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Thyroid Emergencies

ABSTRACT

Myxedema coma and thyroid storm are thyroid emergencies associated with increased mortality. Prompt recognition of these states—which represent the severe, life-threatening conditions of extremely reduced or elevated circulating thyroid hormone concentrations, respectively—is necessary to initiate treatment. Management of myxedema coma and thyroid storm requires both medical and supportive therapies and should be treated in an intensive care unit setting.

Key words: hypothyroidism, hyperthyroidism, ICU, myxedema coma, thyroid emergencies, thyroid storm

The thyroid is a 15- to 20-gram gland located in the anterior neck. It is responsible for the production of the thyroid hormones T4 (thyroxine) and T3 (triiodothyronine). Various factors can affect thyroid hormone synthesis, including acute illness, coexisting morbidities, and certain medications. Both the states of low thyroid hormone concentrations (hypothyroidism) and thyroid hormone excess (thyrotoxicosis) can be transient or permanent. The decompensated, severe forms of hypothyroidism and hyperthyroidism, termed *myxedema coma* and *thyroid storm*, are associated with increased morbidity and mortality. Prompt recognition of both conditions is necessary to initiate treatment and supportive measures. This review will summarize the essential principles of the clinical manifestations, diagnostic methods, and treatments of hypothyroidism and hyperthyroidism, both in the nonacute and life-threatening forms of these diseases.

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THYROID HORMONE PRODUCTION AND METABOLISM

The normal physiology of the hypothalamic-pituitary-thyroid axis involves the production of T4 and T3 by the thyroid gland, a process that is regulated by thyroid-stimulating hormone (TSH) secreted by the pituitary, which is, in turn, regulated by thyrotropin-releasing hormone (TRH) secreted by the hypothalamus. Both serum T4 and T3 concentrations act as negative feedback regulators of TSH and TRH secretion, but can be altered by environmental conditions—including food availability and temperature—and disease states, such as infection.[1]

Thyroid hormone synthesis is achieved first through active transport of circulating iodide, which is taken in from the diet, by the sodium/iodide symporter located at the basolateral membrane of the thyroid follicular cell.[2] Iodide then becomes oxidized by thyroid peroxidase (TPO) and hydrogen peroxide at the apical membrane, which then attaches to the tyrosyl residues on thyroglobulin (Tg) to produce monoiodotyrosine (MIT) and diiodotyrosine (DIT). MIT and DIT are the precursors to the thyroid hormones, which are produced by the linkage of 2 DIT molecules to form T4 and the linkage of MIT and DIT to produce T3. Release of T4 and T3 into the circulation results from the digestion of Tg in MIT and DIT by endosomal and lysosomal proteases.

The metabolic effects of thyroid hormone action result from the binding of the thyroid hormone to thyroid hormone transporters located in specific target tissues, which is mediated by the thyroid hormone nuclear receptor (TR) that is encoded by the genes TRα and TRβ.[3] While the sole source of T4 is the thyroid gland, the majority (approximately 80%) of T3 is produced from the extrathyroidal conversion of T4 to T3 by the action of the 5′-deiodinase enzymes—D1 or D2—located in the liver, brain, brown adipose tissue, and muscles.[4] T4 can also be converted to the inactive thyroid hormones, reverse T3 or T2, by the 5′-deiodinase D3. The activity and expression of the deiodinases are specific to different tissues and environmental conditions.

SERUM THYROID FUNCTION AND ANTIBODIES

Serum TSH is the most sensitive test to suggest thyroid dysfunction, because of the logarithmic-linear relationship between serum TSH and thyroid hormone levels. Overt thyroid dysfunction, whether referring to hypothyroidism or hyperthyroidism, is defined by the sole abnormality of an elevated serum TSH concentration, while subclinical thyroid dysfunction refers to both elevated serum TSH and decreased T3 and/or T4 concentrations. The range of subclinical to overt thyroid dysfunction can be regarded as a continuum of increasingly severe biochemical thyroid disease, which incidentally may or may not correlate to the severity of any corresponding symptoms, if present.

HYPOTHYROIDISM

Hypothyroidism refers to the state of low circulating thyroid hormones. In 2 large US population-based studies of data collected in the 1980s to the 1990s, the prevalence of overt hypothyroidism ranged from 0.3% to 0.4%, while that of subclinical hypothyroidism ranged from 4.3% to 8.5%, among the general population.[5,6] The most common etiology of hypothyroidism in the United States is Hashimoto's thyroiditis, an autoimmune disease that is more prevalent among older women; nutritional iodine deficiency is the most common etiology worldwide. Additional etiologies of hypothyroidism include a history of thyroidectomy, radioactive iodine therapy, and, less commonly, decreased TSH production by the pituitary. Predisposition factors for the development of hypothyroidism include thyroid autoimmunity (which can be assessed by the determination of serum thyroid autoantibodies, such as TPO and [Tg] antibody titers), the use of certain medications (ie, lithium, amiodarone, interferon-alpha), and excess iodine exposure (ie, from iodinated contrast radiographic studies), in which individuals with a history of thyroid disease are at higher risk of iodine-induced hypothyroidism.[7]

Thyroid hormone is important for the metabolic functions of many major organs, including the heart, brain, liver, and muscle. Signs and symptoms of hypothyroidism are widely variable (Table 1), often subtle, and may include fatigue, malaise, weight gain, dry and puffy skin, constipation, cold intolerance, altered cognition, and hyporeflexia. In children, there may be stunted growth, and in women, menstrual abnormalities may be present.

Hypothyroidism Among Women of Reproductive Age and in Children

Normal thyroid function is particularly important among pregnant and lactating women, the developing fetus, and young children. As thyroid hormone is crucial for the complex processes of neurodevelopment and growth,[8] which begins in the first trimester of pregnancy and continues into the first few years of infancy, these groups are especially susceptible to the effects of even mild thyroid dysfunction. Several studies have demonstrated that low thyroid hormone levels among

TABLE 1
Signs and Symptoms of Hypothyroidism

General
Fatigue
Lethargy
Weight gain
Sleepiness
Cold intolerance
Skin and hair
Dry, thick skin
Coarse hair
Eyebrow thinning
Brittle nails
Decreased perspiration
Cardiovascular system
Bradycardia
Elevation of blood pressure
Hyperlipidemia
Respiratory system
Shortness of breath
Hoarse voice
Sleep apnea
Gastrointestinal system
Constipation
Decreased appetite
Reproductive system
Menstrual cycle irregularities
Infertility
Musculoskeletal system
Arthralgia
Neurological system
Paresthesia
Depression
Mental impairment
Slow movements
Hyporeflexia

pregnant women are associated with increased risks of preterm delivery, spontaneous miscarriage, fetal death, and cognitive deficits,[9] including a decrement in intelligence quotient and memory scores of the offspring, compared with euthyroid women.[10-13] Neuroimaging studies also show abnormalities of hippocampal and corpus callosum size, and of gray matter, among children with a form of low thyroid hormone levels at birth termed *congenital hypothyroidism*.[14,15]

Myxedema Coma

Myxedema coma refers to the state of severe, life-threatening, and decompensated hypothyroidism in which thyroid hormone levels are dangerously low. The diagnosis appears to be more common in elderly women with long-standing preexisting hypothyroidism. Triggers may include cold temperature (thus, it is more common during winter months); precipitating comorbidities, such as infection, stroke, and heart failure; or the use of sedative, analgesic, antidepressant, hypnotic, antipsychotic, or anesthetic medications.[16] Patients with preexisting hypothyroidism may also present with myxedema coma following a period of prolonged noncompliance with thyroid hormone replacement.

Signs and symptoms usually are exacerbations of the usual manifestations of hypothyroidism and may include extreme lethargy, which can progress to stupor or coma, hypothermia, respiratory depression, bradycardia, hyponatremia, and renal impairment. The diagnosis of myxedema coma is made with the confirmation of a biochemical thyroid profile consistent with hypothyroidism and corresponding clinical manifestations. A diagnostic scoring system has been proposed to guide the clinician toward a diagnosis of myxedema coma based on body temperature, central nervous system signs, gastrointestinal symptoms, precipitating events, cardiovascular dysfunction, and metabolic disturbances.[17]

Treatment of myxedema coma should be considered as quickly as possible, given the increased mortality of the disease (25%-60% despite treatment),[18] and can be started even before confirmation of laboratory results demonstrating abnormal serum TSH and T4 concentrations. The management of myxedema coma should be in an intensive care unit (ICU) setting. The central tenets of treatment are thyroid hormone replacement, stress-dose corticosteroids if concomitant adrenal insufficiency is suspected, supportive care, and the treatment of any underlying and coexisting conditions (Table 2). Supportive care may include the administration of intravenous (IV) fluids, sodium replacement if hyponatremia is present, and the use of warming blankets (although aggressive rewarming should be avoided, given the risks of vasodilation).[19]

Thyroid hormone replacement should be administered as T4 and/or T3, often intravenously, given the impaired state of the patient. Suggested regimens for the initial and maintenance doses of thyroid hormone in a patient with myxedema coma are provided in Table 2. In general, a loading dose of 200 to 400 μg IV levothyroxine (T4) is to be followed by a maintenance dose of 1.6 μg/kg/d when given orally or 75% of this when given intravenously; consideration can also be made for the coadministration of liothyronine (T3), since T4 to T3 conversion may be impaired in patients with myxedema coma.[20] It is important to note that IV thyroid hormone replacement should be administered only as a push through a syringe, rather than through infusion tubing, in which up to 40% of the starting concentration may be lost from adherence to polypropylene tubing.[21] Improvements in serum T3 and T4 concentrations may be seen before the normalization of serum TSH concentrations, and measurement of serum thyroid function tests every 1 to 2 days during treatment is reasonable.[20] Improvements in clinical cardiovascular, renal, pulmonary, and metabolic parameters may take as much as a week to be observed.[20]

THYROTOXICOSIS

Thyrotoxicosis refers to the state of thyroid hormone excess arising from either overproduction from the thyroid gland (termed hyperthyroidism) or extrathyroidal, including exogenous, sources. Of the etiologies attributable to hyperthyroidism, the most common cause worldwide is Graves' disease, resulting from the autoimmune

TABLE 2
Management of Myxedema Coma

Thyroid hormone replacement
Levothyroxine (T4)
Loading dose of 200-400 μg IV once
Maintenance dose of 1.6 μg/kg/d IV/PO
Liothyronine (T3)
Loading dose of 5-20 μg IV/NG once
Maintenance dose of 2.5-10 every 8 hours IV/PO
Supportive measures
IV fluids containing electrolytes and glucose
Passive rewarming with a blanket
Treatment of any underlying comorbidities, including infection
Glucocorticoids
Hydrocortisone 100 mg IV every 8 hours if adrenal insufficiency is suspected

Abbreviations: IV, intravenous; NG, nasogastric; PO, per oral.

stimulation of the thyroid by serum thyroid-stimulating immunoglobulin, followed by toxic multinodular goiter and toxic adenoma. In the United States, the prevalence of hyperthyroidism from all causes is approximately 1.2%, of which 0.5% is overt and 0.7% is subclinical.[22] Other causes of thyrotoxicosis include overproduction of TSH from a pituitary adenoma, thyroiditis, exogenous thyroid hormone ingestion, ectopic hyperthyroidism (such as from struma ovarii or metastatic thyroid cancer), or human chorionic gonadotropin-mediated hyperthyroidism (such as from hyperemesis gravidarum or a molar pregnancy).

The signs and symptoms of thyrotoxicosis are reflective of the excess concentrations of thyroid hormone present (Table 3) and can include anxiety, fatigue, diaphoresis, heat intolerance, tremors, palpitations, tachycardia, weight loss, hyperreflexia, and warm and moist skin. In women, menstrual abnormalities may be seen. In patients in whom the thyrotoxicosis is due to Graves' disease, specific clinical manifestations may also include thyroid eye disease (ie, exophthalmos, lid lag), a diffuse goiter with a bruit, localized dermopathy, thyroid acropachy (ie, digital clubbing and swelling), and the coexistence of other autoimmune diseases in the patient or the patient's family.

TABLE 3
Signs and Symptoms of Thyrotoxicosis

General
Fatigue
Weight loss
Insomnia
Heat intolerance
Eyes
Exophthalmos, lid lag, or periorbital/conjunctival edema, if thyrotoxicosis is due to Graves' disease
Skin and hair
Warm, moist skin
Thin, fine hair
Brittle nails
Diaphoresis
Thyroid acropachy if due to Graves' disease
Localized dermopathy, if due to Graves' disease
Cardiovascular system
Tachycardia
Palpitations
Atrial arrhythmias
Systolic hypertension
Hyperdynamic precordium
Respiratory system
Shortness of breath
Gastrointestinal system
Loose stools or hyperdefecation
Increased appetite
Reproductive system
Menstrual cycle irregularities
Infertility
Musculoskeletal system
Muscle weakness, especially of proximal muscles
Neurological system
Nervousness
Anxiety
Tremor
Hyperactivity
Hyperreflexia

Thyroid Storm

Thyroid storm is the clinical manifestation of elevated serum thyroid hormone concentrations, resulting in the extreme alteration of usual hyperthyroid symptoms. The diagnosis can occur in patients with or without preexisting hyperthyroidism. It is a rare diagnosis and usually triggered by precipitants such as trauma, myocardial infarction, surgery (including thyroid surgery for hyperthyroidism or other surgeries in general), or infection. In some cases, acute exposure to excess iodine (ie, administration of iodinated contrast radiographic scan) may result in iodine-induced hyperthyroidism to trigger thyroid storm.[23] Patients with known severe hyperthyroidism who are noncompliant with prescribed antithyroid medications may also develop thyroid storm.

Prompt recognition of thyroid storm is essential to initiate treatment, which should be performed in an ICU setting. Clinical manifestations of thyroid storm can be quite varied and may include fever, cardiac arrhythmias, vomiting, and impaired mental status. Patients with thyroid storm have increased inpatient mortality rate, overall hospital and ICU length of stay, and ventilation requirements compared with those with compensated thyrotoxicosis.[24] The mortality rate of thyroid storm ranges from 10% to 20%.[25,26]

Diagnosis of thyroid storm is made using a combination of biochemical laboratory tests confirming thyrotoxicosis in a patient displaying the severe, life-threatening symptoms of hyperthyroidism. Several diagnostic scoring systems have been proposed that can be used to assess the likelihood of thyroid storm in patients. The Burch-Wartofsky scoring system is based

on factors related to temperature, central nervous system effects, gastrointestinal/hepatic dysfunction, cardiovascular dysfunction, heart failure, and any precipitant history.[27] The Akamizu criteria are similar and have also been proposed as another diagnostic scoring system in the assessment of thyroid storm.[28]

Treatment usually consists of multiple measures and medications aimed to target the various causes and effects of thyrotoxicosis, as summarized in Table 4.[19,22] Symptomatic improvement of tachycardia and clinical manifestations reflecting the increased adrenergic tone can be achieved with beta-blocker therapy. Methimazole or propylthiouracil should be initiated to decrease production of thyroid hormone. Saturated solution of potassium iodide can be used to inhibit thyroid hormone release from the thyroid gland. Glucocorticoids decrease the conversion of T4 to T3, which can also be accomplished by the use of propylthiouracil.[29] Supportive measures include IV fluids, oxygen, cooling, and treatment of any precipitating causes. Finally, if necessary when the above treatments cannot be used or are unsuccessful, plasmapheresis can be attempted to decrease thyroid hormone excess, as well as cytokines and putative antibodies, in the circulation.[30]

TABLE 4
Management of Thyroid Storm

Antithyroidal drugs
Propylthiouracil
Loading dose of 600 mg PO/NG/PR once
Maintenance dose of 200-300 mg every 6 hours PO/NG/PR
Methimazole
Loading dose of 20 mg PO every 6 hours
Saturated solution of potassium iodide
5 drops PO every 6 hours; must be started after antithyroid drug therapy is initiated to avoid potential worsening of hyperthyroidism
Glucocorticoids
Hydrocortisone 100 mg IV every 8 hours
Beta-blocker therapy
Propranolol 40-80 mg PO every 4 hours or 2 mg IV every 4 hours
Supportive measures
IV fluids
Oxygen
Cooling
Treatment of any precipitating causes

Abbreviations: IV, intravenous; NG, nasogastric; PO, per oral; PR, per rectum.

CONCLUSION

Hypothyroidism and thyrotoxicosis are common endocrine disorders, each with a variety of etiologies, and most patients with thyroid dysfunction are easily managed. However, in certain patients, severe, life-threatening forms of these states, representing rare thyroid emergencies, can develop on exposure to precipitating triggers or among patients with preexisting thyroid dysfunction or noncompliance with medical treatment. Both myxedema coma, corresponding to extremely low serum thyroid hormone concentrations, and thyroid storm, corresponding to extremely elevated thyroid hormone concentrations, are associated with increased mortality and must be recognized promptly. Treatment of myxedema coma and thyroid storm is multifaceted and should be managed by the interdisciplinary team of an ICU setting.

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