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# Thyrotoxicosis

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## Abstract

Thyrotoxicosis refers to symptoms and signs that arise from excess quantities of circulating thyroid hormones. It can be caused by hyperthyroidism - the hyperfunction of the thyroid gland or by other mechanisms, such as destruction of thyroid follicles with release of thyroid hormones (thyroiditis) or excessive ingestion of thyroid hormones (thyrotoxicosis factitia). There are several causes of thyrotoxicosis, the most common being Graves` disease (GD) followed by toxic nodular thyroid disease - toxic multinodular goitre (TMNG) or toxic adenoma (TA) and thyroiditis of any aetiology. Establishing the underlying cause of thyrotoxicosis is essential for its management. Diagnosis relies on clinical observation, sensitive hormonal and immunological assays and the occasional use of thyroid scintigraphy. Management of thyrotoxicosis includes the use of anti-thyroid medication (ATD), beta-blocking agents, radioiodine, thyroid surgery or a combination of these treatments. Management of thyrotoxicosis in pregnancy and the post-partum period requires special attention and expertise as the correct diagnosis and treatment can significantly influence the outcome of pregnancy, the wellbeing of the mother and of the foetus or the newborn.

Thyrotoxicosis denotes the clinical syndrome that results from tissue exposure to excess of circulating free thyroid hormones - thyroxine (3,5,3`,5`-tetraiodo-L-thyronine) - T4 and/or triiodothyronine (3,5,3`-triiodo-L-thyronine) - T3. It represents one of the commonest endocrine clinical presentations affecting approximately 1-1.5% of population[1] and occurs 5-10 times more commonly in women than in men. Thyrotoxicosis can be caused by several conditions (Table 1), however, the vast majority of cases (up to 80%) are due to Graves` disease (GD). Other common causes include toxic multinodular goitre (TMNG), toxic adenoma (TA) and thyroiditis of any aetiology. Thyroid hormones influence metabolic rate and protein synthesis and have receptors present in virtually all human tissues. It is, therefore, not surprising that clinical signs and symptoms of thyrotoxicosis are pleiotropic (Table 2). Untreated or inadequately treated thyrotoxicosis results in increased risk of atrial fibrillation, cardiovascular mortality, thromboembolic events, osteoporosis and neuropsychiatric states and significant impairment of quality of life.

Anatomy and physiology of thyroid hormone production

The thyroid is located in the anterior part of lower neck, enclosed in the pre-tracheal fascia below the strap of the neck muscles. It consists of the isthmus that lies horizontally just below the cricoid cartilage, two lateral lobes that extend upward over the lower part of the thyroid cartilage and occasionally presence of the pyramidal lobe. A normal-size thyroid weighs 15-20 g and is made up of follicles consisting of a single layer of follicular cells (thyrocytes) that are surrounded by a rich capillary network. The interior of the follicles is filled with clear proteinaceous colloid which contains thyroglobulin (Tg).

Biosynthesis of thyroid hormones requires iodine as a substrate. Iodine uptake from circulation is facilitated by active transport via the sodium/iodide symporter (NIS) at the basolateral membrane of the follicular cell. Iodine gets transferred through the cell and across the apical

membrane into the colloid. Next step is oxidation of iodine, which is a process requiring enzyme thyroid peroxidase (TPO) localised at the apical membrane and hydrogen peroxide ($H_2O_2$). Oxidised iodine gets quickly 'organified' onto the tyrosyl residues in Tg to form mono- or di-iodothyronine (MIT or DIT). TPO then catalyses the coupling reaction in which two DITs form a molecule of thyroxine (T4) and MIT and DIT form a molecule of tri-iodothyronine (T3). Lastly, colloid containing Tg with T4 and T3 gets endocytosed back into the thyrocyte, the T4 and T3 get released from Tg in lysosomes and subsequently get secreted into blood circulation. Most of the T4 and T3 in circulation (>99%) is reversibly bound to thyroxine-binding globulin (TBG), transthyretin (TTR) or albumin. It is however the free fraction of thyroid hormones that correlates with the metabolic state. The active form of thyroid hormone is free T3 (fT3). It binds to the nuclear thyroid hormone receptors (TRs) and this complex then initiates transcriptional changes resulting in physiological effects. Three iodothyronine deiodinases (D1-D3) regulate the availability of fT3 to the tissues. D1 (mainly in liver and kidney) catalyses `5-deiodination to of T4 to form T3 and is responsible for production of most T3 in the circulation. D2 does contribute towards the T3 pool in the circulation and plays a role in T3 generation in the hypothalamus and pituitary. D3 is the main inactivating enzyme catalysing 5-deiodination of T4 to form the inactive reverse T3 (rT3).

fT4 and fT3 regulate secretion of hypothalamic thyrotropin-releasing hormone (TRH) and hypophyseal thyroid-stimulating hormone (TSH) via a classic negative feedback loop. TSH acts through the TSH receptor (TSHR) at the basolateral membrane of thyrocyte resulting in stimulation of thyroid hormone production and trophic effects on the thyroid.

Laboratory diagnosis

Hyperthyroidism is characterised by suppressed or undetectable concentrations of TSH and elevated fT4 and/or fT3concentrations. 'T3-toxicosis' refers to an isolated elevation of fT3 in

the context of a suppressed serum TSH concentration. Subclinical hyperthyroidism refers to a suppressed TSH concentration with normal concentrations of fT4 and fT3. Rarely, serum TSH concentrations may be elevated (or inappropriately normal) in the context of elevated fT4 and/or fT3 concentrations and this is defined as secondary hyperthyroidism due to thyroid hormone resistance (TRH) or a TSH secreting pituitary adenoma. This biochemical picture may also be present in cases of poor compliance with thyroxine replacement therapy, non-thyroidal illness or cases of TSH or fT4/fT3 assay interference. Further discussion is beyond the scope of this article, but an interested reader is referred to an excellent review[2].

Investigation of the cause of thyrotoxicosis should include assessment for autoimmunity against thyroid antigens (TSHR, TPO). Stimulating autoantibodies against the TSHR (TRAb) are present in nearly all cases of GD and their titre tends to correlate with the severity of the disease. Some TRAb inhibit the TSHR and are referred to as TSHR blocking antibodies. These are present in up to 10-20% of patients with autoimmune hypothyroidism. Autoantibodies against TPO are detectable in approx. 70-80% of patients with GD and in the vast majority (>95%) of patients with autoimmune thyroiditis.

Thyroid scintigraphy

Thyroid scintigraphy is not routinely used in the diagnosis of thyrotoxicosis but may be useful in determining the cause if this is not obvious from the history, examination and laboratory findings. Technetium pertechneate ($^{99m}$Tc) is the isotope most commonly used and uptake into the thyroid gland is measured 20 minutes post administration (Figures 1A-D).

Graves` disease (GD)

GD is by far the commonest cause of thyrotoxicosis in iodine replete countries. It is an autoimmune condition in which hyperthyroidism occurs due to binding of stimulating TRAb to the TSHR. Due to the resulting thyroid hypertrophy, a diffuse goitre is present at diagnosis in about 80% of patients. Pathogenesis of GD is not fully understood but it is considered to have a multifactorial aetiology with a polygenic mode of inheritance in which susceptibility genes interact with environmental and constitutional factors to cause disease. The difference in concordance rates between monozygotic and dizygotic twins (0.35 and 0.03 respectively) provides evidence for the role of genetic factors but the lack of 100% concordance in monozygotic twins means that non-genetic factors also contribute to disease development. Susceptibility genes identified include the MHC Class II region, CTLA-4 gene and the TSHR gene. Female gender is the strongest risk factor for GD and oestrogens may play a role. Environmental factors include stress, cigarette smoking and iodine. TRAb are detectable in >95% of patients with GD and TPO antibodies are detectable in 70-80% of cases. $^{99m}$Tc scintigraphy classically shows diffusely increased uptake of the radionuclide in an enlarged gland (Figure 1A).

GD may be associated with extrathyroidal manifestations, the commonest of which is Graves` ophthalmopathy (GO) (Figure 2A). GO is characterised by eye redness, increased tear production, periorbital and conjunctival oedema, proptosis (exophthalmos), diplopia and impaired visual acuity. GO is clinically present in 60% of patients with GD and its presence does not correlate with the severity of thyrotoxicosis. Mild cases of GO may be managed with eye lubricants but more severe cases should be referred to specialised centres[3]. GD may also be rarely associated with pretibial myxoedema which tends to occur in only very severe cases of GD and is detectable in 1-2% of patients (Figure 2B). GO and pretibial myxoedema are caused by pathological accumulation of glycosaminoglycans in retroorbital or pretibial tissues

respectively. Glycosaminoglycans are secreted by TSHR-expressing fibrocytes and adipocytes under the influence of cytokines produced by local lymphocytic infiltration.

Management

1. Anti-thyroid drugs (ATD) and β-blocking agents

ATD represent the first-line treatment of GD in the UK, whereas in the USA there is a preference for radioiodine (RAI). Thionamides used for this indication include methimazole, its pro-drug carbimazole (CBZ) and propylthiouracil (PTU). ATD inhibit iodine oxidation and its organification thus blocking T4/T3 synthesis. ATD also possess immune modifying properties as evidenced by a fall in TRAb and Il-6 concentrations after initiation of the treatment. PTU has the additional effect of blocking T4-to-T3 conversion. In the UK, CBZ is the drug of first choice (with the exception of 1$^{st}$ trimester of pregnancy and thyroid storm) due to a more favourable adverse effect profile and cheaper cost in comparison to PTU. The effect of ATD may not become clinically apparent for up to 2-3 weeks and non-selective β-blockers (propranolol 10-40 mg TDS) may be used in the interim for the relief of symptoms. In cases where β-blockers are contraindicated, calcium channel blockers can be used instead (verapamil 40 mg TDS). ATD are either given in a form of a dose-titration regimen or a block and replace regimen. The typical starting dose of CBZ in dose-titration regimen is 20-30 mg/day and the dose is adjusted based on thyroid hormone concentrations at 4 - 6 weekly intervals until a maintenance dose of 5 -10 mg is achieved when the frequency of follow up is reduced to once every 3months until the course of treatment is completed. The typical duration of a dose-titration regimen is between 12 – 24 months (mean duration 18 months). The starting dose of CBZ in a block and replace regimen is 40-60 mg/day. Once fT4 and fT3 concentrations normalise, levothyroxine typically at a dose of 100 mcg/day is added. The serum TSH concentration alone can not be relied upon to guide treatment as it can remain suppressed for

several months or longer. Subsequently, levothyroxine dose may be adjusted by 25 mcg according to fT4 / fT3 concentrations. The duration of a block and replace regimen is for a minimum of 6 months. The block and replace regimen can also be used in the context of GO or to achieve stable thyroid hormone concentrations when this can not be managed with a dose-titration regimen. Following a course of ATD, the life-long remission rates are reported between 30-50%, with most recurrences occurring within 12 months after ATD cessation. Remission rates following dose titration and block and replace regimens are similar but the latter requires fewer clinic visits and biochemical control is often smoother. PTU is used second line when CBZ is not tolerated or is ineffective and is the drug of choice in the first trimester of pregnancy, breastfeeding and thyroid storm; 50mg of PTU equates to 5 mg CBZ.

Adverse effects of ATD can be divided into mild, the most common of which is a pruritic maculo-papular rash (1-5%, managed with antihistamines or by switching to another ATD) and severe including agranulocytosis, hepatotoxicity and vasculitis. Agranulocytosis denotes a low granulocyte count in particular that of neutrophils. Although idiosyncratic in the context of ATD, its risk is greater with higher doses of ATD and occurs in 0.1-0.3% of patients. It is reversible and should be treated by immediate withdrawal of ATD, hospital admission, treatment of neutropaenic sepsis and administration of granulocyte-colony stimulating factor. Patients who are started on ATD must be fully informed about the possible risk of agranulocytosis and should receive written instructions advising them to stop ATD if they develop a sore throat, mouth ulcers or fever. Hepatotoxicity is another potentially serious side-effect of ATD, however mild increase in transaminases and alkaline phosphatase can be caused by thyrotoxicosis per se. CBZ and PTU cause cholestatic and hepatitic patterns of liver function derangement respectively. Additionally, PTU can cause fulminant liver failure (0.05%) that

can be fatal. For the above reasons it is advisable to obtain baseline FBC and liver function tests when commencing ATD.

2. Radioiodine (RAI)

RAI treatment with the isotope $^{131}I$ may be used as a 'definitive' treatment for relapsed GD[4] after failure of ATD or as a first-line treatment. RAI is also the treatment of choice in toxic nodular disease. Administration of $^{131}I$ results in its accumulation in the thyroid with resulting thyroid cell damage and death due to the emission of beta particles. It is considered safe although a recent meta-analysis has shown a non-significant trend towards increased risk of thyroid, stomach and kidney malignancy. Doses up to 800 megabecquerel (MBq) can be administered in an outpatient setting. Contraindications to RAI include active GO, pregnancy and breast-feeding. ATDs should be stopped before RAI (CBZ for 7 days and PTU for 14 days) but may restarted a minimum of 4 days later if required. Pregnancy should be avoided for 6 months post RAI and men should avoid fathering a child within 4 months post RAI. Patients should adhere to radiation safety precautions such as avoidance of close contact with children and pregnant women for a duration dependent on the RAI dose administered. Side effects which are uncommon include transient worsening of thyrotoxicosis, worsening of GO, radiation thyroiditis and sialoadenitis. Cure is defined as restoration of euthyroidism with the acceptance of hypothyroidism and can be expected in 80-95% of patients after the first dose of RAI. Lifetime prevalence of hypothyroidism post RAI is up to 90% and patients should, therefore, have thyroid function checked at least yearly.

3. Thyroid surgery

Thyroid surgery is an alternative definitive treatment in GD and toxic nodular disease. It is the definitive treatment of choice in patients with active GO, those desiring pregnancy or those who desire a guarantee of cure and patients who can not comply with radiation protection guidance. Thyroid surgery should ideally be performed by a high volume thyroid surgeon.

Patients should be rendered euthyroid pre-surgery with ATDs. Lugol`s solution administered for 10 days prior to surgery inhibits T4/T3 release and reduces thyroid vascularity in cases of GD. Recognised complications include hypocalcaemia due to hypoparathyroidism, superior or recurrent laryngeal nerve damage and bleeding.

Toxic multinodular goitre (TMNG) and toxic adenoma (TA)

TMNG often occurs in patients with long-standing multinodular goitre (MNG) and its incidence increases with advancing age. A MNG is not always palpable in this condition and $^{99m}$Tc scintigraphy may be required to confirm the diagnosis as thyroid autoantibodies are usually not present. In TMNG, $^{99m}$Tc scintigraphy shows focal areas (nodules) of increased uptake (Figure 1B).

TA is characterised by clinical and biochemical thyrotoxicosis with or without a palpable thyroid nodule. Anti-thyroid antibodies are usually absent and $^{99m}$Tc scintigraphy demonstrates a 'hot' nodule with suppressed uptake in the remainder of the thyroid gland (Figure 1C).

Although RAI or surgery are the preferred treatment options for TMNG and TA, this might not always be possible due to comorbitities or patient preference. In such cases, long-term treatment with low doses of ATD is an option.

Thyroiditis

The thyrotoxicosis of thyroiditis (Table 1) is caused by excess circulating thyroid hormones suddenly released from destructed thyroid follicles. Patients typically present with an abrupt onset of thyrotoxic symptoms with the thyrotoxic phase usually lasting for 1-3 months often followed by a phase of transient (or permanent) hypothyroidism in subsequent months. The presence of thyroid autoantibodies and the rate of permanent hypothyroidism varies according to the aetiology but all patients have decreased or absent $^{99m}$Tc uptake on scintigraphy (Figure

1D) As there is no hyperthyroidism, the use of ATD is not required and may result in hypothyroidism.

Autoimmune thyroiditis (silent thyroiditis) can occur spontaneously or in the postpartum period (postpartum thyroiditis, please see below). Most patients will have positive TPO antibodies. There is an increased risk of subsequent hypothyroidism in up to 30% affected individuals. Management is symptomatic with β-blockers and careful monitoring of thyroid biochemistry.

Subacute thyroiditis (de Quervain`s or post-viral thyroiditis) is thought to be caused directly or indirectly by viral infection. It presents with pain in the thyroid region and a small, tender goitre. In the active phase, erythrocyte sedimentation rate (ESR) is grossly elevated, but patients are afebrile and systemically well. Treatment includes β-blockers and NSAIDs but more severe pain may be treated with a short course of steroids (prednisolone 30-40 mg/day for 7 days). It is followed by recovery of normal thyroid function in the vast majority of patients.

Amiodarone-induced thyrotoxicosis (AIT) occurs in 6-10% of patients taking amiodarone. Two distinct mechanisms cause AIT. High iodine content in amiodarone causes AIT type I via the Jod-Basedow effect (10% of AIT cases) and a direct toxic effect of amiodarone on thyrocytes causes destructive thyroiditis (AIT type II in 90% of cases), however mixed forms may occur. The best validated way of distinguishing between AIT type I and II is by colour flow Doppler (AIT type I shows normal or increased and AIT type II shows decreased vascularity). AIT type I should respond to ATD and AIT type II to steroids but both these treatments and adjunctive treatments may be required in mixed forms and more difficult cases. AIT management requires senior endocrinology input and frequent monitoring of thyroid function. Amiodarone withdrawal can help in the management of AIT type I, but this might not always be possible due to the initial indication for its use.

Thyrotoxicosis in pregnancy and postpartum period

The diagnosis of thyrotoxicosis during pregnancy can be challenging as many physiological changes of pregnancy are similar to those of thyrotoxicosis. Gestational hyperthyroidism is a mild and self-limiting form of hyperthyroidism caused by TSHR stimulation from elevated concentrations of human chorionic gonadotropin (hCG). It occurs in the 1st trimester and does not usually require treatment. A more severe form of gestational hyperthyroidism, hyperemesis gravidarum can be managed supportively, with antiemetics, fluids and β-blockers. Approximately 90% of thyrotoxicosis cases in pregnancy are however caused by GD. Management of GD in pregnancy differs significantly from that of GD in non-pregnant women. PTU is the drug of choice in the first trimester but should be switched to CBZ from the 2nd trimester onwards. The lowest possible dose of ATD in a titration regimen should be used to maintain fT4 concentrations in the upper part of reference range in order to minimize effects on the foetus. The block and replace regimen should not be used.

In the postpartum period the main differential diagnosis of thyrotoxicosis is the one of GD and postpartum thyroiditis. Relapses of GD are more common in the postpartum period because the period of immunosuppression during pregnancy is over. Postpartum thyroiditis occurs after 1 in 20 pregnancies and classically presents with thyrotoxicosis 3-6 months after delivery, lasts for 1-2 months and is usually followed by transient period of hypothyroidism (2-9 months) which may be become permanent in up to 30% of cases. Postpartum thyroiditis can also reoccur after subsequent pregnancies.

Thyroid storm

Life-threatening thyrotoxicosis or thyroid storm is a rare condition characterised by multisystem involvement and has a mortality rate up to 25%. Recognised precipitants include acute illness, abrupt cessation of ATDs, thyroidal and non-thyroidal surgery and (rarely) RAI.

Thyroid storm should be considered in an acutely ill patient with a previous history of thyrotoxicosis or previous thyroid treatment under the above circumstances. Although there are several clinical signs suggestive of thyroid storm (alteration in mental status, fever, tachycardia, vomiting, diarrhoea, multisystem decompensation and other signs of thyrotoxicosis) and scoring systems have been developed recently[1], the diagnosis remains a clinical one. Thyroid biochemistry will show a thyrotoxic picture but the actual concentrations of thyroid hormones might not be excessively elevated. Management of thyroid storm is summarised in Table 3.

## Subclinical hyperthyroidism

Subclinical hyperthyroidism (SH) is caused by GD, TMNG or TA. SH confers increased risk of overall and cardiovascular mortality, cardiac arrhythmias (mostly AF) and some studies also suggest increased risk for stroke. This risk is particularly increased in elderly population. European[5] and American[1] guidelines therefore recommend treatment of SH with fully suppressed TSH in people aged >65 years and in those aged below 65 with heart disease, osteoporosis, menopausal or with symptoms of thyrotoxicosis. Treatment should also be considered in patients who do not have a fully suppressed TSH aged over 65 or in those younger than 65 with above listed conditions. Asymptomatic patients younger than 65 years without a fully suppressed TSH should be observed. Treatment is determined by the cause of SH and is the same as for overt hyperthyroidism with the aim of normalising TSH concentrations.

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Table 1. Causes of thyrotoxicosis

| Hyperthyroidism |
| --- |
| 1. Excessive TSH-receptor stimulation |
| - Graves` disease (GD)**, also known as 'von Basedow disease' in continental Europe<br>- Gestational hyperthyroidism (hyperemesis gravidarum)<br>- Trophoblastic disease†<br>- TSH-producing pituitary adenoma††<br>- Resistance to thyroid hormone (RTH)††<br>- Familial non-autoimmune autosomal dominant hyperthyroidism FNAH) and persistent sporadic congenital non-autoimmune hyperthyroidism (PSNAH)†† |
| 2. Autonomous thyroid hormone secretion |
| - Toxic multinodular goitre (TMNG)*<br>- Toxic adenoma (TA)* |
| 3. Excess iodine<br>- Investigations with iodinated contrast<br>- amiodarone¶ |
| Thyrotoxicosis without hyperthyroidism |
| 4. Destruction of thyroid follicles with release of hormones - thyroiditis<br>- Autoimmune thyroiditis (silent thyroiditis, painless thyroiditis, lymphocytic thyroiditis, Hashimoto`s thyroiditis) / postpartum thyroiditis<br>- Subacute thyroiditis† (de Quervain`s thyroiditis, post-viral or granulomatous thyroiditis)<br>- Acute thyroiditis†† (bacterial or fungal)<br>- Drug-induced thyroiditis (amiodarone¶, lithium, interferon-α, interleukin-2, GM-CSF, multi-targeted receptor tyrosine kinase inhibitors (sunitinib, sorafenib etc.) |
| 5. Extrathyroidal sources of thyroid hormone |

- Thyrotoxicosis factitia - ingestion of excess thyroid hormones (iatrogenic, involuntary or surreptitious)
- Metastatic thyroid carcinoma†† (mostly differentiated follicular carcinoma)
- Struma ovarii†† (presence of functional thyroid tissue in ovarian teratoma)

TSH: thyroid-stimulating hormone, GM-CSF: granulocyte/macrophage colony-stimulating factor, ** very common, * common, † rare, †† extremely rare. ¶ amiodarone effects on thyroid are pleiotropic, please see the appropriate part of the text for further discussion.

Table 2. Clinical features of thyrotoxicosis (independent of aetiology)

| |
|---|
| Cardiovascular system<br>- palpitations, sinus tachycardia, atrial fibrillation, congestive (high-output) heart failure |
| Autonomic nervous system<br>- fine tremor, heat intolerance, excess sweating |
| Central nervous system<br>- hyperactivity, irritability, sleep disturbance, dysphoria, psychosis, depression ('apathetic thyrotoxicosis' in the elderly), fatigue, hyperreflexia, hyperkinesia, chorea, hyperkalaemic periodic paralysis (primarily in young Asian men) |
| Gastrointestinal system<br>- increased appetite, weight loss (weight gain in approx. 10% of patients), increased stool frequency |
| Respiratory system<br>- dyspnea |
| Genitourinary system<br>- polyuria and polydipsia<br>- oligomenorrhoea or amenorrhoea, erectile dysfunction, loss of libido |
| Musculoskeletal system<br>- muscle weakness, proximal myopathy, osteoporosis |
| Eyes<br>- retraction of upper or lower eyelid (visible rim of sclera between the lid and the limbus responsible for the typical 'stare' of the patient), lid lag (upper lid lags behind the globe when the patient is asked to shift the gaze downward) |
| Skin and hair<br>- warm and moist skin, pruritus, hair loss, onycholysis, palmar erythema |

* represents signs and symptoms that occur commonly

Table 3. Treatment of life-threatening thyrotoxicosis (thyroid storm)

| |
|---|
| General supportive therapy<br>- best managed in level 2/3 care with close monitoring of vital parameters<br>- treatment of the underlying cause if possible (broad-spectrum antibiotics etc.)<br>- intravenous fluids, cooling if hyperpyrexia present |
| Specific treatment (mechanism of action)<br>- Propylthiouracil (PTU) 500-1000 mg load followed by 250 mg every 4 hours (blocks new T4/T3 synthesis, in high doses blocks T4-to-T3 conversion hence preferred to carbimazole)<br>- Propranolol 60-80 mg every 4 hours (β-adrenergic blockade to control tachycardia, tremor and other adrenergic manifestations, also blocks T4-to-T3 conversion in high doses). Calcium-channel blockers in patients with risk of bronchospasm (verapamil)<br>- Iodine – potassium iodine 60 mg every 6 hours or Lugol`s solution (potassium iodide and iodine) 0.1-0.3 ml every 8 hours, to start at least 1hour post first dose of ATD (blocks new T4/T3 synthesis and release from the thyroid)<br>- Hydrocortisone up to 300 mg iv load followed by 100 mg 6-hourly (blocks T4-to-T3 conversion)<br>- Cholestyramine 4 g 8-hourly, other PO/NG medication to be given 1h before or 4h post cholestyramine (blocks enterohepatic circulation of T4/T3)<br>- Plasmapheresis/plasma exchange or emergency thyroidectomy in extremely severe cases or in those not responding to medical therapy |

Figure captions

Figure 1. $^{99m}$Tc pertechneate scintigraphy of thyroid gland in various clinical conditions. A. Graves`s disease (GD). B toxic multinodular goitre (TMNG) C. toxic adenoma (TA) D. destructive thyroiditis

Figure 2. Extrathyroidal manifestations of Graves` disease (GD). A. Graves` ophtalmopathy (GO) B. Pretibial myxoedema (infiltrative dermopathy).

Key references

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Further reading

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Key points

- Thyrotoxicosis belongs to one of the most common endocrine disorders affecting 1-1.5% of population
- Graves` disease is by far the commonest cause being responsible for approximately 80% of cases, followed by toxic nodular disease – toxic multinodular goitre (TMNG) or toxic adenoma (TA) and thyroiditis of any cause
- Diagnosis of thyrotoxicosis is established by suppressed TSH and elevated fT4 and/or fT3 concentrations
- Establishing the cause of thyrotoxicosis is required for its appropriate management
- Management of thyrotoxicosis includes the use of anti-thyroid drugs (ATD), β-blocking agents, radioiodine (RAI) administration and thyroid surgery or a combination of the above
- The most recent guidelines recommend more active treatment of subclinical thyrotoxicosis especially in the elderly population (>65 years of age)

Self-assessment questions.

1. A 33-year-old-woman attends her GP complaining of 3-months history of increased sweating, palpitations and itchy, red eyes with increased tear production. On examination, her heart rate is 95 bpm and regular, she has bilateral fine tremor present, bilateral proptosis and a smooth non-tender goitre is palpable.

What is the most likely cause of her condition?

A. postpartum thyroiditis

B. anaemia

C. Graves` disease

D. toxic multinodular goitre

E TSH-secreting pituitary adenoma causing thyrotoxicosis

Correct answer: C. Graves` disease.

This lady is thyrotoxic. GD is the commonest cause of thyrotoxicosis. Additionally, she has symptoms and signs of Graves` ophtalmopathy (GO) - itchy, red eyes, increased tear production and proptosis, that are in keeping with GD as underlying condition. A. C. D. not correct as these are far less common and do not present with symptoms of GO. E. very rare condition. B does not present with above signs and symptoms apart from sinus tachycardia.

2. The patient with GD from previous clinical scenario has been started on carbimazole 20 mg twice a day and on propranolol 20 mg three times a day. Three weeks later at her next appointment in the endocrinology clinic she complains of itchy rash in her arms. She is

systemically well, denies sore throat or flu-like symptoms and her palpitations and fine tremor have much improved.

What is the next most appropriate step in her management?

A. request an urgent full blood count

B. stop propranolol immediately

C. switch carbimazole to propylthiouracil (PTU)

D. continue with carbimazole and treat with antihistamines

E. stop carbimazole

Correct answer: D. continue with carbimazole and treat with antihistamines

Mild pruritic rash is not an indication for stopping carbimazole or switching to PTU as in most cases it can be easily managed with antihistamines. The patient should be told that should the rash get worse despite antihistamines she should contact the endocrinologist and then an alternative treatment will have to be considered. A. is not correct as itch rash is not a symptom of agranulocytosis and she does not have pharyngitis or flu-like symptoms and she is systemically well. B itchy rash is not a common side effect of treatment with β-blockers. E. patient should continue with ATD if possible as the benefits of treating thyrotoxicosis outweigh the mild side-effects linked with this treatment in this case.

3. A 24-year old woman has been referred to an endocrinologist by her GP with a 4 weeks history of symptoms of thyrotoxicosis. Her GP has kindly requested thyroid function tests and these show fully suppressed TSH and mildly elevated fT4 concentrations. She has given birth to a healthy child 4 months ago and she has been otherwise fit and well.

What should be the next immediate step in management of this lady`s thyrotoxicosis?

A. she should be started on carbimazole and a β-blocker with close monitoring of thyroid biochemistry

B. her thyroid biochemistry should be repeated together with TRAb and TPO antibodies and a β-blocker can be prescribed

C. she should be referred to a thyroid surgeon for consideration of hemithyroidectomy

D. radioiodine treatment should be offered as ATD are contraindicated in this woman

E. she can be discharged back to her GP and reassured as her thyrotoxicosis is only transient

Correct answer: B. her thyroid biochemistry should be repeated together with TRAb and TPO antibodies and a β-blocker can be prescribed

Given the clinical scenario the most likely cause of her mild thyrotoxicosis 4 months after delivery is postpartum thyroiditis. The differential diagnosis is GD. Thyrotoxic phase lasts for 1-2 months hence repeated thyroid biochemistry might show an euthyroid picture already. Management is symptomatic with β-blockers. A. ATD are not used in treatment of postpartum thyroiditis and the aetiology of thyrotoxicosis has not been established yet. C. and D. thyroidectomy or RAI are not indicated for postpartum thyroiditis as this is transient condition with no actual hyperthyroidism present. E. not correct as one should establish the diagnosis first. In this case, the patient should have repeated thyroid biochemistry done in following months due to the risk of developing hypothyroidism.