Recent developments in thyroid eye disease

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Thyroid eye disease affects an estimated 400 000 people in the United Kingdom. This estimate is based on a UK population of 59 million (www.statistics.gov.uk), a prevalence of Graves' disease of 1.85% (estimates range from 1%¹ to 2.7%²), and a prevalence of thyroid eye disease in Graves' disease of 37.5% (25% to 50%³). For a sizeable minority thyroid eye disease is an extremely unpleasant, painful, cosmetically distressing, and occasionally sight threatening condition. Medical treatment has progressed little in the past 25 years and remains unsatisfactory, but recent advances in other immune mediated disorders indicate that a selective treatment for thyroid eye disease should be a realistic goal.

We discuss the clinical features of thyroid eye disease and what treatments are available. We also explore the current views on the pathogenesis of thyroid eye disease and their clinical implications.

Methods

Sources of information

We retrieved from Medline papers with "thyroid" and "eye" anywhere in the abstract and drew further information from leading medical textbooks. We also consulted with recognised experts (R Bahn, Division of Endocrinology, Metabolism and Nutrition, Mayo Clinic, Rochester, Minnesota, USA; P Kendall-Taylor, Department of Endocrinology, University of Newcastle, Newcastle upon Tyne; A P Weetman, Department of Medicine, Clinical Sciences Centre, University of Sheffield; and W M Wiersinga, Department of Endocrinology, Academic Medical Centre, University of Amsterdam, Netherlands).

Clinical features

Thyroid eye disease is also known as Graves' ophthalmopathy and thyroid associated ophthalmopathy and is usually associated with autoimmune hyperthyroidism (Graves' disease). Its typical ocular manifestations are recognised by a variety of clinical features including pain, gritty eyes, photophobia, chemosis, diplopia, and exophthalmos. Compression of the optic nerve can, in extreme cases, lead to blindness.

Risk factors

Smoking

Once a patient has Graves' disease, the major clinical risk factor for developing thyroid eye disease is smoking.⁴ Patients with thyroid eye disease are four times

Summary points

Thyroid eye disease occurs in 25-50% of people with Graves' disease

Smoking is the most important risk factor for developing thyroid eye disease

Vigilance is needed for any features of possible optic neuropathy, such as blurred vision, impaired colour perception, and reduced visual acuity

Diagnostic pitfalls include uniocular presentation, a lack of history of Graves' disease, and optic neuropathy without obvious proptosis

Thyroid eye disease requires specialist management, preferably by a thyroidologist as well as an ophthalmologist in a combined clinic

The role of orbital radiotherapy in the treatment of thyroid eye disease is controversial

more likely to be smokers or former smokers than never smokers.⁴ The greater the number of cigarettes smoked per day, the greater the risk of developing thyroid eye disease, and giving up smoking seems to reduce this risk.^{w1} Cigarette smoking also increases the risk for progression of ophthalmopathy after radioiodine therapy.⁵

Sex

Women are five times more likely to be affected by thyroid eye disease than men,^{w2} but this largely reflects the increased incidence of Graves' disease in women. Once someone has Graves' disease, his or her sex has little effect on the risk. Thyroid eye disease is clinically evident in 25-50% of patients with Graves' disease,³ and 3-5% of cases develop severe eye disease.⁶ Men older than 60 may be at increased risk of more severe disease.⁷

Radioiodine

Strong evidence exists that radioiodine, which is used to treat the hyperthyroidism, can cause a flare in thyroid eye disease,^{8 w3 w4} although some controversy

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References w1-w38 are on bmj.com

Fig 1 Activity and severity of thyroid eye disease, adapted from Rundle 1957¹³ and Prummel and Wiersinga 2002¹⁴. The lower panel shows the possible outcome of treatment (indicated by the single arrow) which has 50% efficacy, given at 50% of maximal disease severity, and 95% disease activity. Treatment given later, when the disease is less active, is likely to have much less effect on disease severity

remains as to what degree radioiodine worsens thyroid eye disease.^{9 w5}

Genes

No single gene has been identified that is sufficient and necessary for the development of thyroid eye disease, and the genetics of thyroid eye disease has been described as a play in search of a cast of characters.¹⁰ Multiple genes are likely to be involved in the development of thyroid eye disease,^{w6-w9} and these interact with multiple environmental risk factors.

Symptoms and signs

The symptoms of thyroid eye disease depend on how active the disease is (intensity of acute inflammatory reactions) and its severity (extent of anatomical, functional, and cosmetic features). Common symptoms are pain, an oppressive feeling behind the eye, a gritty sensation in the eye, double vision, and photophobia.

The accompanying signs include oedema of the conjunctiva and eyelid, proptosis, and diplopia owing to involvement of extraocular muscles. As the disease progresses the acute inflammation recedes, but signs and symptoms improve only partially because of the residual fibrosis and scarring of the orbital contents (fig 1).

The intensity of inflammation can be measured by using the clinical activity score (box 1) which can be used to assess disease progression and help guide immunosuppressive treatment.^{11 w10} The severity of eye

Box 1: Clinical activity score¹¹

A score of 1 is given for each feature present.

Pain

- Painful, oppressive feeling on or behind the globe during the last 4 weeks
- Pain on attempted up, side or down gaze during the past 4 weeks

Redness

- Redness of the eyelid(s)
- Diffuse redness of the conjunctiva, covering at least one quadrant

Swelling

- Swelling of the eyelid(s)
- Chemosis
- Swollen caruncle
- Increase by 2 mm or more in proptosis during a period of one to three months

Impaired function

- Decrease in eye movements in any direction of 5 degrees or more during a period of one to three months
- Decrease in visual acuity (1 or more lines on Snellen chart, using a pinhole) during a period of one to three months

changes is often classified by using the “NO SPECS” system (box 2).

High vigilance for any features of possible optic neuropathy (such as blurred vision, impaired perception of colour, reduced visual acuity, a relative afferent papillary defect, or visual field loss) is important. Any such findings should prompt urgent review by an ophthalmologist, because the shorter the duration of visual loss, the better the chance of a good outcome of treatment.¹⁵

Extraorbital features

In addition to the eye features, an inflammatory reaction can occur in the skin at various sites. The most common site is the pretibial region (pretibial myxoedema), but sites of skin trauma can also be affected. The skin manifestations are known as thyroid associated dermopathy. Changes can also occur in the fingers nails (acropachy), which are clinically indistinguishable from finger clubbing.

Box 2: “NO SPECS” classification of thyroid eye disease, abbreviated from Werner¹²

Class 0: No signs or symptoms

Class 1: Only signs (limited to upper lid retraction and stare, with or without lid lag)

Class 2: Soft tissue involvement (oedema of conjunctivae and lids, conjunctival injection, etc)

Class 3: Proptosis

Class 4: Extraocular muscle involvement (usually with diplopia)

Class 5: Corneal involvement (primarily due to lagophthalmos)

Class 6: Sight loss (due to optic nerve involvement)

Fig 2 Computed tomography images of orbits of A: normal eye; B: thyroid eye disease with exophthalmos and moderate enlargement of the medial and lateral recti muscles (arrows), the exophthalmos being due to fatty tissue expansion; C: thyroid eye disease with exophthalmos and severe enlargement of the recti muscles, particularly the medial recti (arrows)

Diagnosis of thyroid eye disease

The diagnosis is usually made on clinical grounds by finding typical clinical features on the background of Graves' disease. However, several diagnostic pitfalls exist, including uniocular presentation, a lack of history of Graves' disease, and optic neuropathy without obvious proptosis. Eye changes can occur before Graves' disease, and hyperthyroidism is by no means a consistent finding.

In difficult cases, endocrine assessment should identify the diagnosis of Graves' disease. This includes thyroid function tests (thyroid stimulating hormone (TSH), tri-iodothyronine (T3), and free thyroxine (FT4)), thyroid autoantibodies (antithyroid peroxidase, anti-thyroglobulin, and thyroid stimulating antibodies), and a thyroid uptake scan. Full ophthalmological assessment can help narrow the differential diagnosis. Orbital computed tomography (fig 2) or magnetic resonance imaging can confirm whether soft tissue or extraocular muscles are affected, but the cause of the radiological abnormalities needs to be interpreted in the light of the clinical history and examination, and occasionally orbital biopsy is required to exclude other pathologies such as orbital pseudotumour or lymphoma.

Current treatment

Thyroid eye disease should be managed under the supervision of a specialist with particular expertise and experience of thyroid eye disease, preferably in a combined clinic for thyroidology and ophthalmology. This provides the ideal setting for the accurate and detailed assessment of disease activity and response to treatment that is required. Patients should be referred promptly, as the medical treatment of thyroid eye disease is more likely to be effective when given while the eye tissue is acutely inflamed.

Most patients experience mild disease that requires only symptomatic measures, such as artificial tears, avoiding dust, and sleeping propped up. Smokers should stop smoking, as smoking may influence the course of thyroid eye disease in a dose dependent manner during treatment. The response to treatment is delayed and considerably poorer in smokers.¹⁶

A sizeable minority of patients (10-35%) require medical treatment.^{17 18 w11} This is aimed at modulating the immune response and consists of steroids at high dosages and orbital radiotherapy. Orbital decompression surgery can be used in the acute phase to treat compression of the optic nerve, and in the inactive phase to improve residual functional and cosmetic features. However, these treatments are currently inadequate. After treatment more than half the patients have diplopia, more than a third are dissatisfied with the appearance of their eyes, and more than a quarter have low visual acuity.^{w12 w13}

Judging the effect of treatment in thyroid eye disease is difficult without carefully controlled randomised trials, because, even if no treatment is given, the condition will improve to a variable degree.

Steroids

No large randomised placebo controlled trials of steroids in thyroid eye disease have been conducted, and the observation that steroids dampen down the acute inflammation (response rates to steroids in thyroid eye disease range from 33%^{w14} to 66%^{w15}) would arguably make such a trial unethical. It is not clear to what degree steroids improve thyroid eye disease, or whether they just shorten the time to recovery without improving the final end point.

In general, high doses of steroids are required, but the dosage is titrated against the response and kept to the lowest effective dose, given for as short a time as possible. This should be determined by a specialist using detailed methods for assessment. This approach aims to minimise the potentially serious side effects of steroids, and some centres also use steroid sparing agents such as azathioprine.

Orbital radiotherapy

The role of orbital radiotherapy is controversial. Its use has stemmed from numerous retrospective, uncontrolled studies. Some of these studies may have wrongly attributed the improvements after radiotherapy to the radiotherapy, rather than just the natural course of the disease. Recent, prospective, placebo controlled trials have shown few or no improvements after radiotherapy.¹⁹⁻²¹ In mild thyroid eye disease, radiotherapy does not prevent progression of disease or improve patients' quality of life.²⁰ The reported side effects of radiotherapy include cataracts (12% inci-

Fig 3 Patient after bilateral orbital decompression, lower lid hard palate grafts, and upper lid recessions

dence after a median 11 years^{w16}), radiation retinopathy (usually, but not always, as a result of incorrect radiation doses or targeting^{w17 w18}), and malignancy (calculated risk of 1.2%^{w19}). Radiotherapy is contraindicated in diabetic patients with pre-existing retinopathy. In light of the recent trials the use of radiotherapy for thyroid eye disease may diminish, and currently it should be limited to people with motility defects.¹⁹

Surgery

Surgery is indicated only for more severe disease, either when the disease is sight threatening and unresponsive to other treatment modalities, or for functional and cosmetic reasons once the disease has "burnt out." The usual procedure is an inferior orbital decompression (fig 3), during which a defect is created in the floor and medial wall of the orbit, allowing some of the orbital contents to prolapse down into the maxillary sinus, so reducing the tissue volume within the orbit. Although this improves proptosis, a need for eyelid surgery often arises at a later date, to improve appearance and function.

Pathogenesis of thyroid eye disease

Target antigen

Some patients with Graves' disease also develop changes to the eye, and sometimes to the skin and nails. The mechanisms behind and reasons for this are

becoming clearer. Although the target antigens remain unidentified, the TSH receptor is the leading candidate.^{w20 w21} Concentrations of TSH receptor antibodies have been shown to correlate directly with clinical features of thyroid eye disease,^{w21} and TSH receptors have been found in orbital tissue^{w22} and in affected skin in cases of thyroid associated dermopathy.^{w23 w24} These findings have led to considerable support for the hypothesis that the TSH receptor is the shared antigen that connects the seemingly disparate organs that are affected in thyroid eye disease. However, this hypothesis remains unproved, and the immune processes involved are likely to be complex, with involvement of both antibody and cell mediated responses conducting an orchestra of cytokines.

Role of cellular immunity

Graves' disease is an autoimmune disease in which autoantibodies directed against the TSH receptor are produced. The usual result of this interaction between antibody and antigen is stimulation of TSH receptors located in the thyroid gland, and the consequent overproduction of thyroid hormones.

In thyroid eye disease the orbital autoimmune process is different to that seen in the thyroid gland. The histological appearance of thyroid eye disease is that of an inflammatory cellular infiltrate that is more severe in early disease.²² The identification of sensitised, orbital tissue specific, T lymphocytes in the peripheral blood and orbit from patients with thyroid eye disease strongly supports a role of cellular immunity in the pathogenesis of thyroid eye disease.²³

Role of antibodies

TSH receptor antibodies are responsible for the hyperthyroidism seen in Graves' disease but their role in thyroid eye disease is still uncertain. Although TSH receptor antibody concentrations correlate with the clinical features of thyroid eye disease,^{w21} this may simply reflect the intensity of the autoimmune reaction. The lack of proved cases of neonatal thyroid eye

Patient's story

When I was 42, I developed an overactive thyroid gland. Two years later my eyes became painful, gritty, and dry, with an unpleasant feeling of pressure behind them. One eye began to protrude more than the other. At times I would get double vision, and I had to give up work for a year. I was put on to a big dose of steroids, which was cut down over 15 months. While on steroids my weight shot up by over 3 stones [20 kg], and I became very aggressive. During this time I also had radiotherapy to my eyes, which didn't make a noticeable difference, although things have remained stable since then.

I also have problems with my shins, which have turned a disgusting shade of purple, so I keep them hidden.

Pretty much everything causes me discomfort, such as looking at a computer screen for too long, bright lights, cooking smells, the heat, etc. Although I did go back to work for seven years, my eye problems made it too difficult, and I had to give up work and have been on disability benefit for the past six years.

I am currently waiting for surgery, which I hope will make my right eye look better.

Carmela Squires, 2004

disease (cases of thyroid eye disease in babies born to mothers with active thyroid eye disease, due to placental immunoglobulin G (IgG) transfer) implies that if IgG antibodies have a pathogenic role in thyroid eye disease they are not sufficient for disease expression.

However, IgG from patients with thyroid eye disease can cause orbital fibroblasts from patients with thyroid eye disease (but not those from patients without thyroid eye disease) to produce T lymphocyte chemoattractants (ICAM-1, interleukin (IL)-16, and RANTES) which would be expected to promote thyroid eye disease.^{w25 w26}

Although antibodies are certainly not the only component of thyroid eye disease and may not even be pathogenic at all, it is therefore possible that they contribute to the promotion of the inflammatory response in a susceptible individual.

Recent advances

The signs and symptoms of thyroid eye disease are explained by the orbital accumulation of glycosaminoglycans (GAG) and hypertrophy of adipose tissue, and the orbital fibroblast appears to play a key role in both of these processes.

These fibroblasts have been shown to increase their production of GAG under stimulation from certain cytokines.^{w27-w31} The messenger RNA of a number of cytokines has been detected in orbital samples taken at surgical decompression (IL-1 β , TNF- α , IL-8, IL-10, and γ interferon),^{w32-w34} but the individual functions of these cytokines remains unclear.

Involvement of T cells and activation of fibroblasts have been shown to occur in the early stages of the disease process.²² Successful interruption of the acute inflammatory process therefore probably needs to occur early in the evolution of an individual patient's thyroid eye disease.

There is evidence of increased adipogenesis in the orbits of patients with thyroid eye disease, and a subpopulation of orbital fibroblasts can differentiate into adipose cells with appropriate stimulation.^{w35 w36} Interestingly, peroxisome proliferator activated receptor γ (PPAR γ) agonists (such as the thiazolidinediones) have been shown in vitro to stimulate orbital adipogenesis and increase orbital expression of TSH receptors.^{24 w37} A clinical case is known of a patient who was treated with pioglitazone, who subsequently experienced an exacerbation of his thyroid eye disease that had been stable and inactive for more than two years. As a consequence it has been proposed that PPAR γ agonists may be contraindicated in thyroid eye disease.²⁴

The future

Research into thyroid eye disease is hindered by the lack of either a reproducible animal model or access to orbital tissue from early in the disease process. Despite this it is apparent that numerous cytokines are involved in thyroid eye disease. IL-1 has been shown to stimulate orbital fibroblasts to produce GAG in vitro, and this effect can be blocked by antagonists of IL-1.^{w38} Agents that modulate the effects of certain cytokines, if given early in the course of the disease, may represent a future therapeutic strategy for thyroid eye disease.²⁵

Additional educational resources

Further reading

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Resources for patients

Thyroid Eye Disease Association (www.thyroid-fed.org/members/TED.html)—Provides information, care and support to those affected by thyroid eye disease, including a network of support groups and telephone helplines throughout the United Kingdom

British Thyroid Foundation (www.btf-thyroid.org)—Patient led, charitable organisation dedicated to helping those with thyroid disorders. The foundation works with the medical profession, supporting patients and helping to raise funds for research into all types of thyroid disorders

Thyroid Foundation of America (www.allthyroid.org)—United States based organisation aiming to inform and support patients with thyroid disorders

National Graves' Disease Foundation (www.ngdf.org)—United States based support group dedicated exclusively to patients with Graves' disease

The monophasic nature of thyroid eye disease makes it an attractive candidate for anticytokine treatment—interrupting the disease with an early, short course of these treatments would be expected to have the desired clinical outcome, without the need for repeated, expensive courses of treatment as is the case in other autoimmune conditions such as rheumatoid arthritis and Crohn's disease.

Anti-TNF α agents might seem the obvious choice, as TNF α seems to be involved in the inflammatory process of thyroid eye disease, and the use of these agents in other inflammatory conditions has resulted in extensive clinical experience. However, although anti-TNF- α agents might inhibit GAG production and so improve thyroid eye disease, in vitro evidence has shown that TNF- α inhibits orbital adipogenesis and TSH receptor expression and so anti-TNF- α agents may worsen thyroid eye disease.

Existing anticytokine agents also have a considerable adverse effect profile, and their use in thyroid eye disease would be facilitated by being able to predict which patients are likely to develop more severe eye disease.

Other agents are currently under investigation. These include octreotide and colchicine, but preliminary data do not seem to be particularly promising. With the observed experimental and clinical findings of PPAR γ agonists worsening adipogenesis in thyroid eye disease, it may be that antagonists of PPAR γ present another future therapeutic avenue for thyroid eye disease,²⁴ but

any such agent would have to be judged in the light of what detrimental metabolic effects it might have.

Conclusion

Over recent years important steps have been taken towards understanding thyroid eye disease, and several potential therapeutic targets have been identified. Further progress in the laboratory is likely to translate into real improvement in the treatment options for patients with this challenging condition.

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Interactive case report

Abnormal liver function after an unplanned consultation

This case was described on 31 July and 7 August (*BMJ* 2004;329, 273 and 342). Debate on the management of the patient continues on bmj.com/cgi/content/full/329/7460/273#responses. On 28

August we will publish the outcome of the case together with commentaries on the issues raised by the management and online discussion from the patient and relevant experts.

A memorable patient

The privilege of wisdom is to listen

A 64 year old patient was referred to the emergency department by an oncology nurse. He had metastatic bronchogenic carcinoma and was complaining of bilateral leg weakness of recent onset. The referral note mentioned the possibility of cord compression secondary to bone metastasis. The patient was seen first by the emergency department doctor, who documented the leg weakness and then forwarded the patient for an orthopaedic review. The orthopaedic team agreed with the diagnosis and arranged hospital admission for urgent magnetic resonance imaging. They also discussed the case over the telephone with me (the on-call physician) regarding palliative management.

Late that night, while reviewing another patient, I overheard one of the student nurses telling her colleague that she had checked the blood sugar levels of the patient admitted with spinal cord compression and that they were very high. Armed with this

new information, I reviewed the case history again and this time diagnosed new onset diabetes, precipitated partly by the dexamethasone the patient was taking as a result of his cerebral metastasis. He was discharged after a couple of days.

Since then, I have always paid a little more attention to the discussions of paramedical staff.

Mohammad Imran Khan *consultant in gastroenterology, Wanganui Hospital, New Zealand*

We welcome articles up to 600 words on topics such as *A memorable patient*, *A paper that changed my practice*, *My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. Please submit the article on <http://submit.bmj.com>. Permission is needed from the patient or a relative if an identifiable patient is referred to.