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Thyroid Storm: An Updated Review

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Abstract

Thyroid storm, an endocrine emergency first described in 1926, remains a diagnostic and therapeutic challenge. No laboratory abnormalities are specific to thyroid storm, and the available scoring system is based on the clinical criteria. The exact mechanisms underlying the development of thyroid storm from uncomplicated hyperthyroidism are not well understood. A heightened response to thyroid hormone is often incriminated along with increased or abrupt availability of free hormones. Patients exhibit exaggerated signs and symptoms of hyperthyroidism and varying degrees of organ decompensation. Treatment should be initiated promptly targeting all steps of thyroid hormone formation, release, and action. Patients who fail medical therapy should be treated with therapeutic plasma exchange or thyroidectomy. The mortality of thyroid storm is currently reported at 10%. Patients who have survived thyroid storm should receive definite therapy for their underlying hyperthyroidism to avoid any recurrence of this potentially fatal condition.

Keywords

thyroid storm, thyrotoxicosis, thyroid crisis, therapeutic plasma exchange, hyperthyroidism

Introduction

Thyroid storm was first described by Lahey in 1926 as "the crisis of exophthalmic goiter"[1] due to the large number of patients who presented with an exacerbation of their underlying Graves' disease. Most of the findings in uncomplicated thyrotoxicosis were present but exaggerated in this newly described condition also referred to as thyrotoxic crisis. Over the years, physicians have strived to accurately detail all of the physiologic changes that accompany this morbid diagnosis. Dysfunction of the cardiovascular system, thermoregulatory system, gastrointestinal-hepatic system, and central nervous system (CNS) have all been included in contemporary definitions, and in 1993, Burch and Wartofsky developed a novel scoring system to standardize the diagnosis.[2] Today, physicians continue to have difficulty in diagnosing the condition, and groups around the world are attempting to establish clear diagnostic criteria based on universal clinical parameters.[3] These projects are crucial to improving the morbidity and mortality associated with thyroid storm, because early recognition allows prompt, aggressive treatment, transfer of care to an intensive care setting for supportive care, and rapid identification of the underlying precipitant. However, even with early diagnosis, the overall mortality remains high, between 10% to 30%.[4]

Epidemiology

The incidence of thyroid storm is difficult to approximate due to the rarity of the condition, the absence of laboratory findings that are specific to the diagnosis, and the lack of universally adopted criteria for diagnosis. Most sources report that thyroid storm accounts for between 1% and 2% of hospital admissions for thyrotoxicosis; however, some reports estimate the incidence may be as high as 10%.[4,5] In a recent nationwide survey of hospitals in Japan, the incidence of thyroid storm in hospitalized patients was 0.2 per 100 000 per year, or approximately 0.22% of all patients with thyrotoxicosis and 5.4% of hospital-admitted patients with thyrotoxicosis.[3,6] The recent decline from prior estimations may be due to more frequent screening for thyroid disorders, leading to the earlier diagnosis of hyperthyroidism and improved prevention of thyroid storm.[7] In addition, patients are increasingly more appropriately prepared prior to surgical treatment of their hyperthyroidism leading to a marked reduction in the prevalence of surgically induced storm. Thyroid storm most commonly occurs in women and is more frequently observed among patients with underlying Graves' disease.[8] However, older patients with

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storm may instead have autonomous nodular disease. Although mortality has been reported as high as 75% in hospitalized patients,[9] recent data suggest mortality rates closer to 10% to 30%.[3,4] Multiple organ failure is the most common cause of death, followed by congestive heart failure, respiratory failure, arrhythmia, disseminated intravascular coagulation, gastrointestinal perforation, hypoxic brain syndrome, and sepsis.[3,6]

Pathophysiology of Thyroid Storm

It is essential to understand the normal thyroid hormone physiology in order to appreciate the rationale behind the management of thyroid storm. Normal thyroid function is maintained by feedback mechanisms between the hypothalamus, anterior pituitary, and thyroid gland. The hypothalamus secretes thyrotropin-releasing hormone (TRH) that stimulates the anterior pituitary to release thyroid-stimulating hormone (TSH), which then binds to a specific receptor on the surface of thyroid cells. The synthesis of thyroid hormone first requires the transport of iodide into the thyroid follicular cell via a sodium–iodide symporter. Iodide is then oxidized and organified by the enzyme thyroid peroxidase (TPO). The TPO in turn catalyzes the iodination of tyrosine residues on thyroglobulin, the backbone protein for thyroid hormone synthesis, thereby forming the biologically active hormones, thyroxine (T4) and triiodothyronine (T3). The synthesis and secretion of these active hormones are a TSH-dependent process. The class of medications called thionamides inhibit TPO, whereas iodine therapy in large doses blocks the release of preformed thyroid hormone and decreases iodide transport and oxidation. The major effects of thyroid hormone action occur mostly through the intranuclear action of T3 with T4 acting more as a prohormone.[10] Approximately 10% to 20% of the circulating T3 comes from direct secretion by the thyroid gland, whereas the remaining 80% to 90% is produced by peripheral conversion of T4 to T3. The entire process is controlled by a negative feedback loop with peripheral thyroid hormone inhibiting the release and synthesis of TSH and TRH. In the peripheral tissues, T4 is converted to T3 by the 5′-deiodinases. The deiodinase D2 is the main enzyme active in the euthyroid state as opposed to the hyperthyroid state where deiodinase D1 is the prevailing deiodinase. The deiodinase D1 is susceptible to inhibition by thionamide and propylthiouracil (PTU). Glucocorticoids and propranolol, a β-adrenergic receptor antagonist, also have an inhibitory effect on peripheral conversion of T4 to T3.

More than 99% of both the hormones are bound to thyroid-binding globulin (TBG), transthyretin, and albumin.[11] Bound hormone represents a circulating storage pool, while unbound or free hormone is available for uptake into the tissues. The TBG has a higher affinity for T4 and T3 than transthyretin or albumin, and therefore, it is these latter proteins that are primarily responsible for the immediate delivery of thyroid hormone to peripheral tissues. This will be become important during the discussion of novel treatment strategies such as therapeutic plasma exchange.

The exact mechanisms underlying the development of thyroid storm from uncomplicated hyperthyroidism are not well understood. A heightened response to thyroid hormone is often incriminated along with increased or abrupt availability of free hormones and enhanced binding to thyroid hormone receptors.[2,4,12] Total T4 and T3 concentrations in patients in crisis are not necessarily higher than those with uncomplicated thyrotoxicosis. However, Brooks and Waldstein found that the mean dialyzable fraction of T4 and mean free T4 concentrations were significantly higher in patients with storm compared to those with simple thyrotoxicosis despite the similar levels of total T4.[13] An explanation for this finding is a reduction in carrier protein affinity for T4. A decrease in the hormone-binding capacity associated with various stressors may increase concentrations of free, bioactive moieties in thyrotoxic crisis.[13,14] The rapidity with which free hormone levels rise may be more important than the absolute levels in determining clinical presentation.[12]

The shared clinical manifestations between thyrotoxicosis and adrenergic activation, as well as the dramatic response to antiadrenergic treatment in thyroid crisis, have led to the hypothesis that adrenergic activation also plays a major role in thyroid storm. Prior studies evaluating catecholamine metabolism in patients with hyperthyroidism have failed to demonstrate elevated plasma concentrations or increased secretion rates of epinephrine or norepinephrine compared to patients with hypothyroidism and euthyroidism, which argues against a primary adrenergic system defect.[15,16] Instead, enhanced responsiveness to endogenous catecholamines in the hyperthyroid state has been well described due to a potential increase in tissue-specific β-adrenergic receptor density or modification in postreceptor signaling pathways.[2,17,18] In support of this theory, T3 amplifies the transcriptional response to norepinephrine in brown adipose tissue, an important site of thermogenesis in mammals. Elevated levels of cyclic adenosine monophosphate, the intracellular second messenger for most β-adrenergic receptors, have been identified in patients with hyperthyroidism. This is a key pathway that can be dampened through therapy with a nonselective β-adrenergic antagonist, such as propranolol.[12,18]

Precipitating Factors

Although the exact pathophysiologic mechanism of thyroid storm is not definitive, it is clear that the transition from simple thyrotoxicosis to the metabolic crisis of thyroid storm usually requires a superimposed insult. Thyroid surgery was previously the most common precipitant of storm but adequate preoperative preparation and the increased use of radioactive iodine to treat these patients have now rendered this a rare cause of the disorder. Patients with incompletely treated hyperthyroidism or an interruption in drug therapy place them at increased risk of thyroid storm. Any primary cause of hyperthyroidism can escalate into thyrotoxic crisis; however, the most common etiology is a history of underlying Graves' disease. There are many other well-described causes that can induce thyroid storm

Table 1. Reported Precipitants of Thyroid Storm.

Thyroid surgery/surgical storm
Nonthyroidal surgery
Trauma[68]
Vigorous manipulation of the thyroid gland[5]
Thyroiditis[69]
Parturition
Burn[19]
Myocardial infarct
Pulmonary embolism
Cerebrovascular incidents
Medications such as anesthetics, salicylates, pseudoephedrine, and amiodarone
Interferon treatment[20]
Radioactive iodine treatment
Exposure to iodinated contrast
Withdrawal of antithyroid treatment
Infections
Diabetic ketoacidosis[21]
Hypoglycemia
Acute ingestion of high doses of thyroid hormone[22]
Metastatic thyroid cancer[19]
Struma ovarii[23]
Molar pregnancy[24]
H1N1 infection[25]
Emotional stress
Intense exercise

in patients with unrecognized thyrotoxicosis, including nonthyroid surgery, parturition, major trauma, infection, or iodine exposure from radiocontrast dyes or amiodarone.[4] A comprehensive list is detailed in Table 1. Currently, infection is the most common cause of thyroid storm in the inpatient setting.[2-4] Still, as many as 25% to 43% of the patients present without a clearly identifiable precipitating factor.[10]

Clinical Features and Diagnosis

The diagnosis of thyroid storm is based on clinical findings, and if suspected, treatment should be initiated without delay in order to reduce the mortality risk. The patient will exhibit exaggerated signs and symptoms of hyperthyroidism accompanied by manifestations of multiorgan decompensation.[26] A diversity of clinical presentations may be apparent; however, high fever (104°-106°F has been reported) is near universal, and tachycardia tends to be out of proportion to the underlying illness. The severe hyperpyrexia can induce profuse sweating and contribute to insensible fluid losses and helps differentiate thyroid storm from thyrotoxicosis.[12] The cardiac ramifications from hyperthyroidism are well described and may include palpitations, tachycardia, exercise intolerance, dyspnea on exertion, widened pulse pressure, cardiac ischemia, or atrial fibrillation.[27] In the acute setting of thyroid storm, these findings can become life threatening. The increased cardiac output and accompanying tachyarrhythmia may manifest with heart failure symptoms and can progress to cardiovascular collapse and shock.[28,29] The CNS manifestations are almost invariably seen and range from agitation, delirium, and confusion to stupor, obtundation, and coma.[3] The patient may also exhibit gastrointestinal symptoms including nausea, profuse vomiting, and severe diarrhea. This will also invariably contribute to significant ongoing volume depletion. Liver dysfunction and hepatomegaly secondary to hepatic congestion, hypoperfusion, or direct effect from the hyperthyroidism are also reported.[30] Overall, progression to jaundice is a poor prognostic indicator.[31]

Case reports also exist detailing unusual presentations of thyrotoxic crisis including acute abdomen, status epilepticus, rhabdomyolysis, hypoglycemia, lactic acidosis, and disseminated intravascular coagulation.[32-35] Patients with apathetic hyperthyroidism, first described in elderly patients by Lahey in 1931,[1] may have a propensity to develop thyroid storm due to a delay in their diagnosis of hyperthyroidism and can present with apathy, obtundation, and cardiac failure symptoms with minimal signs of thyrotoxicosis.[30]

In 1993, a landmark article by Burch and Wartofsky assigned a numerical score to each of the different signs and symptoms of thyroid storm and established diagnostic criteria based on the total score calculated (Table 2). The score has been widely accepted; however, it should not replace clinical judgment in making the diagnosis or initiating the treatment. More recently, a group from the Japan Thyroid Association surveyed the incidence of thyroid storm in Japan and formulated population-specific diagnostic criteria based on the presence of the classic organ system manifestations. The diagnostic criteria are based on varying combinations of CNS symptoms, fever, tachycardia, congestive heart failure, and gastrointestinal/hepatic disturbances rather than an absolute score. Japanese hospitals were surveyed for cases of thyroid storm from 2004 to 2008, and clinical and laboratory data were collected. Tachycardia with a heart rate of higher than 130 was found in greater than 75% of the patients, and 84% of the patients had CNS symptoms. In all, 69% of the patients had gastrointestinal manifestations, and 40% of the patients had heart failure. In all, 76% of the patients with thyroid storm had more than 3 major organ manifestations, consistent with multiple organ failure.[3,6] This is the largest single case series of thyroid storm to date and provides valuable epidemiologic data. It may not generalize to all patients with thyroid storm, precisely due to its population-specific nature in an area of high iodine intake[6]; however, the clarification of the clinical presentation of patients with thyroid storm appears to corroborate the available literature.

As discussed previously, the diagnosis of thyroid storm is largely clinical however laboratory values can aid in the diagnosis and treatment. Although the laboratory abnormalities that accompany thyroid storm are not diagnostic, the degree of laboratory derangement can be indicative of the severity of end organ damage. There is no definite serum T4 or T3 cutoff that differentiates uncomplicated thyrotoxicosis from crisis; however, a complete evaluation of TSH, free T4, and free T3 can be useful in the intensive care unit (ICU) setting as many medications and nonthyroidal illnesses can alter the results of these tests. For example, systemically ill patients have a

Table 2. Diagnostic Criteria for Thyroid Storm.[a]

Thermoregulatory Dysfunction: Temperature, F	Score	Cardiovascular Dysfunction: Heart Rate, bpm	Score
99-99.9	5	90-109	5
100-100.9	10	110-119	10
101-101.9	15	120-129	15
102-102.9	20	130-139	20
103-103.9	25	≥140	25
≥104	30		
Central Nervous System Dysfunction	**Score**	**Cardiovascular Dysfunction: Heart Failure**	**Score**
Absent	0	Absent	0
Mild (agitation)	10	Mild (pedal edema)	5
Moderate(delirium, psychosis, extreme lethargy)	20	Moderate (bibasilar rales)	10
Severe (seizure, coma)	30	Severe (pulmonary edema)	15
Gastrointestinal and Hepatic Dysfunction	**Score**	**Cardiovascular Dysfunction: Atrial Fibrillation**	**Score**
Absent	0	Absent	0
Moderate (diarrhea, nausea/vomiting, abdominal pain)	10	Present	10
Severe (unexplained jaundice)	20		
Precipitant History	**Score**		
Absent	0		
Present	10		

[a] Adapted from Burch and Wartofsky[2] with permission of Elsevier. A score of 45 or greater is highly suggestive of thyroid storm; a score of 25 to 44 is suggestive of impending storm, and a score below 25 is unlikely to represent thyroid storm.

decreased ability to convert T4 to T3 and therefore even a minimally elevated, or "normal," free T3 may be inappropriately elevated in that context.[4] A complete laboratory workup is appropriate for these patients as it is for any critically ill patient. Leukocytosis may indicate a concomitant infection however can also be present even in the absence of infection. Elevated blood urea nitrogen has been linked to irreversible complications[3] and liver function abnormalities, with elevation in the transaminases and hyperbilirubinemia, can range from mild to severe. Hypercalcemia can exist due to the high bone resorption that accompanies hyperthyroidism and can exacerbate dehydration. Finally, glucose levels can be affected by thyroid storm with hyperglycemia due to a combination of increased catecholamine inhibition of insulin release and increased gluconeogenesis[7] or rarely hypoglycemia.[32]

Treatment Strategies

The treatment of thyroid storm should be initiated as soon as the diagnosis is suspected due to the high mortality associated with this condition. These critically ill patients are usually best triaged to an intensive care setting to allow for close monitoring and the implementation of timely and aggressive treatment strategies. A multidisciplinary team approach is also important in order to successfully offer the patient all possible therapeutic options. These options should not only target the synthesis and release of thyroid hormone but also attempt to minimize the effects of circulating hormone and prevent end-organ damage (Table 3).

Inhibiting New Thyroid Hormone Synthesis

The first-line therapy in treating thyroid storm consists of halting new thyroid hormone production. This treatment approach most commonly utilizes a class of medications called thionamides. This class includes thiouracils (PTU) and imidazoles (methimazole and carbimazole). Broadly, these medications inhibit thyroid peroxidase, a key enzyme involved in the formation of T3 and T4 from thyroglobulin[36] as well as slow follicular cell growth.[37] Both methimazole and PTU are used to treat hyperthyroidism; however, PTU is favored during thyroid storm due to its added benefit of decreasing the peripheral conversion of T4 to T3. Either of these drugs must be used at much higher doses than the standard regimen recommended for uncomplicated hyperthyroidism with various authors proposing different treatment regimens. The PTU dosing has been described ranging from 600 to 1500 mg per day in divided doses every 4 to 6 hours,[2,4,38] with the option of administering a loading dose of 600 mg. Methimazole dosing may range from 80 to 120 mg daily in divided doses every 4 to 6 hours.[2,4,38] The latest American Association of Clinical Endocrinologist/American Thyroid Association guidelines recommend a 500 to 1000 mg loading dose of PTU followed by 250 mg every 4 hours and 60 to 80 mg per day of methimazole in divided doses.[39]

For the critically ill patient with no enteral access, rectal formulations of PTU and methimazole can be prepared either as suppositories or retention enemas. The bioavailability of this route is lower; however, recently published data demonstrate a measurable clinical response to both rectally administered methimazole and PTU.[40-42] The suppositories exhibit an even

Table 3. Medical Treatment of Thyroid Storm.

	Oral Dose	Rectal Dose	Intravenous Dose
Therapy against new thyroid hormone production			
Propylthiouracil	Loading dose of 500-1000 mg followed by 250 mg every 4 hours	400-600 mg every 6 hours	
Methimazole	60-120 mg per day in 4-6 doses	20-40 mg every 8-6 hours	10-30 mg every 8-6 hours
Therapy against thyroid hormone release			
SSKI	5 drops every 6 hours	250-500 mg every 6 hours	
Lugol's solution	8 drops every 6 hours	80 drops per day/5-10 drops every 8-6 hours	
Sodium iodide			0.5 g every 12 hours
Lithium	300 mg every 8-6 hours		
Blocking the peripheral effects of thyroid hormone			
Propranolol	60-120 mg every 4-6 hours		
Esmolol			50-100 mcg/kg/min
Hydrocortisone			300 mg loading dose IV then 100 mg every 8 hours
Enhancing thyroid hormone clearance			
Cholestyramine	1-4 g twice a day		

Abbreviations: IV intravenous; SSKI, saturated solution of potassium iodine.

lower bioavailability than the enemas but are favored clinically, as their administration is easier for nursing personnel and less uncomfortable to the patient.[43] Different compounding methods exist for both enemas and suppositories, and a discussion with the pharmacist is strongly recommended to ensure proper and timely preparation of the drug.

When the gastrointestinal tract is completely compromised, and neither the oral nor the rectal routes are appropriate for medication administration, thionamides may be prepared for intravenous administration. PTU is relatively insoluble at physiologic pH, therefore its preparation and administration are difficult. Intravenous methimazole on the other hand is available commercially in Europe and can be prepared in a sterile fashion in the United States by dissolving methimazole powder in normal saline. This preparation has been implemented successfully in patients with thyroid storm and recently described in a small case series in the United States.[44]

In addition to thionamides, nonradioactive iodine administration is also known to decrease new thyroid hormone synthesis. This occurs by inhibiting the organic binding of iodide to thyroglobulin in the thyroid gland once plasma iodide levels reach a critical threshold, a physiologic mechanism known as the Wolff-Chaikoff effect. This effect is transient, lasting 26 to 50 hours, as the thyroid eventually escapes or adapts to prolonged iodide excess.[45] Inorganic iodine may be given orally as a saturated solution of potassium iodine by administering 5 drops (0.25 mL or 250 mg) every 6 hours or as Lugol's solution with 8 drops given every 6 hours.[2,39] These are currently the only oral formulations available in the United States, as the oral iodinated contrast agents iopanoic acid and sodium ipodate have been discontinued commercially.

Once again, for the critically ill patients who cannot tolerate oral medications, rectal and intravenous (IV) formulations of iodine are available. Potassium iodide can be prepared for rectal dosing by diluting 1 g of iodide in 60 mL of water and administering 2 g/d in divided doses.[46] Lugol's solution has also been given rectally in doses of 4 mL (equivalent to 80 drops) per day.[47] If the gastrointestinal tract is nonfunctioning, sterile lugol's solution can be added to IV fluids.[48]

There are a few important caveats in the use of iodine to treat thyroid storm. It is critical that iodine be dosed at least 30 minutes after administering thionamides to avoid the iodine serving as a substrate for new thyroid hormone production and worsening the hyperthyroidism. Thionamides must also be continued during therapy with iodine to avoid organification of iodine and increased thyroid hormone production. Iodine administration may also delay definitive treatment of patients' hyperthyroidism with radioactive iodine.[2,4] Iodine is often used when the end goal is an eventual thyroidectomy.

Finally, lithium therapy is known to impede T4 and T3 synthesis by inhibiting the coupling of iodotyrosine residues and can be administered for this effect in patients with thyroid storm. When iodine administration is not possible (secondary to iodine induced anaphylaxis) or desired, lithium may be substituted. It is administered at doses of 300 mg every 6 to 8 hours with frequent monitoring of serum levels (goal is 0.6-1 mEq/L[2,4]) due to the narrow therapeutic range and possibility of toxicity at supratherapeutic doses.

Inhibiting Thyroid Hormone Release

Once the formation of new thyroid hormone has been blocked, the next arm of the treatment strategy should focus on inhibiting the release of preformed hormone into the circulation. In addition to its effect on new hormone synthesis, iodine administration has also been shown to block the release of preformed hormone by inhibiting the proteolytic release of iodothyronines (T3 and T4) from thyroglobulin.[2,49] This secondary effect

affords iodine treatment a faster onset than PTU, which blocks synthesis in a thyroid gland that has a large store of already formed hormone.[10] The combination therapy of thionamides and iodine when used properly can decrease serum T4 levels close to the normal range in 4 to 5 days.[50] Although the mechanism is not well understood, lithium may also be used as a second-line agent to decrease thyroid hormone release in addition to its role in blocking thyroid hormone synthesis.

Inhibiting the Peripheral Effect of Thyroid Hormone

A comprehensive approach to treatment of thyroid storm should include blocking the peripheral effects of circulating thyroid hormone. Since responsiveness to the α-adrenergic stimulation and more so β-adrenergic stimulation is enhanced in cases of thyroid storm, adrenergic blockade is an integral part of the treatment strategy. The first report of the use of β-blockers in thyrotoxicosis dates from 1966 when Hughes used pronethalol in conjunction with carbimazole to treat severe hyperthyroidism in a patient with concomitant diabetic ketoacidosis.[51] Since then, β-blockers have played a cornerstone role in the therapy of both uncomplicated and complicated hyperthyroidism, including thyroid storm. Propranolol is the most commonly used β-blocker in thyroid storm due to its nonselective β-adrenergic antagonism and its ability to decrease the conversion of T4 to T3 in the periphery. The recommended dose can be as high as 60 to 120 mg orally every 6 hours in view of increased drug metabolism in storm.[7] For a more rapid effect, β-blockade can be accomplished intravenously with propranolol or a shorter acting β-blocker such as esmolol. The IV propranolol should be dosed 0.5 to 1.0 mg slow IV push for an initial dose and then 1 to 2 mg at 15-minute intervals while monitoring the heart rate carefully on telemetry. Esmolol is given as an initial bolus of 0.25 to 0.5 mg/kg followed by a continuous infusion rate of 0.05 to 0.1 mg/kg per minute.[10]

Inhibiting Enterohepatic Circulation of Thyroid Hormone

For severe or refractory thyroid storm, targeting thyroid hormone recirculation may be considered as an adjunctive therapy. Thyroid hormone is metabolized in the liver where it is conjugated to glucuronides and sulfates. Conjugation products are excreted into the intestine in bile, where free hormones are released, reabsorbed, and circulate. This process is referred to as the enterohepatic circulation of thyroid hormone. Cholestyramine, by binding the conjugation products, promotes their excretion and, therefore, may be used to decrease thyroid hormone levels. The recommended dosing regimen is 1 to 4 g twice a day, with reported improvement in circulating thyroid hormone levels.[52-54]

Other Therapies

Certain effective therapies are no longer available in the United States but are used in other countries. The oral iodinated contrast agents, used mainly as oral cholecystographic agents, are potent inhibitors of both deiodinases D1 and D2 and lead to a significant decrease in T3 levels. Additionally, in view of their iodine content, they may decrease new thyroid hormone production and prevent the release of preformed hormone from the gland. They have been used in the treatment of thyroid storm administered as a 2g loading dose followed by 1 g daily,[5] and in lower doses for rapid preparation for thyroid surgery[55,56] as well as anadjunct to thionamides in the treatment of Graves' disease.[57]

Supportive and Resuscitative Measures

Patients in thyroid storm are critically ill, and resuscitative measures should be promptly initiated. The treatment of systemic decompensation may require reversal of hyperthermia, dehydration, congestive heart failure, and dysrhythmia, and prevention of adrenal crisis.[10] Hyperthermia can be controlled with peripheral cooling and antipyretics. Acetaminophen is preferred over salicylates. Salicylates can increase free hormone levels by decreasing binding to T4-binding globulin thereby exacerbating thyroid storm.[58] The peripheral cooling can be accomplished with ice packs, cooling blankets, or alcohol sponges.

Intravenous fluids (IVFs) should be administered to correct for fluid losses due to fever, diarrhea, or vomiting. In patients with congestive heart failure, careful monitoring of hemodynamic status is needed when IVFs are being administered, especially with ongoing β-blockade. Often, a central venous pressure catheter, pulmonary wedge pressure monitoring, or both are needed to carefully guide fluid replacement. If hypotension does not respond to IVF resuscitation, vasopressors should be started.

Finally, the hypothalamo–pituitary–adrenal axis has been shown to be impaired in thyrotoxicosis with a decrease in adrenal reserve. Despite increased production of cortisol by the adrenal gland to compensate for accelerated glucocorticosteroid metabolism in hyperthyroid states, a subnormal response of the adrenal glands to adrenocortico-stimulating hormone occurs. Corticosteroids are therefore used as adjunct therapy in thyroid storm to prevent adrenal insufficiency. The therapy serves a dual purpose by also decreasing the peripheral conversion of T4 to T3.[59] Stress dose steroids are therefore recommended with a loading dose of 300 mg of hydrocortisone intravenously followed by 100 mg every 8 hours.[39]

The treatment of thyroid storm is neither complete nor effective if correctable precipitating events are not addressed (Table 1). These events are often readily recognized (such as trauma or surgery); however, some may be more subtle. The thyroid storm patient will most likely be febrile with a leukocytosis and the source for an infectious focus must be investigated. A careful history, or chart review in the stuporous or comatose patient, should look for exposure to iodinated contrast material or recent withdrawal of thionamide medication. In addition, any metabolic abnormalities, such as diabetic ketoacidosis, stroke, or pulmonary emboli, should be treated in the standard fashion.

Therapeutic Plasma Exchange

In refractory cases of thyrotoxic crisis in which clinical deterioration occurs despite the use of conventional therapies or a toxicity emerges (such as leukopenia due to PTU), alternative measures aimed at clearing thyroid hormone from the circulation should be instituted. Therapeutic plasma exchange (TPE) is effective in rapidly reducing thyroid hormone levels with associated clinical improvement. TPE has been used in a variety of illnesses to remove harmful plasma constituents rapidly or to decrease the concentrations of antibodies, immune complexes, and toxins.[60] During plasma exchange, the patient's plasma is extracted from the components of blood, and a colloid replacement such as albumin and/or plasma is infused.[60,61] In thyrotoxicosis, TBG, with bound thyroid hormone, is removed from circulation, and the colloid replacement (usually albumin) provides unsaturated binding sites for circulating free thyroid hormone. Although albumin binds thyroid hormone less avidly than TBG, it provides a much larger capacity for low-affinity binding, thereby decreasing free thyroid hormone concentrations.[14]

The first report of plasmapheresis in thyroid storm was published in 1970 by Ashkar et al[62] and described 3 patients who failed conventional therapy. They were all ultimately treated with plasmapheresis or exchange transfusion with dramatic clinical improvement and decline in their circulating hormone levels. Many subsequent reports have followed describing varying techniques of exchange transfusion, plasma exchange, single pass albumin dialysis, or charcoal hemoperfusion in the treatment of thyroid storm or refractory hyperthyroidism in the absence of storm including amiodarone-induced thyrotoxicosis.

Most series demonstrate a reduction in free T3 and free T4, although the literature contains conflicting reports.[60] Ezer et al published the largest plasma exchange series to date with 11 patients with thyrotoxicosis undergoing preoperative preparation with TPE prior to either thyroid or nonthyroidal surgery. The decrease in free T3 ranged from 22.2% to 89.9% while that of free T4 ranged from 8.3% to 64.8%; yet, the decline in biochemical values was not statistically significant.[61] Signs and symptoms of thyrotoxicosis, nonetheless, improved in all patients. In fact, clinical improvement within a few hours of the first TPE session has often been reported with cardiac manifestations most likely to regress rapidly.[63]

There is no clear consensus on the initiation of TPE in thyroid storm. In 2010, the American Society of Apheresis (ASFA) guidelines on the use of therapeutic apheresis in clinical practice recommended TPE as a grade IIc (weak recommendation, low-quality evidence based on observational studies or case series) and a category III (optimal role of apheresis therapy is not established; decision making should be individualized).[60] TPE becomes an option when clinical deterioration in thyroid storm occurs despite the use of well-established first- and/or second-line therapies. In a small case series and review of the literature, Muller et al recently suggested the early initiation of TPE with the following indications: severe symptoms (cardio-thyrotoxicosis, neurologic manifestations, severe myopathy, etc), rapid clinical deterioration, contraindications to other therapies, and failure of conventional therapeutics.[63] The ASFA recommends that TPE be performed at a frequency of daily to every 2 to 3 days until clinical improvement is noted. Free T3 and T4 should be sampled before and after each session. However, TPE should be continued if clinical stabilization is seen irrespective of hormone levels, since clinical improvement can be dissociated from the decline in hormonal concentration.[63] This effect is usually transient and TPE is considered an adjunct to medical therapy to provide clinical stabilization while awaiting drug efficacy or prior to definitive management with thyroidectomy. Complications of TPE are in the order of 5% and include hypotension, hemolysis, allergic reactions, coagulopathy, vascular injury, and infection.[61,63,64]

Surgical Management

For the elective or nonurgent surgical treatment of hyperthyroidism, the standard protocol would involve gradually achieving euthyroidism prior to surgery utilizing any combination of the aforementioned medical treatment strategies.[4] However, inevitably there are a subset of patients who fail medical management of their thyroid storm despite all of the most aggressive treatment modalities. This occurs more commonly in iodine-deficient areas, where thyroid storm is mostly related to iodine contamination in patients with thyroid autonomy. These patients are particularly resistant to even high-dose thionamides or iodine therapy because of the large intrathyroidal iodine pool.[65] All measures should still be employed to stabilize the patient prior to considering emergent surgical management. As mentioned earlier, a multidisciplinary approach to the patients with thyroid storm is crucial, and the surgical team should be involved early (within 12-72 hours) if the patient is not responding to the therapy.

The surgical approach to thyroid storm is similar to that for Graves' disease and involves a subtotal or near-total thyroidectomy.[10] The surgery produces rapid resolution of the hyperthyroidism, assuming very little thyroid tissue remains, and this allows cessation of the thionamides soon after the operation. Any steroid treatment or β-blockade should be continued perioperatively and slowly weaned off over the ensuing weeks.[4] The patients who require emergent surgical intervention essentially fall into 3 categories. These include those patients who clinically deteriorate or do not improve within 24 to 48 hours despite intensive medical treatment, develop side effects from the treatment (ie thionamide-induced agranulocytosis or severe thrombocytopenia), or need expedient resolution of their hyperthyroidism due to severe underlying cardiac or pulmonary comorbidities.[65] There have been several authors who describe treatment regimens to rapidly prepare these patients for surgery. However, almost all involve using an oral cholecystographic agent (iopanoic acid) that is not commercially available in the United States.[55,56,66] At our institution, we utilize plasmapheresis as an alternative to iopanoic

acid in an attempt to rapidly control refractory hyperthyroidism prior to surgery.

Fortunately, with all of the advances in critical care medicine and the medical treatment for thyroid storm, there is a paucity of patients who require emergent surgery. However, this also limits our ability to study surgical outcomes prospectively in a large series of patients. Dr Scholz and his colleagues from the University of Leipzig in Germany nicely summarize the literature to date examining early thyroidectomy for thyroid storm (not for severe thyrotoxicosis) including their own series of 10 patients. The long-term overall mortality of those patients treated with thyroidectomy was 10% (5 of 49) with a wide range from 0% to 20% in the different series. Obviously, the retrospective nature of these studies imparts a selection bias, and these are mostly patients with iodine-induced thyrotoxic storm which is rare in the United States.[65] Their experience and the results of other groups do suggest that early surgical management may reduce mortality in selected patients. However, essential to the success of the surgery is an experienced surgeon and careful medical management of the patients pre- and postoperatively in an ICU.

Long-Term Management of Hyperthyroidism

After the thyroid storm has subsided, permanent treatment of the hyperthyroidism should be provided. Due to the long half-life of T4 (approximately 1 week), the initial therapy should be slowly weaned off after the acute hospitalization, and the patient should be closely followed as an outpatient prior to definitive therapy. When nonadherence to medical management with thionamide has been identified as the precipitating event, definitive therapy with radioactive iodine ablation or surgery should be pursued. Many of the patients will receive iodine therapy as part of their acute treatment regimen, and ablation will need to be delayed until the intrathyroidal iodine stores have cleared. During this interval, it is important to continue thionamides and monitor serial thyroid function studies to assess stabilization. If surgery is planned, adequate preparation and control of hyperthyroidism should be accomplished prior to proceeding. Finally, continuation of therapy with thionamide agents is an acceptable alternative in compliant patients.

Outcomes

The outcomes of thyroid storm depend largely on prompt delivery of the appropriate treatments described previously. Initial case series described mortality rates as high as 37.5%[67] but more recent reviews report the mortality of treated thyroid storm to be at 10.7%.[3] This can be partly due to the advances made in treatment modalities as well as in earlier recognition of this endocrine emergency. In the nationwide survey of the Japanese cases of thyroid storm, multiorgan failure and congestive heart failure were the leading causes of death. Even when mortality is avoided, significant morbidity, in the form of brain injury, disuse atrophy of the muscles, cerebrovascular disease, renal function impairment, and even psychosis, can lead to long-term complications.

Conclusion

Thyroid storm is an endocrine emergency that is associated with high morbidity and mortality if not promptly recognized and treated. Multidisciplinary treatment in an intensive care setting is usually needed. Treatment involves addressing all steps of thyroid hormone synthesis, release, and action, in a well-defined order, while providing supportive care. Treating precipitating factors is an integral part of the management.

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