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Thyroid Emergencies

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Abstract

Thyroid emergencies are rare, life-threatening conditions resulting from either severe deficiency of thyroid hormones (myxedema coma) or, by contrast, decompensated thyrotoxicosis with the increased action of thyroxine (T4) and triiodothyronine (T3) exceeding metabolic demands of the organism (thyrotoxic storm). The understanding of the pathogenesis of these conditions, appropriate recognition of the clinical signs and symptoms, and their prompt and accurate diagnosis and treatment are crucial in optimizing survival.

Keywords

Myxedema coma; Thyrotoxic storm; Diagnosis; Management

MYXEDEMA COMA

Epidemiology and Precipitating Events

Myxedema coma is the extreme expression of severe hypothyroidism and fortunately is rare, with an incidence rate of 0.22 per million per year.[1] The most common presentation of the syndrome is in hospitalized elderly women with long-standing hypothyroidism, with 80% of cases occurring in women older than 60 years. However, myxedema coma occurs in younger patients as well, with 36 documented cases of pregnant women.[2,3]

The syndrome will typically present in patients who develop a systemic illness such as pulmonary or urinary infections, congestive heart failure, or cerebrovascular accident (Table 1), superimposed on previously undiagnosed hypothyroidism. Sometimes a history of antecedent thyroid disease, thyroidectomy, treatment with radioactive iodine, or T4 replacement therapy discontinued for no apparent reason can be elicited. A pituitary or hypothalamic basis for hypothyroidism is encountered in about 5% or, according to some studies, in up to 10% to 15% of patients.[4]

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Patients with myxedema coma generally present in the winter months, suggesting that external cold may be an aggravating factor.[5] Some abnormalities such as hypoglycemia, hypercalcemia, hyponatremia, hypercapnia, and hypoxemia, may be either precipitating factors or secondary consequences of myxedema coma. Moreover, the comatose state is associated with the risk of aspiration pneumonia and sepsis. In hospitalized patients, drugs such as anesthetics, narcotics, sedatives, antidepressants, and tranquilizers may depress respiratory drive and thereby either cause or compound the deterioration of the hypothyroid patient into coma.[6,7] The effect of these drugs should be taken into consideration as a potential causative mechanism. In fact, Church and Callen[8] described a 41-year-old male patient without any history of thyroid disease who developed myxedema coma after being administered combined therapy with aripiprazole and sertraline.

There is also a report of myxedema coma induced by chronic ingestion of large amounts of raw bok choy. This Chinese white cabbage contains glucosinolates, which break down products such as thiocyanates, nitriles, and oxazolidines, and inhibit iodine uptake and production of thyroid hormones by the thyroid gland. When eaten raw, digestion of the vegetable releases the enzyme myrosinase, which accelerates production of the aforementioned thyroid disruptors.[9]

Clinical Signs and Symptoms

Hypothermia (often profound to 80°F [26.7°C]) and unconsciousness constitute 2 of the cardinal features of myxedema coma.[10] Of importance is that coincident infection may be masked by hypothyroidism, with a patient presenting as afebrile despite an underlying severe infection. In view of the latter and the fact that undiagnosed infection might lead inexorably to vascular collapse and death, some authorities have advocated the routine use of antibiotics in patients with myxedema coma. Underlying hypoglycemia may further compound the decrement in body temperature.

Although coma is the predominant clinical presentation, a history of disorientation, depression, paranoia, or hallucinations (myxedema madness) may often be elicited. The neurologic findings may also include cerebellar signs (poorly coordinated purposeful movements of the hands and feet, ataxia, adiadochokinesia), poor memory and recall, or even frank amnesia, and abnormal findings on electroencephalography (low amplitude and a decreased rate of α-wave activity). Status epilepticus has been also described[11] and up to 25% of patients may experience seizures possibly related to hyponatremia, hypoglycemia, or hypoxemia.

Respiratory System

The mechanism for hypoventilation in profound myxedema is a combination of a depressed hypoxic respiratory drive and a depressed ventilatory response to hypercapnia.[12,13] Partial obstruction of the upper airway caused by edema of the tongue or vocal cords may also play a role. Hypothyroid patients may be predisposed to increased airway hyperresponsiveness and chronic inflammation.[14] Tidal volume may be additionally reduced by other factors such as pleural effusion or ascites. to achieve appropriately effective pulmonary function in myxedema coma, prolonged mechanically assisted ventilation is usually required.

Cardiovascular Manifestations

Patients diagnosed with myxedema coma are at increased risk for shock and potentially fatal arrhythmias. Typical electrocardiographic (ECG) findings include bradycardia, varying degrees of block, low voltage, flattened or inverted T waves, and prolonged Q-T interval, which can result in torsades de pointes ventricular tachycardia.[15] Myocardial infarction should also be ruled out by the usual diagnostic procedures, because aggressive or injudicious T4 replacement may increase the risk of myocardial infarction. Moreover, cardiac contractility is impaired, leading to reduced stroke volume and cardiac output. Reduced stroke volume in severe cases may also be due to the cardiac tamponade caused by the accumulation of fluid rich in mucopolysaccharides within the pericardial sac.

Electrolyte Disturbances and Renal Manifestations

Hyponatremia is a common finding observed in patients with myxedema coma. The mechanism accounting for the hyponatremia is associated with increased serum anti-diuretic hormone[16] and impaired water diuresis caused by reduced delivery of water to the distal nephron.[17] Depending on its duration and severity, hyponatremia will add to altered mental status, and when severe may be largely responsible for precipitating the comatose state. Alterations in renal function observed in myxedema coma include decreases in glomerular filtration rate and renal plasma flow, and increases in total body water. Atony of the urinary bladder with retention of large residual urine volumes is commonly seen. Renal failure may occur as a result of underlying rhabdomyolysis with extremely high levels of creatine kinase.[18–21]

Gastrointestinal Manifestations

The gastrointestinal tract in myxedema may be marked by mucopolysaccharide infiltration and edema of the muscularis, as well as neuropathic changes leading to gastric atony, impaired peristalsis, and even paralytic ileus. Ascites may occur, and has been documented in one report of 51 cases.[22] Another potential complication is gastrointestinal bleeding secondary to an associated coagulopathy.[23] It is important to recognize the underlying mechanisms of these acute gastrointestinal complications so as to avoid unnecessary surgery for an apparent acute abdomen.[24]

Hematological Manifestations

In contrast to the tendency to thrombosis seen in mild hypothyroidism, severe hypothyroidism is associated with a higher risk of bleeding caused by coagulopathy related to an acquired von Willebrand syndrome (type 1) and decreases in factors V, VII, VIII, IX, and X.[25] The von Willebrand syndrome is reversible with T4 therapy.[26] Another cause of bleeding may be disseminated intravascular coagulation associated with sepsis. Patients with myxedema coma have increased preponderance to severe infections, including sepsis, because of granulocytopenia and a decreased cell-mediated immunologic response. Such patients may also present with a microcytic anemia secondary to hemorrhage, or a macrocytic anemia caused by vitamin B_{12} deficiency, which may also worsen the neurologic state.

Diagnosis

To summarize the aforementioned clinical manifestations, the typical patient presenting with myxedema coma is a woman in the later decades of life who may have a history of thyroid disease and who is admitted to hospital, typically in winter, with pneumonia. Physical findings could include bradycardia, macroglossia, hoarseness, delayed reflexes, dry skin, general cachexia, hypoventilation, and hypothermia, commonly without shivering. Laboratory evaluation may indicate hypoxemia, hypercapnia, anemia, hyponatremia, hypercholesterolemia, and increased serum lactate dehydrogenase and creatine kinase. On lumbar puncture there is increased pressure and the cerebrospinal fluid has high protein content.

Although an elevated serum thyrotropin (TSH) concentration is the most important laboratory evidence for the diagnosis, the presence of severe complicating systemic illness or treatment with drugs such as dopamine, dobutamine, or corticosteroids may serve to reduce the elevation in TSH levels.[27,28] There may also be a pituitary cause for the hypothyroidism, in which case an increased TSH would not be found.

Treatment

Myxedema coma as a true medical emergency requires a multifaceted approach to treatment in a critical care setting.

Airways and ventilation—The patient's comatose state is perpetuated by hypoventilation, with CO_2 retention and respiratory acidosis. The maintenance of an adequate airway is the single most important supportive measure, because of the high mortality rate associated with the inexorable respiratory failure. Mechanical ventilation is usually required during the first 36 to 48 hours, but in some patients it may be necessary to continue assisted ventilation for as long as 2 to 3 weeks. The hypercapnia may be rapidly relieved with mechanical ventilation, but the hypoxia tends to persist, possibly because of shunting in nonaerated lung areas.[29] It is advisable, therefore, not to extubate the patients prematurely and to wait until full consciousness is attained.

Thyroid hormone therapy—One of the most controversial aspects of the management of myxedema coma is which thyroid hormone preparation to give and how to give it (dose, frequency, and route of administration). The optimum treatment remains uncertain, because of the scarcity of clinical studies and obvious difficulties with performing controlled trials. There is a necessity to balance the need for quickly attaining physiologically effective thyroid hormone levels against the risk of precipitating a fatal tachyarrhythmia or myocardial infarction. All patients should have continuous ECG monitoring, with reduction in thyroid hormone dosage should arrhythmias or ischemic changes be detected.

Parenteral preparations of either T4 or T3 are available for intravenous administration. Although oral forms of either T3 or T4 can be given by nasogastric tube in the comatose patient, this route is fraught with risks of aspiration and uncertain absorption, particularly in the presence of gastric atony or ileus. The single intravenous bolus of T4 was popularized by reports[30] suggesting that replacement of the entire estimated pool of extrathyroidal T4

(usually 300–600 μg) was desirable to restore near-normal hormonal status. This initial loading dose is followed by the maintenance dose of 50 to 100 μg given daily (either intravenously or by mouth if the patient is adequately alert). Larger doses of T4 probably have no advantage and may, in fact, be more dangerous.[31] There is also evidence showing improved outcomes with lower doses of thyroid hormone.[32] Rodriguez and colleagues[1] performed a prospective trial in which patients were randomized to receive either a 500-μg loading dose of T4 followed by a 100-μg daily maintenance dose, or only the maintenance dose. The overall mortality rate was 36.4%, with a lower mortality rate in the high-dose group (17%) than in the low-dose group (60%). Although suggestive, the difference was not statistically significant.

The rate of conversion of T4 to T3 is reduced in many systemic illnesses (the euthyroid sick or low T3 syndrome),[28] hence T3 generation may be reduced in myxedema coma as a consequence of any associated illness (hypothyroid sick syndrome). As a consequence, some clinicians suggest that small supplements of T3 should be given along with T4 during the initial few days of treatment, especially if obvious associated illness is present. When therapy is approached with T3 alone, it may be given as a 10-to 20-μg bolus followed by 10 μg every 4 hours for the first 24 hours, dropping to 10 μg every 6 hours for days 2 to 3, by which time oral administration should be feasible.[6] T3 has a much quicker onset of action than T4, and increases in body temperature and oxygen consumption may occur 2 to 3 hours after intravenous T3, compared with 8 to 14 hours after intravenous T4. The other advantage of T3 is that it crosses the blood-brain barrier more rapidly than T4, which may be particularly important in patients with profound neuropsychological symptoms.[33] One clinical example of the possible benefit of T3 is a case report of a patient with myxedema coma and cardiogenic shock who responded to T3 therapy but not to T4 therapy.[34] On the other hand, treatment with T3 alone is associated with large and unpredictable fluctuations in serum T3 levels, and high serum T3 levels during treatment have been associated with fatal outcomes.[35] A more conservative but seemingly rational approach is to provide combined therapy with both T4 and T3.[36] Rather than administer 300 to 500 μg T4 intravenously initially, a dose of 4 μg/kg lean body weight (or about 200–300 μg) is given, and an additional 100 μg is given 24 hours later. By the third day, the dose is reduced to a daily maintenance dose of 50 μg, which can be given by mouth as soon as the patient is conscious.[36] Simultaneously with the initial dose of T4, a bolus of 10 μg T3 is given and intravenous T3 is continued at a dosage of 10 μg every 8 to 12 hours until the patient is conscious and taking maintenance T4. Clinical improvement has been seen with even a single dose of only 2.5 μg of T3.[37]

Hypothermia—Treatment with T4 and/or T3 enables restoration of body temperature to normal. Simultaneously, blankets or increasing the room temperature can be used as additional interventions to keep the patient warm until the thyroid hormone effect is achieved. Too aggressive warming may cause peripheral vasodilatation, which may then lead to hypotension or shock.

Hypotension—Hypotension should also be correctable by treatment with T4 and/or T3. However, a hypotensive patient may require additional volume-repletion therapy. Fluids may

be administered cautiously as 5% to 10% glucose in 0.5 N sodium chloride if hypoglycemia is present, or as isotonic normal saline if hyponatremia is present. An agent such as dopamine might be used to maintain coronary blood flow, but patients should be weaned off the vasopressor as soon as possible because of the risk of a pressor-induced ischemic event.

Because of the risk of relative adrenal insufficiency, it is wise to administer hydrocortisone until the hypotension is corrected. The typical dosage of hydrocortisone is 50 to 100 mg every 6 to 8 hours during the first 7 to 10 days, with tapering of the dosage thereafter based on clinical response and any plans for further diagnostic evaluation. Decreased adrenal reserve has been found in 5% to 10% of patients, based on either hypopituitarism or primary adrenal failure accompanying Hashimoto disease (Schmidt syndrome). The other rationale for the treatment with corticosteroids is the potential risk of precipitating acute adrenal insufficiency caused by the accelerated metabolism of cortisol that follows T4 therapy. The clinicians should be aware of signs and symptoms signaling coexisting adrenal insufficiency such as hypotension, hypothermia, hypoglycemia, hyperkalemia, and hyponatremia.

Hyponatremia—Low serum sodium may cause a semicomatose state or seizures even in euthyroid patients, and the severe hyponatremia (105–120 mmol/L) in profound myxedema is likely to contribute substantially to the coma in these patients. Mortality rates in critically ill patients with symptomatic hyponatremia have been reported to be 60-fold higher than in patients without hyponatremia.[38] The appropriate management of severe hyponatremia often requires administration of a small amount of hypertonic saline (50–100 mL 3% sodium chloride), enough to increase sodium concentration by about 2 mmol/L early in the course of treatment, followed by an intravenous bolus dose of 40 to 120 mg furosemide to promote a water diuresis.[39] A small, quick increase in the serum sodium concentration (2–4 mmol/L) is effective in acute hyponatremia because even a slight reduction in brain swelling results in a substantial decrease in intracerebral pressure.[40] On the other hand, too rapid correction of hyponatremia can cause a dangerous complication, the osmotic demyelinization syndrome. In patients with chronic hyponatremia, this complication is avoided by limiting the sodium correction to less than 10 to 12 mmol/L in 24 hours and less than 18 mmol/L in 48 h. After achieving a sodium level of more than 120 mmol/L, restriction of fluids may be all that is necessary to correct hyponatremia. It must be emphasized that fluid or saline therapy requires careful monitoring of volume status based on clinical parameters and measurements of central venous pressure, especially in patients with significant cardiovascular decompensation.

The other therapeutic option is treatment with an intravenous vasopressin antagonist, conivaptan. Conivaptan has been approved by the US Food and Drug Administration for the treatment of hospitalized patients with euvolemic and hypervolemic hyponatremia in a setting of the syndrome of inappropriate secretion of antidiuretic hormone, hypothyroidism, adrenal insufficiency, or pulmonary disorders.[41] The rationale for application of conivaptan in this clinical setting is based on the high vasopressin levels observed in myxedema coma. Current dosing recommendations are for a 20-mg loading dose to be infused over 30 minutes followed by 20 mg/d continuous infusion for up to 4 days. Unfortunately, no data are available on the use of conivaptan in severe hyponatremia (<115 mEq/L) in hypothyroid patients.[42,43]

General supportive measures—In addition to the specific therapies outlined, other treatments will be indicated as in the management of any other elderly patient with multisystem problems. Management might include the treatment of underlying problems such as infection, congestive heart failure, diabetes, or hypertension. The dosage of specific medications (eg, digoxin for congestive heart failure) may need to be modified based on their altered distribution and slowed metabolism in myxedema.

Prognosis

Even with this vigorous therapy, the prognosis for myxedema coma remains grim, and patients with severe hypothermia and hypotension seem to do the worst. In the past the mortality rate was as high as 60% to 70%, but this has now been reduced to 20%–25% with the advances in intensive care management.[44] Several prognostic factors may be associated with a fatal outcome,[1,5,32,35,45] and include older age, persistent hypothermia or bradycardia, lower degree of consciousness by Glasgow Coma Scale, multiorgan impairment indicated by an APACHE II score (Acute Physiology and Chronic Health Evaluation) of more than 20, or SOFA score (Sequential Organ Failure Assessment) of more than 6. The most common causes of death are respiratory failure, sepsis, and gastrointestinal bleeding. Early diagnosis and prompt treatment, with meticulous attention to the details of management during the first 48 hours, remain critical for effective therapy.

THYROTOXIC STORM

Thyroid crisis or thyrotoxic storm is characterized by severely exaggerated manifestations of thyrotoxicosis. The underlying cause of thyrotoxicosis is commonly Graves disease or toxic multinodular goiter. Rarely, thyrotoxic storm may occur with subacute thyroiditis or factitious thyrotoxicosis caused by intentional thyroxine overdose.[46,47]

Epidemiology and Precipitating Events

An accurate estimation of the incidence of thyroid storm is impossible to determine because of the considerable variability in the criteria for its diagnosis. The syndrome does appear to be less common today than in the past, perhaps because of earlier diagnosis and treatment of thyrotoxicosis, thereby precluding its progression to the stage of crisis. Nevertheless, it may occur in 1% to 2% of hospital admissions for thyrotoxicosis.[48] Thyrotoxic storm is rarely seen after thyroid surgery, because of the routine preparation of patients for elective thyroidectomy by treatment with antithyroid drugs. However, several types of nonthyroidal surgeries or other traumas have precipitated surgical thyrotoxic storm in patients with previously undiagnosed thyrotoxicosis. The crisis may be related to perioperative events, such as anesthesia, stress, and volume depletion, because these conditions are associated with increases in the concentration of free thyroid hormone. Thyroid storm has been seen in pregnancy, during labor, and in complicated deliveries such as those with placenta previa.[49] An acute discharge of hormones in the appropriate clinical setting may trigger a crisis, and cases have been reported following vigorous palpation of the thyroid, radioactive iodine therapy,[50] withdrawal of propylthiouracil therapy, or after administration of lithium, stable iodine, or iodinated contrast dyes. The other conditions known to be associated with increased free fraction of T4 and T3 include stress, infections, burns, cytotoxic

chemotherapy for acute leukemia, aspirin overdose, ketoacidosis, or organophosphate intoxication (see Table 1).[45,51–55] Amiodarone, an antiarrhythmic and antianginal drug that is also rich in iodine, may cause either an iodine-induced thyrotoxicosis (type 1) or a destructive thyroiditis (type 2); the latter has been reported as a cause of thyroid storm refractory to the usual treatment.[56] There is also a case report of thyrotoxic storm precipitated by food poisoning with marine neurotoxin after ingestion of seafood.[57] Notwithstanding the multiplicity of precipitating factors, in hospitalized patients the most common event associated with thyrotoxic storm is some type of infection.

Clinical Signs and Symptoms

The clinical diagnosis is based on the identification of signs and symptoms that suggest decompensation of several organ systems. Some of these cardinal manifestations include fever out of proportion to an apparent infection and dramatic diaphoresis. Hyperthermia in thyroid crisis can represent defective thermoregulation by the hypothalamus and/or increased basal metabolic rate, increased oxidation of lipids being responsible for more than 60% of the resting energy expenditure.[58] The other key components of thyrotoxic storm include tachycardia out of proportion to the fever, and gastrointestinal dysfunction, which can include nausea, vomiting, diarrhea and, in severe cases, jaundice. As the storm progresses, symptoms of central nervous system dysfunction simulating an encephalopathic picture will appear, which may include increasing agitation and emotional lability, confusion, paranoia, psychosis, and coma.[59] Patients have been reported who presented with thyroid storm associated with status epilepticus and stroke and with bilateral basal ganglia infarction.[60] In patients with neurologic symptoms, a high index of suspicion for cerebral sinus thrombosis should be considered, because of the higher prevalence of this condition in severe hyperthyroidism.[61] Paralysis observed in thyroid crisis might be due to not only the cerebrovascular accident but also thyrotoxic periodic paralysis with hypokalemia, as frequently may present in Asian men.[62] In older patients, the thyrotoxic storm may present as so-called masked or apathetic thyrotoxicosis.[63]

Cardiovascular Manifestations

The most common cardiovascular manifestations are rhythm disturbances such as sinus tachycardia, atrial fibrillation, or other supraventricular tachyarrhythmias, and rarely, ventricular tachyarrhythmias, which can be observed even in patients without previous heart disease.[64] Congestive heart failure or a reversible dilated cardiomyopathy[65] also may be present even in young or middle-aged patients without known antecedent cardiac disease. A high-output state is present, attributable to the increased preload secondary to activation of the renin-angiotensin-aldosterone axis and to decreased afterload secondary to a direct relaxing effect of thyroid hormones on vascular muscle cells. Therefore, most patients present with systolic hypertension with widened pulse pressure. The hyperthyroid heart is characterized by higher than usual oxygen demands and hence myocardial infarction can be observed, even in young patients.[66,67] A relatively rare complication of severe hyperthyroidism is pulmonary hypertension, which is presumed to be on an autoimmune basis when associated with Graves disease, but which also may be secondary to an augmented blood volume, cardiac output, and sympathetic tone, leading to pulmonary vasoconstriction and increased pulmonary arterial pressure. This condition is usually

reversible after treatment with antithyroid drugs. The other possible reason for pulmonary hypertension is pulmonary embolism caused by the thrombotic or hypercoagulable state that has been observed in severe hyperthyroidism.

Respiratory Manifestations

The main pulmonary symptom is dyspnea and tachypnea related to an increased oxygen demand. The excessive work of the respiratory muscles may eventually lead to diaphragmatic dysfunction.[68] Respiratory failure may result from the hyperdynamic cardiomyopathy but also from preexistent underlying pulmonary disease.[69,70]

Gastrointestinal Manifestations

The most common symptoms are diarrhea and vomiting, which can aggravate volume depletion, postural hypotension, and shock with vascular collapse. The diffuse abdominal pain, possibly caused by impaired neurohormonal regulation of gastric myoelectrical activity with delayed gastric emptying,[71] may even lead to a presentation such as acute abdomen[72] or intestinal obstruction.[73] The liver function abnormalities and presence of jaundice warrant immediate and vigorous therapy. Although most presentations of an acute abdomen in thyrotoxicosis are medical in nature, surgical conditions may also occur.[74]

Electrolyte Disturbances and Renal Manifestations

Increased serum calcium levels, caused by both hemoconcentration and known effects of thyroid hormone on bone resorption, may be seen. The sodium, potassium, and chloride levels are usually normal. Because of the augmented lipolysis and ketogenesis, and the basal metabolic demands that exceed oxygen delivery, ketoacidosis and lactic acidosis are observed.

Hyperthyroidism is often associated with an accelerated glomerular filtration rate, which may progress to glomerulosclerosis and excessive proteinuria. There are case reports of renal failure caused by rhabdomyolysis,[75] urinary retention associated with dyssynergy of the detrusor muscle and bladder dysfunction,[76] and an autoimmune complex–mediated nephritis concomitant with Graves disease.[77]

Hematological Manifestations

A moderate leukocytosis with a mild shift to the left is a common finding, even in the absence of infection. Hyperthyroidism may be associated with hypercoagulability caused by increased concentrations of fibrinogen, factors VIII and IX, tissue plasminogen activator inhibitor 1, von Willebrand factor, increase in red blood cell mass secondary to erythropoietin upregulation, and a tendency to augmented platelet plug formation.[78] Major thromboembolic complications are responsible for 18% of deaths caused by thyrotoxicosis.[79–83]

Diagnosis

Diagnosis can be established predominantly on the basis of clinical presentation, because the laboratory findings may not be much different than those observed in uncomplicated hyperthyroidism. Indeed, serum total T3 levels may be even within normal limits, as these

patients may have some underlying precipitating illness that reduces T4 to T3 conversion as is seen in the euthyroid sick syndrome.[84] Therefore, a semiquantitative scale (Table 2) assessing the presence and severity of the most common signs and symptoms has been developed to aid in the diagnosis.[85]

Other laboratory abnormalities may include a modest hyperglycemia in the absence of diabetes mellitus, probably as a result of augmented glycogenolysis and catecholamine-mediated inhibition of insulin release, as well as increased insulin clearance and insulin resistance. When thyrotoxicosis is prolonged, leading to the depletion of glycogen deposits, hypoglycemia may occur, particularly in older people when aggravated by malnutrition secondary to emesis or abdominal pain.[86] Hepatic dysfunction in thyroid storm results in elevated levels of serum lactate dehydrogenase, aspartate aminotransferase, and bilirubin. Increased levels of serum alkaline phosphatase are also observed, predominantly because of increased osteoblastic bone activity in response to the augmentation of bone resorption.

Of importance, adrenal reserve may be exceeded in thyrotoxic crisis because of the inability of the adrenal gland to meet the metabolic demands and accelerated turnover of glucocorticoids. Moreover, there is known coincidence of adrenal insufficiency with Graves disease. This diagnosis should be considered when there is hypotension and suggestive electrolyte abnormalities.

Treatment

To avoid a disastrous outcome, a complex approach to management is recommended.[87] First, specific antithyroid drugs must be used to reduce the increased thyroid production and release of T4 and T3. The second approach comprises treatment intended to block the effects of the remaining but excessive circulating concentrations of free T4 and T3 in blood. The third arm involves treatment of any systemic decompensation, for example, congestive heart failure, and shock. The final component addresses any underlying precipitating illness such as infection or ketoacidosis.

Therapy directed to the thyroid gland—Inhibition of new synthesis of the thyroid hormones is achieved by administration of thionamide antithyroid drugs, such as carbimazole, methimazole (Tapazole), and propylthiouracil. These drugs in the comatose or uncooperative patient are given by nasogastric tube or per rectum as enemas or suppositories.[88–91] There are no available intravenous preparations of these compounds in the United States, but they are successfully used in some European countries such as the United Kingdom, Germany, and Poland.[92–94] According to the recently published guidelines by the American Thyroid Association and the Association of Clinical Endocrinologists, propylthiouracil can be started with a loading dose of 500 to 1000 mg followed by 250 mg every 4 hours, and methimazole should be administered at daily dose of 60 to 80 mg.[87] It is thought that propylthiouracil will provide more rapid clinical improvement because it has the additional advantage of inhibiting conversion of T4 to T3, a property not shared by methimazole. Because thionamides reduce new hormone synthesis but not thyroidal secretion of preformed glandular stores of hormone, separate treatment must be administered to inhibit proteolysis of colloid and the continuing release of T4 and T3 into

the blood. Either inorganic iodine or lithium carbonate may be used for this purpose. Iodides may be given either orally as Lugol solution or as a saturated solution of potassium iodide (3–5 drops every 6 hours). An earlier mainstay of treatment, the use of an intravenous infusion of sodium iodide (0.5–1 g every 12 hours), has not been feasible recently because sterile sodium iodide has not been available for intravenous use.

It is important that iodine should be administered no sooner than 1 hour after prior thionamide dosage. Otherwise iodine will enhance thyroid hormone synthesis, enrich hormone stores within the gland, and thereby permit further exaggeration of thyrotoxicosis. When iodine is administered in conjunction with full doses of antithyroid drugs, dramatic rapid decreases in serum T4 are seen, with values approaching the normal range within 4 or 5 days.[95] Other agents that theoretically could be used in this manner are the radiographic contrast dyes ipodate (Oragrafin) and iopanoic acid (Telepaque), which act not only by decreasing thyroid hormone release but also by slowing the peripheral conversion of T4 to T3, as well as possibly blocking binding of both T3 and T4 to their cellular receptors. Unfortunately, these agents are no longer available in the United States.

In patients who may be allergic to iodine, lithium carbonate may be used as an alternative agent to inhibit hormonal release.[96,97] Lithium should be administered initially as 300 mg every 6 hours, with subsequent adjustment of dosage as necessary to maintain serum lithium levels at about 0.8 to 1.2 mEq/L.

Therapy directed at the continuing effects of thyroid hormone in the periphery —Given the presence and likelihood of high levels of circulating T4 and T3 in a large vascular pool and tissue distribution space, in severe cases treatment with antithyroid drugs alone is not sufficient. Plasmapheresis and therapeutic plasma exchange are effective alternative therapies, which can reduce T4 and T3 levels within 36 hours. Plasma or albumin solution given during therapeutic plasma exchange provides new binding sites to reduce circulating levels of free thyroid hormones.[98–100] However, this effect is transient and lasts only about 24 to 48 hours, and thus should be followed by a more definitive therapy. Early thyroidectomy has been reported to reduce the mortality rate from 20% to 40% under standard treatment to less than 10%.[101]

Peritoneal dialysis or experimental hemoperfusion through a resin bed[102] or charcoal columns[103] has also been used. Another therapeutic adjunct is the oral administration of cholestyramine resin, resulting in removal of T4 and T3 by binding thyroid hormone entering the gut via enterohepatic recirculation, with the subsequent excretion of the resin-hormone complex.[104]

Hughes[105] was the first to treat a patient with thyrotoxic storm with a β-adrenergic blocker to ameliorate the manifestations of thyroid hormone excess. Propranolol is the most commonly used agent in the United States. The oral dosage of 60 to 80 mg every 4 hours or intravenous doses of 0.5 to 1 mg followed by subsequent doses of 2 to 3 mg given intravenously over 10 to 15 min every several hours are recommended, alongside constant cardiac rhythm monitoring.[87,106,107] There may be a theoretical benefit derived from the inhibitory effect of propranolol on the conversion of T4 to T3,[108] but a significant effect is

seen only with oral doses higher than 160 mg/d. Usage of β-blockers not only corrects the heart rate and diminishes the oxygen demand of the cardiac muscle, but also improves agitation, convulsions, psychotic behavior, tremor, diarrhea, fever, and diaphoresis. In some patients, there may be a relative risks or contraindications to the use of these agents. In patients with a history of bronchospasm or asthma and treatment with either selective β1-blockers or reserpine, guanethidine should be considered instead. A short-acting β-adrenergic blocker, esmolol, has also been used successfully in the management of thyroid storm. An initial loading dose of 0.25 to 0.5 mg/kg is followed by continuous infusion of 0.05 to 0.1 mg/kg per minute.[109,110]

The other important medications characterized by a high therapeutic potency and modest ability to inhibit peripheral conversion of T4 to T3 are steroids. An initial dose of 300 mg hydrocortisone followed by 100 mg every 8 hours during the first 24 to 36 hours should be adequate. Thyroid storm has been reported to recur when steroids had been discontinued after initial clinical improvement.[111] The additional rationale behind the routine use of steroids is perhaps theoretical and unproven, but relates to possible relative adrenal insufficiency secondary to increased metabolic demands and more rapid turnover of cortisol.

Some authorities have suggested that the supplemental administration of 1α (OH) vitamin D_3 might accelerate the reduction of serum T4 and T3.[112] In a recent study, the administration of 2 g/d L-carnitine in thyrotoxic storm facilitated a dose reduction of methimazole. The mechanism appears to be related to an inhibition by L-carnitine of T3 and T4 entry into cell nuclei.[113,114] Although these preliminary findings are of interest, the utility of this adjunct to therapy requires confirmation.

Therapy directed at systemic decompensation—Fluid depletion caused by hyperpyrexia and diaphoresis, as well as by vomiting or diarrhea, must be vigorously replaced to avoid vascular collapse. Appropriate fluid therapy will usually correct hypercalcemia, if present. Judicious replacement of fluids is necessary in elderly patients with congestive heart failure or other cardiac compromise. Intravenous fluids containing 10% dextrose in addition to electrolytes will better restore depleted hepatic glycogen. Vitamin supplements may be added to the intravenous fluids to replace probable coexistent deficiency. Hypotension not readily reversed by adequate hydration may temporarily require pressor and/or glucocorticoid therapy.

For fever, acetaminophen rather than salicylates is the preferred antipyretic, because salicylates inhibit thyroid hormone binding and could increase free T4 and T3, thereby transiently worsening the thyrotoxic crisis. Hyperthermia also responds well to external cooling with alcohol sponging, cooling blankets, and ice packs. Some investigators advocate the use of the skeletal muscle relaxant dantrolene,[115] but significant risk associated with its use precludes routine recommendation. When present, congestive heart failure should be treated routinely. Although less commonly used today, when digoxin is used, larger than usual doses may be required because of its increased turnover in the thyrotoxic state.

Therapy directed at the precipitating illness—The therapy is not complete unless a diagnosis of the possible precipitating event is made and early treatment as indicated for that

underlying illness is implemented. This is not a problem in obvious cases, when trauma, surgery, labor, or premature withdrawal of antithyroid drugs are known to have been the precipitants of thyrotoxic crisis, and which may require no additional management. However, when none of the latter precipitating factors is apparent, a diligent search for some focus of infection must be performed. Routine cultures of urine, blood, and sputum should be obtained in the febrile thyrotoxic patient, and cultures of other sites may be warranted on clinical grounds. Broad-spectrum antibiotic coverage on an empiric basis may be required initially while awaiting results of cultures.

Conditions such as ketoacidosis, pulmonary thromboembolism, or stroke may underlie thyrotoxic crisis, particularly in the obtunded or psychotic patient, and require the same vigorous management as routinely indicated.

Prognosis

Even with early diagnosis, death can occur, and reported mortality rates have ranged from 10% to 75% in hospitalized patients.[85,116,117] In most patients who survive thyrotoxic crisis, clinical improvement is dramatic and demonstrable within the first 24 hours. During the recovery period of the next few days, supportive therapy such as corticosteroids, antipyretics, and intravenous fluids may be tapered and gradually withdrawn, based on patient status, oral intake of calories and fluids, vasomotor stability, and continuing improvement. After the crisis has been resolved, attention may be turned to consideration of the definitive treatment of thyrotoxicosis. Should thyroidectomy be considered, thyrotoxicosis will need to have been adequately treated preoperatively, to obviate any likelihood of another episode of crisis during the surgery. Total thyroidectomy is the procedure of choice, in view of reports of recurrent severe thyrotoxicosis and thyroid crisis after less than total thyroidectomy.[118]

Radioactive iodine as definitive treatment is often precluded by the recent use of inorganic iodine in virtually all cases of storm, but it could be considered at a later date, in which case antithyroid thionamide therapy is continued to restore and maintain euthyroidism until such a time as ablative therapy can be administered. Continuing treatment with antithyroid drugs alone, in the hope of the patient’s sustaining a spontaneous remission, is also possible.

SUMMARY

The life-threatening thyroid emergencies of myxedema coma and thyrotoxic crisis require a high index of suspicion in the appropriate clinical setting, followed by prompt and accurate diagnosis and urgent multifaceted therapy to reduce the risk of fatal outcome.

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Table 1

Factors precipitating thyroid emergencies: myxedema coma and thyrotoxic storm

Precipitating Factors	
Myxedema Coma	**Thyrotoxic Storm**
Drugs	Drugs
Withdrawal of L-thyroxine	Withdrawal of antithyroid drug treatment
Anesthetics	Radioactive iodine treatment
Sedatives	Thyroxine/triiodothyronine overdosage
Tranquilizers	Cytotoxic chemotherapy
Narcotics	Aspirin overdosage
Amiodarone	Iodinated contrast dyes
Lithium carbonate	Organophosphates
Infections, sepsis	Sepsis, infection
Cerebrovascular accidents	Seizure disorder
Congestive heart failure	Pulmonary thromboembolism
Low temperatures	Burn injury
Trauma	Surgery, trauma, vigorous palpation of thyroid
Metabolic disturbances	Metabolic disturbances
Acidosis	Diabetic ketoacidosis
Hypoglycemia	Hypoglycemia
Hyponatremia	
Hypercapnia	
Other	Other
Gastrointestinal bleeding	Parturition
Ingestion of raw bok choy	Emotional stress

Table 2

Semiquantitative scale assessing the presence and severity of the most common signs and symptoms

Criteria	Score
Thermoregulatory Dysfunction	
Temperature 99°−99.9°F (37.2°−37.7°C)	5
Temperature 100°−100.9°F (37.8°−38.2°C)	10
Temperature 101°−101.9°F (38.3°−38.8°C)	15
Temperature 102°−102.9°F (38.9°−39.3°C)	20
Temperature 103°−103.9°F (39.4°−39.9°C)	25
Temperature ≥104°F (40°C) or higher	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, abdominal pain	10
Unexplained jaundice	20
Cardiovascular Dysfunction (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	
Absent	0
Present	10

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

Data from Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin North Am 1993;22:263–77.