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—human herpesvirus
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 had a major role in critically reviewing and revising 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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Human herpesvirus 7 (HHV-7) is a $\beta$-herpesvirus that infects CD4+ T-lymphocytes, and less frequently CD8+ and immature T-cells. 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; $\sim$65% have evidence of infection by 2 years of age and $>90\%$ are seropositive at age 5 years. Primary HHV-7 infection is causally associated with several clinical entities in early childhood including exanthem subitum, febrile illness without a rash, febrile seizures, and febrile status epilepticus. 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. 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). 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 1984 and for which inclusion criteria and investigations have previously been described. 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. Identification of each virus was achieved by restriction enzyme digestion of the amplicon with BamH1 and BstUI, which yielded fragment sizes that were characteristic for each herpesvirus; the details have been described elsewhere.

**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. 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.

**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 × 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 × 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. The potential for severe disease with delayed primary infection is analogous to that seen with other herpesviruses, namely VZV and EBV.

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
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.10

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.18

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 conditions19

### Table 1: Clinical and Laboratory Features of Children Who Had Neurologic Disease Attributable to Delayed Primary HHV-7 Infection

<table>
<thead>
<tr>
<th>Case</th>
<th>Clinical Diagnosis</th>
<th>Age (y); Gender</th>
<th>HHV-7 IgG Titer</th>
<th>Clinical Presentation</th>
<th>CSF Findings</th>
<th>Other Investigations*</th>
<th>Treatment and Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Encephalitis</td>
<td>14.9; F</td>
<td>8</td>
<td>Fever, headache, lethargy, fluctuating level of consciousness, seizures, labial ulcers</td>
<td>&lt;5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ND&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Encephalitis</td>
<td>13, F</td>
<td>64 (low avidity)</td>
<td>Headache, visual hallucinations, emotional liability, seizures</td>
<td>16</td>
<td>100</td>
<td>0.21</td>
</tr>
<tr>
<td>3</td>
<td>Guillain-Barre syndrome</td>
<td>15.8; M</td>
<td>128 (low avidity)</td>
<td>Fever, jaw pain, bilateral facial palsies, symmetric ascending weakness</td>
<td>27</td>
<td>81</td>
<td>4.47</td>
</tr>
</tbody>
</table>

SERUM not available.
<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 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 |
|--------------------------------|--------------------------------|--|}

**AEM.** 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.
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 evidence for this (ie, in subjects who had paired sera there was no rising antibody titer of high avidity; data not presented).

<table>
<thead>
<tr>
<th>HHV-7 Infection (No. of Cases)</th>
<th>Clinical Syndrome (No. of Cases)</th>
<th>Cause* (No. of Cases)</th>
<th>Relevant Clinical Features and Microbiologic Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past (23)b</td>
<td>Encephalitis (6)</td>
<td>VZV (1)</td>
<td>Disseminated VZV infection; clinical diagnosis 6 d before neurologic presentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EBV (1)</td>
<td>Infectious mononucleosis; heterophile antibody+, VCA IgM+, VCA IgG+, IgG EBNA-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anti-NMDAR antibody (1)</td>
<td>Compatible clinical illness; NMDAR antibodies in CSF and serum</td>
</tr>
<tr>
<td></td>
<td>Meningitis (3)</td>
<td>Enterovirus (1)c</td>
<td>Enterovirus RNA detected in CSF by PCR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M. tuberculosis (1)</td>
<td>M. tuberculosis detected in CSF by PCR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N. meningitidis (1)</td>
<td>N. meningitidis isolated from blood culture</td>
</tr>
<tr>
<td>Demyelinating disorders (8)</td>
<td>ADEM (4)</td>
<td>Multiple sclerosis (1)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None identified (3)</td>
<td>Influenza vaccine 3 weeks before neurologic symptom onset in 1 case; none (2)</td>
</tr>
<tr>
<td></td>
<td>Optic neuritis (2)</td>
<td>None identified (2)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Transverse myelitis (1)</td>
<td>None identified (1)</td>
<td>Upper respiratory tract infection 2 weeks before neurologic symptom onset</td>
</tr>
<tr>
<td></td>
<td>Cranial nerve VI palsy (1)</td>
<td>Multiple sclerosis (1)</td>
<td>None</td>
</tr>
<tr>
<td>Other conditions (6)</td>
<td>Fever, lymphadenopathy (1)</td>
<td>EBV-associated PTLD (1)e</td>
<td>Post cardiac transplant; high EBV load in peripheral blood (&gt;1000 cells/10⁶ PBMCs)</td>
</tr>
<tr>
<td></td>
<td>Fever, weakness, paresthesias (1)</td>
<td>EBV-associated HLH (1)</td>
<td>EBV DNA detected by PCR in blood</td>
</tr>
<tr>
<td></td>
<td>Fever, rash, arthralgia (1)</td>
<td>Parovirus B19 (1)</td>
<td>Parovirus B19 DNA detected in skin biopsy</td>
</tr>
<tr>
<td></td>
<td>Fever, myalgia, headache (1)</td>
<td>Benign intracranial hypertension (1)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Psychosis (2)</td>
<td>Bipolar disorder (1)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Depression, substance abuse (1)</td>
<td>None</td>
</tr>
<tr>
<td>Indeterminate (4)c</td>
<td>Meningitis (2)</td>
<td>Enterovirus (1)</td>
<td>Enterovirus RNA detected in CSF by PCR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VZV (1)</td>
<td>Shingles in child who had T-cell ALL; VZV detected by PCR in the CSF</td>
</tr>
<tr>
<td>Demyelinating disorders (1)</td>
<td>Transverse myelitis (1)</td>
<td>Multiple sclerosis (1)</td>
<td>None</td>
</tr>
<tr>
<td>Other conditions (1)</td>
<td>Encephalopathy (1)</td>
<td>RSV (1)</td>
<td>Respiratory failure, BOOP post-BMT; RSV and HHV6B detected on lung histopathology</td>
</tr>
<tr>
<td>Not tested (3)d</td>
<td>Meningitis (5)</td>
<td>Post IVIG (1)</td>
<td>Kawasaki disease, developed meningitis 48 h after IVIG administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enterovirus (1)</td>
<td>Enterovirus RNA detected in CSF by PCR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H. influenzae (1)c</td>
<td>CHD with endocarditis; H. influenzae detected by 16S PCR from PA conduit vegetation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S. lugdunensis (1)</td>
<td>VP shunt infection; S. lugdunensis cultured from CSF</td>
</tr>
<tr>
<td></td>
<td>Neuroborreliosis (1)</td>
<td>Reactive B. burgdorferi western blot IgG and IgM in serum and IgG in CSF by EIA</td>
<td></td>
</tr>
<tr>
<td>Other conditions (4)</td>
<td>Encephalopathy (2)</td>
<td>Hypovolemic shock (1)c</td>
<td>Hurler syndrome 10 mo post-BMT; none</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RSV (1)c</td>
<td>Respiratory failure caused by severe pneumonia; RSV detected in NPA by DFA</td>
</tr>
<tr>
<td></td>
<td>Psychosis (1)</td>
<td>Sandhoff disease (1)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Seizure post epilepsy surgery (1)</td>
<td>Sinus venous thrombosis (1)c</td>
<td>None</td>
</tr>
</tbody>
</table>

* Most likely alternative cause based on chart review of initial presentation, follow-up clinic appointments, and agreed upon by consensus of authors
b High avidity HHV-7 IgG in an acute serum reflecting a primary HHV-7 infection that occurred at least 6 wk previously.
c Antibody avidity could not be determined due to insufficient antibody titer in an acute serum and no later sample available.
d Serum not available.
e Age <6 years.
showed). 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. Granger et al have recently described in detail the difficulties of assigning causality in CNS disease, in particular acute encephalitis, and, as originally proposed by Rivers, 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 seropositive at 5 years old, 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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