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...
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 $\geq 1.1$ is considered positive. A ratio of $\geq 0.8$ but $< 1.1$ is considered equivocal. The recommended quantitative ratios for IgG antibodies are as follows: $< 16$ RU/mL, $\geq 16$ but $< 22$ RU/mL, and $\geq 22$ 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 $58.37 \pm 17.43$ 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 ($P = 0.33$). The mean serum anti-HSV IgG antibody level was significantly higher in patients ($146.78 \pm 60$ RU/mL) than in the controls ($130.61 \pm 52.99$ 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 ($P = 0.042$).

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).
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 the ACM group. 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.

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. 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.

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, 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. 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. 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. In another study, Munani et al. documented positive anti-HSV IgM and IgG antibodies in 35/50 patients with Bell’s palsy. 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. 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. 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-I 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. In another study by Takasu et al. on 17 random dead subjects, PCR and RT-PCR detected the HSV-I in 94% and 88% of TG and GG, respectively. 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. These findings further support the results of our study. Furthermore, two epidemiolog-
The 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: Mehdī 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.

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

References

1. Wald A, Corey L. HSV: Persistence in the population: epidemiology, transmission. In: Arvin A, Campadelli-Fiume G, Mocarski E, Moore P, Roizman B, Whitley R, et al., editors. Human Herpesviruses: Biology, Therapy, and Immunopathogenesis. Cambridge: Cambridge University Press; 2007. p. 656-72. doi: 10.1007/978-0-511-54531-3_17.
2. Marchi S, Trombetta CM, Gasparini R, Temperton N, Montomoli E. Epidemiology of herpes simplex virus type 1 and 2 in Italy: a seroprevalence study from 2000 to 2014. J Prev Med Hyg. 2017;58(1):S27-33. [PubMed: 2855628]. [PubMed Central: PMC542775].
3. Costello MT, M, Sabatini L, Yungbluth P. Herpes simplex virus infections and current methods for laboratory detection. Clin Microbiol News. 2006;28(24):185-92. doi: 10.1096/cminnews.2006.11.005.
4. Fukuda S, Furuta Y, Takasu T, Suzuki S, Inuyama Y, Nagashima K. The significance of herpes viral latency in the spiral ganglia. Acta Otolaryngol (Stockholm). 1994;114:108-10. doi: 10.3109/00034819409127572. [PubMed: 8073871].
5. Klein RJ. The pathogenesis of acute, latent and recurrent herpes simplex virus infections. Arch Virol. 1982;72(1):141-68. doi: 10.1007/BF01344961. [PubMed: 6180702].
6. Kumar SP, Chandy ML, Shanavas M, Khan S, Suresh KV. Pathogenesis and current methods for laboratory detection. Clin Microbiol News. 2006;28(24):185-92. doi: 10.1096/cminnews.2006.11.005.
7. Donofrio PD. Textbook of Peripheral Neuropathy. New York: Springer Publishing; 2012.
8. Lazarini PR, Vianna MF, Alcantara MPA, Scalia RA, Filho HHC. Herpes Simplex Virus in the saliva of patients with vestibular neuritis: a preliminary study. Braz J Otorhinolaryngol. 2006;72(1):77-82. doi: 10.1590/S1808-88942006000100005.
9. Murakami S, Mizobuchi M, Nakashiro Y, Ooi T, Hato N, Yanagihara N. Bell palsy and herpes simplex virus: identification of viral DNA in endoneurial fluid and muscle. Ann Intern Med. 1996;124(1 Pt 1):27-30. doi: 10.7213/0003-4819-124-1_part_1.99601010000005. [PubMed: 7503474].
10. Pollak I, Book M, Smetana Z, Alkin M, Soupavé Z, Mendelson E. Herpes simplex virus type 1 in saliva of patients with vestibular neuritis: a preliminary study. Neurologist. 2011;17(6):330-2. doi: 10.1097/NRL.0b013e31823fa6d. [PubMed: 22045284].
11. Brizzi KT, Lyons J. Peripheral nervous system manifestations of infectious diseases. Neurohospitalist. 2014;4(4):230-40. doi:
1. Arch Clin Infect Dis. 2022; 17(5):e126325. [PubMed: 25160209]. [PubMed Central: PMC421247].

2. Singh A, Preiksaitis J, Ferency C, Romanowski B. The laboratory diagnosis of herpes simplex virus infections. Can J Infect Dis Med Microbiol. 2005;16(2):359-60. doi: 10.1177/194187440501600204. [PubMed: 16159535]. [PubMed Central: PMC2095018].

3. Ashraf Z, Ahurki M, Brandley D, Lam C, Foley K, Meinert E. Tools for the Diagnosis of Herpes Simplex Virus Type 2: Systematic Review of Studies Published Between 2012 and 2018. JMR Public Health Surveillance. 2019;5(2). doi: 10.2196/14216. [PubMed: 3124465]. [PubMed Central: PMC6552407].

4. Reddy SM, Balakrishnan P, Uma S, Thiyagarajan SP, Solomon S. Performance of two commercial enzyme-linked immunosorbent assay kits using recombinant glycoprotein G2 antigen for detection of herpes simplex virus type 2 specific antibodies. Clin Diagn Lab Immunol. 2005;12(2):359-60. doi: 10.1128/CDLI.12.2,359-360.2005. [PubMed: 15699434]. [PubMed Central: PMC549101].

5. Kinchington PR, Leger AJ, Guedon JM, Hendricks RL. Herpes simplex virus and varicella zoster virus, the house guests who never leave. Herpesviridae. 2012;2(1):5. doi: 10.1186/2042-4280-3-5. [PubMed: 22691604].

6. Youssif W, Ibrahim H, Harfoushe M, Abu Hijleh F, Abu-Raddad L. Herpes simplex virus type 1 in Europe: systematic review, meta-analyses and meta-regressions. BMJ Glob Health. 2020;5(7). doi: 10.1136/bmjgh-2020-001236. [PubMed: 32675066]. [PubMed Central: PMC6964498].

7. Tornerup NR, Romsgaard A, Nielsen NV. HSV-1-induced acute retinal necrosis syndrome presenting with severe inflammatory orbitopathy, proptosis, and optic nerve involvement. Ophthalmology. 2000;107(2):397-401. doi: 10.1016/s0144-6652(99)00553-6.

8. Musani MA, Farooqui AN, Usman A, Atif S, Afzal S, Khambaty Y, et al. Association of herpes simplex virus infection and Bell’s palsy. J Pak Med Assoc. 2009;59(2):283-5. [PubMed: 20201772].

9. Behrman S, Knight G. Herpes simplex associated with trigeminal neuralgia. Neurology. 1954;4(7):525-30. doi: 10.1212/wnl.4.7.525. [PubMed: 1376671].

10. Krohel GB, Richardson JR, Farrell DF. Herpes simplex neuropathy. Neurology. 1976;26(6 PT 1):596-7. doi: 10.1212/wnl.26.6.596. [PubMed: 945050].

11. Sekizawa T, Nakamura S, Kogure K, Hayashi K, Yanagi K, Openhaw H. Idiopathic third cranial nerve palsy associated with herpes simplex virus infection. Br Med J (Clin Res Ed). 1987;295(6602):813. doi: 10.1136/bmj.295.6602.813. [PubMed: 319055]. [PubMed Central: PMC127859].

12. Park SM, Han C, Lee JW, Kong TH, Seo YJ. Does Herpes Virus Reactivation Affect Prognosis in Idiopathic Sensorineural Hearing Loss? Clin Exp Otorhinolaryngol. 2017;10(1):66-70. doi: 10.21053/ceo.2016.00306. [PubMed: 27459999]. [PubMed Central: PMC532784].

13. Bachor E, Bonkowski V, Hacki T. Herpes simplex virus type I reactivation as a cause of a unilateral temporary paralysis of the vagus nerve. Eur Arch Otorhinolaryngol. 1996;253(4-5):297-300. doi: 10.1007/BF00178747. [PubMed: 8737789].

14. Tang SC, Jeng JS, Liu HM, Yip PK. Isolated vagus nerve palsy probably associated with herpes simplex virus infection. Acta Neurol Scand. 2000;101(3):174-7. doi: 10.1034/j.1600-0404.2000.00021.x. [PubMed: 1155239].

15. Takas T, Furuta Y, Sato KC, Fukuda S, Inuyama Y, Nagashima K. Detection of latent herpes simplex virus DNA and RNA in human geniculate ganglia by the polymerase chain reaction. Acta Otolaryngol. 1992;112(6):1004-11. doi: 10.3109/00016489209137502. [PubMed: 1136296].

16. Theil D, Arbusow V, Derfuss T, Strupp M, Pfeiffer M, Mascolo A, et al. Prevalence of HSV-1 LAT in human trigeminal, geniculate, and vestibular ganglia and its implication for cranial nerve syndromes. Brain Pathol. 2001;11(4):408-13. doi: 10.1111/j.1750-3639.2001.tb00408.x. [PubMed: 11556685]. [PubMed Central: PMC8098601].

17. Koide J, Yanagita N, Hondo R, Kurata T. Serological and clinical study of herpes simplex virus infection in patients with sudden deafness. Acta Otolaryngol Suppl. 1988;456:21-6. doi: 10.3109/00016488809125072. [PubMed: 2852430].

18. Grinde B. Herpesviruses: latency and reactivation - viral strategies and host response. J Oral Microbiol. 2013;5(1):2276. doi: 10.3402/jom.v5i0.2276. [PubMed: 24167560]. [PubMed Central: PMC3809354].

19. Korczyn A, Jackson WPU. Prevalence of Diabetes Mellitus in Bell’s Palsy. Lancet. 1971;2:772-4. doi: 10.1016/0140-6736(71)92852-3.

20. Yanagihara N, Hyodo M. Association of diabetes mellitus and hypertension with Bell’s palsy and Ramsay Hunt syndrome. Ann Otol Rhinol Laryngol Suppl. 1988;137:5-7. doi: 10.3777/00034894880978302. [PubMed: 3144232].