Dysthyroid orbitopathy (thyroid-associated orbitopathy or Graves’ ophthalmopathy) is the most common cause of both unilateral and bilateral proptosis in adults. This proptosis is usually accompanied by eyelid retraction, orbital congestion or motility disturbances. Each patient experiences a unique combination of symptoms and signs for an unpredictable duration and with varying severity. Although orbital manifestations typically improve within 2-5 years, visual loss due to optic nerve compression does occur. Careful observation and reassurance are helpful and often adequate, but judicious medical and surgical intervention is essential in some patients to prevent irreversible visual loss.

Graves originally described a triad of hyperthyroidism, dermopathy, and eyelid retraction. While most patients with Graves ophthalmopathy have preexisting or simultaneously diagnosed hyperthyroidism, this is not universal. In at least 20%, the diagnosis of a thyroid disorder follows (often by years) the initial orbital manifestations. Furthermore, 3% never develop a clinically apparent thyroid imbalance, although they may demonstrate abnormalities when immune testing is performed. Finally, rather than being characteristically hyperactive, the thyroid may be hypoactive or involved in a neoplastic process. Conversely, only 20% with systemic Graves demonstrate symptomatic and clinically apparent orbital disease. Up to 90%, however, possess extraocular muscle enlargement on computed tomography (CT). Hyperthyroidism and the characteristic orbital signs of Graves disease are therefore definitive but inconstantly liked. Thus the term thyroid-associated orbitopathy is most descriptive and least confusing.

Our understanding of the link between systemic thyroid disease and orbitopathy has expanded greatly over the last 20 years, although the precise pathogenesis remains a point of debate. Activation of the thyroid gland, as a result of inflammation, trauma, surgery, smoking and radiation appears to prompt release into the blood of a thyroid antigen that stimulates both the cellular and humoral arms of the immune system. Then, antibodies to the thyroid stimulating hormone (TSH) receptor and other antigens are produced, enhancing release of thyroid hormone and amplification of thyroid antigen production. Activated T lymphocytes invade the orbital connective tissue at the same time a local humoral immune reaction is initiated. Retrobulbar fibroblasts proliferate, resulting in increased synthesis and release of glycosaminoglycans. Locally produced lymphokines amplify the cascade. A shared orbit-thyroid antigen(s) is then presented and released into the circulation. This combination of cell-mediated and humoral activation promotes inflammatory cell migration and production of edema in the orbit. The result is thickening of extraocular muscle and an increase in orbital fat volume. The specifics of each step are currently the subject of intense investigation.

Thyroid-associated orbitopathy (TAO) is five times more likely to affect women than men (4:1). There is a gender-specific bimodal presentation, with peak incidence between 40-44 and 60-64 in women and 45-49 and 65-69 in men (Mayo study). Although all races may be affected, Caucasians develop TAO much more commonly. Presentation in childhood is unusual but not rare. Genetic factors appear to play a role in development of TAO: 20-60% of affected patients has a family history of a thyroid disorder. Environmental factors are also important; cigarette smoking aggravates and prolongs the orbital inflammation.

Thyroid-associated orbitopathy is a self-limited disease, but each orbital sign varies in prevalence and persistence. Soft tissue inflammation and congestion are common and nonspecific signs and typically resolve within 5 years. Eyelid retraction, either unilateral or bilateral, is common (90% prevalence) and the sign most likely to persist chronically. Although extraocular muscle function occurs in 40% of patients, intermittent diplopia usually resolves over time. One third of patients who develop constant diplopia will also improve spontaneously. Unilateral or bilateral proptosis occurs in 60% of patients. Improvement in proptosis is unusual with fewer than 10% of patients demonstrating significant improvement within 5 years. Vision loss occurs in fewer than 5% of those with orbital involvement. Compressive optic neuropathy is the most common cause of visual loss; corneal scarring or secondary glaucoma is more unusual.

EARLY SIGNS AND SYMPTOMS

Symptoms and subtle signs of TAO are often present for many years prior to diagnosis. Common and nonspecific symptoms include tearing, irritation, aching and photophobia. Early signs include conjunctival injection periorbital puffiness, abnormal tear break-up time, superficial punctate keratitis, and elevation of intraocular pressure. Eyelid retraction is a common early feature of hyperthyroidism, but can occur in euthyroid or hypothyroid patients with orbitopathy. The classic stare of bilateral, symmetric upper and lower lid retraction may abate after thyroid function stabilizes. Eyelid retraction is accompanied by lagophthalmos (retraction of upper lid with passive eyelid closure and in downgaze) and lid lag (a slowing of the descent of the eyelid with downgaze).

After identification of early symptoms and signs of TAO, observation and patient education are indicated. Reassurance and description of the natural course of the disease are helpful. Lubricating drops, cool compresses and sunglasses will improve symptoms during the day. Elevating the head of the bed and taping the eyelids will minimize periorbital edema and irritation due to nocturnal lagophthalmos. Stable, significant eyelid retraction can be improved with appropriate surgical therapy. Corticosteroids and external beam radiation are never indicated for these early TAO symptoms and signs.
ORBITAL INFLAMMATION, CONGESTION AND PROPTOSIS

Some TAO patients experience more significant inflammatory symptoms and signs. Rather than mild conjunctival injection over the recti muscle insertions, interpalpebral chemosis, severe periorbital edema with erythema and proptosis may occur. Increased orbital volume secondary to inflammation is believed to impede venous outflow, which further aggravates congestion and the resulting proptosis. So, although inflammation and congestion are two distinct processes, they are intimately related.

Transient diplopia is very common and can progress to constant diplopia. Difficulties with fusion are usually worse in the morning due to fluid accumulation in the muscles that occurs with recumbency. Infiltration with inflammatory cells and fluid is typically followed by fibrosis that may create a permanent motility restriction. The inferior rectus and medial rectus are most commonly involving resulting in noncomitant esotropia or hypotropia, respectively. Forced duction testing is usually positive due to fibrotic contraction. CT imaging reveals bilateral, typically asymmetric, enlargement of extraocular muscles.

Proptosis, the classic feature of thyroid orbitopathy is actually less prevalent than eyelid retraction. It is caused by infiltration of the eye muscles with inflammatory cells and/or an increase in fat volume, resulting in forward displacement of the globe. Proptosis is usually axial and associated with increased resistance to retropropulsion of the globe. Although typically bilateral, asymmetrical proptosis is not uncommon. Reproducible quantification of the degree of proptosis may be difficult.

Acute, severe orbital inflammation, especially if associated with neurologic visual loss, should be treated immediately with high-dose corticosteroids. A starting dose of 80mg Prednisone is given in divided doses. The high dose should be maintained until visual function approaches normal and then tapered to lower doses slowly over three months. Care must be taken to tailor dosing to the individual’s clinical response. If the patient only initially responds to corticosteroids or can not tolerate the side effects, low-dose radiation (25Gy) is required to counteract inflammation and preserve visual function. Steroids and radiation are most effective during active inflammation.

Corticosteroids and radiation play no role in the management of motility disturbances. The TAO patient with diplopia to be observed for at least 6 months and then offered strabismus surgery when inflammation has subsided and the restrictive component has stabilized.

Although corticosteroids and/or radiation improve proptosis due to active inflammation, proptosis due to chronic inflammatory fibrosis does not respond to these therapeutic interventions. In the presence of corneal compromise or optic nerve compression, steroids are used in a temporizing fashion, sometimes in conjunction with low-dose radiation therapy (25 Gy). If radiation fails or vision deteriorates rapidly, surgical decompression is indicated.

OPTIC NEUROPATHY

The optic nerve has a serpiginous course that allows for several millimeters of proptosis prior to compromise. The orbital apex, conversely, has no room for expansion. Muscle enlargement posteriorly results in compression of the optic nerve just anterior to the optic canal. Proptosis, then, serves a protective function by expanding the total orbital volume. Muscle enlargement in the absence of significant proptosis is most likely to promote optic nerve compression. It is essential to check for signs of afferent dysfunction (e.g., decreased visual acuity, abnormal color vision, afferent pupillary defect and abnormal visual fields) even in apparently asymptomatic patients. The process is often bilateral, so visual field testing remains essential even in the absence of an afferent pupillary defect. The most common clinical presentation is gradual onset of central visual loss, a central scotoma and a normal optic nerve head appearance in a patient with mild to moderate proptosis.

The differential diagnosis includes glaucomatous visual field loss, diabetic papillopathy and ischemic optic neuropathy. Orbital congestion and impaired venous outflow may contribute to an increased prevalence of ocular hypertension in TAO. Although intraocular pressure may fluctuate between 20 mm and 30 mm HG, or higher development of glaucomatous damage is unusual. Patients with a preexisting diagnosis of glaucoma or active TAO or more than 5 years’ duration are at increased risk for glaucomatous optic nerve damage. Visual acuity and color vision are not affected until very late in glaucoma. Glaucomatous field loss (arcuate or nasal step defects) differs from the pattern of loss seen in TAO compressive neuropathy (central or centrocecal defects). Glaucomatous cupping is not observed, rather the optic disc is normal initially but progresses to diffuse pallor over time. Optic disc edema is unusual with TAO compression and not characteristic of glaucomatous damage. In contrast diabetic papillitis or ischemic optic neuropathy (both characterized by disc edema) may occur in TAO patients. Not all afferent dysfunction in TAO patients is due to optic nerve compression from enlarged extraocular muscles and inflammation.

If the clinical examination reveals afferent dysfunction, an orbital CT scan (without contrast) is should be obtained in a timely fashion. Both axial and direct coronal views should be obtained to clarify the optic nerve position with respect to the extraocular muscles. Crowding of the optic nerve at the orbital apex is diagnostic. The significance of intracranial orbital fat herniation is controversial.

High-dose steroids (at least 80 mg in divided doses) should be initiated immediately. In some particularly severe cases, intravenous corticosteroids may be indicated to prevent precipitous visual loss. If the orbit is acutely inflamed, steroids will result in marked visual improvement within 48 hours. Unfortunately steroids are usually only temporarily effective in treating optic neuropathy and significant side effects preclude long-term use. Most patients will require radiation or surgical decompression. Radiation (25 Gy) may be initiated if the afferent function has been stabilized but not returned to normal with a trial of steroids. Radiation is contraindicated in diabetics and children due to the increased risk of radiation retinopathy. Steroids should be continued during the course of radiation and tapered slowly. If vision deteriorates despite corticosteroids and radiation treatment, surgical decompression is warranted.
References