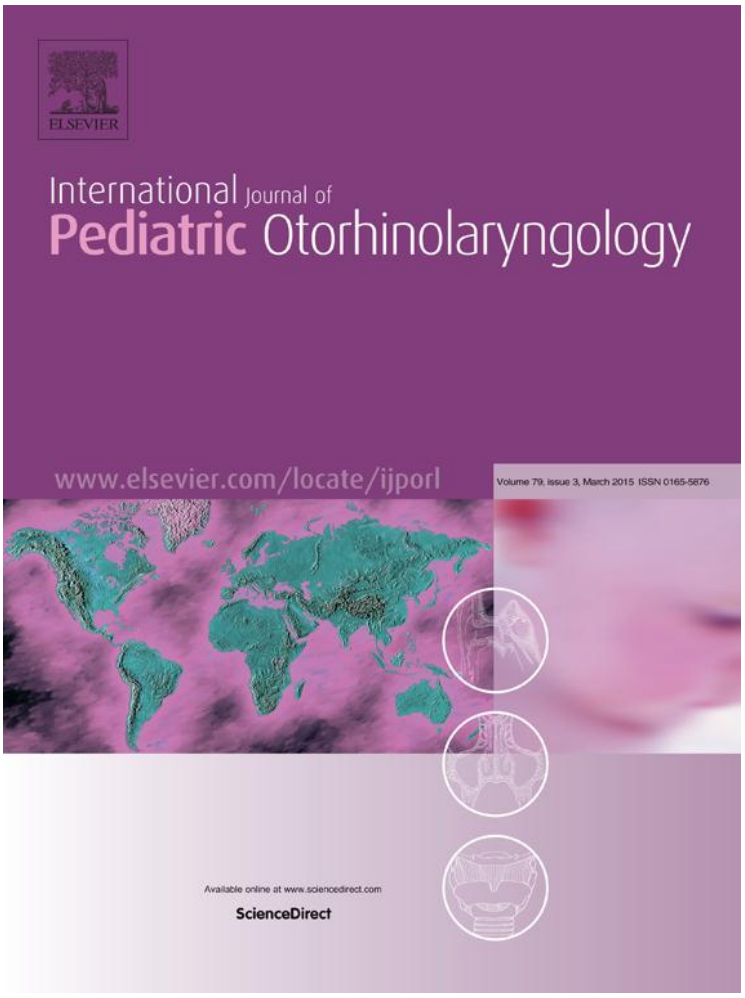

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The association of Varicella zoster virus reactivation with Bell's palsy in children☆

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ABSTRACT

Objectives: Bell's palsy is considered the most common cause of facial nerve paralysis in children. Although different theories have been postulated for its diagnosis, reactivation of the Varicella zoster virus (VZV) has been implicated as one of the causes of Bell's palsy. The aim of the study was to evaluate the association of Varicella-zoster virus infection with Bell's palsy and its outcome in children.
Methods: A total of 30 children with Bell's palsy were recruited and were assayed for evidence of VZV infection. The severity of facial nerve dysfunction and the recovery rate were evaluated according to House–Brackmann Facial Nerve Grading Scale (HB FGS). Paired whole blood samples from all patients were obtained at their initial visit and 3 weeks later, and serum samples were analyzed for VZV IgG and IgM antibodies using ELISA.
Results: A significantly higher percentage of Bell's palsy patients were seropositive for VZV IgM antibodies than controls (36.6% of patients vs 10% of controls) while for VZV IgG antibodies the difference was statistically nonsignificant. HB FGS in Bell's palsy patients with serologic evidence of VZV recent infection or reactivation showed a statistiacally significant less cure rate than other patients.
Conclusions: VZV reactivation may be an important cause of acute peripheral facial paralysis in children. The appropriate diagnosis of VZV reactivation should be done to improve the outcome and the cure rate by the early use of antiviral treatment.

Introduction

Bell's palsy is one of the most common causes of facial paralysis worldwide that has an incidence of 20–30 cases per 100,000 persons and accounts for about 60–75% of all cases of unilateral facial paralysis [1]. In the childhood period, it is considered the most common cause of facial paralysis, with an incidence of around 6.1 in 100,000 in the pediatric population [2]. Clinically, it gives the picture of an acute onset, unilateral, lower motor neuron facial paralysis with aesthetic, functional and psychological disturbance. It may be partial or complete and its diagnosis depends on the exclusion of other causes of facial palsy [3]. However, Taverner [4] proposed minimum diagnostic criteria for the diagnosis of Bell's palsy: paralysis or paresis of all the facial muscles of expression of one side of the face, of sudden onset, absence of signs of central nervous system disease and absence of signs of ear or posterior cranial fossa disease.

Different theories have been postulated for the pathophysiology of Bell's palsy; however, some studies attributed it to an inflammatory process [3,5]. Histopathologic studies of temporal bone obtained from patients with recent episodes of Bell's palsy have revealed an inflammatory process surrounding the nerve fibers, with infiltration of lymphocytes and associated demyelination or axonal degeneration [6]. Many viral infections have been reported to cause acute peripheral facial paralysis (APFP) in children, for example, reactivation of Varicella-zoster virus (VZV), Herpes simplex virus type 1 (HSV-1), Epstein–Barr virus (EBV), cytomegalovirus (CMV), human herpes virus 6 (HHV-6), mumps virus, human immunodeficiency virus (HIV) and hepatitis B virus [5–13]. However, in the majority of patients the cause remains

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unknown and a diagnosis of "idiopathic" peripheral facial paralysis or Bell's palsy is made.

Varicella-zoster virus (VZV) causes Ramsay Hunt syndrome; a characteristic APFP, accompanied by zoster lesions around the auricle or in the oropharynx, and dysfunction of the eighth cranial nerve. However, VZV reactivation might also cause acute peripheral facial paralysis in the absence of zoster, which is a condition termed zoster sine herpete [5]. The aim of our study was to evaluate the association of Varicella-Zoster virus infection with Bell's palsy and its outcome in children.

Methods

This study included 30 children that attended the Rheumatology and Rehabilitation Department, Cairo University and Otolaryngology departments in both Cairo University and Beni Suef University, in the period from May 2012 to December 2013. All cases had acute unilateral peripheral facial nerve palsy with no immediate identifiable causes and were recruited within 10 days of the onset of APFP. None of our patients presented with clinical evidence of Melkersson–Rosenthal syndrome (a triad of recurrent orofacial swelling, relapsing facial paralysis, and fissured tongue) [14]. Patients with other apparent causes of facial nerve palsy were excluded (congenital, traumatic, otitis media. . ..etc). All patients were subjected for full history taking and thorough clinical examination. All patients were treated with corticosteroids. None of the patients was receiving antiviral drugs prior to blood sampling.

Twenty control subjects matched for age and sex were also included in the present study. They were recruited from the pediatric Otolaryngology clinic seeking advice for medical problems other than ear infections.

The severity of facial nerve dysfunction and the recovery rate were evaluated according to House–Brackmann Facial Nerve Grading Scale (HB FGS) at the initial visit and 6 months later to all patients for grading recovery from lower motor neurons facial nerve paralysis. On this scale, grade 1 represents normal face function; 2 mean slight weakness (mild dysfunction); 3 moderate dysfunction; 4 moderate to severe; 5 represents severe dysfunction and grade 6 refers to total paralysis. In 4 and 5 grades patient cannot close the eye and could only barely move the mouth at grade 5 [15]. Recovery was defined as the achievement of HB FGS grade one or two in a patient that initially was grade 3 or more [16]. All children with Bell's palsy were followed up once a week during the first month and subsequently every month until satisfactory recovery.

Blood samples from patients and controls were withdrawn at their enrollment in the study, paired blood samples from patients were obtained at their initial visit and 3 weeks later (convalescence stage) to avoid negative results in suspected early VZV infections [17]. Blood samples were collected and were immediately centrifuged and stored at −20 °C. Serum samples were analyzed for anti VZV IgG and IgM antibodies using a type-specific ELISA kits according to the manufacturer's protocol (MP Biomedicals, Germany). IgG antibodies to VZV were measured with solid-phase enzyme immunoassay (EIA) and IgM antibodies were measured with captured EIA [18]. We scored results for each dilution as positive, negative, or equivocal. For anti VZV IgG antibodies, we defined positive results as an adjusted OD of ≥0.200, equivocal results as an OD of 0.100–0.199, and negative results as an OD of ≤0.100. For anti VZV IgG antibodies, we considered an OD of 0.000–0.099 to be negative, 0.100–0.199 to be equivocal, and ≥0.200 to be positive. Equivocal-range results were interpreted as negative in data analyses. The presence of positive results of IgM antibodies was considered an indication of recent VZV infection, while positive results of IgG antibodies were considered to present a previously immunized individual or a previous VZV infection [18].

A written consent was obtained from parents of all participants in the present study. The protocol for this research conforms to the provisions of the World Medical Association's Declaration of Helsinki. Informed Consent was obtained from all participants prior to the study. Approval from our institutional scientific and ethics committee was also obtained.

Statistical method

Data were analyzed using SPSS statistical package version 17. For numerical data, parametric data were expressed as mean, standard deviation and range. Qualitative data were expressed as frequency and percentage. For comparing categorical data, Chi square (χ^2) test with Yates correction or Fisher exact tests were used. p-Value less than 0.05 were considered significant.

Results

Thirty patients presented with Bell's palsy were included in the present study. They were 13 females and 17 males, their ages ranged from 4 to 15 years (mean 7.87 ± 2.8). The onset of Bell's palsy "in days" at their initial visit ranged from 1 to 9 with a mean of 4.33 ± 1.97. Of those patients, nine patients (30%) were receiving steroids in the form of prednisolone.

Recurrent facial nerve palsy was present in 5 cases out of our 30 patients, two of them had 2 previous attacks on the same side and 3 had a previous one attack on the contra-lateral side. None of our cases presented with clinical herpetic rash.

At the initial visit, out of 30 patients with Bell's palsy, two cases (6%) had HB FGS grade 2, 13 (43.3%) grade 3 and 15(50%) grade 4. After six months, recovery was achieved (HB FGS grade 1 or 2) in 22 (73.3%) patients.

Serological analysis at the initial visit showed that 8 cases (26.6%) were VZV IgM antibodies positive. As for VZV IgG antibodies, 17 cases (56.6%) were positive of them 8 patients were positive for VZV IgM antibodies denoting reactivation of the virus. Three weeks later, VZV IgM antibodies were positive in additional 3 cases (10%), with a total of 11 (36.6%) patients with positive anti VZV IgM and IgG antibodies.

Comparison of patients and control subjects as regards anti VZV IgM and IgG antibodies showed that seropositivity for anti VZV IgM antibodies were significantly higher in patients than controls i.e. 11 patients (36.7%) vs two (10%) of the control cases ($p = 0.034$). However comparison of the frequencies of positive cases with anti VZV IgG antibodies were not statistically significant between patients and controls (Fig. 1), 17 patients (56.7%) vs eight (40%) of the control cases ($p = 0.248$).

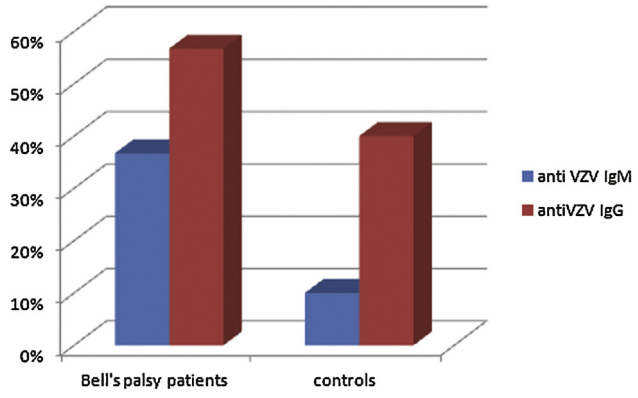

Fig. 1. Anti varicella zoster virus (VZV) IgM and IgG antibodies among Bell's palsy patients and controls described as percentage of the total subjects.

Table 1
House–Brackmann Facial Nerve Grading Scale (HB FGS) grade among Bell's palsy patients at the initial visit and 6 months later described in number of patients (%).

	HB FGS grade at the initial visit					HB FGS grade after 6 months				
	1	2	3	4	5	1	2	3	4	5
Group (I) N (%)	0 (0)	0 (0)	5 (45.5)	6 (54.5)	0 (0)	1 (9.1)	3 (27.3)	7 (63.6)	0 (0)	0 (0)
Group(II) N (%)	0 (0)	2 (10.5)	8 (42.1)	9 (47.4)	0 (0)	15 (8.9)	3 (15.8)	1 (5.3)	0 (0)	0 (0)

According to the serological evidence of VZV recent infection or reactivation of the virus, patients were divided into two groups: group (I) Bell's palsy with serological evidence of VZV recent infection or reactivation of the virus (11 patients) and group (II) Bell's palsy without serological evidence of VZV recent infection or reactivation of the virus (19 patients).

At the initial visit, as regards HB FGS, group (I) patients were 5(45.5%) of grade 3 and 6 (54.5%) of grade 4, none were of grade 1,2 or 5. Group (II) patients were 2 (10.5%) of grade 2, 8 (42.1%) of grade 3 and 9 (47.4%) of grade 4, none was grade 1 or 5. The difference (Table 1) was statistically non significant ($p = 0.536$).

After 6 months, only 4 patients (36.4%) of group (I) achieved recovery (HB FGS grade 1 or 2) compared to 18 (94.7%) patients of group (II), as in Table 1 and the difference was statistically significant ($p < 0.01$).

Discussion

Many infectious causes of acute peripheral facial palsy (APFP) have been identified, such as otitis media, Lyme disease, and some viral infections. Reactivation of Varicella-zoster virus (VZV) is a known cause of APFP [5]. VZV causes APFP without skin lesions; these cases have been termed zoster sine herpete (ZSH), and diagnosis is made by serological assays and/or PCR analysis [19]. In the current study we evaluated the association of Varicella-zoster virus infection with Bell's palsy and its outcome in children.

In this study, VZV reactivation with the absence of zoster (ZSH) occurred in 36.6% of patients clinically diagnosed with Bell's palsy. These findings are in accordance with Furuta et al. [5] who found that VZV reactivation was demonstrated in 11 of 30 (37%) patients with Bell's palsy, while zoster sin herpete was reported in 29% of them. Also, Ogita et al. found that cases of zoster sine herpete were 28.5% among their Bell's palsy patients [20]. However, an antibody response to VZV is not always detected even in patients with Ramsay–Hunt syndrome [5,21]. Because varicella virus latency occurs in sensory rather than motor nerves, it is postulated that during a primary varicella infection, the virus may enter sensory branches of the facial nerve and travel to the sensory fibers of the geniculate ganglion to establish latency. Upon reactivation, the virus travels back along the sensory fibers, at the same time causing inflammation to the adjacent motor fibers of cranial nerve VII, thus leading to facial nerve palsy [22].

In our study, 36.4% of patients in Bell's palsy with serological evidence of VZV recent infection or reactivation of the virus achieved recovery (HB FGS grade 1 or 2) compared to 94.7% of patients in Bell's palsy without serological evidence of VZV recent infection or reactivation of the virus after 6 months and the difference was statistically significant. This comes in accordance with other studies that reported that the complete cure rate for facial palsy among patients with VZV reactivation is lower than the rate among patients without VZV reactivation [22,23]. They also stated that the early administration of antiviral agents and steroids after the onset of paralysis caused by VZV reactivation has been recommended [24,25]. Antiviral agents might inhibit the replication and spread of VZV in the facial nerve, and steroids might reduce its inflammation and edema when paralysis has occurred [5].

It is worth mentioning that our study included a one possible viral cause, because the objective of the study was to assess the association of VZV with Bell's palsy. However, investigation of all viral etiologies on a larger number of patients is recommended in further studies.

In conclusion, this study indicates that VZV reactivation may be implicated as a cause of acute peripheral facial paralysis in children. The appropriate diagnosis of VZV reactivation should be done in those patients to improve the outcome and cure rate possibly by the early use of antiviral treatment.

Conflict of interest statement

None of the authors have financial conflict of interest with regard to this work.

Financial disclosure

None.

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