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VIRUSI I PARODONTOPATIJA

HUMAN VIRUSES AND PERIODONTAL DISEASE

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Apstrakt

Parodontopatija je multifaktorijalno, hronično oboljenje praćeno destrukcijom potpornog aparata zuba. Glavni etiološki faktor za nastanak parodontopatije je oralni biofilm sa anaerobnim mikroorganizmima. Pored bakterija, u parodontalnim džepovima su nađeni i virusi. Uloga virusa je značajna zbog toga što dovode do nepravilnosti u pripajanju, hemotaksi i fagocitozi polimorfonuklearnih leukocita. Udruženi virusi i bakterije imaju jači periodontopatogeni potencijal, nego pojedinačno. Ističe se sinergističko delovanje periodontopatogenih bakterija, Epstein–Barr virusa i Cytomegalovirusa. Za razumevanje patogenetskih dešavanja u toku parodontopatije bitno je poznavanje svih etioloških faktora, kao i imunog odgovora domaćina na ove agense, zbog adekvatnog tretmana ovog oboljenja.

Ključne reči: *Herpes virusi, Cytomegalovirus, Epstein-Barr virus, parodontopatija.*

Abstract

Periodontitis is a multifactorial, chronic disease followed by destruction of supporting structures of teeth. The main etiological factor for development of periodontitis is oral biofilm containing anaerobic microorganisms. Besides bacteria, viruses can also be present within periodontal pockets. The role of viruses is significant, as they may induce abnormalities in the adhesion, chemotaxis, phagocytosis, and bactericidal activities of polymorphonuclear leukocytes. Associated with one another, viruses and bacteria have stronger periodontopathogenic potential than individually. The synergism between periodontopathogenic bacteria, Epstein–Barr virus, and Cytomegalovirus stands out. For full understanding of the pathogenesis of periodontitis, it is significant to know all etiologic factors and host immune response; such an understanding should also guide the adequate treatment of this disease.

Key words: *Herpesviruses, Cytomegalovirus, Epstein-Barr virus, periodontal disease*

Uvod

Parodontopatija je multifaktorijalno, hronično oboljenje praćeno destrukcijom potpornog aparata zuba koji se sastoji od: gingive, alveolarne kosti, cementa i periodoncijuma. Glavni etiološki faktor je oralni biofilm sa anaerobnim bakterijama. U mikrobiološkim kulturama identifikovano je više od 1200 bakterijskih vrsta u usnoj duplji[1]. Najmanje 400

Introduction

Periodontitis is a multifactorial, chronic disease followed by destruction of supporting structures of teeth, including the gingiva, alveolar bone, cementum and periodontal ligament. The main etiological factor for development of periodontitis is oral biofilm containing anaerobic microorganisms. Microbiological culture studies have identified more than 1,200 bac-

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bakterijskih vrsta živi subgingivalno[2], smatra se da 20 različitih vrsta predstavljaju najjače periodontopatogene[3,4]. Zdrav parodoncijum sadrži najveći broj Gram pozitivnih fakultativnih bakterija, dok parodontalne lezije nastanjuje veliki broj raznovrsnih Gram negativnih anaerobnih vrsta[5]. Razvojem oboljenja dolazi do promena u mikrobiološkom sastavu flore. To je rezultat višestrukih interakcija između mikrobioloških osobina infektivnih agenasa, humoralnog i celularnog imunog odgovora domaćina i ekosistema usne duplje[6]. Važnu ulogu u etiopatogenezi parodontopatije, pored specifičnih periodontopatogenih bakterija imaju i herpes virusi. Naime, herpes virusi predstavljaju važan pokretač destrukcije parodontalnih tkiva[7,8]. Njihovi genomi nađeni su u hroničnoj parodontopatiji[9], agresivnoj parodontopatiji[10], kao i parodontopatiji povezanoj sa sistemskim oboljenjima[10]. Produktivna infekcija herpes virusima može da započne ili ubrza destrukciju parodoncijuma. Inflamatorne i neinflamatorne ćelije domaćina pod uticajem virusa otpuštaju citokine i hemokine, ili se povećava virulencija periodontopatogenih bakterija zbog oštećenja odbrane parodontalnog tkiva[10].

Herpes virusi

Opisano je osam različitih humanih herpes virusa. Rodovi herpes virusa su podeljeni na tri podvrste prema patogenosti, tipu ćelije koje inficiraju i prema osobinama njihovog rasta. Alfa herpes virusi su herpes virus tip 1 (HSV-1), tip 2 (HSV-2) i Varicella zoster virus (VZV). Ova podvrsta brzo raste, lizira inficirane ćelije i ostaje latentna u senzornim nervnim ganglijama. Beta herpes virusi su podeljeni na: cytomegalovirus (HCMV), humani herpes virus tip 6 (HHV-6) i humani herpes virus tip 7 (HHV-7). Njihova replikacija je spora i produkuju velike, često višejedarne ćelije. Virusni genom ostaje latentno u limforetikularnom tkivu i sekretornim žlezdama, u bubrezima ili u drugim tkivima. HCMV može da uzrokuje teške forme bolesti kod imunokompromitovanih pacijenata, naročito upalu pluća. Gama-herpes virusi su Epstein–Barr virus (EBV) i humani herpes virus tip 8 (HHV-8). Oni se nalaze latentno u limfnom tkivu[11]. EBV i HCMV se često detektuju kod pacijenata sa agresivnom parodontopatijom[12-15].

terial species in the oral cavity[1]. At least 400 bacterial species inhabit subgingival sites[2], but fewer than 20 species are considered to be major periodontal pathogens[3,4]. Healthy periodontal sites harbor predominantly gram-positive facultative bacteria, whereas periodontitis lesions contain a large variety of gram-negative anaerobic species[5]. The shift of the periodontal microbiota happens with disease development. That is the result of a multifaceted interaction of microbiological-specific traits, host humoral and cellular immune responses and oral cavity ecosystem-based factors[6]. Herpesviruses, besides periodontopathogenic microbiota, have important role in etiopathogenesis of periodontitis. Namely, periodontal herpesviruses comprise an important source for triggering the periodontal tissue destruction[7,8]. Their genomes have been found in chronic periodontitis[9], aggressive periodontitis[10] and periodontitis associated with systemic diseases[10]**.** Herpesvirus productive infection may initiate or accelerate periodontal tissue destruction. Virally mediated release of cytokines and chemokines from inflammatory and non-inflammatory host cells, or a virally induced impairment of the periodontal defense result in a heightened virulence of resident periodontopathogenic bacteria[10].

Herpesviruses

There have been described eight different types of human herpesviruses. The species of Herpesvirus family were divided into three subfamilies according to pathogenicity, the type of cell wherewith they were infected and the properties of their growth. Alpha-herpes viruses include Herpes simplex virus type 1 (HSV-1), type 2 (HSV-2) and Varicella zoster virus (VZV). This subfamily grows rapidly, lyses-infected cells and remains latent in sensory nerve ganglia. Beta-herpes viruses are divided into human cytomegalovirus (HCMV), human herpes virus 6 (HHV-6) and human herpesvirus 7 (HHV-7). Their replication is slow and it produces large, often multinucleated cells. The viral genome remains latent in lymphoreticular tissue and secretor gland, kidneys and other tissues. HCMV can induce severe forms of diseases in immunocompromised patients, particularly pneumonia. Gamma-herpes viruses include Epstein–Barr virus (EBV) and human herpes virus 8 (HHV-8). They are located in lymphoid tissues latently[11]. EBV and HCMV were detected frequently in aggressive periodontitis sites[12-15].

Epstein–Barr virus

EBV-om je inficirano preko 90% populacije[16] i obično se prenosi putem oralnih sekreta ili krvi. Virus se replikuje u epitelnim ćelijama ili B limfocitima orofaringsa. Skoro sve seropozitivne osobe imaju aktivan virus u pljuvački[17]. Memorijski B limfociti su glavno mesto gde EBV opstaje [16], a 1 do 50 cirkulišućih B limfocita u milion je infektivan. Broj latentno inficiranih ćelija među ljudima je stabilan godinama[17].

Cytomegalovirus

HCMV je najčešći uzrok kongenitalne ili perinatalne infekcije. Oko 10% novorođenčadi je inficirano do šestog meseca preko majke, putem placente, tokom porođaja ili preko majčinog mleka tokom dojenja[18, 19]. Smatra se da je HCMV-om inficirano 90% populacije do dvadesete godine života, čak i u industrijskim zemljama[20]. HCMV inficira različite epitelne ćelije, endotelne ćelije, glatke mišićne ćelije, mezenhimalne ćelije, hepatocite, granulocite i monocite izvedene od makrofaga[21]. HCMV je nađen u različitim telesnim tečnostima, uključujući pljuvačku, urin, semenu tečnost i majčino mleko[21].

Interakcija herpes virusa i periodontopatogena

Slots J.[22] povezuje prisustvo herpes virusa i povećano prisustvo periodontopatogenih bakterija u parodontopatiji. Contreras i sar.[23] su u studiji u kojoj su ispitivani odrasli sa gingivitisom i parodontopatijom pokazali statistički značajnu povezanost između EBV tipa 1 i HCMV sa periodontopatogenima: Porphyromonas gingivalis (P.g.), Tannerella forsythia (T.f.), Prevotella intermedia (P.i.), Prevotella nigrescens (P.n.) i Treponema denticola (T.d.). Kvantitativna PCR studija[24] pokazuje povezanost između kopija genoma EBV i HCMV sa P.g. i T.f. kod ispitanika sa teškom kliničkom slikom parodontopatije. Kod pacijenata sa agresivnom parodontopatijom inficirana mesta HCMV-om imaju povećano prisustvo P.g.[25] ili Aggregatibacter actinomycetemcomitans-a (A.a.)[26]. Bliske veze između herpes virusa, bakterija i parodontopatije igraju bitnu ulogu u patogenezi parodontalnog oboljenja.

Epstein–Barr virus

EBV affects over 90% of humans[16], and is usually transmitted by oral secretions or blood. The virus replicates in epithelial cells or B cells of oropharynx. Almost all of seropositive persons have an active virus in the saliva[17]. Memory B cells are the main site of persistence of EBV[16], and 1 to 50 circulating B cells per million are infected. The number of latently infected cells within a person remains stable over years[17].

Cytomegalovirus

HCMV is the most common cause of congenital and perinatal infections. About 10% of infants are infected untill the age of 6 months following transmission from their mother through the placenta, during delivery or by breast feeding[18, 19]. Even in industrialized countries HCMV affects 90% of the population by the age of twenty[20]. HCMV infects many different epithelial cells, endothelial cells, smooth muscle cells, mesenchymal cells, hepatocytes, granulocytes and monocyte-derived from macrophages[21]. HCMV is found in different body secretions including saliva, urine, semen and breast milk[21].

Herpesviruses and periodontopathogenic bacteria interactions

Slots J.[22] associates a periodontal herpesvirus infection with an increased occurrence of periodontopathogenic bacteria. Contreras et al.[23] have found statistically significant associations between periodontal EBV type 1 or HCMV and the pathogens Porphyromonas gingivalis (P.g.), Tannerella forsythia (T.f.), Prevotella intermedia (P.i.), Prevotella nigrescens (P.n.) and Treponema denticola (T.d.) in the study of adults with gingivitis or periodontitis. Quantitative PCR study[24] of severe periodontitis has demonstrated interconnection between genome copy-counts of EBV and HCMV and counts of P. g. and T. f.. HCMV-infected lesions in aggressive periodontitis have an elevated occurrence of P.g. [25] or Aggregatibacter actinomycetemcomitans-a (A.a.)[26]. Close links among herpesviruses, bacteria and periodontitis play an important role in the pathogenesis of periodontitis.

Mehanizam delovanja herpes virusa u parodontopatiji

Patogenost herpes virusa je složena i ispoljava se na dva načina: kroz direktnu virusnu infekciju i replikaciju ili preko oštećenja imunog odgovora domaćina. Herpes virusi mogu imati direktni citopatološki uticaj na fibroblaste, keratinocite, endotelne ćelije i inflamatorne ćelije, uključujući polimorfonuklearne leukocite, limfocite, makrofage i osteocite[27]. EBV i HCMV mogu inficirati i oštetiti funkcije monocita, makrofaga i limfocita u parodontalnim lezijama[28]. Kao rezultat infekcije herpes virusima, lezije u agresivnoj parodontopatiji sadrže manje zdravih ćelija, a više supresornih T i B limfocita (efekat EBV), nego lezije u hroničnoj parodontopatiji ili kod zdravog parodoncijuma[29]. Infekcije herpes virusima mogu povećati patogenost parodontalnih mikroorganizama. Proteini herpes virusa se ponašaju kao nova mesta koja vezuju bakterije na membrani eukariotskih ćelija[27]. HCMV može povećati sposobnost spajanja A.a. sa epitelnim ćelijama parodontalnog džepa i HeLa ćelijama[30].

Herpes virusi mogu potencirati nepravilnosti u pripajanju, hemotaksi i fagocitozi polimorfonuklearnih leukocita[31], koji su od ključne važnosti za kontrolu periodontopatogenih bakterija[32]. Aktivna infekcija EBV-om može stvoriti anti-neutrofilna antitela i neutropeniju, zatim stimulisati poliklonalnu proliferaciju i diferencijaciju B limfocita[27]. Patogeni mehanizam herpes virusa pogoršava kliničku sliku parodontopatije. Zbog toga se dvostruka infekcija sa HCMV i EBV[33] ili HCMV i herpes simplex virusom[34] dešava kod agresivnih parodontopatija. Interakcija herpes virusa i bakterija se najverovatnije dešava u oba pravca, sa bakterijskim enzimima ili sa drugim faktorima koji indukuju inflamaciju, bakterije imaju moć da aktiviraju herpes viruse koji se nalaze u parodoncijumu[22]. Eksperimentalni miš koji je inficiran murin HCMV–P.g. je pokazao značajno veću stopu smrtnosti u poređenju sa mišem koji je inficiran sa murin HCMV–Escherichia coli[35]. Moć P.g. da suprimira interferon-gamma antivirusni odgovor domaćina može delimično razjasniti povećanje patogenosti HCMV[35]. Houri-Haddad i sar.[36] su pokazali da je imuni odgovor vođen T ćelijama aktivniji kod pacijenata sa parodontopatijom. Specifični limfocitni odgovori se odigravaju pod uticajem

Herpes virus mechanism of action in periodontal disease

Pathogenicity of herpesviruses is complex and it is manifested in two ways: via direct virus infection and replication, or through an impairment of the host immune response. Herpesviruses can exert direct cytopathological effect on fibroblasts, keratinocytes, endothelial cells and inflammatory cells, including polymorphonuclear leukocytes, lymphocytes, macrophages and bone cells[27]. EBV and HCMV can also infect and alter the functions of monocytes, macrophages and lymphocytes in periodontitis lesions[28]. As result of a herpesviruses periodontal infection, lesions in aggressive periodontitis contain fewer overall viable cells, more T-suppressor lymphocytes and more B-lymphocytes (EBV effect) than lesions in chronic periodontitis or in healthy periodontal sites[29]. A periodontal herpesvirus infection may increase the pathogenicity of the periodontal microbiota. Herpesvirus proteins expressed on eukaryotic cell membranes may act as new bacterial binding sites[42]. HCMV can enhance the adherence of A.a to primary periodontal pocket epithelial cells and to HeLa cells[30].

Herpesviruses may induce abnormalities in the adhesion, chemotaxis, phagocytosis, of polymorphonuclear leukocytes[31], which are crucial cells for the control of periodontopathogenic bacteria[32]. Active infection with EBV can also generate anti-neutrophilic antibodies and neutropenia, and can stimulate polyclonally proliferation and differentiation of B-lymphocytes[27]. The pathogenic mechanisms of herpesviruses cooperate in exacerbating of periodontitis. Therefore, a dual infection containing HCMV and EBV[33], or HCMV and Herpes simplex virus[34] tends to occur in severe types of periodontitis. The interaction between herpesviruses and bacteria is probably bidirectional, with bacterial enzymes or other inflammation-inducing factors has the potential to activate periodontal herpesviruses[22]. Experimental mice infected with murine HCMV–P.g. exhibited a significantly higher mortality rate than mice infected with murine HCMV–Escherichia coli[35]. The potential of P.g. to suppress the interferon-gamma antiviral host response may partly explain the increase in HCMV pathogenicity[35]. Houri-Haddad et al.[36] have shown that T-cell-driven immune responses are more active in patients with periodontitis.

inicijalnog antigenog stimulusa i podržani su kaskadnim kompleksom, koji se sastoji od citokina, hemokina i drugih medijatora inflamacije[37]. Najvažnija u patogenezi parodontopatije je proinflamatorna i anti-inflammatorna ravnoteža koju kontrolišu limfociti[37]. Prilikom infekcije EBV-om i HCMV-om reguliše se ekspresija interleukin-1beta i tumor necrosis factor-alpha gena od strane monocita i makrofaga[38]. Povišeni nivoi proinflamatornih citokina u parodontopatiji povezani su sa povećanim rizikom od destrukcije parodoncijuma[39]. Udruženi sa herpes virusom, proinflammatorni citokini i hemokini mogu da otežaju antibakterijsku odbranu domaćina, stimulišući resorpciju alveolarne kosti domaćina, a osteoklasti regulišu povećanje matriks-metaloproteinaze, smanjuju nivo tkivnih inhibitora metaloproteinaze tako što sprečavaju tkivni promet i reparaciju; povećavaju rizik od tkivnog propadanja[40, 39]. Takođe, klinička slika parodontopatije ima tendenciju da bude teža ukoliko nosi HLA-DR4 alloantigen[41], najverovatnije zato što je HCMV specifičan za $CD8^+$ T ćelije i može da prepozna HLA-DR4 molekule i tako potencijalno pokrene autoimunu reakciju[42].

Metode identifikacije virusa

Era in vitro kulture ćelija za rutinsku laboratorijsku dijagnostiku virusa odavno je prošla. Izolacija virusa ukazuje na aktivnu (najverovatnije produkujuću) infekciju. Ova metoda je teška, skupa i oduzima dosta vremena. Tehnike koje su bazirane na PCR dijagnostici postale su standard za identifikaciju i kvantitativno određivanje herpes virusa u parodoncijumu[43, 44]. Nested ("ugnježdeni") PCR može da otkrije više pozitivnih parodontalnih mesta na HCMV nego virusna kultura, real time PCR[45] ili end-point PCR[46]. Nested PCR metod je naročito efikasan u otkrivanju virusa koji su malo zastupljeni[47]. Lažno pozitivni rezultati na herpes viruse mogu se pojaviti kada postoje zajednički regioni nukleotidnih sekvenci između herpes virusne vrste i nepoznatog infektivnog agensa. EBV i HCMV su identifikovani u parodoncijumu korišćenjem različitih PCR prajmera u platformi: end-point PCR, nested PCR, reverzne transkripcije PCR i realtime PCR. Rizik od sistemske greške u identifikaciji ovih virusa je mali. Međutim, različiti PCR prajmeri i protokoli mogu detektovati herpes viruse sa

Specific lymphocyte responses are driven by the nature of the initial antigenic stimulus and are supported by a complex cascade of events involving cytokines, chemokines and other inflammatory mediators[37]. Proinflammatory and anti-inflammatory balance controlled by lymphocytes is crucial in pathogenesis of periodontitis[37]. EBV and HCMV infections up-regulate the interleukin-1beta and tumor necrosis factor-alpha gene expression of monocytes and macrophages[38]. Increased levels of proinflammatory cytokines in periodontal sites are associated with an enhanced risk of periodontal tissue destruction[39]. The herpesvirus-associated proinflammatory cytokines and chemokines can hamper the antibacterial host defense, stimulate bone-resorbing osteoclasts, up-regulate matrix metalloproteinase and down-regulate tissue inhibitors of metalloproteinase, thereby impeding tissue turnover and repair, increasing the risk of periodontal tissue breakdown[40, 39]. Also, periodontitis tends to be more severe in carriers of the HLA-DR4 alloantigen[41], perhaps because HCMV-specific $CD8^+$ T cells can cross-recognize HLA-DR4 molecules and potentially induce autoimmune reactions[42].

Viral diagnostic methods

The era of relying upon in vitro cell culture for routine laboratory diagnosis of viral infections has truly passed. Viral isolation indicates an active (possibly disease-producing) infection. This method is difficult, costly and time-consuming. Polymerase chain reaction (PCR)-based techniques have become the standard for identification and quantification of periodontal herpesviruses[43, 44]. Nested PCR may unveil more periodontal sites that are positive for HCMV than viral culture or real-time PCR[45] or end-point detection PCR[46]. Nested PCR technology is particularly efficient in detecting low viral loads[47]. Falsepositive herpesvirus results may emerge when there are shared regions of nucleotide sequences between herpesvirus species and unknown infectious agents. EBV and HCMV have been identified using a variety of PCR primers in platforms of end-point detection PCR, nested PCR, reverse transcription PCR and real-time PCR. The risk of a systematic misidentification of these viruses is small. However, different PCR primers and protocols may detect herpesviruses with a varying degree of proficiency[48], and technical expertise and

različitim stepenom efikasnosti[48], a tehničke mogućnosti i kvalitet metode se razlikuju od laboratorije do laboratorije[49-51]. Priprema ciljane nukleinske kiseline predstavlja posebno osetljivu fazu PCR protokola.

Detektovanje pozitivnih uzoraka subgingivalnih kopija genoma herpes virusa u agresivnoj i hroničnoj parodontopatiji

Procentualna zastupljenost herpes virusa zavisi od tipa parodontalne lezije koja se ispituje, metode identifikacije i etničko-geografske pripadnosti ispitanika[24]. Jedna od najizazovnijih odluka je klasifikacija parodontopatije na agresivnu (aktivnu) i hroničnu (stabilnu). Glavni kriterijum klasifikacije parodontopatije na agresivnu i hroničnu, starost ispitanika, nije pouzdan pokazatelj. Mehaničko uklanjanje kamenca i konkremenata može da rezultira odsustvom ili smanjenjem procenta detektovanog subgingivalnog herpes virusa[52-54]. U studijama bi bilo idealno obuhvatiti ispitanike koji nisu u medicinskoj istoriji imali profesionalni parodontološki tretman. Lokalizovana agresivna (juvenilna) parodontopatija javlja se u pubertetu i karakteriše se gubitkom epitelnog pripoja na aproksimalnim površinama stalnih sekutića i prvih molara. Michalowic i sar.[25] su proučavali prisustvo herpes virusa kod adolescenata sa Jamajke (afro-karipski narod) koji su imali simptome klasične agresivne juvenilne parodontopatije. HCMV i P.g. su delovali sinergistički i uticali na javljanje i napredovanje parodontopatije. Izgledi da osoba oboli od lokalizovane agresivne parodontopatije su 6.6 puta veći ukoliko je prisutan HCMV, dok prisustvo P.g. 8.7 puta povećava taj rizik. Ukoliko su prisutna oba infektivna agensa, P.g. i HCMV, rizik se višestruko uvećava i to 51.4 puta u poređenju sa njihovim odsustvom[25]. Najverovatnije zbog dijagnostičkih poteškoća različite studije su pokazale različitu zastupljenost kopija genoma HSV-1, EBV i HCMV u agresivnoj i hroničnoj parodontopatiji (Tabela 1). Imbronito i sar.[55] su detektovali sličan procenat kopija genoma EBV i HCMV kod hronične i agresivne parodontopatije. Bilichodmath i sar.[56] detektovali su HSV-1, EBV i HCMV kod agresivne parodontopatije u manjem procentu nego u hroničnoj parodontopatiji (Tabela 1).

quality assurance methods varies among laboratories[49-51]. Preparation of the target nucleic acid constitutes a particularly vulnerable stage of PCR protocols.

Detection of positive samples of subgingival genome-copies of herpesviruses in aggressive and chronic periodontal disease

Percentage of periodontal herpesviruses depends on the type of periodontal lesion studied, the viral identification method employed and ethnic-geographical origin of subjects[24]. One of the most challenging decisions in periodontal classification is to allocate to either aggressive periodontitis (active) or chronic periodontitis (stable). The use of patient age as a major criterion for classification of periodontitis may not be a reliable indicator. Also, scaling and root planning of the teeth may reduce the level of subgingival herpesviruses[52-54]. Studies of periodontal herpesviruses should ideally include individuals with no history of receiving professional periodontal treatment. Localized aggressive (juvenile) periodontitis debuts at puberty and attachment loss occurs at the approximal surfaces of permanent incisors and first molars. Michalowic et al.[25] studied the presence of subgingival herpesviruses in Afro-Caribbean adolescents with symptoms of classical localized aggressive periodontitis. HCMV i P.g. seemed to act synergistically to influence the risk for both the occurrence and the extent of disease. Localized aggressive periodontitis was associated with HCMV an odds ratio of 6.6, and with P.g. with an odds ratio of 8.7. The odds of having localized aggressive periodontitis increased multiplicatively 51.4 times in individuals with a co-infection of HCMV and P. g., compared with the odds of harboring neither of the two infectious agents[25]. Probably because of diagnostic difficulties, periodontitis studies have reported a wide variation in the occurrence of genome-copies of HSV-1, EBV and HCMV in aggressive and chronic periodontitis (Table 1). Imbronito et al.[55] describe a similar occurrence of subgingival genome-copies of EBV and HCMV in chronic and aggressive periodontitis. Bilichodmath et al.[56] describe a lower occurrence of genome-copies HSV-1, EBV

Tabela 1. Procenat kopija genoma herpes virusa u agresivnoj i hroničnoj parodontopatiji
Table 1. Percentage of subgingival genome-copies of herpesviruses in aggressive and chronic periodontitis

Virus	Agresivna parodontopatija; Procenat pozitivnih uzoraka Aggressive periodontitis;	Hronična parodontopatija; aprocenat pozitivnih uzoraka Chronic periodontitis;	Referenca Reference
	Percentage of positive samples	Percentage of positive samples	
Herpes simplex virus tip 1 (HSV-1)	7%	100%	Bilichodmath i sar. Bilichodmath et al. (56)
	87%	40%	Imbronito i sar. Imbronito et al. (55)
Epstein –Barr	29%	79%	Bilichodmath i sar. Bilichodmath et al. (56)
(EBV)	33%	47%	Imbronito i sar. Imbronito et al. (55)
Cytomegalovirus (HCMV)	7%	26%	Bilichodmath i sar. Bilichodmath et al. (56)
	47%	50%	Imbronito i sar. Imbronito et al. (55)

Individualne parodontalne lezije mogu skladištiti milione kopija genoma herpes virusa[24], papillomavirusa, kao i humanog virusa immunodeficiencije (HIV), humanog T-limphotropnog virusa tipa 1, torquetenovirusa, hepatitis B i C virusa [57].

Zaključak

Istraživanja uticaja virusa na parodontopatiju imaju za cilj da dovedu do boljeg poznavanja i rasvetljenja njene etiopatogeneze. Na osnovu različitih studija može se zaključiti da virusi utiču na razvoj parodontopatije. Periodontopatogene bakterije, EBV i HCMV deluju sinergistički i utiču na povećanje rizika za javljanje i širenje parodontopatije. Detekcija i određivanje kvantitativnog prisustva virusa značajna je za prognozu parodontopatije. Buduća istraživanja uticaja virusa na parodontopatiju mogu dovesti do napretka u prevenciji i tretmanu ovog oboljenja.

and HCMV in aggressive periodontitis than in chronic periodontitis (Table 1).

Individual periodontal lesions may harbor millions of genomic copies of herpesviruses[24] as well as papillomaviruses, human immunodeficiency virus (HIV), human T-lymphotropic virus type 1, torquetenovirus, and hepatitis B and C viruses[57].

Conclusion

Researches of the virus impact on periodontitis are intended to lead to better understanding and clarification of etiopathogenesis of this disease. Based on different studies it could be concluded that viruses affect the development of periodontitis. Periodontopathogenic bacteria, EBV and HCMV seemed to act synergistically and result in increased risk for the occurrence and spread of periodontitis. Detection and determination of viruses quantitative presence has prognostic significance for periodontitis. Future researches of virus impact on periodontitis can lead to progress in prevention and treatment of this disease.

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