Research Article

A Few Words about Thyroid Eye Disease

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Abstract

The individual parts of the eye need to act in harmony to create a sharp and clear vision. If this is not the case, these situations harm eye health. Minor problems can be solved by wearing glasses or contact lenses, but some diseases may require surgical treatment. Elevated blood sugar, thyroid disease, and hormone imbalances greatly affect the general condition of vision. By treating these diseases and disorders, but also by applying appropriate medications, the harmful consequences of these diseases on the eyes can be remedied.

Keywords: *Thyroid, Eye, Disease, Health*

Introduction

Thyroid eye disease (TED) is an autoimmune disease caused by the activation of orbital fibroblasts by autoantibodies directed against thyroid receptors [**1**]. TED was previously known as thyroid-associated ophthalmopathy (TAO), Graves orbitopathy (GO), and other variations.

TED is most frequently associated with Hyperthyroidism, consisting of approximately 90% of the cases. However, about 10% of patients with TED have either a normal-functioning (Euthyroid) or under-functioning thyroid (Hypothyroidism e.g. Hashimoto's thyroiditis). While strict control of thyroid function is crucial in patients with TED, the course and severity of ocular manifestation do not always correlate with thyroid hormone levels. Thus, treatment of thyroid

dysfunction does not necessarily affect the course of Grave's ophthalmopathy.

Include genetic, environmental, and immune factors. Among the environmental factors, smoking is the most consistently linked risk factor to the development or worsening of the disease. Stress is another environmental factor that may contribute to the worsening of TED. Patients treated with radioactive iodine may experience worsening of TED, especially if they are smokers.

TED has a higher prevalence in women than men. Both men and women demonstrate a bimodal pattern of the age of diagnosis. The median age is 43 years for all patients, with a range from 8 to 88 years old. Patients diagnosed over 50 -years have a worse prognosis overall.

Thyroid eye disease, which is an independent autoimmune process from primary thyroid disease, may mimic cranial nerve palsies due to fibrosis of extraocular muscles [**2**]. The medial rectus is often involved, and this may mimic a VIth nerve palsy on examination. Thyroid eye disease rarely causes actual cranial nerve palsies, unless there is significant extraocular muscle enlargement leading to orbital apex syndrome.

TAO

Thyroid-associated ophthalmopathy (TAO) has a variety of names previously, such as Graves' ophthalmopathy, ophthalmic Graves' disease, and thyroid-associated ophthalmopathy [**3**]. Although their names are different, their clinical characteristics are the same, that is, abnormal thyroid endocrine axis (endocrine hormones secreted by the thyroid, pituitary, and hypothalamus or their interactions), and they have similar orbital lesions. The principle of individualization should also be followed when standardization of TAO treatment is pursued. Therefore, both the diagnosis and treatment of TAO should be taken into account, and the endocrine and ophthalmic departments should cooperate to make an individualized comprehensive treatment regimen.

Thyroid-associated ophthalmopathy (TAO), is a common orbital disease. The main ocular manifestations include eyelids changes, exophthalmos, eye movement disorders, and other signs. The ocular signs occur at the same time as, before, or after abnormal thyroid function occurs. The thyroid can be hyperfunction, hypofunctional, or normal, and most of the patients have thyroid endocrine axis dysfunction.

The pathogenesis of TAO is not clear, but it is generally believed that the disease is an autoimmune disease or immune organ disease, associated with the function of the endocrine system. And orbital tissue and thyroid may be the attack targets of the abnormal immune response. Its pathological features are inflammatory cell infiltration and edema in the early

stage, and degeneration and fibrosis of pathological tissue at the advanced stage. Treatment includes systemic treatment and eye treatment.

Graves ophthalmopathy (an eye disease related to thyroid dysfunction) usually occurs in people with hyperthyroidism, although it can occur in people with normal or even reduced thyroid function [4]. It is characterized by swelling and inflammation of the orbital tissues, including the extraocular muscles, which may lead to retraction of the eyelids, restriction of eye movement (causing double vision), and bulging forward of the eyeball (called exophthalmos, or proptosis). Although exophthalmos arises primarily from inflammation, the associated processes of cellular proliferation and accumulation of fluid in the tissues that surround the eyeball in its socket, or orbit, also are important pathological processes underlying its development. The swelling of tissues in Graves ophthalmopathy can also cause pressure on the optic nerve behind the eyeball, leading to vision loss. In most uncomplicated situations treatment is conservative, relying only on artificial lubrication, but in severe cases, the lids may need to be partially sutured together or surgery may be required to relieve pressure in the orbit. Further eye muscle and lid surgeries may also be needed to correct persistent eye problems related to Graves's ophthalmopathy.

A complete ophthalmic exam should be always be performed [**5**]. The eyes should be examined for clues to an orbital etiology, including proptosis, chemosis, injection, and restrictions of ocular motility. Thyroid ophthalmopathy can cause unilateral or bilateral optic nerve compression and is suggested by the presence of lid retraction and scleral show, lid lag, resistance to retropulsion, and erythema over the insertions of the extraocular muscles. Other findings can include stigmata of neurofibromatosis including café-au-lait spots, axillary freckling, neurofibromas, Lisch nodules of the iris, and Yasunari choroidal nodules visible on infrared fundus photographies. These findings in a patient with optic atrophy would raise the suspicion of an optic pathway glioma. Intraocular pressure should be recorded, especially if the disc appears cupped, but it should be borne in mind that intraocular pressure alone does not necessarily distinguish glaucoma from other causes of optic atrophy, as in population- based surveys 25 to 50% of individuals with glaucomatous optic disc damage have normal intraocular pressures.

Orbitopathy

Thyroid orbitopathy is an inflammatory condition in which a T cell-mediated immune response develops leading to inflammation within the orbital structures, including the muscles and the

orbital fat [6]. Subacute proptosis develops associated with restriction of eye movements, lid retraction, and eye dryness with irritation, tearing, and redness. Untreated, the condition becomes chronic leading to the development of fibrosis within the muscles, which become permanently restricted and atrophic.

All patients possess anti-thyrotrophin receptor antibodies; their level correlates with the clinical features in Graves' disease and thyroid dermopathy, and are associated with a more poor prognosis. 5 % of patients with thyroid orbitopathy are euthyroid, and this is associated with a lower titer of anti-thyrotropin receptor antibody.

There is a clear relationship between the severity of the disease and a poor response to immunosuppression with cigarette smoking, and this too correlates with the severity of cigarette consumption.

How orbital inflammation develops in Graves' disease is as yet undefined, although experimental data are showing that orbital fibroblasts express thyrotropin receptor antigen.

Thyroid orbitopathy is the most common orbital disorder but it is usually not that painful [7]. The next most likely thought would be idiopathic orbital inflammation, also known as orbital pseudotumor, or orbital myositis. It is the most common cause of a painful orbital process. While it occurs at any age and sex (women slightly more than men), it often occurs in middle age. When it occurs in children, it is often bilateral and has evidence of uveitis and even disc edema. The onset can be slowly gradual to acute or subacute. Imaging has been very helpful in defining idiopathic orbital inflammatory disease. Orbital ultrasound is very sensitive to subtle inflammatory disease, but one needs a competent orbital echographer. CT of the orbits with contrast may show enhancing enlarged muscles or a mass in the orbit. MR scan of the orbits with fat saturation and gadolinium enhancement also may be diagnostic—muscle involvement usually does NOT spare the tendon (vs. thyroid ophthalmopathy which does). Further, it has several distinct patterns: muscle only involvement where single muscle or multiple muscles are enlarged and enhancing, lacrimal gland enhancement, and sometimes the sclera wi, ll also enhance. The optic nerve sheath can also be involved and this is often called peri-neuritis. Sometimes it is very difficult to distinguish optic peri-neuritis from optic neuritis. However, optic neuritis almost always causes visual loss, a relative afferent pupillary defect (RAPD), and change in color vision, while optic peri-neuritis may have NO evidence of optic nerve dysfunction. If the enhancement has intracranial extension and cranial nerves are also involved, this is idiopathic cavernous sinus inflammation and called Tolosa Hunt Syndrome.

Occasionally idiopathic orbital disease can be fibrotic and this type does not always respond to steroids.

Inflammations of the orbit are responsible for more cases of exophthalmos than are neoplasms [8]. Among adults, thyroid eye disease causes more unilateral and bilateral exophthalmos than any other disorder. Among children, orbital cellulitis probably produces exophthalmos more often than any neoplasm. Pseudotumors are idiopathic inflammations that resemble neoplasms and are often associated with exophthalmos and pain. The orbit is a common site of occurrence for a wide variety of other inflammatory disorders related to infections, trauma, and systemic disease.

Thyroid eye disease or ophthalmic Graves disease has been defined as multisystem disease of unknown etiology characterized by one or more of three pathognomonic clinical entities: Hyperthyroidism with diffuse thyroid hyperplasia, infiltrative dermopathy, and infiltrative ophthalmology. Histopathologic changes seen within the orbital tissues, which are not diagnostic, include a polytypic infiltrate, increased fibroblastic activity, glycosaminoglycan deposition, edema, and fibrosis.

Ophthalmic Graves' disease includes any of the orbital manifestations of this disorder. Thyroid eye disease appears in 30% to 70% of patients with Graves thyroid disease. Females are affected approximately four times more commonly than males. Orbitopathy may appear before, during, or after thyroid disease and is directly correlated with the level of endocrine dysfunction. Up to 25% of patients present initially to an ophthalmologist prior to detection of systemic disease. The most common finding among patients with thyroid eye disease is widening of the palpebral fissure, termed lid retraction. Lid "lag," or upper eyelid trailing behind the globe on downgaze, is another subtle finding of thyroid eye disease. The orbitopathy seems to be most severe in patients who are smokers, thus patients with signs of orbitopathy are given yet another compelling reason to eliminate smoking. The defining features on the clinical examination include proptosis, eyelid retraction, restrictive myopathy withdiplopia, and compressive optic neuropathy.

Lower eyelid retraction secondary to thyroid eye disease or prior lower eyelid blepharoplasty can be addressed by disinserting the lower eyelid retractors and employing a spacer graft between the tarsus and lower eyelid retractors [9]. Graft materials include hard palate, ear cartilage, sclera, or alloplastic materials. When using ear cartilage or sclera, the graft must be covered with conjunctival epithelium. Hard palate has the benefit of combining the structural

rigidity of tarsus with the mucous membrane epithelium similar to that of the conjunctiva. The biggest disadvantage of hard palate grafting is donor site morbidity. Preoperative fitting of a palate protector and postoperative oral viscous lidocaine (2 %) gel can be used to improve patient discomfort. Anesthesia during hard palate grafting can be obtained with a greater palatine nerve block and direct infiltration of the hard palate. Local anesthesia is injected by the greater palatine foramen, medial to the alveolar process by the third molar. The hard palate is composed of epithelium, lamina propria, and submucosa. Hard palate harvesting is done in the submucosal plane and the submucosa is removed from the graft before implantation. The area of the alveolar process and midline raphe are devoid of submucosa and should therefore be avoided. After harvesting the graft, the graft is rinsed in a 10 % betadine solution, a second set of sterile surgical instruments are opened, and the surgeon's gloves are changed in order to prevent contamination of the eye socket with oral bacteria.

The upper lid retractors comprise levator palpebrae superioris (LPS) and Muller's muscle [**10**]. LPS originates from the orbital apex and runs forward over superior rectus to the orbital rim. At this point, it is stabilized by the superior transverse ligament of Whitnall (a fascial bridge running between the trochlea and the lacrimal gland fascia) permitting the distal LPS to run steeply downward and insert as an aponeurosis into septum, tarsus, and orbicularis. Innervation is via oculomotor nerve (CN III).

Muller's muscle is an accessory retractor muscle supplied by the sympathetic system. Overaction is demonstrated in sympathetic overdrive and thyroid eye disease; underaction is seen in Horner's syndrome.

The lower lid retractors are more rudimentary but are similarly divided into voluntary and sympathetic groups.

Cellulitis

A patient with orbital cellulitis feels unwell and the most obvious physical signs are fever, proptosis, and ophthalmoplegia, with periorbital swelling and chemosis. Other features are reduced vision, desaturation of red, and raised IOP (intraocular pressure). The differential diagnosis includes thyroid eye disease, orbital myositis, idiopathic orbital inflammation (also termed orbital pseudotumor), granulomatosis with polyangiitis (GPA), leukemia, lymphoma, metastatic carcinoma, rhabdomyosarcoma, sarcoidosis, carotid-cavernous fistula, and cavernous sinus thrombosis. The features associating with the presentation with sinusitis are usually evident and an MRI scan of the orbits is likely to show a subperiosteal abscess on the

medial orbital wall. Treatment is with intravenous antibiotics according to local policy, and daily review of signs. Any progression of the signs may indicate the requirement for drainage of an abscess but the management is handled jointly between ENT and ophthalmology.

POP

POPs (Persistent Organic Pollutants) are fat-soluble [12]. They bioconcentrate within the fat of organisms such as fish, cattle, and polar bears, and they are biomagnified as they move from lower to higher trophic levels of food webs. POPs have become widely distributed across the globe, even in ecosystems such as the Arctic, far from where they were ever produced or used.

When POPs are widely distributed through ecosystems, human exposure is unavoidable. Measurement of population tissue levels of POPs has revealed nearly ubiquitous body burdens in human populations. Many of these chemicals are biologically active, affecting neurodevelopmental, endocrine, metabolic, and other delicately balanced systems in humans and animals. Consider the many chemicals collectively known as endocrine disrupters, which either block or activate receptors in sex hormones, thyroid, and other pathways. Synthetic organic chemicals that act in this manner include PCBs, bisphenols (e.g., bisphenol A, or BPA), organochlorine pesticides, brominated flame retardants, and perfluorinated substances (perfluorooctanoic acid, or PFOA, and perfluorooctane sulfonate, or PFOS).

Evidence suggests that these exposures play a role in several non-communicable diseases, through both epigenetic and non-epigenetic mechanisms. POPs exposure has been associated with metabolic conditions such as adiposity, insulin resistance, and dyslipidemias. The concept of chemical obesogens is well established. POPs exposure has also been associated with increased risk of some cancers, especially non-Hodgkin's lymphoma and hormone-responsive cancers such as those of the breast, ovaries, and prostate; to date, the animal evidence is more extensive than the human epidemiologic evidence. POPs may increase the risk of thyroid disease, neurobehavioral disorders, and reproductive dysfunction.

Management

Thyroid eye disease does not usually present as an emergency but is included here because rarely it can present with progressive diplopia and failing vision [**11**]. Thyroid eye disease is a

lymphocytic inflammation of the orbit associated with autoimmune thyrotoxicosis and is commoner in women but tends to be more severe in men and is aggravated by smoking. The orbit becomes progressively congested as the muscle hypertrophy, fat accumulates and glycosaminoglycans are laid down. Most patients are hyperthyroid biochemically.

The progression of symptoms is shown in the classification. Optic neuropathy is characterized by initial loss of contrast sensitivity then blurring and reduced VA, a field defect, RAPD, and disc edema. Visual loss is due to ION or arterial occlusion. Management involves controlling thyroid status. Smokers should be encouraged to stop as there is a strong link between smoking and disease activity. Lubricants and non-steroidal anti-inflammatories are helpful for mild cases, immunosuppression with steroids, steroid-sparing drugs or biologics are required for moderate cases, while severe disease requires high dose steroid, 500 mg/day methylprednisolone iv for 3 days, possibly combined with low dose external beam irradiation. There is a delay before the radiation has an effect and therefore it is of no value alone. If this treatment is not seen to be sufficiently effective, surgical decompression of the orbit is necessary in an attempt to avoid irreversible visual loss.

Today we also see a lot of corporate bodies making philanthropic commitments for various causes in society, and this is opening up the opportunity for eye care as well [**13**]. In some countries like India, this is mandated by law. Corporate social responsibility (CSR) is becoming an accepted deliverable, and many of the corporates are now subscribing to the philosophy of "Triple Bottom Line" – social, environmental (ecological), and financial. Probably as an outcome of the corporate involvement in the social sector and for other reasons, there is an emergence of the new type of funding called social impact funding or development impact funding. This vocabulary and the funding platform are still emerging with initiatives like "Social Impact Bonds" or "Development Impact Bonds". In this approach, funding is done towards measurable beneficial social impact or "results-based financing". Some of them expect a nominal financial return as well when there is a viable business model. In the case of eye care, for example, this could translate into funding "successful sight-restoring cataract surgeries". These are nascent times for this type of funding, though some eye care programs are negotiating funding under this paradigm. If this grows, which we hope it does, it will bring about the much-needed focus on quality, performance, and a much higher level of accountability.

Conclusion

The eye is very specific and partly unique organ in its composition because it contains parts that no other organ in the human body contains, such as the cornea, while on the other hand it

contains typical organ components such as connective tissue, blood vessels, nerves. Because of these similarities, the disease that affects certain organs, affects its symptoms and eyes.

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