CLINICAL REVIEW

Thyroid Storm

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Thyroid storm is a life-threatening emergency that presents with exaggerated symptoms of thyrotoxicosis along with multi-organ system dysfunction. An acute precipitating factor is often present. Diagnosis is based on clinical suspicion, diagnostic systems, and thyroid hormone testing. The most common underlying cause of thyroid storm is Graves' disease. Acute treatment involves supportive measures, controlling increased adrenergic tone, as well as aggressive therapy aimed at reducing thyroid hormone synthesis, release, and peripheral conversion of thyroxin (T_4) to triiodothyronine (T_3). Definitive treatment should be pursued after stabilization. Early recognition and prompt treatment are imperative to prevent mortality.

Case Report

A 53-year-old female with a history of mild intermittent asthma presented to the emergency department (ED) with palpitations and chest pain. She reported several months of dyspnea with exertion and a 15-pound unintentional weight loss. She saw her primary doctor two days prior and was noted to have tachycardia with a heart rate of 130 beats per minute (bpm). An albuterol inhaler was prescribed for possible asthma exacerbation. She used her albuterol inhaler several times with no relief of dyspnea. On the day of admission, she had dyspnea and used several puffs of albuterol without relief and then developed palpitations and chest discomfort for several hours prompting an ED visit. On review of systems, she reported subjective fevers for several weeks and intermittent diarrhea. Her family was also present and reported her to be anxious, agitated, and forgetful at times. The patient noted significant work and home related stressors. She denied edema, cough, dysuria, or abdominal pain. Home medications included a beclomethasone inhaler and the recently prescribed albuterol inhaler.

On examination, the patient was a thin female in moderate distress. She was anxious, tearful, and mildly agitated. She initially declined admission due to concern about contracting COVID-19. Vital signs showed blood pressure 138/99 mmHg, heart rate 168 bpm, respiratory rate 20 breaths per minute, oxygen saturation 98% on ambient air, and body mass index 15.9 kg/m^2. The thyroid was diffusely enlarged and nontender. Cardiovascular exam showed tachycardia with an irregularly irregular rhythm, without peripheral edema. Respiratory effort was normal, and lungs were clear to auscultation bilaterally without wheezes or crackles. Abdomen was benign. The patient was anxious but alert and oriented and appropriately answered all questions. Neurologic exam otherwise revealed only a mild tremor.

Laboratory testing showed normal complete blood count, basic metabolic panel, and liver enzymes. COVID-19 PCR was negative. Thyroid testing showed depressed TSH < 0.2 mcIU/mL, high free T4 > 7.0 ng/dL (range 0.8 – 1.7), total T3 564 ng/dL (rang 85-185), and free T3 > 2,900 pg/dL (range 222 – 383) Troponin was normal, and B-type natriuretic peptide was mildly elevated at 140 pg/mL. EKG showed atrial fibrillation with rapid ventricular response with a heart rate of 140 bpm. Chest x-ray revealed clear lungs with no acute cardiopulmonary process. Thyroid ultrasound showed a diffusely enlarged, hypoechoic, and hypervascular thyroid gland.

In addition to rapid atrial fibrillation, the patient was diagnosed with thyrotoxicosis with high suspicion for thyroid storm based on Burch-Wartofsky Point Scale score of 45 (10 points for agitation, 25 points for HR > 140, 10 points for atrial fibrillation). After further discussion about the severity of her illness, the patient agreed to admission and further treatment. She was initially given intravenous (IV) diltiazem and eventually converted to sinus rhythm. Endocrinology and cardiology were consulted, and the patient was initiated on propylthiouracil (PTU) 200 mg every 4 hours, stress dose hydrocortisone (100 mg intravenous IV every 8 hours), and propranolol 20 mg TID. The following morning, potassium iodide (SSKI) was added. Per endocrinology consult, PTU was stopped and methimazole 20 mg BID was started due to lower risk of hepatic toxicity. On the following day, her heart rate was normal, and she felt much improved. An acute precipitant other than social stress was not identified. The patient was eager to leave the hospital and was counseled extensively on thyrotoxicosis treatment. SSKI was stopped and she was discharged on methimazole, a hydrocortisone taper, and propranolol. Close endocrinology follow-up with twice weekly thyroid testing was arranged.

Thyrotropin binding inhibitory immunoglobulins (TRAb) and thyroid stimulating immunoglobulin levels subsequently returned markedly elevated, consistent with a diagnosis of Grave's disease. Thyroid labs were monitored closely and the methimazole dose was weaned over several weeks to a maintenance dose. Propranolol was continued for several months. Endocrine surgery recommended thyroidectomy for definitive treatment, but the patient declined due to preference of ongoing medical management with methimazole. She slowly regained energy, gained weight, and dyspnea with exertion improved.

Discussion

Thyrotoxicosis is a nonspecific term for the clinical syndrome that results from excess thyroid hormone levels from any cause. Hyperthyroidism refers specifically to disorders leading to an overactive thyroid gland. These include Graves' disease, toxic multinodular goiter (TMNG), and toxic adenoma. Thyroid storm or 'thyrotoxic crisis' is an extreme manifestation of thyrotoxicosis that was first described in 1926 as "the crisis of the exophthalmic goiter" in patients with exacerbations of underlying Graves' disease.[1] Thyroid storm can complicate thyrotoxicosis of any cause but is seen most frequently in the context of Graves' disease. In addition to exaggerated thyrotoxicosis symptoms, patients with thyroid storm also have systemic decompensation with dysfunction of multiple organ systems. Affected systems can include the cardiovascular (CV), thermoregulatory, gastrointestinal (GI)-hepatic, and central nervous system (CNS).[2-7] The exact threshold in which thyrotoxicosis becomes thyroid storm is debated and somewhat subjective. In an attempt to standardize the identification of thyroid storm, diagnostic systems were developed based on the degree of organ dysfunction.[8,9] Early recognition and prompt, aggressive treatment to reduce mortality are warranted for all patients suspected of having this life-threatening condition.

Thyrotoxicosis has a prevalence of 1.2% in the US.[2] The incidence of thyroid storm is <10% of patients hospitalized for thyrotoxicosis but is difficult to accurately estimate as no universally accepted diagnostic criteria exist.[5] Previously, thyroid storm was most frequently seen following manipulation of the hyperactive thyroid gland during thyroidectomy for thyrotoxicosis. Appropriate medical treatment with antithyroid drugs in preparation for thyroid surgery has led to a decline in cases. Graves' disease, now the most common underlying condition in patients with thyroid storm, is more common in women aged 30-50 years, those with a history of autoimmune or thyroid disorders, and smokers.[10] With current treatment, mortality from thyroid storm has improved from nearly 40% in the past to 8-25% in modern series.[7] The most frequent cause of death is multiorgan failure, followed by congestive heart failure (CHF).[3]

An awareness of thyroid hormone physiology is necessary to understand the pathogenesis and management of thyroid storm. The hypothalamus produces thyroid releasing hormone that stimulates the anterior pituitary to secrete TSH. TSH then binds to a receptor on the surface of thyroid cells and initiates the process leading to thyroid hormone release. Transport of iodide into thyroid follicular cells is required for the production of thyroid hormone. Inside the follicle, the enzyme thyroid peroxidase (TPO) is required to oxidize iodide and form the thyroid hormones, T_4 and T_3. T_4 comprises 90% of secreted thyroid hormone. T_3 is the biologically active hormone, while T_4 is a pre-hormone that must be converted to T_3 before becoming physiologically active.[2-3] In the circulation, greater than 99% of both hormones are bound to thyroid-binding globulin (TBG), transthyretin, and albumin which serve as a circulating storage pool of thyroid hormone.[6]

Total hormone levels in thyroid storm are not necessarily elevated but the bioactive free hormone levels are increased. Adrenergic activation is also thought to play a significant role and patients with thyrotoxicosis show increased responsiveness to catecholamines.[3] It is unknown how thyroid storm develops from uncomplicated thyrotoxicosis, but an acute precipitating event is often present. Any systemic stressor such as trauma, surgery, infection, or other acute medical illness can precipitate thyroid storm (***Table 1***).[2-5] In 20-25% of patients, no precipitant can be identified.[6]

Thyroid hormones affect all organ systems. Elevated hormone levels lead to increased metabolic rate, heart rate, GI motility and CNS excitability. Symptoms can vary in thyroid storm, but high fever is nearly universal.[3] Other manifestations may include weight loss, generalized weakness, emotional lability, anxiety, psychosis, tachycardia, atrial fibrillation, heart failure, dyspnea with exertion, sweating, nausea, vomiting, diarrhea, abdominal pain, and abnormal liver function.[4-6] Common physical exam findings in thyrotoxicosis include anxiety, tachycardia and/or an irregularly irregular heartbeat, moist skin, tremor, and eye signs such as stare and lid lag.[2] Atrial fibrillation is reported to occur in 10-35% of patients and is more common in older patients.[10] Increased cardiac output and tachycardia can result in CHF. CNS manifestations are common and range from agitation or delirium to stupor and coma.[2-3] Liver dysfunction can occur, and development of jaundice (total bilirubin > 3 mg/dL) predicts a poor prognosis.[6] Specific findings may suggest the underlying cause of thyrotoxicosis such as diffuse goiter and proptosis in Graves' disease or palpation of multiple thyroid nodules in TMNG. The prevalence of common findings in the largest case series of thyroid storm were tachycardia with HR > 130 (75%), CNS symptoms (84%), GI (69%), and heart failure (40%). More than 3 major organ manifestations were seen in over 75% of patients.[9] It should be noted that elderly patients may present 'apathetic' thyrotoxicosis in which atypical symptoms such as weight loss, weakness, stupor or coma predominate.[1,5]

Since symptoms are nonspecific, the diagnosis of thyroid storm is based on clinical suspicion along with laboratory testing of thyroid function. The differential diagnosis can include infection, sepsis, anxiety, cocaine intoxication, psychosis and pheochromocytoma. Serum TSH is the test of choice for diagnosing thyrotoxicosis. Levels are usually undetectable and should prompt evaluation of *free* T_4 and *total* T_3 levels. Rarely, patients may have normal T_4 levels but elevated T_3 levels ('T_3 toxicosis').[2,6] There is no definite cutoff for T_3 and T_4 levels that distinguish between straightforward thyrotoxicosis and thyroid storm. Other abnormal labs that may be seen in thyrotoxicosis include hyperglycemia, hypercalcemia, leukocytosis, and abnormal hepatic function tests.[5]

Diagnostic systems were created to help distinguish thyroid storm from uncomplicated thyrotoxicosis.[7] In 1993, Burch and Wartofsky published a scoring system based on the degree of

organ dysfunction to help differentiate these conditions. Points are assigned based on temperature, CV dysfunction (heart rate, congestive heart failure, atrial fibrillation), CNS symptoms, GI-hepatic dysfunction, and whether or not an identifiable precipitant is present. A score < 25 points is unlikely to represent thyroid storm, 25-44 points suggests impending storm, and > 45 points is highly suggestive of thyroid storm.[8] This scoring system is sensitive but not specific. In 2012, the Japanese Thyroid Association also specified criteria for thyroid storm based on laboratory evidence and combinations of organ dysfunction to assign diagnostic categories.[9] Use of these systems is suggested to augment diagnosis of thyroid storm.

Once thyrotoxicosis is established, the underlying cause should be identified. Graves' disease may be strongly suggested by the physical exam (diffuse goiter, thyroid orbitopathy). Positive serum thyrotropin receptor antibodies (TRAbs) also suggests a diagnosis of Graves' disease (sensitivity 97%, specificity 99%).[11] If TRAb levels are negative, a radioactive iodine uptake test (RAIU) and a thyroid scan are indicated.[7] RAIU and thyroid scan can distinguish among Graves' disease (diffuse isotope uptake), TMNG (patchy uptake), and toxic adenoma (uptake in a single nodule).[2] Endocrinology consultation is warranted to ensure proper evaluation and treatment.

Suspicion of thyroid storm should result in immediate, aggressive treatment. Supportive care includes management of hyperthermia, IV fluid resuscitation, careful monitoring of volume status in the presence of CHF, treatment of tachyarrhythmias, and nutritional support. Specific management requires a combination of medications to counter increased adrenergic tone and target the steps in thyroid hormone action including synthesis, release, and peripheral conversion of T_4 to T_3 (***Table 2***).[2-7] Identification and treatment of any precipitating factor is also essential.

Halting formation of new thyroid hormone is first-line therapy. Antithyroid drugs, known as thionamides (PTU and methimazole), have been used for thyrotoxicosis for over 60 years. These drugs stop new thyroid hormone synthesis by inhibiting TPO. The starting dose of either drug is based on the free T_4 levels and should be titrated based on response with the assistance of endocrinology specialists. Serious side effects may occur including hepatotoxicity, agranulocytosis, and vasculitis. PTU is more likely to cause hepatic toxicity (0.1%-0.2%) and antineutrophilic cytoplasmic antibody (ANCA) positive vasculitis. For these reasons, methimazole is often preferred.[6] Both drugs can cause agranulocytosis (~0.35% or 1 in 300 patients) at any time during therapy.[5]

Iodine treatment complements the effects of thionamides by blocking the release of preformed thyroid hormone. Iodine can also help temporarily decrease new hormone synthesis by inhibiting binding of iodide to thyroglobulin in the thyroid gland. This action, termed the 'Wolff-Chaikoff' effect, is transient, lasting only 1-2 days, but can be important in acute thyrotoxic crisis. Saturated solution of potassium iodide (SSKI) or Lugol's solutions are iodine formulations available in the United States. Patients must be on thionamides if they receive iodine and the dose must be given at least one hour after thionamides.[3-5] The combination therapy of thionamides and iodine often decrease thyroid hormone levels to the normal range in 4-5 days.[3]

Blocking the peripheral effects of thyroid hormone is another essential aspect of therapy. Peripheral conversion of T_4 to T_3 is responsible for ~80% of T_3 in the circulation and is blocked by PTU, glucocorticoids and propranolol (in large doses) to some degree.[6] ß-blockers, which blunt the enhanced adrenergic tone and help control cardiovascular manifestations, are indicated in all cases of thyrotoxicosis.[4] Propanolol, a nonselective ß-blocker, is commonly used. Caution and close monitoring are warranted in patients with CHF or hypotension.[5] Hypothalamic-pituitary-adrenal axis impairment often exists in thyrotoxicosis. Glucocorticoids inhibit conversion of T_4 to T_3 and also treat this relative adrenal insufficiency. Stress doses of hydrocortisone or dexamethasone are most often used .[2-6]

If patients fail standard therapy or it cannot be given due to toxicity, alternative medical treatments can be tried. Lithium has several effects on decreasing thyroid hormone action and can be used when thionamides and/or iodine are contraindicated. Thyroid hormone is metabolized by the liver and excreted in bile. For severe or refractory cases, cholestyramine can be used to decrease reabsorption of thyroid hormone from the enterohepatic circulation.[3,5] Plasma exchange has also been used in severe cases.[7] Recall that 99% of thyroid hormone pool in the circulation is bound the TBG, transthyretin, and albumin which serves as a circulating storage pool of thyroid hormone. Plasma exchange removes TBG, with bound thyroid hormone from the circulation. Evidence is limited, but case series report plasma exchange leads to a decrease in T_3 and T_4 levels and clinical improvement in patients with thyrotoxicosis.[3]

Despite the most aggressive medical management for thyroid storm, patients may rarely continue to deteriorate, and urgent thyroid surgery may be indicated. For elective surgical treatment of hyperthyroidism, PTU or methimazole are given before surgery to gradually achieve a euthyroid state over several weeks. Urgent preparation for surgery in thyrotoxic patients often includes more aggressive dosing of these medications in attempt to rapidly lower thyroid hormone levels.[6] Some institutions use plasma exchange to prepare patients for surgery.[3] Risk of exacerbating thyroid storm remains if thyroid hormone levels are high prior to surgery.

Following an episode of thyroid storm, close follow-up and hormone level monitoring are necessary. Medications are gradually weaned with clinical improvement. Iodine therapy is often discontinued after 1-2 weeks and steroids are rapidly tapered. Thionamide therapy, at lower doses, is required for weeks to months at a minimum. ß-blockers are continued until euthyroidism is achieved.[4,6] Plans for definitive therapy should be made with the assistance of an endocrinology specialist. For Graves' disease, options include long term methimazole treatment, radioactive iodine (I-131) ablation, or thyroidectomy. For

TMNG or toxic adenoma, I-131 therapy or thyroidectomy is often advised as primary treatment.[2,7]

In conclusion, thyroid storm has high mortality if not recognized early and treated aggressively. Patients classically present with exaggerated symptoms of thyrotoxicosis along with fever and multiorgan dysfunction. Diagnosis requires high clinical suspicion supplemented by diagnostic systems and thyroid hormone testing. Supportive care and immediate treatment aimed at reducing thyroid hormone levels is indicated. A multidisciplinary approach is important for successful management. Close follow-up for medication management and planning for definitive treatment of the underlying cause of thyrotoxicosis is integral to preventing recurrence.

Table 1. **Selected Precipitants of Thyroid Storm***

A. Thyroid surgery (less common currently)
B. Nonthyroidal surgery
C. Trauma
D. Noncompliance to treatment for known thyrotoxicosis
E. Other acute illness (infection, MI, PE, DKA, stroke)
F. Medications: anesthetics, amiodarone, salicylates, interferon alpha, etc.
G. Iodine administration (radiocontrast dye, amiodarone)
H. Other: Childbirth, emotional stress, intense exercise

MI - myocardial infarction, PE - pulmonary embolism, DKA - diabetic ketoacidosis

***** adapted from reference 3

Table 2. **Thyroid Storm Acute Treatment***

A. Supportive care
a. IV fluids, oxygen, acetaminophen, cooling blankets
b. Nutrition support
c. Glucocorticoids for relative adrenal insufficiency
B. Inhibit new thyroid hormone synthesis
a. Methimazole
b. Propylthiouracil
C. Inhibit thyroid hormone release
a. SSKI (Potassium iodide)
b. Lugol's solution
D. Block peripheral effects of thyroid hormone
a. ß-blockers (propranolol,esmolol, metoprolol,)
b. Glucocorticoids (hydrocortisone or dexamethasone)
E. Identify and treat precipitating cause
F. Additional therapies
a. Lithium
b. Cholestyramine
c. Plasma exchange (refractory cases)

***** adapted from reference 2

REFERENCES

1. **Lahey FH**. Apathetic Thyroidism. *Ann Surg. 1931 May;93(5):1026-30*. doi: 10.1097/00000658-193105000-00008. PMID: 17866558; PMCID: PMC1398350.
2. **McDermott MT**. Hyperthyroidism. *Ann Intern Med. 2020 Apr 7;172(7):ITC49-ITC64*. doi: 10.7326/AITC202004070. PMID: 32252086.
3. **Chiha M, Samarasinghe S, Kabaker AS**. Thyroid storm: an updated review. *J Intensive Care Med*. 2015 Mar;30(3): 131-40. doi: 10.1177/0885066613498053. Epub 2013 Aug 5. PMID: 23920160.
4. **Carroll R, Matfin G**. Endocrine and metabolic emergencies: thyroid storm. *Ther Adv Endocrinol Metab*. 2010 Jun;1(3):139-45. doi: 10.1177/2042018810382481. PMID: 23148158; PMCID: PMC3475282.
5. **Nayak B, Burman K**. Thyrotoxicosis and thyroid storm. *Endocrinol Metab Clin North Am*. 2006 Dec;35(4):663-86, vii. doi: 10.1016/j.ecl.2006.09.008. PMID: 17127140.
6. **Idrose AM**. Acute and emergency care for thyrotoxicosis and thyroid storm. *Acute Med Surg*. 2015 May 12;2(3):147-157. doi: 10.1002/ams2.104. PMID: 29123713; PMCID: PMC5667251.
7. **Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, Rivkees SA, Samuels M, Sosa JA, Stan MN, Walter MA**. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid*. 2016 Oct;26(10):1343-1421. doi: 10.1089/thy.2016.0229. Erratum in: *Thyroid*. 2017 Nov;27(11):1462. PMID: 27521067.
8. **Burch HB, Wartofsky L**. Life-threatening thyrotoxicosis. Thyroid storm. *Endocrinol Metab Clin North Am*. 1993 Jun;22(2):263-77. PMID: 8325286.
9. **Akamizu T, Satoh T, Isozaki O, Suzuki A, Wakino S, Iburi T, Tsuboi K, Monden T, Kouki T, Otani H, Teramukai S, Uehara R, Nakamura Y, Nagai M, Mori M; Japan Thyroid Association**. Diagnostic criteria, clinical features, and incidence of thyroid storm based on nationwide surveys. *Thyroid*. 2012 Jul;22(7):661-79. doi: 10.1089/thy.2011.0334. Epub 2012 Jun 12. Erratum in: *Thyroid*. 2012 Sep;22(9):979. PMID: 22690898; PMCID: PMC3387770.
10. **Vaidya B, Pearce SH**. Diagnosis and management of thyrotoxicosis. *BMJ*. 2014 Aug 21;349:g5128. doi: 10.1136/bmj.g5128. PMID: 25146390.
11. **Smith TJ, Hegedüs L**. Graves' Disease. *N Engl J Med*. 2016 Oct 20;375(16):1552-1565. doi: 10.1056/NEJMra1510030. PMID: 27797318.