Thyroid eye disease: a continuing challenge

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Thyroid eye disease represents a significant cause of visual loss. All physicians should be familiar with the eye signs and symptoms and potential complications of this autoimmune disease. This paper reviews the epidemiology, pathophysiology, eye signs and symptoms, and current therapies for thyroid eye disease. It also examines the relationship between smoking and thyroid eye disease and assesses its impact on the Asian population.

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Introduction

Thyroid eye disease is an inflammatory condition which affects the orbital contents including the extraocular muscles and orbital fat. It is almost always associated with Graves' disease (GD) but may rarely be seen in Hashimoto's thyroiditis, primary hypothyroidism, or thyroid cancer. For the purposes of this review, the terms Graves' eye disease and thyroid eye disease (TED) are used interchangeably. Thyroid eye disease can range in severity from mild, almost undetectable changes in the periocular soft tissue, to optic nerve compression which causes total visual loss. Because the underlying aetiology is not known, therapy is currently directed against the consequences of disease.

Epidemiology

The incidence of systemic GD in a well-studied Caucasian population was 15 per 100 000 population annually.[1] The incidence and prevalence of systemic GD among Asians has not been systematically studied. Ocular involvement is clinically apparent in 40% to 50% of systemic GD cases. However, nearly all of these cases have some evidence of eye involvement on orbital ultrasound or CT scan, even if the patient is asymptomatic and the eye appears clinically normal.

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The epidemiology of TED suggests the presence of hereditary factors. A family history is present in 30% of cases and there is a concordance rate of 50% to 60% in monozygotic twins. Although age-specific rates peak in the third and fourth decades, ocular complications are most severe in patients more than 50 years of age.[2] Severe visual loss, which occurs in roughly 5% of patients overall, is more common among men, despite the overall female predominance of TED.

Pathophysiology

The pathophysiology of systemic GD has been fairly well-established. In susceptible individuals, autoantibodies directed against the thyroid stimulating hormone (TSH) receptor on the surface of thyroid follicular cells are produced. These anti-TSH receptor autoantibodies then stimulate thyroid hormone production, leading to the systemic features of thyrotoxicosis. These include heat intolerance, sweating, palpitations, irritability, insomnia, tremor, and nervousness. There is often an associated weight loss and increased appetite.

The pathophysiology of Graves' eye disease has not been elucidated. It is thought that there may be cross-reactivity between orbital and thyroid antigens. However, despite intensive effort, the antigen or antigens responsible for the autoimmune attack on orbital tissues have not been identified. It is further believed that there are defects in both the cellular and humoral components of the immune response. For example, maternal IgG antibodies can cross the placenta and give rise to neonatal GD. In addition, one group has reported a correlation of serum IgE levels with stages of

Graves' eye disease.[3] Defects in T-helper and T-effector lymphocytes have also been implicated in this autoimmune dysfunction.[4]

A number of features support the idea that Graves' orbitopathy may be distinct from Graves' hyperthyroidism. The severity of orbitopathy does not correlate with thyroid function or levels of thyroid-stimulating antibodies. There is also no specific temporal relationship between thyroid dysfunction and eye disease as eye disease may precede, coincide, or follow systemic thyroid dysfunction. Between 10% and 20% of patients with Graves' orbitopathy are euthyroid when their eye disease presents, and some of these will never develop any demonstrable thyroid dysfunction. There is often little or no correspondence between the activity of the systemic disease and the eye disease and in general, there is no correlation between the level of anti-TSH antibodies and the severity of eye disease.

The histology of Graves' eye disease shows characteristic features. There is generalised orbital inflammation that is most severe in the extraocular muscles. Fibrosis and fatty infiltration of muscles occurs, which may lead to muscle hypertrophy up to 10 times the normal volume. Significantly, the tendons of the extraocular muscle are usually spared when examined on CT scanning, which is almost pathognomonic for TED. There is also an influx of inflammatory cells—primarily lymphocytes and plasma cells and lymphocyte activation of quiescent orbital fibroblasts which then secrete collagen and glycosaminoglycan. These extracellular polymers are hydrophilic and lead to increased oedema in orbital soft tissue and extraocular muscle. Continued collagen deposition produces fibrosis of the orbital tissues.

This expansion of orbital tissue volume causes the characteristic proptosis or protrusion of the eyes which is seen in most patients with TED. In severe cases of muscle enlargement, there may be compression of the optic nerve at the orbital apex, with profound and even total vision loss.

Ocular manifestations

The ocular manifestations of TED include soft tissue inflammation, eyelid retraction, proptosis, corneal exposure, and optic nerve compression. The signs and symptoms of the disease are characteristic. These include lid retraction, lid lag, and a delay in the downward excursion of the upper eyelid in downgaze that is specific to TED. Lid retraction in the early phase of disease represents a response to heightened sympathetic tone. The lid margins, which normally cover the cornea slightly, are retracted away from the cornea, causing accelerated evaporation of the tear layer and drying of the ocular surface. As chronic inflammation occurs, there is fibro-fatty infiltration of lid tissues. Soft tissue inflammation may be noted as eyelid or conjunctival oedema or dilated blood vessels over the extraocular muscle insertions.

Thyroid eye disease is the most common cause of bilateral or unilateral proptosis. The appearance of proptosis can be quite distressing to the patient and often imposes a substantial psychological morbidity. The combination of proptosis and lid retraction often leads to poor lid closure and chronic exposure of the cornea. Breakdown of the corneal epithelium can be painful and may lead to secondary bacterial infection with resulting corneal ulceration, perforation, and widespread intraocular infection.

Thyroid eye disease is perhaps the most common cause of acquired diplopia. It also causes a restrictive myopathy—there is actual restriction of the muscle's ability to contract and move the globe. A variety of squint patterns may be present, and these patterns will be incomitant—the degree of squint will be different in different directions of gaze.

The most serious complication is optic neuropathy. This results from direct compression of the optic nerve at the orbital apex. There is no evidence of direct inflammation of the optic nerve. This emphasises the importance of measuring visual acuity, pupiliary response and colour vision, all of which are sensitive indicators of nerve compression. Each eye should be checked carefully to detect early evidence of compromised optic nerve function. If bilateral compression is present, the pupils may react normally, since there will be an equal visual deficit in each eye. In general, there is no strict correlation between the incidence and severity of optic neuropathy and the degree of proptosis. In fact, the proptosis may be quite mild. This emphasises the value of an ophthalmic evaluation for all GD patients who show positive eye findings.

Therapy

The general approach to TED is to prevent ocular complications and to rehabilitate the disfiguring aspects. Patients are often young women and there can be significant psychological consequences. Many patients with the disease require only simple measures such as ocular surface lubricants. For patients with more ex-

tensive disease, a variety of therapies have proven to be effective.

Eyelid retraction and corneal exposure are treated initially with artificial tears and lubricating ointments to reduce corneal desiccation and the incidence of infection and ulceration. If the ocular surface changes persist, then eyelid surgery is indicated. Previously, tarsorrhaphy (suturing together of the eyelids) was a commonly used technique to reduce exposure. Currently, the preferred technique is to relieve eyelid retraction directly, in both upper and lower eyelids. A variety of techniques have been used to lengthen the eyelids, including insertion of spacer materials. These are more effective than tarsorrhaphy at reducing corneal exposure and allowing lid closure.

Extraocular muscle imbalance is very common in patients with GD and is treated with strabismus surgery. Any of the extraocular muscles may be affected. There is a tendency for involvement of the inferior and medical recti. In surgery, the affected muscle is recessed, i.e. weakened, to allow a greater degree of motility. It is often impossible to restore single vision in all directions of gaze to TED patients. The surgical goal is usually to restore single vision in primary (i.e. straight ahead) and reading (downgaze) positions.

Optic nerve compression may be treated either medically or surgically. The mainstay of medical treatment for acute optic nerve compression is oral corticosteroids. Systemic corticosteroids are not recommended for patients with mild disease or as a long term therapy. Chronic steroid use can lead to severe toxic effects such as hyperglycaemia, osteoporosis, and increased susceptibility to infection. The antimetabolites cyclophosphamide and azathioprine have been used with limited success. Their main drawback has been systemic toxicity including bone marrow suppression and increased susceptibility to infection.

Orbital irradiation is usually reserved for patients with severe inflammation who fail to respond adequately to a short course of corticosteroid therapy. Radiation therapy is more successful at reducing inflammation than in restoring vision. It is therefore primarily a temporizing measure while a patient is awaiting the more definitive therapy of orbital decompression.

Orbital decompression remains the definitive surgical procedure for relieving optic nerve compression. The goal of decompression surgery is to remove the inferior and medical orbital walls, allowing prolapse of the orbital contents into the maxillary and ethmoid sinuses, respectively. Adequate decompression of the orbital apex is most important, since this is the primary site of optic nerve crowding and compression. The surgical approach may be transorbital or via the maxillary antrum. Most ophthalmologists find little role for the transcranial approach to orbital decompression. There is an increased chance of morbidity or even mortality using this approach, and the decompression of orbital contents into the anterior cranial fossa is less effective because of the presence of the brain. In general, orbital surgery (if required) should precede muscle and lid surgery. This is because orbital surgery may alter the degree of lid retraction and muscle imbalance.

Smoking and Graves' disease

Several reports have provided evidence that cigarette smoking may be a risk factor for the initiation and exacerbation of TED. In a case-control study of Graves' patients, smokers were disproportionately more likely to suffer from eye disease.[5] Smokers were also more likely than non-smokers to suffer severe eye disease and to have visual loss. Although there is strong evidence of an association between smoking and TED, the mechanism of how smoking causes the disease is unclear. Because stopping smoking may be helpful in reducing the risk of development and progression of eye disease, it is important that physicians urge their thyroid patients to quit smoking.

Thyroid eye disease in Asians

There is preliminary evidence that Asians may be at greater risk of thyroid-related optic neuropathy due to narrower orbits and a subsequent greater degree of crowding in the orbital apex (Rootman J, personal communication). Asians may therefore benefit from earlier orbital decompression, when optic nerve compression is first detected. A natural history study of TED in Chinese individuals is needed to assess the incidence and degree of ocular complications in this population. Such a study is being instituted in Vancouver and Hong Kong and will also measure the effectiveness of current therapies in this population.

Thyroid eye disease represents a continuing challenge for primary care physicians as well as ophthalmologists. Visual loss can be prevented in the vast majority of cases by prompt recognition and appropriate therapy for ocular complications. All patients with GD must undergo careful, regular eye examinations by an ophthalmologist. Until now, TED has not been well-studied in the Asian population.

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