The Egyptian Journal of Hospital Medicine (October 2017) Vol. 69 (6), Page 2743-2749

Diagnosis and Management of Thyrotoxicosis

Awatif Ahmed Althubyani[1], Alaa Jamal Akbar[2], Mohammed Mahmoud Alenezy[2], Abdulilah Ateeq Alsolami[2], Saleha Ahmed Aleid[3], Saud Abdullah Naser Alasmi[1], Al Qahtany. Faisal Hani M[3], Yazeed Waleed O Alfadl[1], Mohammed Taha A Alnoor[1], Manar Ibrahim Y Sangoura[1], Waleed Eid Alraddadi[1], Afnan Shukri A Sharourou[4]

1- Ibn Sina National College, 2- King Abdulaziz University ,

3- Imam Abdulrhman Bin Faisal University, 4- Royal College of Surgeons in Ireland

Corresponding Author: Awatif Ahmed Althubyani - Tofe3636@hotmail.com - 0553348289

ABSTRACT

Background: thyrotoxicosis is a hypermetabolic state due to excessive amounts of thyroid hormone in the circulation. There are several causes and the worst presentation is a thyroid storm, which is an endocrinal emergency. Clinically, thyrotoxicosis can present vaguely leading to misdiagnosis and mismanagement.

Aim of the work: this study aimed to understand the clinical presentation of thyrotoxicosis, its diagnosis and ways of management.

Methodology: we conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE from January 1987 to March 2017.

Conclusion: due to its vague presentation, thyrotoxicosis can be misdiagnosed and managed wrongly, leading to life threatening condition called thyroid storm. Health care physicians must keep a high degree of suspicion in order to provide prompt therapeutic measures to avoid complications as well as death of patient.

Keywords: thyrotoxicosis, diagnosis of thyrotoxicosis, thyroid storm, management of thyroid storm, anti-thyroid drugs, thyroidectomy

INTRODUCTION

Hyperthyroidism is defined more than normal production of thyroid hormone by the thyroid gland and release into circulation which results in excessively high levels in serum. This out of proportion amount of hormone leads to a speeded up metabolic state. The common causes are diffuse toxic goiter also known as Grave's disease, toxic multinodular goiter and toxic adenoma [1].

Thyrotoxicosis, on the other hand, refers to an acute hypermetabolic state that gives rise to an excessive amounts of serum thyroid hormone, but also consists of extrathyroidal sources of thyroid hormone for instance exogenous intake or release of preformed stored hormone from the glands. A frequent cause of thyrotoxicosis is thyroiditis which is inflammation of the thyroid gland leading to release of the stored hormone.

Clinically, thyrotoxicosis presentation can vary from asymptomatic to a life threatening thyroid storm. Thyroid storm is an absolute endocrine emergency. Its diagnosis is derived from history, signs,symptoms and laboratory findings [2].

Thyroid hormone impacts every organ system and therefore, can result in a mixture of complaints that are challenging to recognize. Moreover, if undiagnosed, it can result into serious complications including delirium, anorexia, atrial fibrillation, congestive heart failure (CHF), osteoporosis, thromboembolism, muscle weakness, altered mental status and even death. People at higher risk for serious complication included pregnant women, elderly and children. It is vital that the emergency medicine provider keeps a high clinical suspicion for thyrotoxicosis in patients with a cluster of apparently unrelated symptoms. Thyroid storm needs to be recognized rapidly and managed aggressively in order to avoid multi-organ failure and death [1].

METHODOLOGY

- Data sources and search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed and EMBASE, from January 1987 to March 2017. The following search terms were used: hyperthyroidism, thyrotoxicosis, diagnosis of thyrotoxicosis, thyroid storm, management of thyroid storm, anti-thyroid drugs

- **Data Extraction**

Two reviewers have independently reviewed the studies, abstracted data and disagreements were resolved by consensus. Studies were evaluated for

Received: 21/09/2017
Accepted: 30/09/2017

DOI: 10.12816/0042258

quality and a review protocol was followed throughout.

The study was done after approval of ethical board of King Abdulaziz University.

DIAGNOSIS OF THYROTOXICOSIS

Clinical Presentation

Thyroid hormone upsurges tissue thermogenesis and the basal metabolic rate, hence, thyrotoxicosis results in a hypermetabolic state in which T3 and free T4 affect multiple organs. The range of physical indices depends on a number of factors comprising patient age and period of illness and can vary from asymptomatic in case of subclinical condition to life threatening scenario in thyroid storm. The amount of rise in circulating thyroid does not correlate consistently with severity of symptoms. Younger patients typically present with evident symptoms of increased sympathetic stimulation such as restlessness, anxiety and tremor, while older patients are likely to present with less evident signs. Elderly patients can lack adrenergic symptoms and rather present with weight loss, depression and fatigue known as apathetic hyperthyroidism. Patients usually have a collection of complaints fluctuating from specific ailments linked to one organ system to vague constitutional symptoms. There is an extensive range of differential diagnoses to consider based on such clinical presentation [3].

Hyperthyroidism has severe effects on the nervous system. Cognitive impairment and altered mental status and can present subtly. Anxiety, tremors, seizures, nervousness and emotional lability are other consequences. Unfortunately, patients are often misdiagnosed with psychiatric disorder or substance abuse. Therefore, the emergency medicine physician must consider screening all patients for hyperthyroidism who present with new-onset psychiatric symptoms. Over 50% of patients complain of muscle weakness and easy fatigability especially the shoulder and pelvic girdle areas resulting in difficulty to climb stairs, comb hair or rise out of the seated position. Sometimes these symptoms may be mistakenly ascribed to neuromuscular disorders [4].

Thyroid hormone has important effects on cardiovascular system. Being a lipophilic hormone it effortlessly diffuses through the cytoplasmic membrane of cardiomyocytes. Hyperthyroidism leads to increased expression of myocardial sarcoplasmic reticulum calcium-dependent ATP resulting in increased myocardial chronotropy increasing the heart rate and inotropy increasing contractility, overall resulting in increased left ventricular ejection fraction and cardiac output [5]. It yet remains unclear if thyroid hormone causes sensitivity to catecholamines. The hypermetabolic state leads to higher consumption of oxygen, production of metabolic end products and arterial smooth muscle relaxation. Consequently, systemic vascular resistance decreases is leading to activation of the renin-angiotensin system thus expanding the blood volume. The overall effect is an increased preload and decreased afterload [2].

Subsequently, cardiovascular symptoms include palpitations with a high resting heart rate and amplification during exercise. Younger patients may present with sinus, while atrial fibrillation is the most commonly seen with advanced patient age, with preexisting heart conditions and male sex. Arrhythmias such as flutter, supraventricular tachycardia and ventricular tachycardia are not very common. In thyroid storm, congestive heart failure occurs particularly in patients with preexisting heart disease including ischemic, alcohol cardiomyopathy, or hypertensive and the amplified metabolic demands additionally impair the previously weakened myocardium. Most cases of heart failure are reversible and recover with treatment of primary hyperthyroid state and the heart failure. Hyperthyroidism can rarely unmask silent conditions such as a new-onset atrial fibrillation, angina or heart failure should not be solely secondary to thyroid dysfunction unless until other structural disease has been excluded [5].

The cardiac disorders due to thyrotoxicosis can consequently affect the lungs. High-output heart failure can successively lead to dilatation of the pulmonary artery and lead to pulmonary arterial hypertension. The potential for severe pulmonary artery hypertension attributable to thyrotoxicosis alone remains uncertain. Additional thyroid hormone also changes pulmonary function by making respiratory muscles weaker, increasing airway resistance, and decreasing overall lung compliance [6].

Thyrotoxicosis can have noteworthy effects on the gastrointestinal tract. Surplus sympathetic stimulation can cause increased motor contractions in the intestine leading to an increased intestinal transit time and diarrhea. Nausea and vomiting are

frequent resultant complaints. Dysphagia can also occur due to a decreased closure of upper esophageal sphincter and reduced propulsion of pharyngeal muscles. Thyrotoxicosis can cause substantial issues with the reproductive system, most remarkably infertility.

Women with excess thyroid hormone present with an ovulation, menometrorrhagia, oligomenorrhea and amenorrhea. Men on the other hand, have symptoms related to estrogen excess, resulting in gynecomastia, decreased libido, and spider angiomas. The postmenopausal women can display severe osteoporosis, predisposing them to fractures [7].

Physical Examination

A thorough physical examination is essential in diagnosis of thyrotoxicosis as it may reveal a specific cause. Specific attention should be given to neck and eye examination, along with neurologic, pulmonary, cardiac, and integumentary systems. It is important to assess size, nodularity and tenderness. The gland is usually soft and non-tender. In conditions like Graves' disease, malignancy and thyroiditis the gland could be enlarged, firm, nodular, tender, and asymmetric depending on the pathology [8].

Ophthalmologic examination can reveal further abnormalities such exophthalmos in Grave's disease, and less significant proptosis can occur in thyrotoxicosis from sympathetic hyperactivity leading to elevation of levator palpebrae superioris muscle. Patients may seem to stare and display a lid lag. The neurologic examination may show a nervous, agitated, or restless patient with fine tremor in hand, feet, tongue and facial muscles.

In thyroid storm, the modification of mental status can vary from catatonia with depression to blunt psychosis. Hyperreflexia is a common finding [9].

Almost all patients with thyrotoxicosis display a resting tachycardia and an increased blood flow through the aorta leads to a systolic murmur. Additionally, patients may develop murmurs from noteworthy mitral regurgitation and tricuspid regurgitation. High systolic and low diastolic blood pressures cause a widened pulse pressure that can exacerbate the intensity of the normal heart sounds and present as hyperactive precordium along with bounding peripheral pulses. The carotid upstroke will appear as rapid and brisk.

In the elderly patients, an irregularly irregular pulse may be noticed. Patient may appear dyspneic from tachypnea secondary to the body's increased oxygen demand and carbon dioxide production. Patients with pre-existing pulmonary disease can tire from lengthy respiratory exacerbations; and therefore, profound thyrotoxicosis can cause diaphragmatic fatigue, respiratory muscle weakness, and eventually pulmonary decompensation [5].

Diagnostic Studies

In all types of overt thyrotoxicosis, the value of TSH in serum is decreased and the values of free thyroxine (T4) or free tri-iodothyronine (T3), or both, are high. Around 95% of patients with thyrotoxicosis have a raised T4. A small number (5%) of patients have normal T4 and with high T3 only which is known as T3 toxicosis. Therefore, obtaining a total T3 is crucial in diagnosing.

Subclinical thyrotoxicosis is considered when concentration of TSH is persistently low in serum, with normal free T3 and T4 values. There is no clinical practicality in obtaining a total T4 in the emergency department as several drugs interact with thyroid hormone–binding proteins and hence can confound the diagnosis [2].

After thyrotoxicosis has been recognized by laboratory values, a thyroid radioiodine uptake and scan may be useful in distinguishing the underlying cause. A scan can help differentiate between Graves' disease (with diffused uptake) versus toxic multinodular goiter (with focal areas of increased uptake). The presence of high serum concentrations of thyroperoxidase (TPO) antibodies points to an autoimmune thyroid disorder, while high TSI value indicated Graves' disease. Ultrasonography with Doppler flow is used when radiation exposure is contraindicated, such as in pregnancy and breastfeeding mothers. A summary is depicted in **table 1** [10].

Table 1. Diagnostic Studies for Thyrotoxicosis Causes

Condition	TSH	FT4	FT3	Radio-active Iodine Uptake	Other findings
Grave's Disease	low	high	high	high uptake	thyroid-peroxidase antibody; TSH-receptor antibody
Toxic Thyroid Adenoma Hot Nodule	low	high	high	normal uptake	suppression of other forms of tissue
Toxic Multinodular Goiter	low	high	high	multiple nodules	
Subacute Thyroiditis	low	high	high	low uptake	raised thyroglobulin level
Factitious Thyrotoxicosis	low	high	high	low uptake	absent thyroglobulin level
Iodine-induced Hyperthyroidism	low	high	high	low uptake	history of Amiodarone exposure
Untreated Hyperthyroidism	low	high	high	high uptake	*
T3 Toxicosis	low	normal	high	normal to high uptake	*
Exogenous Thyroid Hormone	normal	normal T4, low T3	high T3, normal T4	low uptake	*

MANAGEMENT OF THYROTOXICOSIS

Therapy for thyrotoxicosis is subjected to on the underlying etiology. Treatment methods include antithyroid drugs as summarized in (**Table 2**) [11], radioactive iodine, surgery and medications for controlling symptom.

Anti-thyroid Drugs

The most frequently used antithyroid drugs are the thionamides which includes propylthiouracil (PTU), and methimazole (MMI). Thionamides inhibit the synthesis of T4 by inhibiting the organification step of tyrosine residues. Additionally, PTU blocks peripheral conversion of T4 to T3. Thionamides decrease thyroid hormone synthesis and control hyperthyroidism within few weeks in majority of patients. They also decrease serum TSI concentrations in Graves' disease aptients. Thionamides are used in patients with Graves' disease in order to induce a remission. Since toxic nodular goiter rarely goes into remission, thionamides are used for the short term management of patients with toxic nodular goiter, to induce euthyroidism before ultimate treatment, but are not suitable for long term therapy. Thionamides are never applicable for the treatment of patients with thyroiditis since no excess synthesis of thyroid hormone takes place [12].

Minor adverse effects—including fever, rash, urticaria, and arthralgias—happen in about 5% of patients who are taking thionamides. More severe adverse effects are rare. The ill effects of methimazole and carbimazole may be dose related. Agranulocytosis can happen in approximately 0.5% of patients being treated with thionamides. Mild increase in transaminase enzyme concentrations are noticed in up to 30% of patients taking PTU, however severe hepatotoxicity is rare. Patients on methimazole or carbimazole may experience reversible cholestasis and rarely, acute inflammatory hepatitis. Lastly, vasculitis has been described as a rare complication of PTU use [13].

Other drugs

For patients who present with severe hyperthyroidism or those with thyroiditis, in whom thionamides are not appropriate, adjunctive medications may be used to improve symptoms or reestablish euthyroidism rapidly. However, these therapies do not treat the underlying causes of thyrotoxicosis. Beta blockers relieve acute symptoms including tremor, tachycardia, and anxiety in a thyrotoxic patient. Beta blockade must be used as the chief treatment only in patients with

thyrotoxicosis owing to thyroiditis. High dose glucocorticoids can be used to inhibit peripheral conversion of T4 to T3 in patients presenting with thyroid storm (which is the most severe form of thyrotoxicosis) [11]. Glucocorticoids are also used to relieve severe anterior neck pain and to reestablish euthyroidism in patients who had painful subacute thyroiditis. Inorganic iodide decreases the production of thyroid hormone and release from the thyroid gland for short term. It is used to manage patients with thyroid storm or, more frequently, to decrease thyroid vascularity prior to thyroidectomy. Iopanoic acid, which is an oral cholecystographic agent rich in iodine, reduces production and release of thyroid hormone and blocks the conversion of T4 to T3. Short term use is effective for the management of thyroid storm or for prompt preparation for thyroidectomy surgery, but it is unsuccessful as long term treatment [14].

Radioactive iodine

Treatment with ^{131}I is beneficial for individuals with hyperthyroidism due to Graves' disease or toxic nodular goiter. In patients with toxic multinodular goiter the radioactive iodine therapy reduces goiter size by 40%. ^{131}I ultimately causes permanent hypothyroidism in nearly all patients. Possible side effects of ^{131}I therapy consist of mild anterior neck pain due to radiation thyroiditis or even worsened thyrotoxicosis for several days, as a result of leakage of preformed thyroid hormones from within the damaged thyroid gland. Therefore, pretreatment with a thionamide can decrease the risk for worsened thyrotoxicosis following treatment with ^{131}I. Graves' ophthalmopathy may occur or worsen after management with ^{131}I, particularly in smokers and in patients with severe stat of hyperthyroidism [15]. Radioactive iodine therapy is comparatively contraindicated in pediatrics age and adolescents due to the lack of data regarding the long term risks linked with radiation. Radioactive iodine is absolutely contraindicated for pregnant and lactating women [16].

Thyroidectomy

Studies suggested that thyroidectomy cures hyperthyroidism in over 90% of cases. It further eradicates compressive symptoms resulting from large toxic multinodular goiters. Contrasting radioactive iodine treatment, it is not related with worsening of Graves' ophthalmopathy. Thyroidectomy is harmless in the second trimester of pregnancy. The procedure stands almost no danger of death when carried out by knowledgeable surgeons. Nevertheless, thyroidectomy is complicated by recurrent laryngeal nerve damage or by permanent hypoparathyroidism as recorded in 1-2% of patients. Transient hypocalcaemia, infection, and bleeding are some potential complications. Surgery also results in permanent hypothyroidism [17].

Before thyroidectomy thionamides are used to restore euthyroidism in order to avoid more severe thyrotoxicosis resulting from leakage of thyroid hormone into the circulation during surgery, and also in order to reduce operative and postoperative complications accompanied with surgery and anesthesia in a thyrotoxic patient [14].

Treatment of Thyroid Storm

Rapid recognition and commencement of treatment is crucial for good results. Medical management is directed at blocking peripheral effects of thyroid hormones and regulating the overactive thyroid gland. These patients are usually serious and must have prompt placement of large-bore intravenous access, cardiac monitoring, and supplemental oxygen. Aggressive volume resuscitation must be started instantly with the exclusion of patients with concomitant heart failure. Since cardiovascular collapse is frequently the cause of decompensation, β-blockers must be started first. β-blockers manage patient symptoms as well as sympathetic hyperactivity [18]. The initial β-blocker can be propranolol, while esmolol infusion may be an alternate choice. High-dose steroid must be administered early to help enhance vascular tone. Both β-blockers and steroids decrease the peripheral conversion of T4 to T3.

PTU is the favored medication for thyroid storm since it also decreases peripheral conversion of T4 to T3. It moreover decreases the synthesis of T4 and T3 inside the thyroid gland. PTU and MMI are accessible in oral preparations. They can be administered orally, by nasogastric tube, or per rectum as clinically specified. The initial loading dose for PTU is 600-1000 mg, then decrease to 250 mg every 4 hours. MMI can be given 20 mg every 4 hours [19].

Acetaminophen and cooling devices may be used in case of hyperthermia. Salicylates must be

avoided because they can surge free thyroid hormone levels by lessening thyroid-binding protein in the serum. If a primary infectious cause is supposed, early broad-spectrum antibiotics should not be forgotten and must be initiated as soon as possible. Patients who display refractory life-threatening symptoms must undergo hemodialysis after medical management has failed [20].

Table 2. Medications Used in Thyrotoxicosis Management

Drug	Drug Type	Action	Adult Dose	Thyroid Storm Dose
Antithyroid agents	Propylthiouracil	Prevents T3, T4 production in thyroid; prevents peripheral conversion of T4 to T3	initial: 100-200mg PO; Maintenance: 50-100 mg/d	500-1000 mg loading dose, then 250 mg Q4-6 h
	Methimazole	Prevents thyroid hormone production	initial: 10-20 mg; Maintenance: 2.5-10 mg/d	60-80 mg/d
Iodides	Lugol solution	blocks release of stored thyroid hormone from gland	4-8 drops Q 6-8 h	10 drops Q12 h
	Potassium iodide	*	5-10 drops Q6-8 h	5-10 drops Q6-8 h
Glucocorticoids	Dexamethasone	Blocks conversion of T4 to T3	2 mgQ6 h	2 mgQ6 h
	Hydrocortisone	*	Prednisone 40-60 mg/d taper	300 mg IV load, 100 mg IV Q 6-8 h
Beta blockers	Propranolol	Symptomatic control, blocks conversion of T4 to T3	10-40 mg Q6-8 h	1 mg/min IV, then 60-80 Q4 h
	Atenolol	*	25-100 mg daily	*
	Esmolol	*	*	500 ug/kg/min for 1 min, then 50-100 ug/kg/min

CONCLUSION

Thyrotoxicosis and hyperthyroidism are hypermetabolic conditions that give rise to significant morbidity and mortality.

The diagnosis can be challenging because signs and symptoms can mimic many other disease states resulting in an inaccurate diagnoses and management. Thyroid storm is the most dangerous form of thyrotoxicosis, manifested by altered sensorium, and, if not promptly treated, can lead to significant mortality.

Thyroid storm must be kept I mind in the differential of any patient who present with altered mental status. The emergency medicine physician must be prepared to rapidly recognize

thyrotoxicosis, recognize the precipitating event, properly and systematically begin medical management, and enable disposition in order to undoubtedly save a life.

REFERENCES

1. **Kravets I (2016):** Hyperthyroidism: diagnosis and treatment. Am. Fam. Physician, 93: 363-370.
2. **Pearce EN (2006):** Diagnosis and management of thyrotoxicosis. BMJ., 332: 1369-1373.

3. **Goichot B, Caron P, Landron F and Bouee S (2016):** Clinical presentation of hyperthyroidism in a large representative sample of outpatients in France: relationships with age, aetiology and hormonal parameters. Clin. Endocrinol. (Oxf.), 84: 445-451.
4. **Song TJ, Kim SJ, Kim GS, Choi YC and Kim WJ (2010):** The prevalence of thyrotoxicosis-related seizures. Thyroid, 20: 955-958.
5. **Fazio S, Palmieri EA, Lombardi G and Biondi B (2004):** Effects of thyroid hormone on the cardiovascular system. Recent Prog. Horm. Res., 59: 31-50.
6. **Silva DR, Gazzana MB, John AB, Siqueira DR, Maia AL and Barreto SS (2009):** Pulmonary arterial hypertension and thyroid disease. J. Bras Pneumol., 35: 179-185.
7. **Doufas AG and Mastorakos G (2000):** The hypothalamic-pituitary-thyroid axis and the female reproductive system. Ann. N. Y. Acad. Sci., 900: 65-76.
8. **Bomeli SR, LeBeau SO and Ferris RL (2010):** Evaluation of a thyroid nodule. Otolaryngol. Clin. North Am., 43: 229-238.
9. **Saraci G and Treta A (2011):** Ocular changes and approaches of ophthalmopathy in basedow - graves-parry- flajani disease. Maedica (Buchar), 6: 146-152.
10. **Wayne EJ (1954):** The diagnosis of thyrotoxicosis. Br. Med. J., 1: 411-419.
11. **Azizi F (2006):** The safety and efficacy of antithyroid drugs. Expert. Opin. Drug Saf., 5: 107-116.
12. **Cooper DS *et al.* (1983):** Propylthiouracil (PTU) pharmacology in the rat. II. Effects of PTU on thyroid function. Endocrinology, 113: 921-928.
13. **Taylor PN, Vaidya B (2012):** Side effects of anti-thyroid drugs and their impact on the choice of treatment for thyrotoxicosis in pregnancy. Eur. Thyroid. J., 1: 176-185.
14. **Nicoloff JT, Fisher DA and Appleman MD J (1970):** The role of glucocorticoids in the regulation of thyroid function in man. J. Clin. Invest., 49: 1922-1929.
15. **Lee SL (2012):** Radioactive iodine therapy. Curr. Opin. Endocrinol. Diabetes Obes., 19: 420-428.
16. **Gorman CA (1999):** Radioiodine and pregnancy. Thyroid, 9: 721-726.
17. **Mittendorf EA and McHenry CR (2001):** Thyroidectomy for selected patients with thyrotoxicosis. Arch Otolaryngol Head Neck Surg., 127: 61-65.
18. **Carroll R and Matfin G (2010):** Endocrine and metabolic emergencies: thyroid storm. Ther. Adv. Endocrinol. Metab., 1: 139-145.
19. **Isozaki O *et al.* (2016):** Treatment and management of thyroid storm: analysis of the nationwide surveys: The taskforce committee of the Japan Thyroid Association and Japan Endocrine Society for the establishment of diagnostic criteria and nationwide surveys for thyroid storm. Clin. Endocrinol. (Oxf.), 84: 912-918.
20. **Sebe A, Satar S and Sari A (2004):** Thyroid storm induced by aspirin intoxication and the effect of hemodialysis: a case report. Adv. Ther., 21: 173-177.