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Prevalence of herpes zoster virus reactivation in patients diagnosed with Bell's palsy

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Main Article

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Abstract

Objective. Herpes zoster virus can cause inflammatory neuropathy of the facial nerve. However, studies evaluating the prevalence of this agent in peripheral facial palsy are heterogeneous regarding sample group selection, laboratory analysis method and variables studied. In addition, there are a lack of epidemiological data in the Brazilian population on this serological phenomenon in peripheral facial palsy. This study estimated herpes zoster reactivation prevalence in serological samples through chemiluminescence immunoassay for quantitative determination of specific antibodies directed against the virus.

Methods. This cross-sectional study sought to determine the prevalence of viral reactivation by herpes zoster in subjects with idiopathic peripheral facial palsy through analysis of serological samples over a year.

Results. Forty-seven patients (32 females and 15 males) participated. Severe paralysis was more common in older patients ($p = 0.017$). Facial pain ($p = 0.02$) and vertigo ($p = 0.001$) were related to a worse evolution of facial palsy. The rate of serological reactivation of the virus was 12.76 per cent.

Conclusion. The rate of serological reactivation of herpes virus in idiopathic peripheral facial palsy in our population is similar to foreign literature data, suggesting similar aetiological mechanisms in the genesis of this morbidity.

Introduction

Peripheral facial palsy is an entity still widely studied, both for the great functional impact of its sequelae on the quality of life of the individuals in whom it manifests itself, and for the differences that we find in the scientific literature with regard to fundamental clinical aspects of the disease, such as aetiology, treatment and prognosis.

Among the aetiological models proposed to explain the disease, infectious, inflammatory, genetic, immunological, vascular and neoplastic causes stand out.[1,2] However, in up to 75 per cent of cases of peripheral palsy, this morbidity is said to be idiopathic,[3] and it is then called Bell's palsy. A Cochrane review estimates that its incidence is around 20–32.7 cases per 100 000 inhabitants per year.[1]

McCormick, in 1972, postulated that the varicella-zoster virus (also known as herpes virus type 3 or herpes zoster) could be latent in the geniculate ganglion of the VIIth cranial nerve and that its reactivation could trigger inflammatory neuropathy.[4] Since then, increased evidence has been found correlating the presence of the herpes virus with the disease. When this agent is related to a condition of Bell's palsy (that is, a condition of paralysis without classic clinical manifestations such as herpetiform rash) and laboratory evidence of viral reactivation, we define it as zoster sine herpete.[5]

The primary importance of establishing a cause for Bell's palsy is to define therapeutic approaches. Although there are conflicting data on the benefits of antivirals in patients with Bell's palsy,[1,2,6–8] many clinical services adopt this therapy based on studies that have demonstrated the reactivation of viruses in the *Herpesviridae* family using polymerase chain reaction analysis of neural and salivary fluids, serology and autopsies, among other methods, to point out this relationship.[1,5,6,9,10]

As demonstrated by Santos *et al.*, in a study that analysed the positivity of varicella-zoster virus through salivary polymerase chain reaction in patients seen at a tertiary hospital in the city of São Paulo, the influence of several infectious agents on the pathogenesis of peripheral facial palsy (including varicella-zoster virus) varies according to population, geographical and cultural aspects of the target population of the study.[10] Therefore, this work starts from the premise that new assessments of prevalence of reactivation of varicella-zoster virus are essential to establish an epidemiological profile for the environment in which we work.

It has been noted, after reading and reviewing the published articles in this field, that the studies have great heterogeneity with regard to the selection of the sample group, the method of laboratory analysis (concerning both the technique used to demonstrate the reactivation of the varicella-zoster virus and the interpretation of results) and the variables

studied, among other factors. The titration of antibodies against the virus, for example, on many occasions becomes biased by: the scarcity of information regarding the measurement method used, the lack of evolutionary analysis (in more than one stage of the disease) of serology, and the not yet detailed aspects of immunoglobulin G (IgG) and immunoglobulin M (IgM) titrations.[11–13]

Furuta *et al.*, in 2000, demonstrated the presence of co-infection of herpes simplex virus type 1 and varicella-zoster virus by evidence of serological reactivation (enzyme-linked immunosorbent assay) of these two agents in 31 per cent of their sample.[9] This was also demonstrated by Kawaguchi *et al.*, in 2007, by the analysis of salivary polymerase chain reaction in 4 per cent of cases.[6]

Our review highlights that the data regarding the prevalence of varicella-zoster virus in cases of idiopathic peripheral facial palsy are very variable, with rates ranging from 0 to 56.5 per cent; these rates vary according to the region studied and the method of analysis employed. Because of the heterogeneity of the analyses and the scarcity of this type of study in Brazil, it was necessary to reproduce this research in our population.

Materials and methods

Data were collected from research subjects diagnosed with Bell's palsy over a period of one year in the city of São Paulo. For the inclusion of research subjects in this work, the following eligibility criteria were considered: (1) individuals with acute peripheral facial paralysis with less than 7 days of evolution; (2) absence of another causal factor that could justify the paralysis; (3) individuals who had not received a chickenpox vaccination; (4) individuals who underwent out-patient follow up for at least 180 days; (5) and individuals who underwent blood collection for serological analysis (two samples).

The project was submitted to and approved by the ethics committee (approval number 2.216.123; Certificate of Presentation of Ethical Appreciation number 67794917.7.0000.5463). There were 59 cases of Bell's palsy during this period. However, only 47 patients were included in the study, because 12 individuals did not meet criteria 4 and/or 5.

The patients eligible for the research completed a questionnaire that assessed the following: age, sex, clinical history, physical examination findings, co-morbidities and the degree of facial paralysis according to the House–Brackmann scale,[14] both at the time of diagnosis and 180 days after the onset of the condition. In addition, a serological sample was collected from each participant at two stages: the first sample was collected in the first 10 days of the disease, and the second sample was acquired 2 to 3 weeks after the onset of symptoms, with at least 7 days between collections.[5,6,9,15]

All patients underwent the same therapeutic protocol in our institution; this consists of oral corticosteroid therapy (prednisone 1–2 mg/kg/day or 60 mg/day for 7 days with gradual reduction every 3 days), an antiviral (acyclovir 1 g/day for 10 days), and eye care, in addition to facial physiotherapy when necessary.

The blood samples were subjected to immunoassay by chemiluminescence for the quantitative determination of specific antibodies of classes IgG and IgM directed against varicella-zoster virus.

According to the product leaflet, the Liaison® varicella-zoster virus IgM test kit has 100 per cent diagnostic specificity (95 per cent confidence interval (CI) = 98.51–100 per cent) and 81.25 per cent sensitivity (95 per cent CI = 63.57–92.80 per cent). For the IgG kit, the diagnostic specificity is 97.14 per cent (95 per cent CI = 90.05–99.65 per cent) and the sensitivity is 100 per cent (95 per cent CI = 98.85–100 per cent).[16] Furthermore, according to the manufacturer, regarding possible cross-reactivity, the method has already been tested for several agents, such as *Borrelia burgdorferi*, rubeola virus, Epstein–Barr virus, measles virus, parvovirus B19, cytomegalovirus, herpes simplex virus types 1 and 2, *Toxoplasma gondii*, mumps virus and rheumatoid factor, among others. All these potentially interfering cross-reactivities have been eliminated.[16]

Specific reagents from the Liaison Control varicella-zoster virus IgG and IgM kit were used to perform the negative control of the samples.

Viral serological reactivation was considered present when at least one of the samples presented IgM above the reference value or when there was a greater than two-fold increase in the IgG titre between the two collections.[6,9,17]

After gathering all data, SigmaPlot® version 12.0 statistical analysis software was used. For all variables, a non-parametric distribution was demonstrated according to the Shapiro–Wilk normality analysis method, which led us to adopt the chi-square test for nominal categorical variables; Kruskal–Wallis analysis of variance (analysis of variance on ranks) was used to analyse multiple groups with numerical data, with the respective Dunn post-test. A p-value of less than 0.05 was considered statistically significant.

Results

Forty-seven patients participated in the study, of whom 32 (68.09 per cent) were female and 15 (31.91 per cent) were male. Of these, four individuals (8.51 per cent) had a previous history of peripheral facial palsy. The average age of the population studied was 48.74 years (± standard deviation of 17.71 years). Regarding co-morbidities, 42.55 per cent of the patients were hypertensive and 34.04 per cent were diabetic. In addition, the associated symptoms (and their respective incidence rates) were: hyperlacrimation (48.93 per cent), otalgia (46.8 per cent), facial pain (23.4 per cent), xerophthalmia (21.27 per cent), vertigo (14.89 per cent), dysgeusia (12.76 per cent), tinnitus (12.76 per cent) and hyperacusis (4.42 per cent).

We found that the groups of patients stratified according to the degree of facial paralysis differed in age group, with the most severe paralysis being more common in older patients ($p = 0.017$). There was no significant relationship between the degree of paralysis at the time of diagnosis and the other variables studied (presence of co-morbidities, sex and associated symptoms).

When we analysed the relation between the degree of paralysis after 180 days and associated symptoms, we found that facial pain ($p = 0.02$) and vertigo ($p = 0.001$) were related to a worse evolution of peripheral facial palsy in our sample.

The rate of serological reactivation of varicella-zoster virus in patients with Bell's palsy was 12.76 per cent. Of all the patients who were positive on the test, five (10.63 per cent) had a significant increase in the titre of IgG antibodies between the two samples (at least a two-fold increase between the two collections), and only one individual (2.12 per cent) showed both an increase in IgG levels and the presence of high IgM titres.

In addition, a positive correlation was found between varicella-zoster virus viral reactivation and the presence of vertigo ($p = 0.009$). There was no significant association between serological reactivation and the other variables studied, such as the severity of facial palsy, sex, presence of co-morbidities and other symptoms.

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Discussion

In agreement with data in the literature,[1,18,19] a greater incidence of the disease was found in women (in the proportion of 2.13:1), with a peak incidence around the fourth and fifth decades of life. Regarding the age range of our patients, we found a positive correlation between the severity of facial paralysis on the House–Brackmann scale and ageing. This association may suggest that older age is a risk factor for more severe peripheral facial palsy. An Italian study conducted by Monini *et al.*, which evaluated 381 patients with Bell's palsy, found that with each passing year the risk of facial paralysis grows at a linear rate of 2 per cent (95 per cent CI = 1–3; $p < 0.05$);[20] therefore, ageing can be considered an important factor in the clinical course of peripheral facial palsy.

- Studies evaluating herpes zoster virus prevalence in peripheral facial palsy are highly heterogeneous regarding samples, methods and variables studied
- In this study, facial pain ($p = 0.02$) and vertigo ($p = 0.001$) were related to worse evolution of peripheral facial palsy
- The serological reactivation rate of varicella-zoster virus in Bell's palsy patients was 12.76 per cent
- There was a positive correlation between varicella-zoster virus viral reactivation and the presence of vertigo ($p = 0.009$)

The main papers dealing with varicella-zoster virus reactivation rates by laboratory analysis are from outside Brazil, and these estimate that zoster sine herpete represents 0–56.5 per cent of Bell's palsy cases. The main Brazilian study carried out in the area – a study also conducted in São Paulo – that evaluated 120 patients with Bell's palsy through salivary polymerase chain reaction, showed the presence of the virus in only 1.7 per cent of cases.[10] This finding was justified by the demographic differences between the different populations studied. However, our study demonstrated the presence of varicella-zoster virus in 12.76 per cent of cases, an index that is close to that of most foreign literature publications. For example, Kawaguchi *et al.*, in Japan, carried out a multicentre analysis with 150 patients, and concluded that zoster sine herpete corresponded to 12 per cent of Bell's palsy cases.[6] This information leads us to believe that the prevalence of viral reactivation by varicella-zoster virus in our country has a distribution similar to that found in other countries.

In our series, patients who had facial pain and vertigo had a worse outcome from the point of view of facial rehabilitation, compared with the patients who did not present these symptoms at the time of diagnosis. Interestingly, our work also demonstrated a positive correlation between the presence of vertigo and viral serological reactivation, which could suggest that patients with zoster sine herpete could have a more severe inflammatory process in the course of the VIIth cranial nerve involvement. As seen in the literature, the involvement of autonomical sensory and motor fibres of the VIIth cranial nerve can cause symptoms other than isolated facial paralysis.[7] Symptoms such as facial pain are already associated with a worse prognosis.[19] In addition, in the last decades, a correlation has also been reported between dysgeusia and hyperacusis and cases of peripheral facial palsy with less functional motor recovery.[5] In these studies, signs of infection by viruses of the *Herpesviridae* family were also found.[5]

The findings that point to inflammatory neuropathy of the VIIth cranial nerve during a varicella-zoster virus reactivation in patients with Bell's palsy are increasingly evident.[5,6,9,10,12,13,17] The importance of prevalence studies in this area, as proposed in this study, lies in the fact that the clinical management of patients with peripheral facial palsy is still controversial in the literature.[1,2,6,8,21] The main aspect under discussion is the benefit of using antivirals, such as acyclovir and valacyclovir. Although it was not the objective of our work to demonstrate the efficacy of this type of medication, laboratory evidence of varicella-zoster virus viral reactivation, as presented in this document, strengthens the need for clinical trials, to guide treatment for this morbidity.

Conclusion

Our study showed a greater distribution of Bell's palsy in women and it identified age as a risk factor for more severe peripheral facial palsy. In addition, we found that, in our population, patients presenting with facial pain and dizziness may have a worse functional outcome concerning facial paralysis. The serological reactivation of varicella-zoster virus in patients with idiopathic peripheral facial palsy was 12.76 per cent, similar to the data found in foreign literature; this suggests that the aetiological mechanisms in the genesis of this morbidity are similar across different countries.

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Competing interests. None declared

References

1 Allen D, Dunn L. Aciclovir or valaciclovir for Bell's palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev* 2004;(3):CD001869
2 Sullivan FM, Swan I, Donnan PT, Morrison JM, Smith BH, McKinstry B *et al.* Early treatment with prednisolone or acyclovir in Bell's palsy. *N Engl J Med* 2007;**357**:1598–607
3 Greco A, Gallo A, Fusconi M, Marinelli C, Macri GF, de Vincentiis M. Bell's palsy and autoimmunity. *Autoimmun Rev* 2012;**12**:323–8
4 McCormick DP. Herpes simplex virus as a cause of Bell's palsy. *Lancet* 1972;**1**:937–9
5 Lee HY, Kim MG, Park DC, Park MS, Byun JY, Yeo SG. Zoster sine herpete causing facial palsy. *Am J Otolaryngol* 2012;**33**:565–71
6 Kawaguchi K, Inamura H, Abe Y, Koshu H, Takashita E, Muraki Y *et al.* Reactivation of herpes simplex virus type 1 and varicella-zoster virus and therapeutic effects of combination therapy with prednisolone and valacyclovir in patients with Bell's palsy. *Laryngoscope* 2007;**117**:147–56
7 Zandian A, Osiro S, Hudson R, Ali IM, Matusz P, Tubbs SR *et al.* The neurologist's dilemma: a comprehensive clinical review of Bell's palsy, with emphasis on current management trends. *Med Sci Monit* 2014;**20**:83–90
8 Zhao Y, Feng G, Gao Z. Advances in diagnosis and non-surgical treatment of Bell's palsy. *J Otol* 2015;**10**:7–12
9 Furuta Y, Ohtani F, Kawabata H, Fukuda S, Bergström T. High prevalence of varicella-zoster virus reactivation in herpes simplex virus-seronegative patients with acute peripheral facial palsy. *Clin Infect Dis* 2000;**30**:529–33
10 Santos MAO, Caiaffa Filho HH, Vianna MF, Almeida AGP, Lazarini PR. Varicella zoster virus in Bell's palsy: a prospective study. *Braz J Otorhinolaryngol* 2010;**76**:370–3
11 Adour KK, Bell DN, Hilsinger RL. Herpes simplex virus in idiopathic facial paralysis (Bell palsy). *JAMA* 1975;**233**:527–30
12 Ogita S, Terada K, Niizuma T, Kosaka Y, Kataoka N. Characteristics of facial nerve palsy during childhood in Japan: frequency of varicella-zoster virus association. *Pediatr Int* 2006;**48**:245–9
13 Turriziani O, Falasca F, Maida P, Gaeta A, De Vito C, Mancini P *et al.* Early collection of saliva specimens from Bell's palsy patients: quantitative analysis of HHV-6, HSV-1, and VZV. *J Med Virol* 2014;**86**:1752–8
14 House JW, Brackmann DE. Facial nerve grading system. *Otolaryngol Head Neck Surg* 1985;**93**:146–7
15 Sauerbrei A, Eichhorn U, Schacke M, Wutzler P. Laboratory diagnosis of herpes zoster. *J Clin Virol* 1999;**14**:31–6

https://doi.org/10.1017/S0022215121004631 Published online by Cambridge University Press

16 Diasorin. LIAISON® VZV IgG and IgM: The fully automated solution for antibody detection. In: https://www.diasorin.com/en/immunodiagnostic-solutions/clinical-areas [15 January 2020]
17 Furuta Y, Ohtani F, Aizawa H, Fukuda S, Kawabata H, Bergström T. Varicella-zoster virus reactivation is an important cause of acute peripheral facial paralysis in children. *Pediatr Infect Dis J* 2005;**24**:97–101
18 Junior NA, Junior JJJ, Gignon VF, Kitice AT, Prado LSA, Santos VGW *et al.* Facial nerve palsy: incidence of different ethiologies in a tertiary ambulatory. *Int Arch Otorhinolaryngol* 2009;**13**:167–71
19 Baugh RF, Basura GJ, Ishii LE, Schwartz SR, Drumheller CM, Burkholder R *et al.* Clinical practice guideline: Bell's palsy executive summary. *Otolaryngol Head Neck Surg* 2013;**149**:656–63
20 Monini S, Lazzarino A, Iacolucci C, Buffoni A, Barbara M. Epidemiology of Bell's palsy in an Italian health district: incidence and case-control study. *Acta Otorhinolaryngol Ital* 2010;**30**:198
21 Hato N, Sawai N, Teraoka M, Wakisaka H, Takahashi H, Hinohira Y *et al.* Valacyclovir for the treatment of Bell's palsy. *Expert Opin Pharmacother* 2008;**9**:2531–6

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