7th EUROPEAN CONFERENCE

FINAL SLIDE SET

HHV-6 update; Sept. 23rd, 2017

Mercure Sophia Antipolis Sophia Antipolis ♦ France
ECIL 7 CMV and HHV-6 update group

Members

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Road map - HHV-6

• Working group
  – Kate Ward (KNW): CIHHV-6 & HHV-6 encephalitis
  – Peter Hubacek (PH): Definitions, diagnosis of infection
  – Josh Hill (JAH): HHV-6B myelosuppression, HHV-6B pneumonitis & other possible end organ disease, HHV-6 B & acute GVHD, increased all cause mortality, antiviral drugs & immunotherapy
  Suggestions further research
  – KNW, PH, JAH joint review of draft paper & slides
Introduction

HHV-6A

? Disease

HHV-6B

1\textsuperscript{st} infection in 1\textsuperscript{st} two years of life

Exanthem subitum

Reactivation post HSCT

Encephalitis

Zerr et al., 2012; Dulery et al, 2012

Wang, 1999; Zerr, 2006

No disease has been proven with HHV-6 in patients with haematological malignancies who have not undergone HSCT
Chromosomally integrated HHV-6 (CIHHV-6)  
*Morisette, 2010; Pellett, 2012; Clark, 2016*

HHV-6A or B always subtelomeric, prevalence about 1%

**Vertical transmission**  
Inherited from mother or father  
1 HHV-6 DNA copy*/leucocyte, & every other nucleated cell type  
HHV-6 DNA also detected in hair follicles & nails (any positive suggestive of CIHHV-6)

**Characteristic persistent high HHV-6 DNA level**  
Equivalent to leucocyte count in whole blood (>5.5 log_{10} copies/ml)  
100-fold lower in serum  
Variable in plasma samples

* Very rarely 2-4 copies
CIHHV-6 & disease associations

Associated with angina pectoris in a large general population screen
*Gravel, 2015*

One proven case of reactivation in vivo:
CIHHV-6A in child with SCID & haemophagocytic syndrome (HPS) pre-HSCT & HPS flare plus thrombotic microangiopathy post-HSCT
*Endo, 2014*

One possible case of reactivation in vivo:
CIHHV-6A in a patient with encephalitis post allogeneic HSCT
*Hill, 2015*

CIHHV-6 in donor or recipient associated with acute GVHD & CMV reactivation
*Hill 2017*
## Findings post-HSCT according to route of HHV-6 acquisition*

<table>
<thead>
<tr>
<th>Clinical/laboratory observations after allogeneic HSCT</th>
<th>Route of HHV-6 acquisition</th>
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<tbody>
<tr>
<td></td>
<td>Donor &amp; recipient postnatal</td>
</tr>
<tr>
<td>One HHV-6 copy/leucocyte</td>
<td>No</td>
</tr>
<tr>
<td>One HHV-6 copy/non-haematopoietic cell</td>
<td>No</td>
</tr>
<tr>
<td>HHV-6 species/prevalence</td>
<td>B/&gt;97%</td>
</tr>
<tr>
<td>Persistent HHV-6 DNA in blood</td>
<td>No</td>
</tr>
<tr>
<td>Proven HHV-6 disease</td>
<td>Yes, encephalitis</td>
</tr>
<tr>
<td>Response of HHV-6 DNA level to antivirals</td>
<td>Yes, decrease</td>
</tr>
</tbody>
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*Adapted from Ward & Clark, 2009
Definitions

• **CIHHV-6**: The viral genome has been inherited vertically and is integrated into a chromosome. HHV-6 DNA can be detected in latent form in every nucleated cell in the body.

• **HHV-6 infection (replication)**: Virus isolation by culture or detection of viral proteins or nucleic acid in any body fluid or tissue specimen. Specify source & diagnostic method. This applies to primary infection and reactivation.

• **Primary HHV-6 infection**: Detection of HHV-6 infection in an individual with no evidence of previous HHV-6 exposure. Normally this would be accompanied by HHV-6 seroconversion but HSCT recipients may not develop antibodies. Donor-derived CIHHV-6 must be excluded.
Definitions (2)

• **HHV-6 reactivation:** New detection of HHV-6 DNA in blood in an individual with evidence of previous HHV-6 exposure. Preceding primary HHV-6B infection can be assumed in individuals > 2 years old. Donor-derived CIHHV-6 must be excluded but also, in the case of relapse, recipient-derived CIHHV-6.

• **CIHHV-6 reactivation:** Reactivation of the integrated virus (HHV-6A or HHV-6B) must be confirmed by virus culture plus sequencing of the viral genome to confirm identity of the viral isolate with the integrated virus.
HHV-6 Diagnostic Testing

• Quantitative PCR that distinguishes between HHV-6A & HHV-6B DNA is recommended for diagnosis of infection.

• For a given patient, repeated HHV-6 DNA testing should be performed using the same DNA extraction method, quantitative PCR, and specimen.

• If CIHHV-6 suspected, pre-HSCT whole blood or serum or cellular samples or leftover DNA from donor and/or recipient should be tested by quantitative PCR that distinguishes between HHV-6A and HHV-6B DNA. Plasma is not recommended.

• CIHHV-6 can be confirmed if there is one copy of viral DNA/cellular genome or viral DNA in hair follicles or nails, or by fluorescent in situ hybridisation (FISH).
HHV-6 Disease: Primary HHV-6 infection vs HHV-6 reactivation after allogeneic HSCT

Only 2 cases of primary HHV-6 infection have been reported. These were accompanied by fever & rash.

*Laure, 1988; Muramatsu, 2009*

In contrast HHV-6B reactivation is common & has been firmly associated with encephalitis.

*Zerr & Ogata, 2015*
**HHV-6B reactivation after allogeneic HSCT: disease associations**

<table>
<thead>
<tr>
<th>Epidemiological associations</th>
<th>In vitro or in vivo support for causation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HHV-6B end organ disease</strong></td>
<td></td>
</tr>
<tr>
<td>Encephalitis (predominantly limbic encephalitis)</td>
<td>Strong</td>
</tr>
<tr>
<td>Non-encephalitic CNS dysfunction e.g. delirium, myelitis</td>
<td>Moderate</td>
</tr>
<tr>
<td>Myelosuppression, allograft failure</td>
<td>Moderate</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Weak</td>
</tr>
<tr>
<td><strong>Hepatitis</strong></td>
<td>Weak</td>
</tr>
<tr>
<td><strong>HHV-6B other</strong></td>
<td></td>
</tr>
<tr>
<td>Fever &amp; rash</td>
<td>Strong</td>
</tr>
<tr>
<td>Acute GVHD</td>
<td>Moderate</td>
</tr>
<tr>
<td>CMV reactivation</td>
<td>Moderate</td>
</tr>
<tr>
<td>Increased all-cause mortality</td>
<td>Weak</td>
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</tbody>
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* Adapted from Hill & Zerr, 2016
### Clinical features of HHV-6B encephalitis*

<table>
<thead>
<tr>
<th>Disease onset</th>
<th>Usually 2-6 weeks after HSCT but can be later</th>
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<tbody>
<tr>
<td>Symptoms/Signs</td>
<td>Confusion, encephalopathy, short term memory loss, SIADH, seizures, insomnia</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>Often normal. Typically but not exclusively, circumscribed, non-enhancing, hyperintense lesions in the medial temporal lobes (especially hippocampus &amp; amygdala)</td>
</tr>
<tr>
<td>CSF</td>
<td>HHV-6B DNA, +/-mild protein elevation, +/-mild lymphocytic pleocytosis</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Memory defects &amp; neuropsychological sequelae in 20-60%</td>
</tr>
<tr>
<td></td>
<td>Death due to progressive encephalitis in up to 25% of all HSCT &amp; up to 50% of cord blood recipients</td>
</tr>
</tbody>
</table>

*Adapted from Hill & Zerr, 2014*
Risk factors for HHV-6B encephalitis in HSCT

- HHV-6 reactivation coincides with or precedes disease ≥ 10,000 copies/ml in blood (whole blood, serum, or plasma) correlates with HHV-6 encephalitis
  
  *Ogata, 2013; Hill, 2012*

- Cord blood HSCT
  Major risk factor - adjusted hazard ratio 20.00 P< .001
  
  *Hill, 2012*

  Incidence 8.3% cord blood & 0.5% PBMC/bone marrow HSCT
  
  *Scheurer, 2013*

- Acute GVHD grades II-IV
  Adjusted hazard ratio 7.5 P<.001
  
  *Hill, 2012*

- Pre-engraftment syndrome
  
  *Ogata, 2015*
Diagnosis of HHV-6B encephalitis

• HHV-6B encephalitis should be based on HHV-6 DNA in CSF coinciding with acute-onset altered mental status (encephalopathy), or short term memory loss or seizures.

• CIHHV-6 in donor & recipient plus other likely infectious or non-infectious causes must be excluded.

• If CIHHV-6 is detected, evidence for CIHHV-6 reactivation in the CSF or brain is necessary to implicate CIHHV-6.
Antiviral therapy for the prevention of HHV-6B encephalitis

- Two prospective, non-randomised studies of prophylactic foscarnet (pre or post-engraftment) did not reduce HHV-6 reactivation or encephalitis
  
  Ogata, 2013; Ishiyama, 2012

- Two prospective, non-randomised studies of preemptive ganciclovir or foscarnet did not reduce HHV-6 encephalitis
  
  Ogata, 2008; Ishiyama, 2011
Prediction & prevention of HHV-6B encephalitis

• Routine screening of HHV-6 DNA in blood after HSCT is not recommended (DIIu)

• Anti-HHV-6 prophylactic or pre-emptive therapy is not recommended for the prevention of HHV-6B reactivation or encephalitis after HSCT (DIIu)
Recent data on treatment of HHV-6B encephalitis

Retrospective study of 145 Japanese HSCT recipients with HHV-6B encephalitis

- Response rates of neurological symptoms:
  - 83.8% foscarnet monotherapy
  - 71.4% ganciclovir monotherapy
    - P=0.10

- Full dose therapy better than lower dose:
  - Foscarnet 93% vs 74% P=0.044
  - Ganciclovir 84% vs 58% P=0.047

Ogata, 2017
Treatment of HHV-6B encephalitis

- Foscarnet or ganciclovir are recommended, the choice of drug being dictated by the patient’s condition (Allu)

- The recommended doses are 90mg/kg b.d. for foscarnet and 5mg/kg b.d. for ganciclovir (Allu)

- Antiviral therapy should be for at least 3 weeks & until testing demonstrates clearance of HHV-6 DNA from blood and if possible CSF (BIII)

- Combined ganciclovir & foscarnet therapy can be considered (CIII)

- Immunosuppressive medications should be reduced if possible (BIII)

- There are insufficient data on the use of cidofovir to make a recommendation
Diagnosis of HHV-6B myelosuppression after HSCT

- Possible disease must be based on failed engraftment together with HHV-6 DNA in blood or bone marrow.

- CIHHV-6 in donor & recipient plus other likely infectious or non-infectious causes must be excluded.
Other possible end-organ HHV-6 diseases

- In suspected end-organ disease, other than encephalitis or failed engraftment, tissue from the affected organ should be tested for HHV-6 infection by culture, immunohistochemistry, in situ hybridization or mRNA.

- PCR for HHV-6 DNA on tissue is not recommended for documentation of HHV-6 disease since the positive predictive value is low.

- CIHHV-6 in donor & recipient plus likely pathogens & other established causes must be excluded.
Treatment for possible HHV-6 associated diseases

• No recommendation can be made.
Areas of research – HHV-6

Improved diagnostic strategies to diagnose HHV-6B end-organ disease (RNA detection to demonstrate active replication through in situ hybridization &/or reverse transcription PCR) after HSCT.

Studies of prevention & treatment strategies for HHV-6B encephalitis using novel therapeutic approaches, including new antiviral drugs & immunotherapy.

Studies of the clinical implications of CIHHV-6 in the HSCT setting & the mechanisms by which this condition affects health outcomes.

All prospective studies on HSCT patients & health outcomes, whether primarily concerned with CIHHV-6 or not, should include HHV-6A & HHV-6B testing of donor & recipient for this condition.