Graves Eye Disease Medical and Surgical Management: A Review

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Abstract

Graves' disease (GD) is the most frequent cause of hyperthyroidism, where iodine levels are abundant.

One of the extrathyroidal symptoms is Graves' ophthalmopathy (GO) which presents with ophthalmic symptoms that can range from minor (e.g., dry eye) to sight-threatening (e.g., corneal ulceration and compressive optic neuropathy) features.

About 79% of Graves' disease cases can be attributed to genetic predispositions, while the remaining 21% are due to environmental factors. Acute stress, active or passive smoking, and past radioactive iodine therapy have all been linked to the development or aggravation of thyroid eye disease (TED).

The devastating effects of GO or TED might include diplopia, ocular hypertension, optic nerve degeneration, and glaucoma.

A low basal serum Thyroid Stimulating hormone (TSH) level has the highest sensitivity and specificity for diagnosing hyperthyroidism. Moreover, the appearance of Thyroid Stimulating hormone receptors (TSHR) autoantibodies (TRAbs) is presumed to be highly specific for the diagnosis of Graves' disease.

Imaging studies of the orbit that use ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), for example, can confirm the diagnosis of TED.

In order to treat Graves's eye disease optimally, a multidisciplinary approach must be applied involving primary care physicians, ophthalmologists, internists and endocrinologists. Therefore, it is essential to restore the euthyroid state and this can be obtained by either antithyroid medications, radioactive iodine or surgical thyroidectomy.

Treatment of GO ranges from supportive treatment (lubricants and moisturizer drops), to medical intervention, preferably corticosteroid, and variable surgical interventions.

Key words: Graves' disease,
Medical and surgical management

List of abbreviations:

GD: Graves disease
TED: thyroid eye disease
GO: Graves ophthalmopathy
TSH: thyroid stimulating hormone
TSHR: thyroid stimulating hormone receptors
TRAbs: Thyroid receptors autoantibodies
CT: computed tomography
MRI: magnetic resonance imaging
RAI: radioactive iodine
ATD: Antithyroid drugs
HLA: human leukocyte antigen

Introduction

Graves' disease (GD) is the most frequent cause of hyperthyroidism, where iodine levels are abundant. The existence of antibodies against the TSH receptor is termed TSH receptor antibodies (TRAb) [1]. The incidence of GD is approximately 40/100,000 per year [2]. Women are more likely than men to have GD, and individuals aged between 30 and 50 years are most commonly affected. Extrathyroidal symptoms such as Graves' ophthalmopathy (GO), thyroid dermopathy, and acropachy may also be present in addition to hyperthyroidism [3].

The development of this autoimmune illness is influenced by both genetic and environmental factors. Antithyroid drugs (ATDs) are the mainstay of medical treatment for GD [4,5]. However, thyroid ablation, either thyroidectomy or radioiodine (RAI) treatment, is necessary in around half of cases due to the high recurrence rate of hyperthyroidism. The devastating effects of GO or thyroid eye disease (TED) might include diplopia, ocular hypertension, optic nerve degeneration, and glaucoma. A patient's quality of life may be negatively impacted by even mild TED [7]. Although TED is more common in younger women, studies suggest that men and older people are at a higher risk of developing this serious illness [8]. Those with unstable thyroid function or specific anatomical features of the orbit, such as a larger lateral orbital wall angle, are also more likely to develop TED [9]. Acute stress, active or passive smoking, and past radioactive iodine therapy have all been linked to the development or aggravation of TED [10,11].

The current review article aims to summarize recent advances in our understanding of the pathophysiology of GD and clinical considerations for diagnosing, prognosticating, and treating GD patients [6].

Methodology

A review of the literature was performed to find scholarly publications about TED through a systematic web search. Multiple keywords, including epidemiology, etiology, pathophysiology, clinical features, diagnosis, medical and surgical interventions of TED, were used to search in research databases Google Scholar and PubMed. Among 84 articles retrieved (published between 1988 and 2021), 48 articles were included in the study. Articles were excluded if they are not directly linked to the research topic. Duplicates were also removed after the final retrieving process.

The Review of Literature

Graves' Disease Epidemiology

Graves' disease is the leading cause of hyperthyroidism. Many studies have examined the incidence of hyperthyroidism, but only a few assessed Grave's disease as a cause of hyperthyroidism. Graves' disease is caused by an immune system malfunction, which fights diseases in the body. About 79% of Graves' disease cases can be attributed to genetic predispositions, while the remaining 21% are due to environmental factors [12]. Common environmental risk factors include vitamin D and selenium deficiency, smoking, and changes in iodine levels. The repletion of iodine in the body can significantly increase its incidence, but the long-term changes in iodine level are not considered a risk factor. It is also believed that stress and pregnancy may increase the risk of developing Graves' disease [12].

Statistics indicate that Graves' disease affects about 40 in every 100,000 people yearly, with an estimated prevalence of 0.4%. However, these statistics are from the retrogressive analysis of available medical records. Hence, these figures may be underestimated and not representative, as patients with mild symptoms are often undiagnosed. The prevalence of Graves' disease is higher in women than men. Its prevalence in the United States was about 0.4% in the 1970s. A United States survey found Graves' disease to be more common among Caucasians than other races [13]. Research conducted in the United Kingdom showed a prevalence rate of about 1.1% to 1.6%. As far as demographics are concerned, people can be affected at any age, but its prevalence is higher between the ages of 30 and 50 years.

The prevalence of Graves' disease is fairly evenly distributed across the globe; however, its incidence is higher in areas with rich iodine consumption, such as India. A recent population study in India indicated that 16.7% of the population suffered from Graves' disease, with those with metabolic syndrome accounting for more than 40%. The same study also indicated that the prevalence was higher in women than in men [14].

Epidemiology of Thyroid Eye Disease (TED)

Graves' ophthalmopathy is a complex inflammation disease of the orbit. Most patients with TED have a biochemical indication of hyperthyroidism, with Graves' disease being the most common. Thyroid eye disease affects about 16 in 100,000 people among women and 3 in 100,000 men, with an average prevalence of about 0.25% [15]. There is no defined ethnic predisposition of TED. The high incidence of TED among women can be attributed to the higher incidence of hyperthyroidism disease among women; however, the disease severity is more pronounced among men [15].

Common risk factors of TED include the female gender, smoking, young age, and hyperthyroidism. The treatment of hyperthyroidism using radioiodine is also a risk factor. The presence of other autoimmune thyroid illnesses can account for up to 15% of the total TED diseases; however, genetic factors are the main risk factors, especially for people with susceptibility alleles [15]. TED usually manifests itself at the beginning of hyperthyroidism and could take five years of treatment. A significantly small proportion of patients have no history of hyperthyroidism. Research shows a decrease in the prevalence in the last two decades, but little justification exists [16]. It is challenging

to determine the definitive prevalence of the TED disease due to insufficient data. However, a study conducted in Olmstead County in the United States showed a bimodal peak for men and women aged between 40 and 44 years and 60 and 64 years. The same study also indicated that about 50% of the patients with Graves' disease have clinically apparent TED [17].

More than 66% of the patients will experience TED either six months before the onset of thyroid disease, or thyroid dysfunction. The natural history of TED consists of two phases; the active inflammatory stage and the static stage. The active inflammatory stage is the first phase; the static stage follows. Only about 5% of TED patients have a late reactivation. Despite TED having no ethical depositions, people of Asian origin tend to have mild manifestations compared to Caucasians [18].

Pathophysiology of GD and GO:
It is widely acknowledged that GD has a substantial hereditary component, with genetic factors playing a key role. Several investigations have established that the main genes causing GD include human leukocyte antigen (HLA), CD40, CTLA-4, PTPN22, Tg, and TSHR. On chromosome 6, the HLA complex contains sequences that code for genes important in controlling the immune response [6]. The involvement of the central tolerance, which is impacted by the production of self-antigens (such as TSHR) within the thymus for negative selection of autoreactive T cell clones, is another factor in the genesis and pathophysiology of GD. Polymorphisms of certain tissue-restricted genes that encode autoantigenes might affect their degree of expression in the thymus, becoming a risk factor for autoimmunity [19,20].

As a component of GD, Graves' ophthalmopathy (GO, often referred to as Graves' orbitopathy) is an autoimmune inflammatory disorder [21]. There are several risk factors for GD-related GO. GO is more prevalent in women than men, and the risk of developing severe GO seems to be higher in males with GD [22]. Moreover, there are ethnic disparities in the frequency of GO, with Asians being less likely than Caucasians to contract the disease [23]. Moreover, the aforementioned hereditary variables are relevant, and smoking is a significant additional risk factor [24]. The activation of autoantibodies to thyroid stimulating hormone (TSH, thyrotropin) receptors (TSHR) appears to be the triggering event in thyroid eye disease, despite the complex underlying molecular mechanisms [25,26]. TSHR is overexpressed in the retrobulbar tissue of Graves' and hyperthyroidism patients compared to controls, especially in orbital fibroblasts, which are crucial to the pathophysiology of thyroid eye disease [21,25,27,28].

Orbital fibroblasts multiply and produce pro-inflammatory cytokines and hydrophilic hyaluronan in the interstitial space when activated [21,25,27]. These mechanisms cause a high osmotic pressure gradient in the orbit, causing greater fluid collection between the muscle fibers. Moreover, some orbital fibroblasts develop into mature adipocytes, resulting in orbital adipose tissue growth [26–28]. This cycle continues, and orbital congestion may result [21,27]. Long-lasting edema causes fibrosis, sclerosis, and the extraocular muscles to atrophy, resulting in restricted strabismus [29].

Clinical Features

Clinical symptoms are linked to both the autoimmune and hyperthyroidism processes. The signs and symptoms of GD can vary greatly and significantly impact general health since excess thyroid hormones affect many different body systems. Tremors, heat sensitivity and warmth, weight loss despite regular eating habits, anxiety and irritability, goiter, and changes in menstrual cycles are common symptoms [30]. Ophthalmic symptoms can range from minor (e.g., dry eye) to sight-threatening (e.g., corneal ulceration and compressive optic neuropathy) problems, and treatment can range from supportive (e.g., lubrication of the ocular surface) to surgical (e.g., orbital decompression) approaches. Due to various clinical presentations, various disorders, such as allergic conjunctivitis and orbital tumors, are included in the differential diagnosis [31].

The devastating effects of GO and TED might include diplopia, ocular hypertension, optic nerve degeneration, and glaucoma [7]. Lid retraction, proptosis, soft tissue edema, strabismus, and compressive optic neuropathy are some of the clinical signs and symptoms of GO. The globe is pushed forward by the enlarged soft tissues inside the bony orbit, which also prevents venous outflow from the orbit. The adipogenesis and glycosaminoglycan buildup that follows the local fibroblasts' activation due to inflammation, causes enlarged soft tissues. Furthermore, lymphocyte infiltration and tissue remodeling are seen in the GD orbital symptoms, which might lead to fibrosis [32].

Diagnosing Graves' Disease

A low basal serum TSH level has the highest sensitivity and specificity for diagnosing hyperthyroidism and should, therefore, be used as an initial screening parameter. However, if Graves' disease is strongly suspected, diagnostic accuracy improves when serum TSH, free T4, and free T3 are also assessed [33]. Moreover, the appearance of TSHR autoantibodies (TRAbs) is presumed to be highly specific for the diagnosis of Graves' disease. Therefore, the diagnosis is usually confirmed by demonstrating elevated TRAbs [34].

Imaging studies of the orbit that use ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), for example, can confirm the diagnosis of TED while excluding other diagnoses such as orbital tumor and idiopathic orbital inflammation (previously known as orbital pseudotumor). Computerized tomography without contrast remains the standard radiographic technique because of its ability to display the bony anatomy of the orbit and its low cost relative to MRI [35].

In ultrasound research, Graves' disease is usually characterized by hypoechoic and heterogeneous parenchyma, diffusely enlarged, and hypervascularity. In

contrast, Technetium-99 (99Tc) scanning of the thyroid is limited in diagnosing GD due to the high sensitivity and specificity of TRAb measurement [36,37].

Diagnosing Graves' Ophthalmopathy

The diagnosis of TED is straightforward based on the clinical history and physical examination of patients. Ophthalmic manifestations are present in up to 50% of Graves' hyperthyroidism patients [25]. TED follows a biphasic course: a progressive or active phase lasting up to three years, followed by a stable or inactive phase [26]. Ophthalmic manifestations can vary from mild (for example, dry eye) to sight-threatening (for example, corneal ulceration and compressive optic neuropathy) problems.

There is no single clinical finding or laboratory test that can diagnose TED. Frequently, the presenting symptoms are non-specific dry eye complaints, such as foreign body sensation, redness, blurring of vision, photophobia, glare, or excessive tearing [3,21]. However, there are many additional symptoms, including concern about cosmesis, retrobulbar discomfort, swelling of the eyelids worse in the morning, diplopia, and uncommon loss of vision [38, 39]. Common clinical signs are upper eyelid retraction, conjunctival and caruncle injection and/or edema, eyelid edema and/or erythema with diurnal variation, ocular motility disruption, or strabismus and proptosis [38,40].
Paradoxically, upper eyelid ptosis can also be a presenting sign of TED [41]. The clinical evaluation for TED focuses on determining clinical activity and severity by assessing visual acuity, pupils, color vision, extraocular movements, visual field, exophthalmometry, external eyelid evaluation, slit-lamp examination, and dilated fundus examination.

Medical and surgical treatment of Graves eye disease

Managing thyroid disease:
In order to treat Graves's eye disease optimally, a multidisciplinary approach must be applied involving primary care physicians, ophthalmologists, internists and endocrinologists [42, 43]. Therefore, it is essential to restore the euthyroid state and this can be obtained by either antithyroid medications, radioactive iodine or surgical thyroidectomy[40]. Some reports have shown that Radioactive iodine may result in the development or aggravation of thyroid eye disease by 15-20% in those who are smokers [44]. These adverse effects could be minimized by using oral corticosteroids post-radioactive iodine [43,45]. Smoking is a known risk factor for the progression of thyroid eye diseases [46,11]. Smoking cessation is considered one of the most important modifiable risk factors in the prevention of thyroid eye disease [47]. Therefore, it is advised for the patient with thyroid disease to stop smoking [42,48].

Graves eye disease treatment

Supportive treatment:
Some mild cases of graves eye diseases can be managed conservatively, for patients with dry eye manifestation, lubricants and moisturizer drops could be used [26]. Sunglasses are recommended to minimize photosensitivity and glare. For eyelids retraction, botulinum toxin injections could be used on the levator palpebrae superioris and Muller's muscles [31].

Medical treatment:
For patients with moderate to severe Graves' eye disease, corticosteroid is the mainstay treatment option. Almost 80% of patients on high intravenous corticosteroid show improvement in their condition in comparison to oral steroid which is less effective and with more side effects [31]. An immunosuppressive agent such as rituximab has shown some potential in the treatment of thyroid eye disease. However, some studies reported conflicting results [31].
Selenium supplementation has been shown to have the potential to improve the quality of life and reduces the severity and progression of thyroid eye disease [31].

Surgical treatment
When there is a significant impact on visual function or quality of life, individuals with moderate-to-severe inactive thyroid eye disease may consider surgical rehabilitation [42, 31]. In general, orbital decompression is done first, then extraocular muscle surgery, and finally eyelid procedures are done while treating inactive thyroid eye illness [26].

Several methods of orbital bone decompression and the amount of removed orbital walls have been researched. One approach hasn't proven itself to be better than the others up to this point [26].

For the purpose of reducing proptosis and improving diplopia, orbital fat decompression can be done either in conjunction with bone decompression or on its own [31]. Temporary tarsorrhaphy can be used to treat exposure keratopathy while waiting for orbital decompression [26].
In order to maintain enough corneal covering, eyelid surgery is only done for symptomatic eyelid retraction or asymmetric lid position [26].

Complications of thyroid eye diseases

Thyroid eye disease may lead to diplopia, ocular hypertension, glaucoma and optic nerve damage. Even mild thyroid eye disease could have a significant effect on the patient's quality of life [7].

Conclusion

Graves' disease is a common condition that can be associated with ocular manifestations that range from mild symptoms like dry eye to severe ones like corneal ulceration and compression to optic disc. Presentation in the eye could be devastating to the patient hence affecting the quality of life. Management of TED can range from medical options to a variety of surgical interventions. Therefore, healthcare providers must be aware of its clinical presentations and treatment modalities.

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