Grave's orbitopathy – an approach to clinical evaluation and management

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Abstract

Grave's orbitopathy (GO), is a potentially sight threatening condition which constitutes a major clinical and therapeutic challenge and occurs in about 50% of patients with Grave's disease with only 3-5% cases posing threat to sight. This autoimmune condition is mediated via cytokines secreted by T lymphocytes infiltrating in to the orbital cavity and thyrotropin receptor antibodies (TRAbs) stimulating thyrotropin receptors (TSHR). Clinical assessment for disease activity and severity in GO is important for decision making in management of both hyperthyroidism and GO. Sight threatening GO should be identified promptly and treated with high dose intravenous (IV) glucocorticoids and/or orbital decompression.

Introduction

Grave's ophthalmopathy also called Grave's orbitopathy, is a potentially sight threatening condition which constitutes a major clinical and therapeutic challenge. It is often mild and self-limiting and probably declining in frequency, with only 3-5% of cases posing a threat to sight (1). Subtle ocular changes of GO occurs in almost all patients with Grave's disease, with clinically recognizable disease only in 50% and 20-30% will have significant ocular disease which needs treatment (4). Its onset may precede or follow the onset of hyperthyroidism, however thyroid disease and GO occur concomitantly or within a few months from each other in more than 80% of cases (2). GO can occur in hypothyroid or euthyroid patients as well. Although clinically apparent unilateral GO is seen occasionally, orbital imaging with either Magnetic resonance imaging (MRI) or computer tomography (CT) confirms asymmetrical bilateral disease in majority of them.

Pathogenesis of Grave's orbitopathy (GO)

GO is an autoimmune process of which precise pathogenic process is not fully unraveled, but is better understood now than ever before. In GO extraocular muscles and adipose tissues are swollen due to accumulation of extracellular matrix of glycosaminoglycans that are secreted by the fibroblasts under the influence of cytokines such as interferon γ, interleukin (IL)-1α and TNFα, which are secreted by T lymphocytes infiltrating the orbital cavity (5). Accumulation of glycosaminoglycans disrupts and impairs the function of ocular muscles leading to fibrosis as the inflammation ceases. The close clinical and temporal relationships between Grave's hyperthyroidism and GO suggest that both conditions derive from a single systemic process and share the thyrotropin receptor (TSHR) as the auto antigen (3). It is now established that full-length TSH receptor is expressed in orbital adipocytes and fibroblasts of GO patients, which are activated by TSHR stimulating antibodies (TRAbs) (5). This is further supported by the fact that patients with most severe orbitopathy have the highest titers of TRAbs and severity of orbitopathy correlates with the level of TRAbs. The type I insulin-like growth factor receptor (IGF-1R) may be another important autoantigen in Grave's ophthalmopathy which is expressed in higher levels in the orbital fibroblasts of patients with Grave's orbitopathy (6).

Clinical presentation of Grave's orbitopthy

Symptoms of GO occur in about 50% of patients with Grave's hyperthyroidism, including a dry and gritty ocular sensation, photophobia, excessive tearing, double vision, and a pressure sensation behind the eyes. The most common clinical features of Grave's ophthalmopathy are upper eyelid retraction, edema and erythema of the periorbital tissues and conjunctivae, and proptosis. Proptosis and exophthalmos can lead to failure of eye lid closure increasing the risk of exposure keratitis. Only about 3 to 5% of patients with GO have severe disease with intense pain, inflammation, and sight-threatening corneal ulceration or compressive optic neuropathy (6). Assessment of visual acuity, colour vision and fundoscopic examination for papilloedema are mandatory to identify sight threatening Dysthyroid Optic Neuropathy

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(DON). Smoking is the single most important risk factor for the development of GO and it is related to the current number of cigarettes smoked per day (7).

Disease activity and severity assessment in GO

Disease activity and severity of orbitopathy should be assessed in all the patients in each visit, and the management be guided upon them. European Group on Grave's Orbitopathy (EUGOGO) has formulated criteria for assessment of clinical activity and severity (Box 1). A clinical activity score (CAS) ≥3/7 (one point assigned to each feature) indicate active GO whereas a CAS <3/7 is considered as inactive disease (1). In follow up patients three additional features should be added which includes, increase of >2mm in proptosis, decrease in uniocular ocular excursion in any one direction of >8º, decrease of acuity equivalent to 1 Snellen line, giving a total score of 10. Grading the severity of GO is fraught with difficulties; however, classifying patients into broad categories as mild, moderate-to-severe or sight threatening facilitates decision making. Careful assessment of the impact of GO on quality of life (QoL) by disease-specific questionnaire is fundamental in deciding whether treatments used for moderate-to-severe GO are justified in patients with mild GO (1).

Sight-threatening GO is defined as presence of Dysthyroid Optic Neuropathy (DON) which is characterized by reduced visual acuity and color vision, presence of relative afferent papillary defect or disc oedema and/or corneal breakdown, which warrants immediate intervention. A visual acuity <6/18 , failure to identify >2 plates in ishihara chart, corneal opacification, papilloedema and globe subluxation are indications for urgent referral to an ophthalmologist (1). Moderate-severe GO is a disease without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression or surgical intervention and they usually have any one or more of the following: lid retraction ≥2 mm, moderate to severe soft tissue involvement, exophthalmos ≥3 mm above normal for race and gender, inconstant or constant diplopia. Mild GO is a disease which have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment. They usually have only one or more of the following: minor lid retraction (<2 mm), mild soft tissue involvement, exophthalmos <3 mm above normal for race and gender, transient or no diplopia, and corneal exposure responsive to lubricants.

Management of Grave's orbitopathy

All patients with GO should be advised to quit smoking and other general measures should be considered where appropriate (Table 1). It is also imperative to make them euthyroid if they are in hyperthyroid state which raises the important question whether the different treatment modalities used to control thyrotoxicosis can affect the course of the eye disease. Most researchers have found that subtotal or total thyroidectomy and thionamide drug therapy do not influence orbitopathy unless they lead to the development of hypothyroidism (8,9). However, long term follow up study by Leo et al (10) on outcome of GO after total thyroid ablation and glucocorticoid treatment has shown that total thyroid ablation with thyroidectomy followed by I^{131} treatment allows best possible outcome and improvement of GO within a shorter period of time as compared to thyroidectomy alone. The effect of radioiodine treatment on GO is researched considerably and several randomized control trials have shown that approximately 15% patients develop new eye disease or experience the progression of existing GO within 6 months after radioiodine therapy(11). This is more likely to occur in patients who already have GO prior to radioactive iodine (RAI) therapy, smoke, have more severe hyperthyroidism and high levels of TRAbs or whose post RAI hypothyroidism is not promptly corrected by thyroxine replacement therapy (11). In these at-risk patients a relatively short course of moderate doses of oral glucococorticoids prevents progression of eye disease and often cures preexisting GO.

Table 1. General measures in management of GO

Problem	*Treatment*
Photophobia and excess tears	Dark glasses
Grittiness	Artificial tears and simple eye ointment
Eyelid retraction	Tape eyelids in the night to prevent corneal damage
Proptosis	Head elevation during sleep
	Diuretics
Ophthalmoplegia	Prisms in the acute phase

Table 2 . Management of hyperthyroidism and orbitopathy of Grave's disease in different clinical settings

Grave's orbitopathy	*Management of hyperthyroidism*	*Management of GO*
Mild active	ATDs, RAI with steroid prophylaxis or surgery	Watch and wait
Mild inactive	ATDs, RAI or surgery	Watch and wait ± rehabilitative surgery
Moderate to severe active	ATDs, RAI with steroid prophylaxis or surgery	High dose steroids ±orbital radiotherapy
Moderate to severe inactive	ATDs, RAI or surgery	Rehabilitative surgery
Sight threatening	ATDs	IV glucocrticoids and/or orbital decompression

Sight threatening GO

Systemic glucocorticoids (GCs) and surgical decompression of the orbit are the only treatments proved to be effective in patients with DON. High dose IV GCs are the first line of treatment for DON and prompt orbital decompression should be carried out if there is inadequate response to IV GCs or poor response after 1-2 weeks, or the dose/duration of steroid required induces significant side effects. Orbital radiotherapy is not recommended in the case of DON unless as an adjunct to proved therapies. High dose IV GCs administered in pulses are more efficacious and associated with fewer adverse effects than oral or retrobulbar steroids (1). The currently recommended treatment for patients with active and moderate to severe GO is a course of 0.5 g of methylprednisolone IV once a week for 6 weeks, followed by 0.25 g/wk for 6 weeks(1). The response rate of this therapeutic regimen is approximately 80% (12). Although IV GCs are tolerated better than oral GCs, acute liver damage and a risk of life threatening liver failure has been reported in association with very high cumulative doses in 0.8% of patients (13). Hence the cumulative dose of IV GCs should not exceed 8 g.

In severe, sight-threatening corneal breakdown hourly topical lubricants are indicated, however this intervention alone may be insufficient to prevent ulceration, thinning, and perforation. In such cases, specific measures to improve eyelid closure such as blepharorrhaphy, tarsorrhaphy, or botulinum toxin injections can help until corneal healing occurs (1). The effect of GCs on severe corneal exposure has never been specifically evaluated. Orbital decompression helps to reduce symptoms associated with exposure keratopathy. Rarely severe corneal ulcers may be refractory to decompression surgery if lagophthalmos persists.

In sight threatening GO hyperthyroidism must be treated by anti thyroid drugs (ATDs) to restore euthyroidism and definitive treatment with RAI or thyroidectomy, if required, should be postponed until DON has improved and orbitopathy has become inactive.

Moderate to severe GO

The treatment of choice for moderate to severe and active (CAS ≥3/7) GO is pulses of IV glucocorticoids, as for sight threatening GO. Orbital irradiation (OR) should be considered in patients with active disease who have diplopia or restricted motility. OR with lower cumulative doses (10 Gy) may be as effective as and better tolerated than with higher doses (20 Gy) and doses>20 Gy are not recommended (1). Orbital radiotherapy is contraindicated in patients with diabetic retinopathy or severe hypertension. The combination of oral GCs (dose of 1mg/kg) with OR is thought to be more effective than either treatment alone, but randomized clinical trials indicating that the combination of IV GCs with OR is better than IV GCs alone are still lacking (1).

Moderate to severe disease with CAS <3/7 (inactive) warrants no immunosuppressive therapy and should be treated with rehabilitative surgery (1), which includes a sequence of orbital decompression, squint correction, lid lengthening and blepharoplasty. Indications for orbital decompression are disfiguring exophthalmos, troublesome retroocular pain/discomfort, and/or grittiness associated with minor exposure keratopathy not amenable to topical therapies (14). Rehabilitative surgery should be performed only in patients who have had inactive GO for at least 6 months (1).

Here the choice of treatment for hyperthyroidism is most controversial. Some argue in favour of ATDs due to prompt correction of hyperthyroidism and stable maintenance of euthyroidism with ATDs. Another argument is that thyroid ablation removes intrathyroidal autoreactive T-lymphocytes and thyroid antigens thereby helping abate the orbital process. Based on these assumptions, after restoration of euthyroidism with ATDs, even in this category of patients the thyroid can be

promptly ablated while managing GO with appropriate therapy (15). If RAI is given in these patients, it should be combined with low dose steroid prophylaxis (0.2mg/kg/day for 6 weeks) (16). In moderate to severe inactive disease, treatment depends on standard criteria and if RAI treatment given steroid prophylaxis can be avoided in the absence of other risk factors for progression of GO.

Mild GO

Local measures and an expectant strategy are sufficient in most cases of patients with mild GO (active / inactive). Glucocorticoids are rarely justified in mild GO as the risks outweigh the benefits. However, if quality of life is profoundly affected, it may be justified to treat as for moderate to severe disease. Rehabilitative surgery can be considered for cosmetic and functional reasons in inactive disease. Treatment of hyperthyroidism in these patients is largely independent of the orbital disease and based on established criteria. Steroid prophylaxis is indicated only if RAI is the treatment of choice in active disease.

Novel treatment modalities

With the better understanding of pathogenesis of GO immunomodulating agents like Rituximab, which is a monoclonal antibody against CD20, has shown promising outcome in management of Grave's disease. Several small studies have shown that rituximab infusion significantly reduces CAS in patients with Grave's orbitopathy (17,18). However large randomized control studies are lacking to recommend rituximab for treatment of GO.

Box 1
Activity and severity assessments in GO – EUGOGO recommendations

(a) Activity measures based on the classical features of inflammation

1. Spontaneous retrobulbar pain
2. Pain on attempted up or down gaze
3. Redness of the eyelids
4. Redness of the conjunctiva
5. Swelling of the eyelids
6. Inflammation of the caruncle and/or plica
7. Conjunctival edema

A CAS ≥3/7 indicates active GO

(b) Severity measures

1. Lid aperture (distance between the lid margins in mm with the patient looking in the primary position, sitting relaxed, and with distant fixation)
2. Swelling of the eyelids (absent/equivocal, moderate, severe)
3. Redness of the eyelids (absent/present)
4. Redness of the conjunctivae (absent/present)
5. Conjunctival edema (absent, present)
6. Inflammation of the caruncle or plica (absent, present)
7. Exophthalmos (measured in millimeter using the same Hertel exophthalmometer and same intercanthal distance for an individual patient)
8. Subjective diplopia score (0=no diplopia; 1=intermittent, i.e. diplopia in primary position of gaze, when tired or when first awakening; 2=inconstant, i.e. diplopia at extremes of gaze; 3=constant, i.e. continuous diplopia in primary or reading position)
9. Eye muscle involvement (ductions in degrees)
10. Corneal involvement (absent/punctate keratopathy/ulcer)
11. Optic nerve involvement (best-corrected visual acuity, color vision, optic disk, relative afferent pupillary defect (absent/present), plus visual fields if optic nerve compression is suspected

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