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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

detection, including different molecular and serological assays, tissue smears, polymerase chain reaction (PCR), and glycoprotein G-based enzyme-linked immunosorbent assay (ELISA) (12). Diagnostic method selection mainly depends on factors such as sample type, turnaround time (especially in infections related to the central nervous system), patient subpopulations, and cost (13). In recent years, detecting antibodies produced against HSV glycoprotein G (gG) has been proven to be a highly sensitive and specific diagnostic method for HSV infection (14).

2. Objectives

The current study aimed to investigate the role of HSV reactivation in acute idiopathic cranial mononeuropathy using ELISA since timely use of diagnostic and treatment strategies against HSV infection will help treat the disease promptly and prevent further complications.

3. Methods

Participants were 35 patients with acute idiopathic cranial mononeuropathy and 35 age and sex-matched healthy controls. We identified and enrolled individuals who visited Vali-Asr University Hospital in Zanjan, Iran, in an outpatient setting, with symptoms of ACM occurring for one week.

We examined the diagnosed patients with typical symptoms of ACM, physical examination findings, and negative neuroimaging results. We used magnetic resonance imaging (MRI) with and without gadolinium and computerized tomography (CT) scan to look for any focal neurological deficits. The clinical symptoms suggestive of cranial neuropathy and the proper physical examinations for evaluating cranial nerve palsy were based on classic semiology.

We excluded patients with concomitant mucocutaneous herpetic lesions, humoral immune deficiency with more than one nerve involvement, focal neurological imaging and physical examination findings leading to another diagnosis, and those who did not consent to participate in the study. After complete evaluations, a list consisting of the patient's age, gender, clinical manifestations, involved cranial nerve, history of cardiovascular diseases, diabetes, hypertension, recent upper respiratory tract infection, and previous cranial mononeuropathy was assembled for final inclusion in the data set.

Matched controls were examined for any signs or symptoms of ACM and excluded if a positive diagnosis was found.

The Ethics Committee of the Zanjan University of Medical Sciences (code: IR.ZUMS.REC.1397.96) approved this project. 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 (113.92) involvement had the highest and the lowest levels of anti-HSV IgG antibody, respectively (Table 3).

Table 1. Positive IgG and IgM HSV Antibodies in Patients and Healthy Controls [a]

Antibody Status	Patients	Controls	P-Value
IgG			0.33
Positive	32 (50.8)	31 (49.2)	
Borderline	0 (0)	2 (100)	
Negative	3 (60.0)	2 (40.0)	
IgM			0.042
Positive	13 (72.2)	5 (27.8)	
Borderline	6 (60.0)	4 (40.0)	
Negative	16 (38.1)	26 (69.1)	

[a] Values are expressed as No. (%).

Also, 11 (31.4%) patients in the ACM group had a previous history of URIs, while only two (5.7%) patients in the control group reported URIs (P-value = 0.006).

5. Discussion

We reported significantly higher positive and borderline anti-HSV IgM antibodies in patients with acute idiopathic cranial mononeuropathy than in the healthy controls, indicating recent HSV reactivation in the patient group. Moreover, all patients with positive anti-HSV IgM antibodies had positive anti-HSV IgG antibodies that excluded primary infection. This is the most valuable finding, supporting our hypothesis on the role of HSV reactivation in patients with ACM. Likewise, in a case-control study by Pollak et al., anti-HSV IgM antibody levels were positive in 14% of patients and 6% of healthy controls' saliva samples, using real-time PCR; whereas 75% and 13% of patients and controls had borderline levels of anti-HSV IgG antibody, respectively, showing a statistically significant difference that supports our findings (10).

Moreover, our results indicated significantly higher serum anti-HSV IgG antibody levels in patients than in the healthy controls, which further implicates the role of HSV in cranial mononeuropathy recurrence (15). However, there were no statistically significant differences in the number of samples with positive anti-HSV IgG antibodies between patients with ACM and the healthy controls. The main explanation for this finding is the high prevalence of HSV infection in the general population, particularly in the 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 infection and the occurrence of cranial mononeuropathy, a four-fold increase in anti-HSV IgG antibody titers six weeks after the beginning of symptoms is suggested (17), which was not attainable in this study due to limitations in time and patient accessibility.

The positive relationship between the prior history of HSV infection (HSV-1/HSV-2) and the occurrence of cranial mononeuropathy has been addressed previously with the application of different diagnostic methods (8-10, 17-24). Most of these studies have evaluated this correlation mainly in fifth and seventh-cranial nerve neuropathies. 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, Musani 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 latently 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 2. Frequency Distribution of IgG and IgM Seropositivity According to Involved Cranial Nerves in Patients [a]

CN	IgM			IgG		
	Positive	Borderline	Negative	Positive	Borderline	Negative
II (3 cases)	1 (33.3)	0 (0)	2 (66.7)	3 (100)	0 (0)	0 (0)
III (4 cases)	2 (50)	1 (25)	1 (25)	4 (100)	0 (0)	0 (0)
IV (2 cases)	0 (0)	0 (0)	2 (100)	2 (100)	0 (0)	0 (0)
V (4 cases)	2 (50)	1 (25)	1 (25)	3 (75)	0 (0)	1 (25)
VI (6 cases)	1 (16.7)	3 (50)	2 (33.3)	6 (100)	0 (0)	0 (0)
VII (6 cases)	4 (66.7)	0 (0)	2 (33.3)	5 (83.3)	0 (0)	1 (16.7)
VIII (10 cases)	4 (40)	1 (10)	6 (60)	9 (90)	0 (0)	1 (10)

Abbreviation: CN, cranial nerve.
[a] Values are expressed as No. (%).

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

CN	Age	IgG Level
II	39.67 ± 4.50	125.73 ± 85.98
III	63.00 ± 30.12	169.42 ± 28.41
IV	58.00 ± 1.41	173.00 ± 18.80
V	62.75 ± 4.57	113.92 ± 75.63
VI	68.67 ± 11.70	155.16 ± 49.11
VII	44.67 ± 2.65	144.80 ± 71.76
VIII	62.50 ± 20.12	148.09 ± 66.95

Abbreviation: CN, cranial nerve.
[a] Values are expressed as Mean ± SD.

cal studies have shown the association between HSV and idiopathic sudden sensorineural hearing loss (ISSNHL) (22, 27). Although both studies did not find any significant association between anti-HSV antibodies and ISSNHL, they reported a higher rate of anti-HSV-1 IgG antibodies in the patient group. Our findings are compatible with the results of these two studies. Koide et al. compared the anti-HSV-1 antibody levels among 61 patients with ISSNHL and healthy controls and demonstrated positive serum HSV-1 in 80% and 77% of patients and controls, respectively (27). In another cohort study of 232 ISSNHL patients, Park et al. documented the positive anti-HSV-1 antibodies in 139 patients; however, they did not observe significant differences in the improvement of symptoms between the two groups after the administration of anti-HSV treatment in the serum-positive group and corticosteroids in the serum-negative group (22).

Consistent with our findings, few case reports have addressed the relationship between HSV infection and the occurrence of optic neuropathy and third-nerve palsy. Tornerup et al., in 2000, documented the presence of HSV-1 in a vitreous biopsy using PCR in patients with acute optic neuropathy following retinal necrosis (17). Similarly, in a study on two patients with oculomotor nerve palsy, Sekizawa et al. demonstrated a possible etiologic role of HSV with a significant increase in anti-HSV antibody levels after evaluation for three consecutive days. Both patients had unremarkable glucose tolerance tests, lumbar punctures, brain angiograms, and CT scan results (21).

Several studies on patients presenting with tenth-nerve palsy, normal lumbar puncture, and brain imaging findings indicated the same results (23, 24); however, we did not evaluate patients with tenth-nerve palsy in our study.

Additionally, in this study, we evaluated the relationships between the occurrence of cranial mononeuropathies and the presence of other medical conditions. We compared the history of recent upper respiratory infection (URI), previous cranial mononeuropathies, diabetes, cerebrovascular accident (CVA), hypertension (HTN), and immune system deficiency conditions such as cancer and HIV in patients with cranial mononeuropathy and healthy controls. The results demonstrated a history of recent URI in 31.4% of patients with idiopathic cranial mononeuropathy one week before the neurological symptoms appeared. This ratio was 5.7% in healthy controls, suggesting a probability of the etiological role of viral infections in cranial mononeuropathies, a relationship that was not studied before. However, it has been speculated that the deterioration of the immune system in response to viral infections may trigger HSV reactivation (28). The rate of disease recurrence was not significantly higher in participants with a history of previous cranial mononeuropathy than in individuals without a disease history. This means that a history of previous cranial mononeuropathy is not a risk factor for its recurrence.

None of the participants reported the presence of can-

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: Mehdi 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.

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

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