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Type 2 diabetic patients with Graves' disease have more frequent and severe Graves' orbitopathy

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Abstract *Background and aims:* Due to the worldwide increasing prevalence of diabetes (DM), patients with both diabetes and Graves' disease (GD) have become more frequent. Sporadic reports indicate that Graves' orbitopathy (GO), a GD complication that affects orbital soft tissues, can be severe in DM patients. The relationship between these diseases is not well understood.

This study aims at evaluating the association of GD and GO with autoimmune and non-autoimmune diabetes (DM) and to assess diabetic features that influence GD and GO prevalence and severity.

Methods and results: This retrospective study evaluated GD, GO and DM association in 1211 consecutive GD patients (447 with GO and 77 with DM). A case-control study was carried out to evaluate DM relationship with GO severity by comparing at 1:2 ratio GO patients with or without DM. A strong association was found between GD and T1DM ($p = 0.01$) but not T2DM. Instead, the presence of GO was strongly associated with T2DM ($p = 0.01$). Moreover, GO was more frequently severe in GD patients with T2DM (11/30 or 36.6%) than in those without T2DM (1/60 or 1.7%, $p = 0.05$). T2DM was the strongest risk factor for severe GO (OR = 34.1 vs. 4.4 $p < 0.049$ in cigarette smokers). DM duration, obesity and vascular complications, but not metabolic control were significant determinants of GO severity.

Conclusions: GD is associated with T1DM but not with T2DM, probably because of the common autoimmune background. GO, in contrast, is more frequent and severe in T2DM, significantly associated with obesity, diabetes duration and diabetic vasculopathy but not metabolic control.

Introduction

Diabetes mellitus (DM) [1,2] has been reported to be a risk factor for Graves' orbitopathy (GO) [3]. GO is a manifestation of Graves' disease (GD) characterized by inflammation and expansion of retroocular soft tissues. Proptosis, malfunctioning of the extraocular muscles and optic nerve damage are the major clinical consequences that impair a patient's quality of life and may be sight-threatening [4–6]. GO severity is the result of a complex interaction between genetic (familiarity, gender, orbit characteristics) and non-genetic factors (smoking, radioiodine treatment, thyroid function) [6].

The mechanisms why diabetes can favor and worsen GO are unclear. One possibility involves the autoimmune background of the disorder. GD, GO and type I diabetes mellitus (T1DM) share an autoimmune nature and, in particular, can share susceptibility as well as involved loci

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of the HLA system [7,8]. Autoimmunity, however, has no role in the etiopathogenesis of type 2 diabetes mellitus (T2DM), which is approximately ten times more prevalent than T1DM [2]. Nevertheless, a number of T2DM cases with severe GO have been described. These cases might be the casual consequence of the high prevalence of T2DM in the population but may also have some unknown pathogenetic mechanism.

We evaluated the frequencies of GD and GO in patients with either autoimmune (T1DM) or non-autoimmune diabetes (T2DM) and evaluated in a case-control study which DM features are associated with more severe orbitopathy in matched groups of GD patients with or without diabetes.

Methods

We investigated two separate aspects of the association between GO and DM:

a) the prevalence of DM in a large series of patients with GD with or without GO; and
b) the severity of GO in GD patients with either T1DM or T2DM compared with matched GD/GO patients without diabetes.

These retrospective studies were carried out according to the guidelines of the ethics committee of our Hospital.

Patients

a) The prevalence of DM was calculated in 1211 patients with GD who received a medical examination and treatment at the Thyroid Clinic, Garibaldi Hospital Medical Center, Catania, Sicily, in the years 2002–2011. DM was diagnosed on the basis of glycosylated hemoglobin (HbA1c) $\geq$6.5% ($\geq$48 mmol/mol), fasting glycemia $\geq$126 mg/dl on two or more separate occasions and anti-diabetes treatment.

Diabetic patients were classified as having T1DM when diabetes was diagnosed before age 40 (with ketoacidosis in two cases) and in all patients with either C-peptide $<$0.2 nmol/l during fasting and positive autoantibodies (to GAD and IA2). Moreover, insulin treatment was required immediately or within a few months after diagnosis in all five T1DM patients. T2DM was diagnosed when diabetes never required insulin treatment or when insulin was added to oral treatment many years after diagnosis (6 cases). In all cases, after insulin addition, the fasting C-peptide was still higher than 0.6 nmol/l. Most of these patients were overweight (10/30) or obese (15/30), and in all cases, DM was diagnosed after age 45. All T1DM patients were treated with insulin, while T2DM patients were treated with either diet alone (6 cases) or with the addition of metformin (23 patients: 11 with only the biguanide, 7 combined with a sulfonylurea and 5 with bed-time insulin). One T2DM patient was treated with basal/bolus insulin injections after ten years of oral therapy.

In all 5 T1DM patients, DM onset preceded GD and GO occurrence. DM occurred before GD in 20/30 T2DM patients (average interval 6.6 years, range 2–24 years), was diagnosed at the same time in 6 cases, while in 4 patients, GD was diagnosed before T2DM.

b) The influence of DM on GO severity was evaluated with a retrospective case-control study carried out in GD patients with GO and DM. GO severity in these patients was compared to that observed in a matched control group of GD patients (1:2 ratio) having GO but not DM. Control patients were matched with the diabetic patients for the following factors that may influence GO: age ($\pm$5 years for T2DM and $\pm$10 years for T1DM), gender, body mass index (BMI), smoking habit, GO activity, thyroid function, presence of anti-TSH-receptor antibodies and GO duration.

The studied GD/GO diabetic series included all five patients with T1DM observed in the period 2002–2011 and 30/36 patients with T2DM observed in the same period. Six T2DM patients were not included in the study because one had maturity-onset diabetes of the young type 2 (MODY 2), one had severe diabetic retinopathy, one did not agree to the use of his clinical data, and three had incomplete anamnestic records and/or orbit data (lost at follow-up).

GO severity evaluation

GO severity and clinical activity stage were evaluated at the patient presentation in our Clinic by trained investigators according to the protocol of our Medical Center.

GO severity was evaluated according to the EuGoGo guidelines [9,10]. Lid fissure width was evaluated in millimeters by a router and proptosis with a Hertel exophthalmometer. Diplopia was classified according to the Gorman score [11]. A complete ophthalmological evaluation was carried out by an expert ophthalmologist. The GO was defined a) mild when features of GO have only a minor impact on daily life and patients had one or more of the following: minor lid retraction ($<$2 mm), mild soft tissue involvement, exophthalmos $<$3 mm above 21 (normal value for caucasian individuals in our experience), transient or no diplopia, corneal exposure responsive to lubrificants; b) moderate to severe when eye disease had sufficient impact on daily life with one or more of the following: lid retraction 2 mm or more, moderate or severe soft tissue involvement, exophthalmos 3 mm or more above 21, inconstant or constant diplopia and c) severe in case of dysthyroid optic neuropathy (DON) and/or corneal breakdown. Severe GO was graded as “clinical” when visual acuity was $<$0.6 pinhole acuity, and it was considered “subclinical” when visual acuity was between 0.6 and 0.9. To confirm the diagnosis of DON one or more of the following had to be present: apical crowding on computed