ENDOCRINE AND METABOLIC DYSFUNCTION SYNDROMES IN THE CRITICALLY ILL

Management of Hypothyroidism and Hyperthyroidism in the Intensive Care Unit

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Alterations in thyroid function occur commonly in critically ill patients; however, they are rarely the primary cause of admission to the intensive care unit (ICU). In this article, the management of patients in whom abnormal thyroid function is the principal cause for ICU management is discussed. These individuals have either severe hypothyroidism or hyperthyroidism, syndromes that require ICU monitoring that are associated with high rates of in-hospital mortality. Early recognition and treatment are critical to successful management. Thyroid function tests, with a focus on the tests that are most relevant for patients with suspected severe thyroid function abnormalities, are discussed, followed by the clinical presentation and management of each disorder.

THYROID HORMONE PRODUCTION

It is critical for the clinician to have a complete understanding of thyroid hormone economy and thyroid function testing to make a rapid and accurate diagnosis of hypo- or hyperthyroidism. This requirement is particularly relevant in the ICU setting, where many medications and nonthyroidal illness can alter the results of thyroid function tests.

Iodine ingested in the diet is absorbed, circulates in the bloodstream, and enters the thyroid follicular cell as inorganic iodide by active transport by means of the Na, I symporter (NIS).[7] After transport, iodide moves down an electrical gradient and is transported into the follicular lumen through the apical membrane by a second

transporter known as Pendrin.[15] At the cell-lumen border, iodide is oxidized and organified by thyroid peroxidase (TPO). TPO then catalyzes iodination of tyrosine residues on thyroglobulin, the backbone protein for thyroid hormone. These tyrosine residues can be iodinated at the 3 and 5 sites on the hexamer ring. After iodination at one or both sites, TPO catalyzes coupling of the iodinated residues to form either 3′, 3, 5-triiodothyronine (T3) or 3′, 5′, 3, 5-tetraiodothyronine (thyroxine [T4]), depending on the combination of iodinated tyrosine residues. Iodine-rich thyroglobulin is subsequently stored in the colloid within the thyroid follicle, creating a large amount of stored thyroid hormone. On stimulation of the thyrotropin (TSH) receptor, thyroglobulin is resorbed through the apical membrane by a poorly defined mechanism, cleaved into thyroxine (T4) and triiodothyronine (T3) by means of proteolysis, and secreted into the circulation. In addition to T4 and T3, iodinated tyrosine precursors, monoiodotyrosine and diiodotyrosine, also are released and may have a role as substrate for formation of additional thyroid hormones.

Over 95% of thyroid hormone produced by the thyroid gland is T4; the remainder is T3. More than 99% of T4 and T3 circulate bound to several binding proteins, including thyroid binding globulin (TBG), transthyretin (prealbumin), and albumin. TBG has a higher affinity for T4 and T3 than transthyretin or albumin; therefore, it is the T4 and T3 bound to transthyretin and albumin that are primarily responsible for the rapid immediate delivery of thyroid hormones to peripheral tissues.[1] At the peripheral tissues, T4 is converted to T3 by deiodinases that remove one of the outer ring iodines from T4. There are two iodothyronine 5′ deiodinases, one located primarily in peripheral tissues such as the liver and kidney, and the second located primarily in the hypothalamus, pituitary gland, and the central nervous system. Alternative metabolism can also occur, with removal of the inner ring iodine rather than the outer ring, resulting in formation of reverse T3, an inactive form of thyroid hormone. Levels of reverse T3 rise in nonthyroidal illness but are not involved in the pathogenesis of hypo- or hyperthyroidism.[19] The effects of nonthyroidal illness on the conversion of T4 to T3 and reverse T3 are discussed in detail elsewhere in this issue.

Thyroid Hormone Action

The vast majority of thyroid hormone actions are initiated by the binding of T3 to nuclear thyroid hormone receptors. Upon entering the nucleus, T3 binds to one of two groups of thyroid hormone receptors (TRs), TRalpha or TRbeta. After binding, the T3/TR complex either homodimerizes with a second T3R or heterodimerizes to a retinoid x receptor (RXR). These complexes directly bind to consensus DNA sequences that are located in the enhancer regions of many target genes, resulting in either activation or inhibition of gene transcription.[18] To add additional complexity to this highly regulated system, the two thyroid hormone receptor families are expressed in different tissues and have unique effector genes. This specific regulation of gene transcription in many tissues accounts for the myriad effects of thyroid hormones in patients.

Through the action of T3-bound T3 receptors, thyroid hormone alters metabolism in the liver, fat cells, bone, and the heart. T3 is known to enhance responsiveness to adrenergic stimuli, alter levels of beta actin in the heart,[9] regulate body temperature, and regulate expression of thyrotropin-releasing hormone (TRH) and thyroid stimulating hormone (TSH) in the hypothalamus and pituitary.

Laboratory and Radiographic Evaluation of Thyroid Function

Thyroid hormones and thyroid regulatory hormones can be measured in several different manners, and the choice of appropriate testing is important. The critical laboratory studies are measurement of TSH with a third-generation assay sensitive at low levels, direct measurement of free T4 by radioimmunoassay or equilibrium dialysis, and measurement of either total T3 or free T3. Measurements of total T4 are not helpful, because this value can be misleading in patients with low levels of albumin or TBG deficiency from chronic liver disease, or other causes. If a total T4 measurement is obtained, a measurement of the percentage of that hormone that is bound to protein is required (T3 or T4 resin uptake) to allow for a calculated estimation of free T4 (free thyroxine index or T7).

Determination of T3 concentrations is important, particularly in hyperthyroidism. The type I monodeiodinase (see previous paragraphs) enzyme is thyroid hormone-responsive. Although this upregulation by thyroid hormone is homeostatic when a person is **hypothyroid**, it can create problems when a patient is **hyperthyroid**. From a laboratory standpoint, it is important to recognize that because there is increased conversion of T4 to T3 in thyrotoxicosis, measuring only TSH and free T4 may underestimate the severity of biochemical hyperthyroidism.[3]

It also is important not to rely solely on a TSH determination in the actually ill population. TSH alone is appropriate when screening for thyroid disease in a healthy population,[8] but in critically ill patients, the clinician is not screening for disease, but rather confirming a clinical impression. In addition, there are a variety of effects of medical illness and medications on one or more thyroid function tests. It is therefore unlikely that a less than complete laboratory evaluation of the entire hypothalamic-pituitary-adrenal axis will result in clinically useful information.

Additional thyroid-related tests that can be performed include measurement of thyroid antibodies. The vast majority of patients in the United States who present with severe thyroid disease have autoimmune thyroid disease, Graves' disease (hyperthyroidism), or Hashimoto's thyroiditis (hypothyroidism). Although they will rarely affect management, measurement of antibodies that bind and activate the TSH receptor (thyroid stimulating immunoglobulins, TSI) can help confirm a diagnosis of Graves' disease. Antithyroglobulin and antithyroid peroxidase antibodies are frequently elevated in all forms of autoimmune thyroid disease and are therefore noncausative markers of thyroid autoimmunity.[1] In general, it is not necessary to perform these tests in a patient with severe thyroid disease requiring ICU-level care. They help confirm the clinical impression but do not alter therapy in the acute setting.

Radiographically, the most useful tests of thyroid function are functional examinations that measure uptake of iodine, or a surrogate marker, into the thyroid gland. These tests all use radioiosotopes, and include I-123, I-131, technetium-99, and thallium-201. Although these tests are more labor intensive, the most useful are those that use the iodine isotopes, because they measure both the uptake and organification of iodine in a physiologic manner. The iodine isotopes can be used to identify nodular thyroid disease, to determine if these nodules are functioning (hot) or hypofunctioning (cold), to determine the cause of the hyperthyroidism (Graves' disease versus thyroiditis), and to determine a dose of radioiodine for treatment. The principal

limitation of iodine scans is the requirement for oral dosing; therefore, in the ICU setting the clinician may need to use alternative intravenous agents. Anatomic tests, such as ultrasound, computed tomography (CT), or magnetic resonance (MR) imaging are useful in preoperative evaluation, but are not usually helpful in the care of the acutely ill patient.

THYROID STORM

Many forms of thyrotoxicosis that are seen in clinical practice can largely be managed in the outpatient setting. These range from Graves' disease that is caused by autoantibodies that activate the TSH receptor to toxic nodules and multinodular goiters, caused by genetic activating mutations in the TSH receptor or its downstream signaling molecules. The following is a more complete list of causes of thyrotoxicosis; some are transient, whereas others require treatment with radioiodine, medications, or surgery.

Causes of Thyrotoxicosis

Endogenous Hyperthyroidism

Graves' disease

Toxic multinodular goiter

Toxic autonomous nodule

Thyroiditis (transient thyrotoxicosis)

Subacute (granulomatous) thyroiditis

Acute (bacterial) thyroiditis

Postpartum thyroiditis

Painless thyroiditis

Riedel's thyroiditis

Struma ovarii (autonomous thyroid function in a teratoma)

Iodine-induced hyperthyroidism

Medications (amiodarone, iodinated radiocontrast agents)

Postradioiodine thyroiditis

Dietary supplements (e.g., kelp)

TSH-mediated

Pituitary tumors

Pituitary resistance to TSH

Metastatic follicular thyroid cancer

Exogenous Thyrotoxicosis

Iatrogenic thyrotoxicosis

Factitious use of thyroid hormone

Dietary supplements containing thyroid hormones

In the ICU setting, the most critical concerns regard the syndrome of decompensated hyperthyroidism (or thyroid storm). Decompensated hyperthyroidism is characterized by the acute onset of enhanced symptoms of hyperthyroidism. It is important to recognize that this condition is a clinical diagnosis. There are no significant differences in the results of thyroid function tests in patients with thyroid storm compared with patients with symptomatic hyperthyroidism who do not have thyroid storm.[2] The classic clinical findings include the following: fever (> 38.5°C), sinus or supraventricular tachycardia (out of proportion to the fever) with or without congestive heart failure, gastrointestinal symptoms (nausea, vomiting, diarrhea, and rarely jaundice), and confusion, delerium, or sometimes coma. The tachycardia and increased bowel movements typically occur in patients without thyroid storm; therefore, it is the full constellation of findings that confirms the diagnosis. Early clinical recognition and initiation of therapy are critical, because thyroid storm carries a 10% to 75% mortality in hospitalized populations.[3] Thus, ICU care is required for patients with thyroid storm.

Precipitating Factors

Levels of thyroid hormone do not distinguish patients with thyroid storm from those with uncomplicated thyrotoxicosis, so it is difficult for a clinician to predict which patients will decompensate. There are several factors that seem to induce thyroid storm in patients with hyperthyroidism. It is first important to recognize that most patients have a history of partially treated hyperthyroidism, have other manifestations of thyroid disease, such as orbitopathy in Graves' disease, or have had symptoms for some time before the diagnosis. Many secondary conditions or factors that induce decompensation of thyrotoxic patients have been described, including surgery, parturition, radioiodine therapy, iodinated contrast materials, stroke, diabetic ketoacidosis, infection, and withdrawal or discontinuation of antithyroid medications.

A recent article by Sherman and colleagues[16] reviewed the recent experience with thyroid storm at Johns Hopkins Hospital. Of interest is that decompensated thyrotoxicosis was more common in medically underserved, poor populations. By contrast, this trend was not seen in patients who were successfully treated as outpatients. The authors suggested that this disparity might be related to barriers to care resulting in delayed diagnosis. In this population, similar to earlier studies, the most frequent indications for admission were, in order, cardiac, neuropsychiatric, fever, and gastrointestinal. The median temperature was 39.3°C, and a significant

minority of patients had definable infections. About one fourth of the patients were hyperglycemic and the same percentage were hypernatremic on admission. The in-hospital mortality rate was 1.8%.

Pathogenesis

The specific mechanism by which thyroid storm occurs remains uncertain. Several hypotheses have emerged, including effects of acidosis or medical illness on thyroid hormone binding to carrier proteins, in particular albumin and prealbumin. Levels of free T4 and free T3, however, do not seem to differ between patients with compensated or decompensated hyperthyroidism. A second hypothesis is that there is an effect at the level of the thyroid hormone receptor in target tissues,[5] perhaps relating to acidosis or release of some other common intermediary during times of metabolic stress. There does seem to be a particularly exaggerated response to adrenergic stimuli. Although levels of catecholamines do not seem to be higher in hospitalized patients with thyroid storm compared with other medically ill patients, clinically, treatment with beta-blockers can induce dramatic improvements in signs and symptoms.[3] Despite these clinical findings, there is no convincing experimental or clinical evidence that altered interactions between the adrenergic system and thyroid hormones cause thyroid storm.

Laboratory Findings

In severe hyperthyroidism, thyroid hormone levels are typical of those seen in thyrotoxicosis in any form, with the exception of patients with exacerbations of chronic illness who may have preexisting euthyroid sick syndrome and have lower levels of T3 than expected. Typically, TSH levels are undetectable (< 0.01 mU/L), and free T4 and T3 levels are elevated. In many cases, the T3 elevation may be much more dramatic than that of the levels of T4, owing to increased conversion of T4 to T3 (in the absence of significant nonthyroidal illness). Thus, it is important to measure the levels of T3 in addition to those of free T4 in patients with suspected decompensated thyrotoxicosis. If obtained, radioiodine uptake will be elevated in nearly all cases.

Serum electrolytes are usually normal with the exception of calcium, owing to increased osteoclast-mediated bone resorption. Alkaline phosphatase levels also are frequently elevated secondary to activated bone remodeling. This can be distinguished from an alkaline phosphate elevation due to thyrotoxic liver disease, because the latter is usually associated with elevated levels of bilirubin or hepatic transaminases. Hyperglycemia is common, particularly for patients with preexisting diabetes, probably because of enhanced glycogenolysis and the effects of catecholamines. Finally, it is important to recognize that individuals with Graves' disease have a higher frequency of adrenal insufficiency than the general population. Because corticosteroids are often used in the acute treatment of decompensated thyrotoxicosis, it is advisable to obtain a serum cortisol level before initiation of therapy. Leukocytosis, with or without a "left shift," commonly occurs, even in the absence of infection, and hemoglobin and hematocrit concentrations are frequently increased.

Treatment

Treatment of thyroid storm is complex and generally requires ICU monitoring. A suggested treatment approach is listed below. Therapy is multifaceted, and may be thought of as a four-pronged approach to the patient: (1) therapy to control the thyroid gland; (2) therapy to block the effects of thyroid hormone on peripheral tissues; (3) supportive measures; and (4) treatment of the precipitating cause for the decompensation.

Therapy to Control the Thyroid

The goal of this arm of the therapeutic plan is to reduce the formation and release of thyroid hormone. The most effective medications that block iodide organification and formation of thyroid hormone are the thionamides, propylthiouracil (PTU) and methimazole (Tapazole). Both medications are effective and can act rapidly when started at high doses. PTU may have the added benefit of inhibiting T4 to T3 conversion at high doses. Neither is available in parenteral formulations, but both can be given as rectal suppositories if the patient is unable to tolerate oral or nasogastric feeding. Typical doses for thyroid storm are 200 to 250 mg every 4 hours for PTU and 20 mg every 4 hours for methimazole. Because of the potential beneficial effects of PTU on peripheral conversion of T4 to T3, it is generally the first choice in this situation, although either medication is effective.

Side effects of the thionamides include allergic reactions, hepatotoxicity, and leukopenia (rarely agranulocytosis). These complications are uncommon, but care must be taken in monitoring for these side effects, particularly in patients in whom hepatic function is abnormal before initiation of therapy.[6] [10]

Treatment of Decompensated Hyperthyroidism (Thyroid Storm)

Therapy to Control the Thyroid

Thionamides (PTU, methimazole)

Iodinated medications (iopanoic acid, stable potassium iodide [SSKI], Lugol's solution)

Lithium carbonate

Therapy to Block Conversion of T4 to T3

PTU

Iopanoic acid

Propranolol

Corticosteroids

Therapy to Enhance Clearance of Thyroid Hormones

Gastrointestinal clearance

Cholestyramine

Blood clearance

Hemodialysis

Hemoperfusion

Plasmapheresis

Therapy to Block the Effects of Thyroid Hormones

Beta blockers

Corticosteroids

Supportive Measures

Antipyretics (acetaminophen)

Cooling

Correction of dehydration

Nutrition

Oxygen

Treatment of congestive heart failure

Therapy for the Precipitating Illness

Because thionamides only block formation of new thyroid hormone, therapy also must be directed to block release of the preformed thyroid hormone stores in the colloid space. Medications to inhibit this release include iodines and lithium carbonate. Of these, iodines have been the best studied and have additional advantages, including inhibition of T4 to T3 conversion.

The iodide preparation of choice is the oral contrast agent iopanoic acid (Telepaque). Iopanoic acid has an extremely high iodine content (1.8 g iodine/3 g dose) and can inhibit thyroid hormone release. This agent also inhibits hepatic uptake of T4 and inhibits T4 to T3 conversion. It is highly concentrated in the liver, and care must be taken in patients with hepatic dysfunction. The usual dose of iopanoic acid is 1 g every 8 hours for the first 24 hours, then 500 mg twice daily. This medication can only be given orally. Additional iodine-containing compounds that can be used include Lugol's iodine or a saturated solution of potassium iodide (SSKI). These are administered as drops and taken orally. For thyroid storm, a typical dose is 4 to 8 drops every 6 to 8 hours. Intravenous iodide (NaI) is no longer available.

An important issue in using this combined approach (i.e. thionamide plus iodide) is that the thionamides must be given before (by at least 2-3 hours) to iodine-containing medications to avoid a rapid rise in thyroid hormone levels. Monotherapy with iodides results in the initial formation and release of new thyroid hormone and can thereby worsen the thyrotoxicosis. In addition, therapy with iodides may prevent future

therapy with radioiodine for several months. Therefore, its use is limited to severe cases and for preparation for surgery. Finally, it is important to recognize that with continued therapy the thyroid gland can escape from the inhibitory iodine effects, so iodide preparations should not be used for more than 2 to 3 weeks.

Lithium also has been used to inhibit thyroid hormone release. The usual dose required is 300 mg every 6 hours initially. It should be used only in patients with a contraindication for iodine and/or thionamide use, because it has not been well studied. The dose should be adjusted to maintain serum levels in the range of 1 mEq/L.

In rare situations, hemodialysis or charcoal hemoperfusion have been used to enhance clearance of thyroid hormones.[3] These procedures have risks such as hypotension and should not be used as first-line measures.

Cholestyramine has been used in the treatment of thyrotoxicosis. Thyroid hormone undergoes resorption in the distal small bowel through the enterohepatic circulation. Cholestyramine will bind thyroid hormones in the gastrointestinal tract, resulting in a modest reduction of circulating thyroid hormone level.[17]

Therapy to Block Peripheral Effects of Thyroid Hormone

The primary therapies to block effects of thyroid hormone include those that inhibit T4 to T3 conversion and those directed at target tissues. Inhibition of T4 to T3 conversion can be achieved most effectively by use of iopanoic acid and PTU. Smaller effects on conversion can be seen with the beta-adrenergic blocker propranolol at high doses and with corticosteroids at high doses.

Beta-adrenergic blockers are a mainstay of therapy for hyperthyroidism. Propranolol has been used most frequently because of its effects on peripheral conversion of T4 to T3, but all beta blockers effectively ameliorate signs and symptoms of thyrotoxicosis, including tachycardia and tremor. In thyroid storm, oral doses in the range of 60 to 120 mg every 6 hours are required. Alternatively, careful administration of intravenous propranolol (0.5-1.0 mg, repeated every 10-15 minutes) can be used to control heart rate. In severe cases, the rapidly acting agent esmolol can be administered as an intravenous infusion (0.05-0.1 mg/kg per minute), but careful monitoring for bradycardia in the ICU is required.

For patients with underlying cardiac disease or impaired left ventricular function, invasive monitoring with a Swan-Ganz catheter may be required. Digoxin and other inotropic agents are sometimes required in complicated cases, and even judicious use of beta blockers may not be tolerated. In these cases, careful monitoring of volume status and aggressive antithyroid therapy are the most important components of therapy.[9]

Corticosteroids, at high doses, may reduce conversion of T4 to T3. This treatment is particularly relevant because of the higher incidence of concomitant adrenal insufficiency in patients with Graves' disease. Hydrocortisone, 100 mg every 8 hours, is administered in thyroid storm.

Supportive Measures and Therapy Against the Precipitating Illness

Many patients with thyroid storm will have a predisposing medical condition. In some situations, the cause is obvious, such as delivery or surgery; in other cases, the cause may be more obscure. Blood cultures, urinalysis, urine cultures, chest radiography, and electrocardiograms are nearly routine in patients with thyroid storm. Antibiotics need not be routinely administered unless there is clinical or laboratory evidence of infection, although empiric therapy with broad-spectrum antibiotics may be warranted in severe cases. If congestive heart failure occurs in this setting, careful monitoring of pulmonary artery and central venous pressures may be useful.

Supportive measures, such as antipyretics, cooling blankets, anxiolytics, intravenous fluids, and corticosteroids may be required. If corticosteroids are to be used, a serum cortisol or adrenocorticotrophic hormone (ACTH) stimulation test should be obtained before initiation of therapy. In most patients who recover from thyroid storm, clinical improvement occurs rapidly over the first 12 to 24 hours. If progression occurs despite aggressive therapy, consideration should be given to hemodialysis, plasmapheresis, or hemoperfusion.

Long-term Treatment Considerations

Once the acute event is controlled, consideration must be given to long-term treatment and control of hyperthyroidism. In the United States, most patients are treated with radioactive iodine; however, if inorganic iodine was used in the treatment of the crisis, this therapy must be delayed for several months. If radioiodine therapy is desired, treatment with iodine should be avoided, and thionamide and beta blocker therapy can be continued until free T4 and T3 levels are near normal. Thionamides, when used for several years, may induce a remission in a minority of patients with Graves' disease, particularly if the degree of thyrotoxicosis is mild.[10] Finally, if iodine is used in therapy, surgical thyroidectomy is a well-established alternative therapy. Rapid patient preparation is possible using beta blockers, thionamides, iodine, and steroids, but care must be taken to ensure normal levels of thyroid hormones at the time of surgery to avoid thyroid storm postoperatively.

MYXEDEMA COMA

Hypothyroidism is among the most common disorders in the United States, affecting approximately 8% of women and 2% of men over the age of 50 years.[4] Although most patients present with mild or minimally symptomatic disease, the most severe form of untreated hypothyroidism, myxedema coma, still occurs and carries significant mortality.[20] Similar to thyroid storm, myxedema coma represents an exaggerated form of thyroid disease associated with precipitating factors that is easily treated once it is recognized.

Precipitating Factors

Myxedema coma is most frequently encountered in patients with a known history of hypothyroidism in the winter months, often after cold exposure. Other factors thought to precipitate the syndrome include pneumonia, cerebral vascular accidents, and medications that can depress central respiratory drive. Other laboratory abnormalities

such as hypoglycemia and hyponatremia are thought to be secondary to the hypothyroidism, rather than causative of the myxedema coma. The following is a list of typical precipitating factors for myxedema coma:

Precipitating and Predisposing Factors for Myxedema Coma

Untreated hypothyroidism

Prior thyroidectomy

Prior radioiodine therapy

Autoimmune or congenital thyroid disease

Hypopituitarism

Hypothermia

Infection

Cerebral vascular accidents

Trauma

Medications

Analgesics

Sedatives

Tranquilizers

Anesthesia

Amiodarone

Lithium carbonate

Narcotics

Clinical Features

The cardinal features of myxedema coma are hypothermia and delerium or unconsciousness. Frequently patients are also bradycardic and, if awake, have slow verbal responses. Respiratory rate is generally reduced because of a reduction in hypoxic ventilatory drive.[21] This effect causes subsequent carbon dioxide (CO_2) narcosis and progressive somnolence that compounds the slowed mental status of the patient. Respiratory muscle weakness also may occur, further compromising the ability to ventilate effectively. Additional anatomic effects of severe hypothyroidism that may further impede effective ventilation include ascites, pleural effusions, and pericardial effusions.

Hypothermia is noted in approximately 80% of patients with myxedema coma[20] and may be dramatic with body temperatures below 80°F. External warming with ordinary blankets is appropriate, but electric heating blankets can cause vasodilation and subsequent hypotension that may require pressor support to correct.

The susceptibility to vasodilation is further aggravated by impaired cardiac function. Cardiac contractility is reduced, resulting in a reduction of stroke volume and cardiac output. These factors, in addition to bradycardia and reduced intravascular volume (but increased total body fluid), result in the inability to respond to peripheral vasodilation that can occur with rapid rewarming. Cardiac output can be further limited by significant pericardial effusions that can cause tamponade. Finally, hypothyroidism causes hyperlipidemia, a factor that may predispose patients with myxedema coma to have underlying coronary artery disease and myocardial infarction.

Neuropsychiatric features of myxedema coma range from unresponsiveness to seizures or delerium with hallucinations (myxedema madness). Patients typically have slow responses to questions, poor short-term memories, cerebellar signs, and somnolence. Electroencephalograms typically reveal low amplitude with reduced alpha signal. If seizures occur, laboratory abnormalities, such as hyponatremia and hypoglycemia, are frequently causative.

Additional features of myxedema coma include constipation or paralytic ileus and bladder atony with large residual urine volumes. Total body fluid overload with hyponatremia caused by impaired water diuresis also is common in myxedema coma. Periorbital edema is common as a result of this fluid overload, and signs of thyroid eye disease can be identified, particularly if a patient has been previously treated with radioioidine.

Laboratory Findings

Laboratory findings in myxedema coma include an elevated TSH concentration with low or undetectable levels of free T4 and T3. The presence of severe, nonthyroidal illness may reduce the degree of TSH elevation expected for particular patients. In addition, if a patient has myxedema coma related to central hypothyroidism, the TSH level may be low or normal. Therefore, in patients with suspected myxedema coma, determination of concentration of TSH along with levels of free T4 and T3 is required to confirm the diagnosis. Because there is a mortality rate of nearly 60%,[20] rapid diagnosis and treatment are important and rest on recognition of the clinical features.

Treatment

The treatment of myxedema coma is directed at replacing thyroid hormone, treating the predisposing underlying condition, and supportive measures.

Hypothermia

Ordinary blankets and keeping the room temperature warm are useful adjuncts to thyroid hormone therapy. The use of external warming blankets is not recommended

because of vasodilation and possible subsequent hypotension and vascular collapse. Ultimately, normal body temperature is restored by administration of thyroid hormone.

Hypoventilation

Hypoventilation, caused by the factors mentioned previously, results in CO_2 narcosis and reduced mental status. Pneumonia is a frequent predisposing illness or complication of myxedema; therefore, all patients with suspected myxedema coma require arterial blood gas determinations and chest radiographs. Although most patients become more alert 48 to 72 hours after initiation of therapy with thyroid hormone, mechanical ventilation is frequently required until this event occurs.

Hyponatremia and Hypoglycemia

Hyponatremia is common in myxedema coma and may even cause seizures or mental status changes. If sodium values are below 120 mEq/L and there are significant mental status changes, isotonic or even hypertonic NaCl must be given to slowly raise levels to above 120 mEq/L. The detailed management of hyponatremia is beyond the scope of this article, but care must be taken to avoid fluid overload and rapid correction of hyponatremia in this clinical situation. Asymptomatic mild hyponatremia (> 120 mEq/L) can be monitored without specific therapy because it usually resolves with l-thyroxine therapy.

Hypoglycemia is common and may reflect underlying adrenal dysfunction. Similar to hyperthyroidism, autoimmune adrenal insufficiency can associate with hypothyroidism (polyglandular autoimmune syndrome) and should be considered in all patients with myxedema coma.[12] Moreover, if a patient has central hypothyroidism, the same lesion may cause low levels of ACTH and subsequent adrenal insufficiency. Therefore, patients with myxedema coma are generally treated with stress dose corticosteroids (e.g., 100 mg of hydrocortisone every 8 hours). To test for adrenal insufficiency, a random cortisol level can be obtained before the initiation of therapy, or a rapid ACTH stimulation test can be performed.

Hypotension

Hypotension frequently occurs in myxedema coma, and its pathogenesis is multifactorial. There is depressed cardiac function, a high likelihood of pericardial effusions, and possible adrenal insufficiency. It is important to assess all of these conditions quickly and treat the patient appropriately. Echocardiography is usually performed in these patients to evaluate for evidence of pericardial effusion and global versus regional hypokinesis. Pressors and fluids should be used carefully, because fluid overload and congestive heart failure and tachyarrhythmias associated with institution of thyroxine therapy may be exacerbated by treatment. Myocardial function improves and pericardial effusions typically resolve over several months of thyroid hormone therapy.

Thyroid Hormone Therapy

The proper initiation of thyroid hormone replacement in myxedema coma is controversial, with disagreement among even the most experienced thyroidologists.

All of the proposed treatment paradigms are designed to reach the same endpoint, the rapid restoration of circulating and intracellular levels of thyroid hormones in a manner that will not induce arrhythmias or sudden death. The major controversy relates to the use of intravenous T3 in addition to, or in place of, intravenous T4 in the acute management of these patients.[13] [20]

T3 is the active hormone and is converted from T4 by the deiodinase enzymes in the peripheral tissues. Because the activity of the deiodinases is reduced in hypothyroidism, there may be relatively less T3 than T4, which may be maladaptive. The drawback to using T3 is the greater potential for arrhythmias because of an acute rise in T3 rather than a slow and gradual rise in T3. T4 has a much longer half-life and is converted to T3 endogenously, resulting in a slower but steadier rise in T3 values.

There are few data to direct clinicians to choose between the use of T4 alone, T4 in combination with T3, or T3 alone. If intravenous T4 is used alone, many clinicians give a loading dose of 200 to 500 mug to restore circulating levels as quickly as possible (higher doses do not seem to be beneficial[14]) and to increase levels of T3 more rapidly. After this initial dose, therapy is continued with 100-mug doses daily for several days and is then reduced to 50 to 75 mug daily as a replacement dose. Using this method, levels of T4 rise quickly, T3 rises secondarily through conversion of T4 in peripheral tissues, and TSH levels decrease. The addition of a low dose of intravenous T3 (10 mug every 8 hours) until the patient is conscious has been advocated and may be rational in younger patients with no known coronary artery disease or arrhythmias.[20] The use of intravenous T3 alone is generally not recommended, because oral T4 is used for long-term replacement therapy.

SUMMARY

Thyroid storm and myxedema coma are uncommon problems in the ICU, but both usually present with typical findings, and when recognized early, are treatable. Thus, rapid recognition with early institution of therapy may be life saving. It is always important to search diligently to determine the underlying cause of the decompensation and to treat that aggressively.

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