“Human Herpes Virus-6 (HHV-6) Etiopathogenesis: New Data and Evidences?”

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Which of the following statements is true?

a) HHV-6 variant A has been associated to Exanthem subitum (Roseola Infantum; Sixth Disease)

b) HHV-6 variant A has been associated with febrile seizures

c) HHV-6 has not been associated with infectious mononucleosis-like syndromes

d) HHV-6 does not cause encephalitis in immunocompromised patients

e) HHV-6 variant B has been associated to Exanthem subitum (Roseola Infantum; Sixth Disease)

f) I don’t know, I’m coming to this meeting to learn
# Herpesviridae family

**DNA-containing, enveloped viruses**

<table>
<thead>
<tr>
<th>Human herpesviridae sub-families</th>
<th>Serial Arabic number designation</th>
<th>Genome length (kb)</th>
<th>Examples of diseases caused by herpes viruses in immunocompromised patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human herpes simplex-1 (HSV-1)</td>
<td>HHV-1</td>
<td>152</td>
<td>Disseminated disease, encephalitis, pneumonia</td>
</tr>
<tr>
<td>HSV-2</td>
<td>HHV-2</td>
<td>152</td>
<td>Disseminated disease, pneumonia, encephalitis</td>
</tr>
<tr>
<td>Varicella zoster virus (VZV)</td>
<td>HHV-3</td>
<td>125</td>
<td>Disseminated disease, pneumonia, encephalitis</td>
</tr>
<tr>
<td><strong>Beta</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>HHV-5</td>
<td>230</td>
<td>Disseminated disease, retinitis, pneumonia encephalitis, gastrointestinal disease, liver and biliary disease</td>
</tr>
<tr>
<td>Human herpes virus 6 (HHV-6)</td>
<td>HHV-6</td>
<td>160</td>
<td>Disseminated, encephalitis</td>
</tr>
<tr>
<td>HHV-7</td>
<td>HHV-7</td>
<td>145</td>
<td>Disseminated disease?</td>
</tr>
<tr>
<td><strong>Gamma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epstein-Barr virus (EBV)</td>
<td>HHV-4</td>
<td>172</td>
<td>Post-transplant lymphoproliferative disease (PTLD), retinitis,</td>
</tr>
<tr>
<td>Kaposi’s sarcoma-associated herpesvirus (KSHV)</td>
<td>HHV-8</td>
<td>165</td>
<td>Kaposis sarcoma, Castleman's disease</td>
</tr>
</tbody>
</table>

Montoya JG. Current Opinion Infectious Diseases. 2007; 20(4): 397-8
- typical structure, genome organization, and expression of herpesviruses
- lymphotropically and neurotropically
- variants A and B genomes share 90% sequence identity
- in vivo, most HHV-6-infected cells express the T-cell marker CD4 but use CD46 as a receptor for cellular entry

HHV-6 infects essentially all humans by age 2 years

- Serological tests do not distinguish between HHV-6A and B variants
- Variant B is present in almost all healthy adults and children
- Variant A is usually isolated from spinal fluid and from ICH

Saliva is the potential transmission vehicle for HHV-6

• Pathogenesis
  • oropharynx
  • regional lymphoid tissue
  • mononuclear cell populations distributed throughout the body
  • lifelong latent infection (latency in CD4+ T cells, monocytes-macrophages?)
  • reactivation of HHV-6B variant
  • primary infection with HHV-6A variant?
HHV-6 and potentiation of HIV-1 pathogenesis

- Replication in CD4+ lymphocytes
- induces CD4 expression
- accelerates HIV-1 transcription and replication
- more rapid progression of HIV disease following HHV-6 infection in infants (J Infect Dis 1999; 180:50-55.)
- progression to full-blown AIDS was dramatically accelerated by coinfection with HHV-6A in SIV-infected pig-tailed macaques (Macaca nemestrina) (Proc Natl Acad Sci USA 2007; 104(12):5067-72)
Fig. 2. Clinical and immunological disease progression in pig-tailed macaques singly or dually infected with SIVsmE660 and HHV-6AGS

Diseases linked to HHV-6

- Exanthem subitum (Roseola Infantum; Sixth Disease)
- infantile Fever
- febrile seizures
- infectious mononucleosis-like syndromes
- Dermatological syndromes (drug-induced hypersensitivity syndrome, Pityriasis rosea)
- immunocompromised hosts:
  - fever
  - encephalitis
  - hepatitis
  - disseminated disease
  - skin rash
  - graft failure in bone marrow transplants
Exanthem subitum (roseola infantum)
# Signs and Symptoms in Febrile Children with Acute HHV-6 Infection

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>Number (%) of Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaise, irritability</td>
<td>28 (82)</td>
</tr>
<tr>
<td>Temperature $\geq 40^\circ$ C</td>
<td>22 (65)</td>
</tr>
<tr>
<td>Inflamed tympanic membranes</td>
<td>21 (62)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>19 (56)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (29)</td>
</tr>
<tr>
<td>Cough</td>
<td>9 (27)</td>
</tr>
<tr>
<td>Rhonchi, wheezing, crackles</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Seizure</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

Of 1653 infants and young children with acute febrile illnesses (ER), 10% had primary HHV-6 infection, as documented by viremia and seroconversion.
Viruses as a major precipitant of seizures in infants

- Role of viral infections in the etiology of febrile seizures
  - Neurotropism
  - Role of the body temperature
  - Cytokine and immune response
  - Genetic susceptibility

Pediatr Neurol. 2006;35(3):165-72
Pediatr Neurol. 2007;36(1):61-3
Human herpesviruses-6 is associated with febrile seizures and status epilepticus in children

- 205 children (2-35 months old) hospitalized with suspected encephalitis and/or severe illness with fever and convulsions in Britain and Ireland
- 26/156 (17%) of children aged 2-23 months had primary infection (11 HHV-6; 13 HHV-7; two with both viruses) coinciding with the acute illness; this was much higher than the about three cases expected by chance
- All 26 were pyrexial; 25 had convulsions (18 status epilepticus), 11 requiring ventilation.

Arch Dis Child 2005 Jun;90(6):619-23
Association of human herpesvirus 6 reactivation with the flaring and severity of drug-induced hypersensitivity syndrome

- Drug-induced hypersensitivity syndrome (DIHS) is an adverse reaction with clinical signs of fever, rash and internal organ involvement.
- In Japan, drugs linked to DIHS include: carbamazepine, phenytoin, phenobarbital, zonisamide, mexiletine, dapsone, salazosulfapyridine and allopurinol.
- Anti-HHV-6 IgG titres increased in 62 of 100 patients, 14-28 days after the onset of symptoms.
- Significant amounts of HHV-6 DNA were detected in serum samples from 18 of the 62 patients.
- All five patients with fatal outcome and 10 patients with renal failure were in the HHV-6 reactivation group.

HHV6 Causes Disease in Immunocompromised Patients

- fever, bone marrow suppression, encephalitis, skin rash, and hepatitis in HSCT and solid organ transplants (J Clin Virol. 2006 Dec;37 Suppl 1:S87-91)
- Tissue immunohistochemistry (if available) and HHV-6 PCR in body fluids may be helpful
Post-transplant acute limbic encephalitis: Clinical features and relationship to HHV-6

- anterograde amnesia, the syndrome of inappropriate antidiuretic hormone secretion, mild CSF pleocytosis, and temporal EEG abnormalities, often reflecting clinical or subclinical seizures.

- MRI showed hyperintensities within the uncus, amygdala, entorhinal area, and hippocampus on T2, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI) sequences.

Seeley et al. Neurology 2007;69;156-165
Post-transplant acute limbic encephalitis: Clinical features and relationship to HHV-6

- nine patients with acute limbic encephalitis after allogeneic hematopoietic stem cell transplantation (HSCT)
- CSF PCR assays for HHV6 were positive in six of nine patients on initial lumbar puncture
- All patients were treated with foscarnet or ganciclovir. Cognitive recovery varied among long-term survivors

Seeley et al. Neurology 2007;69;156-165
Is there a role for HHV-6 in the following diseases?

• encephalitis in immunocompetent patients
  • Clin Infect Dis; 1995 Sep;21(3):571-6
• mesial temporal lobe epilepsy
  • Donati D. et al. Neurology 2003
• multiple sclerosis
• Myocarditis
  • Mahrholdt H et al. Circulation 2006
• chronic fatigue syndrome
• Global amnesia
Encephalitis in immunocompetent patients

• A 34-year-old Asian-American gentleman with past medical history only significant for inactive discoid lupus for which he had required no medications for over a year was transferred to the Stanford University Medical Center in mid summer for further evaluation of worsening meningoencephalitis.

• He had presented to an outside hospital with one week of sore throat, nausea/vomiting, fever, and worsening headache, and had been found on lumbar puncture to have a lymphocytic meningitis with 331 cells/µl (76% lymphocytes), an elevated protein (119), and a normal glucose in his CSF.

• He had been started on Vancomycin, ceftriaxone, and acyclovir, but his mental status had worsened over the week, and he had developed repetitive myoclonic activity.
Encephalitis in immunocompetent patients

- An initial brain MRI had been normal, an EEG had been nondiagnostic, and CSF HSV I and II PCR, West Nile Virus serology, mycobacterium tuberculosis PCR, bacterial culture, AFB stain and preliminary culture, and KOH stain and preliminary fungal culture had all been negative.
- Per discussion with his family, he was a married software engineer with two young children, and his only recent travel had been to Hong Kong and urban China 7 months prior.
- On arrival at Stanford University Medical Center, the patient exhibited continuous severe myoclonic activity, mumbled incoherently, and did not respond to questions or commands. He was intubated for airway protection, his antibiotics were broadened to Vancomycin, cefepime, and unasyn to also cover for possible aspiration pneumonia, and his acyclovir was changed to gancyclovir for broader viral coverage.
Encephalitis in immunocompetent patients

- His initial labs on transfer were significant for leukocytosis with a WBC count of 19.9; he had normal hemoglobin, platelet count, electrolytes, and liver function tests. His clinical status deteriorated to essentially a comatose state, and for the next few weeks his mental status fluctuated between following simple commands to being completely nonresponsive when weaned off all sedation.

- He also developed autonomic dysregulation with hypotension requiring pressors alternating with hypertension requiring IV labetalol, and hypothermia to 35.5 alternating with fevers, all within hours.

- He had serial lumbar punctures which showed continued pleocytosis with a lymphocytic predominance and a glucose that dropped to the low level of 36 on hospital day #8. He was consequently started on isoniazid, rifampin, ethambutol, and pyrazinamide with adjuvant dexamethasone for possible tuberculous meningitis and fluconazole for possible coccidiodal meningitis in addition to his broad-spectrum antibiotics and ganciclovir.
Encephalitis in immunocompetent patients

- PPD, CXR, multiple sputum AFB smears and cultures, and AFB smear and culture of CSF from one small volume and 2 large volume taps were negative. Coccidioides immunodiffusion and complement fixation from serum and CSF were negative, and the fluconazole was stopped on hospital day #11. CSF serology for rubeola, West Nile virus, mycoplasma, LCV, toxoplasma, borrelia, coxiella, bartonella, rickettsia, and cysticercosis and PCR for CMV, HSV I and II, VZV, enterovirus, EBV, toxoplamsa, Whipples, and bartonella were negative for acute infection. CSF VDRL, latex cryptococcal antigen, viral cultures, bacterial cultures, and fungal cultures were negative. Negative blood tests included RPR; WNV PCR; multiple blood cultures; serology for WNV, Western Equine Encephalitis, St. Louis Encephalitis, brucella, legionella, HIV, HAV, HBV, HCV, LCV, rocky mountain spotted fever, poliovirus, coxsackie virus, echovirus, and adenovirus; as well as negative serology for acute infection with EBV, chlamydia, and mycoplasma pneumonia.
Encephalitis in immunocompetent patients

- A brain MRI on hospital day #5 showed three foci of restricted diffusion in the right temporal lobe and left posterior limb internal capsule.
- Multiple EEGs showed diffuse slowing, and an EEG on hospital day #5 showed some frontal epileptiform discharges.
- A repeat brain MRI on hospital day #16 showed symmetric diffuse restricted diffusion involving the white matter only including the subcortical white matter, external and internal capsules extending into the bilateral cortical spinal tracts, splenium of the corpus callosum, and middle cerebellar peduncles.
- As there were no reports of tuberculous meningitis presenting this way, and as all tests for tuberculosis were negative, the isoniazid, rifampin, ethambutol, and pyrazinamide were stopped on hospital day #16.
Encephalitis in immunocompetent patients

• Only one diagnostic test was positive: CSF from a lumbar puncture done on hospital day #4 had a positive HHV-6 PCR at 30,000 copies/ml

• 24 to 48 hours after starting the foscarnet/ganciclovir combination, the patient’s mental status began to improve. He was able to wave hello and answer yes-no questions. He was extubated on hospital day #20, weaned off pressors, and transferred out of the ICU on hospital day #21.

• On the day of his transfer, he was able to converse and answer questions about his children. However, during the transfer his ganciclovir was accidentally stopped, and he did not receive doses for two days. During this period, his mental status worsened, and he became more somnolent and not easily arousable. After ganciclovir was restarted, his mental status improved.
Mesial temporal lobe epilepsy (MTLE)

- Epilepsy is a group of heterogeneous conditions.
- Mesial temporal sclerosis (MTS, also called hippocampal sclerosis) is the most common underlying cause of temporal lobe epilepsy (TLE). CNS infection, head trauma, hamartomas, glial tumors, vascular and congenital malformations, and perinatal injury are other causes.
- Pathologic examination reveals neuronal loss in the hippocampus and dentate gyrus. It is typical for the pathology to be bilateral, although one side is usually more predominantly involved. It is theorized that reorganization of neuronal networks in response to cell loss leads to epileptogenesis.
- Complex partial seizures are the most common manifestation of mesial TLE.

Association of human herpesvirus-6B with mesial temporal lobe epilepsy (MTLE)

- HHV-6B infection in astrocytes and brain specimens was investigated in resected brain material from MTLE and non-MTLE patients using PCR and immunofluorescence.
- Detected HHV-6B by PCR and immunofluorescence in 15 (62.5%) of 24 patients with MTLE, in contrast to zero of 14 with other syndromes.
- HHV-6 gp116/54/64 antigen was detected in primary cultured astrocytes from resected tissue that was HHV-6 DNA positive.
- Astrocyte cultures in vitro with HHV-6 and found a marked decrease in glutamate transporter EAAT-2 expression.

enteroviruses have been considered to be the most common cause of acute viral myocarditis
other viruses are also frequently encountered in these patients
endomyocardial biopsies (EMBs were obtained from 245 consecutive patients with DCM (median left ventricular ejection fraction, 35.0%; range, 9% to 59%).

viral genomes could be amplified by PCR from EMBs of 165 (67.4%) of the 245 DCM patients: EV=23 (9.4%), ADV=4 (1.6%), PVB19=126 (51.4%), \textbf{HHV-6=53 (21.6%)}, EBV=5 (2.0%), HCMV=2 (0.8%), including n= 45 cases (27.3%) with multiple infections

active or borderline myocarditis according to the Dallas classification did not exist in any case. Lymphocyte and macrophage infiltrates were not significantly different in virus-positive versus virus-negative patients.
Chronic fatigue syndrome (CFS) is characterized by a constellation of symptoms - complex and heterogeneous

- severe disabling fatigue and a combination of symptoms including impairments in concentration and short-term memory, sleep disturbances, and musculoskeletal pain

- patients suffering from CFS typically experience these symptoms for 6 months or longer

- many patients with CFS date the onset of their symptoms to a “viral-like” illness

- alternate medical and psychiatric causes of chronic fatiguing illness must be excluded
CFS is a real disease

- experienced by a significant number of patients whose lives have been devastated by its symptoms
- there are no diagnostic tests that can identify with certainty patients with CFS
- a definitive treatment is not available
- some patients spontaneously improve with time but most remain functionally impaired for several years
Is CFS a “real” disease?

an infectious disease?

an immunological disease?

an endocrine disease?

a neurological disease?

a cardiac disease?

a psychiatric disease?
Systemic
Lasting effects
Subsets of patients?
Evolution of the disease over time?
Use of valganciclovir in patients with elevated antibody titers against Human Herpesvirus-6 (HHV-6) and Epstein–Barr Virus (EBV) who were experiencing central nervous system dysfunction including long-standing fatigue

Andreas M. Kogelnik\textsuperscript{a}, Kristin Loomis\textsuperscript{b}, Mette Hoegh-Petersen\textsuperscript{c}, Fernando Rosso\textsuperscript{a,c}, Courtney Hischier\textsuperscript{b}, Jose G. Montoya\textsuperscript{a,c,*}

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\textsuperscript{b}HHV-6 Foundation, Santa Barbara, CA, USA
\textsuperscript{c}Palo Alto Medical Foundation Research Institute, Palo Alto, CA, USA
Change in Physical Activity and Cognitive Performance in 16 Patients Treated with Valganciclovir

Initial worsening!

(Valgancyclovir treatment begins at Year 0)
Change in Ebstein-Barr Virus Viral Capsid Antigen IgG Titer with Valganciclovir Treatment in 12 Patients

Baseline

Final

EBV VCA IgG

P <0.0018
Change in Human Herpesvirus 6 (HHV-6) IgG Titer with Valganciclovir Treatment in 12 Patients

p <0.0082
HHV-6 DNA viral load testing (whole blood) in three patients suffering of CFS and suspected of having CIHHV-6
A randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of valganciclovir (Valcyte) in patients experiencing chronic fatigue syndrome with elevated antibody titers against Human Herpesvirus-6 (HHV-6) and Epstein-Barr Virus (EBV)
¿Which of the following statements is true?

a) HHV-6 variant A has been associated to Exanthem subitum (Roseola Infantum; Sixth Disease)

b) HHV-6 variant A has been associated with febrile seizures

c) HHV-6 has not been associated with infectious mononucleosis-like syndromes

d) HHV-6 does not cause encephalitis in immunocompromised patients

e) HHV-6 variant B has been associated to Exanthem subitum (Roseola Infantum; Sixth Disease)

f) I am sorry, I did not learn