Diabetes mellitus: a risk factor in patients with Graves' orbitopathy

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Abstract

***Aims*—To assess the prevalence of dysthyroid optic neuropathy (DON) in patients with diabetes mellitus (DM) and Graves' orbitopathy (GO) and to investigate the complications of surgery for GO in these patients.**

***Methods*—The records of 482 consecutive patients with GO referred in a 5 year period were studied. Those patients who also had DM were selected for further study. The prevalence of insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM) was registered, as well as the prevalence and course of DON. In the patients who underwent surgery for GO the postoperative complications were recorded.**

***Results*—Out of 482 patients with GO, 15 (3.1%) also had DM. Eight (1.7%) had IDDM, 7 (1.4%) had NIDDM. Five patients (33.3%) three with IDDM and two with NIDDM developed DON with 50% improvement of visual acuity after treatment, whereas in the whole population of 482 GO patients 19 had DON (3.9%), showing 69.4% improvement of vision after treatment. 10 patients with GO and DM were operated for GO; in one of them an optic atrophy developed as a result of a postoperative haemorrhage directly after a three wall orbital decompression by coronal approach. No other postoperative complications occurred.**

***Conclusions*—The prevalence of IDDM in patients with GO is higher than in the normal population. DON occurs much more frequently in patients with GO and DM than in the total group of GO patients and seems to have a worse visual prognosis.**

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Graves' orbitopathy (GO) is a disorder of presumed autoimmune nature, closely related to Graves' thyroid disease.[1] It is the most frequent orbital disorder in adults. Clinical findings typically consist of eyelid swelling, lid retraction, proptosis, acquired double vision, and impaired visual acuity. Blindness resulting from optic neuropathy, is the most threatening complication.[2] Dysthyroid optic neuropathy (DON) is generally accepted as being caused by compression of enlarged extraocular muscles at the orbital apex; vasculopathy associated with smoking and diabetes may be an additional factor.[3–5]

Diabetes mellitus (DM) is the most common endocrine disorder, with a significant morbidity and mortality.[6] The most prevalent form of DM is non-insulin dependent diabetes mellitus (NIDDM) which is caused by a combination of genetic and environmental factors resulting in insulin deficiency and insulin resistance.[7 8] Autoimmunity is supposed to be the major aetiological factor in insulin dependent diabetes mellitus (IDDM).[9] The major long term complication of DM is a generalised vasculopathy with basement membrane disease, blood flow disorders, and platelet abnormalities as the three basic mechanisms of vascular injury.[10]

In a previous study we found that the combination of DON and DM was associated with a worse response to orbital decompression.[11] Therefore, we retrospectively studied those patients in whom the two disorders coexisted. The aims of this study were to assess the prevalence and course of DON in patients with GO and diabetes and to record the complications of treatment for GO.

Patients and methods

We retrospectively studied the records of 482 consecutive patients with GO referred to the Donders Institute of Ophthalmology during the period January 1992 to January 1997. Included in this study were patients with a diagnosis of GO (based on the clinical picture, a characteristic computed tomograph scan, and supported by immunological and/or endocrinological findings) who had diabetes mellitus (insulin dependent or non-insulin dependent) at the time of referral. In the patients who met the inclusion criteria, age at referral and sex were recorded. The course of the orbitopathy was studied. Special attention was paid to the incidence of DON compared with that in the whole population of GO patients. Visual functions were evaluated during 0–12 months after treatment and the final visual acuity was recorded. The response of the visual acuity to treatment was compared with that in the whole group of GO patients. The surgical interventions and postoperative complications such as haemorrhage, delayed wound healing, and infection were recorded.

Differences in percentages (using the standard error of difference between percentages) with an error probability value of less then 0.05 ($p<0.05$) were considered statistically significant.

Results

Out of 482 patients with GO, 15 patients (3.1%) met the inclusion criteria. There were 12 females and three males; mean age at referral was 55.5 years (range 17–68 years). Eight

Table 1 Patients with Graves' orbitopathy, diabetes mellitus, and dysthyroid optic neuropathy (n=5)

Patient (age in years)	*Sex*	*DM*	*Retinopathy*	*VA before DON treatment*	*DON treatment*	*VA after treatment*	*Comment*
1 (60)	F	IDDM	—	0.6 0.6	steroids orally two wall orbital decompression	0.6 0.6	
2 (66)	F	NIDDM	—	0.6 0.6	two wall orbital decompression steroids iv	0.5 0.8	
3 (65)	F	IDDM	—	0.1 0.4	three wall orbital decompression	0.5 0.4	
4 (60)	F	IDDM	background retinopathy, panretinal photocoagulation scars	0.016 0.25	steroids iv two wall orbital decompression	0.25 0.25	
5 (65)	M	NIDDM	—	0.5 0.6	steroids iv	0.6 1.0	also myasthenia gravis

DM=diabetes mellitus; IDDM=insulin dependent diabetes mellitus; NIDDM=non-insulin dependent diabetes mellitus; VA=visual acuity; DON=dysthyroid optic neuropathy.

patients, 1.7% (95% confidence interval 0.53–2.8%) had IDDM, whereas seven patients (1.4%) had NIDDM. All patients were white.

The course and the medical and/or surgical interventions of the patients with DM and DON are shown in Table 1. Five of the 15 patients with GO and DM had DON (33.3%) (patients 1–5), all with visual field defects and two of them with oedema of the optic discs. All of them underwent treatment with high dose steroids (500 mg methylprednisolone intravenously, every 48 hours, four times), orbital decompression or both. One patient (number 5), in whom the DON presented itself on the right side as an anterior ischaemic optic neuropathy (AION) also had myasthenia gravis. In five of the 10 eyes (50%) treatment resulted in an improvement of the visual acuity (0.1 or more), in four eyes (40%) visual function stabilised, and in one eye (10%) vision decreased after treatment. In the whole group of 482 patients with GO, 19 patients (36 eyes) developed DON (3.9%). Twenty five of these eyes (69.4%) improved after treatment, in 10 patients (28.8%) visual function stabilised, and in one patient (2.8%) it worsened.

The difference in incidence of DON in the DM group and the total GO population was significant ($0.01<p<0.05$). The differences in visual outcome after therapy between these two groups appeared not to be statistically significant ($p>0.1$).

The prevalence of diabetic retinopathy in the patients with GO, DM, and DON was the same as in the group of patients with GO, DM, but without DON (respectively 1/5 and 2/10) (Tables 1 and 2).

Patients 6–11 underwent several surgical procedures for the GO (see Table 2). One of them (patient 7) underwent a rehabilitative three wall orbital decompression by coronal approach. She developed an intraorbital haemorrhage on the left side, immediately postoperatively, which in spite of an immediate anterior septum perforation resulted in no light perception and atrophy of the optic disc on that side. She had no blood clotting abnormalities. In the other patients no postoperative complications, such as haemorrhage, delayed wound healing, or infection occurred.

In four patients (Table 2, patients 12–15) no operations for GO were performed.

Discussion

The overall prevalence of DM in our population of GO patients (3.1%) is in accordance with the 2.5% prevalence in the normal Dutch

Table 2 Patients with Graves' orbitopathy and diabetes mellitus (n=10)

Patient (age in years)	*Sex*	*Diabetes mellitus*	*Retinopathy*	*Therapy for GO*	*Complications/comment*
6 (38)	F	IDDM	—	two wall orbital decompression right eye	—
7 (49)	F	NIDDM	—	Recession IRM right eye three wall coronal decompression	postoperative orbital haemorrhage on the left side, resulting in a blind eye
8 (17)	M	IDDM	—	Recession IRM right eye	—
9 (68)	F	IDDM	preproliferative retinopathy for which panretinal photocoagulation was performed	Upper and lower eyelid surgery	—
10 (48)	F	IDDM	background retinopathy	Upper and lower eyelid surgery	—
11 (55)	F	NIDDM	—	Upper eyelid surgery	—
12 (64)	F	NIDDM	Age related macular degeneration	—	Trabeculectomy both eyes because of POAG
13 (49)	F	NIDDM	—	—	—
14 (66)	F	NIDDM	—	—	—
15 (63)	F	IDDM	—	—	—

GO=Graves' orbitopathy; IRM=inferior rectus muscle; POAG=primary open angle glaucoma.

population.[12–14] However, the prevelence of IDDM in this study (1.7%), is significantly higher than that of the normal population in several European countries (0.22–0.26%).[15] This finding is an illustration of the tendency of autoimmune disorders to occur together in one patient. Several papers have demonstrated that 5–8% of people with IDDM have clinical hypo/hyperthyroidism.[16 17] Various immunological theories concerning the comorbidity of Graves' disease and IDDM have been postulated and examined. The overall conclusion is that both diseases share susceptibility as well as resistance gene loci of the human leucocyte antigen system.[18 19] Recently, a paper has been published on a patient with Graves' disease, myasthenia gravis, and polymyositis,[20] but the occurrence of GO, DM, *and* myasthenia gravis in one patient, as presented by the second case has not been published before and is an illustration of the comorbidity of autoimmune diseases. We are aware of the bias which might have occurred in the present study because of its hospital based character. The possible increased diagnostic surveillance of diabetic patients for diabetic retinopathy could also be considered a bias; however, only three patients had a (steady) diabetic retinopathy for which they they were not examined more often than once a year.

The incidence of DON in the patients with GO and DM (33.3%) was significantly higher than in the whole population of GO patients (3.9%) and the 5% incidence of DON described by Char.[2] Neigel *et al* in 1988 already described a group of 58 patients with DON, with 15.5% diabetics, compared with 1.7% in the control GO group.[21] Our findings of 26.3% diabetics in the DON group, compared with 3.1% diabetics in the whole GO population do not differ significantly from their results ($p>0.3$). The higher incidence of DON in diabetics could be explained by a marginal oxygenation of the optic nerve in the diabetic patient, owing to the vasculopathy, which makes the optic nerve more susceptible to pressure by the enlarged extraocular muscles. Patient 5 even illustrates the occurrence of an AION as a result of a disturbed balance in oxygenation of the optic nerve by pressure of the enlarged extraocular muscles. This uncommon manifestation of DON has, to our knowledge, not been described in the literature before. In this study, visual improvement after treatment was seen in 50% of the eyes with DON, which is poor compared with the 69.4% visual improvement demonstrated in the DON patients in the whole population. The difference is however not statistically significant,which may be attributed to the small number of patients. Mourits *et al*, in their study, have already shown that 67% of the patients with DON who did not respond to orbital decompression were diabetic.[11] It is probable that the insufficient vascularisation of the optic nerve in patients with DM is responsible for the poor recovery of DON in these patients.

Diabetic retinopathy did not occur more frequently in the patients with DON than in the patients who did not develop DON, making the presence of retinopathy not a reliable risk factor in predicting its development.

The unilateral orbital haemorrhage after a three wall orbital decompression is a serious postoperative complication we have not encountered before. Although it is casuistry, a generalised vasculopathy and platelet disorders make DM patients more susceptible to haemorrhages. Therefore it may be advisable to operate on these patients side by side in different sessions, to spread the risk.

The conclusion of this study is that the prevalence of IDDM in patients with GO is significantly higher than in the normal population, which underlines the comorbidity of autoimmune diseases. Secondly, probably as a result of diabetic vasculopathic changes, the optic nerve in diabetic patients appears to be much more sensitive to the pressure of enlarged extraocular muscles. As a result, the incidence of DON in diabetic patients is markedly higher. In addition, the visual recovery in patients with DM and DON may not be as good as in non-diabetic patients. Diabetes constitutes an additional risk in patients with GO and therefore the ophthalmologist must be extra vigilant.

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