

Thyroid Emergencies part 1: Thyroid Storm

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Abstract

Thyroid storm is associated with multisystem decompensation and high mortality if untreated. Early clinical recognition and aggressive treatment in a high dependency setting are crucial to a successful outcome. A combination of high-dose antithyroid medication, β -blockade, iodine, steroids and careful haemodynamic management are the essential therapeutic elements, with the potential for a prompt recovery. The pathophysiology, causes and treatment of thyroid storm are reviewed.

Keywords

Thyroid, Graves, Thyrotoxicosis, Emergency Management

Key Points

1. Although rare, thyroid storm has a mortality of 20-30% if untreated
2. Patients usually present with disproportionate sinus tachycardia, fever, CNS disturbance, vomiting and diarrhoea
3. Treatment should include antithyroid drugs, beta-blockade, correction of systemic disturbance and consideration of any precipitating cause

Introduction

Thyroid storm (or Thyrotoxic crisis) is an infrequent presentation in the acute medical setting, but its potential mortality (20-30% untreated)¹ demands early clinical recognition and prompt, comprehensive treatment. The incidence of thyroid storm has probably fallen as a result of more widespread thyroid function testing leading to earlier detection and treatment of milder degrees of thyroid dysfunction. However there is overlap between the degree of thyroid hormone elevation seen in uncomplicated thyrotoxicosis and that of thyroid storm, and the precise molecular basis of the more extreme physiological changes in the latter remains largely unknown. As a result there remains debate regarding some aspects of treatment.

Clinical Features

Patients may have had a recent history of typical symptoms of thyrotoxicosis (tremor, sweating, palpitations, anxiety, weight loss etc.), or be undergoing treatment for thyrotoxicosis. Graves'

disease may be evident in young patients from the presence of a diffuse goitre (with bruit) and ophthalmopathy, or a multinodular goitre detectable in older patients. Rarely thyroid storm has been reported in patients with metastatic thyroid cancer.² There is no universal definition of thyroid storm, but certain cardinal features are recognised, principally fever (usually above 38.5°C), disproportionate tachycardia, central nervous system disturbance, and gastrointestinal upset. Sinus tachycardia is usual, but supraventricular arrhythmias may occur, particularly atrial fibrillation. These may occur in young patients in the absence of underlying heart disease. Cardiac failure may supervene, more so in the presence of existing rheumatic or ischaemic heart disease. Cerebral dysfunction may range from apathy and impaired consciousness (even coma) to confusion, agitation and frank psychosis. Case reports cite thyroid storm in association with status epilepticus and stroke.^{3,4} Nausea, vomiting and diarrhoea are common (and easily overlooked as symptoms of thyrotoxicosis), and may result in hypotension. Severe volume depletion may progress to shock with cardiovascular collapse, which is invariably fatal. Other gastrointestinal presentations reported include acute abdomen, intestinal obstruction and diffuse abdominal pain. Liver dysfunction may progress to frank hepatic necrosis, and the presence of jaundice is regarded as a poor prognostic sign.

Causes

The transition to thyroid storm usually follows a precipitating event or treatment, and may be thyroid-related or systemic in origin (Figure 1). Historically, thyroid storm following thyroidectomy was recognised prior to the routine pre-treatment of patients with anti-thyroid drugs. This is now much rarer, but other types of surgery have been associated with thyroid storm in patients with previously undiagnosed thyrotoxicosis,⁵ perhaps via the effects of anaesthesia, stress and volume depletion. An iodine load, either as radiographic contrast medium or radioactive iodine treatment may act as a precipitant, although it has been argued that pre-treatment with antithyroid drugs before radioiodine

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Figure 1. Precipitants of thyroid storm

Thyroid-related
• Withdrawal of antithyroid drugs • Radioactive iodine (¹³¹I) treatment • Iodinated contrast dyes (e.g. CT scan) • Post thyroidectomy • Amiodarone • Vigorous palpation of Graves' goitre.
General
• Sepsis (especially in hospital) • Surgery • Trauma (e.g. burns) • Parturition • Hypoglycaemia • Diabetic ketoacidosis • Pulmonary embolism • Stroke

therapy may not be necessary in most patients.⁶ Amiodarone may cause an iodine-induced thyrotoxicosis and has been reported as a cause of refractory thyroid storm.⁷ In hospitalised patients the most common precipitating event is probably infection, and distinguishing storm from sepsis in a thyrotoxic patient may be difficult. Exaggerated fever and dramatic sweating are said to be pointers to impending thyroid storm in this setting. However if doubt remains it is advisable to begin treatment for storm, with the option of withdrawing should the patient show a prompt response to antibiotics.

Pathophysiology

The essence of thyroid storm appears to be an increase in free thyroid hormone activity, without necessarily an increase in total circulating levels of thyroxine (T4) or triiodothyronine (T3). Several possible mechanisms have been proposed to explain this observation, including:

- Changes in hormone binding – reduced affinity of thyroid hormone for the natural serum binding proteins occurs in surgery and anaesthesia, burns, infection and ketoacidosis. This may be mediated by the presence of circulating inhibitors.⁸
- Rapid increase in thyroid hormone levels – this may be more important than the absolute hormone levels.
- Sympathetic nervous system (SNS) hyperactivity – absolute levels of catecholamines do not appear to be increased in thyroid storm, but thyroid hormones have been shown to modulate adrenergic receptor expression and post-receptor signalling. An important role for the SNS is clear from the dramatic response of patients to α -blockers (or ganglion blockers such as reserpine).
- Enhanced cellular responsiveness – this has been implicated in cases of sepsis, hypoxaemia and hypovolaemia.

Laboratory findings

Elevation of serum T4 and T3 is usually seen, with suppression of TSH. However T3 levels may be within normal limits as a result of underlying illness driving

thyroid function towards the 'euthyroid sick' picture. Thus obtaining a prompt T4 level takes priority, but if there is a high level of clinical suspicion treatment should not be delayed whilst awaiting results. Glucose may be moderately raised (and more markedly in concomitant diabetic ketoacidosis), along with mild hypercalcaemia due to accelerated bone resorption. Electrolytes are usually normal, but derangement of liver function may occur to varying degrees with elevation of bilirubin, aspartate aminotransferase and lactate dehydrogenase. The full blood count may show a leucocytosis even in the absence of infection. The measurement of serum cortisol (prior to giving corticosteroids) is valuable given the association between Graves' and Addison's disease, but must be interpreted in the context of severe metabolic stress. Thus a 'normal' value would be inappropriately low. Even with underlying normal adrenal function cortisol reserve may be exceeded in thyroid storm because of the increased turnover and clearance of glucocorticoids that occurs.

Treatment

The treatment of thyroid storm should be undertaken in a high-dependency or intensive care unit. Expert endocrine advice should be sought as soon as possible. Management should be directed in a four-strand approach to optimise recovery:

- Control of excessive thyroid hormone production,
- Reduction of the peripheral effects of thyroid hormones,
- Correction of systemic disturbances,
- Treatment of the precipitating event (if known).

These are covered in detail below.

1. Control of excessive thyroid hormone production

Conventional antithyroid drugs (thionamides) block new thyroid hormone synthesis, although in this setting Propylthiouracil is said to be the drug of choice. This is because it has the additional property of limiting conversion of T4 to T3 in the periphery (the latter being the principal active hormone at the cellular level). Large doses are required, i.e. 200 to 300mg 6-hourly. The drug is not available parenterally, so must be given orally or via nasogastric (NG) tube (rectal administration has also been used).⁹

Release of pre-formed thyroid hormone from colloid stores may be achieved by giving "cold" stable iodine (the so-called "Wolff-Chaikoff effect"). This is available either as Lugol's iodine solution (e.g. 10 drops three times daily) or as a saturated solution of potassium iodide (60mg 6-hourly). The timing with administration of antithyroid drugs is important – iodine must be given at least 1 hour *afterwards* to avoid stimulating further thyroid hormone synthesis and release. An alternative is to use radiographic contrast media such as sodium ipodate (Oragrafin), which contains high quantities of organically bound iodine and additionally blocks peripheral T4 to T3 conversion and hormone receptor binding. After a loading dose of 3g a daily dose of 1g orally may be given, often with striking clinical improvement.

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In patients allergic to iodine or with a history of serious side effects to thionamides (e.g. agranulocytosis), lithium carbonate provides an alternative means of inhibiting hormone release. Dosing is 300mg 6-hourly, with therapeutic monitoring (aiming for a serum level around 1 mmol/l). Some have cautioned about its use in the setting of thyroid storm.

2. Reduction of the peripheral effects of thyroid hormones

Many of the manifestations of thyroid storm are soon brought under control by administration of β -blockers. Propranolol is the agent of choice having the added benefit of gradually reducing peripheral hormone conversion. Higher than normal doses are required to compensate for increased metabolic clearance, i.e. 80 to 120mg 6-hourly. Oral or NG treatment is preferred, but if not possible (e.g. severe vomiting) then intravenous treatment may be used, with continuous cardiac monitoring. Doses must be given slowly (over 10 minutes), e.g. an initial 0.5-1mg bolus, followed by 1-3 mg every 4 hours. In patients with a history of asthma an infusion of the short-acting β_1 selective antagonist esmolol has been used.¹⁰ Congestive cardiac failure in the setting of thyroid storm need not necessarily be a contraindication to β -blockade as control of the sympathetic drive may improve cardiac performance.

In rare cases, which prove refractory to these measures the use of peritoneal dialysis or plasmapheresis has been undertaken.¹¹ Adjunctive treatment with cholestyramine is also reported,¹² which in high doses serves to reduce the enterohepatic circulation of thyroid hormones.

3. Correction of systemic disturbances

Hyperpyrexia should be controlled with paracetamol, if necessary in combination with cooling blankets and ice packs. Chlorpromazine (50-100mg IM 8-hourly) may be used to control agitation. Volume depletion should be managed aggressively with normal saline, but inclusion of dextrose will also help replace depleted glycogen stores. Congestive cardiac failure can be treated conventionally with furosemide, and digoxin for co-existent atrial fibrillation (AF). The latter may be required in higher

doses than usual because of increased clearance. Furthermore, AF in thyrotoxic patients carries an increased risk of thromboembolism and prompt anticoagulation is recommended in the absence of contraindications (initially with heparin, followed by warfarin should AF persist).

Finally, steroid treatment is advocated to cover the relative adrenal insufficiency that may exist, and the possibility of associated Addison's disease. In addition, high dose glucocorticoids inhibit thyroid hormone release and inhibit tissue conversion of T4 to T3 conversion. Hydrocortisone should be given as a 200mg bolus, followed by 100mg 8-hourly.

4. Treatment of the precipitating event

As discussed above the recognition of infection during thyroid storm may be difficult. If prior history is suggestive then appropriate broad-spectrum antibiotic cover is recommended until a source is confirmed and sensitivities known. Correction of associated hypoglycaemia or ketoacidosis is mandatory.

Recovery and further treatment

Clinical improvement is usually apparent within 12 to 24hrs. Response to treatment should be assessed by frequent free thyroid hormone (T3 and T4) measurements. Restoration to near normal values is possible within 4 or 5 days with a combination of antithyroid drugs and iodine. TSH levels are unhelpful, as suppression will persist for some time even after normalisation of free hormones. Definitive treatment will need to be planned after recovery. The use of iodine in management of storm will preclude therapeutic use of radioactive iodine for up to 2-3 months, as thyroid gland uptake of iodine remains suppressed. Thyroidectomy is an alternative, after the patient has remained euthyroid for several weeks. Persistence of AF after recovery may require ongoing treatment with β -blockade and/or digoxin (with anticoagulation). Referral for DC cardioversion should be considered if sinus rhythm has not returned after a euthyroid period of 6-8 weeks.

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