HHV-6 & Cognitive Dysfunction

- HHV-6 reactivation is associated with delirium and cognitive decline—especially in processing speed and executive functioning—among stem cell transplant patients (Zerr 2005, 2011).
- Insomnia, agitation and hallucination are more common in patients with HHV-6 reactivation (Provenzale 2010)
- HHV-6 limbic encephalitis occurs in 1-4% of all stem cell transplant patients, often presenting with intermittent confusion, poor coordination, flat affect and somnolence.
- HHV-6 can present as retrograde and anterograde amnesia. These patients have a positive CSF PCR DNA and show signal intensity abnormalities in the medial temporal lobes (Gorniak 2006, Visser 2005, Bollen 2001, MacLean 2002).
- HHV-6 reactivation is suspected as a trigger in a subset of chronic fatigue syndrome patients (Komaroff 2006, Chapenko 2012).
- HHV-6 DNA level is associated with impairment of high-level information processing and decreased EEG power densities (Tanaka 2012)

Selected Abstracts 2006-2012

Fatigue-associated alterations of cognitive function and electroencephalographic power densities.

Tanaka M, Shigihara Y, Funakura M, Kanai E, Watanabe Y.

Fatigue is a common problem in modern society. We attempted to identify moderate- to long-term fatigue-related alterations in the central nervous system using cognitive tasks and electroencephalography (EEG) measures. The study group consisted of 17 healthy male participants. After saliva samples were collected to measure copy number of human herpesvirus (HHV)-6 DNA to assess the level of moderate- to long-term fatigue, subjects were evaluated using EEG, with their eyes open for 2 min, then closed for 1 min sitting quietly. Thereafter, they completed cognitive task trials to evaluate simple selective attention for 3 min (Task 1) and conflict-controlling selective attention for 6 min (Task 2, which included Stroop trials). The percent error of Task 2 for Stroop trials was positively associated with the copy number of saliva.

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*HHV-6 DNA*, although the simple selective attention measures in Task 1 did not differ significantly. **EEG power densities** (especially the alpha power density) *during the eye-closed condition were negatively associated with the saliva HHV-6 DNA level*. Impaired high-level information processing such as that required for conflict-controlling selective attention in the central nervous system may be a characteristic feature of moderate- to long-term fatigue.

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<th>HHV-6 reactivation and its effect on delirium and cognitive functioning in hematopoietic cell transplantation recipients.</th>
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| **Zerr DM, Fann JR, Breiger D, Boeckh M, Adler AL, Xie H, Delaney C, Huang ML, Corey L, Leisenring WM.**  
**Department of Pediatrics, University of Washington, Seattle, WA, USA.**  
**Blood. 2011 May 12;117(19):5243-9.** |

Human herpesvirus 6 (HHV-6) is detected in the plasma of approximately 40% of patients undergoing hematopoietic cell transplantation (HCT) and sporadically causes encephalitis in this population. The effect of HHV-6 reactivation on central nervous system function has not been fully characterized. This prospective study aimed to evaluate associations between HHV-6 reactivation and central nervous system dysfunction after allogeneic HCT. Patients were enrolled before HCT. Plasma samples were tested for HHV-6 at baseline and twice weekly after transplantation until day 84. Delirium was assessed at baseline, 3 times weekly until day 56, and weekly on days 56 to 84 using a validated instrument. Neurocognitive testing was performed at baseline and at approximately day 84. HHV-6 was detected in 111 (35%) of the 315 included patients. **Patients with HHV-6 were more likely to develop delirium (adjusted odds ratio = 2.5; 95% confidence interval, 1.2-5.3) and demonstrate neurocognitive decline (adjusted odds ratio = 2.6; 95% confidence interval, 1.1-6.2) in the first 84 days after HCT.** Cord blood and unrelated transplantation increased risk of HHV-6 reactivation. These data provide the basis to conduct a randomized clinical trial to determine whether prevention of HHV-6 reactivation will reduce neurocognitive morbidity in HCT recipients.

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<th>Association of active human herpesvirus-6, -7 and parvovirus b19 infection with clinical outcomes in patients with myalgic encephalomyelitis/chronic fatigue syndrome.</th>
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| **Chapenko S, Krumina A, Logina I, Rasa S, Chistjakovs M, Sultanova A, Viksna L, Murovska M.**  
**August Kirchenstein Institute of Microbiology and Virology, Riga Stradins University, Riga, Latvia.**  

Frequency of active human herpesvirus-6, -7 (HHV-6, HHV-7) and parvovirus B19 (B19) infection/coinfection and its association with clinical course of ME/CFS was evaluated. 108 ME/CFS patients and 90 practically healthy persons were enrolled in the study. Viral genomic sequences were detected by PCR, virus-specific antibodies and cytokine levels-by ELISA, HHV-6 variants-by restriction analysis. Active viral infection including concurrent infection was found in 64.8% (70/108) of patients and in 13.3% (12/90) of practically healthy persons. Increase in peripheral blood leukocyte DNA HHV-6 load as well as in proinflammatory cytokines' levels was detected in patients during active viral infection. Definite relationship was observed between active betaherpesvirus infection and subfebrility, lymphadenopathy and malaise after exertion, and between active B19 infection and multijoint pain. Neuropsychological disturbances were detected in all patients. The manifestation of symptoms was of more frequent occurrence in patients with concurrent infection. The high rate of active HHV-6, HHV-7 and B19 infection/coinfection with the simultaneous increase in plasma proinflammatory cytokines' level as well as the association between active viral infection and distinctive types of clinical symptoms shows necessity of simultaneous study of these viral infections for identification of possible subsets of ME/CFS.
Clinical and imaging findings suggesting human herpesvirus 6 encephalitis.

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Department of Radiology, Duke University Medical Center, Durham, North Carolina, USA.

We sought to distinguish patients testing positive for human herpesvirus 6 from those testing negative, based on clinical features and magnetic resonance images. Sixteen immunosuppressed patients were tested by polymerase chain reaction for human herpes virus 6 DNA in cerebrospinal fluid (nine positive results). Medical records were examined for agitation, altered mental status, hallucinations, insomnia, memory loss, and seizures. Patients were sorted by viral status. Clinical features were compared with imaging findings. Insomnia, agitation, and hallucinations were preferentially evident in human herpes virus 6-positive patients. Imaging abnormalities were evident in the hippocampus of both groups. However, extrahippocampal involvement was more common in human herpes virus 6-positive patients and among those with insomnia and hallucinations or seizures. Patients with memory loss and imaging abnormalities in the entorhinal cortex or amygdala were likely to test positive, as were patients with hallucinations and abnormal magnetic resonance signal in the hippocampus. Human herpes virus 6 encephalitis patients present with diverse clinical features that are also common among patients who test negative. This entity should be suspected in patients who present with insomnia, seizures, or hallucinations when imaging abnormalities are evident in the hippocampus, amygdala, and limbic structures beyond the medial temporal lobe.

MR imaging of human herpesvirus-6-associated encephalitis in 4 patients with anterograde amnesia after allogeneic hematopoietic stem-cell transplantation.

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MR imaging is typically obtained during the work-up of patients who have undergone allogeneic hematopoietic stem-cell transplant who present with unexplained change in mental status, amnesia, or seizures. Although the differential diagnosis is broad in this setting, the presence of T2 prolongation limited to the medial aspect of one or both temporal lobes with or without associated reduced water diffusion may help limit the possible diagnoses. A frequent etiology seen in this context is human herpesvirus-6 (HHV6) infection. We report the evolution of MR imaging findings and clinical course in 4 patients with limbic encephalitis probably related to HHV6.

Is human herpesvirus-6 a trigger for chronic fatigue syndrome?

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Chronic fatigue syndrome (CFS) is an illness currently defined entirely by a combination of non-specific symptoms. Despite this subjective definition, CFS is associated with objective underlying biological abnormalities, particularly involving the nervous system and immune system. Most studies have found that active infection with human herpesvirus-6 (HHV-6)--a neurotropic, gliotropic and immunotropic virus--is present more often in patients with CFS than in healthy control and disease comparison subjects, yet it is not found in all patients at the time of testing. Moreover, HHV-6 has been associated with many of the neurological and immunological findings in patients with CFS. Finally, CFS, multiple sclerosis and seizure disorders share some clinical and laboratory features and, like CFS, the latter two disorders also are being associated increasingly with active HHV-6 infection. Therefore, it is plausible that active infection with HHV-6 may trigger and perpetuate CFS in a subset of patients.