Graves' thyroid disease is a relatively common disorder in endocrinology and general internal medicine practice. Graves' hyperthyroidism is mediated by circulating stimulating autoantibodies. Up to 60% of patients with Graves' hyperthyroidism develop some form of Graves' orbitopathy. Immune reactivity to the thyroid-stimulating hormone receptor is also thought to play a role in the immunopathogenesis of Graves' orbitopathy. Graves' orbitopathy is characterised by a wide open eye appearance, caused by upper eyelid retraction and soft-tissue swelling that causes exophthalmus. Symptoms include photophobia, sandy feeling in the eye, painful eye movements and diplopia. Visual acuity may be reduced. In some cases emergency treatment is necessary to prevent irreversible vision loss. Smoking should be stopped. Mild to moderate Graves' orbitopathy may be an indication for corticosteroid treatment or radiotherapy. Once inflammatory signs and symptoms have waned, surgery can be performed to correct residual diplopia, exophthalmus or lid retraction. The presence of Graves' orbitopathy has consequences for the management of Graves' hyperthyroidism. Adequately controlled Graves' thyroid dysfunction is likely to improve Graves' orbitopathy, while radioactive iodine treatment can worsen the condition. Due to the wide variety in clinical presentation and the possible interference between treatment of thyroid disease and eye disease, the management of more complicated patients with Graves' orbitopathy can best be performed in combined thyroid-eye clinics, in which the patient is seen simultaneously by the ophthalmologist and the endocrinologist.

**ABSTRACT**

Graves' thyroid disease is a relatively common disorder in endocrinology and general internal medicine practice. Graves' hyperthyroidism is mediated by circulating stimulating autoantibodies. Up to 60% of patients with Graves' hyperthyroidism develop some form of Graves' orbitopathy. Immune reactivity to the thyroid-stimulating hormone receptor is also thought to play a role in the immunopathogenesis of Graves' orbitopathy. Graves' orbitopathy is characterised by a wide open eye appearance, caused by upper eyelid retraction and soft-tissue swelling that causes exophthalmus. Symptoms include photophobia, sandy feeling in the eye, painful eye movements and diplopia. Visual acuity may be reduced. In some cases emergency treatment is necessary to prevent irreversible vision loss. Smoking should be stopped. Mild to moderate Graves' orbitopathy may be an indication for corticosteroid treatment or radiotherapy. Once inflammatory signs and symptoms have waned, surgery can be performed to correct residual diplopia, exophthalmus or lid retraction. The presence of Graves' orbitopathy has consequences for the management of Graves' hyperthyroidism. Adequately controlled Graves' thyroid dysfunction is likely to improve Graves' orbitopathy, while radioactive iodine treatment can worsen the condition. Due to the wide variety in clinical presentation and the possible interference between treatment of thyroid disease and eye disease, the management of more complicated patients with Graves' orbitopathy can best be performed in combined thyroid-eye clinics, in which the patient is seen simultaneously by the ophthalmologist and the endocrinologist.

**KEYWORDS**

Graves, hyperthyroidism, orbitopathy, ophthalmopathy, endocrinology

**INTRODUCTION**

Graves' orbitopathy (also known as Graves' ophthalmopathy, thyroid eye disease and thyroid-associated ophthalmopathy) is a potentially sight-threatening chronic autoimmune disorder characterised by an inflammation of retrobulbar tissues, leading to accumulation of hydrophilic glycosaminoglycans (GAGs) and/or an increase in orbital adipose tissue and thereby in increased volumes of orbital connective tissue and extra-ocular muscles. The annual incidence rate is low: 16 women and 3 men per 100,000. In up to 90% of adults with Graves' hyperthyroidism, extraocular muscle and/or fat enlargement is detected by computed tomography (CT) or magnetic resonance (MRI) scans of the orbit and clinical features are evident in 25 to 50% of patients with Graves' hyperthyroidism. Of all patients with Graves orbitopathy, 5 to 10% have no abnormalities in thyroid function, and up to 10% of patients with Graves' orbitopathy initially present with hypothyroidism. Graves' hyperthyroidism is a relatively common disorder, but the diagnosis and treatment of Graves' orbitopathy may be problematic because of considerable variety in disease presentation and interactions between thyroid and eye disease management. Common clinical features of Graves' orbitopathy are eyelid retraction, proptosis, extraocular muscle dysfunction, periorbital oedema and conjunctivitis. Approximately 5% of patients have severe Graves' orbitopathy with sight-threatening corneal ulceration or compressive optic neuropathy. Here we discuss clinical features of Graves' orbitopathy, imaging modalities and treatment options. The combined approach of an endocrinologist and ophthalmologist will render the best care for a patient with Graves' orbitopathy.

**PATHOPHYSIOLOGY**

The close association between Graves' hyperthyroidism and Graves' orbitopathy suggests a shared underlying
pathophysiological mechanism. Thyroid-stimulating hormone (TSH) receptor-stimulating antibodies bind the TSH receptor on the thyroid gland causing increased thyroid growth and excessive thyroid hormone production known as Graves’ hyperthyroidism. Immune reactivity to the TSH receptor is currently also thought to play an important role in the immunopathogenesis of Graves’ orbitopathy, as the TSH receptor can be detected in orbital adipose tissue of patients with Graves’ orbitopathy. Indeed, elevated TSH receptor expression has been demonstrated in orbital tissues from patients with active Graves’ orbitopathy compared with patients with inactive disease. The receptor autoantibodies titre and the clinical activity of Graves’ orbitopathy correlate, making TSH receptor antibody levels of prognostic value for the severity and the outcome of Graves’ orbitopathy. However, the precise role for the TSH receptor has not been established. There is increasing evidence that orbital fibroblasts, which express the TSH receptor, are major participants in the immunopathogenesis of Graves’ orbitopathy. Orbital fibroblasts can produce excessive amounts of the highly hydrophilic GAG hyaluronan upon stimulation with various cytokines. In addition, a subpopulation, termed preadipocytes, can differentiate into mature adipocytes under strict culture conditions in vitro and may contribute to the increase in adipose tissue. Histology shows accumulation of hydrophilic GAG, predominantly hyaluronan, and an increase in orbital adipose/connective tissue. The different clinical features of active Graves’ orbitopathy are caused by inflammatory processes of retro-ocular connective tissue with infiltration of predominantly type 1 helper T (Th1) cells but also mast cells, B cells, plasma cells and macrophages. The presence of primarily Th1 cells and associated cytokines (interleukin-2, interferon-γ, tumour necrosis factor (TNF)) in early disease indicates that cell-mediated immunity prevails in early disease. In later stages of Graves’ orbitopathy, Th2 cells and cytokines (interleukin-4, interleukin-5, interleukin-10 and interleukin-13) predominate stimulating B-cells to produce autoantibodies.

CLINICAL FINDINGS

Symptoms of Graves’ orbitopathy
In 40% of patients with Graves’ orbitopathy, the signs of the eye disease occur simultaneously with the first symptoms of Graves’ hyperthyroidism. However, Graves’ orbitopathy can occur several years after the diagnosis of Graves’ hyperthyroidism. Approximately 5 to 10% of Graves’ orbitopathy patients are euthyroid at presentation and some of them may not have a history of thyroid dysfunction, which explains why the diagnosis of Graves’ orbitopathy may be delayed. Not surprisingly, these patients are at considerable risk for developing thyroid disease.

As detailed below, the severity of Graves’ orbitopathy can vary between no complaints at all (i.e. just appearance of Graves’ orbitopathy) or (near) blindness. Often, patients only present with a ‘changed appearance’. In case of extensive swelling of the extraocular muscles, compression of the optic nerve may occur in 3 to 5% of patients, leading to loss of vision (dysthryoid optic neuropathy, DON). This is an indication for acute treatment (see treatment of severe Graves’ orbitopathy).

Upper eyelid retraction and proptosis
Many patients with Graves’ hyperthyroidism have subtle signs of Graves’ orbitopathy at physical examination. The ‘wide open eye appearance’ is caused by upper eyelid retraction (UER) and bulging of the eye out of its socket due to increased intraorbital pressure (proptosis or exophthalmus). UER is far more common than increased orbital volume. It is often mistaken for exophthalmus. It can be diagnosed by observing the upper eyelid during downward gaze: the upper eyelid follows the bulb with some delay (lidlag or von Graefe’s sign). Next to increased sympathetic tone, fibrotic attachments around the levator palpabrae muscle cause UER.

Oedema and fibrosis in the external eye muscles and increased intraorbital fat lead to increased intraorbital volume. Since the orbit is bounded by bony walls, except for the anterior side, increased retrobulbar content will move the eye out of the orbit causing exophthalmus. The degree of exophthalmus can be quantified with exophthalmometry, for instance a Hertel exophthalmometer. One should realise that racial, gender, and age-related differences in orbital volume exist. Exophthalmometry is specifically important for longitudinal comparison within patients.

| Table 1. Clinical activity of Graves’ orbitopathy according to Mourits et al. |
|-----------------------------------------|----------------------------------|
| VIII Increase of proptosis of more then 2 mm in one to three months |
| IX Decrease in visual acuity of one or more lines in one to three months |
| X Decrease in eye movement of more then 5° in any direction in one to three months |

Regensburg et al. showed that in Graves’ orbitopathy three subgroups can be distinguished based on the orbital content: 1) no fat or muscle volume increase; 2) only fat or muscle volume increase, and 3) both fat and muscle volume increase. Although the clinical activity score (CAS; see below) between these groups was not different, muscle swelling only was associated with an increased risk of developing DON.

**Activity and severity in Graves’ orbitopathy**

The activity and severity are important determinations in Graves’ orbitopathy and have implications for treatment. Active disease is characterised by inflammatory symptoms and signs such as redness, oedema and pain. Severity of disease is defined by the functional or cosmetic impairment.

Characteristically, the course of Graves’ orbitopathy can be divided into four phases. In the first phase there is an increase of signs and symptoms of Graves’ orbitopathy. The second phase is a plateau phase, during which signs and symptoms are the most severe. In the third phase, signs and symptoms regress, leading to a stable fourth phase in which abnormalities in appearance and functional impairments remain.

Clinical activity can be scored by using the CAS ten-point scoring system, which was developed by Mourits et al. (table 1).10-12 The first seven items are easy to score by the internist, and are used to guide diagnostic and treatment strategies (figure 1). The colour atlas of Graves’ orbitopathy facilitates uniform use of the CAS.

The NOSPECS mnemonic is a useful alternative reminder of what should be assessed in patients with Graves’ orbitopathy regarding severity, but it is of lesser practical value (table 2).13 First, NOSPECS is more of an ophthalmological tool that is not easy to perform in the endocrinologist’s office. In addition, NOSPECS assumes a rank in the various clinical features that is not always present.

**ORTHOPTIC EVALUATION AND IMAGING**

Assessment of eye motility involves the squint angle, the range of fusion, unilateral eye excursions (ductions) and field of binocular single vision. The motility pattern depends on the involved muscles and can be extremely deceptive. A patient with mild unilateral involvement of the inferior rectus muscle may experience constant diplopia, whereas a patient with severe bilateral involvement of the inferior rectus muscle may have single vision (at the cost of elevation impairment and ocular torticollis). Although specific muscle involvement is often suspected when there is gaze limitation in certain directions, imaging (CT, MRI or ultrasound) can be very helpful. Muscle enlargement, and not retrobulbar fat accumulation, is associated with an increased risk of developing DON, as shown by CT and MRI, showing swelling of extra-ocular muscles and disappearance of adipose tissue in the apex of the orbit (apical crowding). The latter is suggestive of developing DON. Also, a stretched optic nerve is associated with an increased risk for visual loss.

**TREATMENT OF GRAVES’ ORBITOPATHY**

The natural course of Graves’ orbitopathy is usually self-limiting as the activity will improve spontaneously. Artificial tears can be of help in reducing symptoms of tearing and burning due to ocular surface exposure. The strongest modifiable risk factor in Graves’ orbitopathy is smoking. Smoking not only increases the chance of developing Graves’ orbitopathy 7-8 fold, it also increases the severity and progression of Graves’ orbitopathy with a less favourable response to treatment. Patients must be encouraged to stop smoking.

Whether or not a patient should be actively treated is based on the level of functional and cosmetic impairment (severity) and on the level of inflammation (activity). The type of treatment is based on the phase of the disease. Active disease is usually treated with immunosuppressive treatment and functional and cosmetic impairment usually by surgery.

**Mild Graves’ orbitopathy: wait and see**

In mild Graves’ orbitopathy the side effects of immunosuppressive treatment or radiation do not weigh against the expected beneficial effects. Progression from mild to moderate to severe Graves’ orbitopathy occurs in about 15%. The best way to predict progression is an increase in the CAS score. Patients who smoke and with high TSH receptor autoantibody titres may be at increased risk. Selenium (a naturally abundant antioxidant) improves the outcome in mild Graves’ orbitopathy.

Table 2. NO SPECS score

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 0</td>
<td>No symptoms or signs</td>
</tr>
<tr>
<td>Class I</td>
<td>Only signs, no symptoms (lid retraction, stare, lid lag)</td>
</tr>
<tr>
<td>Class II</td>
<td>Soft tissue involvement (absent, mild, moderate, marked)</td>
</tr>
<tr>
<td>Class III</td>
<td>Proptosis (&lt; 23, 23-24, 25-27, ≥ 28 mm)</td>
</tr>
<tr>
<td>Class IV</td>
<td>Extraocular muscle involvement (absent, limited motion, evident restriction, fixation)</td>
</tr>
<tr>
<td>Class V</td>
<td>Corneal involvement (absent, stippling, ulceration, clouding/necrosis/perforation)</td>
</tr>
<tr>
<td>Class VI</td>
<td>Sight loss (optic nerve involvement) (&gt;0.67, 0.67-0.33, 0.33-0.10, &lt;0.10, expressed as decimals)</td>
</tr>
</tbody>
</table>

Moderate to severe Graves’ orbitopathy: corticosteroid treatment

Moderate to severe Graves’ orbitopathy is defined as: no threat to vision but sufficient impact on daily life to justify the risks of immunosuppression. The use of immunomodulatory treatment is especially indicated in very active disease.

For a long time corticosteroids have been used in patients with moderate to severe Graves’ orbitopathy, with response rates up to 80%. Intravenous prednisolone treatment is recommended because it has been convincingly shown that it has better results compared with high-dose oral therapy. In addition, intravenous therapy is accompanied by less side effects such as diabetes or weight gain. Preferably, an internist or endocrinologist and the ophthalmologist decide together which patients should be treated with prednisolone (see also the combined thyroid-eye clinic). An internist or endocrinologist should assess possible contraindications for high-dose prednisone treatment, such as gastrointestinal ulcer disease, severe osteoporosis, latent tuberculosis or hepatitis B or C positivity. Blood pressure and plasma glucose levels should be checked frequently and dietary advice should be given in case of weight gain. Fluid retention can be a problem. Additionally, patients must receive osteoporosis prophylaxis (i.e. bisphosphonate, calcium, and vitamin D) and proton pump inhibition.

The cumulative dose of prednisolone should not exceed 8 grams in one course of therapy. However, the exact dose of prednisolone that yields satisfactory therapeutic effect without adverse events is not exactly known. Recently, the inclusion of patients in a large multicentre randomised clinical trial initiated by the European Group on Graves Ophthalmopathy (EUGOGO) was completed. This study compared the effectiveness of three dosage regimens of prednisolone (cumulative dosage of 2.5 g, 5.0 g or 7.5 g). The results will be available at the end of 2011. Whether selenium on top of prednisolone during moderate to severe Graves’ orbitopathy has additive effects remains to be investigated.

Very severe Graves’ orbitopathy or DON

The treatment of DON is difficult because of the absence of randomised trial data and the lack of distinction between possible and definite DON. Data from a small study favour treatment with high-dose intravenous steroids. In this study patients received 1 g methylprednisolone iv daily for three consecutive days, repeated after one week, followed by an oral tapering dose. Usually the iv dose of prednisolone is given in a clinical setting in order to permit regular checks of visual acuity. When there is clinical deterioration, urgent orbital decompression should be considered.

Other immunosuppressive therapy

Whereas corticosteroids are established in the treatment of moderate to severe Graves’ orbitopathy and DON, this is less the case for other immunosuppressive therapies, the only exception being cyclosporine. Prummel et al. compared single cyclosporine vs prednisolone monotherapy use and showed that cyclosporine alone has much lower efficacy. However, cyclosporine in addition to prednisolone has an additive beneficial effect and should be used when steroids alone fail in moderate to severe orbitopathy. Normally, cyclosporine is continued after the tapering down of steroids. The recommended cyclosporine dose is 3 mg/kg/day up to a maximal dose of 5 mg/kg/day.

Intravenous administration of immunoglobulin seems equally effective to prednisolone, but costs, iv administration and the chance of transmitting infections negate the administration of immunoglobulin. Tumour necrosis factor-α blockers may have therapeutic value in Graves’ orbitopathy. Etanercept showed 65% patient-reported improvement and 60% CAS reduction although almost 30% of patients showed Graves’ orbitopathy flare up after cessation of the study drug. The same (decrease in CAS) is true for anti-CD20 monoclonal antibodies (rituximab) although the studies that have been performed are quite small. The value of both etanercept and rituximab needs to be confirmed in larger randomised clinical trials.

Radiotherapy

Retrobulbar radiotherapy may be a good alternative to treat moderate to severe Graves’ orbitopathy since intraorbital lymphocytes are particularly sensitive to radiotherapy. Radiotherapy (10 fractions of 2 Gray (Gy)) compared with sham radiotherapy decreased the NOSPECS score in 63% compared with 31% respectively. A head-to-head comparison between prednisolone and radiotherapy showed equal effectiveness of the therapies. Prednisolone showed a quicker recovery with better effect on soft tissue whereas radiotherapy showed better outcome for muscle motility. The beneficial effect of radiotherapy on muscle motility and diplopia has been established by other studies as well. Usually, the dosage of Rx can be low: 1 Gy per week (compared with 1 or 2 Gy daily) showed to be equally effective in patients with moderate to severe Graves’ orbitopathy. Patients with diabetes (and hypertension) have a relative contraindication for radiotherapy as they have higher risk for developing post-radiotherapy retinopathy.

Surgical treatment

Surgical treatment is usually performed in phase 4, when the activity of the disease has waned. It is only in patients with active disease who have refractory or progressing...
DON or corneal ulcer that urgent orbital decompression surgery may be needed. Indications for orbital decompressions include a stretched optic nerve, prevention of further corneal damage, alleviating complaints of tearing and grittiness, but also cosmetic complaints. During an orbital decompression, part of the bony walls is removed in order to provide more space for the extraocular muscles and orbital fat. Diplopia usually warrants surgery of the extraocular muscles. If orbital decompression is done, extraocular muscle surgery is generally postponed for several months to be able to first evaluate the effect of decompression on the diplopia. Finally, eyelid surgery such as lengthening (in case of upper eye lid retraction) may be a final step in the rehabilitation of the patient with Graves’ orbitopathy.

**TREATMENT OF GRAVES’ ORBITOPATHY WITH CONCOMITANT GRAVES’ HYPERTHYROIDISM**

Apart from the treatment modalities for Graves’ orbitopathy as outlined above, concomitant Graves’ hyperthyroidism may influence the course of the eye disease. Restoration of hyperthyroidism with block and replacement treatment has a neutral effect on the course of Graves’ orbitopathy.69 Stopping block and replacement therapy is associated with a significant risk of recurrence of hyperthyroidism. Some fear a simultaneous flare of Graves’ orbitopathy because of increasing antibody titres. Thyroidectomy also seems to have a neutral effect on Graves’ orbitopathy.5 This may be different for hypothyroidism, which usually shows deteriorating of Graves’ orbitopathy.52–53 131Iodine may induce progression or relapse of Graves’ orbitopathy that is explained by leakage of antigens from the thyroid gland, again eliciting an autoimmune response.8 Progression of Graves’ orbitopathy after 131I treatment can be prevented by corticosteroid treatment.54,55 Also, the occurrence of hypothyroidism after 131I therapy is associated with Graves’ orbitopathy (de novo and pre-existing). Risk factors for progression of Graves’ orbitopathy due to 131I therapy include cigarette smoking, TSH receptor antibody levels, severity of Graves’ hyperthyroidism and pre-existing Graves’ orbitopathy.56–58 If these risk factors are present (smoking in particular) treatment with corticosteroids is warranted to prevent 131I induced Graves’ orbitopathy.19 A study by Bartalena *et al.* showed that prednisolone not only prevents worsening of Graves’ orbitopathy after 131I therapy, but actually also improves Graves’ orbitopathy in some patients.54 In these studies prednisolone 0.5 mg per kg was used for four weeks starting two-three days after 131I therapy. Steroids were tapered down in two months.54,55

**RATIONALE OF COMBINED THYROID-EYE CLINICS**

When patients are assessed in combined thyroid-eye clinics (CTECs), they have a favourable outcome compared with patients who are not managed in such clinics.57 A survey study showed participation in a multidisciplinary setting for management of Graves’ orbitopathy in approximately half of the responders, but this was not the case in more than one third. Moreover, a lack of ‘best practice’ was shown in a significant number of responders for everyday clinical issues such as the referral to an ophthalmologist in case of a possible DON. Therefore, the EUGOGO recommends the implementation of CTECs. The wide variety in clinical presentation and the interactions between the endocrinological and ophthalmological treatment (see ‘treatment of Graves’ orbitopathy with concomitant Graves’ hyperthyroidism’) that

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**Figure 1. Flowchart for patients presenting with Graves’ hyperthyroidism or Graves’ orbitopathy**

- **Patients presenting with Graves’ hyperthyroidism**
  - Hyperthyroidism?: Screen TSH, fT4, total T3 and TSI
  - **GO complaints?**
    - Yes: Reconsider GO diagnosis
    - No: Emergency referral to ophthalmologist/CTEC (same day)
  - **No symptoms and signs and CAS 0/7:** Repeat every 3 months
  - **CAS 1-2/7:** Refer to internist or CTEC
  - **CAS > 3/7:** Emergency referral to ophthalmologist/CTEC (same day)

- **Patients presenting with Graves’ orbitopathy**
  - **GO complaints?**
    - Yes: Refer to internist or CTEC
    - No: Referral to the ophthalmologist/CTEC
  - **Hyperthyroidism?: Screen TSH, fT4, total T3 and TSI**
    - No: Emergency referral to ophthalmologist/CTEC (same day)
    - Yes: Watchful waiting
  - **Loss of colour vision**
    - Yes: Emergency referral to ophthalmologist/CTEC (same day)
    - No: **Strong interference with daily life activities**
      - Yes: Emergency referral to ophthalmologist/CTEC (≤ 2 weeks)
      - No: **Moderate interference with daily life activities**
        - Yes: Emergency referral to ophthalmologist/CTEC (≤ 6 weeks)
        - No: Emergency referral to ophthalmologist/CTEC (≤ 6 weeks)
  - **Loss of vision**
    - Yes: Emergency referral to ophthalmologist/CTEC (≤ 2 weeks)
    - No: **CAS 0-2/7**
      - Yes: Emergency referral to ophthalmologist/CTEC (≤ 6 weeks)
      - No: **CAS > 2/7**
        - Yes: Emergency referral to ophthalmologist/CTEC (≤ 6 weeks)
        - No: Emergency referral to ophthalmologist/CTEC (≤ 6 weeks)

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GO = Graves’ orbitopathy; CAS = clinical activity score; CTEC = combined thyroid-eye clinic; TSH = thyroid-stimulating hormone; TSI = thyroid-stimulating immunoglobulin.
require Graves' orbitopathy to be treated by a multidisciplinary team that includes at least an ophthalmologist and an internist or endocrinologist. In case of endangered vision, emergency referral to a combined thyroid-eye clinic may be necessary, in mild cases 'watchful waiting' is justified (Figure 1). Patients with Graves' orbitopathy may have complicating circumstances that hinder the decision making and subsequent treatment of Graves' orbitopathy and Graves' hyperthyroidism (e.g. toxicity of thyroestatics or pregnancy).

CONCLUSION

Much progress has been made in the diagnosis and treatment of Graves' orbitopathy. Each patient with Graves' hyperthyroidism should be meticulously scrutinised for Graves' orbitopathy. A workup in so-called combined thyroid-eye clinics improves the management of Graves' orbitopathy.

REFERENCES


