

Approach to Thyrotoxicosis

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Abstract

Introduction: Thyrotoxicosis is considered to be one of the common medical conditions. It is generally known to be associated with increasing levels of thyroid hormones circulating in the blood. Thyrotoxicosis might clinically present in several presentations and therefore could be faced by physicians in different medical specialties. In Europe, it impacts about one in two thousand patients every year. Despite the fact that thyrotoxicosis usually manifests with decreased weight, intolerance to heat, and increased heart rate, there are a many other additional manifestations, which present more variably with older age and in patients with relatively mild conditions. It is essential to detect the cause of the thyrotoxicosis, as this helps plan management. Some professionals distinguish between hyperthyroidism and thyrotoxicosis by restricting the former term to explain the cases associated with increased secretion and synthesis of the hormones of the thyroid from the thyroid gland. This clinical review summarizes the latest evidence for the diagnosis and treatment of adult patients with thyrotoxicosis.

Aim of Work: In this review, we will discuss thyrotoxicosis.

Methodology: We did a systematic search for approach to thyrotoxicosis using PubMed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine (<https://scholar.google.com>). All relevant studies were retrieved and discussed. We only included full articles.

Conclusions: Thyrotoxicosis is considered to be one of the common medical conditions. It is generally known to be associated with increasing levels of thyroid hormones circulating in the blood. Decreased weight, intolerance to heat, increased heart rate, tremors, agitation, and exhaustion are generally common clinical manifestations of thyrotoxicosis. The present treatment options for hyperthyroid Graves' disease are thionamide pharmacological agents, using radioiodine, or undergoing thyroid surgery (thyroidectomy). B-blockers (like propranolol modified release one or two times a day) are beneficial to control clinical manifestations in all thyrotoxicosis patients.

Keywords: Thyrotoxicosis; Approach; Management; Diagnosis; Treatment

Introduction

Thyrotoxicosis is considered to be one of the common medical conditions. It is generally known to be associated with increasing levels of thyroid hormones circulating in the blood. Thyrotoxicosis might clinically present in several presentations and therefore could be faced by physicians in different medical specialties. In Europe, it impacts about one in two thousand patients every year [1]. Despite the fact that thyrotoxicosis usually manifests with decreased weight, intolerance to heat, and increased heart rate, there are many other additional manifestations, which present more variably with older age and in patients with relatively mild conditions. It is essential to detect the cause of the thyrotoxicosis, as this helps plan management. Some professionals distinguish between hyperthyroidism and thyrotoxicosis by restricting the former term to explain the cases associated with increased secretion and synthesis of the hormones of the thyroid from the thyroid gland. This clinical review summarizes the latest evidence for the diagnosis and treatment of adult patients with thyrotoxicosis.

Methodology

We did a systematic search for approach to thyrotoxicosis using PubMed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine (<https://scholar.google.com>). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: Thyrotoxicosis, approach, management, diagnosis, treatment.

What are the causes of thyrotoxicosis and who gets it?

Graves' disease is considered to be among the most common condition causing thyrotoxicosis, responsible for about seventy-five percent of cases. It is generally prevalent among females aged between thirty to fifty years but could possibly affect any age in both genders. Patients with a previous history of other autoimmune conditions, those who have a family history of thyroid diseases or other autoimmune conditions, and those who smoke are specifically at a higher risk of developing Graves' disease [2]. Different case-controlled studies [2], but not all [3], have demonstrated a higher reporting of major complications within one year before the diagnosis of Graves' disease, demonstrating that life stress might be a trigger for the medical condition. In addition, several observational studies have demonstrated a higher incidence of new diagnoses or relapses of Graves' disease in females during the postpartum period, indicating that childbirth could be another potential risk factor [4]. Moreover, patients recovering from immunosuppression like HIV patients during highly active antiretroviral therapy also have a relatively increased risk of getting Graves' disease [5]. Thyrotoxicosis that occurs due to toxic nodular goiter is generally commoner among individuals older than sixty years. Those who live in regions deficient with iodine are specifically at a higher risk.

What is the underlying pathophysiology of thyrotoxicosis?

Graves' disease is an autoimmune medical condition that is mediated by anti-bodies which stimulate TSH receptors, causing an increased secretion of thyroid hormones and the development of hyperplastic follicular cells of the thyroid, leading to hyperthyroidism and the development of diffuse goiter. Both environmental (including stress, smoking, and deficient dietary iodine) and genetic factors have essential roles in the pathophysiology of Graves' disease [6]. Hyperthyroidism in a solitary toxic nodule and toxic multinodular goiter is a result of increased secretion of thyroid hormones by one or more nodules. Histologically speaking, these nodules are generally consisted of benign follicular adenomas. Thyroiditis, on the other hand, including subacute, silent, or post-partum, leads to the release of pre-formed hormones into the blood resulting from the inflammatory destruction of the follicles of the thyroid, leading to the development of a transient case of thyrotoxicosis. Gestational hyperthyroidism can also occur in the first trimester of pregnancy due to the higher secretion of thyroid hormone as a response to placental β HCG that is similar structurally to TSH [7]. Gestational hyperthyroidism is specifically common in females who develop hyperemesis gravidarum, as it is linked to higher concentrations of β HCG. Several pharmacological agents, like amiodarone, lithium, iodine, highly active retroviral therapy, interferon α , levothyroxine, and tyrosine kinase inhibitors might potentially lead to the development of thyrotoxicosis in several mechanisms.

What are the clinical features and associated conditions?

Decreased weight, intolerance to heat, increased heart rate, tremors, agitation, and exhaustion are generally common clinical manifestations of thyrotoxicosis. Older individuals usually have less clinical manifestations; a previous study of over three thousand consecutive thyrotoxicosis patients concluded that more than fifty percent of individuals older than sixty years had less than 3 classic clinical manifestations of thyrotoxicosis [8]. Atrial fibrillation is a generally associated character of thyrotoxicosis, specifically among older individuals. A recent large observational study of over half a million individuals demonstrated a thirteen percent cumulative incidence of atrial fibrillation over 8 years among individuals with thyrotoxicosis aged older than sixty-five years. Thyrotoxicosis can sometimes be linked to acute muscle paralysis and/or severe hypokalemia, a case that is sometimes called thyrotoxic periodic paralysis. Thyrotoxic periodic paralysis is generally seen in Asian males who have thyrotoxicosis and is usually stimulated by severe physical activity, relatively high carbohydrate levels, alcohol consumption, or infection [9]. In rare cases, individuals with thyrotoxicosis can manifest with thyroid storm, which is considered to be a severe, potentially-fatal medical condition that it linked to increased heart rate, hyperthermia, severe anxiety, confusion, characteristics of heart failure and abnormal liver function tests [10]. Decreased compliance to treatment, surgery, infections, pregnancy, childbirth and severe trauma are considered to be common predisposing factors of thyroid storm.

How do you determine the cause of thyrotoxicosis?

The diagnosis of a case of primary hyperthyroidism usually depends on the detection of high levels of serum free thyroxine together with the presence of significantly decreased serum TSH levels (less than 0.05 mIU/L). If the concentration of free thyroxine is normal but TSH levels are decreased, then the concentrations of free tri-iodothyronine should be assessed to rule out the presence of a tri-iodothyronine (T3) thyrotoxicosis. This must be taken into consideration as a mild case of hyperthyroidism and is generally seen in cases with toxic multinodular goiter or a toxic thyroid nodule but could possibly also be a character of mild Graves' disease. Low or decreased TSH concentrations in the presence of normal free thyroxine and free tri-iodothyronine concentrations is called subclinical hyperthyroidism.

Obtaining a detailed clinical history and performing a complete physical examination usually help give evidence as to the etiology of the thyrotoxicosis. As examples, dermopathy, ophthalmopathy, and acropachy are important characteristics of Graves' disease. Without the presence of any of these features, establishing a diagnosis of Graves' disease could be done by assessing the serum concentrations of TSH-antibodies. A recently published meta-analysis has demonstrated that such antibodies when measured using immunoassay methods have high sensitivity and specificity for diagnosing Graves' disease (third generation assay can have a sensitivity and specificity that can be as high as 98% and 99%, respectively) [11]. On the other hand, thyroid peroxidase antibodies are only found in about seventy-five of cases of Graves' disease. If TSH receptor antibodies are not detected, a scan of radionuclide thyroid uptake could be useful to determine the etiology of thyrotoxicosis. In cases of subacute thyroiditis, inflammatory markers including erythrocyte sedimentation rate 'ESR' and C reactive protein are often elevated.

When should general practitioners refer?

All individuals who present with a new onset thyrotoxicosis must be evaluated in a secondary care setting, to determine the etiology and to plan management and treatment. Pre-pregnancy consultation for counselling and optimization of management for patients who are currently receiving anti-thyroid pharmacological agents or those who have received radio-iodine therapy or thyroidectomy in the past is also important.

What are the treatment options?

Graves' disease

The present treatment options for hyperthyroid Graves' disease are thionamide pharmacological agents, using radioiodine, or undergoing thyroid surgery (thyroidectomy). B-blockers (like propranolol modified release one or two times a day) are beneficial to control clinical manifestations in all thyrotoxicosis patients. However, they are contraindicated in patients who also have asthma. Anti-coagulation is also important in most thyrotoxicosis patients whose disease is complicated with atrial fibrillation. A randomized trial of anti-thyroid pharmacological agents, thyroidectomy, or radioiodine in Graves' disease demonstrated no significant difference in patients' satisfaction scores with any of the three possible treatment options. Each modality of treatment was found to have its own advantages and disadvantages, and patient preference is usually the most important factor in deciding how to proceed with management.

Thionamide drugs

The thionamide pharmacological agents include propylthiouracil, carbimazole and its active metabolite methimazole, have been used in the treatment of thyrotoxicosis for more than sixty years. A published meta-analysis of randomized trials demonstrated long-term remission of hyperthyroid Graves' disease in over half patients who were treated with thionamide agents for a long-enough period [12]. Carbimazole or methimazole are generally preferred in most cases, as a small risk of serious hepatotoxicity (about one in ten thousand adults) has recently been detected following the use of propylthiouracil [13]. Additionally, carbimazole or methimazole could be administered one a time rather than every eight or twelve hours as with propylthiouracil, and the relatively long half-life leads to better control of the disease. Thionamides decrease concentrations of circulating thyroid hormones by being a preferred substrate for iodination by thyroid peroxidase, the most important enzyme in the synthesis of the thyroid hormone. Most individuals who have hyperthyroid Graves' disease are considered euthyroid (based on the presence of normal free thyroid hormone levels) following four to eight weeks of treatment with methimazole (15 - 30 mg everyday) or carbimazole (20 - 40 mg every day). Patients who suffer from severe hyperthyroidism (free thyroxine more than 70 pmol/L), large goiter, or recent exposure to iodide (this includes exposure to contrast media that is used in computed tomography) might need to be treated for longer, and/or with larger doses of thionamide.

After a state of euthyroidism is achieved, two different treatment regimens could be used. In the first one of them, which is called "block-replace", the dose of thionamide is remained stable (for example, carbimazole 40 mg every day), therefore stopping the production of thyroid hormone, and levothyroxine can then be added in a suitable dose to keep the state of euthyroidism (for example, 100 µg every day for females and 125 µg every day for males). In the other treatment regimen, which is called "titrated", the dose of thionamide is progressively decreased at a regular interval to allow the endogenous synthesis of thyroid hormones to maintain in a regulated manner. In both treatment regimens the remission rate is about fifty percent if the treatment is continued for between six and eighteen months and then ceased [14]. The most important drawback of using any of those two regimens is the unavailability of certainty regarding whether patients could relapse when treatment is stopped and the potential adverse events of the agents used.

A pruritic rash that is usually temporary, is typically seen in about five percent of patients using anti-thyroid agents. The more rare but potentially fatal complication of thionamides used is the induced agranulocytosis that is found in about one in three hundred patients. It typically manifests with sore throat, ulcers of the mouth, and severe fever. All patients receiving anti-thyroid drug treatment must get clear verbal and written information instructing them about this complication with giving advice to immediately stop the agent and get a blood test for full blood count in case they develop any of these warning manifestations. Agranulocytosis happens most commonly during the first 3 months after starting treatment (median thirty days) and is considered to be rare after 6 months have passed [15]. A previous observational study of more than five thousand patients from Japan found that agranulocytosis occurred in 0.8 percent of patients who initiated treatment with 30 mg methimazole compared to 0.2 percent of patients starting with only 15 mg, indicating that dose of the drug is an essential risk factor. Whether administering titrated or block-replace regimens, studies have shown that long-term treatment for more than eighteen months does not improve remission rates, and the agents must usually be stopped at this stage, with assessing thyroid function at four to six weeks to detect the presence of possible early relapse.

The ideal patients to manage with anti-thyroid agents for the treatment of Graves' disease are patients who have a relatively high chance of getting into remission following treatment. Thus females, individuals older than forty years, the presence of a small thyroid, the absence of extra-thyroidal manifestations, the presence of mild hyper-thyroxinaemia, or tri-iodothyronine thyrotoxicosis at initial presentation and a low titre of TSH antibodies are highly likely to develop successful outcomes following pharmacological treatment [16]. Following relapse, a long-term, small dose of thionamide is considered to be an acceptable option where definitive treatment with radioiodine or surgery is not available.

Thyroid surgery

Total (or subtotal) thyroidectomy is considered to be a highly effective and predictable treatment option for patients who have Graves' disease. Graves' disease patients who have relapsed following adequate pharmacological treatment, those who have active ophthalmopathy, or those who have a cosmetically unwanted goiter are all good candidates for surgical intervention. Long term adverse events of thyroidectomy surgery include hypocalcemia resulting from hypoparathyroidism, that is usually temporary, and vocal cord paresis as a result of operative injury of the recurrent laryngeal nerve.

Toxic multinodular goiter and solitary toxic nodule

Anti-thyroid agents do not cause long term remission of cases of thyrotoxicosis when the etiology is toxic multinodular goiter or solitary toxic nodules. Thus, radioiodine treatment is considered to be the best treatment modality for most individuals with these diseases. When radioiodine treatment is not achievable, alternatives include a small long-term dose of carbimazole (or methimazole) or undergoing surgery of the thyroid.

Thyroiditis

Thyrotoxicosis that is associated with thyroiditis is usually temporary, and usually progresses following a hypothyroid phase, and then recovers spontaneously. Anti-thyroid agents are not considered to be effective and must not be administered. Treatment is usually limited to symptoms control using β -blockers. In the cases of subacute thyroiditis, NSAIDs and frequent systemic glucocorticoids might be needed to control the presence of pain.

Pregnancy and lactation

Graves' disease is considered to be the most common etiology of hyperthyroidism that manifests during pregnancy; however, it must be distinguished from gestational hyperthyroidism that is mediated by β HCG. The latter is characterized by the absence of a large goiter or ophthalmopathy, and TSH antibodies, and it spontaneously recovers by twenty weeks of gestation. Anti-thyroid agents are the most important modalities of treatment for hyperthyroid Graves' disease manifesting pregnancy, and a titrated dose regimen is obligatory as block-replace regimens have been linked to a risk of developing fetal hypothyroidism and goiter. A population-based birth cohort study in Denmark demonstrated the development of birth defects in up to nine percent of offspring of pregnant females who used carbimazole or methimazole, when compared to eight percent of pregnant females who used propylthiouracil and five percent in untreated pregnant females with hyperthyroidism.

Thyroid eye disease

Radioiodine must be avoided in the presence of active Graves' ophthalmopathy. Anti-thyroid agents in a block-replace regimen are probably the best treatment modalities until the ophthalmopathy becomes inactive. If this could not be tolerated then surgery with total thyroidectomy is considered to be a good option. Patients with ophthalmopathy might need specific treatment and should be referred early to specialist services [17].

Subclinical hyperthyroidism

The term 'Subclinical hyperthyroidism' refers to the presence of a state of low or suppressed serum TSH levels with normal circulating free thyroxine and free triiodothyronine levels. It occurs in about three of patients over the age of eighty years, with around 0.7 percent having the more important abnormality of suppression of serum TSH levels to less than 0.1 mIU/L. Prospective studies have shown that more than half of patients with subclinical hyperthyroidism, and particularly those with a low but not suppressed TSH level, have a transient abnormality. A low or suppressed TSH level may also be caused by several drugs, including opiates, levodopa, anti-inflammatory doses of glucocorticoid, metformin, and levothyroxine. In addition, persistently low or suppressed serum TSH levels can presage more

major systemic illness, such as chronic infection or covert cancer. Although epidemiological studies show that a low serum TSH level is associated with an increased risk of atrial fibrillation, and in some studies excess vascular mortality, only a few patients have evidence of intrinsic thyroid disease. Current opinion favors consideration of antithyroid treatment in patients aged more than sixty-five years with a persistently suppressed TSH level (< 0.1 mIU/L), particularly in the presence of atrial fibrillation or other cardiac problems. In people with untreated subclinical hyperthyroidism, thyroid function tests should be carried out annually to detect progression to overt thyrotoxicosis

Conclusions

Thyrotoxicosis is considered to be one of the common medical conditions. It is generally known to be associated with increasing levels of thyroid hormones circulating in the blood. Decreased weight, intolerance to heat, increased heart rate, tremors, agitation, and exhaustion are generally common clinical manifestations of thyrotoxicosis. The present treatment options for hyperthyroid Graves' disease are thionamide pharmacological agents, using radioiodine, or undergoing thyroid surgery (thyroidectomy). B-blockers (like propranolol modified release one or two times a day) are beneficial to control clinical manifestations in all thyrotoxicosis patients.

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