Thyroid associated orbitopathy

By Matthew Fanning

Learning objectives

After reading this article you should be able to:

- Identify signs and symptoms of thyroid associated orbitopathy.
- Describe treatment options for thyroid associated orbitopathy.

Competency standards (2010) addressed:
7.1.1, 7.1.2, 7.1.3

Accreditation number:
CAP110707e

Case details

Mrs MB is a 70-year-old nursing home resident in a small Queensland town. Her GP has referred her for her annual RMMR. Her past medical history includes:

- GORD
- Mild cognitive deficit
- Graves’ Disease (2008)
- Radio-iodine thyroid ablation (2008)
- Hypercholesterolaemia
- Paroxysmal AF
- Hypertension

The nursing staff report that she is suffering from dry eye despite twice daily use of the lubricant eye drop. This is confirmed by Mrs MB.

Introduction

Graves’ disease is a common cause of thyrotoxicosis, accounting for approximately 60–80% of presentations. As with many autoimmune disorders, it has a strong female preponderance and has a lifelong risk of up to 2% in women. It typically occurs in the younger population (20–50 years) but also has significant incidence in the elderly.

She is currently taking the following medications:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone tablet</td>
<td>100 mg</td>
<td>1 each morning</td>
</tr>
<tr>
<td>Aspirin tablet</td>
<td>100 mg</td>
<td>1 each morning</td>
</tr>
<tr>
<td>Pantoprazole tablet</td>
<td>40 mg</td>
<td>1 each morning</td>
</tr>
<tr>
<td>Refresh tears plus eye drops</td>
<td>5 mg/mL (0.5%)</td>
<td>1 drop twice daily both sides</td>
</tr>
<tr>
<td>Fish oil caps</td>
<td>1,000 mg</td>
<td>1 each morning</td>
</tr>
<tr>
<td>Movicol sachet</td>
<td></td>
<td>1 three times a day when necessary</td>
</tr>
<tr>
<td>Paracetamol tablet</td>
<td>500 mg</td>
<td>2 four times daily when necessary</td>
</tr>
<tr>
<td>Thyroxine tablet</td>
<td>50 mcg</td>
<td>1 each morning</td>
</tr>
<tr>
<td>Enalapril tablet</td>
<td>20 mg</td>
<td>1 each morning</td>
</tr>
</tbody>
</table>

Matthew Fanning is a consultant pharmacist with experience in community pharmacy and clinical pharmacy and the provision of continuing professional education.
Overview of pathophysiology of Graves’ disease

Graves’ Disease, like most autoimmune disorders is likely caused by a complex interplay of genetic and environmental factors which cause an ‘intolerance to self’. This leads to the production of antibodies directed at proteins which normally occur in a healthy individual (see Table 1).1,2

Usually, the thyroid is controlled by the pituitary gland, which produces thyroid stimulating hormone (TSH) that acts on the thyrotropin receptor to stimulate the thyroid to produce thyroid hormones.1 The hyperthyroidism of Graves’ disease is mediated by the direct stimulation of the thyrotropin receptor by autoimmune antibodies in addition to TSH.2 This leads to raised thyroxine (T4) and triiodothyronine (T3) and subsequent feedback suppression of TSH.2

This produces the typical picture of hyperthyroidism on thyroid function tests (see Table 2), however the detection of auto-antibodies is necessary for the diagnosis of Graves’ disease.

Thyroid associated orbitopathy

Thyroid Associated Orbitopathy (TAO), commonly termed Graves’ Ophthalmopathy, is a common ‘extra-thyroid’ manifestation of Graves’ disease.1 The pathophysiology of TAO can be explained by the targeting of orbital fibroblasts by infiltrating lymphocytes activated by Graves’ disease auto-antibodies.3 Through a variety of mechanisms, activated fibroblasts produce significant inflammation, oedema and fat deposition resulting in increased orbital volume.4 As the orbit has a fixed space, this produces the characteristic eye protrusion (exophthalmos or proptosis) seen in Graves’ disease.4

TAO is present in 25% of those diagnosed with Graves’ disease and usually settles into a more quiescent stage after 1–2 years which is characterised by scarring of the tissues.4 However, symptoms of TAO may first develop or worsen at any time during the course of the disease.4 The typical symptoms of TAO are summarised in Table 3.

Treatment of Graves’ hyperthyroidism

Rapid amelioration of symptoms is the primary treatment goal of hyperthyroidism associated with Graves’ disease.5 Beta blockers relieve symptoms related to thyroid related sympathetic stimulation (e.g. tachycardia, tremor, sweating).6 Antithyroid drugs such as carbimazole and propylthiouracil decrease thyroid hormone synthesis (and additionally propylthiouracil blocks peripheral conversion of T4 to the more potent form, T3).6

Treatment of Graves’ disease often requires specialist advice.3 Since some (usually younger) patients achieve remission after a short time, long term management may include trial cessation of anti-thyroid drugs with monitoring of thyroid function at one, two, three, six and 12 months then annually thereafter.7 However, some may require longer term anti-thyroid therapy or there may be need for radioablation or surgery.7

Treatment of TAO

Treatment of Graves’ hyperthyroidism does not appear to have an impact on the progression of TAO.6 However, hyperthyroidism does appear to worsen eye lid retraction and stare.6 Treatment of hyperthyroidism is also associated with a worsening orbitopathy or even the onset of orbitopathy in a significant number of people.8 Furthermore, hypothyroidism worsens orbital oedema, therefore exacerbating symptoms of TAO.6 This highlights the importance of maintaining a euthyroid state in TAO despite thyroid function not having a direct effect on its pathology.6

The treatment of TAO is dependent on the severity of symptoms and may only require symptomatic management in mild disease.6 More aggressive medical or surgical treatment may be indicated in severe or rapidly progressing cases.8

### Table 1

<table>
<thead>
<tr>
<th>Auto-antigens of Graves’ disease</th>
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<tbody>
<tr>
<td>Thyrotropin (TSH) receptor*</td>
</tr>
<tr>
<td>Thyroglobulin</td>
</tr>
<tr>
<td>Thyroid peroxidase</td>
</tr>
<tr>
<td>Sodium iodide symporter.</td>
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</tbody>
</table>

*Most significant in the development of hyperthyroidism

### Table 2

<table>
<thead>
<tr>
<th>Interpretation of thyroid function tests</th>
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</thead>
<tbody>
<tr>
<td>TSH</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Low</td>
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<td>Low</td>
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### Table 3

<table>
<thead>
<tr>
<th>Typical symptoms of thyroid associated orbitopathy</th>
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<tbody>
<tr>
<td>• Dry eyes</td>
</tr>
<tr>
<td>• Puffy eyelids</td>
</tr>
<tr>
<td>• Angry looking eyes</td>
</tr>
<tr>
<td>• Bulging eyes</td>
</tr>
<tr>
<td>• Diplopia</td>
</tr>
<tr>
<td>• Visual loss</td>
</tr>
<tr>
<td>• Field loss</td>
</tr>
<tr>
<td>• Dyschromatopsia (reduced colour perception)</td>
</tr>
<tr>
<td>• Photopsia on upgaze (flashes of light)</td>
</tr>
<tr>
<td>• Ocular pressure or pain.</td>
</tr>
</tbody>
</table>

Submit your answers online at www.psa.org.au and receive automatic feedback
Symptomatic treatment

Symptomatic treatment may include the regular instillation of artificial tears, protection from sun and wind with dark sunglasses and raising the head of the bed at night. In many people, this may be sufficient and allow them to avoid more aggressive therapy.

More aggressive treatment

Indications for more aggressive therapy include worsening proptosis and soft tissue signs. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be useful in patients with mild eye irritation. However, systemic corticosteroids are considered the accepted treatment for severe TAO despite there being a relative lack of well designed supporting studies. The mechanism for their action is assumed to be related to their anti-inflammatory and immunosuppressant actions. The optimal dose of prednisolone is uncertain but many physicians initiate treatment at 100 mg/day. However, there is some suggestion that lower doses are as effective and have a lower incidence of adverse effects. There is also a small body of evidence for oral or intravenous pulse therapy consisting of slowly reducing once weekly doses.

Some patients with very severe disease may progress to a stage where radiation or surgical intervention is required.

No strong evidence could be found for the use of other immunosuppressants (e.g. azathioprine, methotrexate) nor are they routinely recommended for the treatment of TAO.

Case discussion

Mrs MB is complaining of dry eyes. Although the aetiology of dry eyes is widely varied, given her history of Graves’ disease, TAO must be considered. Appropriate symptomatic treatment with appropriate medical assessment is recommended.

Amiodarone is well known to sometimes cause detrimental effects on thyroid function. This is due to both a direct cytotoxic effect on thyroid follicular cells and its inhibitory effects on the peripheral conversion of T₄ to T₃. Obviously, given her thyroid ablation, the direct effects of amiodarone on the thyroid are not relevant. Furthermore, despite the inhibition of conversion of T₄ to T₃, no clinically significant effects on thyroxine replacement are documented.

Warfarin is considered to be the most effective treatment for prevention of stroke in atrial fibrillation. Mrs MB has a relative lack of risk factors for stroke (diabetes mellitus, previous strokes, heart failure) however considering her (treated) hypertension and her age, warfarin may be appropriate. This needs to be considered in the context of her bleeding and falls risk and overall treatment goals.

Hypercholesterolaemia is listed in the past medical history, however she is not receiving any treatment. Fish oil is useful for hypertriglyceridaemia, however 1 g daily is a subtherapeutic dose.

Actions and recommendations

The following recommendations were made to the GP after discussion with Mrs MB and her carers:

1. Given Mrs MB’s diagnosis of Graves’ disease, her persistent dry eye symptoms may be related to thyroid associated orbitopathy. Further assessment may be required by you with referral for specialist advice if deemed appropriate. For symptomatic relief consider increasing lubricant eye drops to every 4 hours and consider prescribing a lubricating eye ointment for night time use. Non pharmacological interventions such as raising the head of the bed and the use dark wraparound sunglasses when outside may also be helpful.

2. Warfarin is the most effective preventative treatment for thromboembolism secondary to AF. While Mrs MB has few risk factors for stroke, her hypertension and age puts her at a high enough risk that warfarin should be considered. Depending on treatment goals and bleeding risk, warfarin may be preferential to aspirin.

3. Hypercholesterolaemia is listed in Mrs MB’s past medical history however she is not currently receiving any treatment. Consider commencing treatment if indicated by serum cholesterol measurements.

Outcomes

Mrs MB’s doctor commenced a more aggressive treatment with lubricant eye drops and ointment. He referred Mrs MB to an ophthalmologist for assessment of TAO. Aspirin was continued as warfarin was deemed to be not in line with Mrs MB’s treatment goals. Her GP deemed that her serum cholesterol levels did not warrant intervention.

Summary

Graves’ disease is a common cause of hyperthyroidism, usually affecting younger people but has a significant incidence in the elderly. Thyroid associated orbitopathy is a common manifestation of Graves’ disease and can cause significant ophthalmic complications. Treatment may be symptomatic in mild disease or may be more aggressive in severe disease.

References


11. Hypercholesterolaemia is a common cause of atherosclerosis. Hypercholesterolaemia is a common cause of hyperlipidaemia.
Questions

1. Select the INCORRECT answer.
   a) Graves’ disease most commonly affects people aged 20–50 years of age but has a significant incidence in the elderly.
   b) Rapid relief of symptoms is the primary goal in the treatment of Graves’ disease.
   c) Carbimazole blocks peripheral conversion of T₄ to T₃.
   d) Hyperthyroidism of Graves’ disease is mediated by auto-antibody stimulation of thyroid thyrotropin receptors.

2. Select the INCORRECT answer relating to thyroid associated orbitopathy (TAO).
   a) Hyper or hypothyroidism may exacerbate TAO.
   b) Initial treatment of hyperthyroidism of Graves’ disease may be accompanied by a worsening of TAO.
   c) Dry eye is not a common symptom of TAO.
   d) Radiation or surgical intervention may be required in severe cases of TAO.

3. Select the CORRECT answer relating to thyroid associated orbitopathy (TAO).
   a) TAO is worsened by the use of NSAIDs.
   b) In many people, artificial tears, raising the head of the bed and using dark sunglasses is sufficient to manage TAO.
   c) Corticosteroids usually worsen TAO.
   d) Slight hypothyroidism is beneficial to symptomatic control of TAO.

4. Select the CORRECT answer.
   a) Amiodarone blocks peripheral conversion of T₄ to T₃.
   b) Specialist advice is not usually required for the management of TAO.
   c) Graves’ disease has a strong male preponderance.
   d) Environmental factors are not important in the pathogenesis of Graves’ disease.

A score of 3 out of 4 attracts 0.75 CPD credits.