

THYROID STORM



"Miranda, The Tempest" oil on canvas, 1916, John William Waterhouse

"Our revels now are ended. These our actors,

As I foretold you, were all spirits and

Are melted into air, into thin air:

And, like the baseless fabric of this vision,

The cloud-capp'd towers, the gorgeous palaces,

The solemn temples, the great globe itself,

Yea, all which it inherit, shall dissolve

And, like this insubstantial pageant faded,

Leave not a rack behind. We are such stuff

As dreams are made on, and our little life

Is rounded with a sleep”.

William Shakespeare, The Tempest, c.1610-11.

The early Seventeenth century saw the beginning of the migration of large numbers people from the “Old World” to the “New World”. With navigational knowledge being rudimentary and medical knowledge being virtually non-existent, sailing the high seas in those times was an extremely hazardous undertaking. Many ships full of emigrants would sail to the New World and simply never be heard from again. Ships that did make it across the Atlantic would often do so with their crew and passengers decimated by infectious disease and by scurvy. It is little wonder that the image of the storm at sea invoked such a powerful image in the minds of the people of the time. On 23rd May 1610 the crew and passengers of the “Sea Adventure” sailed into Jamestown to the astonishment of the colonists. The “Sea Adventure” had been lost at sea during a storm the previous year with all hands assumed lost, however survivors had managed to get to the island of Bermuda where they survived for a year eventually making their way back to the colony in a small makeshift craft. The incident created a sensation with many accounts written about the event. It is known that William Shakespeare avidly read these accounts and incorporated them into the themes of his last play “The Tempest”. It tells of the literal and emotional storms of the characters’ lives, which they go through, and like the Sea Adventure story eventually concludes with a happy ending for all. The scene where the stranded Miranda watches a ship floundering with her future lover on board was immortalized in John William Waterhouse’s “Miranda” in 1916.

Today it is recognized that patients may undergo physiological storms in addition to physical or emotional ones. We know this condition as the “thyroid storm”. Although a rare event it is vital that it is recognized and treated if there is to be a happy resolution to this tempest.



Left: Lady Hamilton (Emma Hart) as Miranda.

Oil on canvas sketch, Late Eighteenth century, George Romney.

The tempestuous Lady Hamilton was the muse of the painter George Romney, but more notoriously she was also known as the mistress of Lord Nelson.

THYROID STORM

Introduction

Thyroid storm (or thyrotoxic crisis) is a rare, but important condition to recognize as it is life-threatening.

Untreated the mortality is very high, (over 90%).

It is characterized by severe clinical manifestations of thyrotoxicosis. Patients with severe and life-threatening thyrotoxicosis typically have an *exaggeration* of the *usual* symptoms of hyperthyroidism.

There are no universally accepted criteria or validated clinical tools for diagnosing thyroid storm

The diagnosis of thyrotoxic storm is therefore both a biochemical and, more importantly, a clinical one.

Thyroid storm is most often seen in the setting of a patient with severe, undertreated or undiagnosed hyperthyroidism who develops an intercurrent illness or stress.

Urgent specialist endocrine consultation is essential for anyone who presents with this condition.

Pathophysiological Note

It is uncertain why thyroid storm develops in some people.

Hypotheses include:

- A rapid rate of increase in serum thyroid hormone levels
- Increased responsiveness to catecholamines
- Enhanced cellular responses to thyroid hormone

The degree of thyroid hormone abnormality (elevation of T4 and T3 and suppression of TSH) typically is not more profound than that seen in patients with uncomplicated thyrotoxicosis.

However, one study found that while the *total* T4 and T3 levels were similar to those seen in uncomplicated patients, the *free* T4 and free T3 concentrations were higher in patients with thyroid storm.²

The Primary causes of thyrotoxicosis include:

- Grave's disease
- Toxic adenoma
- Toxic multinodular goiter
- Hashimoto's thyroiditis (toxic in early stages, later hypothyroid)

- Infective:
 - ♥ Subacute thyroiditis
- Iatrogenic:
 - ♥ Excess thyroid hormone replacement or acute overdose of thyroxine.

The secondary causes of thyrotoxicosis include:

Elevation of TSH levels due to:

- Pituitary pathology
- Ectopic sources.

Secondary causes are very rare.

Clinical Features

There are no universally accepted criteria or validated clinical tools for diagnosing thyroid storm.

The diagnosis of thyrotoxic storm is therefore both a biochemical and, more importantly, a clinical one.

It is most often seen in the setting of a patient with severe, undertreated or undiagnosed hyperthyroidism who develops an intercurrent illness or stress, including:

1. Development of an intercurrent illness
 - Infection/ acute coronary syndrome
2. Physical stress:
 - Trauma or surgery
3. Pregnancy/ child birth.
4. Enhanced thyroid hormone production:
 - Acute excess iodine load, e.g., Iodinated contrast medium.
 - Thyroxine ingestion

Signs and symptoms are usually abrupt in onset and every organ system is involved to a varying degree:

Features include:

1. Fever:

- This can be marked (up to 41⁰ C) and is an important aspect of making the diagnosis. Pyrexia is not usually a feature of uncomplicated thyrotoxicosis.
- Note that fever may be due to concomitant infection or may represent an alternative diagnosis.

2. CNS:

- Anxiety /agitation
- Delirium/ frank psychosis.
- Tremulousness.
- Altered conscious state/ coma/ seizures.
- Apathy in the elderly:
 - ♥ “Apathetic” thyroid storm, may result in a depressed conscious state and cardiac failure in the elderly.

3. CVS:

- Hypertension.
- Sweaty / warm periphery.
- Tachyarrhythmias:

In particular:

- ♥ Sinus tachycardia will be greater than that expected for the degree of fever - often exceeding 140 beats per minute.
- ♥ Rapid AF, especially in the elderly.
- High output congestive cardiac failure.
- **Ultimately, death can occur from malignant cardiac arrhythmia, cardiovascular collapse and hypotension.**

4. GIT:

- Nausea, vomiting, diarrhea and abdominal cramps

5. Muscle weakness:

- Particularly proximal myopathy.

Differential diagnosis:

As diagnosis is ultimately clinical, there will be a number of important differential diagnoses to consider, including:

1. Sepsis
2. Heat stroke
3. Hyperpyrexic drug reactions:
 - Malignant hyperthermia
 - Neuroleptic malignant syndrome
 - Severe serotonin toxicity
 - Sympathomimetic drug toxicity
4. Severe delirium tremens.
5. Phaeochromocytoma crisis.

Investigations

Blood tests:

- 1 FBE:
 - Leukocytosis, or leukopenia may be seen.
2. U&Es / glucose:
 - Dehydration can lead to pre-renal renal impairment.
 - Mild hyperglycemia may be seen.
 - ♥ This is secondary to a catecholamine induced inhibition of insulin release and increased glycogenolysis.
 - Mild hypercalcaemia may be seen:
 - ♥ This may occur due to hemoconcentration and enhanced bone resorption.
3. LFTs:
 - Abnormal liver function tests can be seen.
3. Thyroid function tests:
 - T3 and T4 levels will be elevated, however this may not necessarily be much above levels seen in “uncomplicated” cases of thyrotoxicosis.

The diagnosis therefore will essentially be a **clinical one**.

This may also be due to an altered tissue response to thyroid hormones rather than any sudden increase in their concentration.

ECG:

Especially for tachyarrhythmias and to look for possible precipitating or secondary ischemic changes.

Others as clinically indicated:

If fever is present infection needs to be considered and ruled out.

Management

Urgent specialist endocrine consultation is essential for anyone who presents with this condition.

The therapeutic options for thyroid storm are essentially the same as those for uncomplicated hyperthyroidism, except that the drugs are given in **higher doses** and **more frequently**.

In addition, full support of the patient in an intensive care unit is essential, since the mortality rate of thyroid storm is substantial (10 to 30 percent).

1. ABC:

- Attend to any immediate ABC issues, IV access
- Supplemental oxygen therapy is useful due to the greatly increased metabolic demand.
- Establish continuous ECG monitoring.

2. Fluid resuscitation:

- Commence IV fluids as required.
- There will often be dehydration, but also beware the possibility of incipient cardiac failure.

3. Sedation:

- This may be with oral or IV benzodiazepines as clinically required.

4. Pyrexia:

If the patient is significantly pyrexic:

- Cooling efforts need to be aggressive. Fans may be used.
- Antipyretic agents:
 - ♥ Paracetamol orally or IV may be used.

- ♥ Aspirin is best *avoided* (may displace further T4 from protein binding sites).
- Antibiotics should be given if **sepsis** is suspected (or cannot readily be ruled out).

5. Beta-blockers:

These are the first line treatment for this condition.

They are used for:

- The control of sympathomimetic features such as tachyarrhythmia, hypertension, palpitations and tremor.

They will give rapid relief of these symptoms whilst awaiting the effects of the more specific but slower acting anti-thyroid medications

- **Non selective** agents such as propranolol also have a beneficial effect by the inhibition of the peripheral conversion of T4 to T3.

Options include:

Propranolol:

- The best oral agent and most commonly used agent is **propranolol**.
- **Usual dosage range is propranolol 40 - 80 mg orally, 4 times daily.**¹

Propranolol can also be titrated intravenously, at 0.5 mg doses, up to around 10 mg. Intravenous propranolol, however is not available in Australia.

Metoprolol and esmolol:

- For more severe symptoms or for those unable to take oral medication, other **IV** beta-blockers may be used such as **metoprolol** or **esmolol**.

These are both *selective* beta-1 agents however and hence will not block the peripheral conversion of T4 to T3, however they will still effectively block the sympathomimetic symptoms of thyroid storm.

- If a patient has a *relative* contraindication to beta-blockers, then cautious use of an esmolol infusion may be considered.
 - ♥ **Give metoprolol 5 mg IV over 2 to 3 minutes, repeated if necessary at 5-minute intervals up to a total of 15 mg.**

Or

- ♥ **Esmolol 250 to 500 micrograms/kg IV, as a loading dose, followed by 50 to 100 micrograms/kg/minute by continuous IV infusion**

- If there is an absolute contraindication to beta blockers, IV diazepam may help to reduce symptoms

Note that the hypermetabolic state will remain despite the relief of overt symptoms with beta blockers and so specific anti-thyroid agents will also be required, (as below).

6. Specific antithyroid drugs:

These are also essential to control the condition.

The **thionamides** block *de novo* thyroid hormone synthesis within one to two hours after administration.

However they have no effect on the release of *preformed* hormone from the thyroid gland.

Three thionamide agents are available:

- Methimazole
- Propylthiouracil (PTU)
- Carbimazole, (this is a *prodrug* which is metabolized to the active form, methimazole).

In Australia there are 2 available options:

- **Carbimazole**
- **Propylthiouracil (PTU)**

High dosages of these drugs are required in cases of thyrotoxic storm.

PTU has some theoretical advantages, as it not only inhibits thyroid hormone synthesis but also inhibits the peripheral conversion of T4 to T3. It also has the most rapid effect (within 1 hour)

Despite safety concerns in *long-term* management of hyperthyroidism, propylthiouracil is preferred to carbimazole in the treatment of **thyroid storm**.

Give:

- **Propylthiouracil 200 mg orally, 4 - 6 hourly.**

PTU may be given via a nasogastric tube or rectally if necessary.

Alternatively:

- **Carbimazole 20 mg orally, 8 hourly.**

7. Glucocorticoids:

These may also be considered in life-threatening situations.

The glucocorticoids have several theoretical benefits in thyrotoxic storm including:

- Reduction of T4 to T3 conversion.
- Immunosuppressant effects:
 - ♥ They may have a direct effect on the underlying autoimmune disease process if the thyroid storm is due to Graves' disease.
- Can treat potentially associated limited adrenal reserve.

The use of glucocorticoids for the treatment of **thyroid storm** appears to have improved outcome in at least one series.

- **Give hydrocortisone 100 mg IV every eight hours.**

Alternatively:

- Dexamethasone 4 mg IV 12 hourly.¹

8. Lugol's iodine solution:

This is also a useful adjunctive agent:

- The specific antithyroid agents inhibit the synthesis of new thyroid hormone, but iodide agents in high doses work to **block the release of thyroid hormone that has already been formed.**
- Iodide administration should be delayed until **1 hour** after the loading dose of antithyroid medication, so that iodide cannot be utilized in the synthesis of new thyroid hormone.
- **Give 0.5 mls orally 3 times a day.**

9. AF:

- If the patient has rapid AF this will be very resistant to drug or electrical treatment until the underlying pathology has been reversed.
- Control of rate with beta-blockers is the best approach.
- Amiodarone should be **avoided** in the management of atrial fibrillation due to thyrotoxicosis.

Its iodine content impairs the response to antithyroid drugs, and may preclude use of radioiodine for some months due to blockage of iodine uptake into the thyroid.¹

10. Treat any underlying precipitating pathology.

11. Surgery:

Urgent surgery may be required for those patients in whom

- Medical therapy has not been able to adequately control the symptoms.
- Cannot tolerate beta blockers and/ or the thionamides.

The advent of appropriate preoperative medical preparation of patients undergoing thyroidectomy for hyperthyroidism has led to a dramatic reduction in the prevalence of surgically-induced thyroid storm.

Disposition:

Urgent referral/ consultation with the Endocrinology Unit.

All patients should be admitted to HDU / ICU.

References

1. Therapeutic Endocrine Guidelines, 5th ed 2014.
2. Douglas S Ross et al. Thyroid Storm in Up to Date Website, December 6, 2013.
3. Maclean A, Thyroid Storm in Thyroid and Adrenal Emergencies, in Cameron et al. "Textbook of Adult Emergency Medicine" Churchill Livingston - Elsevier, 2015.

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