Asthma and hyperthyroidism

A report of 4 cases

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Summary

For many years it has been known that thyrotoxicosis can worsen asthma, increasing both the frequency and severity of asthma attacks and increasing requirements for medication. Clinical recognition of this association may be difficult. Thyrotoxic asthmatics frequently experience side-effects from medications, particularly β-receptor agonists and theophyllines. Four case reports of asthmatics in whom thyrotoxicosis was diagnosed are presented. All 4 patients improved on returning to euthyroid status. The mechanism responsible for the harmful interaction is not known.

Since asthma is a common condition, an occasional chance association with other diseases is to be expected. The fact that the association of asthma with thyrotoxicosis is harmful has been recognised for over half a century. Asthma frequently deteriorates as thyrotoxicosis develops, whether for the first time or after withdrawal of antithyroid drugs, and improves when thyrotoxicosis is successfully treated. An additional problem of this association is that the clinical features of sympathetic overactivity induced by hyperthyroidism may be erroneously attributed to asthma drugs. Four patients seen at the Respiratory Clinic, Groote Schuur Hospital, in whom asthma complicated by thyrotoxicosis resulted in these and other clinical problems, are described.

Case reports

Case 1

A 30-year-old woman, with a 6-year history of asthma when first seen in 1976, reported asthma attacks occurring 2-3 times per month; these attacks were precipitated by upper respiratory tract infections and anxiety. No allergies were identified by history-taking and skin-prick testing. The asthma proved difficult to control and the patient was labelled a 'brittle asthmatic'. Regular doses of both oral corticosteroids and inhaled beclomethasone, and inhaled β2-agonists and oral theophyllines were required. In succeeding years she was admitted to hospital with acute severe asthma attacks on numerous occasions, and her maintenance prednisone dose was gradually increased from 5 mg to 15 mg daily.

On several occasions the patient was noted to be tremulous, anxious and irritable, but there were no other signs of thyroid disease. During January 1990 the asthma deteriorated strikingly, and this was attributed to anxiety related to the discovery of a breast lump which, on investigation, was found to be malignant. Mastectomy was planned but had to be delayed because of extreme difficulty in controlling the asthma. After a week of optimal and intensive inpatient treatment improvement was only slight. Anxiety, irritability, tremulousness and tearfulness were again noted. A sinus tachycardia at rest of 100-150/min was noted. There was no thyroid enlargement or eye signs, but there had been a 6 kg weight loss over the previous 4 months. Thyroid function tests confirmed hyperthyroidism: serum thyroid stimulating hormone (TSH) level 0.1 μU/ml (normal 0.4 - 4 μU/ml), thyroxine (T4) level 70.7 pmol/l (normal 6.3 - 23 pmol/l). Iodine-131 scanning showed diffuse uptake compatible with Graves' disease. Treatment with carbimazole was started and the asthma control improved. Subsequent mastectomy was carried out uneventfully and 131I thyroid ablation therapy was also given. The asthma control has been much improved. She has had no further admissions to hospital for asthma and requires considerably less maintenance therapy, with prednisone having been reduced to 10 mg/d.

Case 2

A 75-year-old woman, first seen in 1984, had a 6-month history of respiratory symptoms. She was troubled by a persistent cough, wheezing related to exertion and reduced effort tolerance. A life-long non-smoker, she had been treated for 10 years with thiazide diuretics for mild essential hypertension. A palpable nodular thyroid gland had been present for several years but thyroid function tests in 1980 had been normal. There were no clinical signs of hyperthyroidism. Pulmonary function tests showed mild airflow obstruction (forced expiratory volume in 1 second (FEV1) of 1300 ml). Skin-prick tests were negative. Primarily based on history-taking, a diagnosis of late-onset asthma was made. On oral corticosteroids, theophylline, inhaled β2-agonists and beclomethasone, her cough and effort tolerance improved and the FEV1 increased to 1600 ml. However, she developed diarrhoea, abdominal pain and palpitations, which resolved when oral theophylline was stopped. Over the next year, the patient required oral corticosteroids in low doses with occasional courses of up to 20 mg prednisone/d. In early 1985 a nodule in the right lobe of the thyroid increased in size, and, although there were no clinical signs of thyrotoxicosis, thyroid function tests confirmed thyrotoxicosis: T4 level 21.3 pmol/l and tri-iodothyronine (T3) level 10.4 pmol/l (normal 3.3 - 8.1 pmol/l). A thyroid scan confirmed the presence of a dominant hot nodule in the right lobe and thyroid ablation with 131I was carried out. When the patient became euthyroid, the asthma was relatively easy to control with inhaled beclomethasone and β2-agonists alone. She has not required oral corticosteroids and her usual FEV1 remains in the region of 1700 ml.

Case 3

A 46-year-old woman with 10-pack/year history of cigarette smoking developed a chronic cough, followed some years later by a first attack of acute asthma. Skin-prick tests were negative. During 1988 and 1989 the patient had almost monthly episodes of acute severe asthma in spite of inhaled β2-agonists,

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oral theophylline and increasing doses of prednisone. By mid-1989 she was receiving prednisone 20 mg/d without good control. Loss of weight was noted in November 1989, together with tremulousness and a resting sinus tachycardia of 100/min. Thyroid function tests confirmed hyperthyroidism: TSH level 0.1 \( \mu \text{U/ml} \), T\(_3\) 13.5 pmol/l and T\(_4\) 24.6 pmol/l. The patient was treated by thyroid ablation using \( ^{131} \text{I} \) and since then has had no further episodes of acute severe asthma. The maintenance prednisone dose and other medications have been progressively reduced.

**Case 4**

In early 1990 a 19-year-old woman was referred to a cardiologist for evaluation of paroxysmal tachycardia. She had had asthma since the age of 4 years but had been well controlled by a combination of inhaled \( \beta \)-agonists and oral theophylline. However, over the preceding 6 months the control of the asthma had worsened, resulting in reduced effort tolerance. The repeated episodes of tachycardia seemed to relate to the use of \( \beta \)-agonists. When seen in our clinic no tremor, weight loss or signs of thyroid disease were evident. There was a resting sinus tachycardia of 100/min. Spirometry showed mild airflow obstruction and skin-prick tests confirmed an atopic status. Previously performed echocardiography, ECG and 24-hour ambulant ECG monitoring had shown only sinus tachycardia. Thyroid function tests showed a TSH level of 0.1 \( \mu \text{U/ml} \), T\(_3\) 45.9 pmol/l and T\(_4\) 26.3 pmol/l. The patient was started on inhaled beclomethasone in addition to her other medications, and carbimazole. Within 3 weeks of starting carbimazole, it was possible to control the asthma solely on inhaled beclomethasone.

**Discussion**

The clinical diagnosis of thyrotoxicosis in asthmatics on symp-athomimetic agents is often difficult. None of our patients had overt clinical signs of thyrotoxicosis beyond those mimicking sympathomimetic overactivity. Similar findings are common in euthyroid asthmatics. Thyrotoxicosis is more common in women and it is not surprising that all our patients were female.

In all 4 patients deterioration of asthma occurred as their hyperthyroidism became symptomatic. In two patients (cases 1 and 3) attacks increased in frequency and severity. In all patients it became necessary to increase therapy. Thyrotoxicosis must be considered as one among several causes of deteriorating asthma in a previously stable or newly-diagnosed asthmatic. Another feature is an apparent intolerance of \( \beta \)-agonists and theophylline seen in thyrotoxic asthmatics, manifesting as paroxysmal or persistent tachycardia, tremulousness, anxiety, agitation, diarrhoea and abdominal pain. This too should alert clinicians to check thyroid function status.

A gratifying consequence of recognising and treating the thyrotoxic state is that the patient's asthma usually improves. This seems to be a consistent feature. It is preferable to perform thyroid function tests too often than to miss patients who will benefit from management of hyperthyroidism. The frequency of the association of asthma and thyrotoxicosis has not been studied prospectively. One retrospective study showed that of 1360 persons admitted to hospital with a diagnosis of asthma, 4 subsequently developed hyperthyroidism. Review of the records of recent attenders at our clinic confirmed 4 cases in 422 asthmatics.

The mechanism of the interaction between asthma and thyrotoxicosis remains obscure. It seems paradoxical that increased \( \beta \)-agonists are required and are effective in a condition characterised by increased sympathetic activity. It might be assumed that airway reactivity to histamine and/or methacholine would be increased in the presence of worsening asthma. This has not been studied. However, in thyrotoxic patients without preceding asthma, bronchial reactivity does not change when they are rendered euthyroid by treatment, nor does bronchial reactivity change when normal individuals are made thyrotoxic by administration of T\(_3\). A similar study has not been conducted in thyrotoxic asthmatics who are rendered euthyroid, although there is 1 case report of a 15-year-old athlete with severe exercise-induced asthma and thyrotoxicosis in whom the provocative concentration dose of histamine reducing the FEV\(_1\) to \( \geq 20\% \) below baseline increased 5-fold after treatment for thyrotoxicosis. Respiratory muscle weakness is well documented in thyrotoxicosis. While this may be associated with a degree of easy fatiguability during an asthma attack, it does not account for exacerbations of asthma. Similarly, pulmonary vascular congestion observed in thyrotoxicosis cannot explain this association.

Some lines of evidence suggest that thyrotoxicosis worsens asthma due either to changes in levels of catecholamines and/or reduced endogenous \( \beta \)-sympathetic activity. Thyrotoxic patients have been shown to have normal or low concentrations of circulating catecholamines and catecholamine-secretion rates. Hydrocortisone clearance and metabolism is increased but concentrations of circulating hydrocortisone remain normal as a result of adrenal compensation. There is at least some evidence that asthmatic patients display reduced \( \beta \)-adrenergic responses and that this is aggravated by the use of \( \beta \)-agonist bronchodilator therapy. Corticosteroids antagonise this effect. Reduced \( \beta \)-adrenergic responses coupled with evidence of \( \alpha \)-adrenergic hyperresponsiveness in asthma may be of particular relevance as a mechanism of asthma in thyrotoxicosis. Direct evidence is not available, but in one study of non-asthmatic thyrotoxic subjects, increased \( \beta \)-adrenergic responsiveness was found after treatment of hyperthyroidism. It was hypothesised that changes distal to the \( \beta \)-adrenoceptor, probably beyond the level of protein kinase, might be responsible for reduced responsiveness. In other studies the number of binding sites and function of \( \beta \)-adrenoceptor sites in circulating lymphocytes from thyrotoxic subjects and in lung tissue of animals exposed to thyroxine appeared to be normal. In rats thyroid hormone administration resulted in increased cardiac \( \beta \)-receptor density. If this finding is relevant in humans, it could explain the susceptibility of thyrotoxic asthmatics to side-effects from \( \beta \)-agonists.

In the management of patients with asthma and hyperthyroidism, \( \beta \)-blockers should never be used. Thyroid function tests should be used to monitor the effect of treatment and during follow-up, since clinical assessment remains difficult. Over-replacement with T\(_3\) has been shown to cause exacerbations of asthma. Attempts at improving asthma by rendering patients hypothyroid should be resisted, because of the long-term complications of this state, including the risk of premature atherosclerosis.

**REFERENCES**

Clinicopathological Conference

A 36-year-old man with complete heart block and shock

Case presentation

A 36-year-old black man was admitted to hospital in a state of collapse. He had been well until 1 week before presentation, when he developed a fever associated with rigors and sweating. Shortly afterwards he noticed that he was becoming short of breath. He also experienced pain over the left chest posteriorly, which radiated down the back and into the left flank. On the day of admission he was dyspnoeic at rest, felt very nauseous, vomited on several occasions and had noted poor urine output. He consulted a general practitioner complaining particularly of abdominal pain. He was found to have haematuria and it was thought that he had renal colic. He was given hyoscine intramuscularly but shortly thereafter he collapsed and was found to be bradycardiac (pulse 40/min) and pyrexial. Following an injection of adrenaline he was urgently referred to Groote Schuur Hospital.

There was a past history of a dislocated left shoulder on two occasions. The patient worked as a labourer for a supermarket, was a mild smoker but drank up to 10 bottles of beer over weekends.

The temperature was 37.5°C, pulse 40/min and irregular, blood pressure 80 mmHg systolic, and respiratory rate 12/min. He appeared very ill. There was no oedema or cyanosis. The peripheral pulses were present and equal; the jugular venous pressure was 4 cm; the apex was not displaced; the heart sounds were normal; no pericardial friction rub or murmurs were heard. The breath sounds were normal and there were no added sounds. The liver was enlarged 4 cm below the costal margin and non-pulsatile but very tender particularly over the left lobe. Neurological examination was unremarkable.

Chest radiography revealed borderline cardiomegaly, some upper lobe venous blood diversion and clear lung fields (Fig. 1). An ECG showed complete heart block with QRS widening and ST-segment elevation in the V leads (Fig. 2). The urine contained 3+ protein and 3+ blood and on microscopic examination granular and hyaline casts together with some debris were noted. The blood urea level was 16.3 mmol/l and the serum creatinine value 286 μmol/l, these rose to 30.8 mmol/l and 565 μmol/l, respectively, 18 hours later. The serum sodium level was 138 mmol/l, potassium 4.9 mmol/l and blood glucose 7.1 mmol/l. The urinary sodium value was 38 mmol/l, potassium 93 mmol/l, urea 148 mmol/l, and creatinine 16.2 μmol/l. Breathing room air, the blood gases

![Fig. 1. Chest radiograph on admission.](image-url)