PERSPECTIVE

Thyroid eye disease

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While the findings of thyroid eye disease were probably described as early as the 12th century, controversy remains regarding the pathogenesis, pathophysiology, and management of this disease.^{1,2} Several recent laboratory and clinical studies have increased our understanding of some of these issues. This review selectively highlights those newer investigations on pathophysiology, epidemiology, and management; established concepts on thyroid eye disease have been reviewed elsewhere.²⁻⁵

Pathophysiology of eye disease

Several hypotheses regarding the pathophysiology of thyroid eye disease are being actively investigated. Most workers believe this to be an autoimmune ophthalmic disease related to the thyroid abnormality. Historically some investigators questioned whether there was a definite link between the eye inflammation and thyroid disease, since approximately 10% of patients were euthyroid; Salvi and colleagues have shown that extensive immunological testing has demonstrated thyroid abnormalities in almost all such cases.⁶

Several systemic immune perturbations have been described in thyroid eye disease patients including increased interleukin 2 receptors in approximately 50% of patients.⁷ As several workers have pointed out, however, there is a paucity of data on immunological abnormalities in the local milieu of the orbit.

Graves' disease develops secondary to autoantibodies secreted by mainly clonally restricted intrathyroidal B cells that bind to, and act as agonists towards, the thyroid stimulating hormone (TSH) receptor.⁸ The large extracellular portion of this G protein linked receptor is antigenic.⁹ Several investigators have queried whether the TSH receptor could be the pathogenic shared thyroid orbital antigen. Some groups have shown messenger RNA (mRNA) transcripts for this receptor in orbital tissue, while others have not.¹⁰⁻¹³ It is also uncertain whether normal TSH receptor protein, altered protein, or what level of expression is present in orbital tissues. While antibodies towards TSH have been demonstrated in some thyroid patients, they do not appear to be either of significantly greater titre or prevalence in patients with eye disease.^{6,10-12,14}

A dichotomy of opinion exists about what is the primary target cell in the orbital autoimmune process; some favour the fibroblast while others argue it is the extraocular muscle. Until a molecular treatment approach can be developed to abort the inciting orbital event, it probably is not vital to know which is the primary cell type for autoimmune attack. In addition to direct inflammatory cell damage to the primary target cell, contiguous spillover effects by both cells and soluble factors alter surrounding orbital tissue. Intuitively, the muscle would appear to be a more likely primary target, since clinically the muscles are almost always involved, while orbital fat less frequently shows signs of lymphocytic infiltration or isolated volume expansion on imaging or at surgery.² In contrast, most histologi-

cal studies have shown little damage to the muscle itself during the acute phase of ophthalmic disease; most inflammation is noted in the perimysial compartment between the individual muscle cells.²

Hiromatsu and colleagues demonstrated a 64 kDa antigen that is shared between the thyroid gland and eye muscle.¹⁵ This antigen has 63% nucleotide homology with tropomodulin which binds tropomyosin.¹⁶ Further analyses with that 64 kDa antigen, cloned from an eye muscle cDNA library, showed there was a much wider tissue distribution than just the thyroid and orbital tissues.^{17,18} Other investigators have noted a minimal correlation between patients' serological reactivity toward this 64 kDa antigen and thyroid eye disease status.¹⁹⁻²² However, as Elisei and colleagues pointed out, the use of expression libraries to identify appropriate antigens is limited by the linear epitopes produced from cDNA libraries that are often not as antigenic as in their native configuration.²³ Antibody reactivity towards this 64 kDa muscle associated antigen is probably a secondary phenomenon; more frequent reactivity in patients with only thyroid disease suggests it is a marker of thyroid autoimmunity, even though there is some cross reactivity with orbital antigens.²⁴⁻²⁶ Other investigators have not found this antigen elicits a demonstrable T cell response.²⁷ It has previously been pointed out that almost all investigations have been on systemic rather than intraorbital antibodies or T cells, and this study design most probably would not detect a localised intraorbital immunological response.²⁸ An intriguing negative study was performed with the middle ear musculature of five patients with thyroid eye disease, because these ear muscles are very similar in structure to the recti muscles. However, no evidence of middle ear muscle abnormalities was noted.²⁹

There are more *in vitro* data consistent with the hypothesis that orbital fibroblasts are central to the inflammatory fibrotic changes that occur in thyroid related orbital disease. Bahn and her colleagues have demonstrated, *in vitro*, that the orbital fibroblasts are both perturbed by, and can alter, intraorbital immune responses.³⁰ Inflammatory cells, including CD4 and CD8 T cells, produce several cytokines including interferon gamma, tumour necrosis factor α , and interleukin 1 α in the orbital connective tissues and these have been demonstrated in orbital decompression specimens.^{31,32}

Several cytokines, as well as corticosteroids, modulate cell surface antigens on fibroblasts by altering expression of heat shock protein, intercellular adhesion molecules, and class II histocompatibility antigens.^{30,33-37} These molecules can upregulate a local immune or inflammatory response and allow the fibroblast to serve as an antigen presentation site. The immunological perturbations in and around the orbital fibroblast could cause inflammation and fibrosis of the contiguous extraocular muscles. Fibroblast proliferation has been shown to be stimulated by several cytokines including interleukin 1 α , interleukin 4, insulin-like growth

factor, tumour growth factor β , and platelet derived growth factors.³⁸ Several of the above cytokines, as well as other factors produced as a result of an inflammatory process, can also increase glycosaminoglycan (GAG) production by the fibroblasts. GAG is a hydrophilic molecule whose production directly increases orbital volume and absorbs extracellular fluid with resultant oedematous changes in the orbital connective tissue.³⁹⁻⁴¹ Hypoxia also increases GAG production; epidemiological data that demonstrate an association between the eye disease and smoking could be partially explained on that basis, although this remains speculative.⁴¹

Several cardinal issues are still unknown about the initiation of the orbital process. Firstly, what is the pathogenic event and antigen? Secondly, why are there a number of incongruities in the clinical pattern such as the more frequent involvement of the inferior recti, marked orbital asymmetry, or the rarity of this disease in non-Graves' thyroid disease including Hashimoto's thyroiditis? Thirdly, what is the role of vascular engorgement? Feldon and others have documented increased size of the superior ophthalmic vein; they proposed that a decrease in venous outflow may be important in the aetiology and maintenance of orbital swelling in this disease.⁴²⁻⁴³ Are these demonstrable venous changes primary or secondary? Finally, among a myriad of unanswered questions, what is the role of the TSH receptor in thyroid eye disease? Bahn and colleagues have noted aberrant TSH receptor mRNA in orbital fibroblasts of some women with a threonine for proline substitution.⁴⁴ What is the significance of these and other findings?

Hyperthyroidism therapy and eye disease

The effect of the systemic hyperthyroidism therapy on the development and progression of the eye disease is uncertain. A compendium of retrospective series did not demonstrate a difference in the incidence of thyroid eye findings as an effect of surgical, medical, or radioactive iodine thyroid therapy.² Thyroid status after systemic Graves' disease therapy does seem important, and several clinical studies have shown a higher incidence of ophthalmopathy in patients who are allowed to become clinically hypothyroid.⁴⁴⁻⁴⁷

Tallstedt and co-workers, in a randomised study of 114 patients between 35 and 55 years old, noted significantly more ophthalmopathy in those treated with radioactive iodine (33%: 13 of 39 patients) compared with patients who had either surgery or antithyroid medicine (10-16%).⁴⁸ The observation of possibly deleterious effects with radioactive iodine has engendered a great deal of controversy.⁴⁹

Several possible explanations were given that might have led to inadvertent, spurious results in the Tallstedt study.⁵⁰ One, in the radioactive iodine group the patients had a higher incidence of smoking; the association between smoking and more severe eye disease is discussed elsewhere in this review. Two, 18 of the patients treated with radioactive iodine required more than one dose of the radioactive iodine-131 isotope; in the 21 who required only a single radioactive iodine dose, only one developed eye disease. Patients with more severe hyperthyroidism have a higher risk of developing eye disease, so that those patients who required additional radioactive iodine were at greater risk of developing ophthalmopathy.⁵¹⁻⁵² Three, the post-treatment management of thyroid status was different in the surgery, medicine, and iodine-131 groups. In the latter subset, patients did not receive hormone replacement until they were hypothyroid in contrast with the other two groups who were treated with thyroxine. The hypothyroid

state that developed in most of the patients treated with radioactive iodine may have adversely affected the eye disease.⁵³

What is the optimal management of hyperthyroid patients to minimise the development of severe eye disease? Previous data have demonstrated that fewer than 5% of patients will develop ophthalmic disease severe enough to require corticosteroids, radiation, or surgery.² Eye status before radioactive iodine is a risk factor for more severe ophthalmopathy.⁵⁴⁻⁵⁵ In one study, 16 of 30 patients with eye disease before treatment with radioactive iodine developed proptosis measurements of >20 mm; in a study with a limited sample size the relative risk was 4.9 for severe ophthalmopathy to develop in patients with eye findings compared with patients without ocular signs before therapy for hyperthyroidism.⁵⁴ These data are compatible with an earlier study that noted 33% of patients with significant eye findings had progression as against 7% of those with only mild eye disease.⁵⁶ In patients with symptomatic eye disease before treatment of the systemic hyperthyroidism, coverage with corticosteroids seems advisable. In a study by Bartalena and colleagues nine of 16 patients treated with radioactive iodine alone had worsening of pre-existing eye disease compared with none of 21 who received radioactive iodine with systemic prednisone.⁵⁷

Prolonged hypothyroidism after therapy is a risk factor for progression of eye disease as is the inability to achieve a euthyroid state.⁵⁵ Tallstedt and co-workers noted that treatment with laevothyroxine immediately after radioactive iodine resulted in a lower incidence of significant eye findings.⁵⁸

Many thyroid specialists, especially in the USA, believe that properly administered radioactive iodine, with complete ablation of the gland, steroid coverage if there is significant inflammation, and thyroid replacement to avoid hypothyroidism is an excellent option in patients with eye disease. There is controversy regarding this point.

Several systemic treatment issues remain unresolved. Thyroid antigens are released after radioactive iodine, and these could make the eye disease worse; isolated case reports have also documented these changes.⁵⁹⁻⁶¹ As an alternative to radioactive iodine, a potential advantage of thiourea drug therapy is that these agents appear to down-regulate intrathyroid lymphoid cells and might mute autoimmune ophthalmopathy, and may decrease class II histocompatibility antigen expression on both the gland and on orbital fibroblasts.⁵⁹⁻⁶² The major problem with these drugs has been their inability to produce complete long lasting remissions in most patients, even when thyroid replacement is added to the regimen.⁶³

Thyroid eye disease epidemiology

Middle aged women are most likely to have both Graves' disease and eye findings, although older men often develop more severe ophthalmopathy.²⁻⁶⁴⁻⁶⁶ In contrast, ophthalmopathy is much less frequent in younger patients with Graves' disease.⁶⁷⁻⁶⁸

In an epidemiological study, Bartley observed that the age-adjusted incidence of thyroid eye disease for women was 16/100 000/year (compared with 2.9 for males), and this was not altered over a 15 year period.⁶⁹ In that latter series, the family history was positive in over 60% of cases, and the risk for therapeutic intervention was significantly higher in patients who presented at over 50 years of old. In older patients the 5 year cumulative risk for ophthalmic surgical intervention was over 20% compared with 12% in younger patients.⁶⁹ Other workers have also noted worse disease in older, male, and white patients compared with Asian subjects.⁷⁰⁻⁷¹

Several studies have demonstrated an association between cigarette smoking and ophthalmopathy.⁷²⁻⁷⁷ In the retrospective study by Bartalena and coworkers of 1730 patients with various types of thyroid disease, 64% of cases with severe eye disease were smokers compared with 48% of non-ophthalmic hyperthyroid patients and 28% of controls.⁷⁴ Heavy smokers had more severe eye disease.⁷¹⁻⁷⁴ Tellez *et al* noted that cessation of smoking did not seem to affect ophthalmopathy.⁷¹ The molecular basis for the association between smoking and eye disease is uncertain. As mentioned above, *in vitro* hypoxia results in increased GAG production by fibroblasts. Other possibilities are the increased thyroglobulin levels in smokers or the adrenergic effects of nicotine.

Management of eye disease

There has been a paucity of major advances in the clinical management of thyroid eye disease since the publication of several comprehensive reviews.^{2, 78} Given the limited amount of new therapeutic data, a few selective alterations in patient management are emphasised in this section.

Fortunately, fewer than 5% of patients with Graves' disease will have severe enough eye findings that require systemic corticosteroids or more aggressive therapy. In the majority of patients, temporary supportive therapy, occasionally augmented with topical β adrenergic blocking agents, are all that is necessary, until this systemic hyperthyroidism is brought under control and the eye disease remits spontaneously.

What are newer therapeutic developments for significant thyroid orbitopathy? One, as previously discussed, hyperthyroid patients with active eye disease, probably should be covered with systemic steroids while the gland is being ablated or suppressed.⁵⁷ Two, several studies have queried the relative efficacy of several agents for patients with significant orbital inflammatory findings. Two prospective studies have been reported on cyclosporine in thyroid eye disease.^{79, 80} Prummel and colleagues compared a 3 month course of prednisone (60 mg/day for 2 weeks then tapered) with cyclosporine (7.5 mg/kg/day) in 36 patients. The steroid treated patients did significantly better than those who received cyclosporine (11 of 18 versus 4 of 18 responders). At 1 year almost 50% required either surgery or radiation.⁷⁹ Kahaly and colleagues compared relatively long term systemic prednisone alone with prednisolone plus moderately high dose (5-7.5 mg/kg/day) cyclosporine for 1 year. The combined group did better than the patients who received only steroids both in terms of a more rapid onset of remission and its maintenance.⁸⁰ Similarly, in another small study it appeared a combination of oral prednisone plus conventional photon radiation (20 Gy in 10 divided fractions) was more efficacious than corticosteroids alone in the control of orbital inflammation.⁸¹

Approximately 1000 patients with thyroid eye disease have been reported after orbital radiation (generally 20 Gy in 10 divided fractions.) This modality has been effective in about two thirds of patients who have mainly inflammatory findings; about 30% of patients still require some surgical procedure at a later date.⁸²

Several studies have demonstrated the potential for magnetic resonance imaging (MRI) or spectroscopy to predict therapeutic response with these non-surgical treatments. A major clinical problem is the differentiation of patients in the inflammatory versus the fibrotic stage of thyroid eye disease. In the former group medical therapy is indicated but cosmetic eyelid or muscle surgery should be delayed. In the latter group medical therapy is not effective and as soon as patients have stable fibrosis, eyelids and muscles can be safely moved. We had previously demon-

strated in an animal model that the delineation between inflammatory and fibrotic changes could be ascertained within 24 hours with ³¹P magnetic resonance spectroscopy (MRS).⁸³ Conventional MRI equipment can be used to approximate some of these factors; however, the sensitivity and accuracy of various approaches is uncertain. In one study, using a low magnetic strength unit with short inversion time recovery (STIR), they noted the signal intensity ratio between muscles and orbital connective tissue could be used to predict response to therapy.⁸⁴ In several studies T₂ extraocular muscle relaxation times have correlated with disease status and response to therapy. Short relaxation times are associated with fibrosis while longer times indicate oedema; those patients with prolonged times were more likely to respond to medicines.⁸⁵⁻⁸⁷ An additional interesting imaging study showed that ultrasound, compared with MRI, was not very accurate in measuring muscle size.⁸⁸

Orbital decompression surgery, in the USA, is being performed more commonly, especially for cosmetic disfigurement as a result of proptosis. Several different approaches including conventional sinus or orbital surgery, advancement of the orbital rim, removal of orbital fat, and nasal endoscopic surgery have been described.^{2, 89-92} Most of these surgical changes are of relatively minor importance. In my experience, if there is compression of the optic nerve with minimal to moderate proptosis, the secondary strabismus, a *bête noir* of that type of surgery, is uncommon. If marked proptosis is the indication for decompression, experience has taught us that adding removal of the lateral wall with relatively less sinus surgery, markedly decreases the incidence of new or increased strabismus to about 15%.

Several authors have commented on the problems of rehabilitating patients with thyroid eye strabismus, especially those with new onset cyclotorsion deviations that can occur after decompression.⁹³ Adjustable sutures are advantageous in the management of thyroid myopathy.⁹⁴ Botulinum toxin has not been shown to be of widespread benefit in this disease. Eyelid surgery remains essentially unchanged.

Finally, several groups are attempting to use newer approaches such as modulating cytokines for thyroid orbitopathy, as has been initiated in some rheumatological diseases; however, there are insufficient data to comment on the possible efficacy of these and other experimental molecular biology approaches.⁹⁵

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