Seroprevalence of herpes simplex and varicella zoster virus among diabetic and non-diabetic patients with acute peripheral facial palsy

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ABSTRACT

Objectives: The aim was to study the prevalence of herpes simplex virus (HSV) and varicella zoster virus (VZV) seropositive patients among diabetic patients with acute peripheral facial paralysis (APFP) as compared to non-diabetics with APFP and a healthy control group.

Methods: Participants consisted of 40 diabetic patients and 40 non-diabetic patients with APFP from Hai Al-Jamea Hospital, Jeddah, Kingdom of Saudi Arabia studied over a period from July 2000 to December 2001. In addition, 20 age and sex matched healthy volunteers were included as a control group. Paired sera were obtained from all participants within the first 4 days of the illness (acute phase) and 2-3 weeks later (convalescent phase). Paired sera were also obtained from the control group within an equivalent period. Detection of immunoglobulin (Ig) M and IgG class antibodies to HSV and VZV in these sera was carried out using enzyme-linked immunosorbent assays kits. The demonstration of IgM antibodies, 2-fold elevations of IgG antibodies or both was considered positive evidence for virus infection.

Results: The present study has shown that there was no statistically significant difference in the prevalence of HSV-seropositive patients in the diabetic and non-diabetic patients with Bell's palsy; however, it was significantly higher in both groups than in the healthy control group. There were no statistically significant differences in the prevalence of VZV-seropositive patients among the 3 groups.

Conclusion: The significantly high prevalence of HSV-seropositive patients among the diabetic as well as the non-diabetic patients with Bell's palsy suggests an equally important role of HSV infection in the pathogenesis of Bell's palsy in the diabetic as in the non-diabetic patients.

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Bell's palsy is an acute idiopathic peripheral facial paresis. Usually, the diagnosis is established without difficulty in patients presenting with unexplained unilateral isolated facial weakness.[1] The incidence is common, with an annual incidence of 20 per 100,000.[2] The prevalence of diabetes mellitus (DM) in patients with Bell's palsy is higher than in the general population.[1,3] Adour et al[4] found that DM is more common among patients with Bell's palsy than among persons who have never had that disease; and that the risk of Bell's palsy is increased in patients with diabetes. Over the years, 4 theories have been suggested to explain the pathogenesis of Bell's palsy: vascular, immunological, compressive and viral. The vascular

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theory (the oldest) has been ruled out by various studies. Subsequently, the immunological and compressive theories were described almost simultaneously. The former established the mechanisms generating a neural inflammatory response, and the later described the morphological basis, which made the nerve sensitive to these mechanisms. Both theories suggested, among other agents, a virus as the agent triggering the process.[5] Recently, herpes simplex virus (HSV) has been identified as the cause of the disease.[4,6-10] Varicella-zoster virus (VZV) reactivation (Ramsay Hunt syndrome) is a less common cause of acute peripheral facial palsy (APFP), but may appear without skin lesions in a form indistinguishable from Bell's palsy (zoster sine herpete (ZSH)), and the diagnosis is only made by serological assays or polymerase chain reaction analysis.[11] These patients are not considered to be true Bell's palsy patients, leaving HSV to be the only other etiological explanation of Bell's palsy when considering the viral hypothesis. Consequently, APFP includes Bell's palsy and ZSH cases.[6] There are still controversies among different studies regarding the etiology of Bell's palsy in diabetic patients.[4,12,13] Some authors still consider the vascular theory as the main etiology of Bell's palsy in diabetic patients.[4,12] To the best of our knowledge, no one has studied the viral theory in diabetics with Bell's palsy yet. The aim of this study was to study the prevalence of HSV- and VZV-seropositive patients among diabetic patients with APFP as compared to non-diabetics with APFP and a healthy control group.

Methods. The study was conducted at Hai Al-Jamea Hospital, Jeddah, Kingdom of Saudi Arabia. Participants consisted of 40 diabetic patients and 40 non-diabetic patients with APFP. In addition, 20 age and sex matched healthy volunteers were included as a control group. All the diabetics had type II DM diagnosed according to the National Diabetes Data Group criteria.[14] Detailed neurological and general examinations were carried out for all patients. Severity of facial paralysis was graded according to House and Brackmann facial nerve grading system.[15] Patients with clinical evidence of Ramsay Hunt syndrome, defined as APFP accompanied by an erythematous vesicular rash on the ear (zoster otitis) or in the mouth were excluded.[16] Also, patients suffering from conditions known to affect the peripheral and central nervous system such as cerebrovascular disorders, hepatic failure, uremia, endocrine disease, chronic infections and neurotoxic drug usage were excluded. Paired sera were obtained from all patients within the first 4 days of the illness (acute phase) and 2-3 weeks later (convalescent phase). Paired sera were also obtained from the control individuals at first visit and 2-3 weeks later. Detection of immunoglobulin (Ig) M and IgG class antibodies to HSV and VZV in these sera was carried out using enzyme-linked immunosorbent assays kits (Enzygnost Anti HSV/IgM and IgG & Enzygnost Anti VZV/IgM and IgG). These are enzyme immunoassays for the detection and quantitative determination of human IgG and IgM antibodies to HSV and VZV in serum. Immunoglobulin M (or IgG) antibodies contained in the test samples which are specific for HSV (or VZV) bind to the antigen in the wells of the test plate. The anti-human IgM (or IgG)/peroxidase (POD) conjugate binds to these specific antibodies. The enzyme component of the conjugate catalyses the working cromogen solution (tetramethylbenzidine plus hydrogen peroxide) producing a blue color. This reaction is terminated by the addition of stopping solution POD. In positive samples, color changes to yellow and is read at 450 nm. The intensity of the yellow color formed is proportional to the activity of the virus-specific IgM (or IgG) antibodies contained in the sample. As indicated by the manufacturer, demonstration of IgM antibodies or 2-fold elevations of IgG antibodies was considered positive evidence for virus infection.

Statistical analysis. Data was analyzed using the Statistical Package for Social Sciences statistical software, version 10, United States of America. All variables showed normal distribution, consequently parametric statistics were used. Comparison of means of 2 continuous variables were carried out using non-paired t-test. Comparison of means of 3 continuous variables were carried out using one-way analysis of variance (ANOVA). Chi-square test was used to compare between 2 or more non-continuous variables. Null hypotheses were rejected at $p < 0.05$.

Results. The age of the patients and controls, and their sex distribution are shown in **Table 1**. One-way ANOVA test showed that there was no significant difference in the mean age between the 3 groups ($p<0.05$). Also, chi-square test showed that there was no statistically significant difference in the sex distribution among the 3 groups ($p<0.05$). In addition, non-paired t-test showed that there was no significant difference between the diabetic and non-diabetic groups in the severity of facial paralysis at first presentation as assessed by House and Brackmann facial nerve grading system ($t = -0.851$, $p<0.05$) (**Table 1**).

The prevalence of antibodies to HSV and VZV among the 3 groups is shown in **Table 2**. Chi-square test showed that the differences in the prevalence of HSV-seropositive patients among the 3 groups were highly significant (Pearson chi-square test = 12.28, $p<0.01$). The difference in the prevalence of HSV-seropositive patients between the diabetic group and the control group was statistically significant (Pearson chi-square = 5.658, $p<0.05$). Also, the difference in the prevalence of the HSV-seropositive patients between the non-diabetic group and the control group was highly significant (Pearson chi-square = 12.251, $p<0.005$). However, the difference of prevalence of HSV-seropositive patients between the diabetic and non-diabetic groups was not statistically significant (Pearson chi-square = 1.978, $p>0.05$). Chi-square test showed that the differences in

Table 1 - Age, sex and severity of facial paralysis of patients in both groups.

Parameter	Diabetics N = 40	Non-diabetics N = 40	Control N = 20	P
Age in years (mean ± SD)	54 ± 8.6	50 ± 11.8	52 ± 9.8	0.48[a]
Males/Females	23/17	21/19	9/11	0.66[b]
Grading of facial paresis[d] (mean ± SD)	4.2 ± 1.44	4.1 ± 1.58	1	0.71[c]

a - one-way analysis of variance; b - Chi-square test; c - Non-paired t-test between diabetic and non-diabetic groups; d - House and Brackmann facial grading system

Table 2 - Prevalence of antibodies to herpes simplex virus (HSV) and varicella zoster virus (VSV).

Parameter	Diabetics N = 40 (%)	Non-diabetics N = 40	Control N = 20	Chi-square	P
Total HSV	23 (57.5)	29 (72.5)	5 (25)	12.28	0.002*
Total VSV	9 (22.5)	11 (27.5)	3 (15)	1.186	0.55
VSV & HSV	4 (10)	7 (17.5)	2 (10)	1.194	0.55
Total seropostive patients	28 (70)	33 (82.5)	6 (30)	16.89	<0.001*

*statistically significant, p < 0.05

Table 3 - Seropositive patients to herpes simplex virus (HSV) and varicella zoster virus (VSV) among Bell's palsy and zoster sine herpete patients.

Parameter	Diabetics n (%)	Non-diabetics n (%)
Bell's palsy	***31/40 (77.5)***	***29/40 (72.5)***
Seropositive to HSV	19/31 (61.3)	22/29 (75.9)
Zoster sine herpete	***9/40 (22.5)***	***11/40 (27.5)***
Seropositive to VZV	5/9 (55.6)	4/11 (36.4)
Seropositive to VZV and HSV	4/9 (44.4)	7/11 (63.6)

the prevalence of VZV-seropositive patients among the 3 groups were not statistically significant (Pearson chi-square = 1.186, p>0.05). Four patients (10%) in the diabetic group, 7 patients (17.5%) in the non-diabetic group and 2 individuals (10%) in the control group had their sera tested positive for antibodies for both HSV and VZV. The difference between the 3 groups in the prevalence of seropositive sera was highly significant statistically (Pearson chi-square = 16.89, P<0.001).

For the diagnosis of Bell's palsy, zoster sine herpete cases were first excluded from APFP patients (9 in the diabetic and 11 in the non-diabetic groups). Also, 17 individuals (85%) in the control group had their sera tested negative for anti-VZV antibodies. The difference in the prevalence of HSV-seropositive patients among the Bell's palsy patients and the healthy individuals in the control groups was highly significant statistically (Pearson chi-square = 15.159, p<0.005). Similarly, when the prevalence of HSV-seropositive patients in the control group was compared with that in the diabetic (Pearson chi-square = 8.423, p<0.005) or non-diabetic (Pearson chi-square = 14.639, p<0.001) groups, the differences were highly significant statistically. However, when the prevalence of HSV-seropositive patients was compared between the diabetic and the non-diabetic groups, the difference was not statistically significant (Pearson Chi-Square = 1.47, p>0.05). (**Table 3**).

Discussion. There are still controversies in the literature regarding the etiology of Bell's palsy in diabetic patients. Some authors have suggested that the etiology of Bell's palsy in diabetic patients is ischemia of the facial nerve (namely, diabetic mononeuropathy).[3,4,12] Korczyn[12] based his ischemic theory only on the increased prevalence of DM among Bell's palsy patients. Pecket and Schattner[3] found that diabetic patients had significantly much less affection of their taste following Bell's palsy than non-diabetic patients. Accordingly, they postulated a diabetic-related pathogenesis and a vascular rather than a generalized "metabolic" impairment. However, Abraham-Inpijin et al[13] assessed the frequency of risk factors for vascular pathology such as hypertension, lipid disturbances and DM in a group of patients with Bell's palsy. Only hypertension proved to be the most single discriminating variable. These results were against diabetes related vascular pathology. The present study showed that there was no statistically significant difference in the prevalence of HSV-seropositive patients in the diabetic and non-diabetic patients with Bell's palsy; however, it was significantly higher in both groups than in the healthy control group. In addition, when ZSH cases were included (all APFP patients), similar statistical results were found. These results suggest that HSV infection has an important role in the pathogenesis of Bell's palsy in diabetic as in the non-diabetic patients.

Whether diabetes mellitus makes the facial nerve more vulnerable to viral infection, or it is the ischemic

theory that explains the increased prevalence of diabetes mellitus among Bell's palsy patients has not been studied yet. The significantly high prevalence of HSV-seropositive patients among diabetics with Bell's palsy in the present study also suggests that the increased prevalence of DM among Bell's palsy patients[1,3,4] might reflect the vulnerability of the facial nerve in diabetics to viral infection. This hypothesis has been supported by the fact that diabetics were found to have high incidence of subclinical facial nerve involvement.[17] Also, a high prevalence of diabetics among patients with different viral infections[18,19] supports the same hypothesis.

The results of the present study have shown that there was a significantly high prevalence of HSV-seropositive patients in the diabetic and non-diabetic Bell's palsy patients. This supports the previous studies, which found that the etiology of Bell's palsy is reactivation of HSV infection.[8,20] However, more recent studies also found that HSV type 1 is the specific type responsible for the etiology of Bell's palsy.[7,9] Being already established, type specific anti-HSV antibodies were not examined in the present study.

In the present study, zoster sine herpete was diagnosed in 22.5% of the diabetic patients and 27% of the non-diabetic patients with APFP. These results are in concordance with the findings of previous studies.[6,21] Furuta et al[6] found that 29% of their patients who were initially diagnosed as having Bell's palsy, actually had herpes sine herpete following serological assay. Also, Suzuki et al[21] found that 28.5% of their patients with APFP had zoster sine herpete. However, these 2 studies[6,21] did not include a healthy control group. In the present study, the prevalence of seropositive patients to VZV in the diabetic and non-diabetic groups was higher than that in the control group, but the difference was not statistically significant.

Recently acyclovir was found to add to the beneficial effect of steroids in improving the functional outcome of Bell's palsy.[2] The significantly high prevalence of HSV-seropositive patients among the diabetics with Bell's palsy suggest that acyclovir would have similar beneficial effect in diabetics as it does in non-diabetics. A trial of acyclovir in the treatment of APFP in diabetic patients is thus suggested.

In conclusion, the significantly high prevalence of HSV-seropositive patients, among the diabetic as well as the non-diabetic patients, with Bell's palsy suggest an equally important role of HSV infection in the pathogenesis of Bell's palsy in diabetic as in the non-diabetic patients.

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