

Graves' orbitopathy: What's new? Case report with diagnostic and therapeutic update

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Abstract

Orbitopathy is the most common extra-thyroidal complication of Graves' disease and is a potentially serious pathology as it threatens the functional prognosis. Its management is complex and requires a multidisciplinary approach. We report the case of a 26-year-old female patient followed for 2 years for Graves' disease with a very severe Graves' Orbitopathy (GO) requiring close monitoring and multidisciplinary collaboration to preserve the visual prognosis. Our article illustrates the seriousness of this pathology and provides an update on the latest diagnostic and therapeutic modalities.

Keywords: Graves' orbitopathy; Graves' disease; Medical treatment; Orbital decompression; Multidisciplinary management

1. Introduction

The orbit is the second most important target after the thyroid gland in autoimmune thyroid diseases, especially Graves' disease. The term orbitopathy is more appropriate than ophthalmopathy because the pathology affects the oculomotor muscles and orbital fat rather than the eye itself. Orbital pathology can be associated with hyperthyroidism in the majority of cases, but also with hypothyroidism or even biological euthyroidism (MEANS or SAINT-YVES syndrome). This is a serious pathology, often poorly tolerated because of the aesthetic damage it causes, and requires a multidisciplinary approach involving the endocrinologist, ophthalmologist, radiologist and maxillofacial surgeon to optimize therapeutic management.(1)

2. Case presentation

Female patient, 26 years old and mother of two children, with no previous medical history. She has been followed for two years for Graves' disease, which was diagnosed on the basis of a very obvious thyrotoxicosis, a laboratory test in favour of peripheral hyperthyroidism and very high levels of anti TSH receptor antibodies. Thyroid ultrasound and scintigraphy confirmed the diagnosis of Graves' disease. The patient initially presented with moderate GO (Figure1) with obvious palpebral oedema and no other extra-thyroidal signs.

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Figure 1 Photograph of our patient with palpebral oedema and moderate Graves' orbitopathy

The patient was treated symptomatically with synthetic antithyroid drugs and selenium. The evolution was marked by the difficulty to control the biological hyperthyroidism, despite high doses of synthetic antithyroid drugs, and by the progressive worsening of the GO. The patient underwent a total thyroidectomy (she had all the predictive factors for an aggressive disease with a high risk of relapse) and was rapidly started on levothyroxine-based replacement therapy to avoid worsening her GO. Several months later, the patient presented with a worsening of her GO. An orbital CT scan showed a worsening of the globe protrusion, which threatened the functional prognosis. The patient was treated with corticosteroids and cyclosporine-based immunotherapy, but to no avail. Orbital decompression was proposed after a collegial decision (patient presented ocular hypertension, corneal complications and compressive optic neuropathy). The course of the disease was initially characterized by a marked reduction in the right-sided GO (Figure 2), followed a few days later by a worsening of the left-sided GO (Figure 3).



Figure 2 Photo of the patient showing significant improvement in right GO after orbital decompression and condition of the left eye before reduction



Figure 3 Worsening of the left GO after orbital decompression

The patient underwent left corneal transplantation with very close ophthalmological monitoring, which stabilized the GO.

3. Discussion

3.1. Epidemiology

Data on the incidence and prevalence of GO are scarce. A recent study by the European Group on Graves' Orbitopathy (EUGOGO) found that GO is a relatively uncommon pathology, but does not meet the main criterion for definition as a rare disease. According to EUGOGO epidemiological surveys, the prevalence of GO in the general population in Europe. It appears that the prevalence of OB, all grades combined, in Europe is between 90 and 155/100,000 population. Graves' disease is much more common in women than in men, although the difference between the sexes varies from study to study. Gender also influences the severity of the disease, which is more severe in men, especially with age. The relevance of ethnic factors in the occurrence of GO is controversial, with Caucasians at increased risk (high prevalence of smoking); conversely, other studies have failed to find an association between ethnic origin and disease prevalence.

The majority of patients with GO present with bilateral disease, but asymmetric or even unilateral GO can occur; asymmetric forms have been described in 4-14% of cases and unilateral forms in 9-34%. The reasons for asymmetric presentation are unknown, but may include differences in the anatomy of the bony orbit or its vascularization. On the other hand, unilateral or asymmetric GO can sometimes progress to bilateral disease.

The main risk factors currently recognized for the development of orbitopathy are smoking, iatrogenic hypothyroidism, iodine treatment and hypercholesterolemia, which is emerging as a new factor (1,2).

3.2. Pathophysiology

The exact mechanisms leading to the development of GO are not yet well understood. However, certain elements are now generally accepted. It is known that the target cell in the orbit is the fibroblast. In patients with a genetic predisposition, these orbital fibroblasts are stimulated by intraorbital humoral and cellular immune mechanisms under the influence of stress. This stimulation triggers a series of reactions: release of water-hungry glycosaminoglycans responsible for inflammatory reactions in orbital tissues (fat, oculomotor muscles), proliferation and differentiation of pre-adipocytes into adipocytes explaining orbital and palpebral fat hypertrophy, and proliferation of fibroblasts leading to fibrosis, mainly of the oculomotor muscles. These cascade reactions explain the clinical signs of this disease (3).

3.3. Clinical presentation

- Functional signs: Pain with increased orbital pressure in certain directions of gaze, photophobia, foreign body sensation, excessive tearing, diplopia, often fluctuating, sometimes intermittent, blurred vision that does not improve with blinking, raising fears of optic nerve damage and reduced color perception.
- Physical signs: reduced visual acuity, keratitis, ulcers, altered tear film quality, chemosis, diffuse hyperemia and hypertonia around the oculomotor muscle insertions.
- Palpebral involvement: upper or lower lid retraction, oculo-palpebral asynergy (von Graefe's sign) and lagophthalmos.
- Exophthalmos, corresponding to forward protrusion of the eyeball, can be measured using the Hertel exophthalmometer.
- Periorbital soft tissue involvement: The main signs are conjunctival erythema, palpebral and periorbital oedema, palpebral erythema, dilation of the vessels at the insertion of the lateral rectus muscles, inflammation of the wattle at the inner angle of the eye and chemosis.
- Oculomotor involvement: leading to binocular diplopia, the most commonly affected muscle is the inferior rectus, but the disease may affect all oculomotor muscles. Diplopia is transient during inflammatory flare-ups, but may be persistent.

A full ophthalmological examination with a detailed report of the above signs is essential to optimize therapeutic management (3).

3.4. Complications

Mainly related to:

- Compressive optic neuropathy in the orbital apex, which should be systematically, investigated even if the exophthalmos is discreet.
- Corneal complications such as ulcers, abscesses or corneal perforation.
- Ocular hypertension, which may lead to true secondary glaucoma.

3.5. Paraclinical

Radiological examination is essential. It has several objectives: to confirm the diagnosis, to measure the exophthalmos, to study the relationship between the orbital cavity and its contents, to determine the extent of muscular masses, to verify the presence or absence of optic nerve compression and to visualize the bony walls.

CT quantifies exophthalmos (grade I, II or III) and is more specific than MRI in demonstrating muscle hypertrophy. MRI, on the other hand, examines the orbital tissues in the case of inflammatory or compressive orbitopathy and assesses the respective volumes of muscle and intraorbital fat, defining the different forms: compressive, fatty and mixed.

At the end of this clinical-paraclinical evaluation, the exophthalmos is classified as a strictly isolated form or an inflammatory form.

3.6. Classification

Several classifications have been proposed to assess the progression of inflammation and the severity of involvement. The most widely used is the modified Morits clinical activity score for inflammatory activity, while the validated score for severity is the 2008 EUGOGO score.

Both scores are essential and help to guide therapeutic management (4,5).

3.7. Treatment

3.7.1. General recommendations

These apply to all patients, regardless of their clinical phenotype and the severity of their hyperthyroidism.

- Thyroid dysfunction must be corrected, as both hypothyroidism and hyperthyroidism adversely affect the clinical activity and severity of GO. Hypothyroidism directly stimulates TSH-receptors expressing orbital target cells to release hydrophilic mucopolysaccharides and pro-inflammatory cytokines, whereas hyperthyroidism is associated with a marked increase in serum levels of Stimulating Anti-TSH Receptor Antibodies. Consequently, both dysfunctions exacerbate the orbital inflammatory process, making it imperative to maintain stable euthyroidism while avoiding transition to hypothyroidism.

Smoking cessation should be recommended for all patients, as smoking is known to worsen orbitopathy but also to reduce the response to immunosuppressive drugs.

- Smoking is a classic factor in worsening orbitopathy, and this risk can be prevented by a short course of oral prednisone corticosteroid therapy. The dose of 0.1-0.2 mg/kg tapered over 6 weeks has shown similar effects to 0.3-0.5 mg tapered over 3 months. According to EUGOGO 2021(6), the higher dose should be reserved for patients who smoke and those with high Anti-TSH Receptor Antibodies levels (> 5 times the norm) and severe hyperthyroidism that is difficult to control.
- Hypercholesterolemia is an emerging and potential risk factor for PAD, statin use has been associated with a reduced risk of PAD, 2 hypotheses are to be considered; the first is probably the pro-inflammatory effect of cholesterol and the second is probably the anti-inflammatory effect of statins, evidence is lacking but statin treatment can be considered in PAD patients.
- Other simple measures are sufficient to alleviate visual discomfort: wearing tinted lenses, perfect lid hygiene, use of artificial tears.
- Treatment with selenium has not been shown to have a beneficial adjuvant effect in patients with moderate to severe OB, so it should be reserved for those with minimal damage.

3.7.2. Medical treatment: (6,7,8)

EUGOGO has divided the treatment of GO into two main lines:

First-line treatment

First-line treatment includes corticosteroid therapy and mycophenolate sodium.

Corticosteroid therapy is the reference treatment, with anti-inflammatory and immunomodulatory effects, reducing the synthesis and secretion of glycosaminoglycans responsible for the oedematous response. Six weekly infusions of 0.5g methyl prednisone followed by six infusions of 0.25g, for a cumulative dose of 4.5g, are very well tolerated and significantly improve quality of life. In the most severe cases, a single dose of 0.75g for a cumulative dose of 7.5 to 8g may be suggested. Treatment on consecutive days should be avoided and infusions should be given slowly over 1 to 2 hours under close supervision.

Sodium mycophenolate: has a dual antiproliferative effect on B cells, T cells and fibroblasts. Studies have shown good results for diplopia, with a lower risk of relapse and reactivation when combined with intravenous or oral corticosteroids.

Second-line treatment

Suggested in cases of cortico-resistance or contraindication to cortico-therapy and include other immunosuppressants and orbital radiotherapy.

Cyclosporine, a potent immunosuppressant, is currently being studied in combination with oral prednisolone. It has been shown to improve ocular outcomes with a lower relapse rate, but there are no trials comparing cyclosporine with intravenous corticosteroids.

Azathioprine, which has a similar mode of action to mycophenolate, has shown benefits in combination with low-dose oral glucocorticoids with a reduction in relapse rate after corticosteroid withdrawal, considered a valuable steroid sparing agent after corticosteroid withdrawal, it is a treatment that still remains poorly tolerated and its benefits with intravenous corticosteroids are unknown. Other immunosuppressants are being evaluated and may be suggested as second-line alternatives, e.g. Teprotumumab, Rituximab and Tocilizumab.

Orbital radiotherapy

at low dose 20Gy fractionated over 10 sessions in 2 weeks. The response rate is about 60%. Particularly effective for oculo-motor disorders and diplopia. Tolerance is generally good with a risk of transient worsening of orbital signs, it is not recommended before 35 years and in diabetic and/or hypertensive retinopathy, however trials have shown a beneficial effect of the combination of orbital radiotherapy and corticosteroid to reduce the activity score.

Surgery:

For orbitopathy, three types of surgery can be done:

- Orbital decompression which aims to modify the ratio of the contents of the orbital cavity. The indications are both functional (ocular hypertonia, corneal complications of proptosis or compressive optic neuropathy) and morphological, allowing the patient to regain a physiognomy compatible with a normal social and affective life. The intervention may be unilateral or bilateral. There are two general ways to correct: fat resection, but not adequate for correcting severe proptosis, and partial resection of one or more of the inner, lower, and outer orbital walls. Decreased bulging can be estimated only after 4 to 6 months.
- Oculomotor surgery: two conditions must be met before surgery is considered: being in a stable period of the disease with no active inflammation. This will be demonstrated by ophthalmological examination and the analysis of an MRI in T2 mode which objectifies the muscular hypertrophy, often greater than the clinical oculomotor impairment suggests; after that other therapeutic resources likely to modify the oculo-motor state, in particular orbital decompression, have been carried out if necessary. Its goal is to make a simple binocular field of vision as wide as possible and to restore oculo-motor symmetry. In general, the milder the initial impairment, the better the outcome.
- Eyelid surgery: the final step in the surgical rehabilitation of thyroid dysorbitopathy. The indications are laid after 6 months of stability. Results are usually good or excellent, but stretching techniques are nonetheless unpredictable. Pending the time of surgery, severe upper eyelid retraction can be corrected by injecting botulinum toxin into the elevator muscle even during a period of progression that can be repeated every 4 months until surgery.

Indications

Minimal active orbitopathy

it is recommended to control risk factors and local treatment with artificial tears especially if dry syndrome as well as protection of the cornea overnight and adjuvant systemic treatment with selenium 200 mg/day for 6 months. Small doses of immunosuppressive therapy may be offered in consultation with the patient. Rehabilitation surgery may be considered if GO is inactive after a thorough discussion and shared decision with the patient.

Moderate to severe active orbitopathy

it is recommended to start a course of corticosteroids for 6 weeks with mycophenolate sodium at a dose of 0.72 g/day for 6 weeks. An ophthalmological evaluation after 6 weeks is required; if no response should be considered, second-line alternatives should be considered, if complete or partial response should be considered, corticosteroids should be maintained at a dose of 0.25 g/weeks/6 weeks with Mycophenolate sodium 0.72 g/day for 18 weeks.

Inactive orbitopathy

all stages of severity, rehabilitation surgery may be offered: decompression surgery, eyelid or oculomotor surgery if needed or required by the patient.

Optic neuropathy

it is recommended to start immediately the corticotherapy with Methyl Prednisone at a dose of 0.5 to 1 g in a single dose renewed on 3 consecutive days or alternating, with daily ophthalmic surveillance and a reassessment on D7; if response is to be repeated on a 2nd course of Methylprednisolone 0.5 g per week (cumulative dose should be less than 8 g per cycle), if partial response or response or worsening is not achieved, urgent decompression surgery should be considered, which should be preceded by imaging.

Orbitopathy and the COVID-19 pandemic

No studies are available on the use of corticosteroids and/or immunosuppressants during the current pandemic. Steroids are known to decrease the efficacy of other vaccines but the impact on COVID vaccination is unknown. It seems reasonable that patients receiving treatment with corticosteroids and/or immunosuppressants should be kept under close observation, GO is an emergency and should be treated as such, independent of the viral pandemic.

4. Conclusion

The pathogenesis of GO is complex, international classifications allow severity to be coded and contribute to the therapeutic management which is often multidisciplinary, the combination of intravenous methylprednisolone and mycophenolate sodium has demonstrated its efficacy with reduced risk of relapse and reactivation. Other immunosuppressive therapies are promising and are under development.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as potential of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

- [1] Front Endocrinol (Lausanne) 2020 Nov 30;11:615993, Collection 2020. Epidemiology, Natural History, Risk Factors, and Prevention of Graves' Orbitopathy Luigi Bartalena 1, Eliana Piantanida 1, Daniela Gallo 1, Adriana Lai 1, Maria Laura Tanda
- [2] Swiss Medical Journal: thematic articles: new in medicine 2012 (first part), Ophthalmology, Mehrad Hamédani, Aurélie Obéric

- [3] , J. Delmas A, B, J.-P. Adenis,, Thyroid Eye Disease [21-453-A-20], Medical-Surgical Encyclopedia of ophthalmology 07/02/20
- [4] George j kahaly management of graves Thyroidal and extrathyroidal disease: an update .J Clin Endocrinol Metab. 2020 DEC 1;105(12):3704-3720.
- [5] S.moraxai.badelonb, Graves' exophthalmia, French journal of ophthalmology, volume 32, issue 8, October 2009, pages 589-599
- [6] The 2021 European Group On Graves' Orbitopathy (EUGOGO) clinical practice guidelines for the medical management of graves' orbitopathy.
- [7] Nadia Bouzehouane a , Françoise Borson-Chazot a, Juliette Abeillon a, Philippe Caron. Annales d'endocrinologie : Treatment of moderate to severe orbitopathy: Current modalities and perspectives - 04/05/21.
- [8] Diagnosis and treatment of dysthyroid orbitopathy: A multidisciplinary disease B. Leraya , P. Imbert b, D. Thouveninc , F. Boutault d, P. Carone, 2013