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POSSIBLE RELATION OF *ROSEOLOVIRUS* INFECTION WITH FIBROMYALGIA

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Fibromyalgia (FM) is a chronic widespread pain disorder that impacts 0.5%–7% of the general population worldwide. The aetiology and pathogenesis of the disease are still unknown. Human herpesvirus-6 and -7 belong to the family Herpesviridae*, subfamily* Betaherpesvirinae*, and genus* Roseolovirus *and are immunomodulating viruses potentially pathogenic to the nervous system. Presence of anti-HHV-6 and -HHV-7 antibodies and viral genomic sequences, viral loads, HHV-6 variant-specificity, and TNF-α level were studied in 41 FM patients and 50 healthy individuals using polymerase chain reactions, restriction endonuclease analysis and ELISA. There was no difference in the presence of anti-HHV-6 and anti-HHV-7 IgG class antibodies between FM patients and control group individuals. Viral sequences were found in 80.5% of FM patients and in 62.0% of controls. Significantly higher rate of concurrent HHV-6 and HHV-7 infection and higher viral loads in peripheral blood were detected in FM patients compared to the control group individuals. Plasma viremia was detected only in FM patients. Significantly higher TNF-α levels were detected in virus positive FM patients. From all positive cases only in two FM patients HHV-6A was revealed. Significantly higher detection frequency of concurrent HHV-6 and HHV-7 infection, simultaneous HHV-6 and HHV-7 activation, higher viral loads and TNF-α expression levels in primary FM patients than in control group individuals indicate the potential involvement of* Roseoloviruses *in development of this disorder.*

Key words: *fibromyalgia, human herpesvirus-6, human herpesvirus-7, infection, molecular diagnostic.*

INTRODUCTION

Fibromyalgia (FM) is a common, chronic widespread pain disorder that is estimated to impact 0.5% to 7% of the general population worldwide (Balon and Wise, 2015). The epidemiology of FM in Latvia has not been studied in detail.

Host individuals diagnosed in clinics are young or middle aged; however, population surveys suggest that frequency of disease increases with age as well as symptom severity and worsening of life quality (Ballantyne *et al*., 2010; Branco *et al*., 2010; Jiao *et al*., 2014; Balon and Wise, 2015). Females suffer from FM eight times more frequently than males (Albin *et al*., 2008).

The term fibromyalgia appeared relatively recently, in 1976. Diagnosis is clinical and is based on the 1990 American College of Rheumatology (ACR) diagnostic criteria. According to these criteria, FM diagnosis may be stated if the patient has chronic widespread pain and 11 or more positive of a possible 18 tender points on physical examination, fatigue, sleep disorders, headaches, memory or concentration problems, mood disturbances, and stiffness.

In 2010, ACR FM diagnostic criteria were supplemented with new details (Hakim *et al*., 2010; Wolfe *et al*., 2011) that include the estimation of the widespread pain index (WPI) and the symptoms of severity (SS) score scale. The SS scale score is the sum of the severity of three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent of somatic symptoms in general.

The aetiology and pathogenesis of FM are still unknown. This disease is probably of multi-factorial nature, since many patients have onset of the clinical phenotype of FM

following a specific trigger. There are many open questions with few or controversial answers. Such triggers can include various viral infections, such as hepatitis C (Kozanoglu *et al*., 2003; Mohammad *et al*., 2012; Rogal *et al*., 2015), parvovirus B19 (Cassisi *et al*., 2011), HIV (Kole *et al*., 2013; Wiffen *et al*., 2013; Fox and Walker-Bone, 2015), and Epstein-Barr virus (Buchwald *et al*., 1987). 55% of patients identify a "flu-like" or viral infection as a precursor to the onset of symptoms, but the role of viral infection in FM development has not been estimated.

One of the major theories is that cytokines may have a role in both the aetiology of the FM and in the intensity of core symptoms (Menzies and Lion, 2010). Goldberg (1989) suggests that the viruses might directly invade central nervous system or are capable of activating cytokines which may in turn cause severe myalgia, fatigue, and neurocognitive disturbances.

According to the current state of knowledge the origin of the pain in FM and variety of FM symptoms are triggered by peripheral as well as central mechanisms (Sprott, 2011; Clauw *et al*., 2011).

Up to date, there are no data on the role of HHV-6 and HHV-7 infection in the FM development. Human herpesvirus-6 (HHV-6) and -7 (HHV-7) belong to the *Herpesviridae* family*, Betaherpesvirinae* subfamily, *Roseolovirus* genus (Berneman *et al.,* 1992) and are ubiquitous (more than 90% of adults have antibodies to the viruses) immunomodulating, and potentially pathogenic to the nervous system. In 2012, the International Committee on Taxonomy of Viruses re-classified HHV-6 as separate viruses HHV-6A and HHV-6B based on biocharacteristics regarding cell tropism and pathological implications (Ablashi *et al*., 2014). After primary infection, the viruses establish a state of life-long subclinical persistence or latency in CNS (Yoshikawa and Asano, 2000) and can be reactivated in cases of immunosuppression. HHV-6A, HHV-6B and HHV-7 DNA are often found in brain tissue from healthy individuals (without pathological changes in the brain) (Chan *et al*., 2001; Yao *et al*., 2010).

HHV-6 infection has been associated with neurologic pathologies such as multiple sclerosis (Ablashi *et al*., 2000; Chapenko *et al*., 2003; Nora-Krukle *et al.,* 2011), which is associated with inflammation, mesial temporal lobe epilepsy in the absence of inflammation in brain tissue (Donati *et al*., 2003; Fotheringham *et al*., 2007; Niehusmann *et al*., 2010), myalgic encephalomyelitis/chronic fatigue syndrome (Ablashi *et al*., 2000; Chapenko *et al*., 2006; Bansal *et al*., 2012; Chapenko *et al*., 2012) and with different neurological complications after allogeneic hematopoietic stem cell transplantation (Bhanushali *et al*., 2013) and solid organ transplantations (Chapenko *et al*., 2009; Massih and Razonable, 2009). The association of HHV-7 infection with these disorders is not sufficiently studied.

HHV-6 and HHV-7 infection profoundly modifies the profile of cytokine and chemokine production, which in turn may significantly affect the generation and functionality of effective immune responses (Lusso *et al*., 2006). Lusso (2006) and Atedzoe *et al*. (1999) have shown that both of the viruses increase the production of inflammatory cytokines.

The aim of this study was to: 1) examine the presence of HHV-6 and/or HHV-7 genomic sequences in whole peripheral blood and cell free plasma DNA samples from patients with FM and practically healthy persons (control group); 2) determine HHV-6 variant-specificity in whole peripheral blood DNA; 3) compare HHV-6 and HHV-7 load in peripheral blood samples from the FM patients and control persons; 4) compare pro-inflammatory cytokine TNF-α plasma level in patients with FM and control group individuals.

MATERIALS AND METHODS

The study was performed during 2013–2015. Clinical and virological (including serology and molecular biology) features were examined in the 41 patients with clinical diagnose of primary FM and 50 practically healthy persons. The primary FM diagnosis was established by a neurologist or algologist in the out-patients' clinic of Pauls Stradiņš Clinical University Hospital. None of the 41 patients with primary diagnosed FM were hospitalised in the Neurology and Neurosurgery Hospital. According to case and drug history, 10 of the 41 patients had not received prior medical treatment; none of the patients had received steroids or statins, but pain relief medication only.

Diagnosis was setup based on ACR 2010 diagnostic criteria for the FM (Widespread pain index (WPI) is equal or more than 7, symptom severity scale score (SS) — equal or more than 5, duration of symptoms at least three months, and the patients do not have a disorder that would otherwise explain the pain). In our FM patients group the mean WPI was 12.7 ± 3.24 (minimal score 4 and maximal score 18), and mean SS scale score — 8.1 ± 1.4 (minimal score 6 and maximal score 11). Mean duration of symptoms was 7.9 ± 6.2 years. Exclusion criteria were previously known polyneuropathy, cervical radiculopathy clinical symptoms, diabetes mellitus, rheumatoid arthritis, liver diseases, myalgic encephalomyelitis/chronic fatigue syndrome, and myocardial infarction.

Of 41 individuals with FM, 40 were females and one was male (mean age 51, range: 24–71) and from 50 control group individuals, 40 were females and 10 were males (mean age 48, range: 35–78). Peripheral blood samples from the patients with FM were received from the Neurology and Neurosurgery Department, Rīga Stradiņš University.

The study was approved by the Ethics Committee of Rīga Stradiņš University, and all of the participants gave informed consent before the examination.

HHV-6 and HHV-7 serology. Testing for antibodies against HHV-6 and HHV-7 in cell free blood plasma samples was carried out using HHV-6 IgG ELISA kits (Panbio,

Sinnamon Park, QLD, Australia) and HHV-7 IgG ELISA kits (ABI, Columbia MD, ASV) in accordance with the manufacturer's recommendations.

Nested polymerase chain reaction (nPCR). The technique of nPCR was used for the detection of viral genomic sequences in DNA isolated from whole peripheral blood (WPB) and cell free blood plasma. Total DNA was isolated from WPB using standard phenol-chloroform extraction. The QIAamp DNA Blood Mini Kit was used to extract DNA from plasma. To assure the quality of the DNA, a β-globin PCR was performed. PCR amplification for the viruses was carried out in the presence of 1 μg WPB DNA and 10 μl plasma DNA (corresponding to 100 μl plasma). HHV-6 and HHV-7 DNA were detected in accordance with Secchiero *et al.* (1995) and Berneman *et al.* (1992), respectively. Positive controls (HHV-6 and HHV-7 genomic DNA; ABI, Columbia, MD, USA) and negative controls (DNA obtained from practically healthy HHV-6 and HHV-7 negative donors and reaction without template DNA), as well as water controls were included in each experiment.

Restriction endonuclease analysis. Restriction endonuclease analysis was carried out using enzyme *Hind*III (Thermo Scientific, USA) which cleaves HHV-6B 163bp amplimer into two fragments: 66 and 97 bp and does not cleave HHV-6A amplimer (Secchiero *et al*., 1995).

Quantitative real-time polymerase chain reaction. HHV-6 load was detected in all positive (according to nPCR data) for viral DNA WPB samples from the patients with FM and controls group individuals using a HHV-6 Real-TM Quant kit (Sacace, Biotechnologies, Italy) and Applied Biosystems 7500 Real-time PCR System (Applied Biosystems, USA), according to the manufacturer's recommendations. The test sensitivity corresponded to five copies of the HHV-6 DNA per 10^5 cells. HHV-7 load was detected in all positive (according to nPCR data) for viral DNA samples from the patients with FM and controls group individuals using Quantification of Human Herpes Virus 7 genomes Major Capsid Protein (U57) (PrimerDesign^{TM} Ltd, genesig detection kits). The test sensitivity is not indicated.

Assay for cytokine determinations. A TNF-α ELISA kit (Biorbyt) was used for TNF-α detection in plasma samples from the FM patients with persistent infection in latent phase and active phase, and without viral infection. The sensitivity of the ELISA assay was < 1 pg/ml. All samples were tested in duplicate.

Statistical analysis. Statistical differences in the detection frequency of HHV-6 and/or HHV-7 genomic sequences in the DNA samples from WPB of the individuals with FM as well as the control group persons were assessed with the Fisher's exact test. The plasma cytokine level (TNF-α) was expressed as mean ± SD. SPSS software was used to assess the continuous variable values of cytokine level with a value of $p < 0.05$ considered as significant.

RESULTS

Seroepidemiology. Specific anti-HHV-6 IgG class antibodies were found in 85.4% (35/41) and specific anti-HHV-7 IgG class antibodies in 83.0% (34/44) of plasma samples from patients with FM. No difference in the prevalence of anti-HHV-6 and anti-HHV-7 IgG class antibodies between FM patients and control group individuals was detected (44/50, 88.0%, $p > 0.05$).

HHV-6 and/or HHV-7 genomic sequences in patients with fibromyalgia. *Roseolovirus* genomic sequences were detected in 80% (33/41) versus 62.0% (31/50) in control group individuals ($p = 0.067$). The detection frequency of single HHV-6, single HHV-7 and concurrent HHV-6+ HHV-7 genomic sequences in the FM patients and control group individuals are summarized in Table 1.

Table 1

FREQUENCY OF HHV-6 AND HHV-7 GENOMIC SEQUENCES IN WHOLE PERIPHERAL BLOOD (WPB) AND CELL FREE PLASMA DNA FROM PATIENTS WITH FIBROMYALGIA (FM) AND CONTROL GROUP INDIVIDUALS BY nPCR[a]

Subjects	Viral genomic sequences					
	single HHV-6		single HHV-7		concurrent HHV-6+HHV-7	
	WPB	plasma	WPB	plasma	WPB	plasma
FM	3/41	2/3	15/41	2/15	15/41*	2/15
Control	3/50	0/3	26/50	0/26	2/50	0/2

[a] nPCR, nested polymerase chain reaction

* Significantly higher rate in FM patients versus control individuals ($p < 0.001$).

No difference in the frequency of single HHV-6 and single HHV-7 infection between FM patients and control group individuals was detected ($p = 0.204$). However, a significantly higher detection rate of concurrent (HHV-6+HHV-7) infection markers was revealed in FM patients in comparison with control group individuals (15/41, 36.6% vs 2/50, 4.0%, respectively; $p = 0.00008$).

Plasma viremia (marker of active viral infection) was revealed only in patients with FM (6/33, 18.2%). As shown in the Table 1, HHV-6 genomic sequence in plasma DNAs upon single HHV-6 persistent infection was detected in two of three patients, simultaneous activation of both viruses upon concurrent persistent infection in two of 15, and HHV-7 genomic sequences in two out of 15 FM patients with single HHV-7 persistent infection.

HHV-6 and HHV-7 load in whole peripheral blood. Mean HHV-6 and HHV-7 load levels were higher in FM patients compared to the healthy persons. The mean HHV-6 load in WPB of FM patients with persistent infection in latent phase was 752.47 [range: 195.5–1129.8] copies/10^6 cells, compared to 125.5 [range: 52.5–192.5] copies/10^6 cells in the control group samples. Mean HHV-7 load was 218.3 [range: 132.0–311.0] copies/10^6 cells in WPB of FM

patients with persistent infection in latent phase and 181.52 [range: 86.63–281.37] copies/10^6 cells in WPB of control group individuals. Higher mean HHV-6 and HHV-7 loads were detected in WPB of FM patients with plasma viremia (5511.6 [range: 1108–21200] and 744.25 [range: 602.0–1058] copies/10^6 cells, respectively).

TNF-α level. To investigate the relationship between the reactivation of HHV-6 and/or HHV-7 and changes in plasma cytokine level, the level of pro-inflammatory cytokine TNF-α was measured in FM patients with persistent infection in latent phase (27/41), FM patients with active viral infection (6/41), and without viral infection (8/41). The TNF-α level was significantly higher in patients with active viral infection (39.33 ± 35.50 pg/ml, $p = 0.018$) and in those with persistent infection in latent phase (19.75 ± 8.84 pg/ml, $p = 0.044$) than in the patients without viral infection (5.33 ± 1.53 pg/ml).

Determination of HHV-6 variant-specificity. HHV-6A was identified in two and HHV-6B in 16 of 18 FM patients positive for HHV-6 infection. HHV-6B was identified in all control individuals.

DISCUSSION

Fibromyalgia (FM) is a chronic disorder that is part of a spectrum of syndromes manifested by diffuse musculoskeletal pain and additional somatic symptoms like fatigue, sleep, emotional disturbance, depression, cognitive symptoms, gastrointestinal symptoms, and headache. The disorder can have a devastating effect on peoples' lives and also imposes large economic burdens on society.

Although inflammatory, infectious, and autoimmune disorders have all been ascribed to be aetiological events in the development of FM, there is very little data to support such a thesis (Borchers and Gershwin, 2015).

At present, clinical diagnostic criteria for FM has been elaborated (Wolfe *et al*., 2010); however, the aetiology and pathophysiology of the disease remains unclear (Albin *et al*., 2008).

Up to date, no data exist on the role of HHV-6 and HHV-7 infection in FM development, although HHV-6 and HHV-7 are ubiquitous viruses with immunomodulating properties and are potential pathogens to the nervous system (Lusso, 2006).

We investigated the detection frequency of single HHV-6, single HHV-7 and concurrent HHV-6+HHV-7 genomic sequences in DNA samples isolated from WPB and cell-free blood plasma from patients with clinically diagnosed FM and control group subjects (Table 1). Although the results of our study show no difference in the detection frequency of single HHV-6 and single HHV-7 infection, the rate of concurrent HHV-6+HHV-7 infection is significantly higher in patients with FM than in healthy individuals ($p = 0.00008$). Active viral infection (plasma viremia) was detected only in FM patients (18.2%).

Increase of mean HHV-6 and HHV-7 loads in WPB of FM patients with persistent infection in latent phase as well as with active infection, in comparison with control subjects, was found.

We found limited empirical evidence to support the association of increased pro-inflammatory cytokine levels with FM development (Menzies and Lyon, 2010). Our results showed that significantly higher TNF-α level occurred in FM patients with active viral infection as well as in patients with persistent infection in latent phase, in comparison with control group individuals. Taking into account the immunomodulating properties of these viruses, quantitative and qualitative changes on system levels of cytokines in the patients with FM cannot be excluded.

At present, the question of potential interaction between HHV-6 and HHV-7 in cases of concurrent infection is not clear. Significantly frequent detection of concurrent infection and simultaneous activation of both viruses only in FM patients allow to suggest the potential interaction between these viruses as well as in development of FM. Our results are in accordance with previous *in vitro* (Katsafanas *et al*., 1996; Tanaka-Taya *et al*., 2000) and *in vivo* (Boutolleau *et al*., 2003; Hall *et al*., 2006) studies.

More frequent detection of HHV-6B in FM patients and healthy individuals indicates that either HHV-6A occurs infrequently in these individuals or that there is a difference in HHV-6A and HHV-6B geographical distribution and the HHV-6B in our area is predominant (Boutolleau *et al*., 2006; Bates *et al*., 2009).

CONCLUSION

Significantly higher detection frequency of concurrent HHV-6 and HHV-7 infection, simultaneous HHV-6 and HHV-7 activation, higher HHV-6 and HHV-7 load, as well as increased expression level of TNF-α in patients with FM, in comparison with control group individuals, indicate a potential association of roseolovirus infection with primary fibromyalgia

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IESPĒJAMĀ ROSEOLOVĪRUSU INFEKCIJAS SAISTĪBA AR FIBROMIALĢIJU

Fibromialģija (FM) ir izplatīta hroniska slimība, kas izraisa sāpes, pasliktina dzīves kvalitāti un samazina dzīvildzi. Tā skar 0.5% līdz 7% no visas pasaules iedzīvotāju populācijas. Slimības etioloģija un patoģenēze šobrīd nav pilnībā skaidra. Cilvēka herpesvīruss-6 (HHV-6) un -7 (HHV-7) ir nervu sistēmas potenciālie patogēni. HHV-6 un HHV-7 antivielu klātbūtne, HHV-6 un/vai HHV-7 infekcijas izplatība, vīrusa slodze, HHV-6 varianta specifiskums un TNF-α ekspresijas līmenis tika noteikts 41 pacientam ar fibromialģiju un 50 praktiski veseliem indivīdiem, izmantojot polimerāzes ķēdes reakciju, restrikcijas endonukleāzes analīzi un ELISA. 85.4% FM pacientu tika atrastas anti-HHV-6 IgG klases antivielas un 83.0% — anti-HHV-7 IgG klases antivielas. Roseolovīrusu genoma secību klātbūtne atrasta 80.5% FM pacientu un 62.0% praktiski veselu indivīdu. Vienlaicīga HHV-6+HHV-7 genomu secību klātbūtne būtiski biežāk konstatēta FM pacientiem. Plazmas virēmija (aktīvas infekcijas marķieris) konstatēta tikai FM pacientiem. HHV-6 un HHV-7 slodze perifēro asiņu DNS paraugos visaugstākā bija FM pacientiem ar aktīvu vīrusu infekciju, taču arī FM pacientiem ar persistentu infekciju latentā fāzē tā bija augstāka nekā kontroles grupas indivīdiem. Būtiski augstāks TNF-α līmenis konstatēts FM pacientiem ar plazmas virēmiju, persistentu infekciju latentā fāzē, salīdzinājumā ar pacientiem, kam netika konstatēta vīrusu infekcija. HHV-6A atrasts diviem pacientiem ar FM, bet visiem pārējiem FM pacientiem un visiem kontroles grupas indivīdiem atrasts HHV-6B. Būtiski biežāk konstatēta vienlaicīga HHV-6 un HHV-7 infekcija, infekcijas aktivācija, augstāka HHV-6 un HHV-7 slodze un augstāks TNF-α ekspresijas līmenis fibromialģijas pacientiem, salīdzinot ar kontroles grupu, liecina par roseolovīrusu iespējamo iesaisti slimības attīstībā.