MAJOR ARTICLE

Characteristics and Acquisition of Human Herpesvirus (HHV)–7 Infections in Relation to Infection with HHV-6

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Although both human herpesvirus (HHV) 6 and HHV-7 infections are ubiquitous during childhood, few acute HHV-7 infections are identified. It is unknown whether HHV-7 viremia indicates primary infection, as with HHV-6, or reactivation, and if these differ clinically. We studied, in otherwise healthy children ≤10 years old, HHV-7 and HHV-6 infections and their interaction by serologic assessment, viral isolation, and polymerase chain reaction. In children ≤24 months of age, HHV-7 infections occurred less often than HHV-6 infections ($P \leq .002$). Of 2806 samples from 2365 children ≤10 years old, 30 (1%) showed evidence of HHV-7 viremia; 23 (77%) of these were primary and 7 (23%) were reactivated HHV-7 infections. Four (13%) showed concurrent HHV-6 viremia, 2 associated with primary HHV-7 infections. The clinical manifestations of primary and reactivated HHV-7 infections were similar, except that seizures occurred more frequently in reactivated infections. These findings, previously unrecognized in otherwise healthy children, suggest that HHV-7 viremia could represent primary or reactivated infection and may be affected by the interaction between HHV-6 and HHV-7.

Human herpesvirus (HHV) 7, first isolated in 1990 by Frenkel et al. [1], is most closely related to HHV-6 genetically, antigenically, and epidemiologically [2–13]. Both HHV-7 and HHV-6 appear to cause ubiquitous infections in early childhood, yet primary HHV-7 infections are rarely recognized. Thus, little is known about the epidemiological characteristics and manifestations of acute HHV-7 infections. This may result, in part, from serologic assessment having been the most frequently used means of determining HHV-7 infection. Combining several methods to detect HHV-7 and HHV-6 infections simultaneously in a large group of children could provide a better assessment of the relative occurrences of HHV-7 and HHV-6 infection in early childhood and a better understanding of the clinical and virologic characteristics of acute HHV-7 infection.

The first aim of the present study, therefore, was to determine the epidemiology and acquisition of HHV-7 infections in comparison with those of HHV-6 infections, in a large group of children ≤24 months of age, the age at which essentially all primary HHV-6 infections have occurred [3, 4, 6, 14–16]. The second aim was to study the characteristics of acute HHV-7 infections occurring during the first decade of life that are detected by viremia, to determine (1) whether HHV-7 viremia indicates primary infection (as is generally the case with HHV-6 viremia) or reactivation, (2) whether reactivation is affected by previous or concurrent HHV-6 infection, and (3) whether the clinical manifestations differ between primary and reactivated infection.

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PATIENTS AND METHODS

Patients. Our first aim—to compare the acquisition of HHV-7 and HHV-6 infections during early childhood—was performed in children ⩽24 months old. The number of samples obtained and the proportion of samples from children with illness are described in table 1. These children presented to Golisano Children's Hospital at Strong for acute infections, noninfectious conditions, and well-child care and had blood samples collected as part of large, ongoing studies of primary HHV-6 infection, beginning in December 1989. In 1995, when we developed methods to detect HHV-7 infection, the study group was expanded by adding children through 10 years of age to the above group of children ⩽24 months of age, to characterize acute HHV-7 infections occurring in younger and older children (our second aim). The preliminary diagnoses of the children's conditions and their demographic data were obtained from the hospital listings of inpatients and outpatients. Initial evaluation of the patients was performed, as medically indicated, by outpatient personnel not involved in this study. Data on the initial illness and evaluation in patients with HHV-7 or HHV-6 infection were obtained from their medical records, families, and private physicians. Families of patients with viremia were contacted for follow-up visits after the private physician's permission was obtained. Interval histories were obtained from the medical records of the child's physician and from the families. Eight children documented in 1995 as having HHV-7 primary infection were previously reported [8] and are not included in this study. The study was approved by the University of Rochester's Research Subjects Review Board and was conducted in accordance with the human research guidelines they had in place at the time.

Laboratory assays. Laboratory assays were initially developed for HHV-6, beginning in 1989. Since HHV-7 was discovered subsequently, our HHV-7 assays were developed later, beginning in 1995.

Specimen preparation. A volume of 0.5–3 mL of whole blood was obtained in EDTA and stored at 4°C until processing within 48 h. The plasma was saved, and the peripheral blood mononuclear cells (PBMCs) were separated by density-gradient centrifugation (Histopaque; Sigma). One-fourth of the visible mononuclear cell pellet was used for viral isolation, one-fourth was digested in 50 μL of 0.5 mg/mL proteinase K (Histopaque; Sigma) for DNA polymerase chain reaction (PCR), and the remainder was saved for future RNA detection.

Viral isolation. The separated PBMCs were cocultivated and maintained with stimulated cord blood mononuclear cells and were observed for cytopathic effect for up to 3 weeks, as described elsewhere [8, 14]. Positive and negative cultures were confirmed by an indirect immunofluorescent assay using specific monoclonal antibodies for both variants of HHV-6, 2D6 for HHV-6A (gift from N. Balachandran), and C3108-103 for HHV-6B (Chemicon International). HHV-7 was similarly identified using a monoclonal antibody to HHV-7, KR-4 (gift from K. Yamanishi).

Serologic assessment. HHV-6 and HHV-7 antibody titers were determined in plasma by indirect immunofluorescent assays, as described elsewhere [8, 15]. The antigen source was a clinical HHV-6 isolate, containing both HHV-6A and HHV-6B genomes, that was grown in HSB-2 cells. For HHV-7 antibody titers, a clinical isolate of HHV-7, which was grown in SupT-1 cells, was used. Each assay included positive and negative plasma controls and uninfected cells as an antigen control. Titers ⩾4.32 $\log_2$ were considered to be positive.

DNA variant–specific PCR. HHV-6 DNA was detected in PBMCs by nested PCR with virus-specific typing with non–cross-reactive oligonucleotide probes, as reported elsewhere [15]. HHV-7 DNA was similarly detected by nested PCR, as designed by Berneman et al. [2], with external primers HV7/HV8, internal primers HV10/HV11, and HV12 probe for hybridization. For PCR amplification, for each HHV-7 primer set we used 2 μL of sample in a final volume of 25 μL containing 50 mmol/L KCl, 10 mmol/L Tris HCl (pH 9.0), 1.5 mmol/L $MgCl_2$, 0.1% Triton X-100, 1.0 U of *Taq* DNA polymerase, 0.2 mmol/L (each) dNTP (all from Promega), and 0.5 μmol/L concentrations of each primer in the appropriate primer set. The external primer amplification profile was denaturation for 5 min at 94°C, followed by 40 cycles of annealing at 60°C (45 s), extension at 72°C (45 s), and denaturation at 94°C (1 min), with 1 final cycle of annealing at 60°C (2 min) and extension at 72°C (8 min). The internal primer amplification profile was the same,

Table 1. Detection of antibody, viral isolation, and DNA evidence of human herpesvirus (HHV) 7 and HHV-6 infection in 7254 peripheral blood samples obtained from 7134 children ⩽24 months of age.

Age group	Total samples, no. (% of total)	Samples from children with illness, no. (% within age group)	Antibody detection, no. of samples		Viral isolation, no. of samples		DNA detection, no. of samples	
			HHV-7	HHV-6	HHV-7	HHV-6	HHV-7	HHV-6
0–12 months	4578 (63)	3140 (69)	205	2516	1080	3259	797	4114
13–24 months	2676 (37)	1600 (60)	59	1163	921	2023	548	2218
Total	7254	4740 (65)	264	3679	2001	5282	1345	6332

Table 2. Acquisition of human herpesvirus (HHV) 7 infections, compared with that of HHV-6 infections, during the first 2 years of life, as determined by detection of antibody, viral isolation, and DNA evidence of HHV-7 and HHV-6 infection in peripheral blood mononuclear cells.

	Antibody detection				Viral isolation				DNA detection			
	HHV-7		HHV-6		HHV-7		HHV-6		HHV-7		HHV-6	
Age group	No. tested	No. (%) positive	No. tested	No. (%) positive	No. tested	No. (%) positive	No. tested	No. (%) positive	No. tested	No. (%) positive	No. tested	No. (%) positive
<1–5 weeks	59	59 (100)	716	686 (96)	235	0 (0)	902	10 (1)	197	3 (2)	1488	143 (10[a])
6–12 weeks	48	34 (71)	544	433 (80)	155	0 (0)	604	34 (6)	150	2 (1)	779	122 (16[a])
3–6 months	53	27 (51)	476	214 (45)	250	1 (0)	667	79 (12[a])	133	13 (10)	663	197 (30[a])
7–12 months	45	8 (18)	780	408 (52[b])	440	3 (1)	1086	174 (16[a])	317	57 (18)	1184	625 (53[a])
13–24 months	59	31 (53)	1163	959 (82[c])	921	12 (1)	2023	126 (6[a])	548	145 (26)	2218	1207 (54[a])
Total (≤24 months)	264	159 (60)	3679	2700 (73[a])	2001	16 (1)	5282	423 (8)	1345	220 (16)	6332	2294 (36[a])

NOTE. PCR, polymerase chain reaction.

[a] $P < .0001$, HHV-7 vs. HHV-6.

[b] $P \leq .001$, HHV-7 vs. HHV-6.

[c] $P = .002$, HHV-7 vs. HHV-6.

with annealing at 55°C instead of 60°C. Southern blot analysis was performed using the HV12 probe 5′ end labeled with [γ-^{32}P]-ATP and 10 U of T4 polynucleotide kinase (Invitrogen). Autoradiograms containing positive and negative controls were evaluated for up to 48 h of exposure at −80°C. Both the HHV-6 and HHV-7 DNA PCR assays were specific and sensitive, detecting <10 genomic copies, and human β-globin primers were included in each PCR tube as performance controls, to confirm the presence of cellular material and the absence of inhibitors.

Statistical analysis. The probability of detecting HHV-7 DNA in PBMCs was compared with the probability of detecting HHV-6 DNA separately within different age groups (<1–5 weeks, 6–12 weeks, 3–6 months, 7–12 months, and 13–24 months), using McNemar's tests. Only samples that had results for both HHV-6 and HHV-7 were included in these analyses, and only the first sample from an individual within a defined age range was used. Similar analyses were used to compare the probabilities of detecting HHV-7 and HHV-6 antibodies and of detecting HHV-7 and HHV-6 infections by viral isolation. Analyses for the total age range included all paired HHV-6 and HHV-7 samples from all subjects. Logistic regression was used, with detection of HHV-6 DNA (or detection of antibody or viral isolation) as the dependent variable and detection of HHV-7 DNA (or detection of antibody or viral isolation) as the independent variable. Because these analyses involved multiple observations per subject, generalized estimating equations [16] were used to account for the within-subject correlation.

RESULTS

HHV-7 and HHV-6 infections during the first 2 years of life, detected by antibody. In children ≤24 months of age, the presence of HHV-7 and HHV-6 antibody was examined in 264 and 3679 serum specimens, respectively (table 2 and figure 1). Maternally derived antibody to both HHV-6 and HHV-7 were uniformly present in infants during the first week of life and remained detectable in almost all infants <6 weeks of age. The subsequent decline over time in the proportion of samples with antibody was similar for both viruses during the first 6 months of life. Thereafter, the acquisition of antibody associated with infection was significantly less frequent for HHV-7 (table 2 and figure 1). In 7–12-month-old children, 18% of samples had HHV-7 antibody, compared with 52% with HHV-6 antibody ($P < .001$).

HHV-7 and HHV-6 infections during the first 2 years of life, detected by viral isolation. HHV-7 viremia was identified infrequently during the first 2 years of life, in comparison with viremic infection with HHV-6 (table 2 and figure 1). HHV-7 viremia was not detected in any of the samples from children ≤12 weeks of age and was detected in only 0%–1% of the samples collected from children in the 3 age groups between 3 and 24 months of age (table 2). In comparison, HHV-6 infection was identified by viral isolation in 12%, 16%, and 6% of samples from children 3–6 months, 7–12 months, and 13–24 months of age, respectively (table 2 and figure 1).

HHV-7 and HHV-6 DNA detection in PBMCs. Although the presence of either HHV-7 DNA or HHV-6 DNA in PBMCs was relatively uncommon during the first 12 weeks of life, HHV-6 DNA was detected significantly more often than HHV-7 DNA in all age groups ($P < .0001$) (table 2). Of the 220 samples in which HHV-7 DNA was detected, 149 (68%) also had HHV-6 DNA, of which 98% were variant B and 2% were variant A. In comparison, of the 2294 samples in which HHV-6 DNA was detected, 97% were variant B and 3% were variant A. However, the proportion of variant A was greater in samples from children ≤12 weeks of age (9.8%) than in samples from children 3–24 months of age (2.3%).

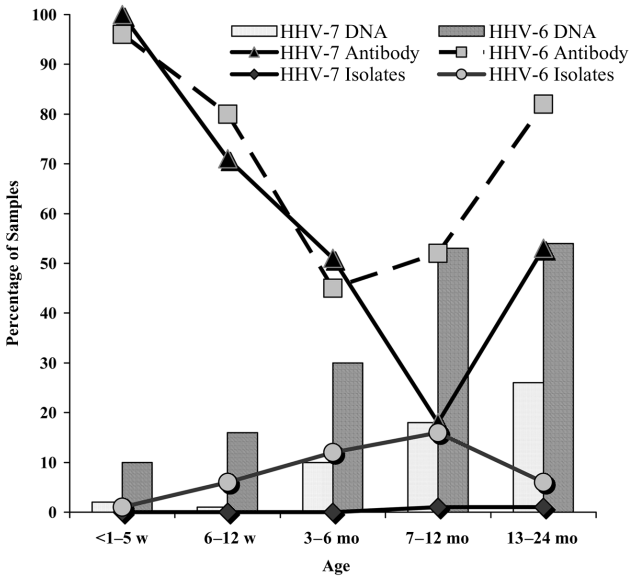

Figure 1. Percentages of peripheral blood samples from children ⩽24 months of age with antibody, viral isolation, and DNA evidence of human herpesvirus (HHV) 7 and HHV-6 infection.

Characterization of acute HHV-7 infections occurring during the first 10 years of life. Acute HHV-7 infection defined by viremia was examined in children ⩽10 years of age, to determine the cause of the viremia (primary or reactivated infection) and whether primary and reactivated HHV-7 infections differed according to age, clinical manifestations, and previous or concurrent HHV-6 infection. From 2365 children, 2806 PBMC samples were collected during 1996–2002. Of these samples, 41% were from children <2 years of age and 62% were from children with an acute illness (table 3). HHV-7 was isolated from 30 samples (1%) from among the total group collected from children within the first 10 years of life. The frequency of HHV-7 viremia was the same in samples from children <2 years of age (1%; 12 of 1149 samples) as it was in samples from children 2–10 years of age (1%; 18 of 1657 samples) (table 3).

In comparison, HHV-6 was isolated from 94 (3%) of the 2806 blood samples from this same group of children 10 years of age or younger. However, most of the samples from which HHV-6 was isolated were obtained from children within the first 2 years of life. HHV-6 viremia occurred in 7% (85/1149) of the samples from children <2 years of age, compared with 1% (9/1657) of the samples from children 2–10 years of age.

Children with HHV-7 viremic infection. The 30 children with HHV-7 viremia ranged in age from 8 to 68 months (mean, 30 months). Twenty (67%) were boys, whereas 55% of the total 2365 children examined for HHV-7 viremia were boys.

To determine the cause of HHV-7 viremia—that is, whether it resulted only from primary infection or also from reactivation—and to delineate its association with previous or concurrent HHV-6 infection, the peripheral blood samples from the 30 children with HHV-7 viremia were examined for the presence of preexisting antibodies to HHV-6 and HHV-7. As summarized in table 4, of the 30 children, 23 (77%) had no detectable HHV-7 antibody at the time of the HHV-7 viremia, indicating that the HHV-7 viremia resulted from a primary HHV-7 infection. Of these 23 primary HHV-7 infections, 15 (65%) occurred in children 2 years of age or older. The other 7 (23%) of the 30 children had HHV-7 antibody at the time of their HHV-7 viremia, suggesting reactivation of a prior HHV-7 infection (table 4). The children with antibody to HHV-7 were beyond the age when passive antibody would be present.

HHV-6 infection in children with HHV-7 viremia. Twenty-three (77%) of the 30 children with HHV-7 viremia had HHV-6 antibody, suggesting a previous infection with HHV-6 (table 4). Four (13%) of the 30 children had concurrent isolation of HHV-6. Three of these children had evidence of prior HHV-6 infection based on serologic assessment and prior HHV-6 DNA detection, and, in 2, the dual viremia occurred at the time of a primary HHV-7 infection. In the third child, both the HHV-6 and HHV-7 viremias appeared to be reactivations, since antibodies to both viruses were already present in the child's serum. The fourth child was found to have developed antibody to HHV-7 previously, and, thus, the HHV-7 viremia was a reactivation that occurred concurrently with a primary HHV-6 infection.

Clinical manifestations associated with HHV-7 viremia. Fever was documented in 26 of the children and occurred both

Table 3. Human herpesvirus (HHV) 7 and HHV-6 viremia in 2806 peripheral blood mononuclear cell samples from 2365 children ⩽10 years of age.

Age group	Total samples, no. (% of total)	Samples from children with illness, no. (% within age group)	HHV-7 viremia			HHV-6 viremia		
			No.	% of total samples	% of isolates	No.	% of total samples	% of isolates
<2 years	1149 (41)	716 (62)	12	1	40	85	7	90
2 to <4 years	865 (31)	251 (29)	14	2	47	8	1	9
4 to <6 years	547 (19)	146 (27)	4	1	13	1	0	1
6–10 years	245 (9)	53 (22)	0	0	0	0	0	0
Total	2806	1166 (42)	30	1	100	94	3	100

Table 4. Concurrent or past human herpesvirus (HHV) 7 and HHV-6 infections in 30 children with HHV-7 viremia.

Culture positive for	Antibody to HHV-7	Antibody to HHV-6	Children, no. (%)	Interpretation of HHV-7 viremia
HHV-7	−	+	15 (50.0)	Primary HHV-7, prior HHV-6 infection
HHV-7	−	−	6 (20.0)	Primary HHV-7, no prior HHV-6 infection
HHV-7	+	+	5 (16.7)	Reactivated HHV-7, prior HHV-7 and HHV-6 infection
HHV-7 and HHV-6	−	+	2 (6.7)	Primary HHV-7, plus reactivated HHV-6 viremia
HHV-7 and HHV-6	+	−	1 (3.3)	HHV-7 reactivated plus primary HHV-6 viremia
HHV-7 and HHV-6	+	+	1 (3.3)	HHV-7 and HHV-6 reactivated, both with viremia
Total, no. (%) of children	7 (23)	23 (77)	30 (100)	

in children with viremia resulting from primary HHV-7 infection and in those with previous HHV-7 infection. The temperature of 4 children was measured after administration of antipyretics or was not documented. The mean temperature was 40.1°C, with a range of 37.9°C–41.6°C. Seizures were the most frequent clinical presentation and occurred in children 12–63 months of age (table 5). The clinical findings did not otherwise appear to be related to age.

The next most frequent diagnosis assigned at the time of the initial evaluation was a nonspecific febrile illness or a febrile viral infection without localizing signs. However, 27% of the 30 children had predominantly respiratory or gastrointestinal symptoms. Six (20%) were hospitalized, primarily because of prolonged or recurrent seizures. No child received a diagnosis of roseola.

White blood cell counts at the initial presentation tended to be low for the child's age (median, 6.1×10^3 cells/μL; 25th and 75th percentiles, 4.8×10^3 and 9.2×10^3 cells/μL; all but 2 were $\leqslant 11 \times 10^3$ cells/μL). The mean proportion of neutrophils was 60%, and that of lymphocytes was 29%.

Detection of HHV-7 DNA in PBMCs after HHV-7 viremia. Thirty-eight blood samples were obtained with consent from 8 children within 7 years (mean, 30 months) of their HHV-7 viremia, to determine whether HHV-7 DNA continued to be present in their PBMCs. In all of the children, HHV-7 DNA was detected in $\geqslant 1$ of the follow-up samples, and, in all but 1 of the children, the HHV-7 DNA was consistently present in all of their follow-up samples.

DISCUSSION

Although the present study was conducted in both well and ill children being evaluated at our medical center, the frequency of the occurrence of acute HHV-7 infection in our sample of children may not be representative of that in the general population of children $\leqslant 10$ years of age. Our findings, however, do indicate that, compared with initial infection with HHV-6, infection with HHV-7 occurs later and at a slower rate. This is unexplained, since contact with HHV-7 during infancy would be expected to be at least as frequent as contact with HHV-6, if not more so. Both viruses are ubiquitous, resulting in essentially all individuals becoming infected during childhood [3–6, 17]. The saliva of previously infected individuals is the presumed major source of infection for infants. Although subsequent to initial infection, both HHV-6 and HHV-7 DNA are detected in saliva, only HHV-7 may be readily isolated from saliva. Indeed, HHV-7 is shed from saliva in up to 90% or more of adults [3–6, 17]. Furthermore, HHV-7 DNA, but not HHV-6 DNA, has been detected in breast milk samples [4, 18, 19]. A child's early exposure to HHV-7, therefore, would be expected to be more likely than exposure to HHV-6.

A more prolonged persistence of passively derived HHV-7 antibody has been suggested as a possible reason for the later onset of initial HHV-7 infection [20]. In our study, the rate of decline of passively derived IgG antibody to both viruses appeared to be similar. However, we did not examine the relative persistence of the neutralizing components of the passive antibody to each virus, which, in one study, was greater for HHV-7 in maternally transferred antibody [21].

HHV-7 was also much less likely than HHV-6 to be isolated

Table 5. Diagnoses at the time of initial evaluation of 30 children with viremic human herpesvirus (HHV) 7 infection in relation to whether HHV-7 infection was primary or reactivated.

Primary diagnosis, secondary diagnosis	HHV-7 infection type: Primary	HHV-7 infection type: Reactivated
Seizure ($n = 12$)		
Fever ($n = 10$)	9[a]	1
Fever, status epilepticus ($n = 2$)	2	0
Nonspecific febrile illness ($n = 10$)		
Cause undetermined ($n = 10$)	5	5[b]
Upper respiratory tract illness ($n = 4$)		
Fever ($n = 2$)	2	0
Fever, otitis media ($n = 2$)	1[a]	1
Gastroenteritis ($n = 4$)		
Fever, vomiting ($n = 2$)	2	0
Fever, diarrhea ($n = 2$)	2	0

NOTE. Data are no. of children.

[a] Concurrent HHV-6 viremia in 1 child.

[b] Concurrent HHV-6 viremia in 2 children.

from the blood samples of children with or without acute illnesses. The infrequent identification of acute HHV-7 viremic infection may result, in part, from HHV-7 infection being less often associated with clinical manifestations because of some cross-protection afforded by a prior HHV-6 infection. Cross-reactive antibodies between these 2 antigenically related viruses exist [4]. However, Yoshida et al. [21] found the neutralizing antibody responses to HHV-6 and HHV-7 to be specific to each virus and not cross-reactive.

Our findings suggest that, in contrast to HHV-6 viremia, an appreciable proportion of HHV-7 viremias are associated with reactivated infections, whereas HHV-6 viremia is almost exclusively associated with a primary infection [14, 15, 22]. Approximately one-fourth of the HHV-7 viremias occurred in children who had had a prior HHV-7 infection. In 2 of these children, the HHV-6 viremia developed during a primary HHV-7 infection, and the clinical manifestations, although more likely related to the primary HHV-7 infection, could have arisen partly from the concurrently reactivated HHV-6 viremia. The HHV-6 viremia in these cases could also be a laboratory reactivation phenomenon, since in vitro experiments have shown that HHV-7 inoculation can reactivate HHV-6 from PBMCs that are latently infected with HHV-6 [23, 24]. If this were the case, however, a greater number of dual viremias would be expected from the in vitro reactivation of the latent virus in the presence of a primary infection with the other virus. However, only 2 of the 23 HHV-7 viremias resulting from primary HHV-7 infection were associated with concurrent detection of HHV-6 viremia, and only 1 of the 7 reactivated HHV-7 viremias was associated with a primary HHV-6 infection.

In humans, an interaction between HHV-6 and HHV-7 has been suggested, primarily in immunocompromised patients in whom the reactivation of HHV-6 or HHV-7 is associated with the reactivation of the other virus or of a closely related β-herpesvirus, such as cytomegalovirus [25–28]. In otherwise healthy children without underlying conditions, demonstration of a similar interplay between HHV-6 and HHV-7 has been lacking. Our findings suggest that this may occur in otherwise healthy children; primary infection with one virus may result in reactivation of and concurrent viremia with the other, and even dual viremias may result from reactivations of both HHV-6 and HHV-7.

The clinical importance of the reactivations and the interaction of HHV-6 and HHV-7 detected virologically is unclear. In these children, the clinical manifestations associated with HHV-7 viremia were similar whether they were caused by a primary or reactivated infection, with the exception of seizures, which appeared to occur more frequently with a primary infection. However, the number of cases was too small to allow us to draw definitive conclusions, and additional long-term prospective studies in otherwise healthy children are needed.

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