Whittle H, Crawford DH (1991) Circulating Epstein-Barr virus carrying B cells in acute malaria. Lancet 337: 876-878.

62. Boom R, Sol CJ, Salimans MM, Jansen CL (1990) Rapid and simple method for purification of nucleic acids. JCM 28: 495-503.

63. Mesquita RA, Anzai EK, Oliveira RN (2001) Evaluation of three methods of DNA extraction from paraffin-embedded material for the amplification of genomic DNA by means of the PCR technique. Pesq Odontol Bras 15: 314-319.

64. Kimura H, Morita M, Yabuta Y, Kuzushima K (1999) Quantitative analysis of Epstein-Barr virus load by using a real-time PCR assay. JCM 37: 132-136.

65. Sugita S, Shimizu N, Watanabe K, Mizukami M (2008) Use of multiplex PCR and real-time PCR to detect human herpes virus genome in ocular fluids of patients with uveitis. British Journal of Ophthalmology 92: 928-932.

66. Luderer R, Kok M, Niesters HG, Schuurman R (2005) Real-time Epstein-Barr virus PCR for the diagnosis of primary EBV infections and EBV reactivation. Molecular Diagnosis 9: 195-200.

67. Hayden RT, Hokanson KM, Pounds SB, Bankowski MJ (2008) Multicenter comparison of different real-time PCR assays for quantitative detection of Epstein-Barr virus. JCM 46:157-163.

68. Brengel-Pesce K, Morand P, Schmuck A, Bourgeat MJ (2002) Routine use of real-time quantitative PCR for laboratory diagnosis of Epstein-Barr virus infections. JMV 66: 360-369.

69. Morishima T (1999) Quantitative analysis of Epstein-Barr virus load by using a real-time PCR assay. JCM 37: 132-136.