Clinical Features and Virological Findings in Children With Primary Human Herpesvirus 7 Infection

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ABSTRACT. *Objective.* **To elucidate clinical features of patients with primary human herpesvirus 7 (HHV-7) infection and serologic and virologic findings between HHV-7 and human herpesvirus 6 (HHV-6).**

Materials and Methods. **During a 19-month observation period, 71 infants and children (35 boys and 36 girls with a mean age of 14.5 months [range, 1 month to 48 months]) who had acute febrile respiratory illness with or without skin rash were examined clinically and virologically. Heparinized blood samples were used for isolation of HHV-6 and HHV-7 and detection of both virus DNA sequences by a nested polymerase chain reaction amplification. Both virus antibody activities were measured by an indirect immunofluorescent assay.**

Results. **HHV-7 infection was observed in 15 (6 boys and 9 girls with a mean age of 12.9 months [range, 7 months to 27 months]), 1 of 10 with upper respiratory infection and 14 (28%) of 50 with febrile exanthem, whereas HHV-6 infection was in 22 (44%) of the 50. Fever (37.5°C) was observed in all 15, with an average maximum body temperature of 38.7°C (range, 37.6°C to 39.8°C), which persisted for 2.9 days (range, 1 to 5 days). Papular, macular, or maculopapular rash was observed in 14 (93%) of the 15, which appeared on day 2.9 of fever (range, days 2 to 5) on the face, trunk, and extremities and persisted for 2.7 days (range, 1 to 5 days). A convulsive seizure that persisted for a few minutes developed in 1 patient on the first day of elevation of fever. HHV-6 antibody was demonstrated in 13 (87%), and a simultaneous significant increase to HHV-6 antibody titers was observed in 8 (53%) of the 15 during primary HHV-7 infection. HHV-7 and HHV-6 DNAs were almost always detected in mononuclear cells (MNCs) during acute and convalescent phases, whereas HHV-7 DNA was positive in some plasma samples obtained during the acute phase of the disease.**

Conclusions. **Primary HHV-7 infection occurred somewhat later than HHV-6, which was confirmed by the isolation of HHV-7 from blood and/or seroconversion to the virus. Clinical features of a virologically confirmed patient with primary HHV-7 infection were comparable with those of primary HHV-6 infection. Preexisting HHV-6 antibody increased significantly in the half of patients with primary HHV-7 infection. HHV-7 DNA was detected in peripheral blood MNCs and plasma in the acute phase and persisted in MNCs thereafter.** *Pediatrics* **1997;99(3). URL: http://www.pediatrics.org/cgi/content/full/99/3/e4;** ***human herpesvirus 7, human herpesvirus 6, exanthem subitum, roseola infantum, polymerase chain reaction.***

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ABBREVIATIONS. MNC, mononuclear cell; HHV-7, human herpesvirus 7; HHV-6, human herpesvirus 6; PCR, polymerase chain reaction; bp, base pair; ES, exanthem subitum.

Human herpesvirus 7 (HHV-7), isolated from purified and activated CD4+ T lymphocytes from the peripheral blood of a healthy individual in 1990 by Frenkel et al,[1] has been recognized as a new lymphotropic herpesvirus.[2–5] The virus was distinct from the six previously identified human herpesviruses and had limited homology to human cytomegalovirus and human herpesvirus 6 (HHV-6) by both molecular and immunological analyses.[1,2] Healthy adults frequently shed the virus into saliva,[3,4,6] and children are infected at a young age but somewhat later than when infected with HHV-6.[5,7,8] Recent reports have suggested that primary infection with HHV-7 is linked to febrile illness with or without rash that resembles exanthem subitum or roseola infantum.[9–14] However, thus far there is limited information about clinical manifestations of virologically confirmed cases. In the present study, we analyzed 15 patients with primary HHV-7 infection to clarify these points.

MATERIALS AND METHODS

Patients

The study was conducted between September 1994 and March 1996 at Fujita Health University Hospital, Akita Hospital, and Nagai Pediatric Clinic. Seventy-one infants and children (35 boys and 36 girls with a mean age of 14.5 months [range, 1 month to 48 months]) who had acute febrile upper and lower respiratory illness with or without skin rash and whose parents agreed to blood sampling more than twice were enrolled in this study. Children with bacterial diseases were excluded from the subjects. Informed consent was obtained from parents of the subjects enrolled in this study after the project was thoroughly explained. A medical history and clinical signs and symptoms were recorded every day by parents for 10 to 14 days on a special form for this project, and we checked the record every 2 to 3 days. The first blood sample was collected within 7 days of the initial visit to our outpatient clinic, and we attempted to collect the convalescent sample 1 week to 2 months later. Children with a history of immune deficiency, those taking cytotoxic or immunosuppressive drugs, and those who had received immunoglobulin were not included in this study.

Antibody Assays for HHV-7 and HHV-6

Antibody titers to HHV-7 and HHV-6 were measured by an indirect immunofluorescent assay, as described elsewhere.[5,15]

Virus Isolation and Identification

Isolation of HHV-7 and HHV-6 was performed by cocultivating peripheral blood mononuclear cells (MNCs) from the patient with

cord blood MNCs, as described elsewhere.[5,6] Virus isolation was considered positive if the following findings were present: (*1*) round large cell formation of the cultured cells, and (*2*) specific immunofluorescence staining with the monoclonal antibody to HHV-7[10] or HHV-6.[16]

Polymerase Chain Reaction (PCR) for HHV-7 and HHV-6

HHV-7 and HHV-6 DNAs were extracted from peripheral blood MNCs according to procedures reported elsewhere.[12,17] The extracted HHV-6 DNA was amplified by the nested double PCR, as described previously.[17] The outer and inner primers were made following the nucleotide sequences reported elsewhere.[18,19] The primers amplify a DNA fragment of 751 base pairs (bp) of putative large tegument protein gene. The extracted HHV-7 DNA was amplified according to procedures reported elsewhere.[2,12,17] The outer (HV7 and HV8) and inner (HV10 and HV11) primers were made following the nucleotide sequences reported by Berneman et al.[2] These primers amplify a DNA fragment of 124 bp. The specific amplification was confirmed by using proven HHV-7 strains RK[1] and JI[2] and our own isolates.[5] HHV-6 primers used did not amplify HHV-7 DNA, even at high copy number and vice versa. To avoid false-positive PCR results, disposable syringes and pipettes were used, and all reagents were assayed for the presence of HHV-7 and HHV-6 DNA sequences.

RESULTS

Blood samples (145; 72 from acute phase and 73 from convalescent phase) were obtained from 71 subjects and used for virus isolation and antibody determination. HHV-7 was isolated from 10 peripheral blood MNCs of 9 patients. Seroconversion or fourfold increase in antibody titers to HHV-7 was observed in 15 of 71. On the other hand, HHV-6 was isolated from 12 of 71, and seroconversion or fourfold increase in antibody titers to HHV-6 was observed in 22 of 71. Thus, HHV-7 infection was confirmed in 15 (6 boys and 9 girls, with a mean age of 12.9 months [range, 7 months to 27 months]), 1 of 10 with upper respiratory infection and 14 (28%) of 50 with febrile exanthem, whereas HHV-6 infection was observed in 22 (44%) of the 50 (Table 1). The results of an isolation of HHV-7 and HHV-6 from peripheral blood MNCs and antibody responses to both viruses in the 15 patients are shown in Table 2. The infection was confirmed by virus isolation in the acute stage and seroconversion to the virus in 8 (cases 1 to 8) of the 15, virus isolation and a 16-fold increase in the antibody titers in 1 (case 9), seroconversion to the virus but no virus isolation from blood in 4 (cases 10 to 13), and a greater than fourfold increase in the antibody titers but no virus isolation in 2 (cases 14 and 15). Case 6 demonstrated seroconversion to both viruses, and case 12 showed seroconversion only to HHV-7.

TABLE 1. Clinical Diagnosis and Human Herpesviruses 7 and 6 Involvement in 71 Subjects With Acute Febrile Respiratory Illness*

Clinical Diagnosis	N	HHV-7	HHV-6
Upper respiratory infection	10	1†	0
Lower respiratory infection	11	0	0
Febrile exanthem	50	14	22

* HHV-7 was isolated from 10 peripheral blood mononuclear cells obtained at the acute stage of 9 patients, and a seroconversion or ≧4-fold increase in antibody titers to HHV-7 was observed in 15 of 71. On the other hand, HHV-6 was isolated from 12 of 71 and a seroconversion or ≧4-fold increase in antibody titers to HHV-6 was observed in 22 of 71.
† Diagnosed as croup.

TABLE 2. Isolation of Human Herpesviruses 7 and 6 From Blood and Antibody Responses to the Viruses in Children With Primary Human Herpesvirus 7 Infection*

Case No.	Day of Illness†	Virus Isolation HHV-7	Antibody Response	
			HHV-7	HHV-6
1	3	+	<8	≧1024
	60	−	256	≧1024
2	3	+	<8	256
	60	−	128	≧1024
3	4	+	<8	256
	45	−	64	256
4	5	+	<8	512
	12	−	128	1024
	30	−	64	512
5	2	+	<8	64
	9	−	64	≧1024
6	4	+	<8	<8
	7	+	<8	16
	30	−	128	≧1024
	60	−	≧256	≧1024
7	4	+	<8	≧256
	13	−	32	≧256
8	2	+	<8	128
	30	−	128	512
9	7	+	8	128
	60	−	128	256
10	4	−	<8	128
	60	−	128	1024
11	3	−	<8	64
	19	−	32	≧256
12	4	−	<8	<8
	17	−	32	<8
13	4	−	<8	128
	11	−	32	≧256
14	3	−	8	≧256
	12	−	64	≧256
15	4	−	8	64
	13	−	64	≧256

* HHV-6 was not isolated from any sample listed here.
† The first day of elevation of fever was defined as day 0.

Clinical information is shown in Table 3. Clinical history of exanthem subitum (ES) was documented from 8 (53%) of the 15, and HHV-6 antibody was detected in 13 (87%) of the 15 at the acute stage of primary HHV-7 infection. A simultaneous significant increase (fourfold) in HHV-6 antibody titers was observed in 8 (53%) of the 15 during primary HHV-7 infection. Fever (37.5°C) was observed in all 15, with an average maximum body temperature of 38.7°C (range, 37.6°C to 39.8°C), which persisted for 2.9 days (range, 1 to 5 days). Skin rash was observed in 14 (93%) of the 15. If the first day of elevation of fever (37.5°C) was defined as day 0, the rash appeared on day 2.9 (range, days 2 to 5) and persisted for 2.7 days (range, 1 to 5 days). The rash appeared on only the trunk of 5 patients, on the face, trunk, and extremities of 4, on the trunk and extremities of 3, on the face and trunk of 1, and on the lower limbs of 1. The rash was papular (rubella-like) in 5, macular (measles-like) in 4, maculopapular in 4, and erythema multiforme-like in 1. One patient (case 13) developed a convulsive seizure, which persisted for a few minutes, on the first day of elevated fever.

HHV-7 and HHV-6 DNAs in peripheral blood MNCs and the plasma of 5 of the 15 with primary

TABLE 3. Main Clinical Features and History of Exanthem Subitum in Children With Primary Human Herpesvirus 7 Infection

Case No.	Age/ Gender	History of Exanthem Subitum	HHV-6 Antibody in the Acute Stage of This Episode	Fever*		Skin Rash			
				Duration (days)	Maximum (°C)	Time of Onset	Duration (days)	Sites	Type
1	10 mo/F	+	+	1	37.6	Day 3	1	Trunk, upper, and lower limbs	Papule
2	10 mo/F	−	+	2	39.3	Day 2	2	Trunk, upper, and lower limbs	Papule
3	9 mo/F	−	+	1	37.8	Day 3	2	Face, trunk, upper, and lower limbs	Papule
4	13 mo/M	+	+	4	39.4	Day 2	5	Face, trunk	Macule
5	15 mo/F	+	+	4	39.3	Day 2	5	Face, trunk upper, and lower limbs	Macule
6	8 mo/M	−	−	5	39.8	Day 5	2	Face, trunk, upper, and lower limbs	Papule
7	15 mo/F	+	+	4	38.5	Day 3	2	Trunk	Macule
8†	7 mo/M	−	+	3	38.6	. . .	. . .	. . .	. . .
9	19 mo/M	−	+	4	38.3	Day 4	3	Trunk, upper, and lower limbs	Maculopapule
10	21 mo/F	+	+	2	38.4	Day 3	2	Trunk	Maculopapule
11	12 mo/M	+	+	3	37.8	Day 3	2	Trunk	Maculopapule
12	9 mo/F	−	−	2	38.6	Day 3	3	Lower limbs	Erythema-multiforme-like
13	10 mo/M	+	+	2	39.5	Day 2	3	Trunk	Papule
14	8 mo/F	+	+	2	38.7	Day 2	3	Trunk	Macule
15	27 mo/F	−	+	4	39.5	Day 3	3	Face, trunk, upper, and lower limbs	Maculopapule

* The first day of elevation of fever was defined as day 0.
† Diagnosed as croup.

HHV-7 infection were evaluated by nested PCR (Table 4). HHV-7 DNA was detected in 11 of 13 MNCs obtained between days 2 and 60 but was not detected in two samples of case 6 obtained on days 4 and 7, whereas it was positive in 3 plasma samples obtained during the acute stage of the disease (days 2 to 4). On the other hand, HHV-6 DNA was detected in all MNC samples from the five patients, except for the day 3 sample of case 11, and in only one plasma sample on day 4 from case 6.

DISCUSSION

In the present study, 15 patients were confirmed as having primary infection with HHV-7, and 14 of them had febrile exanthem. The frequency was 28% among 50 with febrile exanthem, comparable with the frequency reported recently by others, ie, 37%[10] and 31%.[13] A larger prospective cohort study will be required to know the precise frequency of primary HHV-7 infection in patients with febrile exanthem and that of febrile exanthem among primary HHV-7 infection in childhood. As suggested elsewhere,[7,9–13,20] the present data also indicate that primary infection with HHV-7 occurs after development of ES, the primary infection with HHV-6, because 54% had a clinical history of ES and 87% had HHV-6 antibody at the acute stage of HHV-7 infection. This is supported further by the data that the mean age of the present 15 cases was 12.9 months, whereas that of 176 ES patients with primary HHV-6 infection was 7.3 months.[21]

Most of the clinical manifestations of primary HHV-7 infection observed in the present study were comparable with those of primary HHV-6 infection or ES. However, the clinical course of typical primary HHV-7 infection may be milder than that of HHV-6 infection. HHV-6-associated ES is characterized by high fever (mean, 39.4°C) lasting 4.1 days, followed by an erythematous and macular or maculopapular rash of 3.8 days' duration,[21] whereas patients with HHV-7-associated febrile exanthem had a maximum fever of 38.7°C lasting 2.9 days, followed by a skin rash of 2.9 days' duration. It is not known whether preexisting immunological memory to HHV-6 would modify the clinical course of primary HHV-7 infection, although cross-reactions of antibodies[2,8,22] and T-cell clones[23] between HHV-6 and HHV-7 were

TABLE 4. Human Herpesviruses 6 and 7 DNAs in Blood of Children With Primary Human Herpesvirus 7 Infection

Case No.	Day of Illness*	HHV-7 DNA		HHV-6 DNA	
		Mononuclear Cells	Plasma	Mononuclear Cells	Plasma
4	5	+†	−	+	−
	12	+	−	+	−
	30	+	−	+	−
6	4	−†	−	+	+
	7	−†	−	+	−
	30	+	−	+	−
	60	+	−	+	−
8	2	+†	+	+	−
	30	+	−	+	−
10	4	+	+	+	−
	60	+	−	+	−
11	3	+	+	−	−
	19	+	−	+	−

* The first day of elevation of fever was defined as day 0.
† HHV-7 was isolated from the same samples.

reported. However, case 12 without immunological memory to HHV-6 had a maximum fever of 38.6°C lasting 2 days, which was milder than that of cases 4, 5, 7 to 9, and 15 with antibody to HHV-6 at the acute stage of the disease. Additional studies on a larger scale are necessary to clarify this point. Of interest is case 6, the patient of which might have simultaneous infections with HHV-7 and HHV-6. He had both viruses or virus DNA in blood from the acute stage of the disease and revealed seroconversion to both viruses, which may explain the highest fever of 39.8°C and the longest febrile period of 5 days of this patient. Case 8 showed clinical features of croup and had fever lasting 3 days without skin rash. It is likely that this patient had simultaneous infection with other viruses[24] such as parainfluenza virus, because most maternal antibodies are lost by 1 year of age. In the present study, 1 patient (7% of the 15) had a convulsive seizure during the febrile phase of the disease, as observed in primary HHV-6 infection.[17,21] It is not known whether HHV-7 invades the central nervous system, although reports of complications linked to primary HHV-7 infection are increasing.[13,25]

As reported elsewhere,[9–11,13] at least 53% of the 15 showed a significant simultaneous rise in antibody titers to HHV-6 during primary HHV-7 infection. This phenomenon will be explained by antigenic cross-reactivities[2,8,22] between both viruses or by reactivation of HHV-6 in a latent form by HHV-7.[26] Alternatively, the simultaneous rise in HHV-6 antibodies could also be explained by nonspecific B-cell response induced by HHV-7 infection. The true mechanism of this phenomenon remains to be answered. Frenkel and Roffman[27] suggested that infection by HHV-7 may have caused febrile exanthem indirectly by reactivating HHV-6 *in vivo* from latency. However, this was unlikely in our study, because HHV-6 was not isolated from blood during acute phase of the primary HHV-7 infection and case 12, the patient of which had no HHV-6 antibody, developed a skin rash. The present study also indicated that a fourfold increase in antibody titers to HHV-6 does not necessarily mean the primary infection is with HHV-6. This observation has implications for the difficulty of laboratory differentiation of febrile exanthem attributable to these two viruses. Moreover, it is important to remind us that enteroviruses and other viral agents should be carefully excluded for differentiating febrile exanthem from HHV-7 and HHV-6 infections.

PCR findings in our study are of interest. Both virus DNA sequences were frequently detected in peripheral blood MNCs obtained at the acute and convalescent stages of the disease. It is likely that the presence of HHV-7 DNA in blood on the acute stage and its persistence thereafter is attributable to the primary infection with HHV-7, as reported in HHV-6 infection.[28–30] Recent reports from other laboratories[31–33] indicated that HHV-7 DNA was detected in 66% to 83% of peripheral blood MNCs of healthy adults. It is also likely that HHV-6 DNA sequences were just persisting in blood after clinical recovery from ES, as suggested elsewhere.[28–30] Alternatively, HHV-6 DNA may be reactivated by the primary HHV-7 infection,[26] as observed in case 11 in Table 4. Blood sampling before development of the primary HHV-7 infection and quantitative analyses of both virus DNAs by PCR will be required to confirm this point. In cases 8, 10, and 11, HHV-6 DNAs were detected in both peripheral blood MNCs and plasma by PCR. The presence of HHV-7 DNA in plasma of the acute stage may suggest active primary infection with HHV-7, as observed in primary HHV-6 infection.[34] In case 6, it is difficult to interpret data from PCR and virological findings, because HHV-7 was isolated from blood, but the virus DNA was not detected in both MNCs and plasma in the acute phase of the disease. An experimental condition of the methods for detecting virus or virus DNA to compare further may be required. Alternatively, simultaneous infection with both viruses may interfere with replication of each virus, as previously suggested.[24] However, it is likely that this patient had a simultaneous infection with both viruses at this time, based on the temporal relation between HHV-7 viremia, seroconversion to both viruses, and the clinical course of febrile exanthem.

Finally, a consensus is needed on whether the term ES (roseola infantum) should be used only for clinical features by primary infection with HHV-6 or for clinical syndromes featuring febrile exanthem by various infectious agents including HHV-6, HHV-7, enteroviruses, etc.

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