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Consensus

Graves' orbitopathy: Diagnosis and treatment

Orbitopathie basedowienne: diagnostic et prise en charge

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1. Clinical assessment of Graves' orbitopathy

Graves' orbitopathy (GO) is the most frequent extrathyroid complication in Graves' disease. Natural history, described by Rundle, features an initial inflammatory or active phase in which acute episodes and spontaneous remissions alternate, then a fibrotic phase, with regression within 12–18 months.

Diagnosis is based on symptoms and ocular signs. Clinical examination must therefore be rigorous; in case of doubt, the ophthalmologist's opinion is determining.

Various classifications assess clinical signs: most widely used are the EUGOGO (European Group Of Graves' Orbitopathy) and VISA (Vision, Inflammation, Strabismus, Appearance) classifications, the former (http://www.eugogo.eu) in Europe and the latter (http://www.thyroideyedisease.org) more often in the US and Canada. Both have limitations; they are not interchangeable, and each patient must consistently be monitored on one or the other. Expert discussions are ongoing, and alternative classifications are offered to improve assessment [1,2].

Delayed diagnosis and treatment impair ocular progression [3]. Optimal treatment depends on activity status and severity [4]. Clinical activity score (CAS) ≥3/7 indicates active status. Severity is graded as mild, moderate-to-severe or very severe (sight-threatening). Table 1 shows activity and severity criteria.

> R1. GO activity and severity should be assessed on the standardized EUGOGO criteria: active/inactive and mild/moderate-to-severe/sight-threatening, with quality of life taken into account. Grade 1++.

2. Risk factors and prevention

Development of GO depends on environmental factors. The influence of smoking is well-established: smokers show greater GO severity, with higher rates of disease or progression after radioiodine treatment. Smoking slows immunosuppression effects, and cessation is associated with improved progression. Patients should therefore be encouraged to quit smoking and accompanied in this [5].

Rapid recovery of euthyroid status is critical. Antithyroid drugs and thyroidectomy do not impact natural progression, but radioiodine therapy is associated with higher risk of exacerbation or onset of GO, especially in smokers, in case of severe hyperthyroidism (free T3 and anti-TSH-R antibody elevation) or recent hyperthyroidism.

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Table 1
Assessment of activity and severity in Graves' orbitopathy.

Activity: CAS according to Mourits	Initial assessment (score: 1–7 points) CAS ≥3: active GO CAS <3: inactive GO	Spontaneous retrobulbar pain Pain on attempted upward or downward gaze Redness of eyelids Redness of conjunctiva Swelling of caruncle or plica Swelling of eyelids Swelling of conjunctiva (chemosis)	
	Assessment at 1–3 months' follow-up (score: 1–10 points)	>2 mm increased exophthalmos >8° decreased ocular excursion in 1 direction 1-point decrease in acuity on Snellen scale	
EUGOGO severity criteria [8]	Mild GO	Patients whose features of GO have only a mild impact on daily life insufficient to justify treatment. They usually have one or more of the following:	Minor lid retraction (<2 mm) Mild soft-tissue involvement Exophthalmos <3 mm above normal for race and gender No or intermittent diplopia Corneal exposure responsive to lubricants
	Moderate-to-severe GO	Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). They usually have two or more of the following	Lid retraction >2 mm Moderate or severe soft-tissue involvement Exophthalmos ≥3 mm above normal for race and gender Inconstant or constant diplopia
	Sight-threatening GO (very severe GO)	Patients with dysthyroid optic neuropathy and/or corneal breakdown	
NOSPECS classification (severity criteria)	No signs or symptoms Only signs, no symptoms: lid aperture Soft-tissue involvement: swelling/redness of the eyes Proptosis: exophthalmos (using the same Hertel exophthalmometer and same intercanthal distance for an individual patient) Extraocular muscle involvement (intermittent, inconstant or constant diplopia) Corneal involvement: absent/punctuate keratopathy or ulcer Sight loss (due to optic nerve involvement): best-corrected visual acuity, color vision, optic disk, relative afferent papillary defect, visual fields		
VISA criteria [53]	Based on signs and symptoms, with maximum score of 20. Score <4–10: non-operative treatment; Score 5–10 or progression/inflammation: more aggressive treatment	Caruncle swelling Chemosis Redness of conjunctiva Redness of eyelids Retrobulbar pain at rest Retrobulbar pain on gaze Diurnal variation	0: absent 1: present 0: absent 1: minor 2: major 0: absent 1: present 0: absent 1: present 0: absent 1: present 0: absent 1: present 0: absent 2: present

CAS: clinical activity score; GO: Graves' orbitopathy.

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In radioiodine therapy, patients at high-risk of GO must be informed of potential risks and undergo pretreatment assessment by an ophthalmologist.

R2. The physician should encourage and accompany cessation of smoking, even in absence of GO, with help from a smoking cessation specialist or specialized center. Grade 1++.

R3. Euthyroid status should be restored rapidly and held stable, avoiding episodes of hyper- or hypo-thyroidism. Grade 1+++.

R4A. Patients with inactive GO who do not smoke can be treated by iodine-131, avoiding hypothyroid episodes. Grade 1+++.

R4B. High-risk patients treated by iodine-131 should be informed of possible GO complications. Grade 1++.

3. Improving GO management. Graves' Orbitopathy Centers

In 2009, international GO experts from endocrinology and ophthalmology societies and patient associations (including "Vivre sans Thyroïde") met in Amsterdam and signed an agreement to improve GO management with action plans to reduce associated morbidity, improve quality of life and prevent onset in at-risk subjects. The Amsterdam Declaration [6] proved beneficial: treatment improved between 2000 and 2012, with faster (6 versus 12 months) and more widespread referral of orbitopathy cases (increased prevalence of moderate and inactive orbitopathy). Publicity concerning GO networks seems necessary [7].

Health-care organization in France (and, for certain pathologies, in Belgium) is based on a pathway coordinated by the community physician, who may refer the patient either to a specialist or to a specialized structure; the latter should have endocrinological and ophthalmological expertise in GO and can confirm or rule out diagnosis in case of doubt, assist in smoking cessation and provide medical and surgical remedies in moderate-to-severe forms by close teamwork between endocrinologists and ophthalmologists [3]. Patients report greater satisfaction with such a multidisciplinary approach. At present there are no such dedicated approved centers in France; approval by the public authorities and scientific societies should be encouraged. Local organization should be determined by those involved in each center (multidisciplinary consultation and/or team meeting) according to the center's organization.

It is important to promote close and reactive communication between specialized centers and the referring physicians (endocrinologists and ophthalmologists), who are the pillars supporting the management structure.

R5. Management of moderate-to-severe GO should be multidisciplinary, on request by the referring physician, in a "specialized" center. Grade 1++.

4. Patient referral. Viewpoints of the endocrinologist and ophthalmologist

All patients with GO should be referred for specialist assessment, except in case of mild orbitopathy in euthyroid patients responding to artificial tears [8].

Urgency of treatment in the reference center depends on severity [9]. Referral is urgent in suspected dysthyroid optic neuropathy: i.e., recent unaccountable fall in visual acuity and/or altered color vision and/or ocular subluxation and/or risk of corneal ulcer (corneal opacity and/or lagophthalmos) [3].

Referral is non-urgent in GO with CAS$\geq$ 3 requiring multidisciplinary management (endocrinologist, ophthalmologist):

- recently aggravated photophobia (1–2 months);
- conjunctiva irritation unimproved by 1 week's topical lubricants;
- recently aggravated ocular or retro-orbital pain (1–2 months);
- progressive change in aspect of eyes and/or eyelids during the previous 1–2 months;
- altered view troubling the patient and/or diplopia;
- or if clinical examination finds: eyelid retraction, palpebral or conjunctive edema, impaired eyeball motion, clear strabismus or constrained position to avoid diplopia.

Simple diagnostic tools need to be developed to facilitate rapid referral to an expert center (e.g., pilot study by Mitchell et al. [2]).

R6. Primary health-care providers need to be made aware of management of GO. Grade 1++.

5. Achieving euthyroid status

Treatment modalities depend on activity status (inflammation) and severity at time of treatment, requiring

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close teamwork between endocrinologist and ophthalmologist [3,10,11].

Antithyroid drugs are recommended in first line, and should be continued until GO becomes inactive. There are no prospective randomized studies demonstrating superiority of antithyroid drugs or total thyroidectomy in terms of progression. A comparative study of 30 patients after thyroidectomy and 60 patients under antithyroid drugs did not reveal any difference in progression of orbital disease [12].

A prospective randomized study in 60 GO patients found better results at 9 months after total thyroidectomy followed by ablative radioiodine treatment as compared to isolated total thyroidectomy, but without significant difference over a mean 88 months' follow-up [13,14]. However, present literature data are insufficient to recommend systematic total thyroid tissue ablation associated to radioiodine; numerous studies reported that radioiodine could aggravate or induce onset of GO [15–17]. Ophthalmologic assessment of patients with or at-risk of GO (see section 1) should therefore be performed before and after radioiodine treatment. In pre-existing moderate GO, oral corticosteroids prevent deterioration [16,18,19]; the classic dose is 0.3–0.5 mg/kg/day, initiated 1–3 days after radioiodine treatment, with progressive reduction over 3 months.

To avoid hypothyroid episodes, free T4 and TSH should be monitored every 1–2 months for the first 6 months, with the first assay within 2–4 weeks [3]. Systematic early introduction of low-dose levothyroxine 2 weeks after treatment is debatable.

R7. Euthyroid status should be rapidly restored and maintained durably and stably, to avoid aggravation of GO. Grade 1+++.

R8. Hyperthyroidism should be treated and euthyroid status should be restored and maintained by antithyroid drugs during the active inflammatory phase. Grade 1+++.

R9A. In case of radioiodine treatment, ophthalmologic assessment should screen for GO. Grade 1+.

R9B. Hypo-thyroidism should be screened for by free T4 and TSH assay 2–4 weeks after treatment then every 1–2 months for at least 6 months. Grade 1++.

6. Role of medical treatment

As well as stable and lasting euthyroidism and cessation of active and passive smoking, local treatments should always be implemented: dark glasses, artificial tears, raised bed-head.

6.1. In mild orbitopathy

Selenium helps inhibit oxidative stress. A multicenter double-blind randomized study versus placebo [20] demonstrated benefit for 6 months' treatment by 100 μg sodium selenite twice daily (i.e., 93.6 μg per day) in terms of quality of life and inflammatory signs in soft-tissue, maintained 12 months after end of treatment. No side-effects were reported. This treatment is paid for entirely by the patient and is not reimbursed by the French national health insurance scheme.

6.2. In moderate-to-severe orbitopathy

Glucocorticoids are the first line treatment on moderately severe GO. They exert an anti-inflammatory effect by inhibiting cytokines (IL6, INF gamma, IL1).

Intravenous glucocorticoids show better efficacy and tolerance than oral forms [21–24]. A double-blind randomized study versus placebo showed greater efficacy, and a dose-comparison study confirmed the current protocol of 500 mg iv methylprednisolone per week for 6 weeks then 250 mg per week for 6 weeks: i.e., cumulative dose of 4.5 g [25]. Intravenous glucocorticoids show toxicity (mainly liver, with diabetes and psychosis) for cumulative doses exceeding >8 g [23,26].

In case of non-response and persistent active GO, second-line options comprise glucocorticoids associated to external radiation therapy or to cyclosporine or rituximab.

External radiation therapy has a non-specific anti-inflammatory effect. Benefit was shown in 2 randomized studies [27,28]. A retrospective study suggested greater efficacy in oculomotor forms for radiation therapy associated to intravenous glucocorticoids than intravenous glucocorticoids alone, and less recurrence [29]. Contraindications concern patients under 35 years of age or with diabetic retinopathy and severe high blood pressure.

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody that binds specifically to the membrane-spanning antigen CD20, a non-glycosylated phosphoprotein located on matures pre-B and B lymphocytes, inducing rapid B-cell depletion. It is associated with a rare but severe (although reversible) syndrome of cytokine release, requiring precautions in injection. A retrospective study reported efficacy, with 4.9–2.2 reduction in CAS in 91% of patients (39/43). There was a single case of recurrence. One-third of patients (13/43) showed side-effects [30]. However, two recent randomized studies reported conflicting responses, accounted for by selection bias and duration of GO [31,32]. The role of rituximab is thus not yet clear; further randomized studies are needed to determine indications, optimal dose and cost/effectiveness. In many European countries, rituximab

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is available only on compassionate grounds, which further restricts prescription.

Cyclosporine affects hormonal and cellular immunity by inhibiting T-cell activation and cytokine production and activating T-suppressor cells; it acts on lymphocytes in the early stages of activation. Two randomized studies [33,34] showed that association to oral glucocorticoids (initial dose, 100 mg prednisone) improved ocular progression and reduced recurrence; this combined treatment is especially suited to diabetic patients, in whom high-dose glucocorticoids and/or external radiation therapy demand caution. Due to side-effects (blood pressure elevation, renal and hepatic toxicity), recommended doses are 5–7.5 mg/kg/day, with regular blood assay.

Recently, 2 new molecules proved useful in GO, although their role remains to be defined:

- teprotumumab (anti-IGF1-R antibody) proved effective in first line in an American double-blind randomized study versus placebo, with rapid effect (at 6 weeks) in recent GO of less than 9 months' progression, with significant improvement on the main composite assessment criterion (≥2 point reduction in CAS and ≥2 mm reduction in exophthalmos) in 69% of patients (29/42) receiving teprotumumab versus 20% (9/45) for placebo (OR = 8.86; $P < 0.001$). There was no rebound 7 weeks after end of treatment [35];
- mycophenolate mofetil (MMF) (500 mg × 2/day per os for 24 weeks) proved effective in first line in a Chinese randomized study versus glucocorticoids (0.5 g/day IV for 3 days for 2 consecutive weeks, then 60 mg/day per os for 8 weeks, then reduced by 5 mg/week for 14 weeks) in moderate-to-severe active GO (CAS ≥4 with 8 weeks' progression or no improvement over 24 weeks). Response rate was 91% (73/80) for MMF versus 68% (53/78) for glucocorticoids at 6 months ($P = 0.002$). CAS, diplopia on Gorman score and pain showed significantly greater improvement under MMF than glucocorticoids. There were no cases of recurrence under MMF but 5 (6.4%) under glucocorticoids (3 at week 12 and 2 at week 20) [36].

Other older immunomodulation treatments (immunoglobulins and plasmaphereses) no longer have a role. New immunomodulation treatments, such as etanercept, anti-interleukin 6 antibodies or tocilizumab [37], are being regularly assessed but have yet to demonstrate efficacy.

Further prospective clinical studies are needed to determine the roles of these molecules with respect to one another and to initial disease presentation.

6.3. Severe orbitopathy

Any malignant sight-threatening (i.e., severe) orbitopathy should be referred in emergency to a specialized ophthalmology team. Optic neuropathy is not easy to diagnose and requires confirmation before selecting treatment: high-dose iv glucocorticoids (1 g methylprednisolone for 3 days, renewable), followed by orbital decompression in case of insufficient response.

R10. Selenium is recommended for mild active orbitopathy. Grade 2++.

R11A. In moderately severe GO, intravenous glucocorticoids are recommended: 500 mg methylprednisolone per week for 6 weeks then 250 mg per week for 6 weeks (cumulative dose, 4.5 g). Higher doses seem more effective, especially in case of oculomotor disorder. Grade 1++++.

R11B. Treatment should be administered in a center able to assess the risk/benefit ratio, to ensure safety. Grade 2+.

R12. External radiation therapy is recommended in case of corticosteroid dependence or resistance and/or predominantly oculomotor forms. Dosage is 20 Gy in 10 fractions over 12 days. Grade 2+++.

R13. Rituximab is recommended for recent moderate-to-severe active GO, especially with high CAS, in case of corticosteroid dependence or resistance and contraindications to external radiation therapy and in case of diabetes. Grade 2++.

R14. Cyclosporine may be considered in moderate-to-severe active GO in case of corticosteroid dependence or resistance with contraindications to orbital radiation therapy and/or rituximab. Grade 2++.

R15. Other immunomodulation therapies are not recommended except in double-blind randomized clinical studies. Grade1+++.

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R16. In sight-threatening cases, patients should be referred to a GO reference center. Grade 1+++.

7. Specific treatments recommended by ophthalmologists in GO

GO may induce symptoms of dry eye, conjunctivitis and corneal exposure.

Artificial tears play a central role in the treatment of dry eye, compensating for the lack of natural tears and diluting the inflammatory factors causing chronicity. Whatever their viscosity and form (liquid or gel), they should ideally show good tolerance and no corneal toxicity, which precludes preservative agents.

Intraocular pressure should be assessed to prevent glaucoma. Ocular hypertonia may be mechanical, due to increased orbital content and muscle action on the eyeball, which may lead to simple hypertonia or hypertonia in upward gaze; it may also be iatrogenic, related to corticotherapy. Treatment is always initially medical, with eye-drops or oral acetazolamide, adapted secondarily to the etiology.

Binocular diplopia may be induced by oculomotor muscle inflammation followed by fibrosis. Orbital myositis involves, in increasing order of frequency, the inferior, medial and superior rectus muscles. Diplopia and strabismus are found in 15% of GO patients; deviation may be vertical, due to failure of elevation of 1 or both eyes (inferior rectus fibrosis), horizontal, due to abduction defect (medial rectus involvement) or oblique (combined involvement).

Dark lenses improve visual comfort if photophobia is severe. Glasses allow prisms to be fitted from the outset, at the inflammatory stage, if deviation is not too great (<20 diopters). Initially, press-on prisms are fitted to the eye glass, with the ridge along the direction of the deviation; in right-sided hypotropia, the ridge is positioned inferiorly and the base superiorly. Press-on prisms impair visual acuity proportionally to their power, and should therefore not be fitted on both sides; some orthoptists prefer a single oblique prism on the deviating eye. At the sequela stage, in case of mild and stable deviation, or of slight residual deviation following oculomotor surgery, prismatic correction can be integrated in the optical correction, distributing power between the two eyes. If prismatic treatment is impossible or poorly tolerated, occlusion on the glass or on the skin can be proposed, alternating sides day by day to prevent muscle contracture.

Botulinum toxin to treat strabismus was first described by Scott [38]. Several retrospective series demonstrated that efficacy in reducing or abolishing deviation is greater in the muscle inflammation stage than when injected late, in the fibrosis stage [39,40]. Injection is performed under local or general anesthesia for major deviation in primary position, and may be repeated after 3 months. It is especially useful for patients who cannot wait for surgery and in whom prismatic treatment is impossible or poorly tolerated.

Injection in the inferior rectus also lowers intraocular pressure, especially in upward gaze [41]. It can also be used in the inflammatory stage in the levator muscle to correct superior eyelid retraction [42]. In case of severe corneal ulceration resisting medical treatment, therapeutic ptosis can be performed in the acute stage using Botox®.

8. Orbital decompression

GO increases orbital muscle volume and fat, causing orbital hyperpressure and exophthalmos. Orbital decompression, first described in 1911, reduces pressure by reducing orbital content, either by fat removal as described by Olivari in 1984 [43,44], or by increasing orbital volume by boney wall fracture (bony decompression) and periorbital opening. The two techniques are usually associated, fat removal enhancing the effect of bony decompression.

There are many surgical bony decompression techniques, whether endoscopic or not, and approaches (palpebral, conjunctival, or coronal in the lateral approach); the literature, with only 2 randomized studies and many retrospective clinical studies, does not indicate any particular technique [45,46]. Surgery most often involves the medial, followed by the inferior and lastly the lateral wall. Three-wall decompression is more effective than 2-wall surgery, but entails more oculomotor complications and suborbital neuralgia.

Complications in decompression in severe cases (hematoma, cerebrospinal fluid leakage, infection, optic neuropathy) are rare, but need to be known by the patient. Aggravation or onset of oculomotor disorder ranges between 10% and >50% of cases; they are more frequent in bony decompression, with risk increasing with the number of walls involved. Suborbital neuralgia in inferior wall surgery, sinusitis or eyelid malpositioning may follow decompression, which should be performed by an experienced surgeon, ahead of oculomotor or palpebral surgery.

9. Strabismus surgery

When orbital decompression is required, oculomotor surgery should be scheduled afterward. It should be explained to the patient, and aims at restoring the widest possible visual field in primary position and downward gaze. Several procedures may be needed. Surgery is performed under general anesthesia, and consists in recession of the fibrotic muscle or muscles after forced stretch test to determine limits. Several techniques have been described, with identical 80–85% success rates after 1 procedure and 92–93% after ≥2. Recession takes account of preoperative deviation angle, but the muscle is usually reinserted according to the elongation limit or to the intraoperative position after release; adjustable sutures are sometimes used, with adjustment on the day after surgery under local anesthesia [47–50]. Complications comprise over- or under-correction with persistent diplopia and increased lower eyelid retraction after recession of the inferior rectus, of which the patient needs to be warned.

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10. Palpebral surgery

Palpebral lengthening surgery is performed outside of inflammatory phases, under at least 6 months' stable euthyroidism and after any orbital decompression or oculomotor surgery liable to alter eyelid position [51]. There are many techniques, according to the degree of retraction: Müller myotomy, levator palpebrae superioris surgery (recession and/or wing sectioning), or lower eyelid retractor resection. Both eyelids can be lengthened by grafting. Esthetic blepharoplasty may be associated [52], apart from in case of severe acute corneal exposure in the inflammatory stage, where Botox® treatment has made indications for surgical blepharorrhaphy exceptional.

R17A. Systematic assessment of the ocular surface is recommended, with prescription of artificial tears when appropriate. A gel should be applied at bedtime for lagophthalmos. Grade 1++.

R17B. Single-dose products or products contained in a non-chemical antibacterial device are to be preferred. Grade 2++.

R18A. In case of binocular diplopia, the patient should consult an ophthalmologist for correction of near and distant vision, avoiding progressive lenses. Grade 1++.

R18B. Diplopia should be managed jointly by an ophthalmologist and an orthoptist as soon as it appears. Grade 1++.

R19A. Orbital decompression is recommended in case of compressive optic neuropathy, severe corneal exposure or non-controlled severe ocular hypertonia. Grade 1+++.

R19B. When orbital decompression is performed for optic neuropathy, visual recovery may be slow and take as long as 6 months. Grade 1++.

R19C. Esthetic orbital decompression requires inactive GO and at least 6 months' euthyroid status. Grade 1+.

R20. Oculomotor surgery should be performed with inactive GO in the muscular fibrosis stage and in patients with stable euthyroid status and at least 6 months' stable deviation results. Grade 1+++.

Disclosure of interest

The authors declare that they have no competing interest.

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