J Med Microbiol Infec Dis, 2014, 2 (4): 133-137

Original Article

Human Herpesvirus 6 Viremia in Patients with Classic Multiple Scelerosis in Guilan, Iran

Masoumeh Ahmadi Jalali Moghadam[1], *Hamidreza Honarmand[2]

[1]Cellular and Molecular Research Center, Faculty of Medicin, Guilan University of Medical Sciences, Rasht, Iran;
[2]Department of Microbiology, Faculty of Medicine, Guilan University of Medical Sciences, Rasht, Iran.

Received Dec 04, 2015; accepted Jan 17, 2016

Introduction: During the past few years, an increasing body of evidence has suggested a possible role for human herpes virus 6 (HHV-6) in Multiple Sclerosis (MS) pathogenesis. Despite the many reports supporting the relationship between HHV-6 and MS, this association has not been definitely proved or refuted, and the matter remains unresolved. The current study was aimed to investigate any relation between HHV-6 viremia and classic MS in patients in Guilan province, Northern Iran. **Method:** HHV-6 viremia was certified by molecular detection in study group (n=46) and control group (n=46) using nested-PCR. Data were analyzed by using three statistical tests (Chi square, odd ratio, and Relative Risk). **Results:** HHV-6 genomic sequences were found totally in 28 out of 46 (60.8%) plasma DNA samples of patients with MS, but were not found in rest of them. It was also found in 13 out of 46 (28.2%) control group. The difference in prevalence of HHV-6 DNA in blood between patients with MS and control group was statistically significant (*P*=0.0027 and odd ratio=0.277). **Conclusion:** The data of our study showed that HHV-6 can be implicated in the development of MS. We strongly support the need for further, objective, evidence-based examination of the relationship between HHV-6 infection and MS. *J Med Microbiol Infec Dis, 2014, 2 (4): 133-137.*

Keywords: Human Herpes virus 6, Multiple Sclerosis, Nested PCR, Iran.

INTRODUCTION

Multiple sclerosis (MS) is the most common autoimmune inflammatory demyelinating disease of the central nervous system (CNS). MS affects approximately 1,000,000 people between 17 and 65 years old worldwide [1]. The etiology is believed to have both genetic and environmental components [2]. Actually, MS is an autoimmune disease directed against self-neural antigens [2]. Several clinical and epidemiologic observations pointed to the involvement of an infectious process in MS and several studies implicated members of the Herpesviridae family in the pathogenesis of MS [3]. Main characteristic of these viruses is that they have periods of latency and exacerbations within their biological target, the CNS. The Epstein-Barr, cytomegalovirus, human herpes virus 6 (HHV-6) and human herpes virus 7 (HHV-7) are the members that are most studied as being possible triggers of MS [3]. According to evidence in the literature it is unlikely that they are the only components responsible for development of MS [4]. Results from different studies are, however, conflicting and for detecting the viral etiology of MS it is necessary to interpret the HHV-6 findings with great caution. Infection of HHV-6 usually occurs early in childhood, causing exanthema subitum [5]. The primary infection is followed by lifelong latency. HHV-6 is also neurotrophic and primary infection occasionally results in meningitis, encephalitis, and febrile seizures [6]. It can achieve latency in the CNS and can reactivate during periods of stress [7]. Viral infection can also lead to induction of an autoimmune response by molecular mimicry or bystander activation [8]. In the molecular mimicry model, shared antigenic determinants between putative infectious pathogens and myelin antigens in a genetically susceptible individual lead to the development of auto reactivity and ultimately autoimmune demyelization [5]. In the bystander activation model, microbial infections lead to significant activation of antigen-presenting cells (APCs) such as dendritic cells. These activated APCs could potentially activate pre-primed autoreactive T cells, which can then initiate autoimmune disease [7]. Possible role and the evidence for and against a role for HHV-6 in MS is investigated in the present study.

MATERIAL AND METHODS

This cross sectional prospective study was conducted in MS patients (n=46) who were under supervision of MS society of Guilan province, Northern Iran and also with healthy individuals age and gender matched as controls (n=46). This study was performed along April, 2013 to April, 2014. MS patients had been diagnosed by magnetic resonance imaging (MRI) and Evoked Potential (EP) assays and also McDonald criteria were recruited.

***Correspondence:** Hamidreza Honarmand

Department of Microbiology, Faculty of Medicine, Guilan University of Medical Sciences, Saravan Rd, Rasht, Iran, 4415938411.

Email: honarmand.3@gmail.com

Tel: +98 (13) 42226121 **Fax:** +98 (13) 16690036

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Plasma samples were collected by standard method. All Specimens were stored at -70°C until the experiment was performed. Required data were collected by filling out a questioner including main information such as age, gender, duration of the disease, number of crisis, duration of interferon intake, score of Expanded Disability Status Scale (EDSS) which is a method of quantifying disability in MS, result of MRI, result of EP Test and type of antiviral therapy (if prescribed). All patients and control were residents of the area (more than 6 months) with age range 10-50, affected by classic MS (not opticospinal MS). The diagnosis was confirmed by MRI and EP tests for all cases.

Total DNA was extracted from blood plasma. The Genomic DNA Purification Kit (Thermoscientific, Lot: 00155557, Fermentas, Lithuania) was used for extraction of DNA from all blood plasma samples according to the manufacturer's instructions.

Nested PCR was used for the detection of HHV-6 sequences in blood plasma DNA from both patients with MS and the control group. Each PCR contained 1 µg of DNA in a final volume of 20 µl PCR premix (with 10 µl Prime Taq Premix, Genet Bio ,Chorea Lot No 201208, and 0.2 mM of each specific primer and dd H2O for the rest volume). DNA isolated from HHV-6 B virions (purchased from Vircell Company and donated by Dr. S. Yavarian, Tehran University of Medical Sciences, Tehran, Iran) was used as the positive control. To exclude the possibility of contamination during the PCR, water controls were included in each experiment.

The detection of HHV-6 DNA was carried out according to Bandobashi *et al.* [9] with a nested primer set, complementary to the gene coding the major capsid protein, which recognizes both variants (A and B) of the virus. The nucleotide sequence of the primers 5'-GCGTTTTCAGTGTGTAGTTCGGCAG-3' and 5'-GGCCGCATTCGTACAGATACGGAGG-3' (outer pairs); 5'-GCTAGAACGTATTTGCTGCAGAACG-3' and 5'-ATCCGAAACAACTGTCTGACTGGCA-3' (inner pairs) for the first and second round of PCR, respectively.

The inner primers amplify a 258 bp fragment of HHV-6. The first round of PCR was carried out at 94˚C for 5 min, followed by 35 cycles of 94˚C for 1 min, 57˚C for 1 min, and 72˚C for 1 min. Terminal extension of 72˚C for 5 min was carried out after completion of the 35 cycles. A sample (1 µl) of the first round product was used as template for the second round using the conditions described for the first round. The second round of PCR was carried out at 94˚C for 5 min, followed by 32 cycles of 94˚C for 1 min, 55˚C for 1 min, and 72˚C for 1 min. Terminal extension of 72˚C for 5 min was carried out after completion of the 35 cycles. The products of DNA amplification were analyzed by electrophoresis on a 2% agarose gel at 125 volt for 45 min and visualized under UV with safety stain staining, using a Gel Doc Transluminator system (Vilber Lourmat model).

The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), version 16 was used for statistical analysis. Pearson chi square, odd ratio and relative Risk tests were applied to analyze all variables. All *P*-values were regarded two-tailed and significant at $P<0.05$.

The study conformed to the Helsinki declaration and was reviewed and approved by the local research committee and ethics committee. Written informed consent was obtained from all subjects and the control group.

RESULTS

The age range of the patients (n=46) were 10 to 50 years (most frequent around 28-38 and with the average of 32.6). Duration of the disease was more frequent between 2 to 9 years (76.3%). Most patients were women (71.4%). EDSS of most patients were between 2.5 to 3.5 (45.2%). About 28.6% of patients had EDSS score lower than 2.5. EP test and MRI were positive in all patients.

Nested-PCR Set up was performed successfully by using DNA isolated from HHV-6 B virions purchased from Vircell Company (figure 1). HHV-6 genomic sequences were found totally in 28.46 (60.8%) plasma DNA samples of patients with MS (figure 2), but were not found in rest of them. It was also found in 13.46 (28.2%) control group. The difference in prevalence of HHV-6 DNA in blood between patients with MS and the control group was statistically significant. (p=0.0027, odd ratio=2.75 and Relative Risk=2.19).

DISCUSSION

HHV-6 is one of the two herpes viruses associated with MS (the other one is Epstein–Barr virus (EBV)). HHV-6 is ubiquitous, with a seropositivity of more than 90% in the general population [5]. Epidemiological data and the inflammatory nature of the lesions have been main motivation for many researches to find a pathogen in MS. To find a causal association between MS and an infectious agent, the pathogen should be able to (a) cause a chronic inflammatory disorder of the CNS, (b) reside within the CNS and undergo periods of activation and quiescence, and (c) should cause demyelination [5].

An association between HHV-6 and MS has been suggested by: 1) the demonstration of viral antigen expression in the nuclei of oligodendrocytes in inflammatory lesions of brain tissue; 2) the detection of IgM and increased IgG specific anti-HHV-6 antibody titers in plasma or serum and in cerebrospinal fluid; and 3) the detection of HHV-6 DNA in peripheral blood mononuclear cells, brain tissue, blood plasma or serum and Cerebrospinal fluid (CSF) of patients with MS, but not in controls. There is controversy about the application of the above mentioned techniques.

Seropositivity for IgM may be indicative of active viral replication because IgM antibodies are considered in most cases of recent infection, but it is known that, for some pathogens, IgM antibodies may persist for years [10]. On the other hand, HHV-6–specific serum IgM antibodies have been reportedly detected in 5% of healthy adults [11].

The main point in reviewing CSF studies is whether the CSF examined was whole or fractionated. In a cellular CSF sample, a positive result is more likely related to the CNS rather than to the peripheral immune cells. In some studies control CSF samples were obtained from patients with other neurologic diseases rather than from healthy controls.

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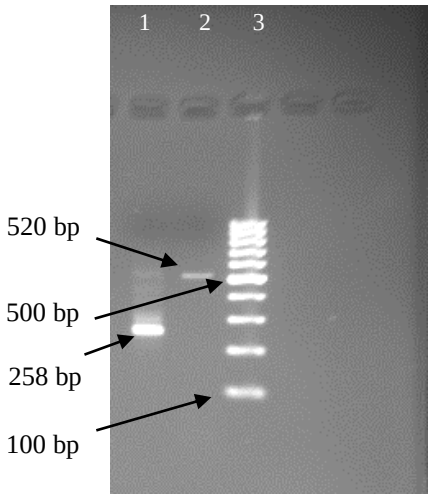

Fig. 1. Results of the first and the second rounds of Nested PCR using for set up the test. Lane 3, 100-1000 bp DNA ladder; lane 2, 520 bp specific band of the first round; lane 1, 258 bp specific band of the second round.

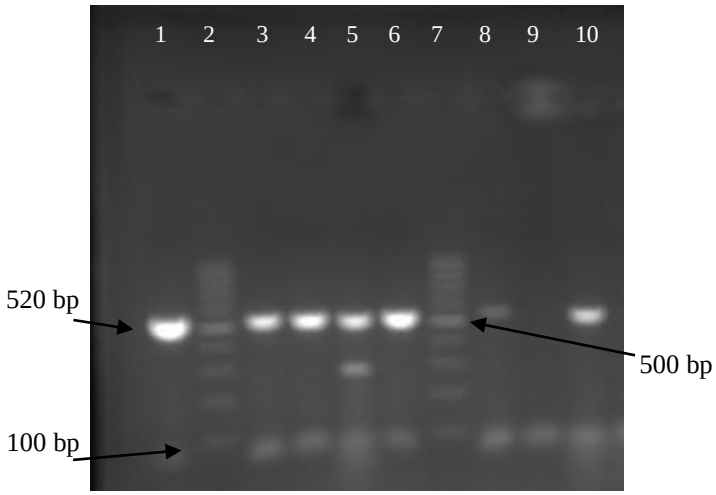

Fig. 2. Results of first round of Nested- PCR for patients' samples. Lane1, specific band of the positive control; lanes 2 and 7, 100-1000 bp DNA ladder; lanes 3, 4, 5, 6, 8, 10, positive cases; lane 9, negative control (water).

Thus, CSF samples were usually selected on the basis of availability rather than from a carefully selected control matched to an MS patient [12].

Because MS is a disease of the CNS, findings from PCR studies performed on CSF samples are important for detection of HHV-6 in the periphery, but a positive result cannot distinguish latent from active infection [12]. Liedtke *et al*. demonstrated the presence of HHV-6 in a cellular CSF samples of MS patients [13] but this finding needs further elucidation and the proportion of positive cases in the rest of the positive studies was consistent with the findings of studies in primary HHV-6 infection in immunocompromised patients [14-16].

Peripheral blood mononuclear cells are the most commonly source of DNA for HHV-6 PCR studies. The results of the studies using PCR techniques on peripheral blood mononuclear cells 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 [17, 18]. It should be noted that many studies did not mention disease duration so it was not possible to locate newly diagnosed cases with positive HHV-6 DNA. It seems that a more clinically relevant finding is MS patients with latent infection or progressive MS [12].

The results of studies using Brain PCR or Immunohistochemistry are not easy to be interpreted. Five studies did not show statistically significant results for MS patients vs controls [19-23] Opsahl reported statistically significant differences between MS patients and controls [24] but it did not provide numeric values, it presented results as higher and lower based on a cutoff value of HHV-6 DNA. Cermelli *et al.* [25] found the presence of HHV-6 DNA in 57.8% of MS plaques and 15.9% of normal brain samples, a result highly statistically significant ($P<0.0005$). Unfortunately these studies didn't manage to clarify whether the isolation of HHV-6 DNA from brain tissue using immunohistochemistry techniques was an evidence of an actual attack on oligodendrocytes or whether it was a bystander phenomenon in which immune cells carrying HHV-6 antigens enter the CNS as a part of the MS disease process [12].

Regarding all above mentioned points we chose a more reliable method. That is why we used PCR assay for plasma because the presence of HHV-6 DNA in blood plasma is a marker of active viral infection [26]. This method was tried by a number of researchers. Study of Chapenko *et al.* Showed statistically significant results between MS patients and controls [27]. Same results were found in other studies [28-31] but these results are not confirmed in several studies [31-36].

Actually the presence of HHV-6 DNA in plasma might be a marker of active infection whether the DNA is originated from cell-free viral particles produced by the active infection of lymphoid tissue or from simple lysis of circulating infected cells in the blood [37]. All data indicated that most plasma HHV-6 DNA, presented in the tested samples is originated from the lysis of infected circulating cells [38].

The present study is the first try to look for any association between HHV-6 and MS in the region. Our results confirmed the causative relationship between HHV-6 and MS. The presence of HHV-6 DNA in blood plasma was detected in 60.8% of patients with MS. This type of viremia was observed only during periods of new disease activity, both in relapsing/remitting and secondary progressive MS in the study of Chapenko *et al.* [24]. Results of the present study are in accordance with those of Soldan *et al.* [28], Ablashi *et al.* [39] and Akhyani *et al.* [40], who reported a higher PCR positivity for HHV-6 in plasma of patients with MS.

We have confirmed the presence of HHV-6 DNA in plasma of MS patients comparing with the control group, but HHV-6 DNA was not found in blood plasma of 39.2% of patients. It should be noted that the absence of HHV-6 viremia in some patients with active MS may be associated

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with an early stage of viral replication [26]. This is consistent with results of some similar studies. Ahram *et al.* did not also detect HHV-6 DNA in serum samples of 26% MS patients in Jordan [33].

HHV-6 DNA could be detected in control plasma from healthy adults which questions its specificity [41]. This may be explained by the variability of cell lysis process which can make difficulty in the standardization of plasma assays. It should be noted that HHV-6 peripheral blood mononuclear cells load has been shown to be correlated to the occurrence of HHV-6 - associated symptoms in stem cell transplant recipients [42]. In addition, recent data have shown that polymorphonuclear leukocytes also provide a major contribution to HHV-6 load in the peripheral blood of patients [43]. It seems that performing study by measuring HHV-6 DNA load in whole blood will be a better quantitation procedure with a higher sensitivity in HHV-6 diagnosis.

There are a number of barriers to make a conclusive argument for a causal connection between MS and an infectious agent because it is not easy to provide a causal connection between pathogen and disease when the pathogen is ubiquitous. The potential association between HHV-6 infection and MS has often been discussed and remains controversial. Some studies provided contradictory results, raising methodological and technical questions. Although some studies have failed to show an association between HHV-6 and MS, our findings support a correlation between HHV-6and MS but for more sensitive diagnosis of HHV-6 viremia we suggest measuring HHV-6 DNA load in whole blood and also the laboratory diagnostic methods would have to be objectively performed and evaluated according to a harmonized, internationally accepted standard.

ACKNOWLEDGEMENT

This work was supported by Guilan University of Medical Sciences.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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