Critical issues on Graves’ ophthalmopathy

By Roberto Rocchi, MD

Graves’ ophthalmopathy (GO) is an inflammatory process that affects tissues of the orbit in patients with Graves’ disease (GD) and, more rarely, with Hashimoto’s thyroiditis. It is the most frequent extrathyroidal manifestation of Graves’ disease. GO is a disfiguring disease that impairs, even in its milder forms, the quality of life of affected patients. It is clinically significant in 50% of patients and severe in 3% to 5%. Approximately 50% of patients with GD do not have clinically relevant ocular involvement, although sub-clinical abnormalities can be shown in many of them by computed tomography scan or magnetic resonance imaging (MRI), or by measurement of intraocular pressure.1,2

In approximately 90% of cases, GO is bilateral, and in 5% to 15% can be monolateral. The natural history of GO is not well understood. Spontaneous disease regression occurred in approximately 66% of patients, whereas eye manifestation remained stable in more than 20% and worsened in 14%. Due to the relative rarity of the disease and the fact that diagnosis and treatment involve physicians of different specialties, GO requires a highly specialized and multidisciplinary approach.1,2

Epidemiology

The onset of hyperthyroidism and ophthalmopathy show a close temporal relationship. GO usually occurs 18 months before or after the onset of hyperthyroidism. The annual incidence of GD in the United States has been reported to be 13.9 cases per 100,000 individuals, with a female/male ratio of about 7:1. The incidence is distributed bimodally by age. Peaks occur in age groups 40 to 44 years and 60 to 64 years in women, and 45 to 49 years and 65 to 69 years in men.

Cigarette smoking has been identified as an important risk factor for GO. Several studies reported that the prevalence of smokers in GO patients is much higher than in any other autoimmune or non-autoimmune thyroid disease. Among patients with GO, smokers have more severe ocular involvement than non-smokers, although there was no significant association between the level of tobacco consumption and the severity of GO. Furthermore, those who stopped smoking reported a relapse of inflammatory eye manifestations. Other studies observed a
Pathogenesis

GO is an autoimmune disease that leads to the enlargement of the extraocular muscles and adipose tissue of the orbit. These changes are consequences of the glycosaminoglycan accumulation and edema of the soft tissue of the orbit, which result in an increase in the volume of fat and muscles with impairment in orbital venous drainage. The current theory is that cross-reacting antigen(s) of the thyroid gland and the orbit induce an autoimmune response with development of humoral and cell-mediated reactions that lead to the inflammatory eye manifestations. Unfortunately, the advancements of basic research in this field are hampered by a lack of a reliable animal model of GO. The debate is still open on which antigen shared by the thyroid and the orbit is responsible for disease development, although TSH receptor is still considered the most important shared antigen. TSH receptor — originally considered a thyroid-specific antigen — has been detected in orbital tissues at mRNA and protein levels, but is also expressed in several other tissues of patients with and without GD.

Marino, et al, recently renewed the old hypothesis by Kriss by which thyroglobulin can be involved in the pathogenesis of GO. This theory postulates that thyroglobulin is initially produced by the thyroid gland, and it migrates to the orbit in a second step. GO is not, however, correlated with the titer of thyroglobulin antibodies. Therefore, thyroglobulin is considered rather a co-factor in the pathogenesis of GO. The development of GO is probably mediated by cytokines that play an important role in the maintenance of the inflammation. Cytokines are produced by inflammatory infiltrating cells and by orbital fibroblasts. Cell-mediated response in the orbit seems to involve the production of IL-2, INF-γ, TNF-α; in the meantime, humoral response requires the production of IL-4, IL-5, and IL-10.

Cytokines are involved in most of the immune responses in the orbit that comprise the antigen recognition, T-cell recruitment, and fibroblast proliferation and secretion of glycosaminoglycans. The orbital cells primarily targeted by the autoimmune response are fibroblasts and adipocytes, but not myocytes that seem to be involved in a second step of the immune reactions. Orbital fibroblasts are very sensitive to the cytokines released during the inflammatory process. Adipocytes are also involved in the pathogenesis of GO: their proliferation — regulated by peroxisome proliferator activator receptor γ (PPR γ) — leads to the increase of orbital fat tissue.

Clinical presentation and diagnosis

Symptoms. Patients with GO, even in the milder forms, usually refer gritty or burning sensation in the eye with or without retro-ocular pressure (due to the expansion of the retrobulbar structures). Other common symptoms are lacrimation, photophobia, and visual blurring due to alteration of the tear film on the surface of the cornea. Patients with GO usually also experience spontaneous ocular pain and with eye movements with restriction of the motility that lead to diplopia. Patients with severe GO can have sight loss with alteration in visual quality in one or more quadrants of the visual field (secondary to an optic neuropathy due to the compression of the optic nerve). Marked proptosis with prolonged exposure of cornea and sclera to air dust can lead to keratitis and corneal ulcers (see Table 1). Signs. The most common presentation of GO comprises proptosis with symmetrical or asymmetrical bright-eyed stare (see Figure 1A). The eyelid retraction can be explained by exophthalmos itself and by a chronic β-adrenergic stimulation of the levator Muller’s muscle secondary to the thyrotoxicosis. Patients also show an extraocular muscle impairment. Eyelid edema, conjunctival injection, and chemosis also occurred frequently as well as lagophthalmos (inability to close the eyelids) (see Table 1).

Table 1. Symptoms and signs of GO

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
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<tr>
<td>Excessive lacrimation</td>
<td>Palpebral edema</td>
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<tr>
<td>Burning sensation</td>
<td>Palpebral hyperemia</td>
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<tr>
<td>Gritty sensation</td>
<td>Increased palpebral width</td>
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<tr>
<td>Spontaneous ocular pain</td>
<td>Lid retraction</td>
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<tr>
<td>Ocular pain with eye movements</td>
<td>Edema of the caruncle</td>
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<tr>
<td>Photophobia</td>
<td>Conjunctival hyperemia</td>
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<tr>
<td>Diplopia</td>
<td>Chemosis</td>
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<tr>
<td>Blurred vision</td>
<td>Lagophthalmos</td>
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<tr>
<td>Sight loss</td>
<td>Proptosis</td>
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<tr>
<td>Increased intra-ocular pressure</td>
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<tr>
<td>Restriction of eye movements</td>
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<tr>
<td>Keratitis and corneal ulcers</td>
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<td>Optic neuropathy</td>
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Activity of the disease. GO’s natural history is not completely understood, but after an initial, active phase of disease progression, there follows a partial regression that leads to an inactive phase in which the chronic manifestations of the disease are unlikely to recur. According to this theory, the activity of the ophthalmopathy is not coincident with the severity of the disease. Mourits, et al, proposed a clinical classification of signs and symptoms that may be related to disease activity. His original Clinical Activity Score (CAS) has been modified by a committee of the four Thyroid Societies as a tool to describe inflammatory ocular changes over time. Other indicators of disease activity are a prolongation of T2 relaxation time at MRI, and the orbital uptake and scintigraphy of [111In]octreotide of soft tissues, which is higher in patients with more severe and active forms of ophthalmopathy. This technique is expensive, however, and further data are necessary to establish its real usefulness.

Figure 1A. Picture of mild, asymmetric GO with proptosis and lid retraction of the right eye

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Treatment

Treating GO (mainly in its severe form) (see Figure 1B) represents a difficult therapeutic challenge. The three major and well-established methods of treatments are high-dose systemic glucocorticoids (GCs), orbital radiotherapy alone or preferably associated with GCs, and orbital decompression. These treatments have indications and contraindications, and frequently do not provide a satisfactory response with complete restitution ad integrum of the functionality and appearance of the eye.²,⁵,⁹

Treatment of mild GO

Most patients with GD have mild ocular manifestations that do not require any important treatment. In such cases, simple locally supportive measures are usually sufficient to obtain a symptomatic relief. Photophobia can be reduced by the use of sunglasses; the foreign body sensation related to a defective tear film is usually controlled by the use of artificial tears. In presence of lagophthalmos, taping the eyelids closed during the night is useful to prevent nocturnal corneal drying. Prisms may be beneficial for correction of mild diplopia, although they are not often well tolerated by the patient. Elimination of risk factors, such as smoking, may be very important and prevents the progression of the disease.⁵

Treatment of severe GO

Glucocorticoids (GC). GC therapy — administered orally, locally (retrobulbar), and intravenously — is a well-established GO treatment because of its anti-inflammatory and immunosuppressive actions — also reduces the synthesis and secretion of glycosaminoglycans by orbital fibroblasts. GCs are particularly effective on active disease including soft-tissue inflammatory changes, optic neuropathy, and also on extraocular muscle dysfunction (if not fibrotic), but lesser on proptosis. Unfortunately, a proportion of 20% to 40% of patients respond only partially or do not respond at all to GC therapy.

High-dose oral GCs for several months — are particularly effective on soft-tissue changes and optic neuropathy.²,⁷,⁸ Intravenous GC have been introduced in the last 15 years with favorable effects on inflammatory signs and optic-nerve involvement, with lesser effects of proptosis, and compared with oral GCs treatment, seems to be more effective and better tolerated, with a lower rate of side effects. Systemic GC therapy, however, presents a high rate of side effects and complications, such as transient Cushinoid features, onset of diabetes, depression, infections, hypertension, osteoporosis, increased body weight, peptic ulcer, and hirsutism.²⁷ Locally (retrobulbar) administered GCs show a lower rate of side effects, although their effectiveness is less if compared with systemic steroids. Retrobulbar GC therapy should, therefore, be considered in patients with active GO and with contraindications to systemic GCs.²

Orbital radiotherapy (OR). The rationale for the use of radiotherapy (RT) for GO resides in its nonspecific anti-inflammatory effect. Moreover, lymphocytes infiltrating the retrobulbar tissues showed a high radiosensitivity. RT can also reduce glycosaminoglycan production by orbital fibroblasts. According to most studies, orbital radiotherapy is especially effective on soft-tissue inflammatory changes and extraocular muscle dysfunction (if not fibrotic) and on optic neuropathy.²,¹⁰ Orbital radiotherapy is usually well tolerated. Cataract is a possible but rare complication; computerized treatment plans and the use of asymmetric beams have significantly reduced the risk. Radiation retinopathy is an extremely rare complication. Orbital radiotherapy combined with glucocorticoids. Systemic GCs and OR are more effective when combined. In addition to synergistic effects, this regimen exploits the more rapid effects of GCs and the more sustained action of irradiation. GCs may also prevent radiation-associated transient exacerbation of ocular inflammatory manifestations. On the other hand, OR may reduce the recurrence of eye disease, sometimes observed with withdrawal of GCs.²,¹¹,¹²

Orbital decompression. Orbital decompression is a very effective procedure for GO — mostly beneficial for proptosis and optic neuropathy but also for congestive manifestations of the disease. Surgical treatment of GO should be afforded by highly experienced orbit surgeons. Orbital decompression does not solve the problem of pre-operative diplopia, and a relevant rate of patients will need a subsequent extraocular muscle correction surgery.²,⁷

Other treatments

Cyclosporine. Cyclosporine is an immunosuppressive drug that has been used in the treatment of GO with favorable results, although most of the studies were uncontrolled. Cyclosporine might be used in association with GC in patients who are resistant to GCs alone. Cyclosporine can induce severe side effects, such as hypertension and liver and kidney toxicity.²

Somatostatin analogues. Somatostatin receptors can be visualized in vivo in orbital tissue of GD patients by octreoscan. Patients with active GO have a higher orbital uptake of [111In]octreotide than those with inactive disease. The rationale of treating patients with active GO with somatostatin analogs came from these observations.

Intravenous immunoglobulins. High-dose intravenous immunoglobulins (IVIG) have been largely evaluated in autoimmune disease with beneficial effects, although the mechanisms of IVIG action are not yet well understood. Positive results for treatment of GO with IVIGs have been reported in three studies. One other study did not show any eye improvement after treatment with IVIGs.

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Cytokine antagonists. Cytokines play an important role in the pathogenesis of GO, particularly in the early stage of the disease. There is only one report of a study of 10 patients with moderately severe GO treated with pentoxifylline, a drug with complex immunomodulatory effects on cytokine production. In this study, eight patients responded favorably. Pentoxifylline was mostly effective on soft-tissue changes and proptosis.

GO and treatment of hyperthyroidism

GO may occur before, at the same time, or after the onset of hyperthyroidism. Therefore, sometimes GO onset follows the treatment for hyperthyroidism, it is uncertain whether the occurrence, amelioration, or aggravation of GO is related to GO natural history or is treatment-dependent. Restoration of euthyroidism by thionamides is associated with GO improvement, but it is unclear whether this is because of a direct effect of thionamides on GO or induced by the normalization of thyroid status. Antithyroid drugs have a high recurrence rate of hyperthyroidism after drug withdrawal; this recurrence implies a reactivation of thyroid autoimmunity that can negatively influence GO course. Radioiodine therapy is a well-established, definitive treatment of Graves’ hyperthyroidism. The relation between radioiodine therapy and GO course had been strongly debated; the treatment can carry a 15% risk of causing progression of pre-existing GO, but can be prevented by concomitant GC therapy. GO progression after radioiodine might be due to the release of thyroid antigens after radiation, with subsequent exacerbation of autoimmune reactions directed against antigens shared by the thyroid gland and the orbit.

Thyroid ablation may be useful for the long-term outcome of GO. Thyroidectomy does not affect GO progression, independently of the extent of surgery. Complete thyroid ablation might be important for removal of thyroid-orbit cross-reacting autoantigens and thyroid-autoreactive T lymphocytes. Although total thyroid ablation may represent an interesting perspective, controlled...
studies supporting this hypothesis are needed. GO should not influence the choice of treatment for hyperthyroidism. This choice is based on established criteria (goiter size, age, first episode versus recurrence of hyperthyroidism, and persistent titer of antibodies against the TSH receptor under thionamides therapy) that do not depend on the presence of GO. 

A coordinated and concomitant approach to the treatment of hyperthyroidism and GO is influenced by the severity of GO, and treatments for GO should promptly follow the ablative therapy for hyperthyroidism. Hypothyroidism secondary to radioiodine treatment or persistent hyperthyroidism should be corrected promptly. In patients with highly severe GO (i.e., in presence of optic neuropathy), treatment of GO should be managed independently of the treatment of hyperthyroidism. In conclusion, it is quite well-established that proper management of GO should comprise a definitive treatment of hyperthyroidism by radioiodine or thyroidectomy, promptly followed by appropriate medical or surgical treatments for GO. 

References