Clinical manifestations associated with human herpesvirus 7 infection

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Abstract

Twenty two cases of human herpesvirus 7 (HHV-7) infection are described. HHV-7 infection occurred later than human herpesvirus 6 (HHV-6) infection and induced exanthem subitum in 47·1% of the children. HHV-7 infection was associated with exanthem subitum and the other symptoms that were observed in HHV-6 infection.

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Human herpesvirus 7 (HHV-7) is a new herpesvirus recently isolated from CD4+ T cells.[1] Recently, we reported that HHV-7 was a causal agent for exanthem subitum.[2] In this report, we examined the clinical manifestations associated with HHV-7, especially exanthem subitum.

Subjects and methods

Fifty one children 2 years of age or less were observed. Twenty four children who had not contracted HHV-7 infection were enrolled in group 1. Fifteen children with symptoms of exanthem subitum were enrolled in group 2. Twelve children who were seropositive for both human herpesvirus 6 (HHV-6) and HHV-7 were enrolled in group 3 (control group). Blood samples were collected regularly (every two to four months) or during acute and convalescent phases of fever or skin rash. An informed consent for blood samplings was obtained from their parents.

The clinical criterion used for the diagnosis of exanthem subitum was as follows: a fever higher than 37·5°C for one day or more followed by a maculopapular skin rash that appeared around the time of defervescence and disappeared within 1–4 days.

ANTIBODY ASSAY

Specific antibodies to HHV-6 and HHV-7 were determined by an indirect immunofluorescence test.[2 3] We confirmed seroconversion to HHV-6 and HHV-7, when the antibody titre was initially <1:10 and subsequently ≥1:80, or when it increased four times or more.

Results

Group 1 was followed up for three to 25 months. Seventeen of the 24 children developed antibodies to HHV-7. Among the 17 who seroconverted to HHV-7, eight (47·1%) had exanthem subitum around the time of their seroconversion. In group 2, 16 episodes of exanthem subitum were observed. Judging by the antibody response, five episodes were associated with HHV-7 infection, seven with HHV-6 infection, and four with neither. Group 3 was followed up for four to 11 months. There was no episode of exanthem subitum during the study.

From groups 1 and 2, 22 children seroconverted to HHV-7 (table 1). Twelve of 20 children's antibodies to HHV-6 that had been positive in the acute phase of HHV-7 infection increased significantly in the convalescent phase of HHV-7 infection (indicated in *italic* in table 1).

Clinical manifestations in 22 children seroconverting to HHV-7 are summarised in table 2. The mean (SD) age of the children seroconverting to HHV-7 was 17·1 (7·0) months. Cases 1 to 12 had exanthem subitum around HHV-7 seroconversion. Among these 12, only four had past histories of exanthem subitum relating to the second episode of exanthem subitum with HHV-7 infection. Two had neurological complications (that is, febrile convulsion and acute infantile hemiplegia). Cases 13 to 22 did not have exanthem subitum around HHV-7 seroconversion. Among these 10, one (case 13) had a skin rash without fever that might have been related to HHV-7 infection and nine had past histories of exanthem subitum. We summarised the other clinical characteristics of cases 1 to 12 with exanthem subitum as follows. The mean (SD) maximum body temperature was 38·9 (0·42)°C and the

Table 1 Antibody titres to HHV-6 and HHV-7 at HHV-7 seroconversion

Case No	Acute phase of illness or before seroconversion		Convalescent phase of illness or after seroconversion	
	HHV-6	HHV-7 (days)*	HHV-6	HHV-7 (days)* [days]†
1	2560	<10 (5)	5120	80 (19)
2	320	<10 (4)	*2560*	640 (21)
3	1280	<10 (−2)	2560	320 (6)
4	160	<10 (−14)	*1280*	640 (30)
5	1280	<10 (3)	*10240*	640 (30)
6	2560	<10 (−7)	*10240*	320 (6)
7	640	<10 (4)	*20480*	640 (11)
8	2560	80 (5)	5120	1280 (21)
9	640	<10 (5)	40	160 (19)
10	320	<10 (2)	320	320 (90)
11	<10	<10 (5)	<10	640 (20)
12	<10	<10 (3)	<10	320 (19)
13	640	20 (3)	*5120*	640 (20)
14	2560	<10	*10240*	320 [120]
15	5120	<10	2560	160 [82]
16	640	<10	*2560*	160 [4]
17	2560	<10	*20480*	640 [196]
18	10240	<10	5120	320 [145]
19	1280	80	*10240*	2560 [57]
20	640	<10	*5120*	1280 [29]
21	80	<10	*320*	320 [400]
22	2560	<10	1280	160 [39]

*Indicates the days after the onset of exanthem subitum or skin rash.
†Indicates the interval in days between blood samplings.

Table 2 Clinical manifestations in children seroconverting to HHV-7

Case No	Past history of exanthem subitum*	HHV-6 antibody	Child's age at HHV-7 seroconversion (months)	Clinical symptoms
1	Yes	Positive	18	Second episode of exanthem subitum*
2	No	Positive	17	Exanthem subitum*
3	Yes	Positive	12	Second episode of exanthem subitum*
4	No	Positive	10	Exanthem subitum*
5	No	Positive	17	Exanthem subitum*
6	Yes	Positive	13	Second episode of exanthem subitum*
7	No	Positive	16	Exanthem subitum*, febrile convulsion
8	No	Positive	20	Exanthem subitum*
9	No	Positive	10	Exanthem subitum*
10	Yes	Positive	31	Second episode of exanthem subitum*
11	No	Negative	18	Exanthem subitum*
12	No	Negative	13	Exanthem subitum*, acute infantile hemiplegia
13	Yes	Positive	15	Skin rash (macular)
14	Yes	Positive	10	No symptoms
15	Yes	Positive	15	No symptoms
16	Yes	Positive	7	Not clear (cough and rhinorrhea?)
17	Yes	Positive	19	Not clear (4 days fever ?)
18	Yes	Positive	23	Not clear (2 days fever ?)
19	Yes	Positive	38	Not clear (macular skin rash ?)
20	Yes	Positive	16	Not clear (2 days fever ?)
21	No	Positive	23	Not clear
22	Yes	Positive	15	Not clear (fever ?)

*Symptoms of exanthem subitum.

mean duration of fever was 2·08 (0·76) days. The skin rash appeared 1–1·5 days after the defervescence in 58·3% of the children. Mean (SD) white cell and platelet counts were significantly lower in the acute phase (white cell count 5·5 (2·1)$\times 10^9$/l and platelet count 159 (32)$\times 10^9$/l) than in the convalescent phase (white cell count 9·2 (2·7)$\times 10^9$/l and platelet count 350 (107)$\times 10^9$/l), as determined by a paired two tail t test ($p=0·0002$ for both white cell and platelet counts).

Discussion

We detected seroconversion to HHV-7 in 22 children and believe that these 22 had primary HHV-7 infections rather than cross reactions to HHV-6. Their mean age at the time of HHV-7 seroconversion was 17·1 (7·0) months. On the other hand, the mean age at the time of HHV-6 seroconversion in 22 different children was 11·5 (4·9) months (data not shown). These results indicated that HHV-7 infection occurred significantly later than HHV-6 infection ($p=0·0042$ by an unpaired two tail t test). The incidence of exanthem subitum among children seroconverting to HHV-7 and HHV-6 was 47·1% (8/17) and 86·7% (13/15; data not shown), respectively in group 1. The difference in incidence was statistically significant ($p=0·015$ by the χ^2 test).

We did not detect obvious cross reactive antibodies between HHV-6 and HHV-7.[4 5] The antibody titres to HHV-6, however, transitionally increased when the antibodies to HHV-7 seroconverted in some children who already had antibodies to HHV-6. HHV-6 which may have been latent, may have been reactivated by the primary infection of HHV-7.

In children who had exanthem subitum with HHV-7 infection, only 33·3% had a history of exanthem subitum. However, in children who did not have exanthem subitum with HHV-7 infection, 90% had a history of exanthem subitum. This difference was statistically significant ($p=0·012$ by the Fisher's exact probability test). It is necessary to evaluate more cases to better understand the meaning of this difference.

We believe that HHV-7 infection induces exanthem subitum and the other symptoms that are observed in HHV-6 infection. Although we observed neurological complications in two children, more work needs to be done to support any relationship between HHV-7 infection and these neurological complications.

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