Human Herpesvirus 6 and Multiple Sclerosis: Systemic Active Infections in Patients with Early Disease

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By means of immunohistochemical staining, cells actively infected with human herpesvirus 6 (HHV-6) were found in central nervous system tissues from 8 (73%) of 11 patients with definite multiple sclerosis (MS). Interestingly, 17 (90%) of 19 tissue sections showing active demyelination were positive for HHV-6-infected cells compared with only 3 (13%) of 23 tissue sections free of active disease (P<.0001). Central nervous system tissues from 2 of 28 normal persons and patients with other inflammatory demyelinating diseases were positive for HHV-6-infected cells (P<.0001), and the 2 positive cases were diagnosed as having HHV-6 leukoencephalitis. By use of a rapid culture assay, blood samples from 22 (54%) of 41 patients with definite MS were found to contain active HHV-6 infections, compared with 0 of 61 normal controls (P<.0001). No significant difference was found between HHV-6 viremia-positive and HHV-6 viremia-negative MS patients with respect to type of disease (relapsing/remitting or progressive). In contrast, patients with active HHV-6 viremia were significantly younger and had shorter durations of disease than did HHV-6 viremia-negative patients.

Work from several laboratories over the past several years has documented that human herpesvirus 6 (HHV-6) is perhaps the most neuroinvasive member of the human herpesvirus family [1]. Numerous studies have implicated CNS infection with HHV-6 as a major cause of seizures in children [2–6]. Other reports have suggested a role for HHV-6 in more severe neurological disease in children, including disseminated demyelination [7] and infarction of the basal ganglia [8]. Fatal HHV-6 encephalitis has been described in an HIV-infected infant [9].

HHV-6 encephalitis has also been documented in bone marrow transplant patients [10–17], and the encephalitis can be fatal [10, 11, 14], although it is amenable in some cases to antiviral drug therapy [12, 15]. Also, HHV-6 can cause encephalitis in liver transplant recipients [18, 19] and chronic, demyelinating myelopathy in immunologically intact adults [20]. HHV-6 frequently infects the CNS tissues of patients with AIDS [21, 22], and this infection has been proposed as the cause of some cases of AIDS dementia [21]. Recently, HHV-6 infections have been associated with focal encephalitis in immunologically intact adults and children, with clinical manifestations ranging from transient signs and symptoms of CNS dysfunction to death [23, 24].

Interestingly, when the neuropathologic changes associated with HHV-6 infections of the CNS have been analyzed, the most consistent findings have been demyelination, ranging from diffuse and extensive loss of myelin [10, 21] to sharply circumscribed foci of demyelination [20, 21, 23, 24], combined with destruction of axons within areas of the most severe pathologic changes [10].

These HHV-6–associated CNS disease patterns become especially interesting in the context of multiple sclerosis (MS), because MS is also associated with prominent demyelination combined with axonal destruction [25, 26]. By use of the molecular technique of representational difference analysis, a high rate of positivity for HHV-6 DNA in the brains of patients with MS was detected, and quantitative PCR analysis confirmed high levels of HHV-6 DNA in the CNS tissues of some patients with MS [27]. Also, earlier studies had shown that MS patients have increased titers of serum antibodies reactive with HHV-6 compared with titers in serum from normal controls [28] and that HHV-6 DNA can be detected in CSF of 14%–17% of patients with MS [29, 30]. Other workers have failed to detect HHV-6 DNA in CSF samples from patients with MS [31], although interpretation of such negative PCR data is difficult because of the frequently observed inhibition of Taq polymerase by CSF and other body fluids [32] and the low level of HHV-6–infected cells present in the CNS tissues of patients with MS (see below). Furthermore, recent studies have demonstrated that at least 50%–70% of MS patients are positive for HHV-
6–specific IgM antibodies [30, 33] and at least 30% of MS patients have HHV-6 DNA in their sera as detected by PCR [33]. Finally, we have reported the case of a young woman who died of clinically and histopathologically proven acute MS who had a dense and active HHV-6 infection of her brain and spinal cord [34]. The virus-infected cells were intimately associated with areas of active demyelination and were not seen in CNS areas free of demyelinating changes.

In the studies described here, these observations have been extended to include detailed analysis for active HHV-6 infections of CNS and lymphoid tissues and peripheral blood leukocytes from patients with MS. Preliminary CNS tissue data have been presented previously [35].

Materials and Methods

Tissue samples. Forty-two paraffin blocks of CNS tissues obtained at autopsy from 11 patients with definite MS [36] were obtained from the Rocky Mountain MS Center in Englewood, Colorado. The mean age of these patients at the time of their deaths was 54 years (age range, 37–82) 50% had relapsing/remitting disease, 30% had progressive disease, and 60% were female. The mean elapsed time from death of the patient to autopsy was 3 h (range, 2–4). By means of hematoxylin-eosin and Luxol fast blue staining of tissue sections, each tissue sample was characterized into the following histopathological categories: normal—no pathological changes present; inactive pathological changes—areas of glial scar with no active demyelination or mononuclear cell inflammation and no detectable myelin debris within phagocytes; active pathological changes—active demyelination with diffuse lesion edges and myelin debris within phagocytes and mononuclear cell inflammation. Tissue sections containing a mixture of both active and inactive disease activity were classified as active for data analysis purposes.

Paraffin-embedded spleen and lymph node tissues from 4 patients with definite MS were provided by Steve Jacobson (National Institutes of Health, Bethesda, MD). Other lymphoid tissue samples were provided by the Armed Forces Institute of Pathology/Army of America Registry of Pathology (Washington, DC). Clinical and detailed demographic information concerning these patients was not obtained.

Control CNS tissues consisted of autopsy-derived, paraffin-embedded samples from a variety of patients. Seven were from normal brains (causes of death: 1 each with liver failure secondary to alcoholic cirrhosis, leukemia, and gunshot wound and 4 with unspecified trauma). Three were from patients with subacute sclerosing panencephalitis (30-year-old woman [autopsy time, 3 h]; 19-year-old woman [unavailable]; 15-year-old man [unavailable]); 3 were from patients with progressive multifocal leukoencephalopathy (11-year-old boy [2 h]; 63-year-old man [16 h]; 55-year-old man [unavailable]); 2 were from patients with postinfectious encephalomyelitis (8-year-old girl [unavailable]; 10-year-old boy [unavailable]); 1 was from a patient with progressive rubella panencephalitis (26-year-old man [6 h]). In addition, 12 were obtained at biopsy from patients with idiopathic leukoencephalitis; the mean age of these patients was 46 years (age range, 6–75) and 67% were male. Two of them (66- and 56-year-old men) were positive for active HHV-6 in the CNS.

Mononuclear cell inflammation with prominent demyelinating changes was present in all samples except those from normal brains. The biopsy samples from idiopathic leukoencephalitis patients represent all CNS samples submitted to our laboratory for immunohistochemical analysis during the period November 1996 through April 1999. These tissues varied in size from 0.5 cm² to >1 cm².

Control lymph node tissues consisted of 4 lymph nodes obtained from organ transplant donors at the time of transplantation and of biopsy samples obtained from 3 HIV-seronegative patients for diagnosis of idiopathic lymphadenopathy. All 3 were diagnosed as idiopathic follicular hyperplasia with no evidence of malignancy.

Immunohistochemical staining of tissues. Sections of CNS and lymphoid tissue were immunohistochemically stained with 2 murine monoclonal antibodies specific for structural glycoproteins of HHV-6. The HHV-6 variant A–specific antibody (clone 2D6) is specific for an epitope encoded by the amino acid sequence KYKD-KNIF [37] within the HHV-6A gp82/gp105 protein [38] and does not react with the HHV-6 variant B homologous sequence KYYDDSIYF. This antibody was the gift of Bala Chandran (University of Kansas, Kansas City). The HHV-6 variant B–reactive antibody (clone OHV-3) is specific for an epitope encoded by the amino acid sequence NVTISRYKW [39] contained within the gH protein of HHV-6B [40] and does not react with the HHV-6 variant A homologous sequence NVTISKYKW. This antibody was obtained from Advanced Biotechnologies (Columbia, MD). An advanced BLAST search of GenBank failed to detect any human or viral proteins having amino acid sequences similar to either of these HHV-6–specific epitopes. Neither monoclonal antibody reacts with the other known herpesviruses, cytomegalovirus and HHV-7, as tested on infected human fibroblasts and mitogen-stimulated peripheral blood mononuclear cells, respectively (unpublished data).

The staining technique used was based on an alkaline phosphatase–labeled avidin–biotin complex system (Vector Laboratories, Burlingame, CA) and has been described in detail previously [9, 10, 18, 20, 21, 34, 35, 41–43].

Rapid HHV-6 culture assay. The rapid cell culture assay used in these studies has previously been used to diagnose active HHV-6 infections in bone marrow and liver transplant recipients [43–45]. In this procedure, purified blood leukocytes from the patient are cocultivated with human diploid fibroblasts. Next, the fibroblasts are stained by indirect immunofluorescence with an affinity-purified rabbit polyclonal antibody specific for the major immediate-early protein (U89/U90 [46]) of HHV-6. Positivity of a sample for an active HHV-6 infection is demonstrated by the presence of >2 fibroblasts with brilliant fluorescent staining restricted entirely to the cell nucleus. The infection in the patient’s leukocytes must be active for the infection to be transferred into the target fibroblasts. This technique has a sensitivity and specificity of 86% and 100%, respectively, compared with isolation of HHV-6 by cocultivation of patient samples with mitogen-stimulated blood mononuclear cells [45]. Positive and negative controls used in each staining run were fibroblasts exposed to mitogen-stimulated peripheral blood leukocytes from a normal donor that were HHV-6 infected and uninfected, respectively. In >400 staining runs, the uninfected control materials have never shown positive staining (unpublished data).

In the studies described here, samples of heparinized peripheral
blood from 41 patients with definite MS were obtained from patients seen at St. Luke’s Medical Center in Kansas City, Missouri. These patients represent a cross-sectional population of patients with MS. The mean age of these MS patients was 45 years (age range, 21–69). 41% had relapsing/remitting disease, 59% had progressive disease, and 76% were female. At the time the blood samples were obtained, 8 patients were receiving therapy with either IFN-β or copaxone. Only 1 of the patients had received immunosuppressive therapy (prednisone) within the previous 3 months. Receipt and analysis of specimens were blinded with respect to patient diagnosis.

Control blood samples were obtained from 13 healthy laboratory and hospital workers and 48 normal blood donors. At the time these control blood samples were obtained, none of the donors were symptomatic of any illness, and all donors were seronegative for HIV-1, HIV-2, hepatitis B virus, and human T lymphotropic virus type 1. Seropositivity for cytomegalovirus among normal controls was 41% (25/61), and 1 normal blood donor was seropositive for hepatitis C virus. The mean age of the normal controls was 50 years (range, 18–79 years).

Blood samples from liver and bone marrow transplant recipients were analyzed by the rapid HHV-6 culture assay contemporaneously with the samples from patients with MS and normal controls. One hundred eighty-three blood samples from 67 liver transplant recipients were obtained and analyzed as part of a prospective study of the clinical manifestations of HHV-6 infections done in collaboration with the VA Medical Center, Pittsburgh, and the Thomas E. Starzl Transplantation Institute of the University of Pittsburgh [47]. Forty-five blood samples were obtained from 33 bone marrow transplant recipients with disease potentially attributable to HHV-6 infections in a study of HHV-6 disease done in collaboration with the Western Pennsylvania Cancer Institute, Pittsburgh [48]. An additional 11 blood samples from bone marrow transplant recipients were obtained as diagnostic specimens from various bone marrow transplantation programs within the United States.

Results

Immunohistochemical staining of CNS tissues from patients with MS. Results are summarized in table 1, and examples of the infected cells are shown in figure 1. Cells actively infected with HHV-6 were found in the CNS tissues from 8 (73%) of the 11 patients studied. No significant differences were observed between HHV-6–positive and HHV-6–negative patients with respect to sex, age, or type of disease.

Three types of cells constituted the majority of the HHV-6–infected cells observed: microglia [34], small cells within white matter undergoing active demyelination (figure 1C), and lymphocytes within perivascular cuffs or adjacent to blood vessels (figure 1D). The appearance of the infected cells illustrated in figure 1C was similar to that of oligodendrogial cells, consistent with the demonstrated ability of HHV-6 to productively infect such cells [22, 24, 49]. Active HHV-6 infection was also observed in cells with the appearance of vascular endothelial cells. Interestingly, the ability of HHV-6 to infect endothelial cells has been demonstrated both in vitro [50] and in vivo [51]. In contrast to a previous report [27], no active HHV-6 infection of neurons was observed in any tissue. The number of HHV-6–infected cells in the tissues was low, ranging from 2 to 10 cells/cm², compared with a mean of 360 infected cells/cm² observed for 2 immunocompromised patients with HHV-6 encephalitis [10, 21]. Of importance, 17 (90%) of 19 tissue sections showing active demyelination (e.g., lymphocyte infiltrates, diffuse lesion edges, and myelin debris within phagocytes) were positive for HHV-6–infected cells. In contrast, only 3 (13%) of 23 tissue sections free of active disease were positive for HHV-6–infected cells. This association between active CNS disease and active HHV-6 infection was highly significant (P < .0001, 2-sided Fisher’s exact test). Interestingly, with respect to these 3 sections, 2 histologically normal tissue sections of CNS tissue from 1 patient contained cells actively infected with HHV-6. These infected cells were several polymorphonuclear leukocytes located within or adjacent to small or medium-sized veins. In the third tissue section free of active disease, obtained from a different patient, the HHV-6–infected cell population consisted of a single infected lymphocyte adjacent to a small blood vessel.

Immunohistochemical staining of CNS tissues from control patients. Reactivation of latent HHV-6 in response to CNS inflammation was excluded as an explanation for the active HHV-6 infections observed in the tissues from patients with MS by the demonstration that numerous CNS tissues from patients with other inflammatory demyelinating diseases were negative for HHV-6–infected cells by the same immunohistochemical staining procedures used with the tissues from the MS

<table>
<thead>
<tr>
<th>Subject group</th>
<th>Active HHV-6 status</th>
<th>Other demyelinating CNS diseases</th>
<th>Histopathologic appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MS patients (n = 11)</td>
<td>Normal controls (n = 7)</td>
<td>(n = 21)</td>
</tr>
<tr>
<td>Active</td>
<td>3 (27)</td>
<td>7 (100)</td>
<td>19 (90)</td>
</tr>
<tr>
<td>Negative</td>
<td>8 (73)</td>
<td>0</td>
<td>2 (10)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. of patients (%).

a Diagnosed as having HHV-6 leukoencephalitis.
b Calculated by means of 2-sided Fisher’s exact test.
c Compared with results from MS patients.
Figure 1. Sections of cerebral cortex from 40-year-old woman with 10-year history of multiple sclerosis. A. Tissue section stained for myelin with Luxol fast blue. Note that myelin is present only in lower left corner and that extensive area of active demyelination extends from myelinated area to vessel with prominent inflammatory cell infiltrates. B. Consecutive serial section adjacent to that shown in A and immunohistochemically stained with murine monoclonal antibody specific for gp82 glycoprotein of human herpesvirus 6 (HHV-6) variant A. Boxed areas in A and B correspond to C and D; arrowheads indicate positions of cells actively infected with HHV-6. Original magnifications, ×6.3. C and D. Higher-magnification (×25) view of portion of tissue section in B. Note small cell actively infected with HHV-6 (arrowhead in C) immediately adjacent to edge of active demyelination (A) and cells actively infected with HHV-6 (arrowheads in D) within inflammatory infiltrate surrounding blood vessel. A. Luxol fast blue with hematoxylin counterstain; B–D, vector red–alkaline phosphatase reaction product with hematoxylin counterstain.

The incidence of active HHV-6 infection in the CNS tissues of MS patients (8/11) was significantly (P < .001, 2-sided Fisher’s exact test) higher than in patients with other neurological diseases (2/21). The 2 control patients with active HHV-6 infections in CNS were diagnosed as having HHV-6 leukoencephalitis, similar to a case described previously by other investigators [24]. In addition, 7 normal brains were also negative for HHV-6–infected cells.

Immunohistochemical staining of lymphoid tissues. The demonstration of active CNS infections by HHV-6 in the CNS...
tissues of patients with MS made it of interest to determine whether the infections could also be detected in peripheral tissues of patients with MS, that is, whether the infections were systemic or restricted to the CNS. To this end, lymphoid tissues from 9 patients with definite MS were analyzed. Active HHV-6 infections were detected in tissues from 6 of them (67%). The majority of the HHV-6–infected cells were lymphocytes within periarterial sheaths. In contrast, lymph nodes from 7 normal controls were negative for HHV-6–infected cells by immunohistochemical staining ($P < .015$, 2-sided Fisher’s exact test).

**Rapid HHV-6 culture assay of blood samples from patients with MS.** Detection of cells actively infected with HHV-6 in lymphoid tissues of patients with MS suggested that infected cells might also be present in the peripheral blood of such patients. This possibility was tested by subjecting samples of peripheral blood from 41 patients with definite MS to virus isolation by a rapid culture technique. Results are shown in table 2. HHV-6 was isolated from the blood of 22 (54%) of the 41 patients. No significant differences were observed between HHV-6–positive and HHV-6–negative patients with respect to sex or type of disease. In contrast, as shown in figure 2, HHV-6–positive patients were significantly younger than HHV-6–negative patients. Similarly, the duration of disease was significantly shorter in HHV-6–positive patients than in HHV-6–negative patients (figure 3). Also, as expected, age of the patients and their duration of disease were significantly ($P < .0005$, Pearson $R$ correlation) correlated with one another. Most interestingly, as illustrated in figure 4, the incidence of positive HHV-6 viremia in patients with disease duration of $\leq 12$ years (18/24; 75%) was dramatically higher than in patients with longer durations of disease (4/17; 24%). HHV-6 was not isolated from any blood sample from 61 carefully screened healthy control subjects ($P < .0001$, 2-sided Fisher’s exact test).

**Rapid HHV-6 culture assay of blood samples from bone marrow and solid organ transplant recipients.** Finally, questions have been raised about whether active HHV-6 infections in patients with MS could be due to immunosuppressive therapies the patients might be receiving [33, 52]. As noted previously, at the time blood samples were obtained from the patients with MS for analysis by the rapid HHV-6 culture assay, only 1 patient had received potentially immunosuppressive therapy (prednisone) within the previous 3 months. We further addressed the possibility of patient immunosuppression contributing to their HHV-6 positivity by comparing the incidence of active HHV-6 infections in peripheral blood lymphocytes of patients with MS with that in peripheral blood lymphocytes from bone marrow and liver transplant recipients. In all, 239 blood samples from 105 transplant recipients were analyzed, and 38 (16%) were positive for active HHV-6 infection. This incidence was significantly ($P < .0001$) lower than the 54% positivity rate observed for peripheral blood lymphocyte samples from patients with MS.

In the course of this study, it was noted that, among patients who had blood samples analyzed at least 4 times over a period of months, the frequency of HHV-6–positive cultures was higher in patients with MS than in liver transplant recipients. Of 14 liver transplant recipients, 9 (64%) had only 1 HHV-6–positive culture. In comparison, all (5/5) of the patients with MS had $>1$ HHV-6–positive culture. This increased positivity

### Table 2.

Detection of active human herpesvirus 6 (HHV-6) infections in peripheral blood leukocytes of patients with multiple sclerosis (MS) and controls according to various demographic parameters.

<table>
<thead>
<tr>
<th>Active HHV-6 statusa</th>
<th>Subject group</th>
<th>Disease type</th>
<th>Sex</th>
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<tbody>
<tr>
<td></td>
<td>MS patients ($n = 41$)</td>
<td>Normal controls ($n = 61$)</td>
<td>Age at time of testing</td>
</tr>
<tr>
<td>Negative</td>
<td>19 (46)</td>
<td>61 (100)</td>
<td>49.6 ± 9.7</td>
</tr>
<tr>
<td>Positive</td>
<td>22 (54)</td>
<td>0</td>
<td>41.5 ± 12.3</td>
</tr>
<tr>
<td>$P$</td>
<td>$&lt; .0001$</td>
<td>$&lt; .0001$</td>
<td>$&lt; .03$</td>
</tr>
</tbody>
</table>

**Note.** Data are no. (%) or mean years ± SD, as appropriate. NS, not significant.

a Determined by rapid culture assay.
b Progressive disease, either primary or secondary, at time of testing.
c Determined by 2-sided Fisher’s exact test.
d Determined by Mann-Whitney test.

Figure 2. Relationship between positivity for active human herpesvirus 6 (HHV-6) viremia and patient age at time of testing in patients with definite multiple sclerosis. Large horizontal bars, means; smaller horizontal bars, 95% confidence intervals. Mean age of patients with active HHV-6 viremia (41.5 years) was significantly ($P < .03$, Mann-Whitney test) less than that of HHV-6 viremia–negative patients (49.6 years).
Discussion

The studies described here used 2 independent technologies to demonstrate that the majority of patients with definite MS have disseminated, active infections with HHV-6 involving their CNS and lymphoid tissues as well as their peripheral blood. That the active HHV-6 infections in the CNS tissues of these patients play a causal role in the pathogenesis of MS is supported by 4 sets of observations. First, active HHV-6 infections are associated with other demyelinating diseases of the CNS [7, 10, 20, 21, 24]. Second, a strong and close relationship was observed here between the presence of cells actively infected with HHV-6 and active demyelination. Third, other investigators have demonstrated a relationship between HHV-6 and MS (summarized in table 3). Fourth, the high degree of neuro-invasiveness of HHV-6 [1–24, 27, 34, 72] combined with the innate ability of herpesviruses to establish latent infections capable of reactivations support the possibility that some of the exacerbations of MS may reflect periodic reactivation of latent HHV-6 in CNS tissues or peripheral blood of the patients.

Numerous previous studies have investigated the possible role of HHV-6 in MS with contradictory results. The results of these investigations can be best interpreted in the context of the diagnostic technology used. A summary of these studies is shown in table 3. When technologies were used that could not distinguish between active and latent HHV-6 infections (PCR analysis of blood leukocytes, CSF-containing cells, or CNS tissue), no differences were noted between samples from patients with MS and control subjects. In contrast, when diagnostic technologies were used that are restricted to the detection of active HHV-6 infections (PCR analysis of acellular specimens, detection of HHV-6-specific IgM antibodies, or immunohistochemical staining of CNS tissues), a strong relationship between HHV-6 and the pathogenesis of MS was reproducibly observed.

The mechanisms by which HHV-6 infection causes the characteristic CNS pathology of MS are likely to be complex. The ability of HHV-6 to infect and destroy oligodendrocytes has been proven by electron microscopy in a case of HHV-6 leucoencephalitis [24] and by investigations in cell culture [49]. Thus, HHV-6 infection may be of importance in the direct destruction of oligodendrocytes and other glial cells in the CNS of patients with MS. HHV-6 has been shown to be capable of productively infecting numerous cell types, including several hematopoietic cell lines [73, 74], glioblastoma cells [74], human astrocytes [75], and human diploid fibroblasts [76]. However, the low number of HHV-6–infected cells in the CNS tissues of patients with MS compared with that observed in the brains of immunocompromised patients with HHV-6 encephalitis [10, 21] suggests that not only direct oligodendrocyte destruction by the virus but also other indirect mechanisms may be involved in the disease pathogenesis.

TNF-α may function as an indirect mediator of HHV-6 damage to the CNS of MS patients. TNF-α has been proposed as a mediator of demyelination in MS [77], TNF-α–producing cells have been identified in MS lesions [78], and the expression of

![Figure 3](https://academic.oup.com/cid/article-abstract/31/4/894/375318/1)

Figure 3. Relationship between positivity for active human herpesvirus 6 (HHV-6) viremia and duration of disease in patients with definite multiple sclerosis. Large horizontal bars, means; smaller horizontal bars, 95% confidence intervals. Mean duration for viremia-positive patients (7.5 years) was significantly (P < .0001) shorter than for viremia-negative patients (15.6 years).

![Figure 4](https://academic.oup.com/cid/article-abstract/31/4/894/375318/2)

Figure 4. Percentage of patients with definite multiple sclerosis who were positive for active human herpesvirus 6 (HHV-6) viremia expressed as function of disease duration. Positivity rate for patients with disease durations of ≤12 years (18/24; 75%) was significantly (P < .005, 2-sided Fisher’s exact test) higher than that for patients with disease durations of >12 years (4/17; 24%).
HHV-6 viremia in MS patients with disease durations of 10–12 years. This suggests that a change in the
peripheral blood and perhaps the CNS.

A second indirect mechanism of demyelinative disease associated with HHV-6 infections of the CNS may be the induction of autoimmunity against CNS tissues. MS is widely considered to have an autoimmune component in its pathogenesis [86, 87]. A potentially important mechanism for such an autoimmune reaction may be molecular mimicry [88]. One or more antigenic determinants on an HHV-6-encoded protein may cross-react with a determinant of a myelin-associated protein, such as myelin basic protein [89] or myelin oligodendrocyte glycoprotein [90].

The finding that active HHV-6 infections can be identified by relatively noninvasive means (e.g., rapid HHV-6 culture) in patients with MS has important implications with respect to therapeutic intervention in those patients. The effectiveness of an antiviral drug on the suppression of the active HHV-6 infections in patients with MS could be monitored by use of blood specimens rather than more invasive samples, such as tissue biopsies or CSF specimens. Also, isolation of HHV-6 from the peripheral blood of MS patients undergoing antiviral drug treatment would allow assessment of its sensitivity to the antiviral agent being used. Interestingly, the antiviral drug acyclovir, which provides effective prophylaxis against HHV-6 infections in bone marrow transplant patients [91], has been shown to reduce significantly the frequency of disease exacerbations in patients with MS [92]. Also, other drugs with even higher suppressive activities against HHV-6 are currently licensed and available for use, including ganciclovir and foscarnet [44].

In summary, most, if not all, patients with MS have active HHV-6 infections in their CNS tissues, lymphoid tissues, and peripheral blood. Such infections are not seen in normal control subjects. The active HHV-6 infections within the CNS are closely associated with areas of active demyelination and are only rarely seen in normal-appearing white matter, gray matter, and areas of old, inactive disease. The incidence of active HHV-6 viremia is significantly increased in MS patients with disease durations of <12 years. This suggests that a change in the pathogenic mechanisms involved in MS may occur over time concurrently with a change in the level of active HHV-6 infection in the peripheral blood and perhaps the CNS.

### Acknowledgments

We thank Gary Tegtmeier and the staff of the Community Blood Center in Kansas City, Missouri, for supplying the blood samples from normal blood donors used in these studies and for their collection of demographic information about the donors.
References


