REVIEW ARTICLE

Thyroid emergencies

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KEY WORDS

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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 patients showing deteriorating mental status, hypothermia, and multiple organ system abnormalities. It typically appears in patients with preexisting hypothyroidism via a common pathway of respiratory decompensation with carbon dioxide narcosis leading to coma. Without early and appropriate therapy, the outcome is often fatal. The diagnosis is based on history and physical findings at presentation and not on any objective thyroid laboratory test. Clinically based scoring systems have been proposed to aid in the diagnosis. While it is 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 is also a rare condition, established on the basis of a clinical diagnosis. The diagnosis is based on the presence of severe hyperthyroidism accompanied by elements of systemic decompensation. Considering that mortality is high without aggressive treatment, therapy must be initiated as early as possible in a critical care setting. The diagnosis cannot be established based on laboratory tests alone, but several scoring systems are available. The usual clinical signs and symptoms of hyperthyroidism are present along with more exaggerated clinical manifestations affecting the cardiovascular, gastrointestinal, and central nervous systems. A multipronged approach has been recommended and has been associated with improved outcomes.

Introduction The entities myxedema coma and thyroid storm represent the respective extremes of thyroid dysfunction. If not promptly and appropriately diagnosed and treated, both conditions are associated with a poor outcome and high mortality. In approaching these as well as other endocrine emergencies, it is important to have a high index of suspicion for the diagnosis and to act counter to usual therapeutic approaches for most disorders by treating the suspected condition 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 myxedema coma and thyroid storm typically occur in patients with preexistent hypo- and hyperthyroidism, respectively, and are precipitated by some superimposed condition or nonthyroidal 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 test or group of laboratory investigations 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 long-standing or previously undocumented, and with the former, there is often a history of discontinuation of thyroid hormone replacement medications. In the precomatose state, the typical clinical findings include hypothermia, decreased mentation, generalized edema, and the usual hallmarks of profound hypothyroidism. A typical presentation is a woman with the above findings, in the age range of 60 to 85 years, and presenting in winter, when the temperatures are low, after

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TABLE 1 Factors known to precipitate myxedema coma

Hypothermia	
Metabolic disruption	Hypoglycemia
	Hyponatremia
	Acidosis
	Hypercalcemia
Infections	
Cerebrovascular accidents	
Drugs	Anesthetics
	Tranquilizers, sarbiturates, sedatives, Narcotics
	Amiodarone, β-blockers, lithium
Discontinuation of thyroxine therapy	
Burns	
Trauma	
Gastrointestinal bleeding	
Respiratory compromise	Hypoxemia
	Hypercapnia

being found down. Severely cold weather is only one of the 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 (TABLE 1). In the overwhelming majority of patients, the basis for the underlying hypothyroidism is autoimmunity, that is, Hashimoto thyroiditis. The occurrence of secondary or central hypothyroidism due to thyrotropin deficiency related to pituitary disease is much more rare. In the latter patients, 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 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, his or 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 and clever or sarcastic responses to questioning have been noted in the precomatose state and have been labelled as "myxedema wit." On physical examination, there is dry and scaly skin, nonpitting edema of the face, 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 are 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 perilaryngeal 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 patients 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 release, further contributing to hyponatremia and impaired free water excretion. The effects of such profound hypothyroidism on the gastrointestinal tract include complaints of anorexia and constipation. Reduced motility, gastric atony, paralytic ileus, and megacolon are not unusual.

It is highly important to consider underlying infection, for example, pneumonia, which is a very common precipitant of myxedema coma. This is because these patients may have the usual signs of infection masked by 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 of the 23 patients (52%) dying of sepsis.[3] Findings in the cardiovascular system include pericardial effusion, cardiomegaly, bradycardia, as well as 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 pointes 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 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 (FT_4) level or how high the elevation in serum thyrotropin concentrations. The FT_4 level is low and can be almost undetectable, while

TABLE 2 Diagnostic scoring system for myxedema coma[a] (adapted with permission from Popoveniuc et al)[5]

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

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

b Other electrocardiogram changes: QT prolongation, or low voltage complexes, or bundle branch blocks, or nonspecific ST-T changes, or heart block

thyrotropin levels have varied widely in reported cases of myxedema coma. Of course, in secondary or pituitary hypothyroidism, FT_4 and thyrotropin levels are low or low "normal," and the presence of biologically inactive thyrotropin may account for the measured normal concentrations.

Other laboratory test abnormalities can include low blood glucose, sodium, and chloride levels, high total and ionized calcium levels, and mild renal failure with elevations in blood urea nitrogen and creatinine levels. In addition to a complete blood count and full chemistry profile, the measurement of adrenocorticotropic hormone and plasma cortisol levels should be considered in view of the likelihood, albeit rare, of a pituitary basis for 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 investigators 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 to 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 indicated only overt hypothyroidism but also a patient 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 should be initiated. Delays associated with failure to diagnose or awaiting confirmation by blood tests have contributed to the high mortality rate 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 multisystem decompensation that is likely to be present. Even in the absence of fever and leukocytosis, broad-spectrum antibiotic coverage should be started on an empirical basis. Low blood sodium levels are likely to be playing a major role in any lethargy, disorientation, or coma when present and must be corrected. When the serum sodium concentration is lower than 120 mEq/l, the slow administration of hypertonic saline is justified with careful continuous monitoring. A too rapid correction can result in worsening of central nervous system function due to central pontine myelinolysis. Otherwise, only normal saline or normal saline with glucose should be employed and will also address the volume depletion present. In addition to the nutritive value provided by 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 antidiuretic hormone levels in these patients. In the United States, there are 2 agents, conivaptan and tolvaptan, that have been used 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/d for 2 to 4 more days. Tolvaptan is initially administered at an oral dose of 15 mg.[7,8]

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 vasodilation and a 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 a great risk of progression to ventilatory failure and death. To ensure adequate ventilation, mechanical means often must be employed with careful monitoring of 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 empirical corticosteroid administration, for example, 50 to 100 mg of hydrocortisone intravenously. Concern for adrenal insufficiency is based on the findings of low blood sugar, low sodium, and high calcium and potassium levels, which are equally compatible with adrenal insufficiency. There is also a belief based on anecdotal cases that adrenal crisis may be precipitated by treatment with thyroid hormone alone. In such a scenario, the patient is believed to have been marginally stable on low plasma cortisol levels 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 (T_4) alone, triiodothyronine (T_3) alone, or a combination of the 2 hormones. Thyroxine is often considered as a "prohormone" with activation of metabolic action achieved by the conversion to T_3, whereas T_3 is a highly active hormone, perhaps 10 to 15 times more active than T_4. Those who recommend use of some amount of T_3, base this belief on the fact that a patient with myxedema is systemically ill and is therefore suffering from reduced deiodination and conversion of T_4 to T_3, analogous to what is seen in euthyroid sick syndrome.[9] Hence, in this situation, reflecting a "hypothyroid sick syndrome," the administration of only T_4 would be associated with inadequate levels of T_3 and a risk of delayed recovery to a more euthyroid state. Concern with T_3 administration has been based on observations of higher mortality rates when T_3 was given in relatively high doses, especially in patients with an underlying cardiac disease. Thus, advocates of T_4 therapy alone point out that the slow conversion of T_4 to T_3 may be more physiologic and probably safer, with a lower risk of an adverse effect that might be seen with high T_3 levels.[10,11] Biokinetic data suggest that the average total body distribution space content of T_4 approximates 500 µg. On this basis, a high T_4 dose (300–600 µg) is given intravenously on the first day to replete the body's stores followed by 50 to 100 µg daily given either intravenously or orally.[12] Advocates of T_3 administration want to provide a faster onset of action and to potentially achieve higher survival rates. For this purpose, a dose of 10 to 20 µg intravenously every 4 hours is recommended for the first day and then 10 µg every 6 hours for 1 to 2 days. Oral administration of T_3 is continued thereafter in a dose of 25 µg twice daily.

Our favorite regimen reflects a compromise approach with administration of both T_4 and T_3. We would administer both T_4 and T_3 simultaneously initially, with T_4 at a dose of 4 µg/kg lean body weight (approximately 200–300 µg), followed by 100 µg 24 hours later and then 50 µg daily either intravenously or orally. We recommend an initial T_3 dose of 10 µg intravenously every 8 to 12 hours until the patient is able to tolerate oral intake. Recently published guidelines for the treatment of hypothyroidism and myxedema coma by the American Thyroid Association[13] emphasize individualizing dosage based on age, weight, and cardiac status, suggesting the initial use of intravenous T_4 at a dose of 200 to 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. There are no objective or specific laboratory tests which, if abnormal, will definitively suggest the diagnosis. Hence, the diagnosis is based on purely clinical features. Two different but similar scoring systems based on signs and symptoms have been developed to facilitate early diagnosis.[14-16] While it is fortunately rare, thyroid storm appears in 1% to 2% of hospital admissions for thyrotoxicosis. In our own 1000-bed hospital, we see 3 to 4 cases per year. In view of the potential for high mortality and like other emergent endocrine situations, treatment should not be delayed and should be initiated once thyroid storm is suspected, without awaiting blood test results indicating severe thyrotoxicosis.

Clinical presentation In the typical patient, it is not difficult to determine the presence of hyperthyroidism. Patients 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 such as an infection, surgical procedure, trauma, burns, emotional stress, or even vigorous palpation of the thyroid gland (TABLE 3). A common cause is

TABLE 3 Events associated with the onset of thyrotoxic storm

Typical associations as compared with rare associations listed below
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
Hydatidiform mole
Organophosphate intoxication
Neurotoxins
Cytotoxic chemotherapy

the inappropriate discontinuation of antithyroid drug therapy in a patient with Graves disease. Storm has also been described in patients with an underlying toxic multinodular goiter (eg, 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 patients with no prior history of cardiac disease. Hepatomegaly and abnormal liver function test results 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 preterminal 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, because the magnitude of hormone levels may not be significantly different with perhaps one exception for the FT_4 level.[18] But increased hormone levels do clearly play a role as demonstrated by the development of storm after radioiodine therapy, with associated acute discharge of the hormone from the thyroid gland, or in rare cases, of iatrogenic thyrotoxicosis from ingestion of a large amount of the hormone. Another example occurs in those patients with Graves disease who without medical advice inappropriately withdraw their thiourea (methimazole, propylthiouracil) therapy. Increased hormone release also plays a key role in iodine-induced thyrotoxicosis (Jod-Basedow disease) with storm.

However, 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 the administration of agents such as reserpine β-adrenergic receptor 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 T_4 and T_3 as well as suppressed, immeasurably low thyrotropin concentrations, this is not always the case. Specifically, serum total T_3 levels may be only slightly elevated or even within normal limits. When a normal T_3 level is seen in storm, it is likely to be due to the presence of reduced deiodination or conversion of T_4 to T_3, much as is seen in the low T_3 or euthyroid sick syndrome.[21] However, in this case, we are dealing with a "hyperthyroid sick syndrome," as expressed by the thyroid function test results. The cause for the low T_3 syndrome, 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 T_4 levels should still be elevated and thyrotropin 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 early (2 hour) measurement of 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, leukocytosis with a mild shift to the left is common,

TABLE 4 Diagnostic criteria for thyrotoxic crisis (adapted with permission from Burch HB, Wartofsky)[14]

Parameter		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
History of precipitating event (surgery, infection, etc.)	Absent	0
	Present	10
Cardiovascular dysfunction		
Tachycardia, bpm	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

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.

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 the bone. 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 levels can be noted as well, but serum electrolytes are usually normal. If serum electrolytes are not normal, for example, with hyponatremia, hyperkalemia, and hypercalcemia, the possibility of coincident adrenal insufficiency must be entertained and serum cortisol and adrenocorticotropic hormone 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, aspartate aminotransferase (serum glutamic-oxaloacetic transaminase), and alanine aminotransferase (serum glutamic pyruvic transaminase).

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 elevation of temperature, but patients with storm exhibit fever, perhaps compounded by coincident infection rendering the patient more ill with other signs such as tachycardia and increased perspiration. Yet 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 on determination of an elevated score consistent with thyroid storm, we then have a 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 authors believe 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

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 electrolytes • 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: T_3, triiodothyronine; T_4, thyroxine

because of any delay in obtaining laboratory confirmation of the diagnosis.

Treatment There are 4 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 4 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 4-pronged therapeutic approach should be neglected. Notwithstanding the usual efficacy of this 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 thyroid gland in Graves disease 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. In the United States, these drugs are given orally as there are no available parenteral preparations, although intravenous propylthiouracil or thiamazole can be found in Europe. In comatose patients, the drugs may be given via a nasogastric tube into the stomach or via the rectum.[24-26] While typical doses of methimazole in uncomplicated hyperthyroidism may average 5 to 45 mg/d, higher doses of 120 mg/d are required in thyroid storm, and are best given on a divided dosage such as 30 mg every 6 hours. It is conceivable that propylthiouracil provides more rapid clinical benefit than methimazole, as it has the additional advantage of inhibiting conversion of T_4 to T_3, and may more rapidly lower serum T_3 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, the administration of inorganic iodine given orally as Lugol's solution or as a saturated solution of potassium iodide (8 drops every 6 hours) is required. The sequence of administration of methimazole and iodine is extremely important. In case of no previous blocking of thyroid hormone synthesis with thionamides, 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 to 60 minutes prior to iodine. In patients allergic to iodine, lithium carbonate may be used as an alternative agent to inhibit hormonal release. Typical dosage is 300 mg 3 to 4 times daily, producing a blood lithium level of 0.9 to 1.2 mEq/l.

Attempts to reduce ongoing effects of thyroid hormone in the periphery The levels of both circulating total and free T_4 and T_3 may be quite elevated in storm, and the goal is to accelerate the loss of hormone to a greater rate than it occurs via metabolism. To achieve this, various means of extracting thyroid hormone from blood have been attempted in cases of severe storm, such as 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, β-adrenergic blockers are used with propranolol as the mainstay of this therapy in the United States.[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 β-blockers, short half-life calcium antagonists such as verapamil have been employed.[32]

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 subside after 24 hours when the therapeutic guidelines suggested herein are applied.

Therapy addressing systemic decompensation Fever should be treated with acetaminophen and a cooling fan and not with aspirin, which can inhibit binding of T_4 to its binding proteins in plasma and result in an increased free T_4 level. 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 younger ones. Use of dextrose–saline 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 T_4 to T_3, and this is an additional justification for their use.[32]

CORRECTIONS

This article was corrected on September 30, 2019. The list of corrections is available at www.mp.pl/paim.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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