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The clinicopathologic basis of Graves' ophthalmopathy: A review

S. KLOPROGGE[1], L. KOWAL[2], J. WALL[3], A.G. FRAUMAN[1]

[1] Molecular Immunology Lab., Clinical Pharmacology and Therapeutics Unit, Department of Medicine, University of Melbourne, Austin Health, Heildeberg, Vic
[2] Dept. of Ophthalmology and Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, East Melbourne, Vic
[3] Department of Medicine, University of Sydney, Western Clinical School, Penrith, NSW - Australia

ABSTRACT. *Graves' ophthalmopathy (GO) is a controversial disease, with disagreement within the medical community regarding its pathogenesis, diagnosis, and treatment. Investigations into the pathogenesis of GO have included possible antigenic targets, orbital cell types, and development of animal models. Diagnosis has been improved recently with new tools and grading systems, but can be complicated by conditions that may simulate one or more of the findings of GO. The new findings of clinical studies also compel practitioners to reassess commonly used GO treatments such as orbital irradiation. The present review critically assesses the current literature from both the endocrinologist's and ophthalmologist's perspective.* (*Eur J Ophthalmol 2005; 15: 315-23*)

KEY WORDS. *Associated Basedow's eye, Graves' ophthalmopathy, Thyroid*

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Graves' disease

Graves' disease (GD) is a relatively common autoimmune disease (approximately 2% prevalence) (1) where the body develops autoantibodies – Graves' antibodies – to the thyroid stimulating hormone receptor (TSH-R), which cause the receptor to be constantly stimulated. Secondary to the constant stimulation of the TSH-R by Graves' antibodies, which are not inhibited by the normal feedback mechanism, there may be uncontrolled secretion of T3 and T4, leading to clinical hyperthyroidism. The thyroid gland itself is often enlarged due to the growth-promoting activity of Graves' antibodies. The most common extrathyroidal association of GD is the ocular disturbance known as Graves' ophthalmopathy (GO) (2), the topic of this review. Other extrathyroidal manifestations are proximal myopathy, acropachy, pretibial myxedema, vitiligo, and eyelash loss (3). GD has a long and variable natural history which makes efficacy of any therapy difficult to evaluate without a control group (4) and makes studies containing control groups particularly valuable (5, 6).

Graves' ophthalmopathy

GO may be associated with other thyroid pathology including Hashimoto's thyroiditis and thyroid cancer (7). The manifestations of GO are diverse and include protrusion of the eye within the orbit (proptosis), upper eyelid retraction, diplopia, and pressure effects including optic nerve compression (8). Diplopia is caused by extraocular muscle involvement, which may include one or more of acute and chronic inflammation, active muscle contraction (9), and fibrotic changes. The spectrum of severity of GO can

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vary from mild ocular discomfort through to diplopia, to abnormal appearance and to sudden visual loss.

GO has been one of the more controversial diseases in modern endocrinology, without a clear consensus regarding pathogenesis, classification, diagnosis, and treatment. During the early stages of GO, a variety of inflammatory cells (macrophages, T cells, mast cells, and occasional plasma cells) infiltrate the orbital connective tissue, adipose tissue, and muscle (10). Several inflammatory cytokines have been associated with the evolution of the orbital tissue changes in GO (11). These include interferon gamma (IFN-g), interleukin-1 (IL-1), and transforming growth factor-beta (TGF-b) (12) and tumor necrosis factor (TNF) (13). Growth factors such as insulin-like growth factor-I (IGF-I) (14, 15) and platelet-derived growth factor (12) have also been implicated.

Diagnosis and treatment

There is much unmentioned and unrecognized selection bias in many studies on GO. Patients seen first by ophthalmologists can be expected to have different clinical and laboratory characteristics to those first seen by endocrinologists. These differences have not been studied.

It is generally accepted that clinically obvious ophthalmopathy develops in 20 to 40% of patients with GD (16). In some populations orbital imaging shows abnormalities in virtually all patients with GD. Magnetic resonance imaging spectroscopy measures more sensitive parameters, e.g., the concentration of chondroitin sulphate proteoglycan in the retrobulbar tissue as a marker for the activity of GO (17).

The onset of GO in relation to GD is variable. GO appears prior to GD in approximately 20% of cases, 40% during GD onset and 40% after the occurrence of hyperthyroidism (18).

To classify the severity of GO, and effectiveness of treatment, there are two main grading systems. The first is the clinical grading NOSPECS, developed and used mostly by endocrinologists with little or no acceptance by ophthalmology (19). Mourits (an ophthalmologist specializing in orbital disease) developed the Clinical Activity Score (CAS), which places greater emphasis on inflammatory changes, giving a range from 0 to 10 to grade the activity of GO (20).

The clinical presentation of GO can be subdivided into predominantly congestive ophthalmopathy and predominantly ocular myopathy. Predominantly congestive ophthalmopathy accounts for about 30% of all GO cases (21) and is characterized by an inflammatory infiltrate seen predominately in the orbital connective tissues and orbital fat with relative sparing of the extraocular muscles (EOM). In the ocular myopathy variant, inflammation, swelling, and dysfunction of the EOM are the major presenting issues, with patients usually complaining of painless diplopia (21). Muscle involvement can rarely present as acute orbital myositis. While up to 10% of GO patients develop isolated ocular myopathy, most have a combination of the myopathy and congestive subtypes (21).

Euthyroid GO

Patients with visual symptoms and no known or suspected biochemical or immunologic thyroid disease typically present to an ophthalmologist. GO is confirmed by the clinical picture (proptosis, diplopia, lid retraction, et cetera).

Euthyroid patients with GO often have multiple thyroid immunologic abnormalities (22). The commonest laboratory abnormality is the presence of TSHR Abs, and if negative, the diagnosis is unlikely. This is not the antibody usually assayed by laboratories when thyroid antibodies are requested, and should be requested in addition to the standard antibodies (and is routinely available).

The tests known as the TSHR Ab assay and the TSH binding inhibitory immunoglobulin assay (TBII) are the same. There are two components of this test: the thyroid stimulating antibodies (TSAb) (aka thyroid stimulating Ig or TSI) and the thyroid blocking antibodies (TBAb) (23). A negative TSHR Ab result in a case strongly suspected of being GD should be discussed with the laboratory and additional antibody tests may need to be performed (see the antigenic target, below). The particular feature of the TSHR Ab may dictate the detail of the clinical presentation (24).

Imaging parameters of GO are fairly well defined. The commonest radiologic abnormality is tendon-sparing enlargement of all the muscles (25). This is different from the clinical situation – it is involvement of medial and inferior rectus, which causes most symptoms (reading). It may be that medial and inferior rectus are more likely to be involved, or it may be that involvement of these muscles causes more symptoms than involvement of other muscles and drives the patient to seek treatment.

Specialized orbital clinics have expertise in ultrasound diagnosis and follow-up. There is a small literature on situations that simulate GO both clinically and radiologically (26). If ordering computed tomography in a patient with diplopia who may have GO/GD, be cognizant of the iodine in contrast and the potential for subsequent disturbed thyroid biochemistry; contrast is better avoided in cases of suspect GD/GO.

The usual diplopia pattern in symptomatic patients is esotropia ± vertical diplopia. The esotropia is due to involvement of the medial recti. Compression of the abducent nerve at the apex of the orbit by swollen muscles may also be a factor in the frequently seen esotropia (27). Exotropia is so uncommon in GO that one should suspect myasthenia gravis as the cause. Vertical diplopia is due to differential involvement of the eight cyclovertical muscles, the most clinically significant usually being the inferior rectus.

Treatment

There are three main treatments of GO: glucocorticosteroids (GCs), orbital irradiation, and surgery (for strabismic, oculoplastic, and orbital complications of GO). There is continuing uncertainty about the place of each of these treatments – when and how to use them – and we need more studies with control groups.

Steroids are used in a number of different ways in GO. With optic nerve compression there is no doubt that high dose (either oral or pulsed) steroids are sight-saving and allow deferment of orbital decompression to a convenient time. High dose steroids usually have an ameliorating effect on GO while they are being used but it is not known if their effect lasts beyond the period of treatment. Bartalena et al (28) found that adding 3 months of oral steroids to thyroid radioablation had a potent positive effect on the outcome that lasted long beyond the duration of therapy. This arm – 3 months of oral steroids independent of other therapy – probably deserves independent evaluation as a treatment that may improve on the natural history in GO. There is the odd patient whose symptoms are markedly improved by low dose steroid (say, 5 mgm a day). One study assessed the effect of oral prednisone combined with cyclosporine versus prednisone alone. The patients who received combination therapy had a greater reduction in proptosis and diplopia and fewer relapses on ceasing treatment (29).

Although orbital radiotherapy is a well established and widely accepted treatment of GO, one prospective, randomized, double-blind, placebo-controlled study of the sort of patients for whom radiotherapy is typically recommended could not demonstrate a beneficial effect (5, 30). Another study using radiotherapy with sham control demonstrated a strabismus surgery-sparing effect in 25% of patients (6), with no change in proptosis or eyelid swelling. Others have shown little or slight effect on strabismus (31, 32). Other studies have shown that any effect may be independent of the actual dose used (33). Many prominent thyroidologists debate the therapeutic nihilism of these studies and still promote the use of orbital irradiation (34).

The oculoplastics specialist is central to the ongoing management of many GO patients. Operations to improve appearance, comfort, and function in these patients include surgeries for upper and lower lid retraction (35, 36), tarsorrhaphy to lessen exposure and the staring appearance, and orbital surgeries for proptosis and for optic nerve compression. Guanethidine eye drops are useful for some patients with upper lid retraction (37).

Orbital decompression surgery for proptosis may cause diplopia de novo (38). The incidence of diplopia is uncertain – reports vary from as low as an 18% incidence of new diplopia in a series undertaken for cosmetic reasons (39), to as high as a 52% worsening of diplopia (40), without any apparent explanation for these differing incidences.

Botulinum toxin appears to be effective in treating some of the manifestations of GO, being effective in the treatment of diplopia (41), upper lid retraction (36, 42), and (anecdotally) optic neuropathy (43). There is some evidence that in the early stages, active muscle contraction, not fibrosis, limits ocular rotations and that this suggests why botulinum toxin injections may help in some cases (27).

Studies into somatostatin analogues such as octreotide as a new treatment for GO look promising. One study saw improvements in 7 out of 12 patients when treated with 0.1 mg of octreotide, three times per day for 3 months, compared to no improvement or worsening of GO in the 8-patient control group (44). A longer acting analogue, lanreotide, has been under investigation, in an attempt to reduce the number of injections required (45).

Plasmapheresis has also been investigated as a therapy for GO, but the literature is inconclusive (46, 47). Until a randomized and controlled study is reported, the useful-

ness of intravenous immunoglobulins is in doubt. Specific TNF treatment has been trialled with some success (13). Prolonged GO can be associated with an increased incidence of glaucoma and these patients should be under periodic review by an ophthalmologist (48).

The course of GO is unpredictable. Though hyperthyroidism typically responds to antithyroid treatment, GO may persist or develop further. Some studies have suggested that thyroid radioablation has a worsening effect on GO (28); following this seminal article, there was much apprehension about using radioablation in patients with any orbitopathy without 3 months of concurrent steroids, a supplementary treatment of some morbidity. The ophthalmologist may be asked for guidance by the endocrinologist who is considering radioablation for a toxic patient. Our advice is as follows:

1. If there are no unusual contraindications to using steroids as in the Bartalena et al article, do so.
2. Some of the worsening documented in the Bartalena et al article was trivial, e.g., increased caruncular edema.
3. Approximately 1/3 of GO is seen prior to, coincident with, and following GD; more of the latter category appears post-radioablation and it is possible that the increased incidence of worsening GO seen in the Bartalena et al article may be a statistical artifact (at least in part).
4. If radioablation is used without steroids, the ophthalmologist can usually mange any subsequent GO.

GO can actively progress for a period of several months to several years (49). It may be quiescent for years then seem to become active again. Consequently, corrective squint surgery for diplopia or oculoplastic surgery for eyelid or orbital pathology is usually deferred until stability has been demonstrated so that changes postsurgery are kept to a minimum (16). Some anecdotal reports suggest that this traditional deferral of surgery until stability has been demonstrated may not be necessary, at least for the treatment of diplopia (3).

Predisposition

There is controversy as to the extent of genetic influences in GD, although the general consensus is that GD is a disorder of multifactorial etiology with a polygenic mode of inheritance. Weak or no links have been demonstrated to specific candidate predisposition genes such as Ig allotypes or T-cell receptor polymorphisms, to HLA-DR3 (50), P1 blood group (51), or CTLA-4 (52). Links have been demonstrated to HLA-B8 (53).

Autoimmune diseases in general are more prevalent in women. While approximately 85% of those with GD will be women (54), of those who already have GD, there appears to be no correlation between sex and frequency of overt ophthalmopathy (55). However, it does appear as though the severity of the disease is more pronounced in older men (10). Other autoimmune diseases are seen with greater frequency in patients with GD, e.g., myasthenia gravis. This can be a difficult diagnosis to appreciate in a patient who already has diplopia from GO (56, 57).

Smoking is strongly associated with GO (58) and patients are very unlikely to quit smoking, even after strong advice from an ophthalmologist (59).

The antigenic target

The most popular theory to explain the association of GO with autoimmune thyroid disease is immunologic cross-reactivity of autoantibodies and/or sensitized T-lymphocytes against antigen(s) shared between the thyroid and the orbit. There have been several proposed antigenic targets for GO:

1. Mitochondrial succinate dehydrogenase flavoprotein subunit (SDHFp, a.k.a. 64 kDa protein) (60-63)
2. Thyroid peroxidase (TPO) (64)
3. Thyroglobulin (Tg) (16, 65, 66)
4. A fusion protein, G2s (67, 68)
5. TSH receptor (24, 69-75)
6. Yersinia enterocolitica (24, 76).

Proposed mechanisms for the EOM cell damage are cytotoxic T-cell mediated apoptosis, antibody-dependent cell-mediated cytotoxicity, and cytokine-medicated cytotoxicity (77). Complement-fixing EOM cell cytotoxic autoantibodies are not seen in patients with GO.

In euthyroid patients with GO, 28.6% were positive for TSH binding inhibitory immunoglobulins (TBII) and 82.9% were positive for thyroid stimulating antibodies (TSAb). Of those with GD and GO, 100% were positive for both TBII and TSAb (78).

Localization of the antigen

Controversy exists between which type of cell(s) are the primary sites for the TSH-R in GO. The main candidate cells are orbital fibroblasts, adipocytes, and muscle cells. Supporting the theory that the fibroblast is the target tis-

sue is that much of the orbital swelling is due to high levels of glycosaminoglycans (GAGs), produced by fibroblasts (79). mRNA transcripts of the TSH-R have also been shown to be expressed in the orbital fibroblast (80).

TSH-R antibodies from the sera of Graves' patients can stimulate fibroblast collagen synthesis in vitro (81). TSH-R protein expression has been found in fibroblasts from several anatomic locations other than the orbit, which suggests other factors (either cell or antigen) are involved in GO manifestations. No currently identified abnormal antigen expressed on fibroblasts results in increased binding of antibodies in GO or enhanced response to TSH (82). A study where extraocular fibroblasts were exposed to recombinant TSH in vitro showed no stimulus of protein synthesis, cAMP, or GAG production, even at high concentrations (83).

It has been shown that the TSH-R mRNA transcript and protein are expressed in adipose tissue (84); however, like fibroblasts, expression is not exclusive to the orbital area (85). More recently, research on interscapular brown adipose tissue (BAT) suggests that TSH stimulates cAMP, but also BAT-specific proteins, which indicates that the TSH-R might be multifunctional, with cell specific properties (86).

Extraocular muscle (EOM) cells are the other obvious target, as EOM enlarges in GO (8). Muscle enlargement has been identified in patients with no other clinical signs of GO, indicating such changes are early manifestations of the disease (2, 87). Dysfunction of the muscles restricts eye movement, and their bulk can cause pressure on the optic nerve in the restricted orbital apex. Antibody-dependent, cell-mediated cytotoxicity against orbital myocytes has been confirmed by in vitro data (77). Most lymphocytic infiltration occurs in or around the EOM (88), and analysis of EOM-infiltrating T cells in GO has shown that they are thyroid-reactive (89). Moreover, antibodies from patients with GO have the ability to stimulate EOM growth in vitro, while not stimulating growth in other skeletal muscle (90). It has also been shown that IgGs bind to porcine eye muscle membranes and increase the growth of myoblast culture (90); however, the same group did not find a correlation between myoblast growth stimulation and thyrotropin receptor (TSH-R) antibody levels. From the biological viewpoint, one study has found 64% of patients with clinically overt GO had sera that reacted with human eye muscle membranes, which did not react with non-ocular skeletal muscle, liver, or fat (91). When sera from patients with GO were tested for antibody dependent cell-mediated cytotoxicity (ADCC), the tests were positive in 10 of 20 patients against EOM cells, but only in 2 of 25 against orbital fibroblasts (92).

EOM also differs from normal muscle by having a greatly increased blood flow, increased cell cycle, and unique innervation and spindle structure (93, 94). EOM fibers also differ from other skeletal muscle with respect to their gene expression profile (95), myosin isotypes, and enzyme profiles (96). Previous studies conducted at our laboratory have shown that the thyroid target of GD, the TSH receptor (TSH-R), is expressed in EOM and thyroid but not in other skeletal muscles at an RNA level (75, 97), and at a protein level (98).

Animal models of Graves' disease and Graves' ophthalmopathy

Very early animal studies have shown that injections of thyroid or pituitary extracts or TSH induces exophthalmos and an increase in retro-orbital tissue (99-103). While there is no reliable animal model for GO at this point in time, there are some recent animal models generated that do show several GD, and some GO characteristics. Using genetic immunization, Costagliola et al reported anti-TSH-R antibodies in 57 of 59 immunized mice, and EOM of the hyperthyroid animals displayed histologic changes typical of GO, such as edema, fibrosis, and cellular infiltration when compared to the control mice (70). More recently, Yamada et al demonstrated another mouse model using a similar technique of immunization with TSHR cDNA and other cDNAs of interest (104).

Summary

There is an incomplete understanding of the mechanisms of Graves' ophthalmopathy, and a lack of effective or complication-free treatment or preventative measures. While not a life threatening disease, GO has the potential to seriously impair a patient's quality of life, with concerns regarding cosmetic appearance and physical discomfort. In its most extreme form GO may lead to visual loss. Identification of the target autoantigen and tissue localization of the antigen may lead to more specific immunotherapies for GO.

Eye muscle is a tissue frequently evaluated in research due to strong evidence that it is a primary target of damage (105). There are some important differences between eye and other skeletal muscles, not least of which is the expression of the TSH-R mRNA (75, 97).

Various researchers consider that due to the TSH-R being the immunologic target in Graves' disease itself, this protein is also a possible candidate autoantigen in GO, if expression can be shown to be restricted to the orbit and thyroid. However, which orbital tissue type(s) are involved or the sequence of their involvement during the immunopathogenesis is in dispute. Once this issue is answered, it will be possible to determine the downstream biochemical pathways by which GO occurs, and consequently find new drug targets.

Reprint requests to:
A/Prof. Albert Frauman
Level 5, Clinical Pharmacology and Therapeutics Unit
Department of Medicine, University of Melbourne
Austin Health
Studley Rd., Heidelberg, VIC 3084, Australia
albertf@unimelb.edu.au

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