Epidemiology

C. Daumerie

Department of Endocrinology, Université catholique de Louvain, Brussels, Belgium

What Is the Present Estimated Prevalence of Graves' Orbitopathy? Has It Changed over the Last Decade?

Estimates of the prevalence of Graves' orbitopathy (GO) are influenced by several variables, including the sensitivity of the detection method.

Graves' ophthalmopathy is clinically relevant in approximately 25% of unselected patients with Graves' disease if eyelid signs are excluded, and 40% if eyelid changes are included. Subclinical abnormalities can be shown in the majority of them by computed tomography or magnetic resonance imaging or by measurement of intraocular pressure. Severe forms of GO account for no more than 3–5% of the cases [1, 2]. The estimated incidence of Graves' ophthalmopathy in the general population is 16 women and 3 men per 100,000 population per year [3].

The prevalence of GO seems to have declined in recent years, as well as that of the more severe expression of eye disease. Review of the clinical records of the first consecutive patients diagnosed at the same eye clinic in 1960 and 1990 showed a significant decrease in clinically relevant ophthalmopathy from 57% in 1960 to 37% in 1990 [4]. This trend might be related to both an earlier diagnosis (facilitated by the introduction of sensitive assays of TSH in the late 1980s) and treatment by the endocrinologists, as well as enhanced attention of the ophthalmologists to the link between the initial ocular manifestations and thyroid dysfunction. Alternatively, smoking behaviour might be involved. In an international survey on the current management of GO, most respondents from Western European countries thought that the prevalence of GO has declined over the last decade, in line with the decreased prevalence of smoking. Conversely, respondents who considered that the prevalence of GO increased originated from countries such as Poland and Hungary, where the prevalence of smoking had increased since 1989 [5].

Is the Age and Sex Distribution of Graves' Orbitopathy Similar to that of Graves' Disease?

GO patients are older than patients with Graves' hyperthyroidism, with a mean age of 46.4 years for patients with GO and Graves' hyperthyroidism, but 40.0 years for patients with Graves' hypothyroidism only [4, 6]. In 152 newly referred GO patients from 8 EUGOGO centers, the mean age of GO patients was 49 years [7].

Graves' ophthalmopathy, like Graves' hyperthyroidism, is more common in women than in men. The female to male ratio was 9.3 in patients with mild ophthalmopathy, 3.2 in those with moderate ophthalmopathy, and 1.4 with severe ophthalmopathy [1–4].

A sex-related difference in the severity of GO has been noted, with men comprising a relatively greater proportion of cases of severe ophthalmopathy. Eye disease tends to be more severe in older patients and in men. The reason for this effect of gender is not clear but the higher prevalence of smoking among men likely plays a role.

Are There Ethnic Differences?

The prevalence of GO has been reported to be lower in several Asian populations (7.5%) than in Caucasians (34%), but only 39 out of the 150 subjects in this study were Asians [8].

In contrast, the prevalence of GO among 167 consecutive multiethnic Malaysian patients with Graves' disease was 34.5%, no different from that in Caucasians [9]. Exophthalmos and lower lid retraction were the most common eye signs in this population. Orientals have a rounder and shallow orbit, black people have a rectangular orbit, and white people are in between [10]. These differences may explain the variation in exophthalmic readings between different ethnic groups. The upper normal limit of proptosis values (defined as 2 standard deviations above the mean) is reported as 24.7 mm for black men and 23 mm for black women, 21.7 mm for white men and 20.1 mm for white women, 19.3 mm for Iranians, 18.6 mm for Chinese and 17.7 mm for Japanese [10]. The figures must be interpreted with caution as the studies vary in design and methodology.

What Are the Risk Factors for the Occurrence of Graves' Orbitopathy?

Several factors may increase the risk of ophthalmopathy in patients with Graves' disease, namely tobacco, gender, genetics, type of treatment for hyperthyroidism, TSH receptor antibodies, drugs, advanced age and stress.

Several susceptibility loci for Graves' disease (like HLA, CTLA-4, TNF, IFN- γ , ICAM-1, TSH receptor) have been proposed to be associated with an additional

risk of developing GO, but the results of these small association studies with candidate genes are either not confirmed or require replication in larger studies [11, 12]. A recent study found a higher frequency of particular polymorphisms in IL-1 α and IL-1RA genes among Graves' patients with GO than in Graves' patients without GO [13]. It seems that in Graves' disease the risk of developing GO depends largely on environmental factors (especially smoking) and less on genetic factors.

Graves' ophthalmopathy, like hyperthyroidism, is more common in women than men. However, men who have GO are more likely to have an increase in severity during follow-up [1–4].

TSH-R autoantibodies (TRAB) might be involved in the disease process of GO and their detection may be of clinical benefit. In a euthyroid Caucasian population, GO activity and proptosis were mainly associated with the TRAb fraction binding inhibitory antibodies (TBII). TBII levels were significantly higher in patients with a severe course of GO compared with patients with a mild course, and this is a risk factor independent of age and smoking. However, this observational study must be confirmed by a prospective study [14].

The type of treatment given for Graves' disease may be a risk factor for GO. Subtotal thyroidectomy and antithyroid drugs do not appear to have a negative influence on the course of GO. In comparison, most but not all studies suggest that radioiodine treatment might lead to the development or worsening of GO [1, 15].

Other possible risk factors for GO include advanced age, stress [16], neck irradiation for Hodgkin disease [17], and drugs such as lithium [18] or interferon- α [19].

Is Tobacco Bad for Graves' Orbitopathy?

Cigarette smoking is the strongest modifiable risk factor for developing GO. Despite various limitations and difficulties in comparing available studies, there is strong evidence of a causal association between smoking and development of GO [20–22].

A positive association between smoking and GO was found in 4 case-control studies when compared with control patients with Graves' disease but no ophthalmopathy (OR 1.94–10.1) and in 7 case-control studies in which control subjects did not have thyroid disease (OR 1.22–20.2) [22].

According to the EUGOGO study, 40% of GO patients are smokers [7]. Among patients with ophthalmopathy, smokers were more likely to have severe disease than nonsmokers. The severity of GO is related to the number of cigarettes smoked per day. The volume of intraorbital connective tissue also correlates well with cumulative smoking [23]. Current smokers were also more likely to experience disease progression or poorer outcome of treatment [1, 2]. The effect of medical treatment of GO may be attenuated in cigarette smokers. Among patients with mild GO, eye disease

progression after radioiodine treatment seems to be significantly higher in smokers than nonsmokers.

Is Ocular Co-Morbidity Relevant for Graves' Orbitopathy?

Cataract and age-related macular degeneration should be excluded as a cause of decreased vision in patients with suspected dysthyroid optic neuropathy (DON). Biomicroscopy, fundoscopy, visual field examination and visual-evoked potential testing can distinguish between DON and the previously mentioned ophthalmological conditions.

Preexistent strabological disorders may complicate the orthoptic assessment in patients with GO and ocular motility disorders. Patients who do not have binocular vision because of congenital eso- or exotropia will not complain of diplopia. Strabismus surgery can be performed for cosmetic rehabilitative reasons in those patients.

Diagnosis of primary open angle glaucoma (POAG) and measurement of ocular pressure should be made with special care.

Is Elevated Intraocular Pressure Relevant in Graves' Orbitopathy?

The intraocular pressure (IOP) is determined by aqueous humor production by the ciliary body, the resistance to aqueous outflow across the trabecular meshwork, and the level of episcleral venous pressure. POAG is characterized by an IOP over 21 mm Hg, an open angle and visual field defects with optic disc cupping. In POAG, the rise in IOP is caused by increased resistance in the drainage channels. Risk factors in the development of glaucomatous optic nerve damage are high IOP, increasing age, family history of glaucoma and black race [24, 25].

Patients with IOP over 21 mmHg but a normal visual field and cup-disc ratio are classified as having ocular hypertension. These patients are usually managed by observation alone. In cases at increased risk, treatment is considered after carefully weighing up the advantages and disadvantages of therapy. Since POAG is a chronic and progressive disease, the diagnosis has serious implications for the patient.

In patients with GO, an absolute increase in IOP of 1–15 mm upon upgaze is a common finding (60–100%) [26]. This phenomenon is explained by the inelasticity of the inferior rectus muscle as a result of fibrosis, and thus the incapacity to relax on the globe when the antagonist pulls the eye upwards causes compression – therefore increasing episcleral venous pressure and orbital congestion. If an elevated IOP is measured in a patient with GO, the question will arise whether the elevated IOP is just a sign of GO or if glaucoma should be considered. In other words, should all patients with elevated IOP and GO be treated?

In a retrospective study of 482 patients with GO, 23 patients (4.8%) had elevated IOPs as measured in primary gaze. They were all using glaucoma medication at referral. Four patients (0.8%) turned out to have real POAG [27]. This prevalence of POAG in the population of GO patients corresponds to the 1.1% prevalence in the Dutch population [28]. That means that although IOP is elevated on upgaze in the majority of GO patients, it does not lead to glaucomatous injury more often than in the normal population. Nineteen patients (3.9%) had elevated IOPs without visual field defects and with normal optic discs [27]. This prevalence of ocular hypertension is higher than the 1.9% prevalence of ocular hypertension in the normal Dutch population [28]. This difference is probably caused by the fact that normally when using the applanation tonometer, the eyes are in mild upgaze, giving rise to a slight elevation in IOP in patients with GO. It is important that when measuring the IOP in patients with GO, the position of the eyes is checked.

Diagnostic confusion may occur in patients with elevated IOP, visual field defects and severe GO. In the above-mentioned study [27], 4 patients were considered to have glaucoma because of elevated IOP and visual field defects. After treatment of their optic neuropathy (orbital decompression and/or steroids intravenously), the visual field defects disappeared. Looking back, the absence of glaucomatous cupping of the optic disc could have been decisive.

The diagnosis of POAG in patients with GO should be made with special care. Increases in IOP when looking up are common in patients with GO, but do not cause glaucoma more often than in the normal population. An increased IOP might be the result of a slight elevation of the eyes during applanation tonometry. Precise assessment of the optic disc can prevent false diagnosis of PAOG in patients with GO and visual field defects.

Is There Significant Non-Ocular Co-Morbidity (Like Diabetes) Which Is Relevant for Graves' Orbitopathy?

In the EUGOGO study, 9% of the 152 new consecutively included patients had diabetes [7]. The prevalence of type 1 diabetes mellitus (DM) or insulin-dependent diabetes mellitus is higher in patients with GO than in the normal population. In a Dutch study, of 482 patients with GO, 3.1% also had diabetes mellitus: 8 (1.7%) had type 1 diabetes, and 7 (1.4%) had type 2 diabetes [29].

Patients with GO and DM seem to have a higher incidence of DON. Several studies show a higher incidence of DON (15–35%) in GO patients with DM compared to GO patients without DM (3–4%) [29, 30]. The higher incidence of DON in patients with GO and DM could be explained by a marginal oxygenation of the optic nerve in diabetic patients, due to the vasculopathy; this makes the optic nerve more suitable to pressure of the enlarged extraocular muscles. Patients with DON and DM also have worse recovery of visual acuity after treatment. Mourits et al. [31] showed that 67% of the patients with DON who did not respond to orbital decompression were diabetics.

In one study, 33% of the diabetics developed DON with 50% improvement in 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 [29].

Patients with GO and DM have also a higher risk of bleeding during or after surgery because of a generalized vasculopathy and platelet disorder.

Myasthenia gravis (MG) is another autoimmune disease which may complicate the diagnosis and course of GO. MG is 50 times more common in patients with GO when compared to the normal population. While GO is a restrictive myopathy, with the inferior and medial rectus muscle involved most frequently, in MG a paresis of the extraocular muscles can be present, with no special pattern. In GO, retraction of the upper eyelids is almost pathognomonic, whereas in MG ptosis is worsening during the day [32]. Therefore, in patients with GO who have ptosis and/or atypical ocular motility, concomitant MG should be suspected. The diagnosis of MG can be established by clinical and serological testing (anticholinesterase antibodies). Forced duction test of the eye muscles can distinguish between restriction and paresis. In patients with GO and MG, prediction of strabismus surgery will be more complicated. Deterioration of diplopia after initial success of strabismus surgery is a common problem in patients with GO and MG.

References

- 1 Bartalena L, Pinchera A, Marcocci C: Management of Graves' ophthalmopathy: reality and perspectives. *Endocr Rev* 2000;21:168–199.
- 2 Wiersinga WM, Bartalena L: Epidemiology and prevention of Graves' ophthalmopathy. *Thyroid* 2002;12:855–860.
- 3 Bartley GB, Fatourehchi V, Kadrmas EF, Jacobsen SJ, Ilstrup DM, Garrity JA, Gorman CA: The incidence of Graves' ophthalmopathy in Olmsted County, Minnesota. *Am J Ophthalmol* 1995;120:511–517.
- 4 Perros P, Kendall-Taylor P: Natural history of thyroid eye disease. *Thyroid* 1998;8:423–425.
- 5 Weetman AP, Wiersinga WM: Current management of thyroid-associated ophthalmopathy in Europe: results of an international survey. *Clin Endocrinol* 1998;49:21–28.
- 6 Prummel MF, Wiersinga WM: Smoking and risk of Graves' disease. *JAMA* 1993;269:479–482.
- 7 Prummel MF, Bakker A, Wiersinga WM, Baldeschi L, Mourits MP, Kendall-Taylor P, Perros P, Neoh C, Dickinson AJ, Lazarus JH, Lane CM, Heufelder AE, Kahaly GJ, Pitz S, Orgiazzi J, Hullo A, Pinchera A, Marcocci C, Sartini MS, Rocchi R, Nardi M, Krassas GE, Halkias A: Multi-Center study on the characteristics and treatment strategies of patients with Graves' orbitopathy: the first European Group on Graves' Orbitopathy experience. *Eur J Endocrinol* 2003;148:491–495.
- 8 Teller M, Cooper J, Edmonds C: Graves' ophthalmopathy in relation to cigarette smoking and ethnic origin. *Clin Endocrinol* 1992;36:291–294.
- 9 Lim SL, Lim AK, Mumtaz M, Hussein E, Wan Bebakar WM, Khir AS: Prevalence, risk factors, and clinical features of thyroid-associated ophthalmopathy in multiethnic Malaysian patients with Graves' disease. *Thyroid* 2008;18:1297–1301.
- 10 Tsai CC, Kau HC, Kao SC, Hsu WM: Exophthalmos of patients with Graves' disease in Chinese of Taiwan. *Eye* 2006;20:569–577.
- 11 Villanueva R, Inzerillo AM, Tomer Y, Barbesino G, Meltzer M, Concepcion ES, Greenberg DA, Maclaren N, Sun ZS, Zhang DM, Tucci S, Davies TF: Limited genetic susceptibility to severe Graves' ophthalmopathy: no role for CTLA-4 but evidence for an environmental etiology. *Thyroid* 2000;10:791–798.
- 12 Bednarczuk T, Gopinath B, Ploski R, Wall JR: Susceptibility genes in Graves' ophthalmopathy: searching for a needle in a haystack? *Clin Endocrinol* 2007;67:3–19.

- 13 Khalilzadeh O, Anvari M, Esteghamati A, Mahmoudi M, Tahvildari M, Rashidi A, Khosravi F, Amirzargar A: Graves' ophthalmopathy and gene polymorphisms in interleukin-1alpha, interleukin-1beta, interleukin-1 receptor and interleukin-1 receptor antagonist. *Clin Experiment Ophthalmol* 2009;37:614-619.
- 14 Eckstein AK, Plicht M, Lax H, Neuhauser M, Mann K, Lederbogen S, Heckmann C, Esser J, Morgenthaler NG: Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of the disease. *J Clin Endocrinol Metab* 2006;91:3464-3470.
- 15 Tallstedt L, Lundell G, Torring O, Wallin G, Ljunggren JG, Blomgren H, Taube A: Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. The Thyroid Study Group. *N Engl J Med* 1992;326:1733-1738.
- 16 Salvi M, Zhang Zg, Haegert D, Wall J: Patients with endocrine ophthalmopathy not associated with overt thyroid disease have multiple thyroid immunological abnormalities. *J Clin Endocrinol Metab* 1990;70:89.
- 17 Jackson R, Rosenberg C, Kleinmann R, Vagenakis AG, Braverman LE: Ophthalmopathy after neck irradiation therapy for Hodgkin's disease. *Cancer Treat Rep* 1979;63:1393-1395.
- 18 Byrne AP, Delaney WJ: Regression of thyrotoxic ophthalmopathy following lithium withdrawal. *Can J Psychiatry* 1993;38:635-637.
- 19 Villanueva RB, Brau N: Graves' ophthalmopathy associated with interferon-alpha treatment for hepatitis C. *Thyroid* 2002;12:737-738.
- 20 Hägg E, Asplund K: Is endocrine ophthalmopathy related to smoking? *Br Med J* 1987;295:634-635.
- 21 Shine B, Fells P, Edwards OM, Weetman AP: Association between Graves' ophthalmopathy and smoking. *Lancet* 1990;335:1261-1264.
- 22 Thornton J, Kelly SP, Harrison RA, Edwards R: Cigarette smoking and thyroid eye disease: a systematic review. *Eye* 2006;15:1-11.
- 23 Szurks-Farkas Z, Toth J, Kollar J, Galuska L, Burman KD, Boda J, Leovey A, Varga J, Ujhelyi B, Szabo J, Berta A, Nagy EV: Volume changes in intra- and extraorbital compartments in patients with Graves' ophthalmopathy: effect of smoking. *Thyroid* 2005;15:146-151.
- 24 Lyons DE: Postural changes in IOP in dysthyroid exophthalmos. *Trans Ophthalmol Soc* 1971;91:799-803.
- 25 Gamblin GT, Harper DG, Galentine P, Bruck DR, Chemow B, Eil C: Prevalence of increased intraocular pressure in Graves' disease-evidence of frequent subclinical ophthalmopathy. *N Engl J Med* 1983;308:420-424.
- 26 Fishman DR, Benes SC: Upgaze intraocular pressure changes and strabismus in Graves' ophthalmopathy. *J Clin Neuro-ophthamol* 1991;11:162-165.
- 27 Kalmann R, Mourits MP: Prevalence and management of elevated intraocular pressure in patients with Graves' orbitopathy. *Br J Ophthalmol* 1998;82:754-775.
- 28 Dielemans I, Vingerling JR, Wolfs RC, Hofman A, Grobbee DE, de Jong PT: The prevalence of glaucoma in a population-based study in the Netherlands: the Rotterdam Study. *Ophthalmology* 1994;101:1851-1855.
- 29 Kalmann R, Mourits MP: Diabetes mellitus: a risk factor in patients with Graves' orbitopathy. *Br J Ophthalmol* 1999;83:463-465.
- 30 Neigel JM, Rootman J, Belkin RI, Nugent RA, Drance SM, Beattie CW, Spinelli JA: Dysthyroid optic neuropathy: the crowded orbital apex syndrome. *Ophthalmology* 1988;95:1513-1521.
- 31 Mourits P, Koornneef L, Wiersinga WM, Prummel MF, Bergout A, van der Gaag R: Orbital decompression for Graves' ophthalmopathy by inferomedial, inferomedial plus lateral, and by coronal approach. *Ophthalmology* 1990;97:636-641.
- 32 Drachman DB: Myasthenia Gravis. *N Engl J Med* 1994;330:1797.

Dr. Chantal Daumerie

Service d'Endocrinologie et Nutrition

Université catholique de Louvain, Cliniques Universitaires St Luc, Avenue Hippocrate 54

UCL 54.74, BE-1200 Brussels (Belgium)

Tel. +32 2 764 54 75, Fax +32 2 764 54 18, E-Mail chantal-daumerie@uclouvain.be