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Human Herpesvirus 6 and Neuropsychiatric Disorders

Human herpesvirus 6 (HHV6) was first found in 1986[1], and type B was identified to be the causative agent in exanthem subitum (roseola) in 1988[2]. Herpesviruses, including herpes simplex viruses (HSV) 1 and 2, Epstein-Barr, and cytomegalovirus, are double-stranded DNA viruses known to be associated with neurological symptoms. The herpesviruses are not eradicated from the body and lie latent, perhaps leading to active infection later in life. HHV6 has been explored for its ability to penetrate the central nervous system and its role in a number of neurological disorders, including multiple sclerosis (MS), human immunodeficiency virus (HIV-1), Guillain-Barre, epilepsy, encephalitis, chronic fatigue syndrome, and Bell's palsy. Studies have often found conflicting results, but the strongest associations currently in the literature seems to connect HHV6 with MS and encephalitis in immunocompromised patients.

Bell's Palsy

Facial palsy was found to be related to herpes simplex virus[3], leading to the exploration of the role of HHV6 in Bell's palsy. PCR studies of the cerebrospinal fluid of patients with facial palsy have shown little evidence of HHV6 infection. HHV6 DNA was not found by PCR in the serum or cerebrospinal fluid of any of 19 patients with facial palsy, nor did the facial palsy patients have significantly higher serum antibodies to HHV6 compared to a control group in one study[4]. Another study found HHV6 DNA by PCR in only one of 34 cerebrospinal fluid samples from patients with Bell's Palsy[5].

While HHV6 DNA has not been found consistently in cerebrospinal fluid, it could still be related to facial palsy peripherally without central nervous system dissemination or the virus could be present in such small numbers as to avoid detection by this assay.

Bell's palsy has been linked anecdotally to HHV6 infection. Facial palsy following exanthem subitum (rash and high fevers with serum positive for HHV6 IgG and IgM at three week intervals) in an infant has been reported, with HSV, CMV, *Borrelia*, varicella-zoster, EBV, and *Mycoplasma* excluded by PCR and ELISA[6]. HHV6 DNA was found in tears of patients with facial palsy significantly more often than in control patients, though not in every patient with Bell's palsy. Since the facial nerve also carries autonomic signals related to lacrimation, assaying tears may be a useful, non-invasive method of study[7]. Though HHV6 has not been definitively linked to facial palsy, given the strong association of HSV with Bell's palsy it seems likely that infection with HHV6 could also be one of many causes of facial palsy. Future studies with greater sensitivity will likely show a stronger association of facial palsy and HHV6; excluding other more well established causes.

Multiple Sclerosis

HHV6 is a good candidate for an autoimmune trigger in multiple sclerosis, as it seems to be more active in patients suffering from MS, and there is a viable mechanism for its action on the immune system. HHV6 DNA has been found in the serum of patients with multiple sclerosis significantly more than healthy and other immune condition controls, and the serum quantity of IgM antibody is greater in MS patients, particularly the relapsing-remitting type more so than the chronic progressive type[8].

Relapsing-remitting MS patients were at any time more likely to have HHV6 (type A) positive PCRs than healthy controls, but HHV6 DNA was more likely to be found during relapse rather than during remission in these patients[14]. Active HHV6 type A in these relapsing-remitting MS patients may be related to their relapses by stimulating the immune system and thereby increasing the amount of autoimmune antibodies.

Viral antigens have been found in the brains of patients with MS[9]. MS patients with a positive HHV6 serum PCR had elevated levels of CD46 in their serum. CD46 is the cellular receptor for HHV6 and measles. The interaction of the virus and CD46 can lead to activation of complement and tissue damage[10]. HHV6 RNA has been found more frequently in the plaques of MS brains than in healthy white matter. The presence of the viral RNA in a few healthy white matter areas may suggest that active viral infection may be related to the formation of the plaque[11]. HHV6 activity may stimulate the immune system and cause damage within the central nervous system that eventually becomes the characteristic white matter lesions in multiple sclerosis.

HHV6's cross-reactivity with myelin basic protein has been tested to further understand the role of HHV6 in MS. Attempts to create T cell lines that cross-react with HHV6 and myelin basic protein have had mixed results. Cirone, *et al* found cross-reactivity between HHV6 and myelin basic protein, but the rate of cross-reactivity was the same for MS patients and healthy controls[12]. In contrast, using an HHV6 peptide with seven identical amino acids to myelin basic protein Tejada-Simon, *et al*, found rates of cross-reactivity greater than 50% and that the frequency of cross-reactive T cells was significantly higher in MS patients than healthy donors[13]. If infection with HHV6 leads to the production of antibodies against myelin basic protein, HHV6 could be an important

autoimmune trigger for multiple sclerosis. Though the story about HHV6 and MS is incomplete, the increased prevalence of active virus, the localization of the virus to damaged tissue, and the ability of the virus to activate complement and generate autoantibodies make it an excellent candidate for an MS trigger. However, active HHV6 does not seem to be present in every patient with MS, not even every patient with relapsing-remitting MS, so it may not be the trigger or at least not the only trigger for multiple sclerosis.

Human Immunodeficiency Virus

Given the association of HHV6 and nervous system complications, it is reasonable to consider the role of HHV6 in immune-compromised human immunodeficiency virus (HIV) patients. HHV6 has been shown *in vitro* to increase the susceptibility of cells to HIV-1 by inducing CD4 expression on cells that had not expressed the protein before[15]. Additionally, infection with HHV6 of cells infected with latent HIV lead to reactivation of the HIV, as measured by reverse transcriptase activity, and eventual cell death *in* vitro[16]. In macaques infected with SIV, co-infection with HHV6 lead to a faster progression to AIDS than those primates infected with SIV alone[17].

HHV6 in patients with neuro-AIDS was studied to determine if HHV6 infection was related to central nervous system complications in HIV. No significant differences were seen in cerebrospinal fluid PCRs or serum antibody concentrations between neuro-AIDS patients and healthy controls, indicating that HHV6 may not have a role clinically[18] despite *in vitro* results and neurological symptoms related to other diseases such as MS.

The promise of *in vitro* studies, however, prevents the exclusion of a role for HHV6 in neuro-AIDS or AIDS dementia complex.

Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS) is a collection of symptoms with severe, chronic fatigue not explained by another medical condition. It is thought that CFS may be a post-viral syndrome because of its often sudden onset with flu-like symptoms and chronic immune activation, so with the knowledge that HHV6 penetrates the central nervous system this virus has been considered as a trigger for the syndrome. Multiple studies have shown a relationship between CFS and active HHV6 by PCR, though evidence of past HHV6 infection was not different between CFS patients and controls. Not all patients with chronic fatigue syndrome have evidence of active HHV6, however, so it is unlikely that HHV6 is the sole infectious agent implicated in CFS[19]. One study found no significant difference between CFS patients and controls for active HHV6 infection alone by serum PCR but did find a significant difference for infection with both active HHV6 and HHV7[20], indicating the likely complex infectious background in these patients.

Studies of success with anti-viral drugs in chronic fatigue syndrome would help illuminate the role of active viral infection in CFS further[19]. One preliminary study of 12 patients with chronic fatigue syndrome and elevated serum antibody titers to EBV and HHV6 showed that six months of valganciclovir (an anti-viral) therapy significantly helped symptoms and decreased antibody titers in nine patients. EBV responded more significantly than HHV6, again indicating that multiple infectious pathogens may be involved in CFS, but this study is promising for the role of anti-viral treatment for these

patients[21]. This study indicates that antibodies against various herpesviruses should be checked in patients with CFS, particularly with other nervous system involvement, to determine if they would benefit from treatment with anti-viral therapy, such as valganciclovir.

Epilepsy

HHV6 primary infection in young children has been associated with febrile seizures related to exanthem subitum, so a role for reactivated HHV6 infection has been explored in adults. Recently, a study of brain tissue resected from patients with seizure disorders was studied for active infection with HHV6. HHV6B viral DNA was found by PCR in nine of sixteen patients with mesial temporal lobe epilepsy (MTLE) but not at all in patients with other types of seizure disorders. Specifically, the virus was located within astrocytes in the brain tissue. MTLE is associated pathologically with mesial temporal sclerosis (MTS), including astrogliosis with surrounding neuron death[22]. The localization of HHV6B to the astrocytes in this brain area with the accompanying astrogliosis suggests a mechanism for how reactivated infection could lead to MTS and MTLE. The researchers also found that HHV6 was specifically localized to the hippocampus and temporal lobe and not present in the frontal or parietal lobes, supporting the virus's role in MTLE further. In one patient, months after initially finding HHV6B in the hippocampus, the virus was found in other lobes of the brain, suggesting that the virus can spread and is not limited to the temporal lobe. MTLE is known to be associated with glutamate transport problems, and this study showed that HHV6B infection was related to decreased transcription of the glutamate transporter EAAT-2 in

the astrocytes cultured from resected brain tissue[22]. The specificity of HHV6B active infection to patients with MTLE versus other types of intractable epilepsy, the localization of virus to the site of MTLE origin, and the relationship of HHV6 activity and decreased glutamate transporter transcription puts together a powerful story of the relationship between active HHV6B and MTLE. However, since not all patients with MTLE had active HHV6 infection, viral reactivation is unlikely to be the only trigger for the development of MTLE.

Encephalitis

Post-transplant acute limbic encephalitis due to HHV6 has been reported in patients who have received hematopoietic stem cell transplants (HSCT)[23]. These patients are immunocompromised, and therefore at risk for reactivation of latent virus, though cases of encephalitis with cerebrospinal fluid HHV6 positive PCRs have also been reported[24]. The age of these patients is much older than the time when most patients are infected with HHV6 (about three years), so it is likely that the encephalitis is not due to primary infection but to reactivation[23].

Although they were being treated prophylacticly with acyclovir for herpes simplex viruses, the post-HSCT patients still developed encephalitis due to HHV6. Symptoms included rapid-onset anterograde and retrograde amnesia, cerebrospinal fluid pleocytosis, and poor control over antidiuretic hormone, though symptoms did not include language or visual problems. Some patients also developed seizures. MRI abnormalities were found in the limbic system, including the hippocampal body and the amygdala. All patients were treated, though recovery varied greatly from none to full.

Six of the nine patients studied had a cerebrospinal fluid HHV6-positive PCR, and all patients were PCR negative for other herpesviruses[23].

Encephalitis due to HHV6 has also been documented with solid organ transplant. A case report of a post-lung transplant patient documented a similar syndrome to the post-transplant acute limbic encephalitis described in the HSCT patients, with MRI lesions in the temporal lobe[25]. Similar cases in a liver transplant patient[26] and a heart transplant patient[27] have also been reported.

Though the number of cases are few, the successful documentation of similar encephalitis profiles is multiple patients with positive cerebrospinal PCRs for HHV6 is strong evidence for the role of HHV6, particularly in immunocompromised patients, to cause temporal lobe encephalitis that may or may not respond to treatment. This evidence highlights the need to test patients, especially post-transplant, with rapid-onset encephalitis for HHV6 DNA so that they might receive the appropriate treatment as quickly as possible.

Guillain-Barre

Guillain-Barre syndrome (GBS) is known to follow viral infection, and is has been reported to follow HHV6 seropositive exanthem subitum in an infant who was seronegative for other known viral causes of GBS[28], suggesting a causal link between the HHV6 and GBS in rare cases. The suggestion of this relationship is encouraged by the finding that GBS patients have higher serum and cerebrospinal fluid antibody titers to HHV6 than healthy controls and patients with other neurological diseases[29], however without PCR testing the current activity of the virus cannot be connected to the time of

onset of GBS. Another group did use cerebrospinal fluid for PCR testing at the time of Guillain-Barre symptoms, and four out of fourteen patients were found to be HHV6 positive[30], giving more power to the association between GBS and HHV6. In contrast, another study found all seven GBS patients serum and cerebrospinal fluid PCR negative for HHV6[4]. However, very few studies have been performed with very small sample size, so HHV6 as a trigger for GBS cannot yet be confirmed or ruled out. The association that has been presented so far, however, is enough to encourage testing for HHV6 in GBS patients to determine the appropriate course of treatment.

Human herpesvirus 6 has been casually associated with many neurological diseases ranging from Bell's palsy to neuro-AIDS. Thus far, no causative relationships have been found between HHV6 and any of these diseases. However, strong associations are currently being heavily researched and likely more substantive relationships will be found. Meanwhile, HHV6 should be included in the differential for symptoms of encephalitis, chronic fatigue, multiple sclerosis, facial palsy, and the other disorders discussed here to ensure the best treatment for the patient. The recommended treatment for HHV6 is ganciclovir or foscarnet[31], which is different than the treatment for the herpes simplex viruses, so care in diagnosis is crucial.

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