TOBACCO SMOKING IN HYPERTHYROID EYE DISEASE

Thesis

Submitted for Partial Fulfillment of MS Degree in Ophthalmology

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تدخين التبغ ومرض العين المصاحب لإفراط الغدة الدرقية

رسالة بحثية

توطئة للحصول على درجة الماجستير
في طب و جراحة العيون

مقدمة من

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INTRODUCTION

Thyroid eye disease (TED) is the most frequent extra-thyroidal manifestation of autoimmune hyperthyroidism. It is clinically relevant in approximately 25 - 50% of patients with Graves' disease (GD), with the severe forms affecting 3% -5% of patients. [(1)] The key pathological features of TED within the orbit are inflammation, excess production of glycosaminglycans (GAG) and adipogenesis. These processes are thought to be driven at least in part by the local release of inflammatory cytokines. [(2)]

The hallmark of TED is increased size of extraocular muscles and retrobulbar fat which have been associated with inflammatory cytokines and excessive glycosaminoglycan (GAG) secretion. Current evidence suggests that orbital fibroblasts (OF) play a key role in the pathogenesis of TED. Previous studies have demonstrated that hypoxic culture conditions not only enhance GAG production but also protein and DNA synthesis in extraocular muscle fibroblasts from healthy individuals. These extraocular muscle fibroblasts are capable of secreting inflammatory cytokines, which are believed to play important roles in the pathogenesis of TED. [(1)]

The incidence and prevalence of GD is 0.1% and 1% respectively in population. The clinical signs include widening of the palpebral fissure, eyelid retraction, lid lag, conjunctival congestion, chemosis, proptosis, corneal exposure, restrictive myopathy and optic neuropathy. In the majority of cases; the ocular manifestations are mild. Severe form of the disease affects 3% to 5% of individuals. [3]

The etiology of TED is complex. Genetic susceptibility, endogenous and environmental factors play a role in its development. The genetic factors are poorly defined and play a minor role. The risk of developing TED increases with age. Women are more likely to develop GD than men. The strongest modifiable risk factor for developing TED is smoking. [4]

Several studies have confirmed that smoking can influence the occurrence and the course of TED and also impairs responsiveness to treatment such as orbital radiotherapy and steroids. [1]

AIM OF THE WORK

It is to assess the incidence of tobacco smoking among patients with hyperthyroid eye disease.

CLINICAL MANIFESTATIONS OF TED

Common Symptoms Of TED

The most common initial symptom of TED is a change in appearance. In over 70% of the patients, this is due to lid retraction, with or without proptosis or periorbital swelling. [5, 6] During early stages of TED, 40% of patients also develop symptoms that relate to ocular surface irritation comprising a gritty sensation, light sensitivity (photophobia) and excess tearing. [7, 8] Double vision is a less common initial symptom but when it develop, it is usually first noticed either on waking, when tired, or on extremes of gaze, sometimes accompanied by aching. [5, 8, 9]

Orbital ache unrelated to gaze is less common but can occur with severe orbital congestion. [10] Only about 5% of patients report visual symptoms such as blurring of vision, which may be either patchy or generalized, or alteration in colour perception. [5, 8] These latter are potentially significant markers of dysthyroid optic neuropathy (DON) and as they may not be volunteered, they should be specifically elicited from all patients with progressive or otherwise symptomatic disease. [8]

Episodes of proptosis (where the eyeball protrudes in front of the eyelids) are extremely alarming for both patient and any witnesses, but fortunately affect only 0.1% of patients. [11]

Common Signs Of TED

Although TED can present with a number of clinical signs, it is very unusual for a patient to present with all of them. [12]

The most frequent sign is of upper eyelid retraction ***(Fig. 1A)***, which affects 90–98% of patients at some stage [6, 12] and frequently varies with attentive gaze which can be moderate lid retraction (Dalrymple sign) ***(Fig. 1B)*** or sever lid retraction (Kocher's sign) ***(Fig. 1C)***. [13] Indeed, if upper eyelid retraction is absent then it is appropriate to question the diagnosis [13] and imaging should be required. The contour of the retracted upper eyelid often shows lateral flare [14], an appearance that is almost pathognomonic for TED. The excursion of the upper eyelid often lags behind eyeball movement on vertical downward pursuit (lid lag) (Von Graefe sign) ***(Fig. 1D)*** and remains high.[14]

Other extremely common signs include the soft tissue signs of periorbital swelling and redness, conjunctival swelling and redness and prominent glabellar rhytids. [12]

Proptosis (also known as exophthalmos) is also very frequent and correlates significantly with lower lid retraction [15]; those patients are more likely to show incomplete eyelid closure (lagophthalmos). Many patients, especially those with a wide palpebral fissure will show punctate inferior corneal staining with fluorescein. [15, 16] Most patients presenting to tertiary

centers show restriction of ocular excursions in one or more directions of gaze ***(Fig. 2)***.

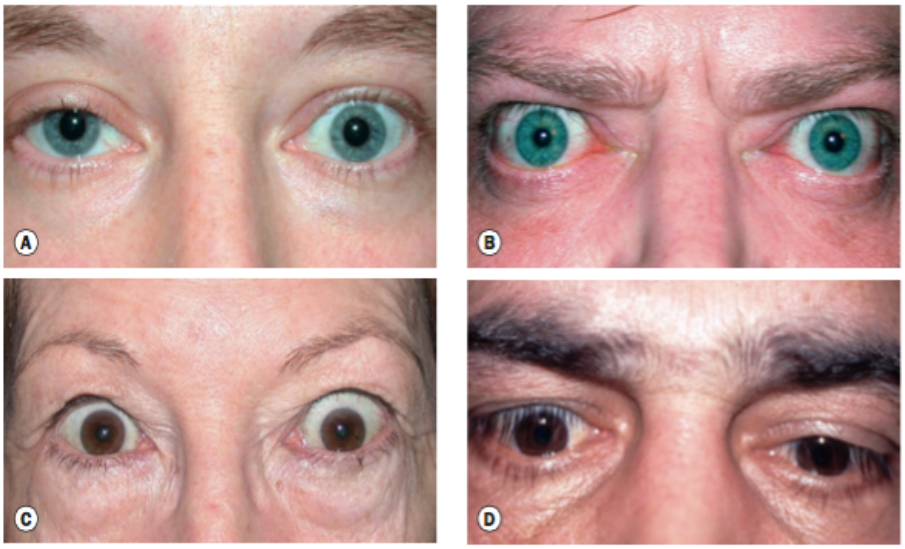

Fig. (1): Lid signs in TED. (A) Mild left lid retraction. (B) Moderate bilateral symmetrical lid retraction – Dalrymple sign. (C) Severe bilateral lid retraction – Kocher sign. (D) Right lid lag on downgaze – von Graefe sign. [17]

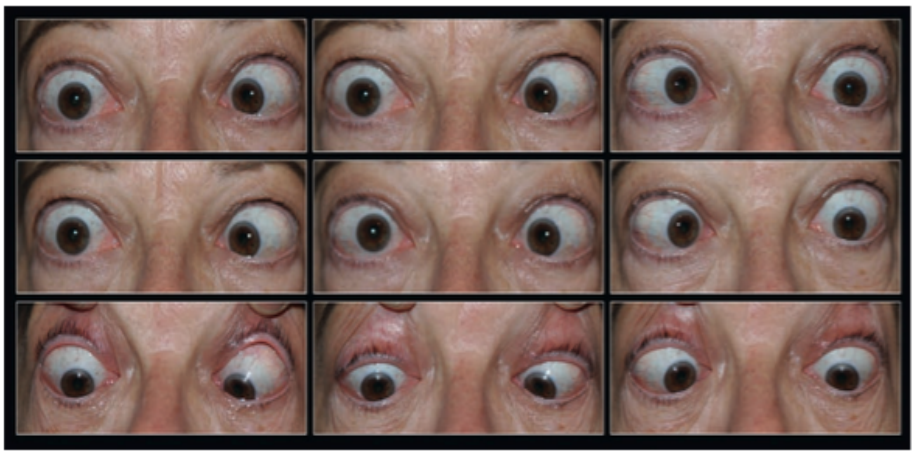

Fig. (2): Restrictive myopathy and bilateral lid retraction in TED – nine positions of gaze. [17]

Unusual Signs Of TED [18]

Less common soft tissue signs include superior limbic keratoconjunctivitis and inflammation of the caruncle and/or plica. It is also unusual to detect signs of DON as this secondary phenomenon of severe disease only affects around 5% of clinical TED. However, detecting subtle evidence of DON is very important and any reduction in corrected vision or colour vision should be elicited. If DON is significantly asymmetrical (30%) then an afferent pupillary defect will also be apparent.

Sight-threatening corneal ulceration is far less common than DON but presents as an area of corneal staining, sometimes with thinning or abscess and very occasionally perforation. Corneal ulceration can only develop when normal corneal protection is lost. This occurs in those patients who not only cannot close their eyes, but whose cornea remains visible when the eyelids are closed due to absent Bell's phenomenon, the normal protecting upward movement of the eyeball. [18]

Although this reflex is absent in 10% of individuals, it is more likely to be lost in TED due to a very tight inferior rectus limiting the upward excursion of the eyeball. It is not known whether patients with extreme eyelid retraction are at greater risk of ulceration, but it is clear that sight-threatening ulceration can develop in patients without severe eyelid retraction. [18]

Although ptosis can develop following longstanding TED, it is very rare for patients to present with ptosis early in the course of their disease: such patient may have concomitant myasthenia gravis and should be appropriately investigated. [18]

Similarly, divergent strabismus does occasionally occur with TED but so rarely that the diagnosis should be questioned and further investigations are required. [18]

The Variability of the Clinical Presentations of TED [14]

It is not fully understood why some patients develop one pattern of tissue involvement while others show a different pattern. However, some differences are likely to be due to anatomical variation: the secondary sequelae of TED relate to the interaction between the degree and speed of onset of the inflammation and the anatomical constraints of the orbit, which are at least in part racially determined. It is clear that there is premorbid variation in the relative position of the globe within the orbit and in the laxity of the orbital septum.

It is also known that muscles are asymmetrically involved. While the majority of patients show some muscle involvement on imaging, less than 10% of patients appear to have normal muscle dimensions with expansion of only orbital fat. This can still lead to proptosis; however, restriction of eye movements is uncommon and when it occur, it is diffuse rather than localized to one or several muscles.

A Short Mechanistic Explanation for the Clinical Manifestations of TED

When inflammation develops in orbital soft tissues, particularly muscle and fat, hydrophilic GAG are produced which promote further tissue swelling. Similar inflammation in the eyelids causes visible edema, erythema and festoons. These are the primary effects of TED and when they affect the muscles, they commonly lead to dysfunction due to a failure of relaxation. This limits movement into the field of the ipsilateral antagonist which if asymmetrical causes double vision. [14]

Unfortunately, the orbit is a tight space which is completely surrounded by bone except anteriorly. Here, instead of bone, there is a fascial sheet extending across the top and bottom of the orbital opening which is known as the orbital septum (OS). The OS limits anterior movement of the orbital contents to a greater or lesser extent. Patients with orbital tissue swelling and a very tight OS cannot develop significant proptosis, but instead will experience a marked rise in intraorbital pressure. Secondary effects of TED may then ensue ***(Fig. 3)***, with pressure on the optic nerve leading to loss of vision, colour impairment and altered pupil responses. In contrast, patients with equivalent intraorbital soft tissue swelling but with a lax OS will 'self-decompress' to develop proptosis (another secondary manifestation) but less rise in

intraorbital pressure. This is the reason that clinicians should be particularly alert to the risk of DON in patients with muscle restriction but without proptosis. [14]

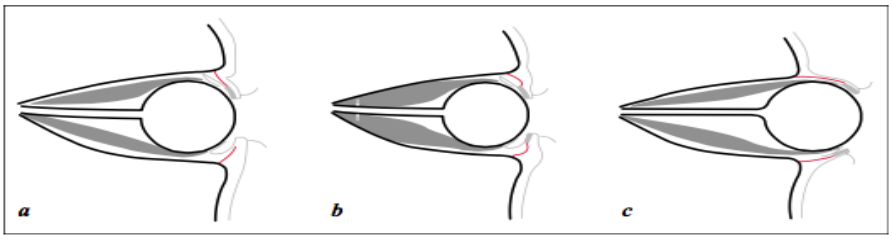

Fig. (3): Diagrammatic representation of secondary effects of TED. Secondary effects depend partly on the laxity of the orbital septum shown in red. (A) Normal relationships of structure within the orbit. (B) Gross compression of the nerve (white arrows) caused by increased orbital muscle volume unaccompanied by significant proptosis: therefore high intraorbital pressure. (C) Gross self-decompression. Stretching may compromise the optic nerve. [19]

Upper eyelid retraction is multifactorial [8, 15, 20] and due to a combination of increased sympathetic stimulation of Müllers muscle, contraction of the levator muscle due to its direct involvement and scarring between the lacrimal gland fascia and levator which specifically gives rise to lateral flare [14]. In addition, tight restriction of the inferior rectus leads to upper eyelid retraction regardless of upper eyelid pathology. [15]

In contrast, lower eyelid retraction correlates with proptosis and may be better described as lower eyelid displacement as no evidence of direct involvement of the lower lid retractors currently exists. [14]

All corneal signs of TED are secondary phenomena of TED. A wide palpebral aperture leads to increased tear evaporation that combined with poor blinking causes superficial punctate erosions and the symptoms of surface irritation. [16] The mechanism for corneal ulceration arises from lagophthalmos and corneal exposure, due to proptosis, lower lid retraction and/or poor levator function, usually accompanied by a tight inferior rectus. [8]

Racial Differences in TED Manifestations

TED can affect people of all races. Genetic susceptibility to GD varies between races [21], and there is some evidence that amongst patients with GD, susceptibility to TED also varies between races. For example, Europeans appear more likely to develop TED than Japanese Asians. [22] There is very little data on racial differences in both prevalence and presentation of TED and the influence of important confounding factors such as smoking needs to be considered. [19]

There is significant variation in normal exophthalmometry values between races [23], with Chinese Asians showing significantly lower values than Caucasians [24], while Negroes have relatively shallow orbits and show higher values. Hence proptosis should be assessed in relation to the normal range for the patient's race. [24]

The Difference in Presentation of TED in Older Compared to Younger Patients

There are some important differences in the presentation of TED at different ages and a tendency for overall severity to increase with age, regardless of gender. [25]

Children and teenagers with GD appear as likely as adults to develop TED, particularly in countries where teenagers are more likely to smoke. However, unlike adults, they rarely develop severe disease and the majority will require no specific treatment. [7, 26] They commonly show a degree of eyelid retraction and mild proptosis but rarely show muscle restriction, corneal ulceration or optic neuropathy [7].

By contrast, some data suggest that patients over 50 years of age are more likely to have impaired motility than those under 50 (32% vs. 12%, respectively) with greater limitation in upgaze [5] while others show no such difference. [25] However, studies consistently show a significantly higher risk of optic neuropathy with age. [5, 18] This may relate at least partly to a higher prevalence of concomitant vascular disease in older patients. [18]

Older patients are also more likely to have unilateral or very asymmetrical disease and are more likely to be euthyroid or hypothyroid at time of presentation. [5]

SCORING AND ASSESSMENT OF SYMPTOMS AND SIGNS OF TED

Activity and Severity

During the course of TED, the disease passes through several phases. From the onset, the first phase involves worsening of symptoms and signs often with visible evidence of inflammation followed by a plateau phase during which no further deterioration occurs. A phase of gradual improvement follows until eventually no further change occurs, although permanent abnormalities in both function and appearance may remain. [8,27]

The 'severity' of TED describes the degree of functional or cosmetic deficit at any stage. [8, 27] What is now apparent is that the first three phases represent a time during which there is inflammation and these are known as the 'active' phases of TED. Hence 'activity' refers to the presence of inflammation. In contrast, the final stage is not accompanied by further spontaneous change as any inflammation has probably resolved and this is therefore referred to as the inactive phase of TED [8, 9, 19]***(Fig 4)***.