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A REVIEW ON TOXIC DIFFUSE GOITRE

Neethu J.*, [1]Amala Alex, [1]Fathima Anwar, [1]Reshma R., [1]Rincy Rajan, [2]Prasobh G. R.

*Associate Professor, Department of Pharmacy Practice, Sreekrishna College of Pharmacy and Research Centre, Thiruvananthapuram, Kerala, India.

[1]Fifth Year Pharm D Students, Sreekrishna College of Pharmacy and Research Centre, Thiruvananthapuram, Kerala, India.

[2]Principal, Head of Department of Pharmacy Practice, Sreekrishna College of Pharmacy and Research Centre, Thiruvananthapuram, Kerala, India.

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***Corresponding Author**
Neethu J.
Associate Professor, Department of Pharmacy Practice, Sreekrishna College of Pharmacy and Research Centre, Thiruvananthapuram, Kerala, India.

ABSTRACT

Grave's disease is an autoimmune disease in which patients own immune system attacks the thyroid gland, causing it to produce too much thyroxine. Graves' disease is the most common autoimmune disease, affecting 0.5% of the population in the US, and represents 50-80% of cases of hyperthyroidism. GD is an organ-specific autoimmune disease whose major manifestations are owing to circulating autoantibodies (Ab) that stimulate the thyroid-stimulating hormone receptor (TSH-R) leading to hyperthyroidism and goitre. Some of the more common symptoms include palpitations, tremulousness, heat intolerance, weight loss, and anxiety. Physical findings include tachycardia, proptosis, thyroid enlargement, and tremor. Ophthalmopathic changes are seen in 20% to 40% of patients and include exophthalmos, proptosis, chemosis, conjunctival injection**,** and periorbital edema. The main diagnostic tests include Thyroid function tests, Radioactive iodine uptake, Antibody tests and Imaging. Hyperthyroidism due to Grave's disease is treated with 1 of the following approaches: use of antithyroid drugs to normalize thyroid hormone production; destruction of the thyroid using RAI; or surgical removal of the thyroid.

KEYWORDS: Proptosis, chemosis, conjunctival injection, exophthalmos.

INTRODUCTION

Grave's disease is an autoimmune disease in which patients own immune system attacks the thyroid gland, causing it to produce too much thyroxine(T4).

Graves' disease, also known as Basedow's disease, primary hyperplasia, exophthalmic goitre, and diffuse toxic goitre, is characterised by a triad of features:
Hyperthyroidism (thyrotoxicosis)
Diffuse thyroid enlargement
Ophthalmopathy.[1]

Graves' disease is the most common autoimmune disease, affecting 0.5% of the population in the US, and represents 50_80% of cases of hyperthyroidism.[2] GD occurs more often in women and has a population prevalence of 1–1.5%. Approximately 3% of women and 0.5% of men develop GD during their lifetime.[3] The peak incidence of GD occurs among patients aged 30–60 years, but all ages can be affected, with an increased incidence among African Americans.[4]

In 80% of patient hyperthyroidism results from the production of TSHR-Sabs. These antibodies have TSH agonist activity, thereby it will help in stimulating hormone synthesis and release. These antibodies cross-react with orbital and fibroblastic tissue, resulting in ophthalmopathy and dermopathy.[5]

Currently, there are no medications or treatment to stop the patient's immune system from attacking their thyroid gland. However, treatments are available which can reduce the symptoms of the disease and bring down the production of thyroxine.

Etiopathogenesis

The emergence of this autoimmune process is probably due to an underlying genetic susceptibility with superimposed environmental factors. Particular HLA alleles on chromosome 6, namely HLA-DRB1-08 and DRB3-0202, are known to confer an increased risk of Graves' disease.[6] Environmental triggers include stressful life events, cigarette smoking, infection, exposure to high doses of iodine and recent childbirth.[2] About 30% of Grave's Disease patients have family members who also have GD.

The trigger for hyperthyroidism in genetically susceptible individuals may be due to infection with viruses or bacteria. Certain strains of gut organisms *Escherichia coli* and *Yersinia*

enterocolitica possess cell membrane TSH receptors. The production of antibodies to these microbial antigens which might cross react with TSH receptor on the thyroid follicular cell could result in development of hyperthyroidism.[7]

GD is an organ-specific autoimmune disease whose major manifestations are owing to circulating autoantibodies (Ab) that stimulate the thyroid-stimulating hormone receptor (TSH-R) leading to hyperthyroidism and goitre. TSH-R-stimulating Ab are predominantly of the IgG1 isotype and bind to a discontinuous epitope in the leucine-rich domain of the TSH-R extracellular domain, bounded roughly by amino acids 20–260.[8,9] TSH-R also interacts with IGF1 receptors (IGF1R) on the surface of thyrocytes and on orbital fibroblasts, with the TSH-R-Ab interaction with TSH-R activating both IGF1R downstream pathways and TSH-R signalling.[10] Circulating stimulatory TSH-R-Ab binding to the TSH-R increase the production of intracellular cyclic AMP, leading to the release of thyroid hormone and thyrocyte growth.

CLINICAL MANIFESTATIONS

Some of the more common symptoms include palpitations, tremulousness, heat intolerance, weight loss, and anxiety. Physical findings include tachycardia, proptosis, thyroid enlargement, and tremor. Older patients are less symptomatic than younger patients.[11] Atrial fibrillation is common in elderly thyrotoxic men with underlying cardiovascular disease,[12] and weight loss with a decrease in appetite is common among older patients with hyperthyroidism.[11]

There are many features of Graves' disease that are distinct from other forms of thyrotoxicosis. Usually apparent ophthalmopathic changes such as exophthalmos, proptosis, chemosis, conjunctival injection**,** and periorbital edema are seen in 20% to 40% of patient. Lid retraction causes a typical staring or startled appearance (Fig. 41–3). Patients may complain of vague eye discomfort and excess tearing. In severe cases, the eyelids are unable to close completely, resulting in corneal damage. In very severe cases, the optic nerve can be compressed, resulting in permanent vision loss. All patients with suspected or known Graves' disease must be evaluated and monitored by an ophthalmologist.

Dermopathy occurs in 5% to 10% of patients with Graves' disease, It is usually associated with severe ophthalmopathy. Clinical manifestation observed on skin include hyperpigmented, non-pitting induration of the skin, typically over the pretibial area (pretibial

myxedema), the dorsa of the feet, and shoulder areas. Clubbing of the digits (thyroid acropachy) is associated with long-standing thyrotoxicosis.[5]

DIAGNOSIS

Thyroid function tests

A blood sample is sent to a lab to see body has the right amount of thyroid hormone (T4) and TSH. A high level of thyroid hormone in the blood plus a low level of TSH is a sign of overactive thyroid. Sometimes patient with mild overactive thyroid function will not show symptoms in routine screening. In such cases doctors will start treatment or wait to see if levels return to normal.

Radioactive iodine uptake:

How much iodine the thyroid takes up will tell by RAIU. The thyroid takes up iodine and uses it to make thyroid hormone. High uptake suggests Grave's disease. This test can be helpful in clearing other possible causes of overactive thyroid.

Antibody tests

A blood sample is sent to a lab to check for antibodies that suggest Grave's disease.

Imaging

In addition to thyroid function and TSH-R-Ab determination, most clinicians would request thyroid ultrasound (US) and less often isotope scanning.[13] In a study conducted among 263 endocrinologists in 992 hyperthyroid patients, thyroid US and scintigraphy were used in 93.8 and 40.3%, respectively.[14]

TREATMENT

Hyperthyroidism due to Grave's disease is treated with 1 of the following approaches:[3] use of antithyroid drugs to normalize thyroid hormone production;[4] destruction of the thyroid using RAI; or[15] surgical removal of the thyroid.

Antithyroid drug therapy

Thionamide

The two thionamides that have been in use since the 1940s are propylthiouracil (PTU) and action and side effects. These drugs show action by blocking the synthesis of thyroid hormone. PTU has the additional action of inhibiting peripheral conversion of T4 to the more

active T3. These drugs may also possess immunosuppressive and anti-inflammatory properties, but this is controversial.

Depending on the severity of the patient's hyperthyroidism, the usual starting dose for methimazole is 10 to 30 mg per day. Most patients do not require more than 30 to 40 mg per day. Methimazole given in single daily dose can improves medication adherence. A split dose may be more effective initially in case of severe hyperthyroidism.[16] Higher methimazole doses may achieve faster normalization of thyroid function and are used in more severe thyrotoxicosis (e g, FT4 >3 times greater than the reference range) but are also associated with more adverse effects.[17]

Patients should be informed its possible side effects including rash, arthralgia, ANCA-positive vasculitis, hepatitis and agranulocytosis. Patients should be advised to stop antithyroid drugs if any potential symptoms of agranulocytosis develop, such as fever, oral ulceration or painful throat. This rare idiosyncratic reaction affects 0.1-0.3% of patients on antithyroid drugs. It occurs acutely without prior warning and is not dose related.

Antineutrophil cytoplasmic antibody–associated vasculitis occurs much more frequently with propylthiouracil than it does with methimazole or carbimazole60 and can occur after months to years of therapy. Typically, patients present with polyarthritis, fever, and purpura, and more severely affected individuals develop glomerulonephritis and pneumonitis. Therapy started by stopping drug and using glucocorticoids and other immunotherapies.

RAI Therapy

Within the thyroid gland, RAI is incorporated into thyroid hormone, releasing beta particles that cause ionizing damage to thyroid follicular cells, resulting in gradual destruction of the gland.

The hypothyroidism occurs depends on the size of the thyroid, the RAI uptake, the degree of thyrotoxicosis, and the activity of RAI administered. The goal of RAI therapy is to render the patient hypothyroid.

Most patients develop hypothyroidism within 2 to 3 months after a single 12- to 15-mCi (444-555 MBq) administration of RAI. Usually patients require a longer time, with repeated treatment generally not considered before 6 months after the initial therapy. Patients with a delayed response to RAI often require antithyroid drug therapy while awaiting the beneficial

effects of surgical removal treatment. The destruction of thyroid tissue occasionally results in transient worsening of thyrotoxicosis in the weeks following RAI therapy.[20,21]

The particular dose of RAI that is administered may be fixed or determined on the basis of the gland's radionuclide uptake and volume in addition to the duration of time that the patient is able to remain in isolation. Patients administrating a fixed doses of RAI may have higher response rates but these patient will be exposed to more radiation and also have higher rates of long-term hypothyroidism.[22]

After RAI therapy, thyroid hormone measurement should be done at 2- to 6-week intervals. Patients should be started on levothyroxine therapy immediately when free T4 levels fall below the normal range[23] because untreated hypothyroidism is another risk factor for the worsening of orbitopathy.[24]

Surgical removal

Surgery was the first definitive treatment for Grave's disease, but with the development of antithyroid drugs and RAI therapy in the 1940s and 1950s, surgery is now recommended by fewer than 1% of experts for the initial management of Grave's disease. However, recent data indicate that surgery has become the main definitive therapy (vs RAI) in some US centers, particularly among patients with low socioeconomic status.[25]

Total thyroidectomy is an effective means of achieving remission but poses risks associated with general anaesthesia, recurrent laryngeal nerve palsy and transient or permanent hypoparathyroidism. Amongst most thyroid physicians it is therefore third line therapy. Surgery is particularly useful for patients who decline or cannot tolerate treatment with thionamides or RAI, or those with large, compressive goitres or suspicious nodules. There is some suggestion that thyroidectomy may prevent the later development of thyroid eye disease but this is anecdotal and should not be an indication for surgery in most patients.

CONCLUSION

Grave's disease is a common autoimmune disorder, if untreated, may result in severe complexities. Several treatment modalities are available for treatment. Early detection of the disease through identification of signs and symptoms as well as through diagnostic methods can ease the symptom manifestations. Since each of the treatment modalities has unique

limitations and adverse consequences, physicians need to be familiar with the advantage and disadvantages of each therapy in order to best counsel their patients.

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