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SALIVARY VIRAL SHEDDING

CHATTERJEE S.*

Department of Oral Pathology, MMCDSR, M. M. University, Mullana- 133203, Haryana, India.
*Corresponding Author: Email- shailjachatterjee@gmail.com

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Abstract- Viral shedding in salivary secretions is a ubiquitous phenomenon in infected as well as carrier states. Transmission of different viruses via person-to-person can occur on a much large scale through parenteral routes. Prominent viruses that can be detected in saliva include- herpes simplex virus type 1, cytomegalovirus, human immunodeficiency virus, hepatitis C virus, Epstein barr virus. This paper reviews various viruses that can be detected in saliva either as whole or as RNA fragments.

Keywords- viral shedding, saliva, HHV, EBV, HIV, HCV, CMV

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Introduction

Viruses are particulate entities comprising of nucleic acids (DNA or RNA) and protein coat structures. They affect all living organisms, plants, animals and humans alike. Interspecies transmission can occur through various routes, for example, respiratory, salivary, serum etc. These organisms are shed at regular or intermittent intervals despite presence or absence of symptoms. Salivary shedding can be responsible for transmission of various viruses and can inadvertently affect human population. Viruses that are transmitted through saliva include human herpes virus (HHV) groups, Epstein Barr virus (EBV) and human immunodeficiency virus 1 (HIV-1). The dynamics of viral shedding and reactivation varies among individuals. The reactivation of latent or persistent virus among immunocompetent individuals may be due to: specific biological features of a virus; presence of local stimuli (for example, allergen) and specific changes in immune system [1].

Human Herpes Virus Group

Herpes simplex type I (HSV-1) is a DNA virus belonging to the family Herpesviridae. This family comprises of more than 100 herpes viruses. The clinical spectrum of HSV-1 infection includes asymptomatic shedding, oral and genital vesiculoulcerative lesions, encephalitis and disseminated neonatal infection. DNA sequence analysis has identified three clades (A – C) with a genetic distance between the most distant isolates of approximately 2% as well as recombinants. Same individual can harbor and secrete non-identical HSV-1 strains. A second strain can infect and replicate in an already infected cell thus, creating recombinants. Same individual can harbor and secrete non-identical HSV-1 strains. Hence, it can be surmised that the same neuron can be superinfected by different HSV-1 strains. Moreover, a single human trigeminal neuron can be dual infected by HSV-1 and Varicella zoster virus (VZV). Homologous recombination is dependent on replicating viruses and increases with the high viral dose [2].

Kaufman studied the frequency of HSV1 (Herpes Simplex Virus 1) in tears and saliva of asymptomatic individuals. They found that the percentage of asymptomatic individuals shedding the virus in saliva was greater than in tears. Hence, asymptomatic shedding of HSV can be considered a major route of transmission [3]. Thus; an asymptomatic HSV-1 infected individual can shed two different as well as recombinant strains in salivary secretions.

Cytomegalovirus

Cytomegalovirus (CMV) is a ubiquitous human herpes virus that establishes latency in myeloid progenitor cells. Equilibrium between the virus and host relates to its latency with occasional intermittent release into urine, saliva, semen, cervical secretions and breast milk. Early childhood CMV infections are characterized by more prolonged, active viral replication. CMV-specific T cell proliferation is impaired in children with congenital or perinatally acquired CMV infections as well as in immunocompromised patients. Experimentation involving adoptive transfer of CMV-sensitized cytotoxic T cells to bone marrow-transplant recipients provides direct evidence that CD8 T cells restricted CMV replication in CMV seropositive individuals. Hence, it can be surmised that CMV replication is controlled by CD8+ T cells and healthy adults with chronic infection maintain high numbers of CMV-specific CD8 T cells. Antiviral immunity differs widely in children and adults in number of virus-specific T cells quantitatively and qualitatively in effector role. CD8 T cells in children with active CMV infection have the functional capacity to produce perforin. Hence, deficient perforin production by antiviral CD8 T cells is not the reason for persistent viral shedding. Diminished IFN-ϒ production by CD4 T cells has been observed in young children evaluated for cell-mediated immunity to HSV and measles.

Natural vertical CMV transmission can occur in mothers to infants via breast milk. These asymptomatic CMV infected children persistently release infectious virus and transmit it to susceptible contacts [4].

Cytomegalovirus (CMV) shedding is a major cause of morbidity and mortality in HIV patients. Most clinical manifestations are due to reactivation of latent CMV reservoirs during progression of HIV-induced immune deficiency. CMV strains comprise of 1 to 4 glycoprotein B genotypes (gpB). In bone marrow transplant cases, subtype gpB1 infection is associated with high morbidity. CMV inclusion bodies are frequently found in parotid salivary glands of immunocompetent infants during early course of CMV infection. Oropharyngeal shedding is a well-established source of infant-to-infant and infant-to-adult transmission. Salivary CMV shedding has been observed in 1% to 2% of immunocompetent adults and 30% of HIV-positive adults with asymptomatic CMV infection. CMV genotype gB2 is the predominant viral strain in saliva regardless of ethnic origin and HIV transmission risk factors [5].

Human Herpesvirus 7 (HHV-7)

HHV-7 was originally isolated from peripheral blood mononuclear cells obtained from healthy adults in 1990. This virus belongs to the β-herpesviridae subfamily and is closely related to HHV-6. Primary HHV-7 infection is considered to be benign and self-limiting. Most children acquire primary HHV-7 infection till five years of age, hence, it is widespread in adult population. Like other HHV, HHV-7 can reactivate in immunosuppressed patients. Its reactivation is associated with cytomegalovirus disease in organ-transplant recipients. The mode of infection is through horizontal transmission i.e., households, door handles etc. Salivary glands are considered to be the sites for persistent infection due to the high frequency of salivary detection in healthy adults [6].

Human Herpes Virus-8 (Kaposi sarcoma-associated herpesvirus, Human Herpesvirus-8)

Kaposi sarcoma associated herpes virus (HHV-8) infection is required for Kaposi sarcoma development. However, many HIV-infected persons appear to be infected with KSHV but do not have clinical Kaposi sarcoma manifestation. Kaposi sarcoma herpes virus transmission may occur through sexual transmission. However, it has been found in older persons in Mediterranean and infants in Africa. Hence, it appears that a nonsexual route also exists. Studies have shown that HHV-8 shedding rate is higher in saliva as compared to semen, urine or stool suggesting a horizontal spread [7].

Kaposi sarcoma is a lymphotropic virus similar to Epstein Barr virus with latency in B lymphocytes. Among HIV-infected patients, the prevalence of KSHV DNA in saliva is equal regardless of the presence or absence of clinical Kaposi sarcoma lesion [8]. There is an increased salivary KSHV shedding in individuals with HLA-A68, HLA-DRB104 and HLA-A43 alleles [9].

Human Immunodeficiency Virus (HIV)

Shedding of HIV-1/-2 is present in cervicovaginal fluid, semen, breast milk and anorectal mucosa. It has been proposed that HIV is inactivated by inhibitory salivary factors. Pavlinac et al have shown that oral HIV-1 RNA is present in low levels in oral cavity and reflect systemic burden. The authors found that HIV-1 infected patients with periodontal disease are more likely to have oral HIV detected in the patients as compared to those without the disease. There was no association between CD4 cell count and oral HIV-1/-2 RNA. Hence, it can be surmised that plasma viral load and periodontal disease are associated with oral HIV-1 shedding [10].

HIV RNA is detectable in oropharynx, however, it is rarely cultured from saliva suggestive of neutralization by innate salivary factors. Hence, HIV cannot be transmitted through saliva but through orogenital transmission route. Antiretroviral therapy (ART) affected pharyngeal HIV level independent of plasma HIV level due to differential penetration of antiretroviral drugs into lymphoid tissue or different viral replication kinetics in oropharynx. Moreover, the epithelial surface of tonsils with its lectin glycocalyx surface may provide a surface permitting survival of cell-free HIV. Hence, posterior oropharynx is a potential site for obtaining culturable HIV [11].

Epstein Barr Virus (EBV)

EBV can be transmitted from person-to-person by means of saliva. It persists in infected persons in lymphoid or epithelial cells within the oral cavity or salivary glands and is intermittently reactivated, leading to its shedding in saliva. EBV DNA is detectable at high levels in saliva in healthy individuals in addition to individuals with Burkitt's lymphoma. EBV infection can be influenced by multiple factors such as- socioeconomic levels, age at time of infection, quantity of inoculums and frequency of repeated exposures [12].

Hepatitis C Virus (HCV)

The most common routes of HCV infection are through intravenous, sexual or parenteral routes. Saliva may be one of the nonparenteral routes of viral transmission. However, this claim is refuted by studies [13]. However, detectable levels of salivary HCV RNA have been observed with high serum HCV RNA load [14].

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