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Editorial
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Impact of Chronically Ongoing Infections - HHV-6 and HHV-7 on the Course of Various Diseases

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Editorial

The spectrum and dynamics of infectious diseases have changed significantly over the last decades, with the increase in the number of chronic infections and the importance of these diseases in healthcare - in the medical context, in its impact on the quality of life and socio-economic context.

Latest studies and observations in medical practice indicate that infectious agents which do not always originally cause illnesses manifesting with symptoms that are severe or significantly impair patient's well-being, e.g., herpesviruses, HIV, Hepatitis C virus, eventually cause serious chronic diseases and also has significant impact on the course and outcome of other diseases [7].

Several herpesviruses are such infectious agents causing chronically ongoing infections and adversely affecting the course of other diseases. Among those herpesviruses Human Herpes virus 6 (HHV-6) and Human Herpes virus 7 (HHV-7) are considered to be very significant.

Despite the fact that HHV-6 was discovered only in 1986, it soon became apparent that this virus was spreading rapidly among the population of almost all continents. Experts' attention was drawn to the fact that these viruses were often found in patients with other infectious diseases, such as HIV/ AIDS, non-communicable diseases, dermatologic diseases and even healthy people [1]. A similar situation in terms of prevalence was detected in the context of another virus - HHV-7 which turned out to be morphologically similar to HHV-6.

Taking into account the above mentioned and considering the fact that rates of HHV-6 and HHV-7 among newborns are not detected at birth, but within the next three years of life, according to many literary sources, the rates of those infections are approaching 100% [9], many researchers around the world, including infectologists and virologists in Latvia have expressed interest about the impact of those viruses on human health. Along with the active research process on the association of Chronic Fatigue Syndrome (CFS) with HHV-6 and HHV-7, which demonstrated the close association of these viruses with CFS, a wide range of diseases and pathological conditions was studied, which resulted in discovering the significance of the above mentioned viruses in creating an adverse background for development of other diseases. Let me list the range of diseases studied, which revealed the impact of HHV-6 and HHV-7 on specific diseases. HHV-6 and HHV-7 were detected in patients after renal transplantation, including the correlation between the virus and the incidence and severity of and post-transplant complications; in patients involved in autologous stem cell transplantation processes; in patients with nervous system disorders including demyelinating diseases, multiple sclerosis, encephalopathies of unspecified etiology, changes in the olfactory processes; in cases of gastrointestinal cancers; in cases of autoimmune diseases-thyroid and rheumatoid arthritis and even in prolonged microvascular free flap surgery. Almost all studies have shown that HHV-6 and HHV-7 have a more or less negative effect on the course of underlying disease or comorbidity.

In my opinion, Latvian specialists along with scientists from other countries are playing a significant role in the research of HHV-6 and HHV-7 and in the assessment of the impact of HHV-6 and HHV-7 on various pathologies.

The quantitative and qualitative detection of viruses in different biological fluids, assessment of their activity or latency and other research was carried out in Latvia by August Kirchenstein Institute of Microbiology and Virology of Rīga Stradiņš University.

By performing a qualitative assessment of the genomic sequence of HHV-6 and HHV-7 in DNA samples isolated from peripheral blood lymphocytes, obtained results were used as markers

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of infection's latency or persistence. While the sequence of viral genomes in DNA samples derived from blood plasma was considered as a marker of active infection. Synovial fluid was also studied in case of necessity. The study found that both, HHV-6 and HHV-7 have practical role in the development of many other diseases discussed later, with HHV-6 activation more frequent than HHV-7.

For example, it was found that after prolonged microvascular free flap surgery the activation of the HHV-6 and HHV-7 infection was triggered in the postoperative period, the complications were more frequent and postoperative period was longer [10].

When assessing the progression of multiple sclerosis, it was concluded that HHV-6 and HHV-7 reactivation could be implicated in the exacerbation of multiple sclerosis via activation of Th 1 lymphocyte subsets [4].

In the context of chronic allograft nephropathy (CAN) the following could be concluded. The tendency to shorten the period of CAN development and loss of grafts in renal transplant patients with simultaneus activation of HHV-6, HHV-7 suggest that both viruses may be involved in the CAN development via their immunomodulatory ability [3].

As regards Myalgic Encephalomyelitis (ME/CFS) the following was found: The association between occurrence of ME/CFS clinical symptoms, HHV-6, HHV-7 infection/coinfection reactivation and increased expression levels of TNF-α and IL-6 allows suggesting that these immunomodulating pathogens are involved in ME/CFS etiopathogenesis. Their role as trigger factors could no be excluded. The correlation of distinctive active viral infection with various types of clinical symptoms shows necessity of simultaneous study of these viral infections for identification of possible subsets of ME/CFS [5].

Effect of HHV-6 and HHV-7 infection on the post-transplant process and the development of complications in patients after autologous stem cell transplantation un pētot the relationship between HHV-6 and HHV-7 reactivation and development of post-autologous peripheral stem cell transplantation complications was examined. The presence of viral genomic sequences in whole peripheral blood and cell free plazma was determined by nested PCR, HHV-6 and HHV-7 load by real-time PCR, virus specific antibodies and cytokines in serum by ELISA, and HHV-6 variants by restriction endonuclease analysis. Clinical features, reactivation of virusies and serum TNF-α, and IL-6 concentrations were determined in seventy-six patients with HH6 and HH7 infection before and after transplantation. Citing certain figures, as an example, we noticed that Anti-HHV-6 antibodies were fund in 62 of 76 (81,6%) patients before transplantation. A significantly higher rate of single HHV-7 infection was found in patients with viral infection in comparison with single HHV-6 infection (p=0,0003) and concurrent (HHV-6 and HHV-7) infection (p=0,0017). Complications after transplantation developed in 30,3% of patients and reactivation of viruses was detected in all of these patients. Significant increase of HHV-6 and HHV-7 reactivation with simulltaneous increase of pro inflammatory cytokines serum levels suggests that both viruses may be involved in the development of complications after autologous peripheral blood stem cell transplantation via their immunomodulatory ability. The kinetics of the Roseolvirus reactivation may reflect the potential role of HHV-7 as a co-factor for HHV-6 activation [6].

The high incidence of gastrointestinal cancer (GIC) combined with high mortality of the disease if diagnosed at a late stage, signifies the need for better diagnostic, prognostic and predictive tools. Human beta-herpesviruses have been suggested as possible cofactors in the development of gastrointestinal cancer [7].

HHV-6 and HHV-7 can be reactivated in immunosuppressed conditions and can lead to severe complications. Malignancy also is associated with immunosuppression in hematological tumors and in solid organ cancers as well [7].

HHV-6 and HHV-7 share a high degree of genomic homology and have some similar biological properties. Thus, these herpesviruses might share a similar oncogenic potential [5]. For both, HHV-6 and HHV-7, main target cells appeared to be CD4+ lymphocytes , bat natural killer cells, CD8+ T cells, macrophages, epithelial, endothelial, neural cells and fibroblasts may also be infected [6, 7].

In conclusion, activation of HHV-6 and HHV-7 may lead to decrease of lymphocytes' total count and worsening of immunsuppresion in patients with GIC. High frequency of beta-herpesviruses infection in patients with GIC is contributing into increase of IL-6, sIL-2R and decrease of TNF-α expression levels what could lead to the worse clinical outcomes. Estimation of the viruses-associated impairment of immunological functions may be useful for clinical application to monitoring of GIC patients [7].

A detailed study of patients with rheumatoid arthritis (RA) identified the effect of HHV-6 and HHV-7 infection on the clinical course of rheumatoid arthritis. Viruses and viral infections are considered to be the main risk factors for autoimmune disease development (especially for individuals with genetic predisposition).

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease affecting joints and causing symmetrical chronic progressive aseptic synovitis and erosive-destructive changes in humans. The goal of this study was to evaluate the frequency of HHV-6 and HHV-7 persistent infection and its activity phase in RA and osteoarthritis (OA) patients, and healthy persons. Tika examined the influence of HHV-6 and -7 infections on RA activity, aggressiveness, radiographical stage, and frequency of complications as well as the presence of HHV-6 infection markers in synovial fluid and synovial tissues of RA joints of affected patients. Despite the lack of significant correlation between frequency of persistent single HHV-6, single HHV-7, and concurrent HHV-6 and HHV-7 infection and RA clinical course, were found that both active and latent HHV-6 and/or HHV-7 infection increasec RA activity and progression in several clinical and laboratory parameters. Regarding the severity of the course of RA, was observed also a high prevalence of RA complications in the patient group with active single HHV-6 infection and also a more severe radiographical stage in RA patients with active concurrent HHV-6 and HHV-7 infection. Moreover, viral infection markers were found in synovial fluid and synovial tissues of affected joints of RA patients. This suggests that HHV-6 and/or HHV-7 infection has effect on the disease clinical course, but virus reactivation may be a conequence of immunosuppresive treatment [8].

To emphasize the ability of HHV-6 and HHV-7 to affect the immune system, I also listed some markers indicating the condition of the immune system, which indirectly confirms the immunosuppressive ability/ activity of HHV-6 and HHV-7 that can affect the course of many other diseases.

Summary

Based on the above mentioned results and according to many

other important sources of literature, it is clear that infectious processes, especially chronic ones, have increasingly important role in the development of other diseases and pathological conditions, leading to more severe course of other diseases, more complications and longer recovery period. This is explained by the fact that HHV-6 and HHV-7 have immunosuppressive activity, which is confirmed by the association with TNF-α and IL-6 as well as with other important parameters.

The above would be a reason for physicians to pay attention timely to the underlying infection in the background of the specific disease of the patient. This is important also in the context of invasive manipulations, including transplantation cases in patients with chronic HHV-6 and HHV-7 infection. Detection and activity clarification of HHV-6 and HHV-7 would allow to do the immuno-correction in order to inactivate these infections, which would be preventive therapy in the preparation of patients, for example, for transplantation procedures, but in other cases, a non-standard course of underlying disease could be expected.

Hoping that effective etiological medications for the treatment of HHV-6 and HHV-7 infection will be developed in future it can be expected that the outcome of many diseases, surgical manipulations, large-scale operations and transplantations will be more predictable and better.

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