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صدق الله العظیم

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Background And Historical Note

Thyroid-associated ophthalmopathy **(TAO)**, frequently called Graves ophthalmopathy, is an organ-specific autoimmune process that is strongly associated with dysthyroidism. The earliest recorded case of **TAO** may be Bodhidharma, also known as Daruma, who, in the sixth century, was the founder of Zen Buddhism and Kung Fu. In the medical literature, **TAO** was formally described by Graves in 1835 and by von Basedow in 1840. **TAO** may precede, coincide, or follow the systemic complications of dysthyroidism (***Perros*** *et al* .,1995).

An estimate made in 1993 showed that thyroid eye disease affects 400 000 people in the United Kingdom. This estimate is based on a UK population of 59million , a prevalence of Graves' disease of 1.85% (estimates range from 1%), and a prevalence of thyroid eye disease in Graves' disease of 37.5% (25% to 50%) for a sizeable minority thyroid eye disease is an extremely unpleasant, painful, cosmetically distressing, and occasionally sight threatening condition (***Bahn*** & **Heufelder** ,1993) .

Twenty percent of patients indicate that the ocular morbidity of **TAO** is more troublesome than the thyroid problems. It may result in eyelid retraction, proptosis, chemosis, periorbital edema, and altered ocular motility, with significant functional and cosmetic consequences (***Perros*** et al.,1995).

Although the muscles are enlarged on computed tomography **(CT)** scan, the myocytes themselves appear fairy normal histopathol-ogically.Formerly,decreased circulating suppressor T-cells and increased circulating autoantibodies against extraocular muscles were proposed as the mechanism of disease but this autoantibodies proved to be neither tissue nor disease specific (***Rizk*** et al.,2000).

It seems that the retrobulbar fibroblasts are playing a key role in the pathogenesis of Graves' ophthalmopathy. They secrete glycosaminoglycans which is the hallmark of Graves' ophthalmopathy. Furthermore, these cells can produce major histocompatibility complex class II, heat shock protein, and lymphocyte adhesion molecules. In addition, in a majority of patients with Graves' ophthalmopathy, autoantibodies against fibroblast antigen have been

found. It has been suggested that these cells act as target and effector cells in the Graves' ophthalmopathy (***Heufelder & Bahn*** ,1994).

The inferior rectus muscle is the most commonly involved followed by the medial rectus, superior rectus-levator complex, and lateral rectus. The physical examination reveals lid edema, retraction, chemosis, restricted extraocular motility, and proptosis.Although proptosis can be measured with various instruments (e.g., Hertle exophthalmo-meter), medical imaging is another way to provide objective measurements of proptosis. **CT** scan, furthermore, can demonstrate enlargement of extraocular muscles, crowding of the orbital apex, optic nerve swelling, and anatomical variation of the bony framework of the ethmoid sinuses(***Trokel & Hilal*** ,1979).

For soft tissue changes and to demonstrate the direct compression of the optic nerve at the orbital apex, magnetic resonance imaging **(MRI)** with its T_2 weighted sequence is more appropriate.Although most cases of **TAO** can be managed medically and without visual loss, it may result in vision-threatening exposure keratopathy and compressive optic neuropathy. As such, all clinicians should be able to recognize **TAO** (***Rizk*** , et al. ,2000).

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. Orbital decompression is indicated for patients who are resistant to medical treatment. Surgical decompression is still the primary therapy for sight threatening Graves' disease and is the most effective procedure for compressive optic neuropathy at the level of the orbital apex. By expanding the orbital confines it reduces intraorbital pressure, corneal exposure, proptosis, and optic nerve compression (***Rizk*** et al. ,2000) .

Historically, in 1911 Dollinger performed the first lateral orbitotomy for exophthalmos and subsequently other approaches were described by Naffziger, Sewall, and Hirsch, but the most popular surgical procedure was described by Walsh and Ogura in 1957 . They proposed a technique for

decompressing the orbital contents transantrally into the maxillary sinus and the ethmoid space. In 1990, Kennedy et al, first proposed to perform the Ogura technique transnasally under endoscopic guidance. The endoscopic approach allows for complete medial orbital wall decompression with excellent visualization of the key landmarks (***Kennedy*** et al. ,1990).

Epidemiology

The epidemiology of **TAO** has recently been reviewed, It is clinically relevant in approximately 50% of patients with Graves' disease. Two age peaks of incidence are observed in the fifth and seventh decades of life ,The natural history of Graves' ophthalmopathy is incompletely defined but in many instances, especially in mild forms, the disease may remit or improve spontaneously , The onset of the ophthalmopathy is in most cases concomitant with the onset of hyperthyroidism,but eye disease may precede or follow hyperthyrodism (***Wiersinga & Prummel***, 2001).

The disease may be unilateral or bilateral, may begin in one eye, or may always be more severe in one eye than in the other. Usually the syndrome accompanies hyperthyroidism and is at its worst when the diagnosis is first made. Infiltrative ophthalmopathy frequently occurs in patients with Graves' disease without clinical evidence for ophthalmic involvement. This was shown by the prevalence of increased intra-ocular pressure in 61% of such patients (***Gamblin*** et al.,1983) .

However, if more sophisticated techniques are used to detect infiltrative ophthalmopathy, for instance ultrasound, virtually all patients with Graves' disease, including those without clinical eye signs, show signs of extra-ocular infiltration (***Werner*** et al.,1977).

It was reported that measurements of proptosis in Graves' disease fit a normal distribution curve, but the curve is shifted to higher values. This finding suggests that the complication is not sporadic, but rather that all patients have it to some extent and that we clinically recgonize as unique those with the most severe symptoms (***Amino*** et al.,1980).

The course of thyrotoxicosis therapy has been evaluated in a study of 59 patients with Graves' hyperthyroidism and **TAO**, treated with antithyroid drugs but without any specific eye treatment. Eye signs improved substantially in 22%, to a minor extent in 42%, did not change in 22% and deteriorated in 14%, suggesting "spontaneous" improvement in 64% of patients (***Perros*** et al.,1995).

No more than 2 - 5% of patients with Graves' disease develop progressive severe exophthalmos. This progression often happens without a

clear correlation with the severity of stage of the thyrotoxicosis. In some of these patients, the process continues inexorably to complete blindness unless heroic therapeutic measures are taken, and sometimes despite these efforts (***Perros*** et al.,1995).

Although thyrotoxicosis occurs in women about five times more frequently than in men, progressive ophthalmopathy occurs relatively more frequently and is relatively more severe in men and increases with age. It is rare in children. Since exophthalmos usually improves with treatment of thyrotoxicosis, the patient should be restored to the euthyroid state as soon as possible and kept there (***Perros*** et al.,1995).

In treating the hyperthyroidism of these patients, it is important that they not be allowed to become hypothyroid later. Hypothyroidism seems to accentuate the signs and symptoms of the ophthalmopathy, possibly by increasing the water content of the tissues ***(Perros*** et al.,1995).

Risk factors:

Smoking:

Once a patient has Graves' disease, the major clinical risk factor for developing thyroid eye disease is smoking. Patients with thyroid eye disease are four times more likely to be smokers or former smokers than never smokers. 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. Cigarette smoking also increases the risk for progression of ophthalmopathy after radioiodine therapy ***(Vestergaard*** , 2002).

Age:

TAO mostly affects persons aged 30-50 years.Severe cases of **TAO** are thought to be more frequent in patients who are older than 50 years (***Bartley*** *et al.* ,1995).

Sex:

Women are five times more likely to be affected by thyroid eye disease than men, 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, and 3-5% of cases develop severe eye disease. Men older than 60 may be at increased risk of more severe disease ***(Bartalena*** et al., 2000)

Radioiodine:

Strong evidence exists that radioiodine, which is used to treat the hyperthyroidism, can cause a flare in thyroid eye disease, although some controversy remains as to what degree radioiodine worsens thyroid eye disease (***Manso*** et al.,1998).

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. Multiple genes are to be involved in the development of thyroid eye disease, and these interact with multiple environmental risk factors (***Farid & Marga*** , 2003).

Pathogenesis

A possible explanation is that the orbital antigen cross-reacting with a thyroid antigen might be located on eye muscle cells. A 64-kDa antigen shared by the thyroid and the orbit was reported by Salvi et al., but the role and specificity of this antigen have been questioned because of its expression in other tissues . Wall et al., reported that under nondenaturing conditions a 64-kDa protein, expressed in eye muscle cells but not in skeletal muscle, reacted with serum antibodies present in 67% of **GO** patients but not in patients with Hashimoto's thyroiditis or in controls (***Wall et al.,***1995)

The 64-kDa protein was partially sequenced and identified as the flavoprotein subunit of mitochondrial succinate dehydrogenase, with a corrected molecular mass of 67 kDa. Autoantibodies reactive with purified succinate dehydrogenase were detectable in 67% of patients with active **GO**, 30% of patients with stable eye disease, 30% of Graves' patients without clinically apparent ophthalmopathy, and 7% of normal subjects . It has been claimed that the appearance of these antibodies in the circulation might predict the subsequent development of **GO** (***Wall et al.,***1995)

Over the years many aetiological factors have been suggested for the development of **TAO**. Among others, these factors include genetic influence, immunological, hormonal, stress, smoking, and infections. Despite intense research over a long period, the pathogenesis of **TAO** is not yet fully understood (***Bahn*** , 2000)

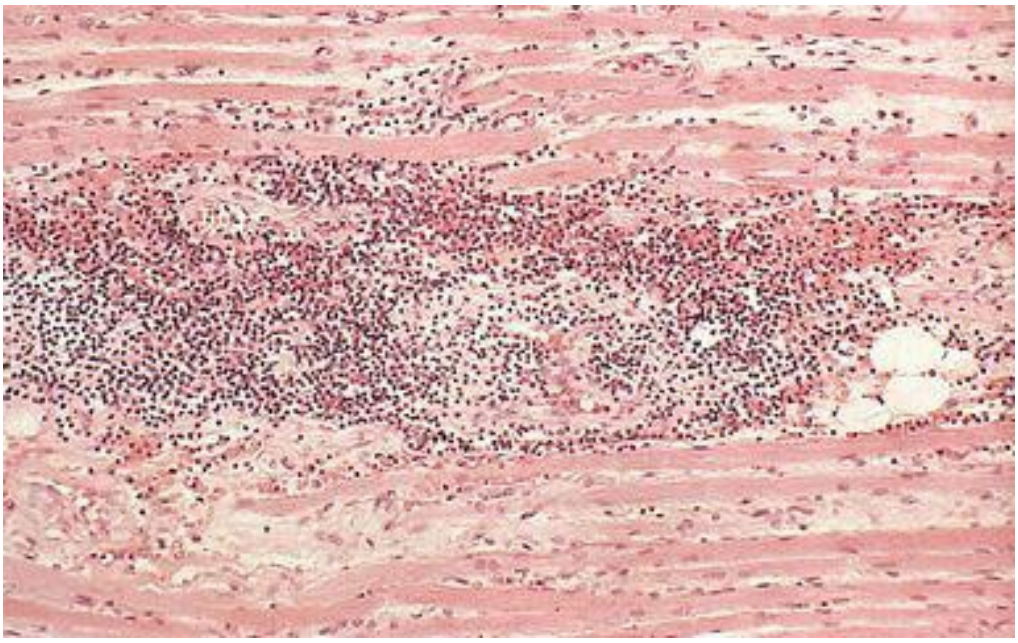
It is generally believed, however, that **TAO** is foremost the result of autoimmune reactions in the orbit, and that the thyrotropin **(TSH)** receptor is the most likely candidate auto antigen. The disease affects several cell types in the orbit (primarily fibroblasts and adipocytes and secondarily myocytes (***Bartalena et al.*** 2000)

In the early stages of **TAO**, cell mediated immune reactions dominate the process while humoural autoimmunity probably becomes more important in later stages. In severe and active **TAO** there is an accumulation of hydrophilic glycosaminoglucans **(GAGs)** and an infiltration of immunocompetent cells, especially macrophages and T-lymphocytes. The accumulation of **GAGs** leads to thickening of extraocular muscles as well as retrobulbar fat and connective tissue (***Valyasevi et al***. 2001).

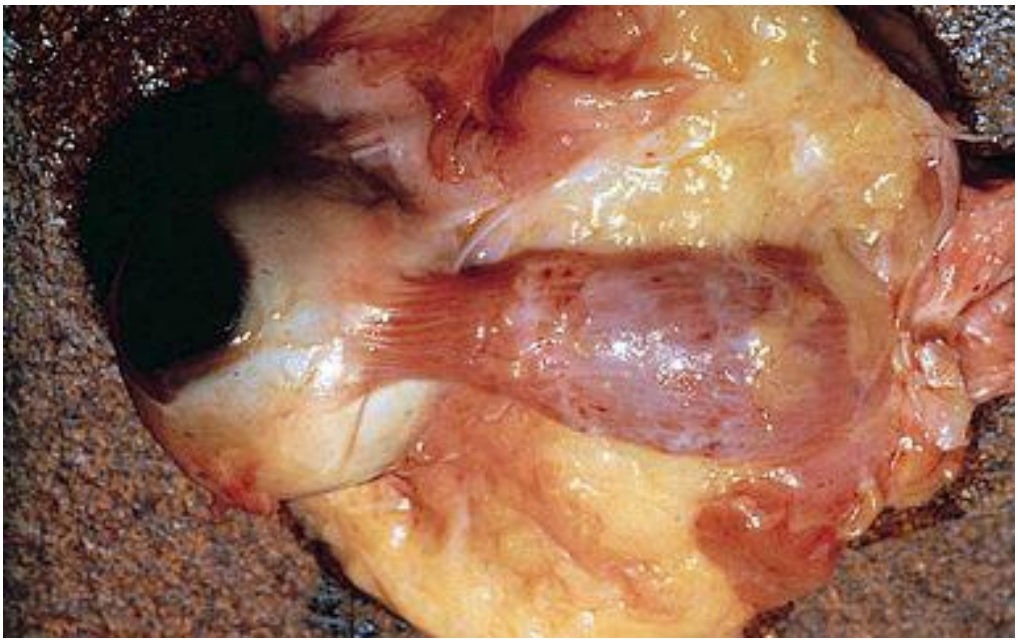
Even though the extraocular muscles enlarge, the muscle fibres are initially intact, but may, in later stages, become fibrotic. Activated T-cells produce different cytokines including interferon-γ, tumour necrosis factor-α **(TNF-α)** and interleukin − 1α. These cytokines stimulate the proliferation of orbital fibroblasts and their production of **GAGs** but **TNF**-α and interferon-γ may also inhibit the differentiation of orbital fibroblasts into adipocytes as well as the expression of the TSH receptor (***Valyasevi et al***. 2001).

It was found in a small series of patients with **TAO** , that the expression of messenger RNA (mRNA) for TSH-R , the pro-inflammatory cytokines interleukin − 1b , interleukin − 6 , interleukin − 8 and interleukin − 10 , and the T-helper-1 derived cytokine interleukin − 2 to be significantly higher among patients with active disease . With further research, it is possible that cytokines or cytokine antagonists can become part of the therapeutic battery in **TAO** (***Wiersinga & Prummel*** 2001).

Many studies have shown a relationship between cigarette smoking and Graves' thyreotoxicosis. Smokers are also over-represented among those who develop **TAO** and are prone to more severe **TAO** than non-smokers. Cigarette smoking may also reduce the effect of retrobulbar irradiation and systemic glucocorticoids.The exact mechanisms for these effects are still unclear (***Eckstein et al***. 2003).



figuer 1 : simpel microscopic examination (x 25) of Extraocular muscle from a patient with Graves' disease and infiltrative ophthalmopathy **(Wiersinga & prummel ,** 2001 **) .**



figuer 2 : postmortam end stage in severe involvement of extraocular muscles in ophthalmopathy **(Wiersinga & prummel ,** 2001 **) .**

Clinical picture

Noninfiltrative Ophthalmopathy :

Almost all patients with active thyrotoxicosis have some abnormality that is detectable on careful examination of their eyes. This abnormality may be only widening of the palpebral fissure, lag of the globe on upward gaze, or lag of the upper lid on downward gaze, producing an increase in the visible segment of the sclerae and a bright-eyed or pop-eyed appearance (***Lee*** et al.,1961).

These abnormalities cause the eyes to appear exophthalmic, but measurement may show that there is no proptosis. Similar changes may be produced by administration of thyroid hormone or by local action of sympathetic stimuli on Müller's superior palpebral muscle, causing spasm and retraction of the upper lid (***Lee*** et al.,1961).

This variety of ophthalmopathy is valuable diagnostically, and although it may have some undesirable cosmetic effect, it carries no hazard to ocular function (***Lee*** et al.,1961).

Infiltrative Ophthalmopathy :

Infiltrative ophthalmopathy is considered a characteristic and unique feature of Graves' disease. It may coexist with the noninfiltrative ophthalmopathy described above, but it is a separate disorder. Paralysis, or paresis, of the extraocular muscles occurs. Upward gaze is affected first and most seriously; and loss of convergence is common (***Sommer*** et al.,1993).

Oculomotor paralysis may be severe when exopthalmos is minimal or absent, but the changes are usually more or less parallel. These changes in ocular muscle function often initially produce diplopia. As the lesion progresses, a permanent strabismus may develop, with coincident suppression of the visual image in one eye and loss of the diplopia. Oculomotor function is occasionally lost completely (***Sommer*** et al.,1993).

The initial inflammatory lesion is followed gradually by recovery and fibrosis, and often the scarred and fibrotic muscle causes a fixed strabismus