Graves' Opthalmopathy

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Graves' opthalmopathy/orbitopathy (GO) is an autoimmune inflammatory disorder also known as thyroid eye disease (TED); it is associated with Graves' disease (GD) and affects ocular and orbital tissues [1]. GO is the most common and important extrathyroidal manifestation of GD [1]. It generally occurs in patients with current or past hyperthyroidism but may sometimes be seen in patients who are euthyroid or even in a hypothyroid state [2]. About 50–70% of patients with GD have mild (or subclinical) orbital involvement, whereas 3–5% of patients show significant GO with exophthalmus and pain [3,4]. The estimated incidence of GO is 16/100,000 women and 3/100,000 men [5]. GD hyperthyroidism is caused by autoantibodies directed against the thyroid-stimulating hormone receptor (TSHr). These autoantibodies activate the receptor and stimulate thyroid follicular hypertrophy and excessive hormone production [3]. The fact that TSHr are highly expressed in orbital tissues points to the possible role of TSHr autoantibodies in the pathogenesis of GO [3]. Here we review the pathogenesis, clinical, laboratory and histological findings, as well as diagnosis, assessment and treatment of GO.

Graves' orbitopathy is a frequent feature of Graves' disease. Fortunately, the vast majority of the cases are subclinical or mild

PATHOGENESIS OF GO

The precise etiology of Graves' disease is not defined, although hormonal, environmental and genetic factors were shown to play a role in the pathogenesis of the disease [6]. One of the hallmarks of GD is the presence of anti-TSHr autoantibodies, which stimulate the receptor leading to thyroid gland enlargement and hyperthyroidism [1]. Several lines of evidence support the possible role of those autoantibodies in the pathogenesis of GO as well. First, TSHr is expressed by orbital adipose cells and fibroblasts [4]. Second, the levels of anti-TSHr autoantibodies correlate with the severity of GO and it is used as a prognostic marker [7]. Moreover, the immunization of BALB/c female mice with the human TSHr A subunit was shown to induce murine anti-TSHr autoantibodies with GO-like clinical manifestations [8]. It appears that after stimulation, orbital fibroblasts and adipose cells generate and secrete the glycosaminoglycan hyaluranan, which contributes to the soft tissue changes seen in GO [9]. Concomitantly, pro-inflammatory cytokines, such as interleukin 1 (IL-1) and interferon-gamma (IFNγ), and chemokines (e.g., CXCL9, CXCL11) promote retro-ocular inflammation with infiltration of TH1 cells [10]. Only in later stages of GO can TH2 cells and the relevant cytokines, IL-4 and IL-5, mast cells and B cells be observed [3,9]. The predominance of TH2 cells in the orbital tissue was shown to be associated with GO remission [11].

HISTOPATHOLOGY OF GO

The soft tissue enlargement of GO involves both the extraocular muscles and the adipose tissue. Fat expansion is more prevalent among patients younger than 40 years, whereas patients over age 60 have more prominent muscle swelling [12]. Electron microscopy evaluation reveals intact extra-ocular muscle fibers with accumulation of amorphous material between the fibers. This material consists primarily of collagen fibrils and glycosaminoglycans [9]. It is extremely hydrophilic and capable of binding significant amounts of water which leads to edematous enlarged muscles [4]. In active GO disease, the extra-ocular muscles, lacrimal glands and orbital adipose tissues are diffusely infiltrated by CD4+ T cells, mainly TH1 cells. During inactive disease, muscle atrophy and fibrosis are mainly evident [13].

GO CLINICAL MANIFESTATIONS

Like most autoimmune disorders, GD is more prevalent among women, with a male to female ratio of 1:5 [1]. Although GD can be apparent at any age, its peak incidence is between the fifth and sixth decades of life [1]. In most patients ocular symptoms are presented simultaneously with Graves' hyperthyroidism or within 18 months of each other [4]. However, GO can develop several years after the diagnosis of GD, and up to 5–10% of patients who present with GO are euthyroid [4]. Between 50% and 70% of patients with GD have mild or subclinical (evident only by imaging) opthalmopathy. About 3–6% of GD patients have moderate to severe active GD, while less than 1% of GD

patients will have sight-threatening disease [14]. In most cases of GO, clinical symptoms and signs of GD are present [4]. Thus, diffuse enlargement of the thyroid gland (goiter), which may vary from a prominent to a minimally enlarged gland, is usually observed. In addition, signs of hyperthyroidism such as nervousness, palpitations, sweating, heat intolerance, weight loss, diarrhea and fatigability are quite common [1].

The most common sign of GO is upper eyelid retraction, which causes the "wide open eye appearance." Diagnosis of upper eyelid retraction is made by observing lid lag: when gazing downwards, the upper eyelid follows the bulb with some delay. This sign is also called von Graefe's sign [9]. Upper eyelid retraction is caused by increased sympathetic tone due to excess of thyroid hormone and by fibrosis around the levator palpabrae muscle. Exophthalmos (proptosis) is a consequence of increased intra-orbital volume. Increased retrobulbar content, caused by either orbital fat accumulation or enlarged extra-orbital muscles, pushes the eye in anterior direction out of the orbit where there are no bony boundaries [9]. The severity of exophthalmos is dependent on the depth of the orbit and the degree of retro-ocular muscle and/or fat enlargement. Measurements of exophthalmos by an experienced ophthalmologist are important for longitudinal follow-up. Exophthalmos may be symmetrical or asymmetrical. One-sided exophthalmus was also reported [15]. It should be noted that edema of the periorbital tissue may mask the exophthalmus. The most common symptoms/complaints of patients with exophthalmus, aside from the cosmetic issue, are increased tearing, grittiness, photophobia, dry eye, conjunctival redness and eyelid swelling [4]. Swelling and hypertrophy of ocular muscles may impair their function and cause pain during eye movements, restricting ocular motility with various degrees of diplopia [16]. In a severe case, extensive ocular muscle involvement can compress the optic nerve, leading to loss of vision known as dysthyroid optic neuropathy [17].

GO disease has a biphasic disease course with an active inflammatory phase and an inactive phase. Mild GO is treated with local measures

LABORATORY FINDINGS

The laboratory workup of patients with GO is aimed to assess thyroid function. In most patients hyperthyroidism is observed with undetected levels of TSH and elevated free thyroxine (T4) and free triiodothyronine (T3) levels. Autoantibodies directed against the TSHr can be found in 98% of patients [12]. A correlation between the presence and severity of GO and the titers of these autoantibodies has been reported [18]. Other anti-thyroid autoantibodies such as anti-thyroid peroxidase (anti-TPO) and thyroglobulin antibodies were also reported in those patients [1].

IMAGING STUDIES

Imaging studies in GO patients include thyroid and orbital evaluation. Thyroid ultrasound provides information regarding thyroid size and the presence of thyroid nodules. Typical findings include a hypoechoic thyroid gland with reduction of colloid content and increased vascularity. Color flow Doppler of the thyroid is likely to demonstrate increased blood flow. Thyroid radioiodine uptake is increased in most patients. Computed tomography (CT) or magnetic resonance imaging (MRI) scans of the orbit are mandatory. A finding of muscle enlargement, rather than retrobulbar fat accumulation, is associated with an increased risk for the development of dysthyroid optic neuropathy [9]. Moreover, the demonstration of stretched optic nerve by CT/MRI was associated with high risk for visual loss [10].

ACTIVITY AND SEVERITY SCORING SYSTEMS OF GO

In most patients GO has a biphasic disease course. The active inflammatory phase, which generally lasts for 18–36 months, is followed by a chronic non-inflammatory inactive phase [16]. GO disease activity is related to the inflammatory process, whereas disease severity is more related to ocular functional and cosmetic impairments [16]. It is crucial to differentiate between the active inflammatory and inactive chronic phases since treatment modalities are different in the different stages of GO [16].

Several scoring and grading systems of GO disease activity and severity have been developed. However, there is little uniformity among the various scoring systems [19-25].

- **NO SPECS** (**N**o physical signs or symptoms, **O**nly signs, **S**oft tissue involvement, **P**roptosis, **E**xtraocular muscle signs, **C**orneal involvement and **S**ight loss). This classification was first reported by Werner in 1969 [19] and modified in 1977 [20]. It exclusively addresses clinical severity (symptoms) but does not relate to the acute inflammatory status [20].
- **Clinical Activity Score (CAS),** described in 1989 by Mourits et al. [21], is based on both disease activity (inflammation) and severity. This scoring system was further modified in 1997 [22]. The CAS system consists of 10 items. For each item present one point is given. The first seven items are easily scored by any internist, while the last three require precise measurement by an experienced ophthalmologist [Table 1].
- **VISA** score system was developed in 2006 by Dolman and Rootman [23]. The system is based on evaluation of vision, inflammation, strabismus, and eye appearance. The parameters assessed include **V**ision (1 point), **I**nflammation/congestion (10 points maximum: chemosis, conjunctival erythema, lid erythema, retrobulbar pain and diurnal variation), **S**trabismus/motility restriction (6 points max) and **A**ppearance (3 points max). Each feature is graded independently with a total maximal score of 20. Moderate inflammation is defined when inflammation is scored at less than 4 points. Inflammation scores above 5 points should be treated aggressively [23].

Table 1. The 10 items evaluated in Clinical Activity Score (CAS) of Graves' ophthalmopathy [22]

	Item	Evaluation made by:
Pain	Pain around the globe lasting for 4 weeks	Internist
	Pain during eye movement (up/side/down gaze)	Internist
Redness	Eyelid redness	Internist
	Redness extends to the conjunctiva, covering at least one-quarter	Internist
Swelling	Eyelid swelling	Internist
	Chemosis	Internist
	Swollen caruncle	Internist
	Proptosis increases by ≤ 2 mm during 1–3 months	Experienced ophthalmologist
Impaired function	Eye movements decrease by more than 5° to any direction during 1–3 months	Experienced ophthalmologist
	Decrease in visual acuity during 1–3 months	Experienced ophthalmologist

- **EUGOGO** (the European Group On Graves' Orbitopathy) classification study group recommended the stratification of GO patients according to disease activity and severity into three groups: mild GO, moderate to severe GO, and sight-threatening severe GO. Disease activity grading is based on the modified CAS score. Severity is evaluated by comparison with an image atlas. Each group of patients should be treated differently. Thus, the EUGOGO classification is therapeutically oriented [24,25]. In mild GO the disease has a minimal impact on patients' daily life. Signs and symptoms include minor lid retraction, mild soft tissue involvement, mild exophthalmus, without diplopia or significant corneal involvement. In those GO patients, immunosuppressive or surgical treatment is not justified [24,25]. In the moderate-to-severe GO group of patients, the impact of the disease on daily life may justify the risks of immunosuppression for active inflammatory disease or surgery for severe inactive disease. In this group of patients, the eyelid retraction, soft tissue involvement and exophthalmus are all more prominent and the patients may suffer from inconstant or constant diplopia [24,25]. Patients with sight-threatening severe GO suffer from either dysthyroid optic neuropathy or corneal breakdown. These patients warrant immediate intervention [16,24,25].

Active moderate to severe GO is treated with glucocorticoids. Surgery is considered when GO is inactive. Sight-threatening GO is treated with intravenous glucocorticoids

TREATMENT OF GO

GD management should be individualized according to disease activity and severity. Initial medical treatment with anti-thyroid drugs (thionamides: propylthiouracil or methimazole) is generally recommended to all hyperthyroid patients in order to restore euthyroidism. Anti-thyroid treatment has a complex effect on GO. The reduction of thyroid hormone levels decreases eyelid retraction. On the other hand, the development of hypothyroidism can cause fluid retention that adversely affects GO [26]. Interestingly, the effect of anti-thyroid therapy on GO varies with the type of treatment. Anti-thyroid drugs and subtotal thyroidectomy do not have a negative effect on orbitopathy [27], whereas radioiodine therapy (RAI) can lead to deterioration of GO [28,29].

GO is usually a self-limiting disease and is expected to improve spontaneously or after successful anti-thyroid treatment [30]. Symptomatic treatment including artificial tears and dark glasses to relieve photophobia and sensitivity to wind and cold air should be offered to all GO patients. Patients with incomplete eyelid closure may benefit from nocturnal ophthalmic ointment and from elevation of the head of their bed during the night. Smoking cessation should be encouraged, as smoking increases the risk for developing and exacerbating GO by seven- to eight-fold [9].

Beyond symptomatic relief, treatment should be given according to the degree of functional and cosmetic impairment (disease severity) and disease activity (inflammation).

Mild GO (according to EUGOGO classification) is treated by relieving symptoms as described above. Supplementation of the trace mineral selenium may decrease the inflammatory activity and ameliorate GO [31]. Botulinum toxin injections can improve upper eyelid retraction. Immunosuppressive agents or surgical treatment are not indicated in these patients [24]. Progression of mild GO occurs in about 15% of patients. Smoking and high titers of TSHr autoantibodies increase the risk for GO progression [9].

In patients with moderate-to-severe GO (EUGOGO classification) there is no immediate threat to eyesight, although exopthalmus with diplopia is present and has a significant impact on patients' daily life. In these patients, treatment with corticosteroids should be initiated. The usual regimen includes weekly injections of 500 mg of methylprednisolone for 6 weeks followed by 250 mg of weekly methylprednisolone for another 6 weeks [32]. Extension of the treatment beyond 12 weeks should not exceed a total cumulative dose of 8 g. Although efficacious, this treatment may cause adverse effects, including liver dysfunction, hypertension, peptic ulcer disease, diabetes, infection, psychosis, or glaucoma. When high dose corticosteroids are contraindicated, not tolerated or not effective, extra-orbital radiotherapy (10–20 Gy in 10 sessions over 2 weeks) may be a good therapeutic option, since intra-orbital lymphocytes are highly sensitive to radiotherapy [9,33]. The best radiotherapy results are seen in patients treated shortly after onset of symptoms. It should be noted that patients with diabetes and hypertension are at increased risk for developing post-radiotherapy retinopathy [9,34]. Alternatively, patients who are not responsive to corticosteroids may be treated with

combination therapy of cyclosporine A, azathiopirine or retuximab (anti-CD20 monoclonal antibody) [9]. Other promising treatments such as TSHr antagonists are currently under development [35]. High dose of intravenous immunoglobulins (IVIG, 1–2 g/kg) was also shown to be effective in the treatment of GO, with or without corticosteroids [36].

Corticosteroids (or other immunosuppressive agents) and orbital radiotherapy are only effective in the treatment of active inflammatory GO. When the disease reaches its quiescent phase, the clinical manifestations result mainly from fibrotic changes of the orbital tissue [37]. At this later phase, surgical orbital decompression, eye muscle surgery or rehabilitative eyelid surgery should be considered [9]. For cosmetic correction of severe proptosis, decompression surgery should be withheld for as long as possible, until the active inflammatory disease is controlled with corticosteroids [38].

Patients with dysthyroid optic neuropathy or with corneal breakdown require immediate intervention. The treatment of choice is methyprednisolone given intravenously for 3 consecutive days (1 g/day). The same regimen should be given again after 1 week (three additional methyprednisolone injections) and then tapered down with oral prednisone [39]. Although effective, this treatment may be accompanied by major side effects including severe hepatic damage. Thus, careful patient selection and monthly monitoring during treatment are necessary [40]. About 80% of patients respond to the methylprednisolone treatment (1 g x 6). Unresponsive or partially responsive patients require immediate surgical orbital decompression, which may be performed either by removing parts of the orbital walls or removing orbital fat, leaving the bony orbit intact [37,39].

CONCLUSIONS

Subclinical/mild GO is quite common in patients with GD, while significant sight-threatening GO is rare (1%). Treatment for mild GO is based on treatment of GD (anti-thyroid drugs and surgery are preferred). Severe GO should be treated immediately with high dose corticosteroids and/or orbital decompression surgery.

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