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

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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, asymptotically, 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 Y-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

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hybridization to too much for a high level be explained by replication in B cells in the virus being released at a much higher rate than previously thought makes it a reliable source of study and analysis. The results showed that the release of saliva EBV is continuous and fast so that the virus dynamics of spread of the virus in healthy carriers. The study confirms more detailed models on the persistence of EBV, the study of the 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: nephroptrophy 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].

Urinary 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 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, when 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 cytolgy as a less invasive alternative in the diagnosis of hairy leukoplaikia has been postulated by some authors. However, the cytological characteristics of the lesion, stained with Papanicolaou 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 cytolgy 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.

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Author Contribution

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Conflicts of Interest

The authors declare no conflict of interest.

References


