Graves Disease - A Comprehensive Review

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Graves Disease (GD) is an inflammatory disorder that often results in hyperthyroidism. GD is particularly prone to affecting women, African Americans, individuals with pre-existing autoimmune conditions, and first-degree relatives of those with GD. GD presents through a breakdown of immune tolerance against thyroid antigens. This occurs through a multifactorial autoimmune dysfunction of environmental and mainly genetic contribution. Hereditary predisposition accounts for 79% of the GD risk and increases susceptibility to dysfunction by environmental risk factors such as smoking, vitamin D deficiency, and stressful life events. GD is caused by a disruption of the thyroid gland on a molecular level. The disease is characterized by an overstimulation of the thyroid gland causing hyperthyroidism. This issue is caused by thyroid-stimulating immunoglobulin (TSI) synthesized by B cells. These immunoglobulins bind to the TSH receptors on the thyroid gland, activating it and producing an abundance of the thyroid hormones, levothyroxine (T4) and triiodothyronine (T3). The clinical presentation of GD encompasses a diverse array of signs and symptoms, from common manifestations such as palpitations, weight reduction, and exophthalmos, to less conventional presentations like cardiac complications and cholestatic hepatic injury. There are many methods of diagnosis that are used for GD including the gold standard, which tests for TSI and antibodies against the TSH receptor. Other methods include radioactive iodine uptake and CT scans that test for thyroid enlargement and are used to substitute radioactive iodine uptake tests for pregnant women. The three classical treatments for GD are antithyroid drugs, radioiodine treatment, and thyroidectomy. Additional treatments include corticosteroids which are used to decrease exophthalmos. Beta-adrenergic blockers are used for tachycardia, palpitations, and also blocking the peripheral conversion of T4 to T3. Immunotherapies, such as Mycophenolate mofetil and Azathioprine show promise as potential treatments are currently being investigated. This comprehensive review provides an up-to-date compact analysis of literature pertinent to the epidemiology, etiology, risk factors, genetics, pathophysiology, classifications, clinical presentation, diagnosis, and treatments of GD.

1. Introduction

Graves Disease (GD) is an autoimmune disorder that leads to hyperthyroidism. GD is named after Irish physician James Graves who first reported the symptoms of goiter and exophthalmos in 1835 in the London Medical and Surgical Journal [1]. GD, characterized by an enlarged thyroid gland and eye involvement, was previously known as exophthalmic goiter [2]. GD leads to chronic inflammation, increased thyroid size, the appearance of antibodies specific to the thyroid gland, an eye disease that involves intra-orbital structures, dermopathy, and negative effects on multiple organ systems [3]. GD is the most prevalent cause of hyperthyroidism, affecting 1.2 % of the population in the US, and represents 60–80% of cases of hyperthyroidism [2,3]. GD has a proclivity to affect individuals in the age group of 20-50 [2]. GD is more common in women [3]. Individuals with previously diagnosed autoimmune conditions have a greater risk of developing GD compared to those without any history [4]. It was also reported that GD has a familial component to its genesis as there is a sixteenfold increase in risk among
children and siblings with autoimmune thyroid diseases [5]. Black Americans are affected more by GD compared to other races [6].

2. Etiology and risk factors

GD presents through a decrease in immune tolerance against thyroid antigens, clinically characterized by high levels of circulating thyroid hormones and serum anti-thyroid antibodies [8]. Immunogenic abnormalities of thyroid-stimulating hormone receptor (TSH-R), thyroid peroxidase (TPO), and thyroglobulin (Tg) contribute to GD manifestation [8]. Females are 5 to 10 times more likely to develop GD than men [8]. The breakdown of immune tolerance towards the thyroid in individuals with GD typically occurs through an autoimmune dysfunction prompted as a result of an interconnection of environmental factors and mainly genetic predisposition [8,9]. A genetic predisposition increases susceptibility to the environmental factors associated with GD incidence [8,9]. A family history of GD is a known risk factor [7,8]. Previous studies demonstrated a concordance rate of GD amongst monozygotic twins ranging between 0.29 to 0.36, meanwhile, dizygotic twins showed a concordance rate between 0.00 and 0.04 [7]. Concordance rates being higher for monozygotic twins implies that there is genetic association. Using these values and structure equation modelling, hereditary contribution was calculated to be 79% of the GD risk, and environmental factors account for 21% [8]. Some other endogenous factors relative to GD onset are estrogens, X-inactivation, and microchimerism [8].

Environmental risk factors include smoking, immune modulators, iodine excess, selenium, vitamin D deficiency, and Agent Orange through occupational exposure [7,8]. Previous studies suggest that life strains may play a causative role in GD occurrence [9]. A case-control study conducted by Janković et al. supports the claim that the presence of stressful life events and circumstances is associated with increased GD occurrence [9]. According to the collected data, patients with GD reported change in time spent at work, unemployment for at least a month, increased arguments with spouses, and familial disharmony at a significantly higher rate than the control group of participants without GD [9].

3. Pathophysiology

Molecularly, GD is an autoimmune disease, where issues arise when the immune system functions abnormally, leading it to attack its own healthy cells. GD impacts the thyroid gland, causing an overproduction of thyroid hormones, a condition referred to as hyperthyroidism [3]. These thyroid hormones regulate body temperature, heart rate, and metabolism [3].
GD is caused by thyroid-stimulating immunoglobulin (TSI) which can be synthesized by B lymphocytes primarily in the thyroid cells, but also in the lymph nodes and bone marrow [3]. B lymphocytes are stimulated by T lymphocytes which get sensitized by antigens in the thyroid gland [3]. TSI binds with TSH-R on the thyroid cell membrane and stimulates the action of TSH [3]. TSH stimulates the thyroid gland and causes an increase in the thyroid hormones, levothyroxine (T4) and triiodothyronine (T3). The heightened synthesis of thyroid hormones and the growth of the thyroid gland manifest clinically as hyperthyroidism and thyromegaly [3].

GD can lead to orbital issues in patients, manifesting as protruding eyes. This complication is caused by inflammation, cellular proliferation, and increased growth of extraocular muscles and retro-orbital connective and adipose tissues [3]. This presentation occurs due to the actions of the thyroid-stimulating antibodies and cytokines released by cytotoxic T lymphocytes [3]. These cytokines and thyroid-stimulating antibodies activate periorbital fibroblasts and preadipocytes, causing the synthesis of excess hydrophilic glycosaminoglycans [3]. This results in muscle swelling, congestion, and periorbital edema by retaining water in the area.

In GD patients, antibodies often target the TSH receptor and other thyroidal antigens [10]. Other antigens that are frequent targets in the disease include TPO and thyroglobulin, and recent studies suggest that the thyroidal iodide transporter may also represent an autoantigen [10]. Antibodies against the TSH receptor are important in the pathogenesis of the disease and are the main antibody signal that a patient has GD. Conversely, anti-TPO and anti-thyroglobulin seem to have little role [10]. These other antibodies can be high in lab tests for other thyroid issues such as Hashimotos so they may not be used as the best indicator that a patient has GD.

4. Classification:

GD is classified as an organ-specific autoimmune disease and is also characterized by manifestations of eyes, joints, and skin [11]. GD is characterized by thyrotoxicosis as well as extrathyroidal characteristics. It can present in a mild, moderate, or severe form which can include minimal eyelid swelling, lid retraction, and proptosis with some dysfunction affecting the extraocular muscles [12]. Graves ophthalmopathy (GO) is a common extrathyroidal manifestation of GD which often presents with edema, caused by the accumulation of glycosaminoglycans and collagen in orbital tissue. The NO
SPECS classification chart expands on the severity of the eye changes which states class 0 as no symptoms or signs, class 1 as only signs and no symptoms, class 2 as soft tissue involvement, class 3 as proptosis, class 4 as extraocular muscle involvement, class 5 as corneal involvement and class 6 as slight loss [13].

Figure 1: The NO SPECS classification of GD based on eye changes

<table>
<thead>
<tr>
<th>Class</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms or signs</td>
</tr>
<tr>
<td>1</td>
<td>Upper lid retraction with or without lid lag</td>
</tr>
<tr>
<td>2</td>
<td>Edema of the conjunctiva, lid, conjunctival injection</td>
</tr>
<tr>
<td>3</td>
<td>Forward bulging of eyes</td>
</tr>
<tr>
<td>4</td>
<td>Extraocular muscle involvement</td>
</tr>
<tr>
<td>5</td>
<td>Unable to close eyelids</td>
</tr>
<tr>
<td>6</td>
<td>Loss of vision due to optic nerve impairment</td>
</tr>
</tbody>
</table>

5. Clinical Presentation:

In the intricate domain of GD, the clinical exhibition discloses a varied array of cues and indications, intricately interconnecting the physiological complexities of this autoimmune condition. Chiefly, individuals diagnosed with GD regularly show a range of symptoms, including palpitations, tremors, heat intolerance, fatigue, weight reduction, goiter, anxiety, modified menstrual cycles, frequent bowel movements, and diminished libido or erectile dysfunction, indicative of inherent hyperthyroidism [14]. Remarkably, palpitation, tremors, heat intolerance, fatigue, and weight reduction are widespread, affecting over fifty percent of individuals diagnosed with this autoimmune disorder [15].

The overdriving function of the thyroid is the cause of thyrotoxicosis, occasionally causing severe hypokalemia and acute muscle paralysis, collectively referred to as thyrotoxic periodic paralysis. This phenomenon is observed more frequently in individuals of Asian descent and is associated with factors such as alcohol consumption, intense physical activity, and an elevated carbohydrate diet [16].

A distinct morbidity observed in 30% to 50% of GD patients is ophthalmopathy, characterized by ocular symptoms including diplopia, blurry vision, retro-ocular discomfort, foreign particles in their eyes, and, in severe cases, loss of sight. Orbitopathy, particularly exophthalmos, is a common manifestation, often accompanied
by preorbital edema. In severe instances, patients may present with conjunctivitis and ulcers due to excessive exposure [17]. Patients with GD, following ocular symptoms, infrequently develop pretibial myxedema, occurring at an incidence of 1% to 5%. This condition manifests as firm plaques with non-pitting edema, predominantly located in the anterior and lateral aspects of both legs [18,19].

Within the realm of GD, instances of unconventional clinical presentations have been documented, emphasizing the importance of recognizing diverse manifestations. In a study by Kumar et al., a case was expounded in which a lack of adherence to hyperthyroidism medication unveiled significant cardiac implications. The patient displayed a mere 28% left ventricular ejection fraction and elevated troponin T levels, indicative of cardiac damage [20]. Moreover, a notable case study highlighted complications in a GD patient, encompassing cholestatic hepatic injury, pancytopenia, and pulmonary hypertension leading to right-sided heart failure [21]. The cholestatic hepatic injury exhibited a distinctive pattern of biliary obstruction, resulting in liver impairment, marked by increased direct bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT). Hepatic abnormalities in GD can manifest with varied clinical features, ranging from extreme presentations to asymptomatic cases [22]. Pancytopenia, a recognized complication of hyperthyroidism, has been observed in GD, with anemia occurring in 34% of cases, leukopenia in 5.8%, and thrombocytopenia in 3.3% [23, 24]. A specific variant of anemia, termed "GD anemia," affecting 22% of GD patients, is associated with the condition, often resembling anemia of chronic disease [25]. These distinct clinical presentations underscore the heterogeneous nature of GD manifestations, necessitating a comprehensive understanding for accurate diagnosis and management. The intricate interplay of endocrine and systemic effects in GD requires heightened clinical vigilance to address the diverse spectrum of signs and symptoms associated with this autoimmune thyroid disorder.

6. Diagnosis

Since GD is a malfunction of the immune system that leads patients to overproduce thyroid hormones, the gold standard for diagnosis is testing for the TSH receptor antibody or TSI. These tests are cost-effective and readily available [2]. A high level of these specific antibodies confirms GD. Blood tests can also help determine TSH levels which are responsible for stimulating the thyroid gland to make more thyroid hormones. This test is used frequently as people with GD tend to have higher levels of thyroid hormones and lower levels of TSH [2]. Another means of diagnosis is a thorough physical examination, due to the fact that 70% of patients with GD also have subclinical ophthalmopathy, and patients may present with symptoms such as bulging eyes and pressure or pain in the eyes [26].

Radioactive iodine uptake is another commonly used option as it shows clinicians the rate at which the thyroid takes up iodine to produce thyroid hormones [27]. However, for pregnant women, it is contraindicated because of the consumption of radioactive iodine.
Studies show that ultrasounds are especially useful for the pregnant population as they can show enlarged thyroids for the diagnosis of GD without risk to the patient. If the diagnosis is still uncertain after utilizing the above methods, physicians can also order additional imaging tests such as CT scans or MRIs [27].

7. Treatment

Treatment of GD consists of managing the symptoms and reducing the excessive levels of thyroid hormones. There are three classical long-term therapy options for reducing the levels of thyroid hormone:

1. Antithyroid Drugs (ATD)
2. Radioactive Iodine Treatment
3. Total or subtotal thyroidectomy

The ATDs include methimazole, carbimazole, and propylthiouracil. These drugs work by blocking the enzyme thyroid peroxidase in the thyroid gland, thus blocking the eventual production of the T4 and T3 hormones [3]. While methimazole and carbimazole pose teratogenic risks in the first trimester of pregnancy, propylthiouracil does not. Thus, propylthiouracil is the preferred choice of treatment for pregnant patients during their first trimester [28]. After the first trimester, it is recommended to go back to methimazole to avoid the hepatic failure complications associated with propylthiouracil [29].

Radioactive Iodine treatment normally becomes an option if there are continued symptoms of hyperthyroidism for more than 12 to 18 months after beginning ATD [29]. Radioactive Iodine is taken up by iodide transporters of follicular cells in the thyroid and leads to their destruction [30]. Nonetheless, the major concern of this treatment is that most patients end up with hypothyroidism symptoms due to damage to the thyroid gland [31].

A thyroidectomy is considered to be the most definitive treatment for GD. Patients have the lowest relapse rate (10%) when compared to the other treatments discussed above [32]. Nonetheless, the patient will be started on T4 supplementation post-operatively to manage the hypothyroidism symptoms that may occur after the thyroidectomy. This procedure is normally indicated for patients with large goiters (typically obstructive) or patients with severe hyperthyroidism that cannot be managed with the other treatments [33].

The decision of which treatment to use comes after consideration of the severity of the disease, the side effects, and the likelihood of success from treatment. In most cases, patients are started with ATD and then the other treatments are considered if ATD is not sufficient or is causing side effects [34].
There are other therapies that can help with common symptoms. Cardiac involvement of GD is typically seen as sinus tachycardia, supraventricular arrhythmias, and atrial fibrillation in elderly patients [32]. To address this, beta-adrenergic blockers are used in the early stages of GD. This reduces the symptoms of palpitations, excessive sweating, nervousness, tremors, and tachycardia. High doses of propanol (160-200 mg) have been shown to decrease the peripheral conversion of T4 to T3 and decrease the release of thyroid hormone from the thyroid gland [29]. While beta-adrenergic blockers have minimal effect on the actual disease process, they are useful to treat the symptoms before seeing the effects of other major therapies [27].

GO is another autoimmune consequence that can occur with GD. The disease process is not fully understood, but it is thought that inflammation and lymphocytes play a role [35]. Thus, corticosteroids have proved to be the standard treatment for GO as they are potent anti-inflammatory agents [35]. Corticosteroids, specifically methylprednisolone, were also shown to reduce the risk of relapsed hyperthyroidism after treatment with ATD had stopped [36].

Other immunosuppressants are being investigated to see their usefulness in treating GD and GO such as Mycophenolate mofetil and Azathioprine. Mycophenolate mofetil has been shown in clinical trials to be more effective than corticosteroids in reducing the symptoms and pains associated with GO [35]. Mycophenolate mofetil is an inhibitor of inosine monophosphate dehydrogenase (IMPDH) and this is commonly used in patients who have received transplant organs. By blocking the proliferation of T and B cells, this drug reduces the activity of the adaptive immune system. Azathioprine is another drug being investigated as an adjunct therapy with ATD. Azathioprine is a purine analog that also stops lymphoid proliferation. A recent study showed that the addition of azathioprine to ATD increased the remission rates from 33.4% to 87.5% [37]. Other clinical trials have used monoclonal antibodies to treat GD. These include rituximab (an anti-CD-20 antibody), teprotumumab (an anti-IGF-1R antibody), and tocilizumab (an anti-IL6 antibody). All have shown success in either reducing the symptoms of GO or modifying the disease process of GD [38]. However, further research is needed before these treatments can be established as primary treatment options.

The three classical treatments for GD have been around for quite some time, with Theodor Billroth being the founder of modern thyroidectomies back in the late 19th century [39]. While radioactive iodine therapy and thyroidectomies have high rates of remission, patients are left with little to no function of their thyroid gland and tend to experience hypothyroid symptoms. Newer treatments targeting the immune system or thyroid gland aim to enhance remission rates and symptom reduction without the necessity of damaging the thyroid gland.

**Abbreviations:** Graves’ Disease (GD), thyroid-stimulating hormone receptor (TSH-R), thyroid peroxidase (TPO), thyroglobulin (Tg), thyroid-stimulating immunoglobulin (TSI), Graves ophthalmopathy (GO), inosine monophosphate dehydrogenase (IMPDH)

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