Chapter 5

THYROTOXIC CRISIS

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Thyroid storm, also known as thyrotoxic crisis, is a severe and potentially fatal complication of thyrotoxicosis. This condition manifests rapidly and is associated with high rates of morbidity and mortality, requiring immediate recognition and treatment. Although rare, thyroid storm can be triggered by factors such as surgery, trauma, infection, or changes in medication. The diagnosis and treatment of

this condition remain challenging as there are no specific laboratory abnormalities to identify it, and the available scoring system is based on clinical criteria (Ross, 2023).

Thyroid hormones affect all body systems and, in excess, can increase metabolic rate, heart rate, ventricular contractility, and gastrointestinal motility, as well as cause excitability of the muscles and central nervous system. Thyrotoxicosis results from an excessive concentration of these hormones, and thyroid storm is its most extreme form. While the exact mechanism of thyroid storm is not fully understood, it is believed to occur due to an increased tissue response to thyroid hormones, greater binding to thyroid receptors, decreased binding protein affinity, or a sudden increase in the availability of free thyroid hormones (Idrose, 2015).

In emergency and critical care settings, thyroid storm is a critical condition requiring immediate attention and intensive treatment, often in an ICU environment. It is essential to provide advanced supportive care to manage potential complications, such as severe cardiovascular events, liver dysfunction, and even mortality. Despite available treatments, mortality rates remain high, underscoring the importance of early diagnosis and rapid intervention (Chiha, Samarasinghe and Kabaker, 2015).

Thyrotoxicosis is relatively common, with the prevalence of hyperthyroidism ranging from 0.05% to 1.3% in the U.S. Thyroid storm, though rare, has a high mortality rate, reaching 80-100% without treatment and 10-50% with treatment. Studies in Japan show an incidence of 0.20 cases per 100,000 people per year among hospitalized patients. Rates of thyrotoxicosis vary geographically, being more common in regions with iodine deficiency. Graves› disease is the primary cause of hyperthyroidism in areas with adequate iodine intake and is 10 times more common in women. Thyroid storm is more frequent in young women but can affect any age group. Risk factors include a history of thyroid disease, female gender, reproductive age, iodine intake, use of medications such as amiodarone, and precipitating conditions like infections and trauma. Understanding these epidemiological aspects is crucial for early diagnosis and proper management of these conditions to reduce associated mortality (Idrose, 2015).

The diagnosis of thyrotoxicosis and thyroid storm involves identifying clinical signs such as weight loss, tremors, heat intolerance, tachycardia, and hypertension, confirmed by laboratory tests, including measurements of high T3 and T4 levels and low TSH levels, elevated CRP (C-reactive protein) levels, and monitoring of liver and kidney function. Biotin can interfere with laboratory results, leading to falsely low TSH and thyroglobulin readings, and falsely high T3 and T4 (Ylli, Klubo-Gwiezdzinska and Wartofsky, 2019).

Clinical criteria, such as the Burch-Wartofsky scoring system, are used to assess severity. Additional tests like ECG and chest X-ray may be performed to evaluate complications, while a detailed medical history is crucial to identify precipitating factors such as amiodarone use or iodine exposure. Rapid and accurate diagnosis is essential to initiate appropriate treatment and reduce associated mortality (Ross, 2023).

Imaging technologies include ultrasound to evaluate the thyroid gland, thyroid scintigraphy to assess radioactive iodine uptake, ECG to monitor and detect arrhythmias, and echocardiography to evaluate cardiac function in patients with heart failure symptoms. Emerging biomarkers are also being studied to improve diagnostic accuracy and monitor treatment response, although they are not yet widely implemented in daily clinical practice (Algell *et al*., 2015).

The treatment of thyrotoxicosis and thyroid storm involves multiple therapeutic approaches. Antithyroid medications such as methimazole and propylthiouracil reduce hormone production, while beta-blockers control adrenergic symptoms. Iodine can be used to temporarily block hormone production. In severe cases, corticosteroids may be administered. Definitive options include surgery and radioactive iodine for selected cases. Clinical support is essential, with rigorous monitoring and intensive care when necessary. The therapeutic approach is personalized, aiming to stabilize patients and prevent severe complications (Chiha, Samarasinghe and Kabaker, 2015). Updated guidelines for thyroid storm have been developed by the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE), focusing on the efficacy of new therapeutic approaches such as plasmapheresis and combined therapies of antithyroid drugs and glucocorticoids, showing improvements in clinical outcomes (Algell *et al*., 2015).

Recent treatment techniques with pharmacological therapy include the use of beta-blockers to control adrenergic symptoms, antithyroid drugs to inhibit thyroid hormone synthesis, potassium iodide to inhibit hormone release from the thyroid, and glucocorticoids to reduce the conversion of T4 to T3 and treat relative adrenal insufficiency. In severe cases, intravenous administration of levothyroxine (T4) or triiodothyronine (T3) may be used (Ylli, Klubo-Gwiezdzinska and Wartofsky, 2019).

Adjuvant therapies include plasmapheresis in refractory or severe cases and rectal administration of medications in patients unable to take oral medications. Supportive management involves intensive care, rigorous monitoring to manage severe complications, treatment of precipitating causes, and fluid and electrolyte replacement (Algell *et al*., 2015).

EPIDEMIOLOGY

Thyroid storm is a rare but severe condition, with an incidence ranging from 0.20 to 0.76 per 100,000 people per year, and 4.8-5.6 per 100,000 hospitalized patients. It is a high-mortality condition that requires immediate recognition and treatment. Understanding its epidemiology, risk factors, and demographics is crucial to improving early diagnosis and effective management, reducing mortality, and enhancing clinical outcomes for affected patients. In the United States, 16% of hospitalized patients with thyrotoxicosis are diagnosed with thyroid storm (Farooqi *et al*., 2023). The reduction in the incidence of this condition is largely due to early diagnosis and screening for hyperthyroidism (Idrose, 2015).

The mortality rate of untreated thyroid storm is alarming, ranging from 80% to 100%, while with treatment, this rate decreases to between 10% and 50%. Recent studies indicate significant improvement in the United States, with mortality rates reduced to 1.2% to 3.6%, thanks to intensive and high-quality treatments (Idrose, 2015; Farooqi *et al.*, 2023). Patients with high levels of total bilirubin (>3 mg/dL) have significantly higher mortality.

The most common causes of death include multiple organ failure, congestive heart failure, respiratory failure, arrhythmias, disseminated intravascular coagulation, gastrointestinal perforation, cerebral hypoxia, and sepsis (Idrose, 2015). Graves› disease is the main cause of thyroid storm due to excessive and uncontrolled stimulation of thyroid hormones, being more common in young women, who are affected ten times more than men at any age (Chiha, Samarasinghe and Kabaker, 2013).

Precipitating factors include trauma, thyroiditis, excessive manipulation of the thyroid gland, use of medications such as anesthetics, salicylates, pseudoephedrine, and amiodarone, withdrawal of antithyroid treatment, cerebrovascular incidents, and acute ingestion of high doses of thyroid hormone (Idrose, 2015; Chiha, Samarasinghe and Kabaker, 2013). Infections are currently the most common cause of thyroid storm in hospitalized patients. In about 25% to 43% of patients, no clear precipitating factor is identified.

Exogenous causes, such as metastatic thyroid carcinomas, ectopic thyroid tissue, or excessive thyroid hormone ingestion, can also lead to thyrotoxicosis (Idrose, 2015). Thyroid storm is an extreme response of thyrotoxicosis, more common in women and often associated with Graves› disease, with an estimated incidence of 0.2 per 100,000 per year among Japanese patients (Chiha, Samarasinghe and Kabaker, 2013).

Although the overall incidence of thyroid storm has declined due to early screening for hyperthyroidism, thyrotoxicosis continues to have a significant incidence, between 0.05% and 1.3% in the United States, with most cases being subclinical (Idrose, 2015). Early screening allows for faster diagnosis and better prevention, reducing associated mortality.

Thyrotoxicosis without thyroid storm is more common in middle-aged adults, Caucasians, and women. Among hospitalized patients in the United States, thyroid storm is more frequent among Hispanics and African Americans. Graves› disease, discontinuation of medications, and younger age (18-40 years) are significant risk factors (Galindo *et al.*, 2019). Patients with Graves› disease have a higher prevalence of thyroid storm, with a significant incidence of medication discontinuation, reflecting the importance of continuous and proper management of antithyroid treatment. Young and adult patients have a lower risk of mortality, underscoring the need for constant vigilance and early interventions.

DIAGNOSIS

The use of scoring systems based on clinical findings, such as the Burch-Wartofsky Point Scale, is crucial for identifying this condition (Banerjee; Bala and Aggarwal, 2019). Additionally, other important diagnostic systems include the Japanese Thyroid Association criteria and the Akamizu Criteria, which integrate clinical findings with laboratory results and thyroid hormone levels (Elendu *et al.*, 2024).

The role of imaging studies, such as ultrasound and fine-needle aspiration biopsy (FNAB) for incidental nodules, needs to be re-evaluated (Shnadig, 2014). Recent research highlights elevated levels of C-reactive protein (CRP) and interleukin-6 (IL-6) as important markers for screening thyroid storm (Elendu et al., 2024). Technological innovations, such as artificial intelligence algorithms, promise to revolutionize early diagnosis and prevention of this emergency by cross-referencing laboratory data, imaging studies, and clinical symptoms (Elendu *et al.*, 2024).

The condition can be excluded if the patient presents with unexplained diseases such as pneumonia, malignant hyperthermia, psychiatric disorders, cerebrovascular disorders, acute myocardial infarction, viral hepatitis, and acute liver failure (Akamizu *et al.*, 2012). However, these disorders can trigger thyrotoxic crises. Triggering factors for thyrotoxic crises include irregular use or discontinuation of antithyroid medications, thyroid surgery, radioactive thyroid therapy, excessive palpation or biopsy, infection, trauma, pregnancy and childbirth, adrenal insufficiency, diabetic ketoacidosis, administration of iodinated contrast media, cerebrovascular disorders, pulmonary thromboembolism, ischemic heart diseases, tooth extraction, severe emotional stress, and strenuous exercise (Akamizu *et al.*, 2012).

The Burch-Wartofsky Point Scale is widely used, based on clinical signs and symptoms, while the Japanese Thyroid Association Criteria rely on clinical findings and laboratory results, and the Akamizu Criteria include clinical characteristics and thyroid hormone levels such as free thyroxine (FT4). Diagnosis is particularly challenging due to the variety of symptoms overlapping with other diseases such as sepsis, drug intoxication, and heart failure. For pediatric patients, the Adapted Burch-Wartofsky Criteria are used, considering the specific vital signs and symptoms for each age group. In elderly patients, diagnosis requires caution, as they may not present common symptoms such as high fever and hyperactivity (Akamizu *et al.*, 2012).

The differential diagnosis of thyrotoxic crisis is extensive and depends on the systems involved, but it should be considered in situations of sepsis, hyperthermia, and altered mental status. Cardiovascular dysfunction, such as atrial tachyarrhythmias and congestive heart failure, includes ischemic heart disease. Hyperpyrexia manifestations include sepsis from pneumonia and malignant hyperthermia, while changes in mental status, such as agitation, delirium, and coma, should be differentiated from psychiatric and cerebrovascular disorders (Akamizu *et al.*, 2012). Recent research highlights the importance of CRP and IL-6 in the search for thyroid storm, as their elevation indicates classic inflammatory processes, aiding in diagnostic accuracy. Additionally, technological innovations, such as the use of artificial intelligence to cross-reference laboratory data and clinical symptoms, promise to improve early diagnosis and prevent future complications. Standardizing diagnostic criteria globally with the best technologies is essential to provide early diagnosis and avoid complications in thyroid storm, ensuring adequate and effective management of the condition.

TREATMENT

Laboratory tests for patients with thyroid storm often show thyroid-stimulating hormone (TSH) levels that are very low or undetectable (<0.01mU/L), elevated free thyroxine (fT4) and/or free triiodothyronine (fT3), and positive thyroid receptor antibody (TRab) if the underlying etiology is Graves› disease (De Almeida; McCalmon; Cabandugama, 2022). Early diagnosis is crucial to initiate aggressive treatment and reduce associated morbidity and mortality (Chiha; Samarasinghe and Kabaker, 2015).

Given the severity of the condition and the potential systemic repercussions such as thermoregulatory dysfunction, tachycardia, congestive heart failure (CHF), hepatic and gastrointestinal manifestations, and central nervous system alterations, all patients should be admitted for intensive treatment. Transfer to an intensive care unit is necessary to halt the damage and achieve a euthyroid state (De Almeida; McCalmon; Cabandugama, 2022). Even with early intervention, mortality remains high, with multiple organ failure being the most common cause, followed by CHF, respiratory failure, cardiac arrhythmias, disseminated intravascular coagulation (DIC), intestinal perforation, and sepsis (Chiha; Samarasinghe and Kabaker, 2015).

Therapeutic efforts aim to contain clinical deterioration, provide symptomatic support, and initiate initial treatment to achieve a euthyroid state before definitive treatment. The use of antithyroid drugs that inhibit hormone synthesis by acting on thyroid peroxidase, such as propylthiouracil (PTU), carbimazole, and methimazole (MMI), is essential. Definitive treatment involves total thyroidectomy or radioactive iodine ablation, depending on the severity of the clinical condition (Chiha; Samarasinghe and Kabaker, 2015).

To achieve a euthyroid state, therapeutic management includes inhibiting the synthesis of new thyroid hormones, inhibiting the release of preformed hormones, and blocking the peripheral effects of excess thyroid hormones. Regarding synthesis inhibition, antithyroid medications like PTU and methimazole are administered orally or via nasogastric tube. The recommended PTU dose is 200 to 250 mg every 4 hours, while the methimazole dose is 20 mg every 4 to 6 hours (Ross, 2023).

To inhibit the release of preformed hormones, inorganic iodine is administered in the form of Lugol›s solution or saturated potassium iodide solution, with a dosage of 8 drops every 6 hours. Patients allergic to iodine can use lithium as an alternative, with a dosage of 300 mg three to four times a day (Ylli; Klubo-Gwiedzinska and Wartofsky, 2019).

In severe or refractory cases, cholestyramine can be used to inhibit the enterohepatic recirculation of thyroid hormones by binding to conjugated products and promoting their excretion. The recommended dose is 1 to 4 g twice a day (Chiha; Samarasinghe and Kabaker, 2015). To control peripheral effects, the beta-blocker propranolol is used. Patients contraindicated for beta-blockers can use short-acting calcium channel antagonists like verapamil (Ylli; Klubo-Gwiedzinska and Wartofsky, 2019).

Glucocorticoids, such as hydrocortisone, are administered to reduce the conversion of T4 to T3, promote vasomotor stability, and treat relative adrenal insufficiency associated with Graves› disease. The recommended dose is 300 mg intravenously, followed by 100 mg every eight hours (Ross, 2023). Supportive therapy includes controlling hyperthermia with acetaminophen and other physical measures, such as cooling blankets and cold fluids. Volume depletion and hypotension, often resulting from fever, vomiting, diarrhea, and sweating, should be treated with intravenous fluid replacement, preferably combined dextrose/saline solution to provide nutritional content and multivitamins (Ylli; Klubo-Gwiedzinska and Wartofsky, 2019).

When thyroid storm is triggered by an infection or when the precipitating factor is unidentified, broad-spectrum antibiotic therapy and a thorough search for infectious foci are considered while awaiting culture results (Ylli; Klubo-Gwiedzinska and Wartofsky, 2019).

Definitive therapy for thyrotoxic crisis is surgical thyroidectomy or treatment with radioactive iodine, essential for preventing recurrences and associated mortality. However, it is crucial that the patient reaches a euthyroid state before any definitive intervention (McGonigle *et al*., 2018).

Therapeutic plasma exchange (TPE) is an option for patients with thyroid storm who do not respond to conventional medical treatment or have contraindications to standard therapies. TPE removes plasma from the blood and replaces it with another fluid, such as albumin or fresh frozen plasma, helping to reduce levels of thyroid hormones, autoantibodies, catecholamines, and cytokines (McGonigle; Tobian; Zink and King, 2017). TPE can effectively restore euthyroidism or improve clinical manifestations of severe thyrotoxicosis. It is especially indicated in refractory thyroid storm cases or to prepare patients for thyroidectomy or other urgent surgeries. Current guidelines recommend using albumin or plasma as replacement fluids during TPE due to their advantages in providing additional binding sites for newly synthesized thyroid hormones. This procedure is a safe and effective treatment option, though limited by cost and the need for specialized resources. It is a valuable option in specific situations where other forms of treatment are contraindicated or insufficient (Montaño; Arrieta and Gonzalez, 2021).

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