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THYROID EMERGENCIES

Dorina Ylli, MD, PhD,
Endocrinology Division, University of Tirana, "B.Curri" St, 114 Tirana, Albania

Joanna Klubo-Gwiezdzinska, MD, PhD,
Lasker Tenure Track Investigator, Metabolic Disease Branch, NIDDK, National Institutes of Health, Bethesda, Maryland USA 20814

Leonard Wartofsky, MD
Professor of Medicine, Georgetown University School of Medicine, Endocrinology Division, Department of Medicine, MedStar Health Research Institutem, MedStar Washington Hospital Center, 110 Irving Street, N.W., Washington, DC USA 20010-2975

Abstract

Myxedema coma and thyroid storm are among the most common endocrine emergencies presenting to general hospitals. Myxedema coma represents the most extreme, life threatening expression of severe hypothyroidism with subjects presenting with deteriorating mental status, hypothermia, and multiple organ system abnormalities. It typically appears in patients with pre-existing hypothyroidism via a common pathway of respiratory decompensation with CO_2 narcosis leading to coma. Without early and appropriate therapy, there is often a fatal outcome. It is a clinical diagnosis based on history and physical findings at presentation and not on any objective thyroid laboratory tests. Clinically based scoring systems have been proposed to aid in the diagnosis. While a relatively rare syndrome, the typical patient is an elderly woman (thyroid hypofunction being much more common in women) who may or may not have a history of previously diagnosed or treated thyroid dysfunction. Thyrotoxic storm or thyroid crisis also is a rare condition and it too reflects a clinical diagnosis. Diagnosis is based upon the appearance of severe hyperthyroidism accompanied by elements of systemic decompensation. Based upon the prospect of high mortality without aggressive treatment, therapy must be initiated as early as possible in a critical care setting. There are no clues to diagnosis based upon laboratory tests alone, but several scoring systems have been developed to aid in diagnosis. The usual clinical signs and symptoms of hyperthyroidism will be present along with more exaggerated clinical manifestations affecting the cardiovascular, gastrointestinal, and central nervous systems. A multi-pronged treatment approach has been recommended and has been associated with improved outcomes.

Corresponding Author: Leonard Wartofsky, leonard.wartofsky@medstar.net.

Keywords

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Introduction

The entities of "Myxedema Coma" and "Thyroid Storm" represent the respective extremes of thyroid dysfunction, each of which if not promptly and appropriately diagnosed and treated, have a poor outcome with high mortality. In approaching these as well as other endocrine emergencies, it is important to have a high index of suspicion for the diagnosis, to act counter to usual therapeutic approaches for most disorders by treating the suspected diagnosis before it is actually confirmed. This approach proves valid because in these conditions the treatment indicated will rarely be harmful in contrast to the risks inherent in not treating. Moreover, because both entities typically occur in patients with pre-existent hypo- or hyperthyroidism, respectively, and to have been precipitated by some superimposed condition or non-thyroidal illness, it is important to identify and address the precipitating event. Otherwise, the abnormal thyroid state may continue, worsen, or recur at a later time.

MYXEDEMA COMA

It should be appreciated that myxedema coma is a clinical diagnosis as there is no single or group of laboratory test results that establish the diagnosis in any definitive way. The most dramatic clinical finding is of course, coma or precoma appearing in the setting of hypothyroidism. The hypothyroidism may have been longstanding or previously undocumented, and with the former there is often a history of discontinuation of thyroid hormone replacement medications. In the pre-comatose state, the typical clinical findings include hypothermia, decreased mentation, generalized edema and the usual hallmarks of profound hypothyroidism. A typical presentation is of a woman with the above findings in the age range of 60–85 presenting in the cold of winter after being found down. Severely cold weather is only one of many possible precipitating factors that may convert the clinical status of the patient from hypothyroidism to myxedema coma. Other possible precipitating events include hypoglycemia, hyponatremia, hypoxemia, and hypercapnia (see Table 1). In the overwhelming majority of subjects, the basis for the underlying hypothyroidism is autoimmunity, i.e., Hashimoto thyroiditis. But, much more rarely is the occurrence of secondary or central hypothyroidism due to thyrotropin deficiency related to pituitary disease. In the latter subjects it is critical to keep the possibility of associated hypoadrenalism in mind, which constitutes a justification for consideration of empiric corticosteroid therapy. Medications that can precipitate myxedema coma include sedatives, analgesics, antidepressants, hypnotics, antipsychotics, and anesthetic drugs via a shared mechanism of the tendency to suppress respiration. Drug-induced myxedema coma is more common in patients not known to have hypothyroidism and who are hospitalized for other problems (1).

Clinical Presentation

If the patient is conscious and communicative, her slow speech and hoarse voice may be the clue to hypothyroidism. A history of radioiodine therapy for nodular or diffuse toxic goiter may be elicited, or of having discontinued taking thyroid hormone medication prescribed previously. Rarely, laconic clever or sarcastic responses to questioning have been noted in the pre-comatose state and have been labelled as "myxedema wit". On physical examination there will be dry, scaly skin, nonpitting edema of the faces, hands, and feet, macroglossia, delayed deep tendon reflexes, and thinning or sparse body hair. There may be a surgical scar in the neck indicating earlier thyroidectomy. Even in the absence of pulmonary infection, there will be hypoxemia and hypercarbia secondary to a reduced ventilatory drive triggered by hypercapnia that forms the basis for respiratory depression. In the presence of pneumonia, the downhill process is accelerated and torpor with slowed respiration coupled with airway obstruction from peri-laryngeal edema and the large tongue lead to progressive depression of the central nervous system and coma. The pathway to respiratory decompensation is further exacerbated by depressed function of respiratory musculature due to hypothyroidism and the tendency for reduced lung volume due to fluid collections in the lung (pleural effusion), heart (pericardial effusion), and abdomen (ascites). Ono, et al, (2) analyzed 149 hospitalized subjects with myxedema coma and noted that two-thirds were women and the group had an average age of 77 years. Death was seen in 30% and with higher frequency in winter.

Manifestations of myxedema coma like those of thyroid storm reflect multisystem decompensation. Renal function is impaired due to decreased glomerular filtration leading to symptomatic hyponatremia as the kidneys lose their ability to excrete a free water load because of decreased delivery of water to the distal nephron, Decreased cardiac output and hypovolemia sensed by baroreceptors may lead to a stimulation of antidiuretic hormone (ADH) release, further contributing to hyponatremia and impaired free water excretion. The effects of such profound hypothyroidism on the gastrointestinal tract will include complaints of anorexia and constipation, and reduced motility, gastric atony, paralytic ileus and megacolon are not unusual.

It is highly important to consider underlying infection, e.g., pneumonia, which is a very common precipitant of myxedema coma, because these patients may have the usual signs of infection masked by the bradycardia and hypothermia, thus not demonstrating the fever or tachycardia typical of infection. In one retrospective series, sepsis was highly correlated with mortality with 12/23 (52%) of patients dying of sepsis (3). Findings in the cardiovascular system include pericardial effusion, cardiomegaly, bradycardia, and reduced ejection fraction and cardiac output due to decreased cardiac contractility. Findings on electrocardiography include bradycardia, various degrees of heart block, and low voltage. Although bradycardia is almost always present, occasional patients may present with *torsades de pointe* ventricular tachycardia (4). As implied above, the most dramatic aspect of the presentation is the coma per se which typically evolves from initial lethargy, then progressing to a history of increased sleeping throughout the day, and then inability of family members to awaken the patient. Seizure can occur, doubtless facilitated by the metabolic abnormalities.

Laboratory Findings

As indicated above, there is no laboratory test result that indicates the presence of myxedema, no matter how low the free thyroxine (FT4) level or how high the elevation in serum thyroid-stimulating hormone (TSH) concentration. FT4 levels will be low and can be almost undetectable, while TSH levels have varied widely in reported cases of myxedema coma. Of course, in secondary or pituitary hypothyroidism the FT4 and TSH levels will be low or low 'normal' and the presence of biologically inactive TSH may account for the measured normal concentrations.

Other laboratory test abnormalities can include low blood glucose, low sodium and chloride levels, high total and ionized calcium, and mild renal failure with elevations in blood urea nitrogen (BUN) and creatinine. In addition to complete blood counts and a full chemistry profile, measurement of ACTH and plasma cortisol should be considered in view of the likelihood, albeit rare, of a pituitary basis for the hypothyroidism or coincident primary adrenal insufficiency (Schmidt syndrome).

Diagnosis

Because a definitive diagnosis of coma due to myxedema cannot be made on the basis of laboratory tests, several workers have attempted to develop scoring systems based on history, physical findings, and symptoms in order to objectify a diagnosis and differentiate between the presence of just overt or severe hypothyroidism and myxedema coma (5, 6). At our medical center, Popoveniuc et al. (5) assigned a numerical value for the presence of specific signs and symptoms (Table 2) and calculated a total or cumulative score. Based on the outcome of the patients studied, a diagnostic score of equal to or greater than 60 correlated with the presence of myxedema coma, whereas a score between 45 and 59 only overt hypothyroidism but a subject at increased risk for myxedema coma if not treated.

Management

Patients in whom myxedema coma is suspected should be immediately admitted to an intensive care unit and treatment initiated. Delays associated with failure to diagnose or awaiting confirmation by blood tests have contributed to the high mortality associated with this condition. Although the obvious primary cause of the situation is thyroid hormone deficiency, treatment by the replacement of thyroid hormone alone does not fully address the multi-system decompensation that is likely to be present. Even in the absence of fever and leukocytosis, broad spectrum antibiotic coverage should be started on an empiric basis. Low blood sodium is likely to be playing a major role in any lethargy, disorientation or coma when present and must be corrected. When serum sodium concentration is less than 120 mEq/L, the slow administration of hypertonic saline is justified with continuous careful monitoring. Too rapid correction can result in worsening central nervous system function due to central pontine myelinolysis. Otherwise, only normal saline or mixed saline/glucose should be employed and will also address the volume depletion present. In addition to the nutritive value provided by the glucose, multivitamins may be added to the intravenous fluids. We believe that treatment with a vasopressin antagonist should be considered with severe hyponatremia related to the high ADH levels in these patients. In the USA, there are two agents, conivaptan (7, 8) and tolvaptan that have been employed in euvolemic and

hypervolemic hyponatremia. Conivaptan is given by intravenous infusion as a loading dose of 20 mg over 25 to 30 minutes followed by continuous intravenous infusion at a rate of 20 mg/day for 2 to 4 more days. Tolvaptan is initially administered as an oral dose of 15 mg.

To address the hypothermia urgently until the effect of thyroid hormone on body temperature is realized, ordinary blankets rather than electric heating blankets are recommended. Too rapid warming can be associated with peripheral vasodilatation and drop in blood pressure and even shock, particularly because total blood volume tends to be low.

As myxedema coma is often precipitated by pneumonia and impaired ventilation (see above), there is great risk of progression to ventilatory failure and death. To ensure adequate ventilation, mechanical means often must be employed with careful monitoring blood oxygen and carbon dioxide levels. As recommended above, a baseline plasma cortisol having been drawn, the patient's vascular stability may be enhanced by administration of empiric corticosteroid administration, e.g., 50–100 mg hydrocortisone intravenously. Concern for adrenal insufficiency is based upon findings of low blood sugar, low sodium, and high calcium and potassium which are equally compatible with adrenal insufficiency. There also is a belief based upon anecdotal cases, of a risk of precipitation of adrenal crisis by treatment with thyroid hormone alone; in such a scenario, the patient is believed to have been marginally stable on low plasma cortisol but the enhanced metabolism afforded by thyroid hormone provokes acute adrenal crisis

Thyroid Hormone Therapy

One of the most controversial aspects of the management of myxedema coma is related to its treatment with thyroid hormone. The controversy is whether to use thyroxine (T4) alone, triiodothyronine (T3) alone, or some combination of the two hormones. T4 is often considered as a 'pro-hormone' with activation of metabolic action achieved by the conversion to T3, whereas T3 is highly active, perhaps some 10–15 times more active than T4. Those (like myself) who recommend use of some amount of T3 base this belief on the fact that the myxedema patient is systemically ill and is therefore suffering reduced deiodination and conversion of T4 to T3 analogous to what is seen in the 'euthyroid sick syndrome' (9). Hence, in this situation reflecting a 'hypothyroid sick syndrome', the administration of only T4 would be associated with inadequate levels of T3 and a risk of delayed recovery to a more euthyroid state.

Concern with T3 administration has been based on observations of higher mortality rates when T3 was given in relatively high doses, especially in subjects with underlying cardiac disease. Thus, advocates for T4 therapy alone point out that the slow conversion of T4 to T3 may be more physiologic and probably safer with less risk of an adverse effect that might be seen with high T3 levels (10, 11). Biokinetic data suggest that the average total body distribution space content of T4 approximates 500 μg. On this basis, a high T4 dose (300–600 μg) is given intravenously the first day to replete the body's stores followed by 50–100 μg daily given either intravenously or orally (12). Advocates for T3 administration want to provide a faster onset of action and to potentially achieve higher survival rates. For this purpose, a dose of 10–20 μg intravenously every 4 hrs is recommended for the first day and

then 10 μg every 6 h for 1–2 days. Oral administration of T3 is continued thereafter in a dosage range of 25 μg twice daily.

Our favorite regimen reflects a compromise approach with administration of both T4 and T3. We would administer both T4 and T3 simultaneously initially, with T4 at a dose of 4 μg/kg lean body weight (approximately 200–300 μg) followed by 100 μg 24 h later and then 50 μg daily either intravenously or orally. We recommend an initial dose of T3 as 10 μg intravenously every 8–12 h until the patient is able to tolerate oral intake. Recently published guidelines for treatment of hypothyroidism and myxedema coma by the American Thyroid Association (13) emphasize individualizing dosage based upon age, weight, and cardiac status, suggesting the initial use of intravenous T4 in a dose of 200–400 μg with a lower dose given to older patients or those with cardiac disease.

THYROTOXIC STORM

Thyrotoxic storm or thyroid crisis is the most extreme clinical expression of thyrotoxicosis and typically represents an exacerbation of previously existent hyperthyroidism but with a dramatic clinical picture. Because of the potential for a fatal outcome in the absence of aggressive management, it demands early diagnosis and aggressive therapy in an intensive care setting to avoid a disastrous outcome. There are no objective or specific laboratory tests which if abnormal will definitively suggest the diagnosis and hence the diagnosis is based on purely clinical features. Two different but similar scoring systems based upon signs and symptoms have been developed to facilitate early diagnosis (14 – 16). While it is fortunately rare, thyroid storm appears in 1–2% of hospital admissions for thyrotoxicosis. Our own 1000 bed hospital will see 3–4 cases per year. Like other endocrine emergent situations, treatment should not be delayed and should be initiated once suspected in view of its potential for high mortality, without awaiting blood test results indicating severe thyrotoxicosis.

Clinical Presentation

In the typical patient, it is not difficult to determine the existence of hyperthyroidism. They will present with many of the usual signs and symptoms of hyperthyroidism including weight loss, tremor, tachycardia, goiter, brisk reflexes and proptosis. However, with the advent of thyroid storm, features become exaggerated with the appearance of fever, more marked tachycardia, arrhythmias, cachexia, a sense of impending doom, and even coma. Very commonly, the transition from uncomplicated hyperthyroidism to thyroid storm is associated with some precipitating event (Table 3) such as an infection, surgical procedure, trauma, burns, emotional stress, or even vigorous palpation of the thyroid gland. A common cause is the inappropriate discontinuation of anti-thyroid drug therapy in a patient with Graves' disease. Storm has also been described in subjects with an underlying toxic multinodular goiter, for example following radioiodine therapy, and in elderly patients the presentation may be less dramatic and has been called masked or "apathetic" thyrotoxicosis. Without treatment, systemic decompensation occurs and tachyarrhythmias and atrial fibrillation may lead to congestive heart failure even in subjects with no prior history of cardiac disease. Hepatomegaly and abnormal liver function tests can occur from hepatic congestion due to heart failure. Jaundice with hepatic necrosis has also been seen. Volume

depletion occurs with voluminous diarrhea, vomiting and fever leading to postural hypotension although systolic hypertension with a widened pulse pressure is common in hyperthyroidism. In patients with thyroid storm who do not survive, a pre-terminal event can be vascular collapse with shock. Other manifestations affecting the gastrointestinal system include acute abdomen, intestinal obstruction, diffuse abdominal pain, and splenomegaly. As the thyroid crisis progresses, symptoms of central nervous system dysfunction may appear, including increasing agitation, confusion, paranoid ideation, psychosis, and finally even frank coma (17).

Pathogenesis

It is unknown or at least uncertain what constitutes the pathophysiologic mechanism that underlies the transition of a patient from uncomplicated hyperthyroidism to thyrotoxic storm. However, there does seem to be a common theme inherent in a number of the clinical situations that either precede or appear to precipitate the storm. What does appear clear is that this transition is not simply due to more thyroid hormone synthesis and secretion into the bloodstream as the magnitude of hormone levels may not be significantly different, with perhaps one exception the level of free T4 (18). But increased hormone levels do clearly play a role as is demonstrated by the development of storm after radioiodine therapy with associated acute discharge of hormone from the thyroid gland or in rare cases of iatrogenic thyrotoxicosis from ingestion of large amount of the hormone. Another example occurs in those Graves' disease patients who without medical advice inappropriately withdraw their thiourea (methimazole; propylthiouracil) therapy. And increased hormone release also plays a key role in Jod-Basedow iodine-induced thyrotoxicosis with storm.

But there is something else at play here as well, and there is evidence for an interaction between the effects of excessive levels of circulating thyroid hormone and catecholamines. The clinical expression of this interaction includes tachycardia, anxiety, and tremors, all of which may be mitigated by administration of agents such as reserpine β-adrenergic receptors blockers which reduce expression of catecholamine effects (19, 20). These agents play an adjunctive role in the management of storm as indicated below.

Laboratory Findings

As previously indicated, one cannot rely on any given laboratory result to definitively diagnose storm. While we should expect to see markedly elevated levels of both total and free T4 and T3 and suppressed, immeasurably low TSH concentration, this is not always the case. Specifically, serum total T3 may be only slightly elevated or even within normal limits. When a normal T3 level is seen in storm, it is likely to be due to presence of reduced deiodination or conversion of T4 to T3, much as is seen in the "low T3" or "euthyroid sick syndrome" (21) but in this case we are dealing with a "hyperthyroid sick syndrome" as expressed by the thyroid function test results. The cause for the low T3, just as in the euthyroid sick syndrome, is a systemic or underlying illness that may have been the original stimulus for the patient's evolution into storm. However, in such cases, free T4 should still be elevated and TSH undetectable. When it can be arranged between a Nuclear Medicine Department and the intensive care unit based on patient stability, diagnosis can be facilitated by performance of a rapid or 2-hr radioiodine uptake which should be markedly elevated.

Routine admission blood counts may disclose mild anemia and relative lymphocytosis typical of uncomplicated Graves' disease, but in storm a leukocytosis with a mild shift to the left is common raising the question of superimposed infection. Although this pattern is seen even in the absence of infection, infection must be ruled out (see below). On the basis of volume depletion or hemoconcentration, hypercalcemia may be seen, perhaps fueled by the resorptive action of thyroid hormones on bone. The hypercalcemia should resolve with fluids and other therapy, but if not, the possibility of coincident primary hyperparathyroidism should be considered. Modest elevations in blood glucose can be noted as well but serum electrolytes are usually normal. If serum electrolytes are not normal, e.g., with hyponatremia, hyperkalemia, and hypercalcemia, the possibility of coincident adrenal insufficiency must be entertained and serum cortisol and ACTH levels measured (22). However, the result of cortisol measurements must be interpreted in the context of storm in which setting the existent stress will provoke higher cortisol levels. Thus, a low normal cortisol level may be inappropriately low and distinctly abnormal. Adrenal insufficiency does occur with increased frequency in patients with Graves' disease and the presence of the above electrolyte disturbances together with hypotension, cachexia and any other suggestive physical findings demands consideration, ruling out diagnostically and empiric steroid coverage that can be started immediately after drawing blood for cortisol determination.

The severe hypermetabolic state leads to increased lipolysis and ketogenesis and reduced clearance of lactic acid by the liver promotes development of lactic acidosis and ketoacidosis. Both renal and liver function abnormalities can be seen in hyperthyroidism, with the degree of dysfunction directly related to the severity of the thyrotoxicosis. However, in thyroid storm, either hepatic necrosis or the liver dysfunction due to heart failure noted above will be associated with even more abnormally high levels of bilirubin, serum lactate dehydrogenase (LDH) and aspartate aminotransferases (SGOT, SGPT).

Diagnosis

As noted above, the diagnosis of thyroid storm is a clinical one, a diagnosis made after assessing a patient presenting with indisputable thyrotoxicosis and determining that the condition has advanced to a dangerous state. Laboratory findings in thyrotoxic storm are useful but can be misleading with results that are difficult to distinguish from those in uncomplicated thyrotoxicosis. Hence, both true storm and uncomplicated hyperthyroidism may have tachycardia, but is there a difference in the degree of tachycardia, and in addition, is atrial fibrillation or signs of heart failure present? Similarly, uncomplicated thyrotoxicosis may exhibit mild temperature elevation, but storm patients exhibit fever, perhaps compounded by coincident infection rendering the patient more ill with other signs such as tachycardia and increased perspiration. Or on other occasions in storm, an infection may be quite minor but the degree of fever and toxicity seems out of proportion to the infection. Such apparent paradoxes make rendering of a diagnosis problematic, and this dilemma led us (14) and subsequently others (15) to develop a scoring system to derive the diagnosis of storm. Based upon determination of an elevated score consistent with thyroid storm, we then have full license to initiate an intensive treatment plan. Otherwise, experience has shown that these patients will continue an inexorable decline of vital functions at the risk of early mortality. As indicated in Table 4, the author believes it best to err on the side of assuming

storm in present or imminent when scores are marginally elevated and to initiate therapy rather than miss the diagnosis. In any event, initiation of therapy should not be postponed when there is a high index of suspicion because of any delay in obtaining laboratory confirmation of the diagnosis.

Treatment

There are four components that represent the approach to therapy of thyroid storm (Table 5). They are: 1) treatment directed at thyroid hormone synthesis and secretion by the thyroid gland ; 2) addressing the distribution, content, and action of the thyroid hormones already in the peripheral circulation; 3) determining the precipitating cause of storm when possible and ensuring that there is no ongoing contribution to the exacerbation of the thyrotoxicosis; and finally, 4) supportive and symptomatic therapy for the systemic decompensation present. Experience has shown that addressing all four components of treatment provides the best opportunity to avoid a fatal outcome. Although the relative importance of each arm of therapy for an optimal outcome will vary in each patient, no one component of this four-pronged therapeutic approach should be neglected. Notwithstanding the usual efficacy of this four-pronged approach to medical therapy, there is the rare patient who does not respond and in whom the ravaging effects of unbridled severe thyrotoxicosis continue unabated. For such patients, surgical thyroidectomy on an emergent basis (23) has been attempted with mixed results.

Therapy Directed against the Thyroid Gland

The Graves' disease thyroid gland is typically quite rich in hormone stores and this is especially true in circumstances when storm was precipitated or aggravated by exposure to excessive amounts of iodine. Treatment must address both new hormone synthesis and the secretion of already preformed, stored thyroid hormone. Blockade of new synthesis is achieved by inhibition of organification of iodide and the coupling of iodotyrosines in the synthetic process by the administration of thiourea antithyroid drugs, such as propylthiouracil (PTU) or methimazole (Tapazole). In the USA, these drugs are given orally as there are no available parenteral preparations although intravenous PTU or tiamazole can be found in Europe. In comatose patients the drugs may be given via nasogastric tube into the stomach or via the rectum (24–26). While typical doses of methimazole in uncomplicated hyperthyroidism may average 5 – 45 mg daily, higher doses of 120 mg daily are required in thyroid storm, and best given on a divided dosage such as 30 mg every 6 hours. It is conceivable that PTU provides more rapid clinical benefit than methimazole as it has the additional advantage of inhibiting conversion of T4 to T3, and may more rapidly lower serum T3 levels than will methimazole.

After addressing blockade of new hormone synthesis, it is next mandatory to attempt to inhibit release of preformed hormone into the circulation (27). To do so requires administration of inorganic iodine given orally as Lugol's solution or as a saturated solution of potassium iodide (eight drops every 6 h). The sequence of administration of methimazole and iodine is extremely important. Absent prior thionamide blockade of hormone synthesis, administration of iodine will provide extra substrate for even greater hormone production

and enrichment of hormone stores within the gland, thereby potentially causing worsening storm. This is easily avoided by administering at least one large dose of thionamide 30–60 minutes prior to iodine. In those patients allergic to iodine, lithium carbonate may be used as an alternative agent to inhibit hormonal release. Typical dosage is 300 mgms three to four times daily producing a blood lithium level of 0.9–1.2 mEq/liter.

Attempts to Reduce Ongoing Effects of Thyroid Hormone in the Periphery

Levels of both circulating total and free T4 and T3 may be quite elevated in storm and the goal is to accelerate the loss of hormone to a greater rate than occurs via metabolism. To achieve this, various means of extracting thyroid hormone from blood have been attempted in cases of severe storm to include peritoneal dialysis, plasmapheresis, and hemadsorption or perfusion through a resin bed or charcoal columns (28–30).

Apart from removal of thyroid hormone from the peripheral circulation, we also can attempt to block the effects of the thyroid hormones that are typically exaggerated in storm. For this purpose, beta adrenergic blockers are used and the mainstay of this therapy in the USA is the agent, propranolol (19, 20). Large doses, such as 60 to 120 mg every 6 h, are used in crisis or impending crisis. As occurs with almost all drugs given in thyrotoxicosis, the drug metabolism is accelerated and larger than usual oral doses, or preferably intravenous doses, will need to be given. The benefits of β-adrenergic blockade include reduced agitation, convulsions, psychotic behavior, tremor, diarrhea, fever, and diaphoresis. In the intensive care setting, very short-acting β-adrenergic antagonists, such as esmolol (31) or landiolol, can be given intravenously instead of propranolol. For esmolol, an initial intravenous dose is 0.25 to 0.5 mg/kg given in 5 to 10 minutes, followed by a continuous infusion of 0.05 to 0.1 mg/kg/min. For patients with asthma or who present other concerns if treated with beta blockers, short half-life calcium antagonists such as verapamil have been employed.

Therapy Directed against the Precipitating Event

When thyroid storm may have been precipitated by infection or some other non-thyroidal illness or toxins, it will be less than optimal to treat the thyroid gland but run the risk of recurrent storm because the precipitating event or cause was not addressed and eliminated. Conditions such as ketoacidosis, pulmonary thromboembolism, and stroke may underlie thyrotoxic crisis, particularly in the obtunded or psychotic patient, and require identification and appropriate aggressive management. When no precipitating cause is apparent, a diligent search for some focus of infection should be done with consideration given to use of empiric, broad-spectrum antibiotics while awaiting culture results. An ongoing underlying problem should be suspected if storm does not relent after 24 hours when the therapeutic guidelines suggested herein are applied.

Therapy Addressing Systemic Decompensation

Fever should be treated with acetoaminophen and a cooling fan and not with aspirin which can inhibit binding of T4 to its binding proteins in plasma and result in an increased free T4. Volume depletion with hypotension is the result of fever, vomiting, diarrhea and increased

sweating and can lead to vascular collapse and shock. While use of vasopressor agents is not encouraged due to the sensitivity to these agents and the patient's fragile vascular status, they are sometimes required in the acute shock situation and should be employed sparingly. Shock may respond instead to only fluid replacement but even providing fluids alone may provoke congestive heart failure in elderly patients while being relatively safe in the younger decades. Use of dextrose/saline combination fluids is recommended over normal saline alone in order to also provide nutritional content, and multivitamins should be added in view of the likely deficiencies that accompany the hypermetabolism of thyrotoxicosis. Stress dose glucocorticoids have been given on empirical grounds on the basis of postulated relative adrenal insufficiency insofar as adrenal reserve may be exceeded in thyrotoxic crisis due to the inability of the adrenal gland to meet the demand placed on it as a result of the accelerated metabolism and disposal of glucocorticoids that occur in thyrotoxicosis. This approach has the added benefit of further blockade of peripheral conversion of T4 to T3, and this is an additional justification for their use.

REFERENCES

1. Kwaku MP, Burman KD Myxedema coma. J Intensive Care Med 3007; 22:224–31

2. Ono Y, Ono S, Yasunaga H, Matsui H, Fushimi K, Tanaka Y Clinical characteristics and outcomes of myxedema coma: Analysis of a national inpatient database in Japan. J Epidemiol 2017; 27:117–122 [PubMed: 28142035]

3. Dutta P, Bhansali A, Masoodi SR, Bhadada S, Sharma N, Rajput R Predictors of outcome in myxoedema coma: a study from a tertiary care centre. Crit Care 2008; 12:R1 [PubMed: 18173846]

4. Schenck JB, Rizvi AA, Lin T Severe primary hypothyroidism manifesting with torsades de pointes. Am J Med Sci 2006; 331:154–6 [PubMed: 16538077]

5. Popoveniuc G, Chandra T, Sud A, et al. A diagnostic scoring system for myxedema coma. Endocr Pract 2014; 20:808–17 [PubMed: 24518183]

6. Chiong YV, Bammerlin E, Mariash CN Development of an objective tool for the diagnosis of myxedema coma. Transl Res 2015; 166:233–43 [PubMed: 25647622]

7. Naidech AM, Paparello J, Liebling SM, et al. Use of Conivaptan (Vaprisol) for hyponatremic neuro-ICU patients. Neurocrit Care 2010; 13:57–61 [PubMed: 20568023]

8. Ferguson-Myrthil N Novel agents for the treatment of hyponatremia: a review of conivaptan and tolvaptan. Cardiol Rev 2010; 18:313–21 [PubMed: 20926941]

9. Wartofsky L, Burman KD Alterations in thyroid function in patients with systemic illness: the "euthyroid sick syndrome". Endocr Rev 1982; 3:164–217 [PubMed: 6806085]

10. Rodriguez I, Fluiters E, Perez-Mendez LF, Luna R, Paramo C, Garcia-Mayor RV Factors associated with mortality of patients with myxoedema coma: prospective study in 11 cases treated in a single institution. J Endocrinol 2004; 180:347–50 [PubMed: 14765987]

11. Yamamoto T, Fukuyama J, Fujiyoshi A Factors associated with mortality of myxedema coma: report of eight cases and literature survey. Thyroid 1999; 9:1167–74 [PubMed: 10646654]

12. Holvey DN, Goodner CJ, Nicoloff JT, Dowling JT Treatment of Myxedema Coma with Intravenous Thyroxine. Arch Intern Med 1964; 113:89–96 [PubMed: 14067598]

13. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association task force on thyroid hormone replacement. Thyroid 2014; 24:1670–751 [PubMed: 25266247]

14. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis: thyroid storm. Endocrinol Metab Clin North Am 1993;22:263–277. [PubMed: 8325286]

15. 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. Diagnostic criteria, clinical features, and incidence of thyroid storm based on nationwide surveys. Thyroid 2012; 22:661–679 [PubMed: 22690898]

16. Angell TE, Lechner MG, Nguyen CT, Salvato VL, Nicoloff JT, LoPresti JS. Clinical features and hospital outcomes in thyroid storm: A retrospective cohort study. J Clin Endocrinol Metab 2015; 100: 451–459. [PubMed: 25343237]

17. Nayak B, Burman KD. Thyrotoxicosis and thyroid storm. Endocrinol Metab Clin North Am 2006; 35:663–686. [PubMed: 17127140]

18. Brooks MH, Waldstein SS. Free thyroxine concentrations in thyroid storm. Ann Intern Med. 1980; 93:694–7. [PubMed: 7212477]

19. Feely J, Forrest A, Gunn A. Propranolol dosage in thyrotoxicosis. Journal of Clinical Endocrinology & Metabolism 1980; 51:658–661. [PubMed: 7410541]

20. Eriksson MA, Rubenfeld S, Garber AJ, et al. Propranolol does not prevent thyroid storm. N Engl J Med 1977; 296:263–264 . [PubMed: 831110]

21. Wartofsky L, Burman KD. Alterations in thyroid function in patients with systemic illness: the euthyroid sick syndrome. Endocr Rev 1982; 3:164–217. [PubMed: 6806085]

22. DeKeulenaer BL, Lahaye FJ, Schepens DR, et al. Thyroid storm presenting with no fever and an absolute adrenal insufficiency. Intens Care Med 2002;28:1192.

23. Scholz GH, Hagemann E, Arkenau C, et al. Is there a place for thyroidectomy in older patients with thyrotoxic storm and cardiorespiratory failure? Thyroid 2003; 13:933–940. [PubMed: 14611702]

24. Hodak SP, Huang C, Clarke D, Burman KD, Jonklaas J, Janicic-Kharic N. Intravenous methimazole in the treatment of refractory hyperthyroidism. Thyroid. 2006;16:691–5, [PubMed: 16889494]

25. Jongjaroenprasert W, Akarawut W, Chantasart D, et al. Rectal administration of propylthiouracil in hyperthyroid patients: comparison of suspension enema and suppository form. Thyroid 2002;12:627–631. [PubMed: 12193309]

26. Nareem N, Miner DJ, Amatruda JM. Methimazole: an alternative route of administration. J Clin Endocrinol Metab 1982; 54:180–181. [PubMed: 7054215]

27. Wartofsky L, Ransil BJ, Ingbar SH. Inhibition by iodine of the release of thyroxine from the thyroid glands of patients with thyrotoxicosis. J Clin Invest 1970; 49:78–86. [PubMed: 5409810]

28. Ashkar FS, Katims RB, Smoak RM, Gilson AJ. Thyroid storm treatment with blood exchange and plasmapheresis. JAMA 1970; 214:1275–1279. [PubMed: 5536311]

29. Burman KD, Yeager HC, Briggs WA, Earll JM, Wartofsky L. Resin hemoperfusion: A method of removing circulating thyroid hormones. J Clin Endocrinol Metab 1976; 42:70–78. [PubMed: 55416]

30. Herrmann J, Hilger P, Kruskemper HL. Plasmapheresis in the treatment of thyrotoxic crisis (measurement of half-concentration tissues for free and total T3 and T4). Acta Endocrinol (Copenh) 1973; 173: Suppl. 22.

31. Brunette DD, Rothong C. Emergency department management of thyrotoxic crisis with esmolol. Am J Emerg Med 1991; 9:232–234. [PubMed: 1673341]

Table 1.

Factors known to precipitate Myxedema Coma

•   Hypothermia
•   Metabolic Disruption
Hypoglycemia
Hyponatremia
Acidosis
Hypercalcemia
•   Infections
•   Cerebrovascular accidents
•   Drugs
Anesthetics,
Tranquilizers, Barbiturates, Sedatives, Narcotics
Amiodarone, Beta blockers, Lithium
•   Discontinuation of thyroxine therapy
•   Burns
•   Trauma
•   Gastrointestinal bleeding
•   Respiratory compromise
Hypoxemia
Hypercapnia

Table 2

Diagnostic Scoring System for Myxedema Coma

Thermoregulatory dysfunction (temperature, °C)		Cardiovascular dysfunction	
>35	0	Bradycardia	
32–35	10	Absent	0
<32	20	50–59	10
Central nervous system effects		40–49	20
Absent	0	<40	30
Somnolent/lethargic	10	Other EKG changes[b]	10
Obtunded	15	Pericardial/pleural effusions	10
Stupor	20	Pulmonary edema	15
Coma/seizures	30	Cardiomegaly	15
Gastrointestinal findings		Hypotension	20
Anorexia/abdominal pain/constipation	5	**Metabolic disturbances**	
Decreased intestinal motility	15	Hyponatremia	10
Paralytic ileus	20	Hypoglycemia	10
Precipitating event		Hypoxemia	10
Absent	0	Hypercarbia	10
Present	10	Decrease in GFR	10

Abbreviations: EKG = electrocardiogram; GFR = glomerular filtration rate.

[a] A score of 60 or higher is highly suggestive/diagnostic of myxedema coma; a score of 25 to 59 is suggestive of risk for myxedema coma, and a score below 25 is unlikely to indicate myxedema coma.

[b] Other EKG changes: QT prolongation, or low voltage complexes, or bundle branch blocks, or nonspecific ST-T changes, or heart blocks.

TABLE 3.

EVENTS ASSOCIATED WITH THE ONSET OF THYROTOXIC STORM

Infection

Other acute medical illness

Acute emotional stress

Acute psychosis

Non-thyroid surgery

Parturition

Trauma

Metastatic differentiated thyroid cancer

Discontinuation of antithyroid drug therapy

After radioiodine therapy

Post-thyroidectomy

After high-dose iodine administration

Iodinated radiographic contrast agents

RARE ASSOCIATIONS:

Vigorous palpation of thyroid gland

Subacute thyroiditis

Thyroxine overdosage (thyrotoxicosis factitia)

Aspirin intoxication

Subacute thyroiditis

Thyroxine overdosage (thyrotoxicosis factitia)

Aspirin intoxication

Hydatidiform mole

Organophosphate intoxication

Neurotoxins

Cytotoxic chemotherapy

TABLE 4.

DIAGNOSTIC CRITERIA FOR THYROTOXIC CRISIS

		Points
Thermoregulatory dysfunction		
Temperature (°F):	99–99.9	5
	100–100.9	10
	101–101.9	15
	102–102.9	20
	103–103.9	25
	104	30
Central nervous system effects		
Absent		0
Mild agitation		10
Delirium, psychosis, lethargy		20
Seizure or coma		30
Gastrointestinal dysfunction		
Absent		0
Diarrhea, nausea, vomiting, or abdominal pain		10
Unexplained jaundice		20
Cardiovascular dysfunction		
Tachycardia (beats/min):	90–109	5
	110–119	10
	120–129	15
	130–139	20
	140	25
Congestive heart failure:	Absent	0
	Mild (edema)	5
	Moderate (bibasilar rales)	10
	Severe (pulmonary edema)	15
Atrial fibrillation:	Absent	0
	Present	10
History of precipitating event (surgery, infection, etc.)		
	Absent	0
	Present	10

Points are assigned and the score totaled. When not possible to distinguish a finding due to an intercurrent illness from that of thyrotoxicosis, a higher point score is given in order to favor empiric therapy given the potential high mortality.

Interpretation: Based on the total score, the likelihood of the diagnosis of thyrotoxic storm is unlikely if <25, impending if between 25–44, likely if between 45–60, and highly likely if >60.

TABLE 5.

TREATMENT OF THYROTOXIC STORM

I.	Reduction of thyroid hormone production and secretion	
	Inhibition of T_4 and T_3 synthesis	
		Propylthiouracil, methimazole
	Inhibition of T_4 and T_3 secretion	
		Inorganic iodide (potassium iodide, Lugol's solution)
		Radiographic contrast agents (sodium ipodate, iopanoic acid)
		Lithium carbonate
		Thyroidectomy
II.	Therapy directed against systemic disturbances	
	Treatment of fever	
		Acetaminophen
		External cooling
	Correction of volume depletion and poor nutrition	
		Intravenous fluid and electrolyes
		Glucose (calories)
		Vitamins
	Supportive therapy	
		Oxygen
		Vasopressor drugs
	Treatment for congestive heart failure (diuretics, digoxin)	
III.	Amelioration of the peripheral actions of thyroid hormone	
	Inhibition of extrathyroidal conversion of T_4 to T_3	
		Propylthiouracil
		Radiographic contrast agents (sodium ipodate, iopanoic acid)
		Glucocorticoids
		Propranolol or other β-adrenergic antagonist drugs
	Removal of T_4 and T_3 from serum	
		Cholestyramine, plasmapheresis, hemodialysis, hemoperfusion
IV.	Treatment of any precipitating or underlying illness	

Abbreviations: T3, triiodothyronine; T4, thyroxine.