

HHV-6/7 ENCEPHALITIS

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There are no conflicts of interest or support that may bias my presentation

HUMAN HERPESVIRUSES 6 & 7

HHV-6**A** (Variant A) ? disease

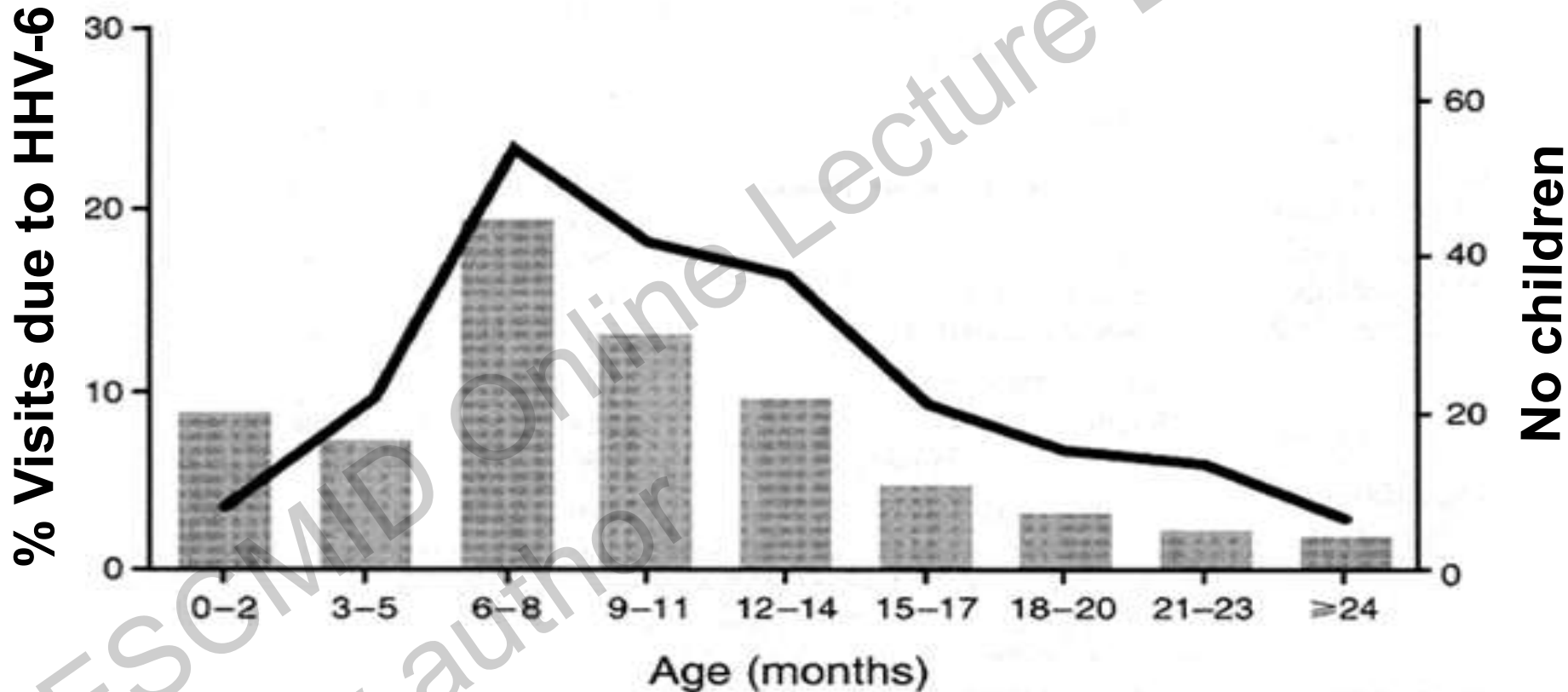
HHV-6**B** (Variant B) Exanthem subitum

HHV-7 Exanthem subitum

PREVALENCE OF HHV-6/HHV-7 INFECTIONS IN BRITISH CHILDREN IN RELATION TO AGE



CHILDREN PRESENTING WITH 1^o HHV-6^B



13% (21/160) fever & convulsions – 2 hospitalised

1^o HUMAN HERPESVIRUSES-6 & -7 (HHV-6/-7) INFECTIONS

MAY BE

IMPORTANT CAUSES OF ENCEPHALITIS IN 1ST 3 YEARS

BRITISH ISLES-WIDE SURVEY OCT 1998 – SEPT 2001

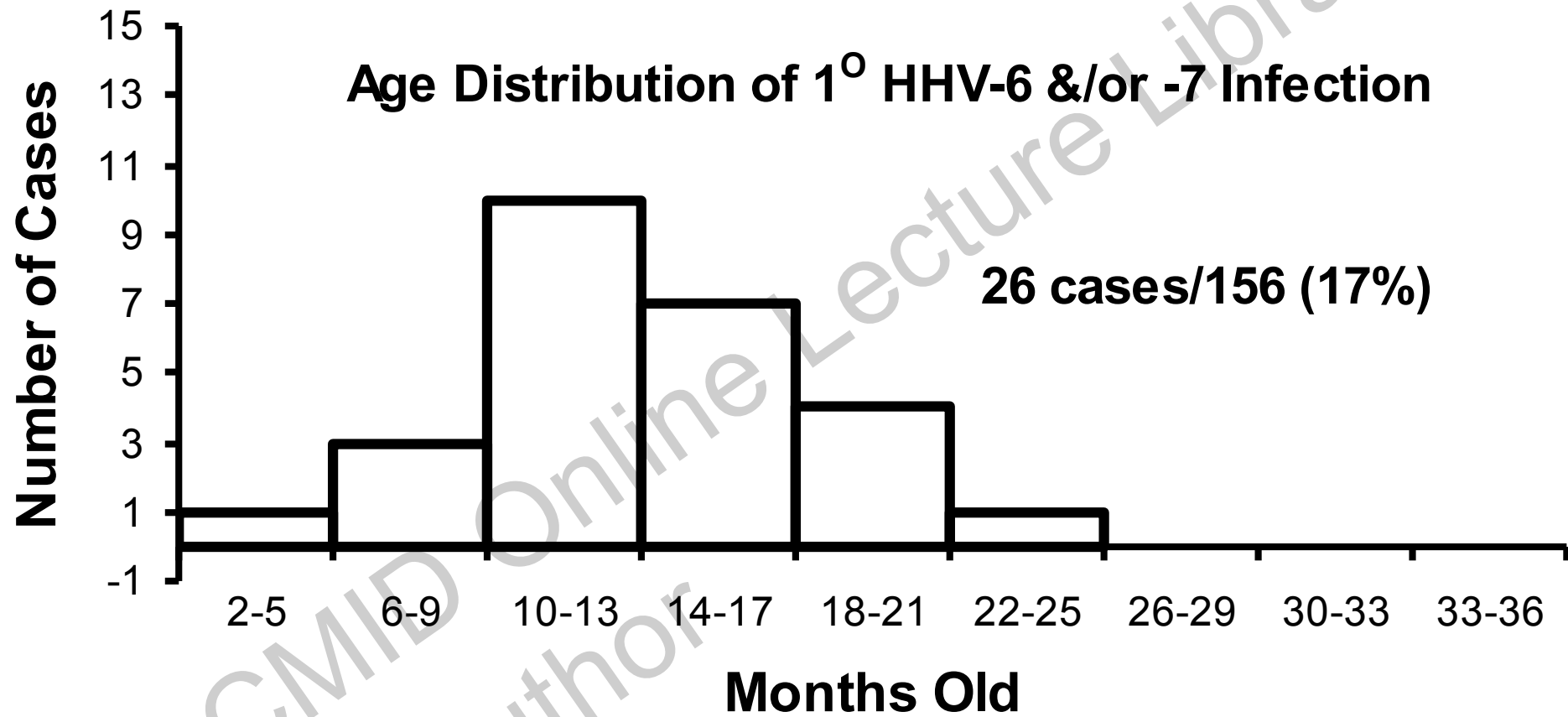
**USING THE NETWORK OF THE BRITISH PAEDIATRIC
SURVEILLANCE UNIT (BPSU)**

EXAMPLE: 1^o HHV-6^B INFECTION

Case 6 - Age: 11 months

Days	Serum		CSF
	HHV-6 IgG Titre	Avidity	DNA
0	<8	-	HHV-6 ^B
3			-
4	<8	-	HHV-6 ^B
5			HHV-6 ^B
10	2048	Low	-
55	512	High	-

BRITISH ISLES-WIDE SURVEY of ENCEPHALITIS



Note – peak at 10-13 months

COMPARISON of 1^o HHV-6 & -7 CASES

	<u>HHV-6</u> B	<u>HHV-7</u>
No. of cases	13	15
Days in hospital	9	5
CSF pleocytosis	0	2
Max temperature °C	39	38.7
No. c. convulsions		
None	1	0
≤ 30 minutes	5	2
>30 minutes		
(status epilepticus)	7	13
No. ventilated/sedated	6	6

1° HHV-6B & -7 INFECTIONS

Are equally important causes of status epilepticus with fever in the first 2 years of life

Ward, 2005; Epstein, 2012

BUT

Low level viral DNA only in CSF of 50% cases

CSF pleocytosis unusual

All patients recovered at discharge

Ward, 2005; Ward, 2007

BUT

Do these viruses cause encephalitis?

1° HHV-6B & ENCEPHALITIS/ENCEPHALOPATHY: NATIONWIDE SURVEY in JAPAN

- Incidence 5.5/100,000
- 38/77 neurological sequelae & poor prognosis
- HHV-6 DNA in CSF of 21 (50%)
- Pleocytosis in only 4 patients

Yoshikawa 2009

?Genetic susceptibility to acute encephalopathy

ACUTE ENCEPHALOPATHY in JAPAN

Shinohara, 2011; Hoshino, 2012; Kubota 2012; Kobayashi, 2013

- **Acute encephalopathy with biphasic seizures & late reduced diffusion**
- **a.k.a. febrile status epilepticus followed by recurrent seizures & encephalopathy**
- **Highest incidence in infancy**
- **Neurological sequelae common**
- **Commonly triggered by 1^o HHV-6^B infection**
- **Linked to thermolabile carnitine palmitoyltransferase 2**

CONCLUSIONS – YOUNG CHILDREN

HHV-6/7 status	CNS disease	Rx antiviral
1^o HHV-6^B/7 infection	Complex febrile seizures/status epilepticus/acute encephalopathy	No??
	?? encephalitis	???
1^o HHV-6^A infection	???	???

DELAYED 1^o HHV-7 INFECTION - 19 YEAR OLD WITH ENCEPHALITIS & FLACCID PARALYSIS

Days	Serum				CSF*
	HHV-6 IgG		HHV-7 IgG		HHV-6/7
	Titre	Avidity	Titre	Avidity	DNA
2					-/+
5	16,384	High	2,048	Low	
14	8,192	High	4,096	Low	

* 63 lymphocytes, 2 neutrophils x 10⁶/l, protein 0.8g/l;
 HSV, VZV & enterovirus negative

Ward, 2002

HHV-7 & ENCEPHALITIS IN CHILDREN: A 14 YEAR SURVEY

- 1998 – 2011: 159 encephalitis cases aged 6-17 yrs
- Diagnostic workup included CSF test for HHV-7 DNA
- 2 adolescents with delayed primary HHV-7 infection
- 2/159 children aged 6-17 years – 1.3% (0.2-2.4*)

* 95% confidence limits

Schwarz 2014

?SIGNIFICANCE OF CSF HHV-6 DNA IN OLDER CHILDREN & ADULTS

? HHV-6 chromosomal integration (CIHHV-6)

Luppi, 1993, Torelli, 1995, Morris 1999

FISH of CIHHV-6 9q TELOMERIC

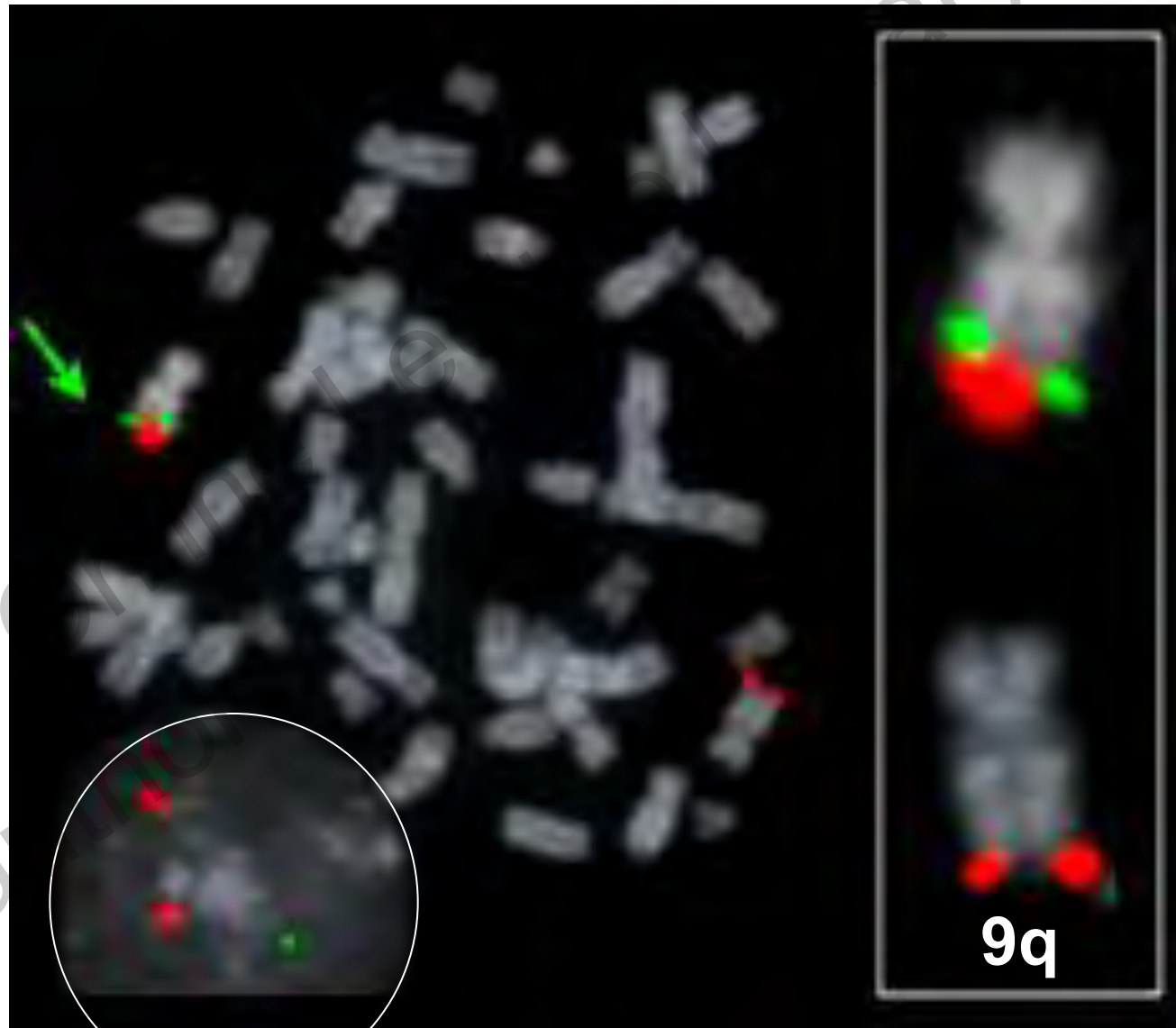
Hybridisation probe

■ HHV-6

■ 9q telomeric

Main figure
representative
dividing cell

NB Lower left
interphase
nucleus with
uncondensed
nucleic acid



CIHHV-6

- About 1% of humans - HHV-6A or B (about ¼ A)
- Always telomeric
- Vertical transmission
 - Inherited from mother or father
 - Daibata, 1998, 1999, Tanaka-Taya, 2004*
 - ~ 1 copy HHV-6 DNA/leucocyte, hair follicle or nail cells
 - Tanaka-Taya, 2004, Ward et al., 2006, Hubacek, 2009*
- Mean HHV-6 DNA concn (\log_{10} copies/ml)
 - Whole blood 7.0 (95% confidence limits 6.9-7.2)
 - Serum 5.3 (95% confidence limits 3.7-6.0)
 - Ward et al., 2006*
 - c.f. Whole blood (latent unintegrated) ≈ 2
 - Clark, 1996/2005*

HHV-6 DNA in CSF: PREVALENCE IN IMMUNOCOMPETENT – ALL AGES

Patients with CIHHV-6

UK <i>Ward, 2007</i>	8/510	1.6%
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Patients with unknown status

Sweden <i>Studahl, 1999</i>	6/407	1.5%
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UK <i>Davies, 2005</i>	9/753	1.2%
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Austria <i>Kleines, 2014</i>	4/2417	0.17%
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Patients with encephalitis

USA <i>Glaser, 2003</i>	1/320	0.3%
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USA <i>Isaacson, 2005</i>	4/1000	0.4%
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USA <i>Tavakoli 2007</i>	23/1408	1.6%
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CONCLUSIONS HHV-6/7 in OLDER IMMUNOCOMPETENT

HHV-6/7 status	CNS disease	Rx antiviral
1 ⁰ HHV-6 ^B infection	?	?
1 ⁰ HHV-7 infection	Encephalitis	?
HHV-6/7 reactivation post 1 ⁰ infection	??	??
CIHHV-6	No	No

HHV-6 & POST-TRANSPLANT LIMBIC ENCEPHALITIS (PALE)

- Uncommon 1-2% & **B >> A**
- More common after cord blood tx (8%)
- Usually 1-2 months post-HSCT
- Clinical picture - short-term memory loss, seizures, hyponatraemia, hippocampus (temporal lobe) abnormalities on MRI
- Memory defects & neuropsychological sequelae (up to 50%); mortality (up to 25%)

SIGNIFICANCE of CSF FINDINGS

- **Pleocytosis – often absent or delayed**
- **Raised protein – often absent or delayed**
- **HHV-6 DNA – level variable but usually high**
Kawamura, 2011
- **HHV-6 DNA – spectrum of disease from headache alone to delirium & neurocognitive decline to fulminant encephalitis**

Zerr, 2011; Hill, 2014

What about CIHHV-6?

CIHHV-6A Reactivated in SCID

Endo, 2014

- **One case post HSCT**
- **Definite proof for virus reactivation**
- **Presumed association with haemophagocytic syndrome (HPS) & thrombocytic microangiopathy (TMA)**
- **Can CIHHV-6B reactivate & cause encephalitis??**

Hill, 2015

2 HSCT patients with limbic encephalitis

- is HHV-6 the likely cause?

1. HHV-6 **B** DNA positive – 5.1*

No CSF pleocytosis

Copy number/cell about 200

HHV-6 encephalitis diagnosed

2. HHV-6 **A** or **B** DNA positive – 3.9*

No CSF pleocytosis

Copy number/cell about 1

Consider other causes

* Log₁₀ copies/ml

CONCLUSIONS - IMMUNOCOMPROMISED

HHV-6/7 status	CNS disease	Rx antiviral
HHV-6 A reactivation post HSCT	?	?
HHV-6 B reactivation post HSCT	Encephalitis <i>Wang, 1999; Zerr, 2001, 2002, 2006</i>	Yes - ganciclovir, foscarnet
HHV-7 reactivation post HSCT	?	?
CIHHV-6 A or B	No?	No?