Comparison of Herpes Simplex Virus Reactivation Frequency in Acute Idiopathic Cranial Mononeuropathy and Normal Population by Serological Assay

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Abstract

Background: Herpes simplex virus (HSV) is a neurotropic DNA virus with a high prevalence. Following primary infection, HSV remains dormant in the neural ganglia. Secondary infection can emerge after the reactivation of latent infection, presenting as neurological manifestations. Previous studies have demonstrated the relationship between HSV reactivation and selective involvement of cranial nerves. Depending on the affected nerve, cranial mononeuropathies can present with symptoms, including diplopia, blurred vision, vertigo, unilateral facial palsy, speech impairment, swallowing difficulties, and hoarseness.

Objectives: This study used a serological assay to compare HSV reactivation frequency between patients with recent idiopathic cranial mononeuropathies and normal individuals.

Methods: Plasma samples from 35 idiopathic cranial mononeuropathy cases (57.2% women, mean age 58.37 years) and 35 age and sex-matched healthy controls were analyzed for anti-HSV immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies by enzyme-linked immunosorbent assay (ELISA).

Results: Anti-HSV IgG antibody was positive in 91.4% of patients and 88.6% of controls. The mean serum anti-HSV IgG antibody level was significantly higher in patients (146.78 ± 60 RU/mL) than in the controls (130.61 ± 52.99 RU/mL) (P-value = 0.037). Anti-HSV IgM antibody was positive in 37.1% of patients and 14.3% of controls (P = 0.042).

Conclusions: The frequency of HSV reactivation was significantly higher in patients with acute idiopathic cranial mononeuropathy than in the healthy controls, indicating the possible role of HSV as an etiology of cranial mononeuropathy.

Keywords: Herpes Simplex Virus, Cranial Mononeuropathy, HSV, IgG, IgM

1. Background

Herpes simplex virus (HSV) establishes primary infection in approximately 60% to 94% of the adult population worldwide (1). There are two subtypes of HSV, with type-1 (HSV-1) accounting for 67% of the population globally (2). This neurotropic virus can present neurological manifestations and cause primary and secondary infections (3). Following primary infection, HSV remains dormant in the neural ganglia (4). Secondary infection can emerge subsequently from the reactivation of latent infection (5). The activated virus travels from the neural ganglia along the sensory nerves, manifesting neuropathy symptoms (6).

Cranial mononeuropathy occurs as a result of injury to the cranial nerves. The disease's clinical manifestations are diverse depending on the affected cranial nerve (CN) and can present symptoms including diplopia, blurred vision, vertigo, unilateral facial palsy, speech impairment, swallowing difficulties, and hoarseness. Cranial mononeuropathy can develop for several causes; infections, autoimmune abnormalities, microvascular injuries, tumors, and trauma have been identified among possible etiologies (7).

Previous studies have indicated HSV reactivation as an etiology for selective acute cranial mononeuropathy (ACM) (8). Most of these studies are case reports showing a relationship between the reactivation of HSV and the occurrence of cranial neuropathy with the aid of different diagnostic methods (8-10). However, this association is not yet firmly established (11).

Numerous diagnostic methods are available for HSV...
diagnosis. All participants were enrolled in the study with informed consent, and data collection was confidential.

About 10 cc blood sample was drawn from each individual and then split into two 5 cc samples. Extracted plasma samples were stored at -70°C in Vali-Asr Hospital Laboratory. After data collection, a total of 140 plasma samples (70 samples for each group) were analyzed for anti-HSV immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies using the EUROIMMUN anti-HSV kit. Kits detected IgM qualitatively (positive or negative) and IgG quantitatively.

EUROIMMUN recommends the following index values for IgM antibodies: A ratio of < 0.8 is considered negative, and a ratio of ≥ 1.1 is considered positive. A ratio of ≥ 0.8 but < 1.1 is considered equivocal. The recommended quantitative ratios for IgG antibodies are as follows: < 16 RU/mL, ≥ 16 but < 22 RU/mL, and ≥ 22 RU/mL, which are considered negative, borderline, and positive, respectively.

The frequency distribution table, t-test, chi-square test, and Mann-Whitney U test were applied to determine the group differences. We used SPSS software version 25.0.0.1 for statistical analysis, and p-values less than 0.05 were considered statistically significant.

4. Results

There were 35 ACM cases and 35 healthy controls in the analysis. There were 20 (57.14%) women in each group, and the mean age, at the time of sampling, was 58.37 ± 17.43 years among both patients and controls (using t-test analysis).

There were 32/35 (91.4%) patients and 31/35 (88.6%) healthy controls with positive anti-HSV IgG antibody (P-value = 0.33). The mean serum anti-HSV IgG antibody level was significantly higher in patients (146.78 ± 60 RU/mL) than in the controls (130.61 ± 52.99 RU/mL). Using the Mann-Whitney U test, the p-value was found to be 0.037. There were also 13/35 (37.1%) individuals with positive anti-HSV IgM antibody among patients and 5/35 (14.3%) among healthy controls (P-value = 0.042).

The frequency distribution of positive anti-HSV IgG and IgM antibodies in patients with ACM was compared with the healthy controls, as shown in Table 1.

The association between anti-HSV IgG and IgM antibodies and cranial nerve involvement is shown in Table 2. Quantitative variables (such as age and anti-HSV IgG antibody level) were measured for each cranial nerve separately. The results showed the highest mean age for CN VI involvement (67.68) and the lowest mean age for CN II involvement (39.67). Patients with CN IV (173.00) and CN V (133.92) involvement had the highest and the lowest levels of anti-HSV IgG antibody, respectively (Table 3).
After the beginning of symptoms is suggested (17), which four-fold increase in anti-HSV IgG antibody titers six weeks after the infection and the occurrence of cranial mononeuropathy, a latent form. This indicates that most people have been infected with the virus at least once, and the anti-HSV IgG antibodies have already been produced in their sera (16). To document the correlation between the recent HSV in cranial mononeuropathy recurrence (15). However, we tried to investigate the presence of anti-HSV antibodies in various cranial neuropathies.

In a case-control study by Lazarini et al., consisting of 38 Bell’s palsy patients and 10 healthy controls, HSV-1 was found in the saliva of 29% of patients using PCR (8). Additionally, HSV-1 was found in the perineurium of the seventh cranial nerve in 11 out of 14 patients with Bell’s palsy using PCR in a study by Murakami et al. (9). In another study, Mansani et al. documented positive anti-HSV IgM and IgG antibodies in 35/50 patients with Bell’s palsy (18). Our findings agree with the results of these studies, suggesting the possible role of HSV-1 in Bell’s palsy. In case-report studies, serological anti-HSV antibody testing documented the reactivation of HSV in trigeminal sensory neuropathy (19, 20). The results of these studies favor the role of HSV in trigeminal sensory neuropathy, which further supports the findings of our study.

Two randomized studies evaluated the prevalence of different neural ganglia involvement by HSV (25, 26). Theil et al. removed the trigeminal ganglia (TG), geniculate ganglia (GG), and vestibular ganglia (VG) from both sides of seven dead subjects and examined HSV-1 DNA in tissue sections using in situ hybridization. The results showed the HSV-1 presence in all TG, 70% of GG, and 0% of VG. However, they were not able to detect the virus in the VG. In a second experiment, using reverse transcription-polymerase chain reaction (RT-PCR) only on the VG of 10 random dead subjects, HSV-1 was detected in almost all VG samples (26). In another study by Takasu et al. on 17 random dead subjects, PCR and RT-PCR detected the HSV-1 in 94% and 88% of TG and GG, respectively (25). These findings suggest that HSV-1 remains dormant in TG and GG of adults and latent migrates along the sensory nerves during secondary infection.

In line with the results of previous studies, our findings showed the association between HSV and eighth-cranial nerve palsy. Pollak et al. studied anti-HSV IgG antibody levels using immunofluorescence assay (IFA) in 21 patients with vestibular neuritis compared to the healthy controls. Although the positive anti-HSV IgG antibody results between both groups were equal, the serum anti-HSV IgG antibody levels were significantly higher in patients than in the healthy controls (10). These findings further support the results of our study. Furthermore, two epidemiologi-

<table>
<thead>
<tr>
<th>Antibody Status</th>
<th>Patients</th>
<th>Controls</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td></td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>Positive</td>
<td>32 (50.8)</td>
<td>3 (49.2 )</td>
<td></td>
</tr>
<tr>
<td>Borderline</td>
<td>0 (0)</td>
<td>2 (100)</td>
<td></td>
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<tr>
<td>Negative</td>
<td>3 (60.0)</td>
<td>2 (40.0)</td>
<td></td>
</tr>
<tr>
<td>IgM</td>
<td></td>
<td></td>
<td>0.042</td>
</tr>
<tr>
<td>Positive</td>
<td>13 (72.2)</td>
<td>5 (27.8)</td>
<td></td>
</tr>
<tr>
<td>Borderline</td>
<td>6 (60.0)</td>
<td>4 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>16 (58.1)</td>
<td>26 (69.1)</td>
<td></td>
</tr>
</tbody>
</table>

*Values are expressed as No. (%).
Table 2. Frequency Distribution of IgG and IgM Seropositivity According to Involved Cranial Nerves in Patients

<table>
<thead>
<tr>
<th>CN</th>
<th>IgM</th>
<th>IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Borderline</td>
</tr>
<tr>
<td>II (3 cases)</td>
<td>(33.3) 1</td>
<td>(0) 0</td>
</tr>
<tr>
<td>III (4 cases)</td>
<td>(50) 2</td>
<td>(25) 1</td>
</tr>
<tr>
<td>IV (2 cases)</td>
<td>(0) 0</td>
<td>(0) 0</td>
</tr>
<tr>
<td>V (4 cases)</td>
<td>(50) 2</td>
<td>(25) 1</td>
</tr>
<tr>
<td>VI (6 cases)</td>
<td>(16.7) 1</td>
<td>(50) 1</td>
</tr>
<tr>
<td>VII (6 cases)</td>
<td>(66.7) 4</td>
<td>(0) 0</td>
</tr>
<tr>
<td>VIII (10 cases)</td>
<td>(40) 4</td>
<td>(10) 1</td>
</tr>
</tbody>
</table>

Abbreviation: CN, cranial nerve.
*Values are expressed as No. (%).

Table 3. Comparison of Quantitative Variables in Each Involved Cranial Nerve in Patients

<table>
<thead>
<tr>
<th>CN</th>
<th>Age</th>
<th>IgG Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>39.67 ± 4.50</td>
<td>125.73 ± 85.98</td>
</tr>
<tr>
<td>III</td>
<td>63.00 ± 30.32</td>
<td>169.42 ± 28.41</td>
</tr>
<tr>
<td>IV</td>
<td>58.00 ± 1.41</td>
<td>173.00 ± 18.80</td>
</tr>
<tr>
<td>V</td>
<td>62.75 ± 4.57</td>
<td>113.92 ± 75.63</td>
</tr>
<tr>
<td>VI</td>
<td>68.67 ± 11.70</td>
<td>155.16 ± 49.31</td>
</tr>
<tr>
<td>VII</td>
<td>44.67 ± 2.65</td>
<td>144.80 ± 71.76</td>
</tr>
<tr>
<td>VIII</td>
<td>62.50 ± 20.32</td>
<td>148.09 ± 66.95</td>
</tr>
</tbody>
</table>

Abbreviation: CN, cranial nerve.
*Values are expressed as Mean ± SD.

cers, a known immune deficiency state, or a history of the mentioned conditions, which could further activate the latent form of the virus and affect our study. We found a positive history of diabetes in eight patients with ACM and three healthy controls. Diabetes can cause cranial neuropathy through two mechanisms, including vasculopathy and collateral vessel thrombosis or immune system dysfunction, leading to HSV reactivation (29). In our study, although diabetes history was higher in patients than controls, the difference was not highly significant, suggesting further in-depth clinical trials. Hypertension, cerebrovascular disease, and ischemic heart disease can cause systemic vasculopathy and result in cranial neuropathies (30). However, there were no significant differences between the two groups to affect the study results.

Our study has certain limitations. We included patients with mononeuropathies of various cranial nerves. Although some were not detectable during the study, current evidence may present preliminary data on HSV’s role in acute idiopathic cranial mononeuropathies. Detection of group-specific HSV (for example, HSV-1/HSV-2) in cranial mononeuropathies was not possible in our study due to a lack of access to group-specific laboratory kits. Other limitations included the qualitative measurement of anti-HSV IgM antibodies and virus detection through indirect serological tests with lower sensitivity than the PCR.

In conclusion, HSV reactivation frequency was significantly higher among patients presenting with acute idiopathic cranial mononeuropathy than among healthy controls, indicating the potential role of HSV in cranial mononeuropathy development. Further studies are needed to expand our knowledge of the role of HSV reactivation in idiopathic cranial mononeuropathies. We suggest case-control studies with more participants using direct serological methods (for example, PCR) with high sensitivity and specificity to investigate the role of HSV in a particular cranial nerve neuropathy. We also suggest clinical trials evaluating the effect of timely HSV treatment on acute idiopathic cranial mononeuropathy symptoms and prognosis improvement.

Footnotes

Authors’ Contribution: Mehdí Maghbooli: Study conception and design, statistical analysis, manuscript editing, data collection, manuscript writing, and final approval of the manuscript; Amin Mirzaei: Study conception and design, statistical analysis, data collection, and manuscript writing; Zahra Jourahmad: Manuscript editing, writing, reviewing, and final approval of the manuscript; Hesam Mirshahabi: Study design, statistical analysis, data collection, and manuscript writing; Nazanin Azizi: Manuscript editing, writing, reviewing, and final approval of the manuscript.

Conflict of Interests: The authors declare no conflict of interest.

Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after its publication.

Ethical Approval: The Ethics Committee of Zanjan University of Medical Sciences (code: IR.ZUMS.REC.1397.96) approved this project.

Funding/Support: This study was supported by a grant from Zanjan University of Medical Sciences (Number: A12-205-19).

Informed Consent: All participants enrolled in the study with informed consent, and data collection was confidential.

References

Herpes simplex neuropathy.

Association of herpes simplex virus infection and Bell’s palsy.

Herpes simplex virus type 1 in Europe: systematic review, meta-analysis and host response.

Isolated vagus nerve palsy probably associated with herpes simplex virus infection.

Detection of latent herpes simplex virus DNA and RNA in human geniculate ganglia by the polymerase chain reaction.

Detection of herpes simplex virus type 2 specific antibodies.


Isotonic necrosis syndrome presenting with severe inflammatory orofacial pain.

Herpes simplex virus and varicella zoster virus, the house guests who never leave.

Idiopathic third cranial nerve palsy associated with herpes simplex virus infection.

Prevalence of HSV-1 LAT in human trigeminal, geniculate, and vestibular ganglia and its implication for cranial nerve syndromes.