

# Delayed Primary HHV-7 Infection and Neurologic Disease

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## KEY WORDS

HHV-7, encephalitis, Guillain-Barré syndrome, meningitis, CNS, child

## ABBREVIATIONS

CMV—cytomegalovirus  
 CNS—central nervous system  
 CSF—cerebrospinal fluid  
 EBV—Epstein-Barr virus  
 GBS—Guillain-Barré syndrome  
 HHV-7—human herpesvirus 7  
 PCR—polymerase chain reaction  
 VZV—varicella-zoster virus

Dr Schwartz carried out the chart reviews and data extraction and drafted the original manuscript; Dr Richardson conceptualized the design of the study, helped identify relevant microbiology results, reviewed each case as part of a multidisciplinary panel, and had a major role in critically reviewing and revising the manuscript; Dr Ward performed the serology testing and had a major role in critically reviewing and revising the manuscript; Mr Donaldson performed and reviewed the serology testing and reviewed and revised the final manuscript as submitted; Dr MacGregor reviewed all cases as part of a multidisciplinary team and reviewed and revised the manuscript; Dr Banwell reviewed all demyelination cases and had a major role in critically reviewing and revising the manuscript; Dr Mahant reviewed all cases as part of a multidisciplinary team and reviewed and revised the manuscript; Dr Bitnun conceptualized the study design, reviewed all cases as part of a multidisciplinary team, and had a major role in reviewing and revising the manuscript; and all authors approved the final manuscript as submitted.

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**WHAT'S KNOWN ON THIS SUBJECT:** Primary HHV-7 infection is almost universal by age 5 years and is causally associated with exanthem subitum, febrile seizures, and febrile status epilepticus. The consequences of delayed primary infection are unknown, although encephalitis has been reported in one adult.



**WHAT THIS STUDY ADDS:** Delayed primary HHV-7 infection can cause serious neurologic disease as identified in 3 adolescents, 2 with encephalitis and 1 with Guillain-Barré syndrome. Serologic tests to distinguish primary from past HHV-7 infection are imperative when HHV-7 DNA is present in CSF.

## abstract

**BACKGROUND:** Primary human herpesvirus 7 (HHV-7) infection occurs almost universally during the first 5 years of life and is rarely accompanied by central nervous system (CNS) symptoms such as febrile seizures. The present retrospective study investigated the role of primary HHV-7 infection in CNS disease in children, including adolescents.

**METHODS:** The study included all children who had neurologic disease aged younger than 18 years seen at the Hospital for Sick Children, Toronto, Canada, between April 1, 1998 and December 31, 2011, whose cerebrospinal fluid (CSF) was found by polymerase chain reaction to contain HHV-7 DNA. Where sera were available, HHV-7 IgG antibody titers and avidity were measured to differentiate primary from past infection.

**RESULTS:** HHV-7 DNA was detected in the CSF of 57 (1.9%) of the 2972 children tested. In 3 adolescents primary HHV-7 infection (low avidity IgG) was confirmed as the cause of neurologic disease, 2 who had encephalitis and 1 who had Guillain-Barré syndrome. Eighteen children had possible HHV-7 disease (no alternative cause identified and indeterminate antibody result or serum not available), 7 encephalitis, 8 meningitis, and 3 demyelinating disorders. HHV-7 disease was excluded in 36 children on the basis of past infection (high IgG avidity) and/or an alternative cause.

**CONCLUSIONS:** Primary HHV-7 infection delayed into adolescence can cause serious neurologic disease. HHV-7 DNA in CSF alone is insufficient to prove an etiologic association. Combining CSF polymerase chain reaction with serology is essential to prove primary infection when investigating HHV-7 CNS disease. *Pediatrics* 2014;133:e1541–e1547

Human herpesvirus 7 (HHV-7) is a  $\beta$ -herpesvirus that infects CD4+ T-lymphocytes, and less frequently CD8+ and immature T-cells.<sup>1</sup> Similar to all other herpesviruses, HHV-7 persists for life after primary infection in a combination of latent and lytic phases. Primary HHV-7 infection occurs predominantly in young children; ~65% have evidence of infection by 2 years of age<sup>2,3</sup> and >90% are seropositive at age 5 years.<sup>3,4</sup>

Primary HHV-7 infection is causally associated with several clinical entities in early childhood including *exanthem subitum*,<sup>5,6</sup> febrile illness without a rash,<sup>5</sup> febrile seizures,<sup>7</sup> and febrile status epilepticus.<sup>8,9</sup> The possibility of HHV-7 encephalitis in young children was first invoked by a description of 2 cases of *exanthem subitum* accompanied by encephalopathy and hemiplegia.<sup>6</sup> The consequences of delayed primary HHV-7 infection in older children are unknown. However, a single case of encephalitis in a 19-year-old man has been reported in whom primary HHV-7 infection was established on the basis of low IgG avidity in acute serum together with HHV-7 DNA in the cerebrospinal fluid (CSF).<sup>10</sup>

The present paper reports on a 14-year retrospective study in Toronto, Canada, of children (including adolescents) who had HHV-7 DNA detected in CSF. The children had a variety of neurologic syndromes, including meningitis, encephalitis, and demyelinating disorders. The objective was to investigate the relationship between primary HHV-7 infection and central nervous system (CNS) disease in these children.

## METHODS

### Study Population

All children aged younger than 18 years admitted to the Hospital for Sick Children, Toronto, Canada, presenting with neurologic disease from April 1, 1998 to December 31, 2011 whose CSF contained HHV-7 DNA, were included in the

study. Encephalitis cases were identified from the hospital's Encephalitis Registry, which has been in place since 1994 and for which inclusion criteria and investigations have previously been described.<sup>11,12</sup> All other cases were identified from the hospital's Microbiology Laboratory database. Clinical data were extracted from the hospital charts. The study was approved by the Hospital for Sick Children's Research Ethics Board.

### Herpesvirus Detection by Polymerase Chain Reaction on CSF

The range of known human herpesviruses was detected by conventional polymerase chain reaction (PCR) using 2 assays based on consensus sequences for the 9 viruses. Primers for each assay were designed to target well-conserved regions of the genomes. The first assay used primer pair HSV-P1 and HSV-P2 to amplify herpes simplex virus 1 and 2, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus 8. The second assay used primer pair VZV-P1 and VZV-P2 to amplify varicella-zoster virus (VZV) and human herpesviruses 6A, 6B, and 7.<sup>13</sup> Identification of each virus was achieved by restriction enzyme digestion of the amplicon with BamHI and BstUI, which yielded fragment sizes that were characteristic for each herpesvirus; the details have been described elsewhere.<sup>13</sup>

### HHV-7 Antibody Avidity Testing

HHV-7 serology was performed at the Virus Reference Department of the Health Protection Agency Microbiology Service Division, London, United Kingdom, using a previously described antibody avidity assay.<sup>14</sup> HHV-7 IgG antibodies were detected by indirect immunofluorescence using Sup-T1 cells infected with HHV-7. Serum samples were tested in doubling dilutions and those whose antibody titers were reduced eightfold or greater by urea were defined as having

low avidity; conversely, sera whose titers were reduced fourfold or less were defined as having high avidity.

### Serologic Classification of HHV-7 Infection

Serum samples were defined as acute if taken within 14 days of hospital admission and convalescent if taken >14 days after hospital admission.

#### Primary HHV-7 Infection

A change from seronegative in acute serum to low avidity HHV-7 IgG in convalescent serum or low avidity HHV-7 IgG in an acute serum.

#### Delayed Primary HHV-7 Infection

Primary HHV-7 infection at or beyond 6 years of age.

#### Past HHV-7 Infection

High avidity HHV-7 IgG in an acute serum reflecting a primary HHV-7 infection that occurred at least 6 weeks previously.

#### Indeterminate HHV-7 Infection

Antibody avidity could not be determined owing to insufficient antibody titer in an acute serum and no later sample available.

### Classification of Disease Etiology

Each patient's illness was classified in terms of the likelihood of disease attributable to HHV-7 and any alternative cause. This process involved a thorough case-by-case review of clinical, radiographic, laboratory, and microbiologic results by a multidisciplinary team consisting of a pediatrician, pediatric infectious disease specialist, microbiologist, and pediatric neurologist. Our criteria for HHV-7 disease were modified from those proposed by Granerod et al.<sup>15</sup>

#### Confirmed HHV-7 Disease

Neurologic symptoms, HHV-7 DNA detected in CSF by PCR, primary HHV-7

infection confirmed serologically, and no alternative cause identified.

#### Possible HHV-7 Disease

Neurologic symptoms, HHV-7 DNA detected in the CSF by PCR, indeterminate HHV-7 infection, or serum not tested and no alternative cause identified.

#### HHV-7 Neurologic Disease Excluded

HHV-7 DNA detected in the CSF by PCR, but serologic evidence of past HHV-7 infection and/or an alternative cause identified.

## RESULTS

A total of 2972 pediatric inpatients had CSF tested for HHV-7 in the 14 years covered by the study. The median age of all patients tested was 2.3 years (0–17.99 years), 65% were younger than 6 years of age and 55% of the whole cohort was male. HHV-7 DNA was detected in 57/2972 (1.9%) patients; their median age was 10.1 years (range, 1.4–17.6 years), 65% were male, and 3 were immunocompromised. Only 12/57 children (21%) were younger than 6 years of age at presentation and none had typical features of *exanthem subitum* or simple febrile seizures. The most common clinical syndromes in the 57 patients were meningitis ( $n = 18$ ; 32%), encephalitis ( $n = 15$ ; 26%), and demyelinating disorders ( $n = 12$ ; 21%). Demyelinating disorders included acute disseminated encephalomyelitis ( $n = 6$ ), optic neuritis ( $n = 3$ ), transverse myelitis ( $n = 2$ ), and cranial nerve VI palsy ( $n = 1$ ). HHV-7 DNA was also detected in the CSF of patients who had other neurologic conditions ( $n = 12$ ; 21%) including Guillain-Barré syndrome (GBS). Sera were available for HHV-7 antibody testing in 32 of the 57 children, including 13 who had both acute and convalescent sera and 19 who had only acute sera.

#### Confirmed HHV-7 Disease

There were 3 cases, all with delayed primary infection, 2 with encephalitis

and 1 with GBS. Table 1 gives clinical and laboratory features of these 3 cases together with their excluded infectious causes.

#### Possible HHV-7 Disease

Of the 18 cases, 7 had encephalitis, 8 meningitis, and 3 demyelinating disorders (Table 2). Three of the 18 children were younger than 6 years of age, 2 had meningitis and 1 had acute disseminated encephalomyelitis.

#### HHV-7 Neurologic Disease Excluded

This was the case for 6/15 (40%) patients who had encephalitis, 10/18 (55%) patients who had meningitis, 9/12 (75%) patients who had demyelinating disorders, and 11/12 (92%) patients who had other neurologic conditions (Table 3). All 3 children who had immunocompromising conditions had HHV-7 neurologic disease excluded.

#### Encephalitis

All 15 cases were in older children (median age, 10.1 years; range, 7.6–15.6). HHV-7 was excluded as the cause in 6 cases (Table 3). Of the remainder, 9 had either confirmed ( $n = 2$ ; Table 1) or possible ( $n = 7$ ; Table 2) HHV-7 encephalitis. The median age of the 9 confirmed/possible cases was 12.0 years (range, 7.6–14.9); 3 were male. Common presenting clinical manifestations included altered level of consciousness persisting for 24 hours or more (100%), fever (78%), headache (67%), and seizures (56%). CSF pleocytosis tended to be mild (median, 16; range, 0–2200  $\times 10^6/L$ ), and predominantly lymphocytic (60%–100%). Neuroimaging was normal in 7 of the 9 cases, including both of those with confirmed HHV-7 encephalitis. One of the 2 children who had confirmed HHV-7 encephalitis and 4 of the 7 who had possible HHV-7 encephalitis made full recoveries by the time of discharge. One child who had possible HHV-7 encephalitis

died. He was a 7.6-year-old child diagnosed with a seizure disorder 8 months previously. He was subsequently hospitalized with fever and intractable seizures and showed progressive brain atrophy over his month-long admission. Despite extensive investigation, no cause was identified. An autopsy was not performed.

#### Meningitis

Of the 18 cases, HHV-7 was excluded as the cause in 10 (Table 3). The median age of the 8 children who had possible HHV-7 meningitis was 9.8 years (range, 3.4–16.1) and 5 were male. Six of 8 children were 6 years of age or older (Table 2). The median CSF white blood cell count was  $235 \times 10^6/L$  (range, 44–1060); lymphocytes predominated in 50%. Common presenting clinical signs were fever (100%), headache (63%), meningism (50%), and rash (25%). All 8 made full recoveries by the time of discharge.

## DISCUSSION

Our observation that delayed primary HHV-7 infection was responsible for severe neurologic disease in 3 adolescents, 2 who had encephalitis and 1 who had GBS, strengthens the evidence for delayed primary HHV-7 infection as a cause of more severe disease than is typically observed in young infants. To our knowledge there is only 1 previous report of delayed primary HHV-7 infection and this concerned encephalitis in a 19-year-old.<sup>10</sup> The potential for severe disease with delayed primary infection is analogous to that seen with other herpesviruses, namely VZV<sup>16</sup> and EBV.<sup>17</sup>

In the 14 years covered by our study there were 260 cases of encephalitis included in the Encephalitis Registry. It is notable that of the 101 children aged 5 years or younger who had encephalitis, none had HHV-7 DNA in their CSF, supporting our hypothesis that it is delayed

**TABLE 1** Clinical and Laboratory Features of Children Who Had Neurologic Disease Attributable to Delayed Primary HHV-7 Infection

Case	Clinical Diagnosis	Age (y); Gender	HHV-7 IgG Titer		Clinical Presentation	CSF Findings			Other Investigations <sup>a</sup>	Treatment and Outcome
			Acute Serum	Convalescent Serum		WBC ( $\times 10^6/L$ )	Lymphocytes (%)	Protein (g/L)		
1	Encephalitis	14.9; F	8	64 (low avidity)	Fever, headache, lethargy, fluctuating level of consciousness, seizures, labial ulcers	<5 <sup>b</sup>	ND <sup>b</sup>	0.5 <sup>b</sup>	CT scan and MRI normal; EEG generalized slowing	Acyclovir 8 d; minor neurologic sequelae with learning disability (11 mo of follow-up)
2	Encephalitis	13; F	64 (low avidity)	ND	Headache, visual hallucinations, emotional lability, seizures	16	100	0.21	MRI normal; EEG generalized slowing and frontal intermittent $\delta$ activity	Acyclovir 8 d; full recovery (9 mo follow-up)
3	Guillain-Barré syndrome <sup>c</sup>	15.8; M	128 (low avidity)	ND <sup>d</sup>	Fever, jaw pain, bilateral facial palsies, symmetric ascending weakness	27	81	4.47	MRI: enhancement of cauda equina and cranial nerves V, VII, VIII; nerve conduction: polyneuropathy	IVIg $\times$ 2 doses; slow improvements in mobility (2 mo of follow-up)

CT, computed tomography; EEG, electroencephalography; IVIG, intravenous immunoglobulin; ND, not done.

<sup>a</sup> Microbiologic workup: Case 1: CSF HHV-7 DNA detected by PCR but PCR negative for HSV-1/2, EBV, CMV, HHV-6A and B, HHV-8, enteroviruses, *M. pneumoniae*; nasopharyngeal aspirate for respiratory virus antigen detection, throat swab for *M. pneumoniae* PCR were negative. Serology for CMV, EBV, HSV, VZV, influenza A, influenza B, syphilis, West Nile virus, *B. henselae*, measles, mumps, *M. pneumoniae* IgM, and parvovirus B19 was not suggestive of acute infection; Case 2: CSF HHV-7 DNA detected by PCR but PCR negative for HSV-1/2, EBV, CMV, HHV-6A and B, HHV-8, enteroviruses, *M. pneumoniae*; nasopharyngeal aspirate for respiratory virus antigen detection, stool for electron microscopy, and viral culture were negative. Serology for CMV, EBV, HSV, VZV, parvovirus B19, West Nile virus, flaviviruses (St Louis, eastern equine, western equine and Powassan encephalitis viruses), *M. pneumoniae*, *B. henselae*, influenza A and B, measles, mumps, and syphilis was not suggestive of acute infection; Case 3: CSF HHV-7 DNA detected by PCR but PCR negative for HSV-1/2, EBV, CMV, HHV-6A and B, HHV-8, enteroviruses, parechoviruses; nasopharyngeal aspirate for respiratory virus antigen detection, throat swab for *M. pneumoniae* PCR, and stool for bacterial culture and ova and parasite examination were negative. Serology for CMV, EBV, HSV, Lyme disease, anti-streptolysin O, rabies, West Nile virus, measles, mumps, and VZV was not suggestive of acute infection.

<sup>b</sup> A second lumbar puncture was performed within 5 days of the first; results were identical to those from the first lumbar puncture.

<sup>c</sup> This case was included in the "other neurologic condition" category.

<sup>d</sup> Serology was not performed as IVIG administered 1 day after acute serum taken.

primary HHV-7 infection that causes this condition. Of the remaining 159 children 6 years of age or older, 2 had HHV-7 encephalitis. The incidence of confirmed HHV-7 encephalitis attributable to delayed primary HHV-7 infection was therefore 1.3% (95% confidence limits,

0.2%–2.4%). However, given that there were 7 additional cases of possible HHV-7 encephalitis, the incidence may be as high as 5.7% (95% confidence limit, 3.5%–8.0%) in this older age group. As to the long-term sequelae of encephalitis after delayed primary

HHV-7 infection, it is of interest that, although 1 of our cases made a full recovery, the other went on to suffer minor learning disability (Table 1). In the previously reported case of delayed primary HHV-7 infection and encephalitis, good recovery was evident after a prolonged hospitalization.<sup>10</sup>

Ours is the first report of an association of primary HHV-7 infection with GBS. Whereas *Campylobacter jejuni* is the commonest microorganism causing this condition, herpesviruses other than HHV-7 (namely CMV and EBV) have also been reported.<sup>18</sup>

The interpretation of a positive PCR for HHV-7 DNA in CSF is complicated because the virus has been detected in normal brain tissue of 5% of adults who died of non-neurologic conditions<sup>19</sup>

**TABLE 2** Cases of Possible HHV-7 Disease in Children Who Had HHV-7 DNA in CSF ( $n = 18$ )

HHV-7 Infection (No. of Cases)	Clinical Syndrome (No. of Cases)	Alternative Cause
Indeterminate (2) <sup>a</sup>	Meningitis (2)	None identified
Not tested (16) <sup>b</sup>	Encephalitis (7)	None identified
	Meningitis (6) <sup>c</sup>	None identified
	Demyelinating conditions (3)	None identified
	ADEM (2) <sup>d</sup>	
	Optic neuritis (1)	

ADEM, acute disseminated encephalomyelitis.

<sup>a</sup> Antibody avidity could not be determined because of insufficient antibody titer in acute serum and no later sample was available.

<sup>b</sup> Serum not available.

<sup>c</sup> Two children aged younger than 6 years.

<sup>d</sup> One child aged younger than 6 years.

**TABLE 3** Causes of Disease in Children Who Had HHV-7 DNA in CSF but HHV-7 Disease Excluded ( $n = 36$ )

HHV-7 Infection (No. of Cases)	Clinical Syndrome (No. of Cases)	Cause <sup>a</sup> (No. of Cases)	Relevant Clinical Features and Microbiologic Evidence	
Past (23) <sup>b</sup>	Encephalitis (6)	VZV (1)	Disseminated VZV infection; clinical diagnosis 6 d before neurologic presentation	
		EBV (1)	Infectious mononucleosis; heterophile antibody+, VCA IgM+, VCA IgG+, IgG EBNA-	
		Anti-NMDAR antibody (1)	Compatible clinical illness; NMDAR antibodies in CSF and serum	
		None identified (3)	None	
	Meningitis (3)	Enterovirus (1) <sup>c</sup>	Enterovirus RNA detected in CSF by PCR	
		<i>M. tuberculosis</i> (1)	<i>M. tuberculosis</i> detected in CSF by PCR	
		<i>N. meningitidis</i> (1)	<i>N. meningitidis</i> isolated from blood culture	
	Demyelinating disorders (8)	ADEM (4)	Multiple sclerosis (1)	None
			None identified (3)	Influenza vaccine 3 weeks before neurologic symptom onset in 1 case; none (2)
		Optic neuritis (2)	None identified (2)	None
	Transverse myelitis (1)	None identified (1)	Upper respiratory tract infection 2 weeks before neurologic symptom onset	
	Cranial nerve VI palsy (1)	Multiple sclerosis (1)	None	
	Other conditions (6)	Fever, lymphadenopathy (1)	EBV-associated PTLD (1) <sup>c</sup>	Post cardiac transplant; high EBV load in peripheral blood (>1000 cells/10 <sup>6</sup> PBMCs)
			EBV-associated HLH (1)	EBV DNA detected by PCR in blood
		Fever, weakness, paresthesias (1)	Parvovirus B19 (1)	Parvovirus B19 DNA detected in skin biopsy
Fever, rash, arthralgia (1)		Benign intracranial hypertension (1)	None	
Fever, myalgia, headache (1)		Bipolar disorder (1)	None	
Psychosis (2)		Depression, substance abuse (1)	None	
Indeterminate (4) <sup>c</sup>	Meningitis (2)	Enterovirus (1)	Enterovirus RNA detected in CSF by PCR	
		VZV (1)	Shingles in child who had T-cell ALL; VZV detected by PCR in the CSF	
	Demyelinating disorders (1)	Transverse myelitis (1)	Multiple sclerosis (1)	None
			Other conditions (1)	Encephalopathy (1)
	Not tested (9) <sup>d</sup>	Meningitis (5)	Post IVIG (1)	Kawasaki disease, developed meningitis 48 h after IVIG administration
Enterovirus (1)			Enterovirus RNA detected in CSF by PCR	
<i>H. influenzae</i> (1) <sup>e</sup>			CHD with endocarditis; <i>H. influenzae</i> detected by 16S PCR from PA conduit vegetation	
<i>S. lugdunensis</i> (1)			VP shunt infection; <i>S. lugdunensis</i> cultured from CSF	
Other conditions (4)		Encephalopathy (2)	Neuroborreliosis (1)	Reactive <i>B. burgdorferi</i> western blot IgG and IgM in serum and IgG in CSF by EIA
			Hypovolemic shock (1) <sup>e</sup>	Hurler syndrome 10 mo post-BMT; none
Psychosis (1)	Encephalopathy (2)	RSV (1) <sup>e</sup>	Respiratory failure caused by severe pneumonia; RSV detected in NPA by DFA	
Seizure post epilepsy surgery (1)	Psychosis (1)	Sandhoff disease (1)	None	
	Seizure post epilepsy surgery (1)	Sinus venous thrombosis (1) <sup>e</sup>	None	

ADEM, acute disseminated encephalomyelitis; ALL, acute lymphoblastic leukemia; BMT, bone marrow transplant; B00P, bronchiolitis obliterans organizing pneumonia; CHD, congenital heart disease; DFA, direct fluorescent antibody; EBNA, Epstein-Barr nuclear antigen; EIA, enzyme immunoassay; HLH, hemophagocytic lymphohistiocytosis; IVIG, intravenous immune globulin; NMDAR, N-methyl D-aspartate receptor; NPA, nasopharyngeal aspirate; PA, pulmonary artery; PTLD, posttransplant lymphoproliferative disease; RSV, respiratory syncytial virus; VCA, virus capsid antigen.

<sup>a</sup> Most likely alternative cause based on chart review of initial presentation, follow-up clinic appointments, and agreed upon by consensus of authors

<sup>b</sup> High avidity HHV-7 IgG in an acute serum reflecting a primary HHV-7 infection that occurred at least 6 wk previously.

<sup>c</sup> Antibody avidity could not be determined due to insufficient antibody titer in an acute serum and no later sample available.

<sup>d</sup> Serum not available.

<sup>e</sup> Age <6 years.

and HHV-7 establishes lifelong latency within lymphocytes (cells that are present in normal CSF albeit in small

numbers). Lifelong latency carries with it the possibility of reactivation, but in our cohort, we found no serologic evi-

dence for this (ie, in subjects who had paired sera there was no rising antibody titer of high avidity; data not

shown). Indeed HHV-7 reactivation has never been causally associated with any disease. Moreover, an alternative cause was identified for 47% (27/57) of the children who had HHV-7 DNA in their CSF and 72% (23/32) of those tested serologically had evidence of past HHV-7 infection as manifested by the presence of high avidity antibody at the time of illness (Table 3). Thus, in the cases in which HHV-7 disease was excluded, the detection of HHV-7 in CSF was most likely attributable to virus in latently infected cells, or to asymptomatic reactivation.

There are several limitations to this study that arise because of its retrospective nature. Entry into the study was based on HHV-7 detection by PCR in the CSF, and therefore, with the exception of encephalitis cases (prospectively enrolled), interpretation of the data is limited because of inherent bias in the choice of subjects for testing. In addition, there can be subjectivity in retrospective disease classification, and we attempted to balance this with a detailed multidisciplinary review

of all cases. It is also possible that some cases of primary HHV-7 infection went undiagnosed, because sera were not available for testing from every case. Strengths of our study included the large number of children who had various neurologic syndromes whose CSF was tested for HHV-7, and the comprehensive nature of investigations afforded by the Encephalitis Registry.

Ever since the discovery of viruses, assigning causality to clinical diseases has presented challenges that could not be met by application of the Henle-Koch postulates.<sup>20</sup> Granerod et al<sup>15</sup> have recently described in detail the difficulties of assigning causality in CNS disease, in particular acute encephalitis, and, as originally proposed by Rivers,<sup>21</sup> describe definitions combining identification of the microbe in CSF together with an appropriate antibody response. Our definitions of HHV-7 disease were based on this concept and included serological evidence of primary infection. Additionally, because >90% of children are HHV-7 seroposi-

tive at 5 years old,<sup>3,4</sup> the likelihood of identifying primary infection in 3 adolescents coinciding with the onset of rare diseases such as encephalitis or GBS in these same 3 individuals merely by chance is extremely low, especially in the absence of an alternative cause.

## CONCLUSIONS

Our study identifies important new observations regarding HHV-7 in relation to CNS disease. First, our confirmed cases of HHV-7 disease in adolescents, 2 who had encephalitis and 1 who had GBS, demonstrate that delayed primary HHV-7 infection can cause serious neurologic illness, a point that clinicians must now keep in mind when dealing with this age group. Second, PCR applied to CSF must always be combined with antibody avidity testing of peripheral blood to confirm or exclude primary infection when evaluating the role of HHV-7 in CNS disease. The availability of a commercial assay for HHV-7 antibody avidity testing would aid in this regard.

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