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THYROTOXICOSIS- REVIEW

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INTRODUCTION:

The thyroid hormone is the one the major hormone that regulates body metabolism, growth, reproduction, and neuronal development. One of the common presentations of thyroid dysfunction is thyrotoxicosis. Essentially, inappropriately higher amounts of circulating thyroid hormone results in excessive thyroid hormone action at the tissue level which is clinically manifested as Thyrotoxicosis. Thyrotoxicosis results from hypothalamic-pituitary-thyroid axis dysfunction that results in excessive production of thyroid hormone. Hyperthyroidism is a subset form of thyrotoxicosis wherein there is a high amount of production of thyroid hormone(s) by the thyroid. The prevalence of hyperthyroidism is 1.3% in the USA and occurs more commonly in the female population (2%) than the male population (0.2%) (Sharma and Stan 2019).

The high amount of thyroid hormone in thyrotoxicosis, results in a high metabolic rate in an individual, leading to a condition known as the hyper-metabolic state. Consequently, thyrotoxicosis patients have a fast heart rate, a huge reduction in weight, and are heat-intolerant. Additionally, these patients also exhibit signs such as- persistent nervousness, sweating, high blood pressure, hand-tremors, irregular heart-beat, fatigue, hair loss, weakness, difficulty in sleeping, nausea & vomiting, vision problem, palpitations, worsening of psychiatric condition, reduced bone density, infertility, gynecomastia, irregularity in menstrual cycle, hyperglycaemia and hypercalcemia (Hubbard, 2011).

The most common causes of thyrotoxicosis are-

- Grave's diseases (accounts for almost 70-80% of cases),
- Nodular thyroid disease,
- Thyroiditis

Iodine is a vital component of the thyroid hormone; however, the global distribution of iodine varies throughout the world. Few areas are rich in iodine while others are deficient. The level of iodine intake affects the cause of thyrotoxicosis. In iodine-deficient areas, almost 50% of cases are due to nodular thyroid disease

and thyroiditis while areas with an adequate amount of iodine, 80% of thyrotoxicosis cases are owing to Grave's disease (Sharma & Stan, 2019). Although various other factors viz., genetics, age, sex, ethnicity, alcohol consumption, etc also affect the cause of thyrotoxicosis (Taylor et al., 2018).

GRAVE'S DISEASE:

Grave's disease is also known as Parry disease or Basedow syndrome. Grave's disease is the most common cause of hyperthyroidism with an estimated annual incidence of 50 cases per 100,000 people, with a higher incidence risk in women (3%) as against men (0.5%). Nearly 80% risk for Grave's disease is due to genetic factors. Although, stress, environmental factors, smoking, dietary iodine, antibodies to infections including *Yersinia enterocolitica* etc can also trigger Grave's disease. Exact underlying mechanism of Grave's disease is not known, however it is well established that Grave's disease is an auto-immune disorder wherein thyroid-stimulating hormone (TSH) receptor on the thyroid cell membrane is stimulated by the binding of thyroid-stimulating immunoglobulin (TSI) resulting in excessive production and secretion of thyroid hormone (Thadani, Deacon, & Peters, 2000). Associative hyperplasia and hypertrophy of thyroid follicles resulting in goiter formation have also been reported (Hubbard, 2011). Grave's disease is manifested by hyperthyroidism and diffuses goiter; ophthalmopathy, pretibial myxedema and thyroid arthropathy (Taylor et al., 2018). Diffuse thyroid uptake of radioisotope helps to distinguish between Graves', toxic multinodular goiter and a toxic nodule.

The retraction of eyelid and lid lag is a clinical common feature of thyrotoxicosis. Additionally, Grave's ophthalmopathy has a few characteristic features viz., proptosis, extra-ocular muscle involvement, discomfort, and grittiness. The reason for this peculiar ophthalmological condition is thought to be an immunological response to antigens in retro-orbital tissues that are similar to those in the thyroid. Alternatively, antigens can also cross-react with the TSH receptors present on orbital adipocytes and fibroblasts. This results in edema, glycosaminoglycan deposition, and fibrosis of retro-orbital tissue and extraocular muscles (Hubbard, 2011). Treatment modalities for severe Grave's ophthalmopathy condition include- steroids at high dose, orbital radiotherapy, while the last treatment modality is ocular surgical intervention.

TOXIC NODULAR GOITRE

Benign thyroid tumors (either a single autonomous thyroid nodule or multiple autonomous nodules) that secrete excess thyroid hormone autonomously results in thyrotoxicosis. Multinodular goiter is also known as Plummer's disease (Thadani, Deacon, & Peters, 2000). This kind of thyrotoxicosis is commonly seen in patients aged 60 years or more. The risk factors for toxic nodular goiter include age and iodine levels. Ophthalmopathy and other symptoms of Graves' disease, including antithyroid antibodies, are absent in toxic nodular goiter. The diagnosis of toxic nodular goiter requires confirmation using Thyroid scintigraphy. Toxic nodular goiter can be controlled using Anti-thyroid drugs, however, complete treatment using anti-thyroid drugs is not possible. For a complete treatment, surgical intervention (Total thyroidectomy for multiple nodules while Thyroid lobectomy is carried out for single nodule) is mandatory while treatment with radioiodine provides a cosmetic relief to patients who wish to avoid surgical intervention (Hubbard, 2011).

THYROIDITIS

Thyroiditis is basically an inflammation of the thyroid gland due to a multitude of factors viz., infectious, autoimmune, drug-associated, viral infections, pregnancy/post-partum, etc. In sub-acute thyroiditis, transient thyrotoxicosis may occur due to inflammation that results in lymphocytic infiltration resulting in thyroid destruction. Consequently, the thyroid hormone is released from the damaged

thyroid leading to temporary mild thyrotoxicosis. However, further, this condition advances to hypothyroidism as the thyroid gland becomes depleted of thyroid hormone. In 80% of cases, the normal condition of the thyroid is restored in 12-18 months (Thadani, Deacon, & Peters, 2000). Post-partum, the female body has elevated levels of thyroid antibodies that may lead to transient thyrotoxicosis similar to sub-acute thyroiditis. Lymphocytic infiltration in thyroid due to unestablished etiology is also observed during auto-immune thyroiditis or Struma lymphomatosis or Hashimoto's thyroiditis.

Bacteria, most commonly, gram-positive *streptococcal* and *staphylococcal* species may spread to thyroid via bloodstream resulting in Infective thyroiditis. Infective thyroiditis is manifested as tenderness of thyroid, pain, and fever.

Amiodarone, an anti-arrhythmic drug that contains two iodine molecules in its chemical structure, is known to cause thyrotoxicosis. Amiodarone can result in two types of thyrotoxicosis-

- Type 1 (iodine-induced thyrotoxicity-similar to toxic multinodular goiter) or
- Type 2, amiodarone-induced thyroiditis.

Other drugs that can cause thyrotoxicosis include IFN-α, lithium, tyrosine kinase inhibitors, highly active antiretroviral therapies, immune checkpoint mediators and the humanized monoclonal antibodies used in the treatment of multiple sclerosis (Taylor et al., 2018).

Chronic inflammation leading to fibrosis of thyroid tissue results in Reidel's thyroiditis. The fibrotic thyroid tissue expands beyond the thyroid capsule resulting in hard and painless goiter. This may eventually lead to hypothyroidism, hypoparathyroidism, hoarseness due to recurrent laryngeal nerve involvement and tracheal and oesophageal compression (Hubbard, 2011). Complete thyroidectomy is usually not feasible hence, surgical decompression of the airway may be carried out.

DIAGNOSIS OF THYROTOXICOSIS

The serum TSH levels, free thyroxine (T4) and free tri-iodothyronine (T3) are measured for the diagnosis of thyrotoxicosis. In overt thyrotoxicosis, the serum TSH levels are low, while T4 and T3 are high. Whereas in subclinical thyrotoxicosis, persistent low levels of serum TSH along with normal levels of T4 and T3 are found. Further to establish the cause of thyrotoxicosis, radioiodine uptake and scan may be carried out. Radioiodine uptake and scan help to distinguish the cause of thyrotoxicosis. A high radioiodine thyroid uptake and a diffused scan are observed in Grave's disease, while, a patient with toxic nodular goiter may exhibit a raised or normal radioiodine uptake and increased uptake in focal areas of upon scanning. Differentiating, low or undetectable uptake of radioiodine is observed in thyroiditis. The elevated serum concentration of thyroperoxidase (TPO) antibodies indicates autoimmune thyroid dysfunction (Thadani, Deacon, & Peters, 2000).

TREATMENT OF THYROTOXICOSIS

ANTI-THYROID DRUGS:

Chemically, anti-thyroid drugs belong to thionamides class, containing a sulfhydryl group and a thiourea moiety. The most commonly used drugs are methimazole (MMI), carbimazole, and Propylthiouracil (PTU) (John, Sundrarajan, & Gomadam, 2015). These drugs inhibit thyroid hormone synthesis by interfering with thyroid peroxidase-mediated iodination of tyrosine residues in thyroglobulin (Cappa et al., 2011). Additionally, PTU prevents the conversion of T4 to T3 within the thyroid and in peripheral tissues (John, Sundrarajan, &Gomadam, 2015). MMI is widely used in Europe, Asia, and the United States while, carbimazole (CBZ), a methimazole analog, is available in the United Kingdom and British Commonwealth countries. MMI is administered once a day while PTU is given two-to-three times a day.

Both MMI and PTU are rapidly absorbed from the gastrointestinal tract. PTU exhibits extensive protein binding ~80-90% albumin binding whereas MMI is freely available in serum (Hudzik &Zubelewicz-Szkodzinska, 2016). Due to high protein binding, PTU is less likely to cross the placenta and is, therefore, preferred in pregnancy (Hubbard, 2011).The recommended starting dose is 0.5–1.0 mg/kg/day for MMI and 5–10 mg/kg/day for PTU (Cooper, 2005). There are two treatment regime) (Hubbard, 2011)-

- **Titration regime:** The medications are initiated at a high dose and are gradually reduced every 4–8 weeks, post verification of resolution of symptoms and thyroid function tests. Later, the dose is maintained at a minimum that is required to maintain a clinical and biochemical euthyroidism (Normal T3 and T4) for a period of 12–24 months. Following that the anti-thyroid drugs are discontinued, and the patient is kept under follow-up for the recurrence of symptoms.
- **Block and replace regime:** Therapy is initiated at a high dose (e.g. 40 mg carbimazole daily) to fully block endogenous thyroid hormone production and later to maintain euthyroid state thyroxine (e.g. 100 mg daily) is added. Continuous therapy monitoring and corresponding dose adjustment is required for thyroxine. Treatment usually lasts for 12-18 months.

In Grave's disease, the two-fold treatment approach is followed: Control of symptoms using Propranolol and treatment of hyperthyroidism. Overstimulation of β-adrenergic receptors results in the appearance of the majority of the symptoms of Grave's diseases, hence β-blockers (viz., Propranolol) are used for symptomatic treatment and anti-thyroid drugs are used for the treatment of hyperthyroidism (Sharma & Stan, 2019).

RADIOIODINE THERAPY: Radioactive iodine is the preferred definitive treatment, as a first-line approach or for treating recurring thyrotoxicosis post subtotal thyroidectomy or treatment with anti-thyroid drugs. Radioiodine therapy is the favored first-line therapy in the USA, while anti-thyroid drugs are preferred in Asia and Europe (Hubbard, 2011). Prior to radiotherapy patients are rendered clinically euthyroid with anti-thyroid drugs. Anti-thyroid drugs are stopped days prior to radiotherapy, in order to achieve maximum therapeutic benefit. Radioiodine, ^{131}I, is administered orally and it emits β particles that destroy thyroid follicular cells. The therapeutic effect of ^{131}I is not immediate but is observed after months of treatment. Hypothyroidism is the immediate consequence of the therapy and patients are monitored for the rest of the life (Hubbard, 2011). Radioiodine therapy is completely contraindicated in patients with pregnancy, lactation, Grave's disease with severe ophthalmopathy (Thadani, Deacon, & Peters, 2000).

SURGERY OR THYROIDECTOMY

It has been found that thyroidectomy can cure almost 90% of the cases (Palit et al., 2000), even in patients with Graves's disease with severe ophthalmopathy (Bartalena et al., 1998). Even compressive symptoms from large toxic multinodular goiters are eliminated following thyroidectomy. Thyroidectomy can even be performed during pregnancy (Thadani, Deacon, & Peters, 2000). Thyroidectomy is the choice of treatment for large or symptomatic goiters, severe ophthalmopathy, suspected malignancy of thyroid tissue and in children. Depending on the patients' condition, total or a subtotal Thyroidectomy is performed. Patients are certainly rendered hypothyroid post total thyroidectomy (Hubbard, 2011). Although most patients eventually become hypothyroid irrespective of total or subtotal thyroidectomy. Recurrent laryngeal nerve injury or permanent hypoparathyroidism is the manor complication of thyroidectomy. Transient hypocalcemia, bleeding, or infection has also been reported post-surgery (Thadani, Deacon, & Peters, 2000).

CONCLUSION:

Thyrotoxicosis is one of the common endocrinological diseases that majorly affects patients in the age of a group of 20-60 years. A number of treatment modalities are available; however, their choice is dependent on the patient's condition.

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