

Thyrotoxicosis-A Review

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Abstract: Thyrotoxicosis or hyperthyroidism is a fairly common endocrine disorder in clinical practice and it is the clinical syndrome caused by an excess of circulating free thyroxine (T₄) or free triiodothyronine or both. The interdependence of this thyroid disorder with disorders of the mind and emotions, as well as with mental disorders, is not being given the required consideration in many clinical settings. Similarly, many clinical symptoms suggesting thyrotoxicosis are sometimes overlooked, such as palpitations, agina, breathlessness, tremor, infertility, pruritus, bone pains, excessive sweating and insomnia. In addition, a lot of metabolic derangements can be secondary to thyrotoxicosis, such as hyperglycemia, hypercalcemia, hypoparathyroidism, hypocalaemia and hypocholesterolaemia. Despite the enormity of the several problems associated with a thyrotoxic condition, very inadequate attention is given to these problems in many clinical settings. Although both hyperthyroidism (thyrotoxicosis) and hypothyroidism are the two common thyroid disorders, thyrotoxicosis is more prevalent. Therefore, thyrotoxicosis should be part of regular differentials in any clinical setting and hence there is need for a review of this endocrine metabolic disorder. This review discusses thyrotoxicosis and its various clinical manifestations, its relationships with the mind and emotions/mental disorders and finally the metabolic manifestations. It also highlights on the approach to handling suspected cases of thyrotoxicosis.

Key word: Thyrotoxicosis • Manifestations • Causes • Treatment

INTRODUCTION

Thyrotoxicosis (hyperthyroidism) is the syndrome that develops after body tissues are exposed to increased concentrations of the thyroid hormones (T₃ or T₄ or both) [1] and the clinical manifestations of thyrotoxicosis can affect every organ [1]. It is a common endocrine metabolic disorder, affecting about 2% of women and 0.2% of men. The presentation varies with age, the classical symptoms and signs being seen in young and middle aged patients but less so in the elderly [1]. A number of causes are in literature as the causes of thyrotoxicosis [1, 2] and they include:

- (a) Common causes in order of decreasing frequency are Graves disease (70-80%), thyroiditis, Toxic nodular goiter, Toxic thyroid adenoma and exogenous hyperthyroidism (iatrogenic, factitious, iodine induced).

- (b) The rare causes include excess thyroid stimulating hormone (trophoblastic tumors, pituitary tumors) and ectopic thyroxine production.

The common symptoms of thyrotoxicosis include [3]: Nervousness and increased activity; increased sweating; hypersensitivity to heat; palpitations; fatigue; increased appetite; weight loss; tachycardia, insomnia; weakness; and frequent bowel movements. The common signs include [3]: Goitre; tachycardia; widened pulse pressure; warm, fine, moist skin; tremor; and eye signs (stare, lid lag, lid retraction and photophobia). Atrial fibrillation and atrial flutter [4] are rare signs.

Thyrotoxicosis is found in various age groups and in different clinical situations. For instance, a study by Luboshitzky *et al.* [5] reported a prevalence of 0.8% for hyperthyroidism in children of various age groups, with lowest occurrence in age 1-2 years and peak occurrence in puberty. Muller *et al.* [6] reported the occurrence of hyperthyroidism in the elderly.

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Clinically, almost every organ is affected and patients may initially present to various medical specialists before they eventually get diagnosed for thyroid dysfunction [7]. Also, thyrotoxicosis usually develops insidiously and most patients have had symptoms for at least 3-6 months before presentation [7]. All these facts suggest that a thyrotoxic patient often has delayed diagnosis in spite of the available knowledge on this disease, this is avoidable.

This review therefore summarizes the various manifestations of thyrotoxicosis in the different medical specialties, the causes and investigation of thyrotoxicosis, recent works on the disease and an overview of the treatment modalities available for the disease.

The different manifestations of thyrotoxicosis: These shall be discussed under 3 subheadings, namely-clinical features, metabolism and psychiatry.

(a) Clinical features [7]: Apart from the general clinical features mentioned under introduction, specific manifestations have been noted for each system affected. These include:

(i) Cardiovascular: It manifests as palpitations, dyspnoea, angina, tachycardia, atrial fibrillation, cardiac failure and thyrotoxic cardiomyopathy.

(ii) Neuromuscular: It is seen as tremor, agitation, chorea, psychosis, emotional liability, proximal myopathy, bulbar myopathy and periodic paralysis.

(iii) Reproductive: It is demonstrated as loss of libido, gynaecomastia, oligomenorrhoea and infertility.

(iv) Gastro intestinal: Features here include nausea, vomiting, diarrhoea, steatorrhoea, hepatomegaly and splenomegaly.

(v) Dermatological: Symptoms and signs to note here include pruritus, thinning of hair, palmar erythema and spider naevi

(vi) Bone: Common problems here are osteopenia and osteoporosis.

(b) Thyrotoxicosis and Metabolism

Metabolic Manifestations: Thyrotoxicosis manifests metabolically in a number of ways depending on the severity of thyroid hyperfunction. The metabolic features include:

i) Hypercalcaemia: Increased serum calcium is very common. This is because the thyroid hormone (T₃) is essential for normal bone growth and bone metabolism. T₃ stimulates bone formation directly through T₃ receptors in osteoblasts. It also stimulates bone resorption by osteoclasts probably secondarily through the osteoblasts [8]. So in thyrotoxic state, there is high turn-over bone loss causing elevated bone metabolic markers such as calcium.

ii) Parathyroid hormone and phosphorus: The T₃ effect on bone metabolism in thyrotoxicosis had been reported to cause decreased serum levels of both parathyroid hormone and phosphorus [9].

iii) Alkaline phosphatase: In thyrotoxicosis the serum level of alkaline phosphatase remains variable [9].

iv) Osteocalcin: Increased level of serum osteocalcin had been reported in thyrotoxicosis [9].

v) Plasma Cholesteryl Ester Transfer Protein (CEPT) activity. CETP is a plasma protein that mediates the exchange of cholesteryl ester and triglyceride between plasma lipoproteins and plays an important role in high-density lipoprotein metabolism and in the reverse cholesterol transport pathway. In thyrotoxicosis, plasma CEPT activity was increased [10].

vi) Serum cholesterol: Thyroxine is a catabolic hormone, thyrotoxicosis therefore decreases serum cholesterol level, hence atherogenesis is not usual in thyrotoxicosis [11].

vii) Hyperuricemia: In thyrotoxicosis of Grave's disease hyperuricaemia had been reported [12], resulting from the catabolic feature of thyroxine hormone.

viii) Hypokalaemia: Hypokalaemia occurs in thyrotoxicosis. This manifests as periodic paralysis and weakness of muscles at the extremity [13].

ix) Hyper glycemia: Thyroxine is an antagonist of insulin. Hyperglycemia is seen in severe thyrotoxicosis [14].

x) Hyperbilirubinaemia: Hyperbilirubinaemia had been documented in a thyroid storm [15].

(c) Thyrotoxicosis and Psychiatry:

i) The thyroid and the mind and emotions [16]. The psychiatric disturbances which accompany

hyperthyroidism mimic mental illness. People with hyperthyroidism may exhibit marked anxiety and tension, emotional lability, impatience and irritability, distractible over-activity, exaggerated sensitivity to noise and fluctuating depression with sadness and problems with sleep and the appetite. In extreme cases, they may appear schizophrenic, losing touch with reality and becoming delirious or hallucinating.

In instances of hyperthyroidism, some patients have been wrongly diagnosed, hospitalized for months and treated unsuccessfully for psychosis.

The relationship between depression and stress and the thyroid remains unclear. Patients with depression and thyroid dysfunction benefit from thyroid hormone therapy, but whether such therapy is useful to those with depression without thyroid dysfunction remains unclear. Also, stress can lead to thyroid dysfunction and vice versa.

- ii) Thyroid dysfunction and mental disorders [16]. Attention has been directed to the possible role of stress or emotional disturbance in precipitating hyperthyroidism. Psychological disturbances are quite common with thyroid hyperactivity and can be part of the early picture. More serious mental disturbances accompany thyroid crisis and thyroid hormones have been used to treat certain psychiatric disorders. Similarly, drugs used to treat mental illness have also been used in treatment of thyroid dysfunction. Hence thyroid disorders and psychiatry are somehow related. Obembe & Abengowe reported a prevalence of 0.6% for hyperthyroidism in Nigeria psychiatric outpatients [17].

(d)Other Features reported in thyrotoxicosis: Uncommon clinical problems in thyrotoxicosis include Urticaria [18], Pleural effusion [19], Embolic episodes [20] and wernicke encephalopathy [21]. Craniofacial deformities had been documented as in juvenile hyperthyroidism [22].

Causes of Thyrotoxicosis

1.Grave's Disease: This is the commonest cause of thyrotoxicosis. It is an autoimmune disorder that is distinguished clinically from other forms of hyperthyroidism by the presence of a painless diffuse goiter (90%), ophthalmopathy (60%), pretibial myxoedema (1-5%) and less often, thyroid acropachy (<1%). The disease is rare in children, but the frequency increases to a peak in the fourth decade, thereafter declining. There is a female preponderance of 10:1 and there may be a family history of thyroid disease or other autoimmune endocrine disease.

Pathogenesis of Graves' Thyrotoxicosis:

Hyperthyroidism of Graves' disease is mediated by the stimulant action of thyroid stimulating hormone receptor antibodies of thyrocytes. The major thyroid stimulating hormone receptor antibody in Graves' disease is referred to as the thyroid stimulating antibody (TsAb), which binds to and activates the thyroid stimulating hormones receptor, mimicking the effects of thyroid stimulating hormone, namely biosynthesis and secretion of thyroid hormone.

Thyroid stimulating hormone receptor antibodies in Graves' disease may also stimulate thyrocyte proliferation, leading to goiter (thyroid growth stimulating antibodies), or they may block synthesis of thyroid hormone (thyroid stimulating hormone blocking antibodies).

2.Other causes of thyrotoxicosis:

- a) Toxic multinodular goiter
Commonest in women. Here, atrial fibrillation and cardiac failure predominate because the patients here are older than in Graves disease.
Treatment is usually by radioiodine treatment or surgery.
- b) Toxic solitary adenoma
Mostly in females over 40 years.
Treatment is by radioiodine or surgery.
- c) Subacute (de Quervain's) thyroiditis.
It is characterized by the presence of a small tender goiter, caused by an inflammation of the thyroid gland which is induced by viruses such as coxsackie or enteroviruses. The thyrotoxic phase (4-6 weeks) is followed by a similar period of hypothyroidism and finally by full recovery of thyroid function in 4-6 months. Treatment is with Aspirin or other non-steroidal anti-inflammatory drugs, but occasionally a short course (3-4 weeks) of steroids may be required.

Hyperthyroid Crisis (thyroid storm): It is an uncommon medical emergency and is a life threatening exacerbation of thyrotoxicosis. It occurs in patients with untreated or poorly treated hyperthyroidism, in response to stress factors (infection, surgery, trauma), may be precipitated by administration of radioiodine, iodinated contrast agents, or withdrawal of anti-thyroid drugs.

In thyroid storm, clinical features include those of severe thyrotoxicosis, seizure, coma, hyperpyrexia, dehydration, multi-system failure and death within a few hours or days.

Treatment includes rehydration, broad spectrum antibiotic, propranolol, sodium ipodate and carbimazole. Intravenous hydrocortisone or dexamethasone may be helpful.

Investigations of Thyrotoxicosis (7): When thyrotoxicosis is suspected, the diagnosis should be confirmed by measurement of thyroid stimulating hormone and free thyroxine in the serum (TSH, T4), which are usually present in low and high concentration respectively. The concentration of thyroid stimulating hormone may, however, be normal or increased if the cause of thyrotoxicosis is either a pituitary adenoma secreting thyroid stimulating hormone or resistance to thyroid hormone. When the concentration of TSH is low but that of thyroxine (T4) is normal, serum concentration of free triiodothyronine (T3) should be measured to diagnose T3 toxicosis.

Recent Studies on Thyrotoxicosis: Results of active research work activities are available on thyrotoxicosis. In Thailand increasing prevalence of thyroid dysfunction has been reported in HIV-infected patients, both hyperthyroidism and hypothyroidism were recently reported in these patients [23].

In another study the long-term outcome of thyroid function was assessed in patients with amiodarone-induced thyrotoxicosis and compared to sub acute thyroiditis [24]. It was found that 17% of the amiodarone-induced thyrotoxic patients and 5% of the sub acute thyroiditis thyrotoxic patients developed hypothyroidism after correction of thyrotoxicosis, this showed that the Long-term outcome of thyroid function in thyrotoxic patients on treatments depends on the cause of thyrotoxicosis.

The rate of occurrence of thyroid carcinoma in thyrotoxicosis was also reported recently, for instance, incidental thyroid carcinoma was found in 6.9% of subjects with thyrotoxicosis treated by surgery [25]. Thyrotoxicosis and hypothyroidism have been implicated in gynaecological disorders. A recent study reported that about 25% female infertility and 15% menstrual cycle disorders result from thyroid dysfunction [26].

Thyrotoxic hypocalcemic periodic paralysis is becoming increasingly common in the western countries. The diagnosis should not be overlooked in any case presenting with extremity weakness and paralysis, especially considering its irreversible nature. In Tennessee a case of thyrotoxic hypocalcemic periodic paralysis was reported on a Vietnamese patient [27].

Thyrotoxicosis and cardiology remains inseparable. A relatively recent study has reported reversible dilated cardiomyopathy as an unusual presentation of thyrotoxicosis [28]. Thyrotoxicosis is a rare cause of Atrial fibrillation, as reported in a study which evaluated the prevalence of thyrotoxicosis and coexistent disease in patients with atrial fibrillation admitted to a general medicine ward in Iceland [29].

An Overview of the Treatment of Thyrotoxicosis: The management of Graves' disease is primarily directed towards the treatment of hyperthyroidism, but also aims to prevent the development or deterioration of the extrathyroidal manifestations like dermopathy and ophthalmopathy (particularly ophthalmopathy).

Graves' Hyperthyroidism

There are three principal treatments

- Medical (drugs)
- Treatment with radioiodine
- Surgery

All these are effective, but the choice of treatment depends on factors such as local circumstances and experience, characteristics and preference of the patients and access to a specialist centre.

(a) Medical Treatment (drugs)

(i) Antithyroid drugs:

- Carbimazole, methimazole and propylthiouracil constitute the thionamide group of antithyroid drugs.
- They inhibit the organification of iodide and coupling of iodothyronines, thus reducing production of triiodothyronine and thyroxine.
- Propylthiouracil also inhibits the peripheral conversion of thyroxine to triiodothyronine.
- In addition to blocking thyroid hormone biosynthesis; these drugs also lower concentrations of thyroid stimulating hormone receptor antibodies and increase activity of suppressor T cells, which suggests that they have immunosuppressive effects.
- Carbimazole is given 15-20mg tds and later 15-20mg once daily, which makes it the drug of first choice.
- Once patients are taking maintenance dose, serum concentrations of free thyroxine and thyroid stimulating hormone are measured every three months. The duration of antithyroid treatment has been debated (6-24 months) but is usually 18 months.

Adverse effects of antithyroid drugs include:

- *Minor- Maculopapular rash and pruritus, fever, arthralgia, alopecia, nausea, vomiting, abnormal taste sensation.
- *Serious- Agranulocytosis, cholestatic jaundice, hepatitis, lupus-like syndrome, aplastic anaemia and thrombocytopenia.

Outcome of treatment: The relapse rate after 18 months treatment is around 50%. The longer the duration of treatment the lower the relapse rate. The larger the goiter and the more the concentrations of thyroid stimulating hormone receptor antibodies the higher the relapse rate.

ii). B-Blockers: These are useful adjunctive agents and ameliorate some of the clinical features, such as tremor, palpitations and anxiety.

Propranolol (120-240 mg/day) is the most commonly used B blocker, although any could be used. Once euthyroid state has been reached, the b blocker is discontinued or at least reduced (40-80 mg/day).

(b)Radioiodine treatment: Radioiodine acts by destroying functioning thyroid cells and inhibits their ability to replicate; iodine 123 is the isotope used. It is appropriate in nearly all types of hyperthyroidism, especially in elderly people, those with recurrent treatment for hyperthyroidism with anti thyroid drugs, or those in whom drug treatment or surgery is contraindicated. Radioiodine is contraindicated in children, pregnancy and women who are breastfeeding; pregnancy is reportedly safe 4 months or more after treatment.

Treatment regimens, which may vary from centre to centre, include administering either an ablative (large) dose or a calculated (small) dose of radioiodine; there is no evidence that the calculated dose has any advantage over the ablative dose.

Antithyroid drugs are stopped 3-4 days before radioiodine to allow for its effective uptake and resumed 4 days after treatment to prevent thyroid storm, or, more often, radiation thyroiditis.

Thyroid function should be assessed 6-8 weeks after treatment. Given that radioiodine works slowly, it is usual to wait 6 months before giving a further dose of it for persistent hyperthyroidism.

Hypothyroidism, which can occur at any stage after radioiodine treatment, is usually transient in the first 3 months of treatment. Permanent hypothyroidism occurs in 50% of those given high doses of radioiodine by 1 year

(in 10% of those given low doses); its incidence remains at 1-3% per year thereafter.

Radioiodine treatment of Graves' hyperthyroidism carries a small, but definite, risk of the development of worsening of ophthalmopathy.

c)Surgery: Surgery is indicated in the following cases;

- i) Allergic reaction to medical treatment
- ii) Disease refractory to high dose medical treatment.
- iii) Relapsing disease.
- iv) Contraindication to treatment with iodine 123.

Details of surgery is beyond the scope of this review. However, two most important things to remember for surgery are:

- i) Surgery can damage the recurrent laryngeal nerve, so the vocal cords must be checked preoperatively.
- ii) Parathyroid glands may be removed too, so repeated measurements of the serum concentration of calcium must be made in the immediate post operative period.

d)Management of Graves' Ophthalmopathy: The aims of treatment are to relieve the symptoms, to suppress the process of the disease, to restore muscle motility and to improve cosmetic appearance. These measures are necessary in severe cases only and include:

- i) Simple measures-Elevation of the head of the bed.
 - Diuretics
 - Dark glasses
- ii) Local measures-Artificial tears
 - Orbital radiotherapy
 - Prism lense for diplopia
 - Tape eyes shut at night
- iii) Surgical measurements-Tarsorrhaphy
 - Squint/eyelid surgery
 - Orbital decompression
- iv) Immunomodulation-
 - Plasma exchange
 - Cyclosporin, azathioprine

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