Role of beta-herpesviruses infection in the development of chronic fatigue syndrome/myalgic encephalomyelitis

Santa Rasa, Svetlana Chapenko, Angelika Krumina[1], Maksims Chistyakovs, Ludmila Viksna[1], Inara Logina[2], Sandra Gintere[3], Modra Murovska

August Kirchenstein Institute of Microbiology and Virology, Riga Stradins University, Latvia;

[1]Department of Infectology and Dermatology, Riga Stradins University, Latvia;

[2]Department of Neurology and Neurosurgery, Riga Stradins University, Latvia;

[3]Department of Family Medicine, Riga Stradins University, Latvia

ERAF EIROPAS REĢIONĀLĀS ATTĪSTĪBAS FONDS

IEGULDĪJUMS TAVĀ NĀKOTNĒ

EIROPAS SAVIENĪBA

"Promotion of International Cooperation Activities of Riga Stradiņš University in Science and Technologies", Agreement No. 2010/0200/2DP/2.1.1.2.0/10/APIA/VIAA/006

13. 10.2011.

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is defined as severe, unexplained, chronic fatigue lasting at least six months, accompanied by four of eight symptom criteria:

- sore throat,
- tender cervical or axillary lymph nodes,
- muscle pain,
- impaired memory,
- impaired concentration,
- un-refreshing sleep,
- post-exertional malaise,
- headaches

Possible triggers of CFS/ME

- Human herpesvirus-6 (HHV-6)
- Human herpesvirus-7 (HHV-7)
- Cytomegalovirus (CMV)
- Epstein-Barr virus (EBV)
- Enteroviruses
- Human parvovirus B19 (B19)
- Lyme disease and Q fever causing bacteria
- Xenotropic murine leukemia virus related virus (XMRV)

CFS/ME

- Came to attention in 1988
- Complex and incompletely understood illness
- International Consensus Panel developed criteria and suggest to use term “myalgic encephalomyelitis” (ME)
- Heritable predisposition
- Genetic basis, environmental factors, viral illnesses, stressful life and traumas
- Worldwide prevalence is 0.4 – 1%
- Affects 17 million people, over 800 000 people in US, 240 000 - in United Kingdom

CFS/ME

- Reactivation of HHV-6 and HHV-7 is detected in patients with CFS/ME and it could be result of latent herpesvirus reactivation
- Amount of HHV-6 and HHV-7 reactivation can be an objective biomarker for fatigue
- CFS/ME may have multiple causes and some viruses or infectious agents might contribute a subset of CFS/ME
- There are no effective standardized and reproducible diagnostic tests, medical treatment and prevention strategies
- Etiology, risk factors, and pathophysiology of CFS/ME remain obscure

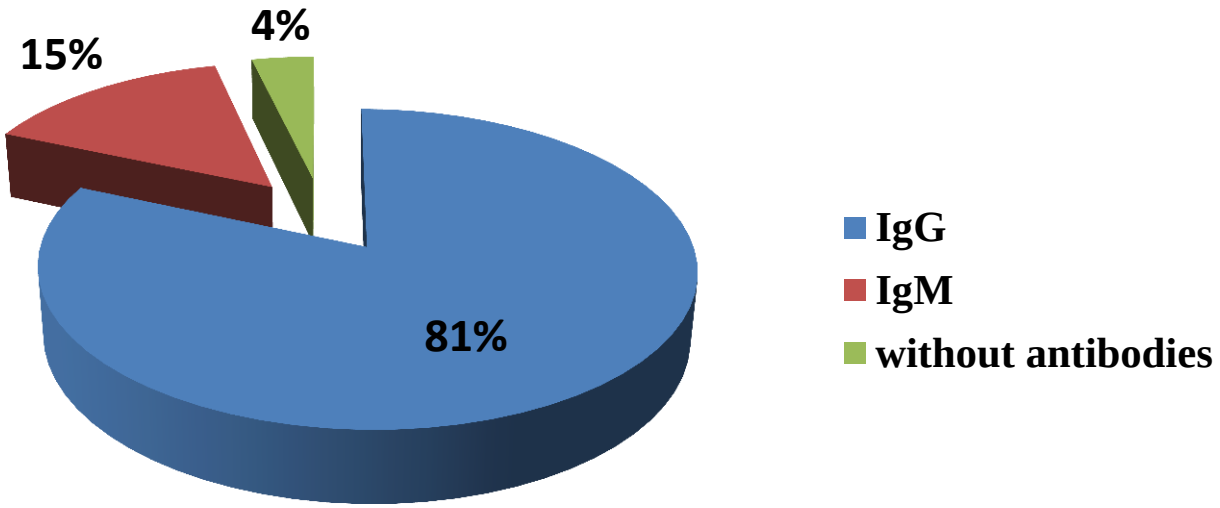
The aim

- This study was done to evaluate frequency of HHV-6 and HHV-7 infection association with clinical findings in CFS/ME patients in Latvia

Materials and methods

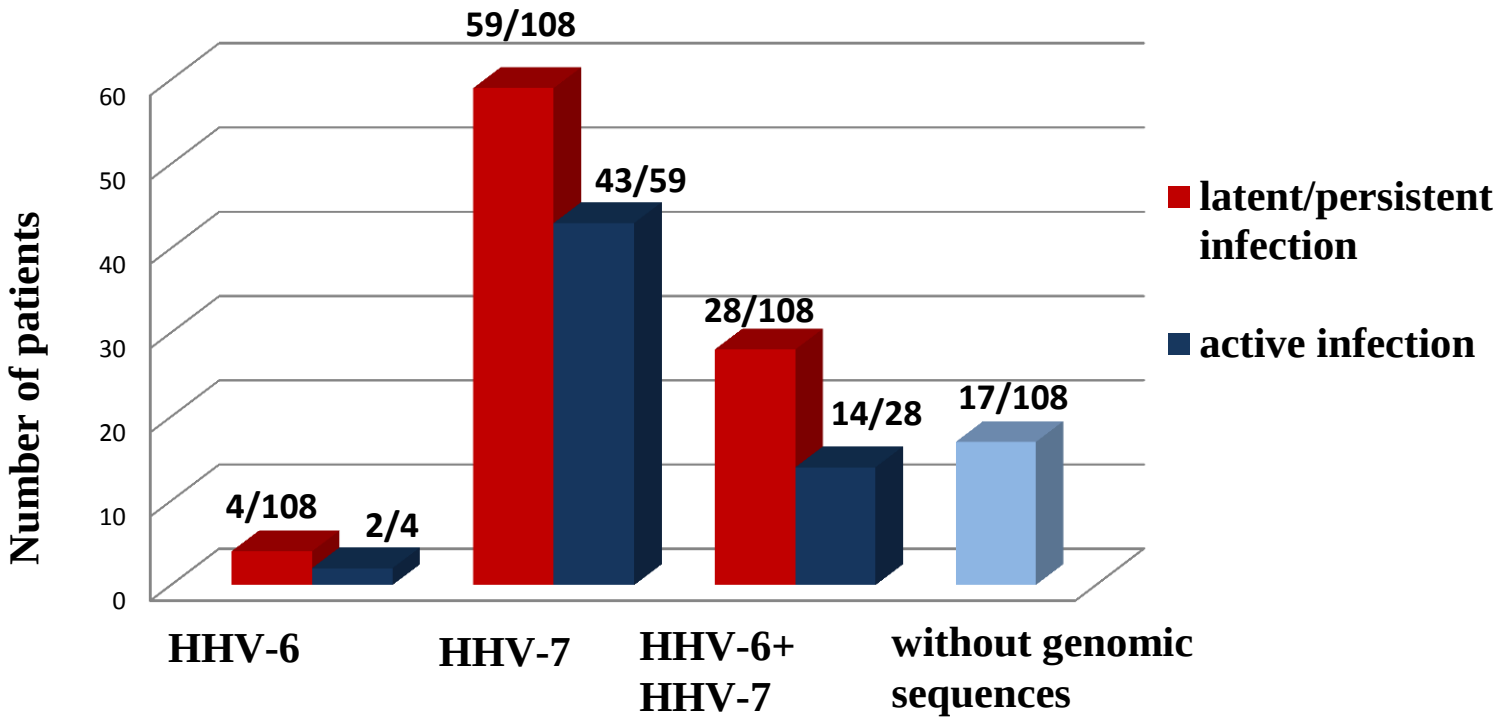
- 108 patients (34% male; 66% female, mean age 37 years) with clinically diagnosed CFS/ME corresponding to CDC diagnostic criteria
- Plasma samples were tested for the presence of HHV-6 IgM and IgG class antibodies using ELISA
- DNA from peripheral blood leukocytes (PBL) and cell free blood plasma was isolated using the phenol-chloroform method
- β-globin gene polymerase chain reaction (PCR) was carried out
- Nested PCR (nPCR) was performed to determine presence of HHV-6 and HHV-7 genomic sequences in DNA isolated from PBL and from cell free blood plasma
- Amplicones were analyzed by agarose gel electrophoresis
- Viral load of HHV-6 in PBL was determined by real time PCR

Results

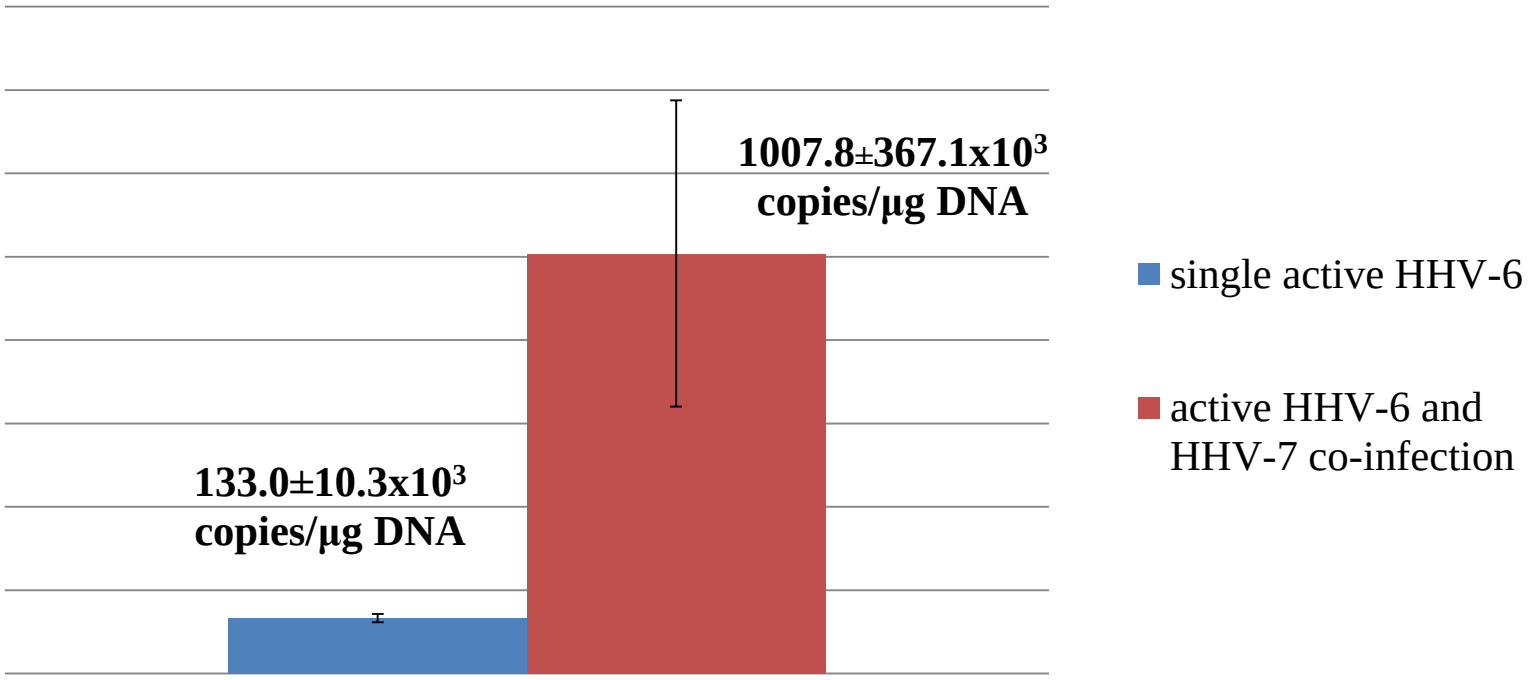


Presence of HHV-6-specific antibodies in plasma samples of patients with chronic fatigue syndrome/myalgic encephalomyelitis

HHV-6 and/or HHV-7 specific genomic sequences were detected in 91 out of 108 (84.3%) CFS/ME patients' DNA samples

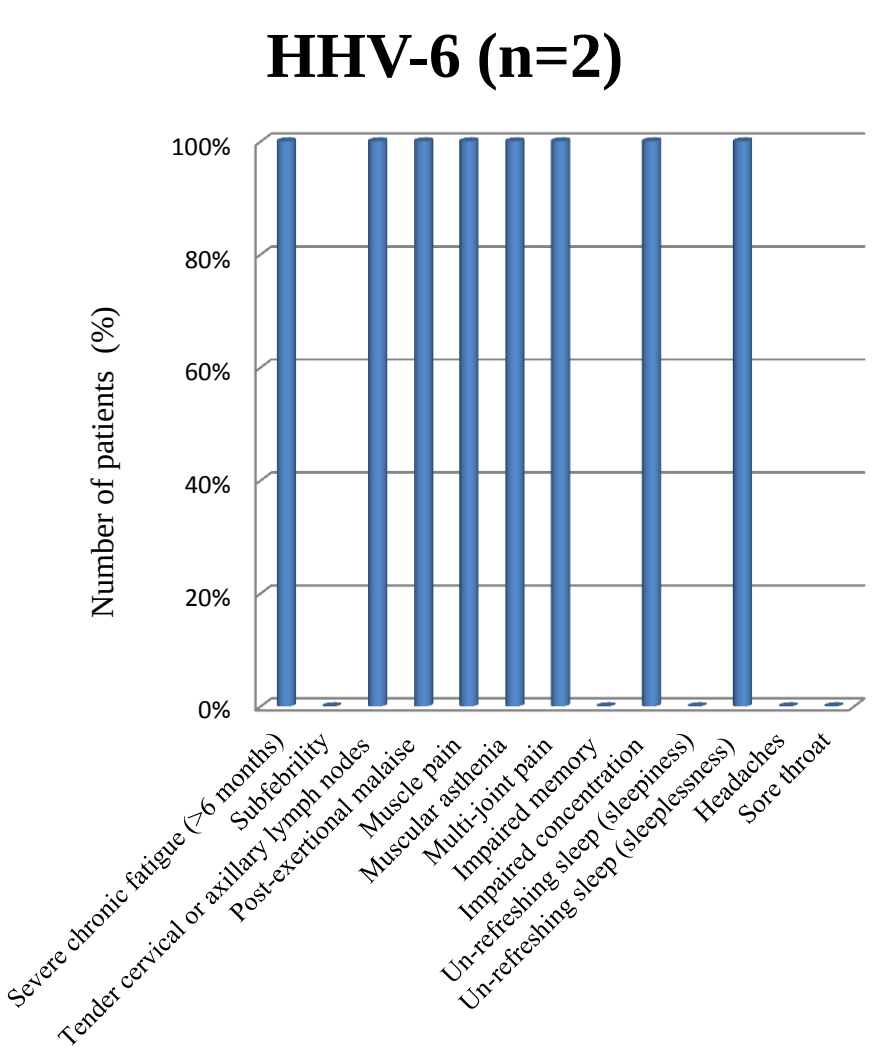


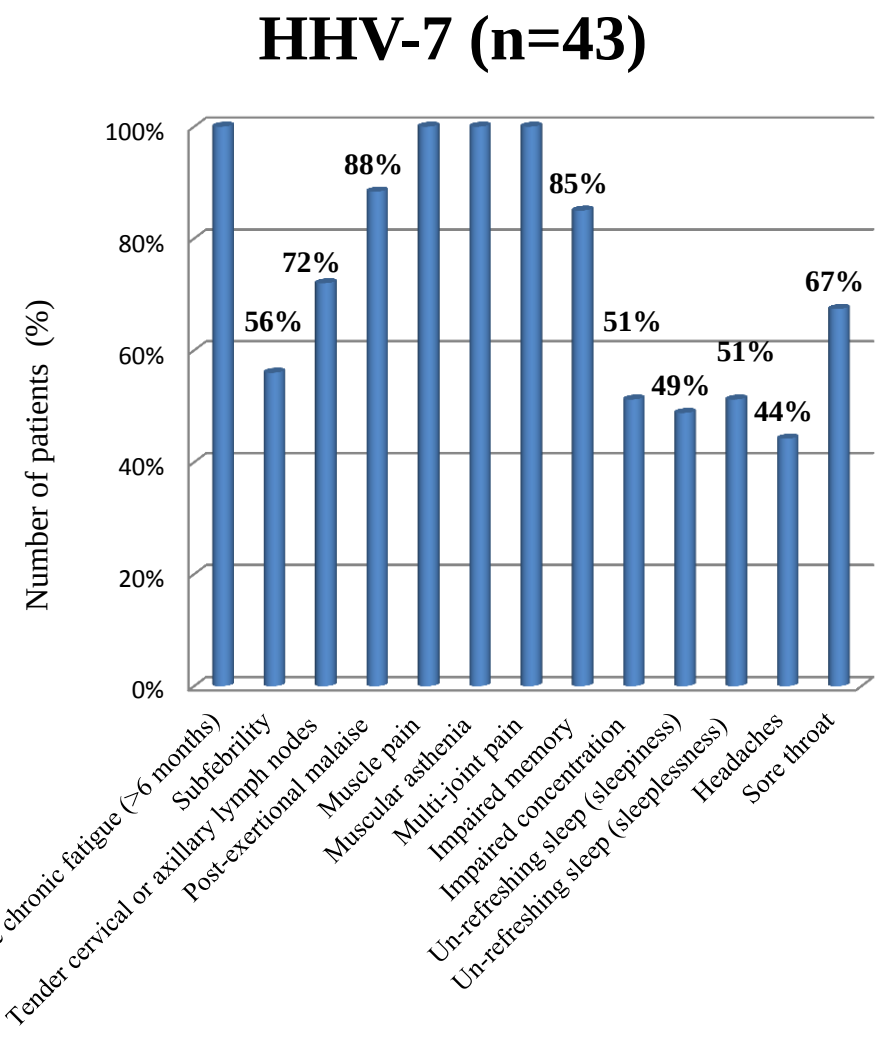
Latent/persistent and active infection of HHV-6 or HHV-7, and concurrent (HHV-6+HHV-7) infection in patients with chronic fatigue syndrome/myalgic encephalomyelitis

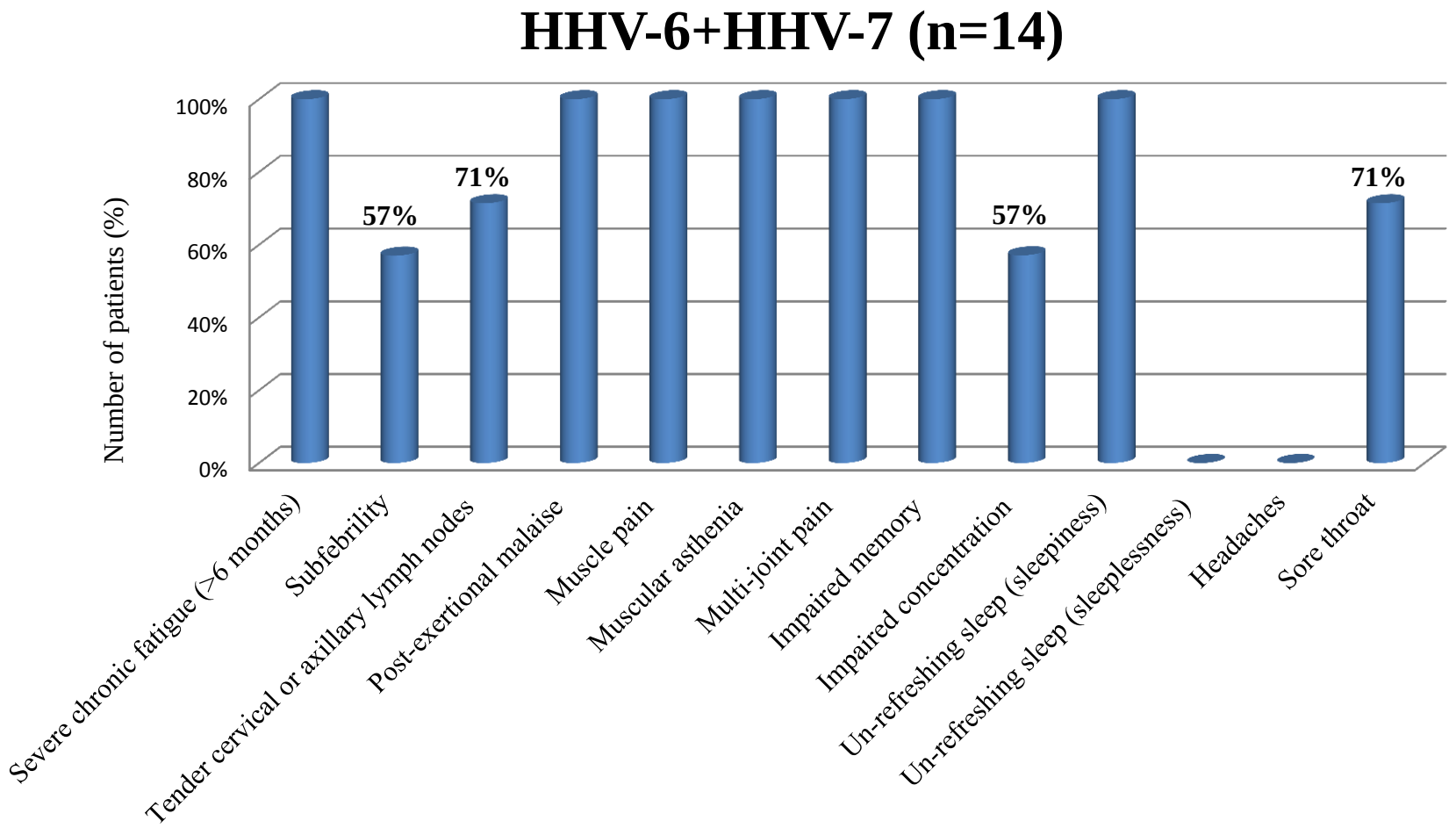


HHV-6 PBL load in patients with active HHV-6 and HHV-7 co-infection and single HHV-6 infection (copies/µg DNA)

Characteristic clinical symptoms of CFS/ME were more often observed in patients with active HHV-6 and/or HHV-7 infection







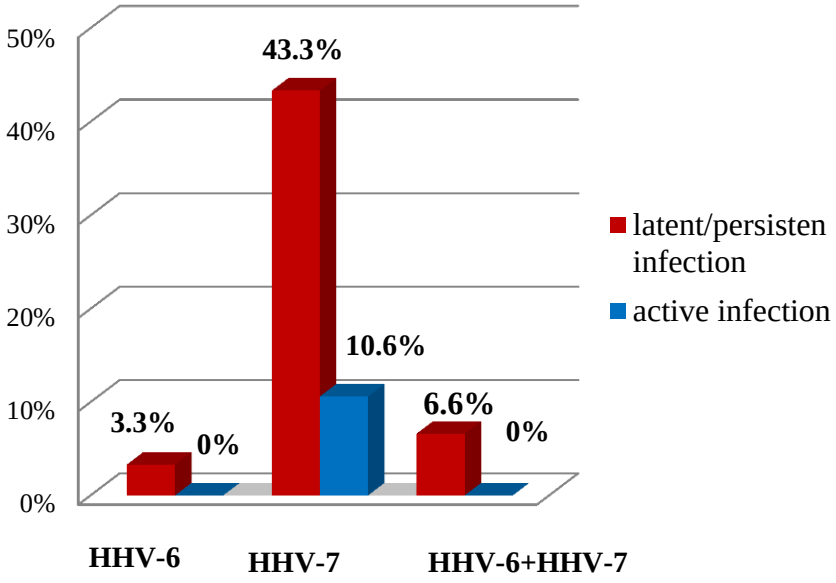
Characteristic clinical symptoms of CFS/ME in patients with active HHV-6 and HHV-7 infection

Discussion

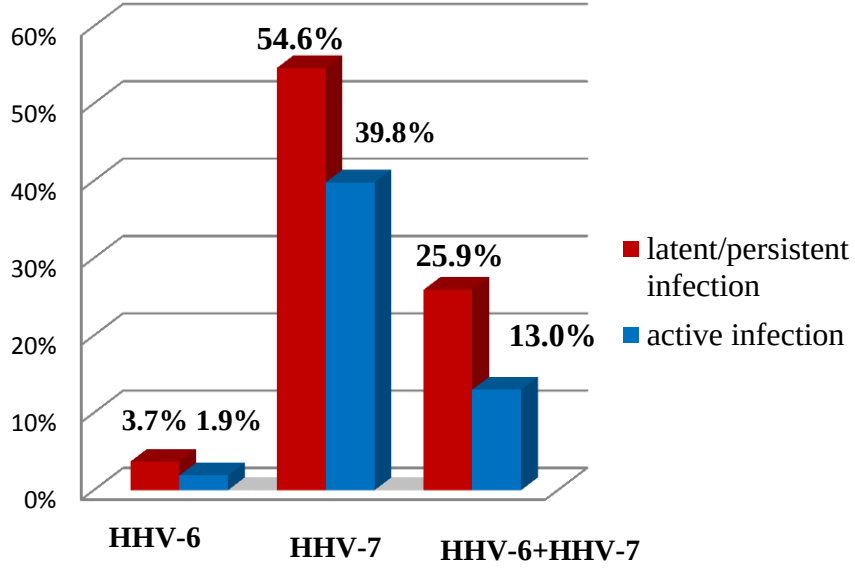
- Majority of researchers have reported on association between HHV-6, HHV-7 and CFS/ME
- Several researchers find no differences in prevalence of HHV-6 and HHV-7 between CFS/ME patients and healthy controls

- In this study HHV-6 specific IgM and IgG class antibodies were detected in 15% and 81% CFS/ME patients, respectively
- In other studies elevated titres of HHV-6 IgM class antibodies are detected in 57% of CFS/ME patients versus 16% healthy controls
- Our study find no differences between HHV-6 specific IgM and IgG class antibodies' prevalence

Latent/persistent and active infection of HHV-6 or HHV-7, and concurrent (HHV-6+HHV-7) infection in healthy blood donors



Latent/persistent and active infection of HHV-6 or HHV-7, and concurrent (HHV-6+HHV-7) infection in patients with chronic fatigue syndrome/myalgic encephalomyelitis



- High load of HHV-6 DNA is detected in 15-30% CFS/ME patients

- In this study we find higher HHV-6 PBL load in patients with active HHV-6 and HHV-7 co-infection than in patients with single HHV-6 infection, suggesting on more important role of dual infection in CFS/ME

Severe clinical course of disease was observed in all patients with active HHV-6 and/or HHV-7 infection:

- chronic fatigue for at least six months or longer
- muscle pain
- muscular asthenia
- multi-joint pain
- un-refreshing sleep

Conclusions

- High rate of active HHV-7 and concurrent HHV-6+HHV-7 infection suggest that these immunomodulating pathogens could be trigger factor for CFS/ME development

- The association between active viral infection and severe clinical symptoms show necessity of simultaneous study of these viral infections to define possible subsets of CFS/ME

RĪGA STRADIŅŠ UNIVERSITY
ERAF EIROPAS REĢIONĀLĀS ATTĪSTĪBAS FONDS
IEGULDĪJUMS TAVĀ NĀKOTNĒ
EIROPAS SAVIENĪBA
"Promotion of International Cooperation Activities of Riga Stradiņš University in Science and Technologies", Agreement No. 2010/0200/2DP/2.1.1.2.0/10/APIA/VIAA/006