Review

Thyroid Emergencies

LNR Bondugulapati[1], MA Adlan[1], LDKE Premawardhana[1,2]
[1]Section of Endocrinology, Department of Medicine, Caerphilly Miners' Hospital, UK [2]University Hospital of Wales, Heath Park, Cardiff, UK

Abstract
Thyroid emergencies though rare, are associated with a high mortality rate. They usually occur in subjects known to have thyroid dysfunction and are precipitated often by recognisable events. A high index of suspicion, early diagnosis and appropriate management in an intensive care setting may help reduce mortality and morbidity. We describe the diagnosis, investigation and managment of thyrotoxic crisis and myxoedema coma in detail below.

Introduction

Thyroid emergencies are rare and form a small proportion of admissions to critical care units. Urgent appropriate treatment may reduce mortality which usually is high (1). The most severe form of thyrotoxicosis, a thyrotoxic crisis, occurs in about 1-2% of patients hospitalized for this disease and has a mortality as high as 10-75% (2,3). At the other extreme, the most severe form of hypothyroidism, myxoedema coma, accounts for only about 0.1% of all cases of hypothyroidism (4). Recent data suggest its mortality has improved to 15-20%. The falling incidence of both conditions may be related to early diagnosis and treatment following the ready availablility of sensitive diagnositc tests. However, early recognition of thyrotoxic crisis and myxoedema coma depends on a knowledge of their clinical features and the ability to interpret biochemical abnormalities in the critical care setting which these patients are managed in, which may be sometimes confusing.

Critical illness alters biochemical thyroid function in several well recognised patterns in subjects without pre-existing thyroid or hypothalamo-pituitary disease. The most common pattern is one of low serum triiodothyronine (T3) and high reverse T3 (rT3) (5). A low thyroxine (T4) pattern emerges with increasing disease severity (6). Physicians should be alert to thyroid hormone perturbations in this "non thyroid illness syndrome" (NTIS) and drug therapy in patients who are hospitalized with acute unrelated illness - about 10% have abnormally low thyroid stimulating hormone (TSH) values (7).

The hypothalamo-pituitary-thyroid axis and control mechanisms in health

In healthy iodine replete humans, thyroid follicular cells produce T4, which is converted peripherally to bioactive T3 or to the inactive metabolite rT3(8). T3 binds to specific nuclear receptors to modify gene transcription and to induce down stream effects. Thyroid hormones play a very important role in growth, development and cellular metabolism. Thyroid hormone secretion is regulated primarily by TSH which in turn is regulated by thyrotrophin-releasing hormone (TRH). T4 and T3 through a negative feedback loop, act on the pituitary and hypothalamus dampening their secretions of TSH and TRH respectively. Other substances may intervene in this loop at various levels (8). The availability of optimal amounts of thyroid hormone peripherally at target tissue level is determined mainly by enzyme dependent peripheral deiodination of free T4 to free T3 (Deiodinases types 1 and 2 causing outer ring deiodination).

An understanding of these mechanisms is essential for the interpretation of thyroid test results in

Correspondence to: Dr. LNR Bondugulapati, Department of Medicine, Caerphilly Miners' Hospital, St. Martin's Road, Caerphilly, CF83 2WW, UK

critical care settings, in view of the known effects of systemic illness and drugs which some times make thyroid tests difficult to interpret e.g. the NTIS.

The Non thyroid illness syndrome (NTIS)

NTIS describes a constellation of abnormalities in thyroid function that occurs in acute or chronic disorders which are not due to intrinsic thyroid disease. The prevalence of NTIS with its hallmark abnormalities of low T3 and low T4, is high in intensive therapy units (ITU) – 70 and 50% respectively (9). TSH is usually low. However, undetectable TSH is usually a result of intrinsic thyroid disease – thyrotoxicosis. Currently there is no unanimity about the need to treat these patients with thryoid hormone replacement (10).

Thyroid hormone activity in NTIS

Free T3

Peripheral deiodination of T4 gives rise to about 80% of T3. In acute illness, reduced peripheral tissue activity of the deiodinase enzymes reduces T3 levels (tissue clearance remains unaltered) and elevates rT3 levels (due mainly to reduced clearance rates) – this combination is called the "low T3 syndrome". In NTIS free T3 levels are about 10% lower than in healthy individuals and is often proportional to the severity of the illness (11). The low T3 state is compounded by a low tissue uptake of T4. The diminished deiodinase activity is either a primary enzyme defect or a defect of its co-factors NADPH or Glutathione (12).

FreeT4

There is less agreement about the levels of free T4 in NTIS. Study methodology and assay techniques were variable in several studies addressing this question and may have contributed to this uncertainty. Free T4 was elevated in a significant proportion of patients using an equilibrium dialysis method in one study (13). Another study revealed a reduction in free T4 in ITU patients using multiple methods of analysis (14).

TSH

Both basal and stimulated concentrations of TSH are decreased in acute illness. Its diurnal rhythm is altered too. Third generation immunometric assays able to detect very low levels of TSH (0.001 mU/ml) are useful in the diagnosis of primary thyrotoxicosis as TSH in NTIS is usually above 0.05 mU/ml (15). These changes of TSH are due to the development of "central hypothyroidism" in acute illness. About 10% of patients with NTIS have abnormally low TSH values and 3% of patients have TSH level <0.1mU/L (typical TSH ref range 0.3-4.0). The most ill group have the highest incidence of suppressed TSH. On recovery TSH may rise above normal transiently.

Mechanisms causing NTIS

NTIS is the result of disruption of several mechanisms involved in thryoid hormone production and its controlling apparatus. Effects on the hypothalamo-pituitary-thyroid (HPT) axis, thyroid binding proteins in the plasma, thyroid transporters, and thyroid hormone receptors all play a role.

(a) Abnormalities of the HPT axis in NTIS

There appear to be multiple mechanisms causing abnomalities of the HPT axis in NTIS (16). Central to these is a loss of TRH drive, the result of cytokine secretion, hypercortisolaemia, increased glucagon secretion and exogenous drug therapy. TRH gene expression in the paraventricular nucleus is leptin driven, and is reduced in malnutrition and reduced calorie intake accompanying critical illness (17). Recent animal studies have highlighted the importance of tanycytes from the floor of the 3rd ventricle. These cells express increased levels of deiodinase 2 and increase T4 to T3 conversion in sepsis (18). In turn, increased levels of T3 inhibit hypothalamic TRH levels. The cytokines that are implicated in inhibiting TRH do so by their action on pituitary TSH secretion (e.g. IL-6, TNF alpha, Interferon gamma) particulary in sepsis, autoimmune disease and trauma (19).

(b)Plasma thyroid hormone binding globulin (TBG) in NTIS

The widespread availability of assays for free thyroid hormones have somewhat diminished the effects of TBG in the assessment of thyroid function in NTIS in the clinical setting. Although TBG falls in acute illness and produces low total T4 leves in about 50% of ITU patients, the concentrations of free thyroid hormones are largely unaffected by changes in TBG (19).

(c) Thyroid hormone transporters and tissue uptake

There is no convincing evidence in NTIS to suggest down regulation of thyroid hormone transporters which help transport thyroid hormones across cell membranes (20). Other mechanisms may play a part in impairing tissue uptake of thyroid homones in this condition. In vitro studies have implicated non-esterified fatty acids in impairing free T4 transport across hepatocytes in hepatic and renal disease (20).

(d) Thyroid hormone receptors

There is evidence that thyroid hormone receptors are down regulated in acute illness (21).

Hormone replacement in NTIS

There is no consensus about hormone replacement in these low hormone syndromes. The few studies addressing the issue have been of variable design and have examined a variety of parameters and outcomes.

In an early randomised study in a medical ITU, Brent and Hershman (22) found no survival benefit with thyroxine treatment. Neither was there a survival benefit in a group of burns patients given T3 in a separate study (23). A more recent double blind study in patients with renal failure showed no benefit with thyroxine treatment (24). There are further studies using TRH and growth hormone (25) and other trophic hormone combinations with variable results (26). However, studies in cardiac surgery, cardiac transplantation and cardiac failure have indicated that T3 treatment may be of some benefit in improving cardiac function and stability (27). A very recent study in heart failure patients demonstrated an improvement in the hormonal milieu and left ventricular end diastolic volume (28).

Recovery from non thyroid illness syndrome

Thyroid tests usually resolve when patients recover from their acute illness (29). Occassionally there is a transient increase in TSH during recovery in some patients. This is a physiological response restoring to normal hitherto abnormal levels of thyroid hormones.

Conclusion

NTIS is common in ITU patients. Low T3 and TSH are the commonest abnormalities, followed by low T4. The mechanisms involved in NTIS are multiple and include central hypothyroidism, abnormalities in thyroid hormone binding proteins and binding inhibitors, reduced tissue thyroid hormone uptake and down regulation of thyroid hormone receptors. There is no compelling evidence for hormone replacement treatment except in some patients with cardiac disease. Most studies are short term and long term studies are now needed. Recovery from non thyroid illness syndrome is usually complete and could be associated in some patients with a transient rise in TSH.

Thyrotoxic crisis

It is estimated that 1-2% of all thyrotoxic patients admitted to hospital will have a thyrotoxic crisis, the most severe form of thyrotoxicosis. Dysrhythmias, cardiac failure and respiratory failure secondary to respiratory muscle paralysis are recognised causes of death in these patients. The incidence of thyrotoxic crisis has decreased in recent years due to early diagnosis and treatment of thyrotoxicosis. An increased awareness and the ready availability of thyroid tests in primary and secondary care have helped in this regard.

Aetiology

Graves' Disease remains the most common cause of thyrotoxic crisis. However, toxic multinodular goitre and toxic adenoma may also progress to a crisis.

Rarely, TSH secreting pituitary adenomas, subacute thyroiditis (30), struma ovarii and hydatidiform mole (secreting HCG) may also give rise to a crisis (31). Drug induced thyrotoxic crisis has ben reported but is very rare (32).

Clinical features

Thyrotoxic crises are usually precipitated by a recognisable event or illness in a patient known to have thyrotoxicosis (Box 1).

Body temperature is usually high (up to 41° centigrade). In the cardiovascular system, sinus tachycardia, atrial tachydysrhythmias, systolic hypertension, heart failure and cardiogenic shock are well recognised. Neuromuscular features include tremor, thyrotoxic myopathy, rhabdomyolysis, encephalopathy, status epilepticus and even coma. While dyspnoea is common gastrointestinal symptoms like nausea and vomiting, diarrhoea, jaundice and hepatosplenomegaly may also occur. Rarely, patiens with a thyrotoxic crisis may present with an acute abdomen (33).

BOX 1. Events precipitating a thyroid crisis

- Withdrawal of anti-thyroid medication
- Surgery (thyroid/non thyroid)
- I 131 treatment
- Sepsis
- Child birth
- Emotional stress
- Iodinated contrast media
- Burns
- Acute coronary syndrome
- Strokes
- Pulmonary embolism
- Diabetic ketoacidosis
- Vigorous palpation of the gland (rare)

Burch and Wartofsky devised a scoring system which helps to differentiate a thyrotoxic crisis from an impending cirisis or uncomplicated thyrotoxicosis (Box 2) (34).

Box 2. Burch and Wartofsky Scoring system for diagnosing thyroid storm[34]. This scoring system may be used to differentiate between the increasingly more severe forms of thyrotoxicosis.

CUMULATIVE SCORE	DIAGNOSIS
45 or more	Thyroid storm
25-44	Impending storm
<25	Unlikely to be thyroid storm

Table 1. Abnormalities recognised in thryotoxic crisis. Numerous metabolic and biochemical abnormalities have been identified in thyrotoxic crisis

Abnormality	**Mechanism**
Hyperglycaemia in the absence of diabetes mellitus	Catecholamine induced inhibition of insulin release and increased glycogenolysis
Hypercalcaemia	Haemoconcentration and bone resorption
Sinus tachycardia (40%), atrial fibrillation (10-20%)	Adrenergic overdrive
Leukocytosis with a left shift	Stress response +/- infection
Liver enzyme abnormalities	Thyrotoxicosis related
Abnormal serum cortisol	Relative hypoadrenalism

Investigations

The following abnormalities have been recognised in thyrotoxic crisis (Table 1) (35-37).

FT4 and FT3 are increased although they do not correlate with clinical severity. TSH is usually undetectable. Radioactive iodine uptake scanning would reveal increased uptake of radioiodine as early as 1-2 hours if available and performed.

In the intensive care setting, a thyroid sonogram with doppler flow should be considered to assess gland size, vascularity and nodules. Typically, a thyroid gland secreting excessive hormones would be enlarged and have enhanced doppler flow (38). On the other hand, in the setting of iatrogenic hyperthyroidism, subacute thyroiditis and postpartum thyroiditis, the thyroid gland may be small and doppler flow may be decreased (38).

Management

The management of patients with thyrotoxic crisis requires a multidisciplinary approach in a critical care setting. Although ventilatory support is not always needed, intensive monitoring with anticipation and prompt treatment of complications may reduce morbidity and mortality (36). However, mortality remains high in subjects who are elderly and in those with diminished cardiorespiratory reserve.

Table 2. Drugs used to reduce thyroid hormone levels in thyrotoxic crisis[38]. Thyroid hormone production and release may be inhibited and adjunctive therapy used in the management of thyrotoxic crisis.

	Medication	**Dosage**	**Action**	**Use**
Inhibition of thyroid hormone production	Propylthiouracil	200-400 mg, po 6-8h (NG or PR if necessary)	Inhibits new hormone synthesis and decreases T4 to T3 conversion	First line therapy
	Methimazole (or equivalent doses of carbimazole)	20-25mg,PO,6h (NG or PR if necessary)	Inhibits new hormone synthesis	First line therapy
Inhibition of thyroid hormone release	Potassium iodide (SSKI)	5 drops po, 6h	Blocks hormone release	Given 1 hr after thionamide
	Lugol's solution	4-8 drops po, 6-8h	Blocks hormone release	Given 1 hr after thionamide
Adjunctive therapy	Lithium carbonate (close monitoring needed)	300mg, po 8h	Blocks hormone release	When thionamide or iodine therapy contra-indicated
	Potassium perchlorate	1g, po, once daily	Inhibits iodide uptake by thyroid gland	With thionamides in AIT2

(a) Reducing circulating thyroid hormone levels

Thionamides (carbimazole/methimazole and propylthiouracil) inhibit the synthesis of thyroid hormones. In addition propylthiouracil (PTU) also inhibits peripheral conversion of T4 to T3 reducing the concentration of the active hormone in peripheral tissues (Table 2). In those unable to take thionamides Lithium is a suitable option with close monitoring of serum lithium levels. Rarely, excess thyroid hormones may need to be removed from the circulation through peritoneal dialysis, plasma exchange, or haemoperfusion using resin or charcoal (39,40).

(b)Beta-adrenergic blockade

The control of cardiovascular manifestations of a thyrotoxic crisis is a vital part of the management. The effects of thyroid hormones on the heart are mediated partly by genomic (activating transcription of alpha-myosin heavy chain and repressing the transcription of the beta-myosin heavy chain) and partly by non-genomic actions (directly causing disruption of the sodium, potassium and calcium channels). A rapid and dramatic improvement in the heart rate, cardiac work, and cardiac output improves the clinical status substantailly. The following betablockers are useful in a thyrotoxic crisis (Table 3).

Table 3. Beta blockers used in thyrotoxic crisis.

Medication	Dosage	Action	Use
Propranolol	40-80mg po, 4 - 6h (or 0.5 to 1mg i.v increments)	Adrenergic block and reduces T4 to T3 conversion	Control symptoms of adrenergic overdrive
Atenolol	50-200mg po, once a day	Adrenergic blockade	Cardioselective (eg: presence of reactive airways)
Esmolol	50-100 µg/kg/min i.v. infusion	Adrenergic blockade	oral agents unsuitable (eg:comatose patients)

However, haemodynamic deterioration following beta blockers has been reported even in young patients. Hence judicious administration under close monitoring is warranted (41). Cardiac evaluation with echocardiography and pulmonary artery pressure monitoring is recommended in patients with heart failure. Relative contraindications to beta blockade include the presence of moderate-severe heart failure or the history of reactive airways. Selective beta-blockers (beta-1 antagonists) such as atenolol and metoprolol may be used in patients with reactive airway disease.

(c) Anticoagulation

There are conflicting views about the incidence of thromboembolic disease in atrial fibrillation (AF) complicating thyrotoxicosis (42). The standard risk factors for embolic events in AF, including increasing age and underlying heart disease, apply to these patients as well. The current recommendations are to apply these criteria in decisions about anticoagulation (43). Thyrotoxic patients may require a lower maintainance dose of warfarin because of the increased clearance of vitamin K dependant clotting factors (44).

(d) Fluid and supportive therapy

Fluid losses caused by reduced oral intake, increased sweating, fever, vomiting and diarrhoea should be vigorously treated, with central venous or arterial monitoring. Intravenous fluids containing isotonic saline with 5-10% dextrose will better restore depleted hepatic glycogen (45).

For fever, acetaminophen is preferred to salicylate as salicylates inhibit thyroid protein binding and increase free hormone levels. External cooling measures such as alcohol sponging, ice packs or a cooling blanket may also be used. Multivitamins, particularly thiamine supplementation is necessary to prevent Wernicke's encephalopathy which could result from administering glucose rich fluids in the presence of thiamine deficiency.

(e) The role of glucocorticoids

The role of glucocorticoid therapy in thyrotoxic crisis has been contentious but is almost universally accepted. Glucocrticoids have a dual role in this situation. They inhibit peripheral conversion of T4 to T3 and will potentially reduce active homone levels. Furthermore, they will also correct possible adrenal insufficiency which may be present in patients who have a thyroid crisis on the basis of uncontrolled Graves' disease. Hydrocortisone should be given at a dose of 100mg every 8 hours (46).

(f) The precipitating condition

A precipitating cause should be actively sought and treated. Thorough screening for infection (urine, blood and sputum cultures, chest X ray) should be done in a febrile thyrotoxic patient and cultures of other sites may be considered depending on the clinical context. Broad spectrum antibiotics should be initiated on an empirical basis whilst awaiting culture results. If the precipitating cause is obvious (surgery, trauma, labour) no additional investigations are needed. In cases of thyrotoxic storm precipitated by diabetic ketoacidosis, myocardial infarction, pulmonary embolism or stroke, appropriate management should be initiated.

(g) Definitive treatment of thyrotoxicosis and prognosis

Patients who survive the crisis, improve clinically in the first 24 hours (47). They should be monitored closely with plans for definitive therapy to prevent a recurrence. If iodine has been used to treat the thyrotoxic crisis (in any form), radioactive iodine ablation may need to be postponed for a few weeks to months. Surgery is therefore preferred by many clinicians after complete biochemical remission.

Myxoedema coma

Myxoedema coma can be precipitated in patients with treated or untreated hypothyroidism and has a mortality of 15-20% currently. The crisis occurs most commonly in elderly women. Common precipitating events are shown in box 3.

Box 3. Myxoedema coma may be precipitated by drugs, physical disease and metabolic abnormalities.

Infection/ sepsis
Hypothermia
Trauma
Surgery
Drugs- Amiodarone, anaesthetic drugs, beta-blockers, lithium, narcotics, phenytoin, rifampicin.
Myocardial infarction
Heart failure
Gastrointestinal bleeding
Acidosis
Hypoglycaemia
Stroke
Hypercapnia

Clinical features

Although myxoedema coma is rare in modern practice, the presence of clinical features of hypothyroidism (e.g. dry, coarse skin, sparse hair, oedema of periorbital tissues/hand/feet, macroglossia, delayed deep tendon reflexes, bradycardia etc.) together with decreased sensorium and hypothermia, makes diagnosis relatively easy. However, atypical presentations may occur.

(a) Hypothermia

Hypothermia results from decreased thermogenesis and occurs in approximately 75% of patients. Mortality is proportional to the degree of hypothermia (48).

(b) Cardiovascular

Bradycardia is common and may accompany hypotension secondary to impaired myocardial contractility. Pericardial effusions may occur but rarely cause tamponade as fluid accumulation is

slow. An acute coronary syndrome must be excluded as a precipitant of the crisis. A resting ECG may show bradycardia, varying degrees of heart block, low voltage complexes, a prolonged QT interval, and non-specific ST-T wave changes. Because of the potential for serious dysrhythmias and profound shock, patients should be admitted to an ITU for close monitoring. The cardiovascular abnormalities are reversible with cautious thyroid hormone replacement, although severe hypotension and shock may supervene before the effects of thyroxine becomes obvious.

(c) Respiratory

Hypercapnia which is often found in these patients is due to a combination of a decreased hypoxic drive and depressed ventilatory response to hypercapnia (50). This is compounded by obesity when present. Partial upper airway obstruction may be seen secondary to swelling of the tongue or laryngeal oedema. Mechanically assisted ventilation may be needed in some patients.

(d) Gastrointestinal

Gastric atony, impaired peristalsis and paralytic ileus are well recognised (51).

(e) Neuropsychiatric manifestations

Mentation is altered to some extent in the majority of patients. Approximately 25% of patients experience seizures prior to coma (48,52).

Investigations

Thyroid function tests reveal low free T4 and free T3 levels. TSH is high in primary and low in secondary and tertiary hypothyroidism.

Other abnormalities include :

- hyponatraemia
- hypoglycaemia (due to hypothyroidism alone or as a result of concurrent adrenal insufficiency)
- abnormal renal function due to multiple causes
- respiratory acidosis and type-2 respiratory failure

Management

Thyroid hormone replacement should not be delayed once the diagnosis is suspected and should be initiated even if confirmatory biochemical results are delayed. Delay in initiating treatment may affect outcome.

(a) Thyroid hormone replacement

The optimum thyroid hormone replacement regime is unclear. The rarity of myxoedema coma and the paucity of clinical trials in this area, have hampered the discussion about the type of hormone, optimum replacement dose, frequency, and route of administration (53). Most authorities recommend T4 as the drug of choice (54). Parenteral admistration is preferred because of the risks of aspiration and uncertain absorption. A loading dose of 100-500 mcg levothyroxine intravenously is recommended as this saturates the binding proteins (55). A maintenance dose of 50-100 mcg daily is given after that until conversion to the bioequivalent oral formulation is possible.

Some experts favour T3 as the drug of choice as it is biologically active and has a quicker onset of action. It also bypasses potentially impaired peripheral deiodination which may occur in severe hypothyroidism. 10-20mcg of T3 should be given intravenously as a bolus dose followed by 10 mcg every 4 hours for the first 24 hours, and 10mcg every 6-8 hours on days 2 and 3. However, close monitoring is essential as high serum T3 concentrations are associated with increased mortality. Some authorities recommend the use of T4 and T3 in combination (56).

The above dosage schedules are guidelines only and individual factors such as the patient's age, weight and co-morbidities should be taken in to account when decisions are made.

(b) Corticosteroids

A random cortisol level should be checked prior to commencing hydrocortisone therapy at a dose of 100mg every 6-8 hours until the patient is stable, as absolute or relative hypoadrenalism may occur concurrently with hypothyroidism (36). Acute hypoadrenalism may also occur

due to accelerated metabolism of cortisol that follows thyroxine therapy.

(c) Supportive therapy

Hypothermia: Passive rewarming should be used because rapid, active rewarming can cause marked peripheral vasodilation and vascular collapse.

Ventilatory support: Mechanical ventilation should be initiated in the presence of type-2 respiratory failure. Frequent monitoring of arterial blood gases will guide subsequent management.

Hypotension: Intravascular fluid depletion should be treated with judicious administration of intravenous fluids under close cardiac monitoring. Vasopressors and inotropes should be used with utmost care because of their potential to cause cardiac ischaemia and malignant arrhythmias.

Hyponatraemia: Thyroid hormone replacement combined if necessary with mild fluid restriction (<1000 ml/day) improves hyonatraemia. Occasionally severe hyponatraemia (sodium <120 mmol/l) may contribute to neurolocial dysfunction, in which case hypertonic saline should be used cautiously with invasive monitoring (57).

As with all critically ill patients, microbial cultures should be taken as necessary and antibiotics initiated. Protection against venous thromboembolism and peptic ulceration should be provided.

There is recent evidence to suggest that patients with pre-existing thyroid failure who default on treatment present with more severe symptoms and have a higher mortality rate than those who develop thyroid failure de novo and present with myxoedema coma. The same study suggested that outcome was not influenced by either the aetiology of thyroid failure or route of administration of thyroxine. But the outcome prediction tool, the Sequential Organ Failure Assessment (SOFA) was useful in predicting outcome (58).

Conclusions

The high mortality associated with thyroid emergencies makes early detection, and appropriate specific and supportive therapy of vital importance. Fortunately they are rare in current practice because of the free availability of cheap and sensitive thyroid hormone assays. In the critical care setting the detection of intrinsic thyroid disease is often difficult because of the changes associated with NTIS. However, it is worth remembering that TSH levels which are undetectable (<0.02mU/L) or significantly elevated (> 20-30 mU/l) are usually due to primary thyroid disease. Thryoid emergencies are usually associated with a precipitating cause which needs to be addressed.

Standard treatment protocols are available for these emergencies but multi organ failure with the need for intensive monitoring and support, and the possible need for venilatory assistance makes the ITU the best place for managing these patients. If standard drug therapy is only partially successful other interventions such as plasmapheresis may need to be used. Investigations may help in diagnosis and management but above all clinical suspicion in the appropriate circumstances and prompt intervention are of vital importance.

Acknowledgements: none

Conflict of interest: none

References

1. Sarlis NJ, Guorgiotis L. Endocrine emergencies. Rev Endocrinol Metab Dis 2003; 4: 129-136.
2. Dillman WH. Thyroid storm. Curr Ther Endocrinol Metab 1997; 6: 81-5.
3. Tietgens ST, Leinung MC. Thyroid storm. Med Clin North Am 1995; 79: 169-84.
4. Schraga E D. Hypothyroidism and Myxoedema Coma, e-medicine, Dec 10, 2009, article 768053. Accessed 15.06.2011
5. Peeters RP, Wouters PJ, Kaptein E et al. Reduced activation and increased

inactivation of thyroid hormone in tissues of critically ill patients. J Clin Endocrinol Metab 2003; 88: 3202.
6. De Groot LJ. Dangerous dogmas in medicine: the nonthyroidal illness syndrome. J Clin Endocrinol Metab 1999; 84: 151-64.
7. Aytug S, Shapiro LE. Euthyroid sick syndrome, e-medicine, April 5, 2010, article 118651.
8. Theo J. Visser. Biosynthesis, transport, metabolism, and actions of thyroid hormones In: John A.H. Wass, Stephen M. Shalet, Edwin Gale, Stephanie A. Amiel (eds), Oxford Textbook of Endocrinology & Diabetes, 1st Edition: 2002; The Thyroid; 287-301.
9. Ray DC, Macduff A, Drummond GB, Wilkinson E, Adams B. Beckett GJ. Endocrine measurements in survivors and non-survivors from critical illness. Intensive Care Med. 2002; 28: 1301-308.
10. Warner M H, Beckett GJ. Mechanisms behind the non thyroid illness syndrome: Update. J Endocrinol. 2010; 205: 1-13.
11. Faber J, Siersbaek NK. Serum free 3,5,3'-triiodothyronine (T3) in non-thyroidal somatic illness, as measured by ultrafiltration and immunoextraction. Clin Chim Acta. 1996; 256: 115-23.
12. Sato T, Maruyama S, Numora K. On the role of NADPH and glutathione in the mechanisms of hepatic thyroxine deiodination. Endocrinol Jpn. 1986; 28: 451-9
13. Fritz KS, Wilcox RB, Nelson JC. Quantifying spurious free T4 results attributable to thyroxine-binding proteins in serum dialysates and ultrafiltrates. Clin Chem. 2007; 53: 985-88.
14. Beckett GJ. Thyroid Function and thyroid function tests in non-thyroidal illness. CPD Bulletin Clinical Biochemistry. 2006; 7: 107-16.
15. De Groot L J. Dngerous Dogma in Medicine: The nonthyroidal illness syndrome. The Journal of Clinical Endocrinology & Metabolism. 1999; 84: 151-64.
16. Fliers E, Alkemade A, Wiersinga WM, Swaab DF. Hypothalamic thyroid hormone feedback in health and disease. Prog Brain Res. 2006; 153: 189-207.
17. Coppola A, Liu ZW, Andrews ZB, Paradis E, Roy MC, Friedman JM, Ricquier D, Richard D, Horvath TL, Gao XB et al. A central thermogenic-like mechanism in feeding regulation: an interplay between arcuate nucleus T3 and UCP2. Cell Metab 2007; 5: 21-33.
18. Lechan RM. The dilemma of the nonthyroidal illness syndrome. Acta Biomed 2008; 79: 165- 71.
19. Boelen A, Kwakkel J, Platvoet-ter Schiphorst M, Baur A, Kohrle J, Wiersinga WM. Contribution of interleukin-12 to the pathogenesis of non-thyroidal illness. Horm Metab Res 2004; 36: 101-106.
20. Hennemann G, Docter R, Friesema EC, de Jong M, Krenning EP, Visser TJ. Plasma membrane transport of thyroid hormones and its role in thyroid hormone metabolism and bioavailability. Endocr Rev 2001; 22: 451-76.
21. Rodriguez-Perez A, Palos-Paz F, Kaptein E, Visser TJ, Dominguez-Gerpe L, Alvarez-Escudero J, Lado-Abeal J. Identification of molecular mechanisms related to nonthyroidal illness syndrome in skeletal muscle and adipose tissue from patients with septic shock. Clin Endocrinol (Oxf). 2008; 68: 821-27.
22. Brent GA, Hershman JM. Thyroxine therapy in patients with severe nonthyroidal illnesses and low serum thyroxine concentration. J Clin Endocrinol Metab. 1986; 63: 1-8.
23. Becker RA, Vaughan GM, Ziegler MG, Seraile LG, Goldfarb IW, Mansour EH, McManus WF, Pruitt BA, Jr., Mason AD, Jr. Hypermetabolic low triiodothyronine syndrome of burn injury. Crit Care Med. 1982; 10: 870-75.
24. Acker C G, Singh AR, Flick RP, Bernardini J, Greenberg A, Johnson JPA. Trial of thyroxine in acute renal failure. Kidney Int 2000; 57: 293-8.
25. Van den Berghe G, Baxter RC, Weekers F, Wouters P, Bowers CY, Iranmanesh,

Veldhuis JD, Bouillon R. The combined administration of GH-releasing peptide-2 (GHRP-2), TRH and GnRH to men with prolonged critical illness evokes superior endocrine and metabolic effects compared to treatment with GHRP-2 alone. Clin Endocrinol (Oxf) 2002; 56: 655-69.

26. Van den Berghe G, Wouters P, Weekers F, Mohan S, Baxter RC, Veldhuis JD, Bowers CY, Bouillon R. Reactivation of pituitary hormone release and metabolic improvement by infusion of growth hormone-releasing peptide and thyrotropin-releasing hormone in patients with protracted critical illness. J Clin Endocrinol Metab 1999; 84: 1311-23.
27. Hamilton MA, Stevenson LW, Fonarow GC, Steimie A,Goldhaber JI, Child JS,Chopra IJ, et.al. Safety and hemodynamic effects of intravenous triodothyronine in advanced congestive cardiac failure. AmJ Cardiol. 1998; 81: 443-7.
28. Pingitore A, Iervasi G. Triiodothyronine (T3) effects on cardiovascular system in patients with heart failure. Recent Pat Cardiovasc Drug Discov. 2008; 3: 19-27.
29. Stockigt JR. Guidelines for diagnosis and monitoring of thyroid disease: nonthyroidal illness. Clin Chem. 1996; 42: 188-92.
30. Swinburne JL. Kreisman SH. A rare case of subacute thyroiditis causing thyroid storm, Thyroid 2007; 17: 73-6
31. Chiniwala NU, Woolf PD, Bruno CP, Kaur S, Spector H, Yacono. Thyroid storm caused by a partial hydatidiform mole. Thyroid. 2008; 18: 479-81.
32. Al-Anazi KA, Inam S, Jeha MT, Judzewitch R. Thyrotoxic crisis induced by cytotoxic chemotherapy. Support Care Cancer. 2005; 13: 196-8.
33. Bhattacharyya A, Wiles PG. Thyrotoxic crisis presenting as acute abdomen. J Roy Soc Med 1997; 90: 681-2.
34. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin North Am 1993; 22: 263-77.
35. Pimental L, Hansen K. Thyroid disease in the emergency department : a clinical and laboratory review. J Emerg Med 2005; 28: 201-9.
36. Sarlis NJ, Gourgiotis L. Thyroid emergencies. Rev Endocr Metab Disord 2003; 4: 129-36.
37. Wartofsky L. Thyrotoxic storm. In: Braverman LE, Utiger RD. Editors. Werner & Ingbar's The Thyroid. 9thedition. Philadelphia: Lippincott, Williams & Wilkins; 2005. p. 652-7.
38. Nayak B, Burman K. Thyrotoxicosis and Thyroid storm. Endocrinol Metab Clin N Am 2006; (35): 663-686.
39. Burman KD, Yeager HC, Briggs WA et al. Resin hemoperfusion: a method of removing circulating thyroid hormones. J Clin Endocrinol Metab 1976; 42: 70-8.
40. Kokuho T, Kuji T, Yasuda G, Umemura S. Thyroid storm-induced multiple organ failure relieved quickly by plasma exchange therapy. Therapeutic Apheresis & Dialysis: 2004; 8: 347-
41. S.Y.A. Ngo, H.C. Chew. When the storm passes unnoticed – A case series of thyroid storm. Resuscitation 2007; 73:485-490.
42. Peterson P, Hansen JM. Stroke in thyrotoxicosis with atrial fibrillation. Stroke 1988; 19: 15-8.
43. Singer DE, Albers GW, Dalen JE. Antithrombotic therapy in atrial fibrillation: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004; 126: 429-56.
44. Fadel BM, Ellahham S, Ringel MDl. Hyperthyroid heart disease. Clin Cardiol 2000; 23: 402-8.
45. McKeown NJ, Tews MC, Gossain V et al. Hyperthyroidism. Emerg Med Clin N Amer 2005; 23: 669-85.
46. Handy J, Thyroid emergencies. In: Andrew D Bersten, Neil Soni (eds), Oh's Intensive Care Manual, 6th Ed: 2009; 637-645.
47. Wartofsky L. Thyrotoxic storm. In: John A.H. Wass, Stephen M. Shalet, Edwin Gale, Stephanie A. Amiel (eds), Oxford Textbook of Endocrinology & Diabetes, 1st Edition: 2002; The thyroid, pp 482-486.

48. Wartofsky L, Myxedema Coma. Endocrinol Metab Clin N Am 2006; 35: 687-698.
49. Schenck JB, Rizvi AA, Lin T. Severe primary hypothyroidism manifesting with torsades de pointes. Am J Med Sci 2006; 331: 154-6.
50. Behnia M, Clay A, Farber M. Management of myxedematous respiratory failure: review of ventilation and weaning principles. Am J Med Sci 2000; 320: 368-73.
51. Wartofsky L. Myxedema coma. In: John A.H. Wass, Stephen M. Shalet, Edwin Gale, Stephanie A. Amiel (eds), Oxford Textbook of Endocrinology & Diabetes, 1st Edition: 2002; The thyroid, pages 514-518.
52. Sanders V. Neurologic manifestations of myxoedema. N Eng J Med 1962; 266: 547-551.
53. Rodriguez I, Fluiters E, Perez-Mendez LF et al. Factors associated with mortality of patients with myxoedema coma; prospective study of 11 cases treated in a single institution. J Endocrinol 2004; 180: 347.
54. Smallridge RC. Metabolic and anatomic thyroid emergencies: a review. Crit Care Med 1992; 20: 276-91.
55. Holvey DN, Goodner CJ, Nicoloff JT, Dowling JT. Treatment of myxedema coma with intravenous thyroxine. Archives of Internal Medicine, 1964; 113: 139-46.
56. Wartofsky L. Myxedema coma. In: Braverman LE, Utiger RD (eds). The Thyroid. Philadelphia: Lippincott-Raven; 1996: 871-7.
57. Pereira VG, Haron ES, Lima-Neto N, Medeiros-Neto GA. Management of myxedema coma: report on three successfully treated cases with nasogastric or intravenous administration of triiodothyronine. J Endocrinol Inv, 1982; 5: 331-4.
58. Dutta P, Bhansali A, Masoodi SR, Bhadada S, Sharma N, Rajput R. Predictors of outcome in myxoedema come; a study from a tertiary centre. Crit Care 2008; 12: R1 (doi: 10.1186/cc6211)