

Thyroid Emergencies

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Abstract

Thyroid storm and myxoedema coma is both uncommon but life threatening disorders. Early recognition and aggressive multifaceted treatment has changed mortality figures in these patients from 90% to 10-20%. More commonly encountered entity in intensive care unit is the "sick euthyroid syndrome"¹ where thyroid function tests give aberrant results in presence of any intercurrent medical or surgical illness without obvious thyroid disorder. In following section thyroid storm and myxoedema coma are reviewed. (The Ind. Pract. 1998; 51(11): 902-909)

Thyroid Storm

Introduction

The clinical spectrum of thyrotoxicosis ranges in severity from asymptomatic biochemical abnormalities to cataclysmic metabolic crisis with multisystem dysfunction. Thyroid storm is relatively rare, accounting for approximately 1.2% of hospital admissions for thyrotoxicosis. It is characterized by exaggerated manifestations of thyrotoxicosis. Thyroid storm or crisis is precipitated when the aggregate effect of parameters such as intercurrent illness, or cardiovascular disease surpasses the individual ability to maintain adequate metabolic, thermoregulatory and cardiovascular compensatory mechanisms. Despite the absence of uniform criteria for defining the point at which severe thyrotoxicosis becomes storm, certain clinical features, such as advanced fever, mental status aberration and evidence of multisystem involvement are harbingers of storm. Mortality rates of hospitalized patients have ranged from 20-30%².

Clinical Presentation

The clinical features of uncomplicated thyrotoxicosis are generally present and often accentuated in thyroid storm. Although usually present a key clinical feature is the presence of a precipitating event of intercurrent illness. Thyroid surgery, once the most common precipitant of storm, has now become relatively uncommon. Table one enumerates known precipitant of thyroid storm.

Typical presentation includes the presence of a goiter and in the presence of Graves disease, concurrent ophthalmopathy. The heat intolerance and diaphoresis common in simple thyrotoxicosis manifest as severe hyperpyrexia with temperatures occasionally in excess of 106°F. There is accelerated tachycardia, often more than 140/min and a high propensity for atrial dysrhythmia as well as ventricular dysfunction a congestive cardiac failure.

Although the latter are more likely to occur in elderly patients, cardiac decompensation is also seen in young³ or middle aged patients with no antecedent heart disease. Gastrointestinal manifestation includes diffuse abdominal pain, hepatosplenomegaly and various abnormalities in liver function tests. Presence of liver tenderness and jaundice are poor⁴ prognostic signs. Severe agitation, delirium or frank psychosis progressing to stupor and coma are often seen in storm. In its atypical presentation, the thyroid storm is often masked⁴ as first described, by Lahey, in the older patient population, without prominent goitre or exophthalmos, with a low pulse rate and a tendency to lapse comfortably, leisurely into semistupor and death.

**Table 1
Known Precipitant of Thyroid Storm**

I. Conditions associated with a rapid rise in thyroid hormone levels

Thyroid surgery, withdrawal of antithyroid drug therapy, radioiodine therapy vigorous thyroid palpation

II. Conditions associated with acute or subacute nonthyroidal illness

Nonthyroidal surgery, infection, cerebrovascular accident, parturition, diabetic ketoacidosis, emotional stress and trauma.

Pathophysiology

No clear distinction can be made between uncomplicated thyrotoxicosis and storm on the basis of absolute levels of circulating thyroid hormones. Recent studies have shown however significant elevation in the free⁵ thyroid hormone levels, in-patients with thyroid storm, despite similar levels of total T₄ as compared to patients with simple thyrotoxicosis. There may be a transient thyroxine binding globulin deficiency at the inception of storm, which reverses with recovery.

Adrenergic system activation plays an important contributory role in the pathogenesis. Many of the clinical features are directly attributable to direct catecholamine action or an interaction between adrenergic system and excess thyroid hormones.

Mechanism of thyroid storm remains largely incompletely understood. Factors including poor nutrition and emotional stress on the hormone binding as well as metabolic clearance are important contributors. It is net effect of multiple such influences, superimposed on a susceptible patient substrate that results in this metabolic crisis.

Diagnostic Criteria

In a given patient the net effect of multiple contributing aberrances and unique predisposition will culminate in thyroid storm; therefore a diagnostic point scale⁴ for the purpose of enabling a semiquantitative distinction between uncomplicated thyrotoxicosis, impending thyroid storm, and established thyrotoxic storm has been laid down. Here, temperature dysregulation; CNS status; gastrointestinal and hepatic dysfunction; cardiovascular dysfunction and CC; and precipitating cause each are score. A score of 45 or greater is highly suggestive of thyroid storm, a score of 25-44 is suggestive of impending storm and a score below 125 is unlikely to represent thyroid storm.

Investigations

Values of serum total thyroxine (T₄) and triiodothyronin (T₃), T₃ resin uptake and 24 hrs radio active iodine uptake (RAIU) are elevated above the normal range, but may⁹ not be particularly different from values in uncomplicated thyrotoxicosis. In patients with concurrent systemic illness, decreased serum T₃ may obscure the diagnosis of toxicosis, mild to moderate hyperglycemia in the absence of diabetes mellitus may be present. Leucocytosis with a mild shift to the left, in the absence of infection, with other haematologic values being normal is often present.

Hypercalcaemia as a result of haemoconcentration and bone resorption caused by excess thyroxine may be present. Liver dysfunction is associated with elevated enzymes and bilirubin. Even in the absence of adrenal insufficiency adrenal reserve may be exceeded in crisis.

Treatment

The therapy of thyroid storm may be considered in terms of four components i.e. therapy directed against the gland, antagonism of peripheral action of thyroid hormone, reversal or

prevention of systemic decompensation, therapy against precipitating event and finally, definitive therapy.

Therapy Directed Against The Gland

A near complete blockade of new hormone synthesis is established early with the use of antithyroid drugs such as propylthiouracil (PTU) or methimazole (MMI). These are not available as parenteral preparations and therefore have to be given orally or per nasogastric tube in stuporous, comatose or otherwise unco-operative patient. Rectal administration with adequate absorption has also been used. Following a loading dose of 600-1000 mg, PTU is given as 200-250 mg every four hourly daily. MMI is given as 20mg every four hourly following loading dose of 80-120 mg. Initial blockade of iodine organification is established within an hour. PTU has the added advantage of inhibiting peripheral conversion of T4 to T3. A history of minor adverse reaction such as urticaria or rash is not significant to abandon this therapy, though a previous history of agranulocytosis is a definite contraindication⁷.

Inorganic iodine directly inhibits colloid proteolysis and release of T3 and T4 as well as inhibits new hormone synthesis transiently. Recommended oral doses range from 0.2-2 mg / day, given as either Lugol's solution, 8 drops every six hourly, or saturated solution of potassium iodide (SSKI) 5 drops every 6 hrly. Parenteral administration by slow infusion of sodium iodide, 0.5-1 gm every 12 hours has also been used, oral use however is found to be more efficacious. It is essential that iodine therapy should not be administered until an effective blockade of new hormone synthesis has been established with antithyroid drugs (approximately one hour)⁸ as iodine will further fortify the thyroid hormone stores, thus increasing the risk of exacerbation of the toxic state. In those with a history of iodine induced anaphylaxis, lithium carbonate 300mg six hourly may be used. Beside limited experience with this agent in thyroid storm, significant renal and neurologic toxicity impairs its clinical utility.

Another agent now widely used is the radiographic contrast dye ipodate. By the virtue of its large iodine content (300mg / 500mg cap) it has effect on release of thyroxine similar to inorganic iodine. It is given as 1-3 gm daily, only after hormonal synthesis is blocked by PTU / MMI.

Treatment Directed against the Peripheral Effects of Thyroid Hormone

This category includes treatment given to antagonize the adrenergic symptoms of hyperthyroidism. Of the adrenergic receptor blockers, propranolol is the most frequently used. In addition to antiadrenergic effect, these agents have the added benefit of modest inhibition of peripheral conversion of T4 to T3. The dose of propranolol in crisis is 60-80mg every four hourly. Plasma levels in the excess of 50ng/ml may be necessary to maintain adequate block. For rapid effect, intravenous propranolol may be given initially in the dose of 0.5-1 mg with continuous cardiac monitoring, subsequent intravenous doses as high as 2-3 mg may be given over 15 minutes, to be repeated every few hours if required. Recently an ultra short acting blocker, esmolol⁹ has been used successfully as a loading dose of 250-500 mcg/kg followed by a continuous infusion of 50-100 mcg/kg/min. Alternative therapy with reserpine¹⁰ 2.5-5 mg IM every four hours or guanethedine 30-40 mg PO every six hours may be used effectively. Reserpine is found to be useful in cases, refractory to propranolol. Glucocorticoids are administered in-patients with storm, in an attempt to treat the accelerated turn over and decreased effectiveness of corticosteroids. In addition, glucocorticoids such as dexamethasone and hydrocortisone have inhibitory effect on peripheral T4 to T3 conversion. Use of these agents has led to improved survival of these patients. Hydrocortisone is given IV initially as dose of 300 mg, followed by 100 mg every 8 hours. The dose is subsequently tapered and discontinued when patient's condition settles down.

Removal of circulating hormone in storm has been done with plasmapheresis,¹¹ with clinical

improvement. It is generally reserved for patients who deteriorate despite therapy for crisis.

Measures Directed Against Systemic Decompensation

These include measures for treatment of hyperthermia, dehydration, congestive cardiac failure, dysrhythmia and prevention of concomitant adrenal failure. Acetaminophen is given as antipyretic therapy and cooling techniques such as alcohol washes, ice packs, and cooling blankets are used to enhance the patient's ability to dissipate thermal energy. Salicylates² are specifically avoided owing to their ability to displace thyroid hormone from its binding sites.

Fluid requirements of 3-5 L/d are not uncommon in thyroid storm. Depletion of hepatic glycogen stores occurs readily during the storm. Hence, IV fluids containing 5% - 10% dextrose in addition to required electrolytes should be used. Vitamin supplementation, particularly, thiamine, should be added to replace any co-existing deficiency. Congestive cardiac failure occurs largely as a result of impaired myocardial contractility and is aggravated by atrial dysrhythmia. Hence larger dose of digoxin may be required.

Measures Directed Against Precipitating Events

Though events precipitating the storm may be quite obvious this is frequently not the case. This is especially true in case of an infection. A careful culture of blood, urine and sputum is therefore required in a febrile individual. In those cases where the cause is apparent standard therapeutic measures apply and should be instituted simultaneously with the treatment of storm.

Definitive Therapy

As the patient improves clinically, gradual withdrawal of drugs is usually possible. Steroids should be rapidly tapered and discontinued. Antithyroid drugs should be continued till such time that the patient becomes euthyroid and there after continued on maintenance dose for a period of 12-24 months, in case drug therapy is contemplated. Due to the use of a large dose of iodine, radioactive iodine (RAI) as means of ablative therapy is not immediately possible. In case surgery or RAI therapy is chosen as a definitive mode of therapy, it should be done following continued medical therapy, with antithyroid drugs till glandular stores of thyroid hormone is depleted and the patient is bio-chemically proven to be euthyroid.

Conclusion

Although important studies in the recognition and therapy have significantly reduced the mortality from nearly 100%, survival is by no means guaranteed. Recent studies have yielded fatality rates between 20-50%. An unwavering commitment to an aggressive multifaceted therapeutic intervention is critical for a satisfactory outcome.

Myxoedema Coma

Introduction

Myxoedema coma is the term describing a rare, life-threatening clinical state associated with longstanding untreated hypothyroidism in which a variety of precipitating illnesses or events intervene to produce dysfunctional cardiovascular and central nervous systems (CNS) which, if not rapidly recognized and reversed, may lead to a fatal outcome.

The principal cause of this decompensation relates to the inability of the hypothyroid patient to adapt effectively to functional or actual losses in blood volume or impairments in the CNS function.

Pathophysiology

In severe hypothyroidism there is depression of hypoxic and hypercapnic ventilatory drive leading to alveolar hypoventilation and carbondioxide retention. Respiratory failure is compounded by inefficiency of respiratory muscles that are laden with myxoedematous material.

Pneumonia, which often accompanies myxoedema coma, worsens hypoxia, by causing ventilation perfusion mismatches.

Lack of thyroid hormone influence contractile properties of the myocardium, which is reduced. The problem is compounded by diastolic hypertension and pericardial effusion, which is usually present in severe hypothyroidism.

Impaired free water clearance results from syndrome of inappropriate secretion of anti-diuretic hormone and diminished renal flow, leading to development of hyponatraemia. Low sodium can further contribute to impaired sensorium.

Clinical Presentation

Myxoedema coma is usually seen in elderly women in winter. There is almost always a history of long standing hypothyroidism, which may be secondary to autoimmune thyroiditis, postablative Grave's disease, high dose neck irradiation for neoplasia, hypopituitarism, or antithyroid medications. In such patients a precipitating factor can usually be identified. The broad categories of precipitating events are shown in Table 2. Patients are pale and have a characteristic oedematous facies with notable periorbital oedema. There may be macroglossia. The skin is dry and cold to touch. Hypothermia is usual, but not invariably present, and is accompanied by subnormal temperature; values as low as 23.3°C have been recorded. Because the ordinary clinical thermometer is graduated only to 32.4 - 34.5°C, true depth of hypothermia may not be appreciated. Other classic features are bradycardia, distant heart sounds, and delayed relaxation of the deep tendon reflexes. Body hair, including axillary and pubic hair, may be sparse and does not necessarily indicate hypopituitarism. The neck may show a scar from a prior thyroidectomy. The extremities have non-pitting oedema. Family members often notice that there has been a progressive decline of intellectual status, apathy, neglect, emotional liability, confusion, or true psychosis. Coma may not be present, but mental acuteness is always depressed.

Table 2 Common precipitating events for myxoedema coma	
infection	stroke
hypothermia	hypoglycemia
CO2 narcosis	trauma
diuretics	sedatives

Laboratory Testing

The diagnosis is straight forward when the T4 is low and the TSH is strikingly elevated. A finding of a low T4 and a normal or low TSH presents a diagnostic dilemma because the patient could have secondary hypothyroidism or, more likely, the low T4/ low T3 syndrome (sick euthyroid syndrome,). The presence of typical physical findings of hypothyroidism described previously is sufficient¹² evidence to diagnose myxoedema coma despite a low TSH.

Ancillary laboratory testing that supports the presence of hypothyroidism is as follows:

- A high creatinine phosphokinase (CPK) level, which may be as high as 500 U/L and may exceed 1000 U/L. The predominate CPK isoenzyme is the MM fraction, which comes from skeletal muscle.
- Serum cholesterol is often elevated.
- Several haematological abnormalities occur. The decrease in RBC mass is seen as

normochromic normocytic anaemia. Less commonly it may be macrocytic due to pernicious anaemia.

- The increase in total body water results in hyponatraemia³, which normalizes with thyroid hormone replacement.
- Uncommonly patients with myxoedema coma develop hypoglycemia. The exact mechanism is not known, but may be because of increased insulin sensitivity⁴ and appetite that is characteristically poor.
- ECG changes include sinus bradycardia, prolonged PR interval low amplitude of P wave QRS complex, alteration of ST segment and flat or inverted T wave.

Treatment

The key to the successful management of myxoedema coma is its early recognition and rapid institution of appropriate therapeutic measures. Once the diagnosis is entertained seriously, there should be no hesitation in initiating the therapeutic measures immediately even in the absence of supportive laboratory data. The overall goal is to resuscitate and stabilize the patient's condition in the first 24 to 48 hours which is the time required for thyroid hormone therapy to begin reversing the underlying impaired metabolic state of hypothyroidism. As the disease is uncommon systematic evaluation of possible treatment strategies has been difficult.

Thyroid Hormone Replacement

There is universal agreement that all the patients with myxoedema coma should receive parenteral form of thyroid hormone therapy. The principle is to replace the thyroid hormone deficit quickly and to saturate the large binding capacity on thyroxine binding proteins in order to provide an effective circulating level of free T₄. Oral reabsorption of thyroxine is poor and unpredictable, varying from 50-80%.

The concern about enhancing cardiac workload with thyroxine therapy in an individual with diminished cardiac reserve is overridden by life threatening state of myxoedema coma.

Single injection of 500 mcg L-T₄ is administered IV followed by 100 mcg every 24 hours, which is changed to oral preparation as soon as patient's condition improves. T₄ in loading doses has predictable onset of action and avoids adverse cardiac effects that might be produced by loading doses of T₃. Because of impaired conversion of T₄ to T₃ in sick euthyroid patients, some recommend IV T₃ rather than T₄. The loading dose of T₃ is 10-25 mcg⁸ IV and same dose is repeated every 8 or 12 hours if indicated.

Alternatively T₃ can be given orally as it is well absorbed¹² even in severely hypothyroid state. The dose is 25 mcg every 8 hours by nasogastric tube on day one, followed by 12.5 mg every 8 hours till patient regains consciousness and can take oral T₄.

A treatment schedule combining T₄ and T₃ is also advocated. It has been suggested that 200-300 mcg of T₄ should be given simultaneously with 25 mcg of T₃, both IV. The T₃ dose is repeated 12 hours later followed by 100 mcg of T₄ at 24 hours. A 50 mcg daily dose of T₄ is begun on the third day and continued until the patient regains consciousness. T₄ being firmly protein bound replaced the pool deficit early, and serves as reservoir of T₃.

There is little justification in using T₃ alone as therapy as it has rapid clearance and it

cannot replete body pool thyroid hormone. There is no strong basis for advocating any of the three methods of thyroid hormone replacement. However, most experts recommend IV T4 alone as therapy.

Specific Management Issues

Infection And Antibiotic Therapy

Bacterial infection probably constitutes the most common precipitating event and should be assumed to be present in all cases. As total white cell count rarely exceeds 10,000 cells, even in seriously infected hypothyroid patients, considerable emphasis must be placed on the differential count in which the presence of any band forms should be interpreted as the presence of a bacterial infection. In all such patients broad spectrum IV antibiotic coverage should be given until culture results are reported. If results are negative and there are no other signs of infection, the therapy can be stopped.

Respiratory Assistance

These patients often require respiratory assistance because of a tendency to retain CO₂ and hypoxia. Endotracheal intubation and mechanical respiratory assistance should be instituted promptly at the first sign of respiratory failure. As CO₂ retention or hypoxia may lead rapidly to cardiovascular collapse. Despite intubation and respiratory assistance, however, many of these patients continue to display hypoxaemia, which presumably results from arteriovenous shunting, through unaerated portions of the lung. This hypoxia may be worsened if concurrent anaemia is present. For this reason transfusion of packed red cells should be given if the haematocrit level is below 30%.

Cardiovascular Assistance

The development of any degree hypotension should be considered as an ominous sign of an irreversible phase of illness. Even a normotensive state should be considered with some alarm, because mild to moderate hypertension is expected with uncomplicated long-standing hypothyroidism. Therefore, a reduction in blood pressure in hypothyroidism must be assumed to result from bleeding or a functional loss of blood volume. Any reduction in blood volume is tolerated poorly because of the pre existing hypovolaemia. Common causes of volume loss include silent gastrointestinal bleeding, pooling of blood secondary to sepsis, reduction in blood volume secondary to overuse of diuretics and a silent myocardial infarction. The placement of a Swan-Ganz catheter to monitor pulmonary capillary-wedge pressure is critical in distinguishing whether the lack of cardiac performance is due to intrinsic myocardial disease or secondary to diminished cardiac return. If congestive heart failure is present, the patient should be digitalized, but the maintenance dose should be reduced because of diminished digoxin clearance. The use of diuretics and afterload reducing agents should be done with caution. Vasoactive drugs, such as dopamine 4, should be avoided, because they are not effective in maintaining perfusion to vital organs and at the same time may provoke ventricular arrhythmias.

Other Supportive Measures

Hypothermia

General, no specific therapy is required other than preventing further heat loss by use of passive rewarming techniques, such as blankets or increasing the ambient room temperature. Gradual internal warming generated by the patient's own metabolism

allows vascular expansion. External warming on the other hand should be avoided because it can cause peripheral vasodilatation and precipitate cardiovascular collapse.

Steroid administration

Virtually all experts recommend giving large doses of glucocorticoids (hydrocortisone 100 mg every 8 hourly). This is to prevent the precipitation of adrenal crisis in-patients with coexisting adrenal insufficiency. A blood sample for cortisol should be drawn before initiating the therapy. If low, the case of hypocortisolaemia requires evaluation.

Hyponatraemia

In most instances the hyponatraemia is mild to moderate and can be managed by fluid restriction to 1000 ml / day. This gets corrected once thyroid hormone replacement is started. Severe hyponatraemia may occur and may be responsible for mental status changes. Such patients require cautious administration of normal saline or hypertonic saline (3% NaCl).

Treatment of Precipitating factors

Infection is present in about 35% of patients. The most modest suspicion of infection requires the addition of broad spectrum antibiotics. Sedatives and tranquilizers should be avoided. Cold causes coma in a simple case of hypothyroidism.

Course Of Therapy

Body temperature usually starts to increase by 24 hours, low body temperature of less than 93°F that does not respond in 2-3 days are associated with poor prognosis. Vital signs usually show some improvement within 12 hours.

Factors Associated With Poor Prognosis

Advanced age, body temperatures less than 93°F, hypothermia less than 44 beats/min, sepsis, myocardial infarction and hypotension are poor predictor of survival.

Patient Education

It is important to begin patient education in the early convalescent phase, emphasising the life long nature of illness and need to take regular treatment.

Conclusion

Myxoedema Coma is the most severe expression of hypothyroidism. Recognition is hampered by its insidious onset and its rarity. The syndrome is often or never entertained as a diagnosis. The key to therapeutic success includes a high level of suspicion, early recognition of the syndrome, rapid institution of therapy and employment of supportive care. With adequate treatment the mortality rates have decreased from 60-70% in the past to 15-20%. Keeping these factors in mind, the successful treatment of myxoedema coma is one of the most gratifying events experienced by the physician.

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