Human Herpesvirus 6 Infection as a Trigger of Multiple Sclerosis

Konstantine I. Voumvourakis, MD, PhD; Dimitrios K. Kitsos, MD, PhD; Sotirios Tsiodras, MD, PhD; George Petrikkos, MD, PhD; and Eleftherios Stamboulis, MD, PhD

We systematically reviewed the existing evidence to determine whether a relationship exists between infection with human herpesvirus 6 (HHV-6) and multiple sclerosis (MS) and, if so, to define the strength of that relationship. The following terms were used in searches of the Entrez-PubMed database (1966-2009): *human herpes virus 6*, *HHV 6*, *demyelination*, *multiple sclerosis*, *pathogenesis*, *diagnosis*, *serology*, *cerebrospinal fluid*, *IgG antibodies*, *IgM antibodies*, *PCR*, and *lymphoproliferative techniques*. Study quality was assessed using the criteria proposed by Moore and Wolfson and by the classification criteria used by the Canadian Task Force on the Periodic Health Examination. Studies were categorized both by experimental technique and by quality (high [A], intermediate [B], and low [C]) as determined by the Moore and Wolfson criteria. Overall, 25 (41%) of 61 studies, 15 (60%) of which were classified as A quality, reached a statistically significant result. According to the Canadian Task Force classification, all studies were categorized as evidence of quality II-1. Limitations of the available experimental techniques and perspectives for future research are discussed. The current review supports the need for further, objective, evidence-based examination of the relationship between HHV-6 infection and multiple sclerosis.

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CSF = cerebrospinal fluid; CTF = Canadian Task Force; HHV-6 = human herpesvirus 6; MS = multiple sclerosis; PBMC = peripheral blood mononuclear cell; PCR = polymerase chain reaction

Infection with various viral agents has been implicated as a potential triggering event for the onset of multiple sclerosis (MS).[1] A possible viral etiology for MS is suggested by the following observations: several viruses are associated with encephalomyelitis, and demyelination can be induced in animals through viral infection[2]; axonal damage, usually observed in association with a viral infection of the nervous system, may well precede demyelination in MS[3]; $CD8^+$ T cells, which are the main cells involved in viral immunity, rather than $CD4^+$ cells predominate and expand in active MS plaques[4]; gray matter lesions and axonal damage without lesions, which are both frequently observed in virus-induced demyelination, are commonly seen in MS[5]; and some viruses, including human herpesvirus 6 (HHV-6), are characterized by latency and periodic reactivation, which is a behavior very similar to the pattern of relapsing-remitting MS.[6]

No virus has been definitively implicated as a causative factor of MS, but certain HHVs have been linked with the development of MS because they exhibit neurotropic behavior, establish latency, and are ubiquitous.[7] Human herpesvirus 6 is a very probable candidate because it is neurotropic and a primary infection with this agent may cause several neurologic complications; it is lymphotropic with immunomodulating properties; it is characterized by latency and periodic reactivation; and it is ubiquitous.[8] A number of hypotheses have been proposed to explain how HHV-6 may act as a causative agent in MS, including direct cytopathic action, molecular mimicry or modulation of cytokine production during acute infection or virus reactivation, and an increase in an already present immune response during virus reactivation, a phenomenon also known as *bystander effect*.[9,10]

Many epidemiological and serologic studies during the past 15 years have used a variety of methods to investigate a probable correlation between HHVs and MS. We systematically surveyed the existing evidence to determine whether a relationship exists between infection with HHV-6 and MS and, if so, to define the strength of that relationship.

METHODS

Three authors (K.I.V., D.K.K., S.T.) independently performed the literature search, study selection, and data extraction. The following terms were used in searches of the Entrez-PubMed database (1966-2009): *human herpes virus 6*, *HHV 6*, *demyelination*, *multiple sclerosis*, *pathogenesis*, *diagnosis*, *serology*, *cerebrospinal fluid*, *IgG antibodies*, *IgM antibodies*, *PCR*, and *lymphoproliferative techniques*. We also screened articles related to the initially identified publications to expand our data sources. Classification of study quality was performed using the criteria proposed by Moore and Wolfson[11] (see eTable 1 in Supporting Online Material, a link to which is provided at the end of this article) and by the classification criteria used by the Canadian Task Force (CTF) on the Periodic Health Examination.[12] We used 2 methods for the evaluation of studies to increase objectivity. For example, the lowest-quality studies based on Moore and Wolfson criteria were the ones in which a

From the 2nd Department of Neurology (K.I.V., D.K.K., E.S.) and 5th Department of Internal Medicine (S.T., G.P.), Attikon University Hospital, University of Athens Medical School, Athens, Greece.

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Individual reprints of this article are not available. Address correspondence to Konstantine I. Voumvourakis, MD, PhD, Department of Multiple Sclerosis, Attikon University Hospital, University of Athens Medical School, 1 Rimini Str, Chaidari, Athens, Greece (cvoumvou@otenet.gr).

control group was not properly defined or not defined at all, ones that included heterogeneous MS and control groups, and ones in which MS diagnostic criteria were not accurately defined. The criteria were used for all studies, regardless of whether they reached statistical significance.

RESULTS

Serologic Studies

An increased frequency of anti–HHV-6 antibodies in MS patients compared with controls would suggest a relationship between HHV-6 and the pathogenesis of MS. The identified studies were divided into 4 subgroups according to the antibody type (IgM/IgG) and the fluid in which the antibodies were measured (serum vs cerebrospinal fluid [CSF]).

Serum IgG. The results of 19 studies assessing seropositivity for anti–HHV-6 serum IgG antibodies in MS patients vs controls are presented in eTable 2. Four studies found a statistically significant difference between the proportion of MS patients who had anti–HHV-6 serum IgG antibodies compared with controls and were classified as high quality (A).[14,15,17,28] Four studies were classified as A quality but did not reach statistical significance.[13,16,18,19] Of those 4 studies, 2 considered mean antibody titers rather than an arbitrary positive titer.[18,19]

Four studies were classified as intermediate quality (B), and none of them showed a statistically significant difference between MS patients and controls.[20,24-26] One of those studies considered mean antibody titers,[20] and another reported only that the IgG titers of MS patients were higher than those of controls without providing absolute values.[24]

The remaining 7 studies were classified as lower quality (C), mostly because of a failure to define and provide details about the study patients with MS.[21-23,27,29-31]

According to the CTF classification, 18 of the 18 studies were classified as quality II-1.

The main problem with the existing studies was the variety of the techniques applied and the fact that no definition of a positive result had been uniformly accepted by laboratories. Although some investigators define as positive the specified dilution of the sample, others do not define an absolute level of positivity but report average antibody titers. Moreover, anti–HHV-6 IgG detection is not by any means a definitive indication of an ongoing lymphoproliferative response to HHV-6. It is interesting to note that 4 of the high-quality studies achieved statistical significance despite the high seropositivity in healthy controls.

Serum IgM. The results of 13 studies assessing seropositivity for anti–HHV-6 serum IgM antibodies in MS patients vs controls are presented in eTable 2. Two studies were classified as A quality and reached statistical significance when correlating IgM anti–HHV-6 antibodies with MS.[16,28] Three more studies were classified as A quality but did not reach statistical significance when comparing MS patients and controls.[13,19,20] Of these 3 studies, 2 reported mean antibody titers.[19,20]

Two studies were classified as B quality.[24,25] Ongradi et al[24] reached statistical significance and reported only "high" and "low" antibody titers in MS patients and controls without providing actual values, whereas Ablashi et al[25] did not find significant differences in titers.

The remaining 6 studies had too many methodological limitations and were classified as C quality.[21-23,27,31,32]

All of the IgM studies were classified as quality II-1 on the basis of the CTF criteria.

It is quite difficult to compare the aforementioned studies because of differences in the method or in the definition of a positive result. For example, including a lower cutoff value for considering a titer positive would create a more concentrated sample of test-positive patients and thus generate a bias in assessing whether there is a true difference between the 2 groups (type I error).

Furthermore, seropositivity for IgM may be indicative of ongoing viral replication because IgM antibodies are considered in most cases evidence of recent infection. However, albeit more rarely, IgM seropositivity may also indicate reactivation. It is also well known that, for some pathogens, IgM antibodies may persist for years.[33] Indeed, HHV-6–specific serum IgM antibodies have been reportedly detected in 5% of healthy adults[34]; whether this indicates a persistent subclinical infection that is only clinically relevant in certain subpopulations (eg, immunocompromised individuals) remains unknown.

Cerebrospinal Fluid IgG/IgM. The results of 18 studies assessing CSF IgG/IgM antibodies in MS patients are presented in eTable 3. Of the 18 studies presented (12 detecting CSF IgG antibodies and 6 CSF IgM antibodies), only 3 were classified as A quality and achieved statistical significance.[14,15,17] Another 3 were classified as A quality but did not achieve statistical significance[13,18] (Kuusisto et al[13] on both CSF IgG and IgM correlations and Gutierrez et al[18] on HHV-6A subtype IgM antibodies).

Three studies were classified as B quality and did not achieve statistical significance[24,25] (Ongradi et al[24] for both CSF IgG and IgM correlations).

Nine studies had severe methodological issues, were classified as C quality, and found no statistically significant difference between MS patients and controls[22,23,29-32] (Ablashi et al,[22] Friedman et al,[32] and Taus et al[23] on both CSF IgG and IgM correlations).

All the aforementioned studies were classified as II-1 (CTF classification criteria).

Overall, the 3 high-quality statistically significant studies showed higher rates of anti–HHV-6 detection in the

CSF of MS patients than in that of controls, a finding supporting the correlation between HHV-6 infection and MS.[14,15,17]

The 2 main considerations/limitations in reviewing CSF studies are whether the CSF examined was whole or fractionated (in the case of an acellular CSF sample, a positive result is more likely to derive from the central nervous system rather than from peripheral immune cells) and whether, as was often the case, control CSF samples were obtained from patients with other neurologic diseases rather than from healthy controls. Thus, CSF samples were usually selected on the basis of availability rather than from a carefully selected control matched to an MS patient.

Polymerase Chain Reaction Techniques

The polymerase chain reaction (PCR) technique in the studies examined was typically performed using either serum or a specific cell population (ie, peripheral blood mononuclear cells [PBMCs]). When using this technique, it is important to realize that the absence of DNA in one sample does not exclude its presence in another sample from the same individual.

Sera PCR Techniques. The results of 20 studies evaluating the relationship between MS and the detection of HHV-6 in serum by PCR are presented in eTable 4. One study was classified as A quality and had statistically significant results between MS patients and controls.[17] Another 6 studies were classified as A quality but did not reach statistical significance.[18,36,38,39,41,49] Two of those studies did not present any HHV-6–positive patients or controls.[18,49] Four studies were classified as B quality and achieved statistical significance.[27,37,43,45] Alvarez-Lafuente et al[37] did not provide the number of HHV-6–positive MS patients and controls, whereas Tejada-Simon et al[43] provided only percentages for both MS patients and controls. Seven additional studies were classified as B quality without achieving statistical significance.[40,42,44,47,48,50,51] Hollsberg et al[40] presented only rates without absolute numbers of HHV-6 antibody–positive MS patients and controls, whereas Ma rtin et al[51] did not present any HHV-6 antibody–positive MS patients. The final 2 studies had severe methodological problems and were classified as C quality.[35,46]

All the aforementioned studies were classified as II-1 studies by the CTF classification criteria.

Overall, the studies reporting statistically significant results suggested a lack of relationship between HHV-6 infection and MS. However, comparison with healthy controls is extremely difficult because adequate data are lacking regarding the detection of HHV-6 by PCR in serum from healthy individuals.[52] Whether the positive results in bone marrow transplant patients and in patients infected with the human immunodeficiency virus in one of the aforementioned studies (Clark et al, 2002, personal communication) represent active infection or reactivation resulting from immunosuppression remains uncertain.

Cerebrospinal Fluid PCR Techniques. The results of 15 studies evaluating the relationship between MS and the detection of HHV-6 in CSF by PCR are presented in eTable 5. Two studies achieved statistically significant results between MS patients and controls and were classified as A quality.[28,53] Liedtke et al[28] studied both cellular and acellular samples. Another 2 studies were classified as A quality.[18,49]

Two studies classified as B quality achieved statistical significance,[25,45] whereas 6 studies classified as B quality did not[23,31,48,50,51] (Clark et al, 2002, personal communication).

The 3 remaining studies were classified as C quality because Ahram et al[36] used very small groups and the other 2 studies[20,54] did not use PCR controls.

All the aforementioned studies were classified as II-1 by the CTF classification criteria.

Because MS is a disease of the central nervous system, findings from PCR studies performed on CSF samples are more important than detection of HHV-6 in the periphery. The same considerations regarding positive results apply as for detection of anti–HHV-6 antibodies in the CSF. A positive result cannot distinguish latent from active infection.

Of the studies that achieved statistical significance, only Liedtke et al[28] demonstrated the presence of HHV-6 in acellular CSF samples of MS patients, a finding that needs further elucidation. The proportion of positive cases in the remainder of the positive studies was consistent with the findings of studies in primary HHV-6 infection in immunocompromised patients.[55-57]

Peripheral Blood Mononuclear Cell PCR Techniques. Peripheral blood mononuclear cells have been the most commonly used source of DNA for HHV-6 PCR studies. The results of 22 studies using PBMC PCR techniques are presented in eTable 6. Two studies reported statistically significant differences between MS patients and controls and were classified as A quality.[17,37] Alvarez-Lafuente et al[37] presented DNA prevalence rather than total values and distinguished between high and low values. Another 2 studies were classified as A quality without reaching statistical significance.[39,58]

Of the studies classified as B quality, 1 study reached statistical significance,[44] whereas 8 studies did not.[23,47,59-62,67,68] In most B-quality studies, a greater proportion of MS patients had detectable HHV-6 DNA in their PBMCs than controls; however, the results were not statistically signifi-

cant. One B-quality study used nested PCR techniques that could assist in discerning early/active from latent infection; in most cases with a positive result, only samples of "latent" HHV-6 DNA were detected.[61]

The remaining 9 studies presented significant methodological problems and were classified as C quality.[22,30,46,54,63-66,69]

All the aforementioned studies were classified as II-1 studies by the CTF classification criteria.

Overall, the results of these studies are difficult to interpret because up to 90% of healthy blood donors are positive for HHV-6 DNA, and serial testing shows significant variability in any individual.[29,70] Because many of the studies did not mention disease duration, it was not possible to locate newly diagnosed cases with positive HHV-6 DNA, a more clinically relevant finding in an MS patient with latent infection or progressive MS.

Polymerase chain reaction techniques cannot distinguish an active from a latent infection, thus diminishing the relevance of a positive result, as it may only represent prior exposure. Furthermore, individual studies exhibited an immense variety of use and description parameters of the PCR technique, and so no standardized technique could be assumed in reviewing the studies. Finally, some studies used standard PCR, whereas others used nested PCR, which is more sensitive without being more specific.

Rapid Culture Assay and Lymphoproliferative Techniques

In contrast to most of the techniques already described, rapid culture assay techniques detect the virus itself rather than indirectly identifying the immune reaction to the virus. In these studies, PBMCs from patients or controls were grown in culture with purified HHV-6–negative human cells (such as cultured human fibroblasts or human cord blood mononuclear cells) that were taken from neither the patients nor the controls. After an incubation period, the cells were stained with HHV-6–specific antibodies. Positive staining of the cell nuclei of the fibroblasts or cord blood cells was indicative of active HHV-6 infection because the virus must have been transmitted from the cells of the patient or control to the fibroblast or cord blood cells. Lymphoproliferative techniques are intended to measure the actual immune response to specific antigens, and therefore the results may be more important than those obtained with simple serology or PCR techniques.

The results of 2 studies (rapid culture assays) are presented in eTable 7. Knox et al[71] presented an A-quality study in which MS patients testing positive for HHV-6 by this technique tended to be younger and to have a shorter disease duration. A higher rate of active HHV-6 infection was observed when closer to the time of MS onset, supporting a potential role for HHV-6 in triggering an autoimmune central nervous system event such as MS. The other available study was C quality and will not be discussed further.[25]

A similar technique can be used to measure the immune response to specific antigens by incubating cultured PBMCs of patients or controls with the purified antigen of interest and then measuring the uptake of a radioactive tracer incorporated on the proliferating cells. This technique reportedly may be useful for evaluating the relationship between viral infection and recent MS onset.[31,60,72]

The results of 3 studies using this methodology (lymphoproliferative techniques) are presented in eTable 8. Soldan et al[72] showed that a higher proportion of MS patients than controls had a lymphoproliferative response to HHV-6A antigen, which has not yet been implicated as a cause in human disease but which is routinely identified in human CSF.[73] The other 2 studies[31,60] were B and C quality, respectively, and their results were not statistically significant.

Brain PCR/Immunohistochemistry

Eleven studies using brain samples as PCR material are presented in eTable 9. Of these, 4 were classified as A-quality studies.[32,58,76,78] Blumberg et al[78] presented the results as high and low values of HHV-6 DNA.

One B-quality study reported statistically significant differences between MS patients and controls.[74] It did not provide numeric values but rather presented results as higher and lower based on a cutoff value of HHV-6 DNA.

The results of the 3 remaining B-quality studies did not reach statistical significance.[68,75,79] Only Coates and Bell[79] provided nonsignificant differences in both patients and controls without giving numeric values.

The final 3 studies were C quality and will not be discussed further because they did not provide control groups and had significant methodological errors.[56,77,80]

All the aforementioned studies were classified as II-1 by the CTF classification criteria.

These pathology studies present a number of methodological issues. First, brain specimens were not selected in a systematic way; instead, MS and non-MS brain tissues were used on the basis of availability. Therefore, it is difficult to compare the results from 2 heterogeneous groups because the samples may come from different populations. Second, the studies differed in the techniques used and the areas of the brain examined. None of the studies explained how they sampled their specimens other than stating that they looked for white matter–gray matter plaques. Third, MS has characteristic pathologic findings, and therefore it is difficult for a researcher who interprets the experiment to remain blinded unless other demyelinating diseases are included in the control brain tissue. Fourth, all the specimens were postmortem and likely represented cases of progressive MS rather than active newly diagnosed MS. Finally, a

TABLE. **Studies That Achieved Statistically Significant Results**

Study	Method	MS patients (%)	Controls (%)	Classification	
				Moore and Wolfson	Canadian Task Force
Virtanen et al,[14] 2007	IgG serum	100, 100	69	A	II-1
Derfuss et al,[15] 2005	IgG serum	21	0	A	II-1
Chapenko et al,[17] 2003	IgG serum	61.5	29	A	II-1
Liedtke et al,[28] 1995	IgG serum	39	18	A	II-1
Villoslada et al,[16] 2003	IgM serum	22, 16, 10	10	A	II-1
Liedtke et al,[28] 1995	IgM serum	3	2	A	II-1
Ongradi et al,[24] 1999	IgM serum	Higher titers	Lower titers	B	II-1
Virtanen et al,[14] 2007	IgG CSF	11, 21	0	A	II-1
Derfuss et al,[15] 2005	IgG CSF	21	0	A	II-1
Chapenko et al,[17] 2003	IgG CSF	61.5	29	A	II-1
Chapenko et al,[17] 2003	Sera PCR	61.5	29	A	II-1
Tejada-Simon et al,[43] 2003	Sera PCR	83	55	B	II-1
Tejada-Simon et al,[45] 2002	Sera PCR	66	33	B	II-1
Soldan et al,[27] 1997	Sera PCR	30	0	B	II-1
Alvarez-Lafuente et al,[37] 2007	Sera PCR	NA (n=62)	NA (n=62)	B	II-1
Alvarez-Lafuente et al,[53] 2008	CSF PCR	10	2	A	II-1
Liedtke et al,[28] 1995	CSF PCR	39, 11	35, 4	A	II-1
Tejada-Simon et al,[45] 2002	CSF PCR	66	33	B	II-1
Ablashi et al,[25] 1998	CSF PCR	8	0 (n=4)	B	II-1
Chapenko et al,[17] 2003	PBMC PCR	61.5	29	A	II-1
Alvarez-Lafuente et al,[37] 2007	PBMC PCR	↑DNA prevalence	↓DNA prevalence	A	II-1
Alvarez-Lafuente et al,[62] 2002	PBMC PCR	49	22	B	II-1
Soldan et al,[72] 2000	Lymphoproliferative techniques	67, 78	33, 71	B	II-1
Knox et al,[71] 2000	Rapid culture	54	0 (n=61), 16	A	II-1
Opsahl & Kennedy,[74] 2005	HHV-6 brain immunohistochemistry	Significantly higher levels of HHV-6 mRNA	Significantly lower levels of HHV-6 mRNA	B	II-1

CSF = cerebrospinal fluid; HHV-6 = human herpesvirus 6; mRNA = messenger RNA; MS = multiple sclerosis; NA = not available; PBMC = peripheral blood mononuclear cell; PCR = polymerase chain reaction.

positive result on PCR to detect HHV-6 in the brains of MS patients at autopsy does not provide any information on the overall presence of HHV-6 in the brain, whereas a negative result does not exclude the absence of HHV-6 from the brain.

The results of 7 studies using immunohistochemistry results are provided in eTable 9. Two studies were classified as A quality without providing statistically significant results for MS patients vs controls.[58,78]

Of the 4 B-quality studies, 1 (Opsahl and Kennedy[74]) reported statistically significant differences between MS patients and controls, whereas 3 did not.[32,71,79] The one C-quality study will not be discussed further.[77]

None of the aforementioned pathology studies managed to clarify whether the isolation of HHV-6 DNA from brain tissue using immunohistochemistry techniques was evidence of an actual attack on oligodendrocytes or whether it was a bystander phenomenon in which immune cells that happen to carry HHV-6 antigens enter the central nervous system as a part of the MS disease process.

Overall Results

Of the 61 studies evaluated using the Moore and Wolfson criteria, 67% were identified as A-quality studies and the rest as B- or C-quality studies. Furthermore, 41% of studies reached a statistically significant result; of these, 60% were A-quality studies and the remainder were B-quality studies (Table). According to CTF criteria, 100% belonged to the II-1 quality scale.

DISCUSSION

The studies reviewed in this article attempted to establish a correlation between HHV-6 infection and MS. Most were serologic studies. All studies attempted to delineate the nature of the relationship between HHV-6 infection and MS. Studies reporting a relationship between HHV-6 and MS speculated that HHV-6 has a pathogenetic role in MS. Nevertheless, the same findings could reflect the breakdown of the blood-brain barrier during an acute infection with HHV-6 and not necessarily suggest a direct role for HHV-6 in triggering MS. Moreover, reactivation or exacerbation of MS could lead to some of these antibodies being detected as a sign of immune system hyperactivity rather than a true infection (either reactivation of a latent infection or a new infection). This is known to happen with other herpesviruses such as cytomegalovirus. Use of serology to implicate HHV-6 in MS pathogenesis overempha-

sizes the importance of a positive result without taking into consideration whether HHV-6 seropositivity is the result of a previous childhood infection or whether it is evidence of an ongoing infection that could be an active influential factor in MS pathogenesis.

A more specific sign of true infection and the active presence of HHV-6 may be PCR identification of HHV-6–specific DNA in either CSF or blood from MS patients. However, highly specific PCR cannot readily distinguish between reactivation of latent disease and a new infection. Quantification of the exact viral load may assist in this regard, because acute infections are usually associated with much higher loads. More studies should examine a possible relationship between new-onset MS and the actual HHV-6 load present. Theoretically, a higher viral load could lead to an increased immune response and a more pronounced adverse neurologic manifestation. The use of newer nested PCR techniques needs to be further evaluated. Rapid culture assays or lymphoproliferative techniques that are more direct indicators of ongoing HHV-6 activity can also assist in this regard. Postmortem PCR experiments to detect HHV-6 in the brains of MS patients are limited by similar methodological uncertainties because a positive result does not provide any information on the overall presence of HHV-6 in the brain, whereas a negative result does not by any means exclude the presence of HHV-6 from other brain sites.

The current study could assist in the future design of trials attempting to elucidate the role of certain pathogens (eg, HHV-6) in the pathogenesis of MS. The 3 following conditions should be met when designing such a trial:

(1) Controls Should Be as Similar as Possible to Patients With MS

Apart from age, sex, and race distribution, it would be ideal to draw the controls from the same population pool used for the patients. Although the high global prevalence of HHV-6 is well established, more data are necessary on local variations in its prevalence and in the populations affected. Further, the rate of neurologic complications associated with primary HHV-6 infection may differ according to geography or genetic predisposition (to either the virus or the disease) of the individuals. Multiple sclerosis is known to be associated with genetic predisposition in certain individuals or populations. Selection of controls from geographically diverse populations may help ensure that controls exhibiting different genetic predispositions to MS are included, but it might harm the comparison regarding the role of HHV-6. When possible, investigators studying the role of a pathogen in MS pathogenesis should ensure that MS and control groups differ only in the diagnosis of MS.

(2) Diagnostic Criteria of MS Must Be Well Defined and Patients May Have to Be Matched According to Disease Onset

Multiple sclerosis is a broad term that refers to a range of clinical manifestations that include subtle, overt, and serious progressive disease. In patients with progressive forms (eg, long-term MS variable), the detection of a pathogen such as HHV-6 does not implicate the virus in the pathogenesis of disease as a triggering first event (cause and effect) and does not necessarily mean that HHV-6 was present at the time of diagnosis or that its presence was more than a chance event. Nevertheless, it may implicate the virus in the maintenance of the observed phenotype. Thus, careful classification of patients according to onset and pattern of disease will be helpful in establishing a clearer picture of the relationship between MS and HHV-6 infection.

(3) Laboratory Diagnostic Methods Must Be Objectively Evaluated and Harmonized

Valid and accurate diagnostic methods would greatly enhance our understanding of the role of newer pathogens in complex diseases like MS. It is essential that both positive and negative results be presented to rule out the possibility of a group of negative controls resulting from technical errors in the experimental process. It is preferred that results be evaluated by observers blinded to the diagnosis.

Study Limitations

Our attempt to objectively present data on the relationship between HHV-6 infection and MS has a number of limitations. These include the different techniques used in each study, the different areas of the brain examined, and the fact that tissue collection was based on tissue availability rather than a careful match between a patient and a control group. In addition, subjective bias could not be avoided when examining brain tissue because MS lesions have a characteristic morphology. Finally, because most brain tissue was taken from patients with progressive MS and examined postmortem, relapsing-remitting MS brain tissue was not readily available for study.

CONCLUSION

This review of the literature supports the need for objective, evidence-based clinical studies of the relationship between HHV-6 infection and MS. Useful studies should use controls as similar as possible to patients with MS. Moreover, the diagnostic criteria of MS must be well defined in these studies, and patients should be matched according to disease onset. Finally, the laboratory diagnostic methods would have to be objectively performed and evaluated according to a harmonized, internationally accepted standard.

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