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Bell's palsy: a manifestation of prediabetes?

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Background – Idiopathic peripheral facial nerve palsy or Bell's palsy (BP) is the most common cause of facial nerve palsy.
Objective – To evaluate the role of glucose metabolism abnormalities in BP. *Methods* – We identified 148 patients with unilateral BP and 128 control subjects. In all we evaluated glucose level at fasting and after a 2-h oral glucose tolerance test (2h-OGTT). In addition we determined insulin resistance (IR), by HOMA-index. Patients and controls were divided in to two groups, according to their Body Mass Index (BMI). *Results* – Following a 2h-OGTT, the prevalence of glucose metabolism abnormalities was significantly higher in patients with BP than in controls ($P < 0.001$). Impaired glucose tolerance (IGT) was found in 57 (38%) patients and in 23 (18%) controls, while a new-diagnosed DM (NDDM) was found in 29 (19%) patients and in 8 (6%) controls. The IR was significantly increased only in BP patients with BMI ≥ 24.9 ($P = 0.005$). BMI, waist circumference, blood pressure, tryglicerides, serum lipid, drugs use were not significantly different between patients and controls. *Conclusions* – In this study we found that prediabetes is frequently associated with facial palsy. We propose to perform a 2h-OGTT in patients with peripheral facial palsy and normal fasting glycaemia. HOMA-index should be evaluated in obese facial palsy patients.

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Key words: Bell's palsy; peripheral facial palsy; facial palsy and prediabetes; neuropathy and diabetes; 2-h oral glucose tolerance test; hyperinsulinemia

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Introduction

Idiopathic peripheral facial nerve paralysis, or Bell's palsy (BP), is the most common cause of facial nerve palsy. BP accounts for approximately 49–51% of all cases; other causes may be trauma, infection of the middle ear and mastoid bone, geniculate herpes, tumours along the intracranial roots, acoustic neuroma, diabetes, Lyme disease and sarcoidosis (1). The annual incidence of BP is 15–30 per 100,000 persons, with equal number of men and women affected. There is no predilection for either side of the face. BP has been described in patients of all ages, with peak incidence noted in the 40s. It occurs more commonly in patients with diabetes and in pregnant women (2, 3). Prediabetes is defined as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) following a 2-h oral glucose tolerance test (2h-OGTT). The relationship between BP and diabetes mellitus (DM) is well known (4), while association with prediabetes is contentious (5). However, several studies have demonstrated that IGT is an important contributor to peripheral neuropathy (6, 7).

In the present study performed in our country (Calabria, Southern Italy), we assessed glucose metabolism abnormalities in 148 subjects with BP and normal fasting glycaemia.

Methods

Patients and ethical committee approval

The study was approved by the Ethical Committee of 'S. Giovanni di Dio' Hospital, Crotone, Italy. All patients gave their consent, in accordance with the official standards of the 1964 declaration of Helsinki, local laws and regulations. We studied prospectively 148 patients with BP associated with normal fasting glycaemia and 128 control subjects between January 2007 and February 2009. Exclusion criteria were: (i) family history of facial nerve palsy; (ii) distal symmetric neuropathy; (iii) alcohol overuse according to the DSM-IV criteria (8); (iv) drug intake that could interfere with glucose metabolism (i.e. steroids); (v) autoimmune conditions such as connective diseases, human immunodeficiency virus and/or other active infections; (vi) abnormal

results on blood tests including electrolytes, blood glucose, HbA_{1c}, renal function, liver function, complete blood cell count, B_{12} level, serum protein electrophoresis; (vii) pregnancy; (viii) sarcoidosis; (ix) Lyme disease; (x) multiple sclerosis. As controls, we enrolled normal subjects coming from the same geographical area of the patients and a similar life style. Control subjects did not have clinical evidence of BP and/or systemic disorder, DM, autoimmune and infective conditions or signs of peripheral neuropathy. Patients and controls were divided into two groups, according to their body mass index (BMI). We used WHO-defined categories of BMI: normal weight (BMI: ≤24.9) and overweight and/or obese (BMI: ≥25) (9).

Evaluation

Every patient was evaluated by an endocrinologist and a neurologist. All of them showed a unilateral peripheral facial palsy of moderate-severe grade. After a first-level check-up, all patients underwent the following tests: magnetic resonance imaging (MRI) and Angio-MRI (MRA) with gadolinium of the brain, electromyography (EMG) evaluation with an extensive nerve conduction study, HIV-test, Vit B_{12}, folic acid, Anti-Borrelia antibodies (IgM–IgG), angiotensin converting enzyme (ACE) levels and chest X-ray. All tests were normal in every subject. Recorded medical data for patients and controls included anamnestic data (dietary habits, life style, drug use), demographic information (age, gender), BMI, waist circumference, glucose and insulin values at fasting and after 2h-OGTT, serum HbA_{1c}, cholesterol, triglyceride, iron and ureic levels. Procedure for the 2h-OGTT required fasting after mid-night, obtaining a baseline fasting glucose level and administration of the oral glucose load within a 5-min period. Blood specimens to determine plasma glucose and insulin levels were subsequently drawn at 120 min, timed from the beginning of the glucose load. Insulin resistance (IR) was calculated by the homoeostasis model assessment (HOMA) formula: basal glucose plasma (mg/dl) × basal insulin plasma (UI/ml)/405, with a cut-off value of 2.7 (10). Patients and controls were established as having IGT if the 120-min venous plasma glucose value fell between 140 and 200 mg/dl. Criteria for new-onset DM were fasting plasma glucose level higher than 126 mg/dl or 120-min venous plasma glucose level higher than 200 mg/dl on the 2h-OGTT (11). The 2h-OGTT and every other metabolic assessment (i.e. glucose and insulin values, HbA_{1c}, HOMA index, etc.) was performed before starting corticosteroid treatment.

Data analysis

Data were expressed as mean ± SD. Patients were compared with controls with respect to variables representing their current status and potentially, the aetiology of the condition. For categorical variables, this was performed by comparing distributions using χ^2 tests and for calculated variables by comparing means using *t*-tests with correct test of the normal assumption required. When they were not satisfied because of skewed data distributions, logarithmic transformations were used. Finally, to assess and allow for discrepancies among the clinical characteristics in the group comparisons and to assess the relative significance of potential aetiological variables, logistic regression was used. In all cases, a *P*-value of 0.05 was considered statistically significant.

Results

Demographic features

During the period of 2 years, from 2007 to 2009, we recruited prospectively 148 (98 women and 50 men) patients with BP. Mean age in the patients group was significantly higher than in control group (56.1 ± 8.9 vs 50.5 ± 6.8 years; $P = 0.002$); all subsequent statistical comparisons of the two groups took age into account. In the control group, 88 were women and 40 men: there was no significant difference as regards gender between patients and controls ($P = 1.25$) (Table 1).

Table 1 Features of 148 patients with facial palsy and 128 control subjects

	Patients	Controls	*P*-value
Number of patients	148	128	0.005
Age (years)	56.1 ± 8.9	50.5 ± 6.8	0.002
Gender (M/F)	98/50	88/40	1.25
Fasting glycaemia (mg/dl)	74 ± 9.1	79 ± 6.8	0.45
Fasting insulinaemia (UI/ml)	10.9 ± 1.9	13.4 ± 2.9	1.72
Glycaemia 2-h-OGTT (mg/dl)	176 ± 15.9	136 ± 12.4	0.002
HbA_{1c} (%)	5.1 ± 0.6	4.8 ± 0.9	0.623
Triglycerides (mg/dl)	139 ± 10.9	143 ± 9.1	0.412
Serum lipid (mg/dl)	146 ± 14.9	135 ± 10.1	3.12
Waist circumference (cm)	86.5 ± 8.8	79.8 ± 5.8	1.1
HOMA index	2.7 ± 1.2	2.4 ± 0.5	3.2
Systolic pressure (mmHg)	128 ± 8.9	119 ± 9.7	0.25
Diastolic pressure (mmHg)	75.6 ± 7.4	69 ± 9	0.82
Anti-depressant or/antipsychotics use (no)	9	11	2.4

BMI, body mass index: [weight (kg)/height^2 (h^2)]; IR, insulin resistance; HOMA index: basal glucose plasma (mg/dl) × basal insulin plasma (UI/ml)/405.

The differences between the proportions with insulin resistance >2.7 on the HOMA formula. Values are expressed as mean (SD) unless otherwise indicated. *P*-value was evaluated after adjustment for age.

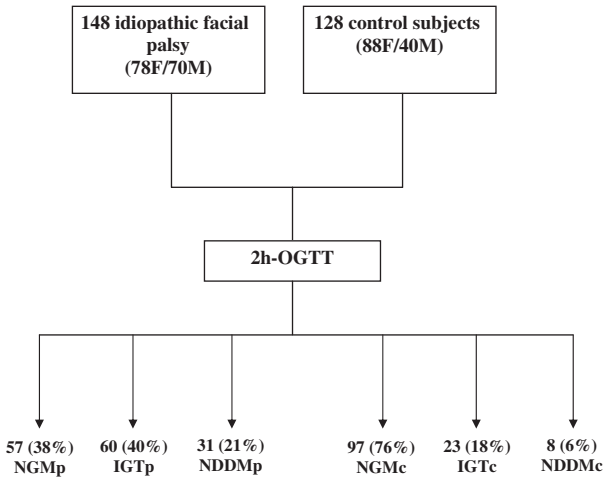

Figure 1. Clinical features of 148 idiopathic facial palsy and 128 control subjects divided into three subgroups (NGM, IGT and NDDM) according to 2h-OGTT response. In patients: normal glucose metabolism (NGM*p*), impaired glucose tolerance (IGT*p*) and newly diagnosed diabetes mellitus (NDDM*p*). In controls: NGM*c*, IGT*c* and NDDM*c*.

Impaired glucose tolerance and insulin resistance

The mean fasting glucose value was 74 ± 9.1 mg/dl in patients group and 79 ± 6.8 mg/dl in controls group respectively ($P = 1.8$). Following the 2h-OGTT, we found an abnormal glucose metabolism in 91 (61%) patients (60 with IGT and 31 with DM) and in 31 (24%) control subjects (23 with IGT and 8 with DM). After adjustment for age, the difference between patients and controls was significant ($P < 0.001$) (Fig. 1). Eighty-six (58%; 57 women and 29 men) patients with facial palsy showed a BMI ≥ 25, while in the control group, 61subjects had a BMI ≥ 25 (48%; 44 women and 17 men), after adjustment for age, this difference was not significant ($P = 1.1$). Among overweight and/or obese (BMI: ≥25) subjects, IR calculated with HOMA formula was present in 60 patients (40%) and in 21 controls (16%) respectively; after adjustment for age, this difference was significant ($P = 0.005$). Among normal weight subjects (BMI: ≤24.9), IR was present in 26 patients (17%) and in 25 controls (19%) respectively; this difference was not significant ($P = 2.2$) (Table 2).

Clinical features

Waist circumference, HbA_{1c}, mean values blood pressure, triglycerides, serum lipid, iron and uraemic levels were not significantly different between patients and controls, after adjustment for age. History of antidepressant or antipsychotics use was similar in patients and controls (patients vs controls: 9 vs 11; $P = 2.4$) (Table 1).

Table 2 Prevalence of insulin resistance in 148 patients and 128 controls divided into two groups, according to their BMI. We used WHO-defined categories of BMI: normal weight (BMI: ≤24.9) and overweight and/or obese (BMI: ≥25). A total of 148 patients with Bell's palsy and 128 control subjects

	Patients *N* (%) 148	Controls *N* (%) 128	*P*-value
BMI ≥ 25	86 (58%)	61 (48%)	1.5
BMI ≥ 24.9	62 (42%)	67 (52%)	301
BMI ≥ 25 + IR	60 (40%)	21 (16%)	0.005

BMI, body mass index: [weight (kg)/height^2 (h^2)]; IR, insulin resistance; HOMA index: basal glucose plasma (mg/dl) × basal insulin plasma (UI/ml)/405. Values are expressed as mean (SD) unless otherwise indicated. *P*-value was evaluated after adjustment for age.

Discussion

In this study, we investigated the prevalence of abnormal glucose metabolism (IGT and DM) by 2h-OGTT in subjects with BP. Sixty-one per cent of subjects showed abnormal glucose metabolism after a 2h-OGTT, 40% having an abnormal IGT and 21% DM. These percentages were significantly higher than those reported in the control group ($P < 0.001$). Several works emphasizing the microvascular and axonal injury of diabetic neuropathy and strict research criteria for diagnosis reinforced the popularly held notion that development of neuropathy required a prolonged period of hyperglycaemia (12). A decade of small epidemiology studies (13, 14) offers evidence that early hyperglycaemia is sufficient to damage distal peripheral nerves. In fact, various clinical studies suggest that neuropathy is more common in patients with prediabetes. As a matter of fact, a prospective study of 187 patients with idiopathic neuropathy found 45% of patients with IGT and a further 15% with previously unrecognized diabetes (14). In a previous case–control study performed on 162 patients, we found that blepharoptosis is frequently associated with prediabetes (IGT and IR) (15). The relationship between facial palsy and DM is well-known; conversely, there are no controlled studies on the association of facial palsy and manifestation of prediabetes. Our data documented a strong linkage between facial palsy and glucose metabolism abnormality (IGT and DM) after 2h-OGTT in patients with normal fasting glycaemia. Nevertheless, our data highlight IR as a risk factor for neuropathic injury depending on BMI. In fact, HOMA index had a significant higher value only in patients with BMI: ≥25, while no differences were found in normal weight patients vs controls. It is not surprising that facial palsy is frequently associated with both IGT and IR. The EuroDiab study that followed 3000 subjects with type 1 diabetes for up to 7 years,

found that among the 1200 subjects without neuropathy at baseline, hypertension, serum lipids, triglycerides, BMI and smoking were independently associated with increased risk of neuropathy during follow-up (16). A methodological limitation of our study is the control group: to obtain a convenient sample of control subjects, we recruited people matched for gender, geographical areas, ethnic background, dietary habits and life style; they were not matched for age. Nevertheless, after adjustment for this variable, we did not find any difference in waist circumference, blood pressure, triglyceridaemia, iron, uraemic and serum lipid levels and antipsychotic use between facial palsy patients and controls, while the association between abnormal glucose metabolism and facial palsy remained strongly significant. Neuropathy in IGT and diabetes seem to share similar pathogenetic mechanisms, the final common pathways of which include direct metabolic effects on nerve and injury to small blood vessels leading to nerve ischaemia. Hyperglycaemia causes direct nerve injury by several mechanisms including increased oxidative stress, accumulation of advanced glycation endoproducts, impaired axonal transport and impaired flow through the polyol pathway (12). Animal model and cell culture data suggest that intermittent hyperglycaemia, similar to those observed in IGT, results in nerve injury. Embryonic rat dorsal root ganglionic cell cultures demonstrate apoptotic cell death and reduced neurite outgrowth when exposed to acute hyperglycaemia (17). The microangiopathy may also be a compensatory response to endoneurial ischaemia/hypoxia induced by chronic hyperinsulinaemia (18). IR is a self-reinforcing process that is intimately associated with obesity, and strongly promote hyperglycaemia (19). Obesity is central to this process. Adipocytes respond to reduced skeletal muscle insulin sensitivity by increasing glucose uptake. This increases adipocyte size, stimulating production and release free fatty acids and triglycerides. Elevated circulating free fatty acids in turn promote hyperglycaemia by stimulating hepatic gluconeogenesis and potentially inhibit endothelian nitric oxid (NO) synthesis and vasodilatation (20). Tumour necrosis factor-α is also related to enlarged adipocytes, where it increases oxidative stress reducing insulin receptor expression and promoting endothelial injury (21). Conversely, enlarged adipocytes reduce expression of the vasoprotective agent adiponectin, accelerating endothelial cell proliferation and macrophage-mediated atherosclerosis injury (22). Altogether, these findings support an aetiological relationship between prediabetic status and neuropathy. Although our findings suggest that facial palsy is an early event in subjects with subclinical glucose metabolism imbalance, causes of facial palsy different from those investigated cannot be excluded. Our study could be criticized because the 2h-OGTT was not performed after loading the diet with carbohydrates for 4 days, which is known to increase the proportion of patients in the IGT range (23). This may represent a possible bias to our results. Nevertheless, the test was performed in the same way for patients and controls and hence it is likely that the relative proportions of patients and controls in the IGT could remain unmodified. In conclusion, to evaluate an early impaired glucose metabolism, we propose to perform a 2h-OGTT in all patients with idiopathic facial palsy and normal fasting glycaemia. IR compared with OGTT does not provide adjunctive information about facial palsy risk. In our study, IR was predictive of facial palsy risk only in obese patients. Additional case–control studies matched for gender are needed before defining causal relationship between facial palsy and prediabetes.

Disclosure

The authors report 'no conflict of interest'.

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