
September
22th & 23th
2017
7th EUROPEAN
CONFERENCE
ON INFECTIONS IN
LEUKAEMIA
HHV-6 update
FINAL SLIDE SET
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

1^0 infection in 1^{st} two years of life

Exanthem subitum

Reactivation post HSCT

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

Encephalitis

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*

Clinical/laboratory observations after allogeneic HSCT	**Route of HHV-6 acquisition**			
	Donor & recipient postnatal	Donor CIHHV-6 /Recipient postnatal	Donor postnatal /Recipient CIHHV-6	Donor & recipient CIHHV-6
One HHV-6 copy/ leucocyte	No	Yes	No	Yes
One HHV-6 copy/ non-haematopoietic cell	No	No	Yes	Yes
HHV-6 species/ prevalence	B/>97%	A or B/ about 1%	A or B/ about 1%	A or B About 1%
Persistent HHV-6 DNA in blood	No	Yes	+/-	Yes
Proven HHV-6 disease	Yes, encephalitis	None due to CIHHV-6	None due to CIHHV-6	None due to CIHHV-6
Response of HHV-6 DNA level to antivirals	Yes, decrease	No decrease	No decrease	No decrease

**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- and/or recipient-derived CIHHV-6 must be excluded.

- *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.

Lau, 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*

	Epidemiological associations	In vitro or in vivo support for causation
HHV-6B end organ disease	Encephalitis (predominantly limbic encephalitis)	Strong
	Non-encephalitic CNS dysfunction e.g. delirium, myelitis	Moderate
	Myelosuppression, allograft failure	Moderate
	Pneumonitis	Weak
	Hepatitis	Weak
HHV-6B other	Fever & rash	Strong
	Acute GVHD	Moderate
	CMV reactivation	Moderate
	Increased all-cause mortality	Weak

* *Adapted from Hill & Zerr, 2016*

Clinical features of HHV-6B encephalitis*

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

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

These slides are open for public consultation until November 1st, 2017

Any comment, question, suggestion, should be sent by @mail to Kate Ward at :

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by Nov 2, 2017