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Incidence, clinical characteristics and outcome of congestive heart failure as the initial presentation in patients with primary hyperthyroidism

Chung-Wah Siu, Chun-Yip Yeung, Chu-Pak Lau, Annie W C Kung, Hung-Fat Tse

Background: There are limited systematic data on the incidence, clinical characteristics and outcomes of congestive heart failure (CHF) in patients with hyperthyroidism. The aim of this study was to investigate the incidence, clinical characteristics and outcome of CHF as the initial presentation in patients with primary hyperthyroidism.

Methods: The prevalence, clinical characteristics and outcome of CHF was studied in 591 consecutive patients (mean (SD) age 45 (1) years, 140 men) who presented with primary hyperthyroidism.

Results: CHF was the presenting condition in 34 patients (5.8%) with hyperthyroidism. The presence of atrial fibrillation at presentation (OR 37.4, 95% CI 9.72 to 144.0, p<0.001) was an independent predictor for the occurrence of CHF. Of the 34 patients with CHF, 16 (47%) had systolic left ventricular dysfunction with left ventricular ejection fraction (LVEF)<50%. They were predominantly male (OR 26.6, 95% CI 2.6 to 272.5, p=0.006) and had a lower serum thyroxine level (OR 0.93, 95% CI 0.87 to 0.99, p=0.044) than patients with preserved left ventricular systolic function. In these patients, LVEF (55 (4)% vs 30 (2), p<0.001) and New York Heart Association functional class (1.2 (0.1) vs 2.5 (0.2), p<0.001) improved significantly 3 months after achieving euthyroid status. Systolic left ventricular dysfunction (mean (SD) LVEF 38 (4)% persisted on long-term follow-up in five patients: no clinical parameter could be identified to predict the occurrence of this persistent cardiomyopathy (p>0.05).

Conclusion: CHF was the initial clinical presentation in approximately 6% of patients with hyperthyroidism, and half of them had left ventricular systolic dysfunction. Symptoms of CHF subsided and LVEF improved after treatment for hyperthyroidism. Nonetheless, one-third of these patients developed persistent dilated cardiomyopathy.

Hypothyroidism is a common metabolic disorder with prominent cardiovascular manifestations. It creates a hyperdynamic circulatory state because of a marked fall in peripheral vascular resistance and an increased total blood volume and heart rate. These cardiovascular changes can aggravate pre-existing cardiac disease or directly lead to thyrotoxic heart disease. Although symptoms and signs of congestive heart failure (CHF) are common in patients with hyperthyroidism, dilated cardiomyopathy with impaired left ventricular systolic function is only rarely reported. Hypothyroidism is a very rare (<1%) cause of dilated cardiomyopathy. Nonetheless, there has been no systematic study of the incidence, clinical characteristics and outcome of heart failure caused by hyperthyroidism. The purpose of this study was to determine the incidence, clinical characteristics and outcome of heart failure in a large cohort of patients with hyperthyroidism.

METHODS

Study population

We studied 618 consecutive Chinese patients diagnosed with hyperthyroidism from January 2001 to December 2002 in the Cardiology Division, Department of Medicine and Metabolic and Endocrinology Division, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong, China, the only large regional general hospital to accept emergency referrals from the western region of Hong Kong Island. Patients were referred directly or from hospital wards to our thyroid and general medical outpatient clinics for treatment of primary hyperthyroidism. Data were prospectively collected on their demographic characteristics, symptoms of heart failure and hyperthyroidism, ECG at presentation and clinical outcome during follow-up. Patients were excluded from study if they had documented pre-existing coronary artery disease, or a history of myocardial infarction, CHF and cerebrovascular and peripheral vascular disease (n = 8) or incomplete clinical data (n = 12). A further seven patients with previously diagnosed persistent atrial fibrillation in the presence of a normal thyroid function test, and who subsequently developed hyperthyroidism after treatment with amiodarone were also excluded from the analysis. A total of 591 patients were included in the final analysis.

Definitions

The diagnosis of primary hyperthyroidism was established in the presence of a serum-free thyroxine (T4) level >23 pmol/l, and a concomitant suppressed thyroid-stimulating hormone level <0.03 pmol/l. A diagnosis of Graves’ disease was based on the clinical presentation of hyperthyroidism, usually in the presence of a diffuse goitre with or without thyroid eye signs and positive immunological markers. Presence of CHF diagnosis was retrieved from the medical records and validated with the use of modified Framingham criteria. Hypertension was defined as a systolic blood pressure of >140 mm Hg, a diastolic blood pressure of >90 mm Hg, or if the patient was prescribed drugs for hypertension. Smoking status was also recorded, with patients classified as non-smoker or current smoker.

Abbreviations: CHF; congestive heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association
Transthoracic echocardiography
Two-dimensional and M-mode transthoracic echocardiographic examinations were performed in all subjects using the System V machine (GE Medical System, Waukesha, Wisconsin, USA) with a 3.5 MHz transducer, according to the recommendations of the American Society of Echocardiography.\textsuperscript{11} Left ventricular systolic dysfunction was defined as left ventricular ejection fraction (LVEF) $<$ 50%. All studies were performed and analysed by the same experienced operator who was unaware of the patients’ clinical status.

Follow-up
In patients with hyperthyroidism and CHF, initial transthoracic echocardiography was performed after stabilisation of heart failure symptoms and adequate ventricular rate control in those with atrial fibrillation. Clinical and ECG evaluation, laboratory measurements and transthoracic echocardiography were repeated 3 months after completion of treatment (antithyroid drugs or radioactive iodine-131) for hyperthyroidism to achieve euthyroid status. Examinations were performed in all subjects using the System V machine (GE Medical System, Waukesha, Wisconsin, USA) with a 3.5 MHz transducer, according to the recommendations of the American Society of Echocardiography.\textsuperscript{15} Left ventricular systolic dysfunction at presentation was defined as left ventricular ejection fraction $<$ 50%. All studies were performed and analysed by the same experienced operator who was unaware of the patients’ clinical status.

Statistical analysis
Continuous variables are expressed as mean $\pm$ SEM. Statistical comparisons were performed using Student’s $t$ test or Fisher’s exact test, as appropriate. A logistic regression model was applied to determine clinical predictors for the occurrence of CHF and left ventricular systolic dysfunction in patients with hyperthyroidism. Multivariate analyses were performed with an enter regression model, in which each variable with a $p$ value $<$ 0.1 (based on the univariate analysis) was entered into the model. Calculations were performed using SPSS software (V.10.0). $p$ value $<$ 0.05 was considered significant.

RESULTS
Incidence of CHF
Table 1 presents the baseline demographic and clinical variables of 591 consecutive patients diagnosed with hyperthyroidism. Their mean age was 45 (1) years (range 18–97 years), and 140 patients (24%) were male. All patients were Chinese in origin. A total of 34 patients (5.8%) had symptoms of CHF at presentation. The Hong Kong West Island adult population remained stable at approximately 300,000 during the study period giving an annual incidence of CHF related to hyperthyroidism of 5.6 per 100,000 general population.

Clinical characteristics of CHF
Patients with CHF were older, most of them were male, had a higher prevalence of a history of hypertension and diabetes, and cigarette smoking, and had a higher incidence of atrial fibrillation and resting heart rate at presentation compared with patients without CHF (Table 1; $p$ value $<$ 0.05). There were no significant differences in the duration of symptoms of hyperthyroidism, serum free T$_4$ level or the incidence of Graves’ disease (Table 1; $p$ value $>$ 0.05). In multivariate analysis, only the presence of atrial fibrillation at presentation (OR 37.4, 95% CI 9.72 to 144.0, $p$ value $<$ 0.001) was an independent predictor for the occurrence of CHF in patients with hyperthyroidism.

In the 34 patients who presented with symptoms of CHF, an echocardiogram showed no evidence of marked valvular lesion, pericardial disease, or hypertrophic or infiltrative cardiomyopathy, and 16 (47%) had left ventricular systolic dysfunction, LVEF $<$ 50%. None had a history of alcohol or illicit drug misuse or exposure to cardiotoxic agents. Patients with left ventricular systolic dysfunction were also repeated at 12 months after establishment of a euthyroid state to detect delayed recovery of left ventricular systolic dysfunction.

Table 2
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Absent (n = 18)</th>
<th>Present (n = 16)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>72 (3)</td>
<td>58 (4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Male</td>
<td>6 (33)</td>
<td>14 (88)</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (17)</td>
<td>8 (50)</td>
<td>0.07</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (17)</td>
<td>2 (13)</td>
<td>1.0</td>
</tr>
<tr>
<td>Smoking history</td>
<td>4 (22)</td>
<td>9 (56)</td>
<td>0.07</td>
</tr>
<tr>
<td>Free thyroxine, pmol/l</td>
<td>66 (12)</td>
<td>39 (4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Aetiology of hyperthyroidism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves’ diseases</td>
<td>11 (61)</td>
<td>5 (31)</td>
<td>0.10</td>
</tr>
<tr>
<td>Toxic multinodular goitre</td>
<td>7 (39)</td>
<td>11 (69)</td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms of hyperthyroidism</td>
<td>40 (25)</td>
<td>38 (16)</td>
<td>0.85</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>18 (100)</td>
<td>14 (88)</td>
<td>0.21</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>140 (5)</td>
<td>137 (9)</td>
<td>0.79</td>
</tr>
<tr>
<td>LV end-diastolic dimension, cm</td>
<td>4.3 (0.1)</td>
<td>5.3 (0.2)</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>62 (2)</td>
<td>29 (2)</td>
<td>$&lt;0.01$</td>
</tr>
</tbody>
</table>

LV, left ventricle; LVEF, left ventricular ejection fraction.
Values are in n (%) or mean (SEM).
ventricular systolic dysfunction were significantly younger, with a higher prevalence of males, lower serum free T4 level and LVEF and a larger left ventricular end-diastolic dimension compared with patients without left ventricular systolic dysfunction (table 2; p<0.05). There were no significant differences in the prevalence of hypertension, diabetes and smoking, duration of symptoms of hyperthyroidism, incidence of atrial fibrillation and resting heart rate at presentation or incidence of antithyroid antibodies (table 2; p>0.05). In multivariate analysis, male sex (OR 26.6, 95% CI 2.6 to 272.5, p = 0.006) and lower serum T3 level (OR 0.93, 95% CI 0.87 to 0.99, p = 0.044) were independent predictors of left ventricular systolic dysfunction with LVEF ≤ 50% in patients with hyperthyroidism.

Clinical outcome
In the 34 patients with CHF, all achieved euthyroid status with either radioactive iodine (n = 21) or carbimazole (n = 12) treatment, except one patient who died of refractory heart failure during the initial presentation.

In the 18 patients with LVEF ≥ 50%, all had atrial fibrillation at presentation. The time to achieve satisfactory resting mean heart rate control (<90 bpm) was 3.5 (0.5) days. Symptoms of heart failure subsided after treatment with diuretics, β-blocker and carbimazole at initial presentation. Spontaneous sinus conversion from atrial fibrillation was observed in 8 of 18 patients (44%) at a mean of 121 (46) days after treatment of hyperthyroidism. During a mean follow-up of 42 (6) months, none reported any symptoms of CHF, including the 10 patients in whom atrial fibrillation persisted.

In the remaining 15 patients with LVEF ≤ 50%, 13 had atrial fibrillation at presentation. The time to achieve satisfactory mean resting heart rate control (<90 bpm) was 4.7 (0.8) days. Spontaneous sinus conversion from atrial fibrillation was observed in 6 of 13 patients (46%) at a mean of 328 (131) days after treatment of hyperthyroidism. Three months after achieving euthyroid status, LVEF (55 (4)% vs 30 (2)%, p<0.001) and New York Heart Association (NYHA) functional class (1.2 (0.1) vs 2.5 (0.2), p<0.001) had significantly improved compared with initial presentation. In 10 patients (67%), LVEF had completely recovered (65 (2)% vs 32 (2)%, p<0.01, fig 1) and none of them reported any symptoms of CHF 3 months after achieving euthyroid status. In the remaining five patients (33%), left ventricular systolic dysfunction persisted with LVEF ≤ 50%, although LVEF (36 (4)% vs 26 (5)%, p<0.01, fig 1) and NYHA functional class (1.4 (1) vs 3.2 (1), p = 0.03) had significantly improved.

There were no significant differences (p>0.05) in the demographic features of patients with or without persistent left ventricular systolic dysfunction in terms of duration of symptoms of hyperthyroidism, incidence of atrial fibrillation and resting heart rate, serum free T3 level, incidence of Graves’ disease, LVEF and left ventricular end-diastolic dimension at presentation of hyperthyroidism and time to achieve satisfactory heart rate (table 3). In addition, among those patients with atrial fibrillation at presentation, there were no significant differences in the percentage of patients with spontaneous conversion to sinus rhythm (50% vs 44%, p = 1.0) and their time to conversion (265 (260) days vs 361 (67) days, p = 0.3) between patients with and without persistent left ventricular systolic dysfunction.

In five patients with persistent left ventricular systolic dysfunction after achieving a euthyroid state, a coronary angiogram was normal in four, and a thallium SPECT scan in the remaining patient showed no evidence of myocardial ischaemia. At 1-year follow-up, three patients were in sinus rhythm and two had persistent atrial fibrillation with satisfactory heart rate control (average heart rate <80 bpm at 24 h ECG recording). Despite optimal medical treatment for heart failure in these patients, including use of an ACE inhibitor (n = 5), digoxin (n = 4), frusemide (n = 4), β-blocker (n = 3), spironolactone (n = 2) and angiotensin II antagonists (n = 2), there was no further improvement in LVEF at 1 year compared with those at 3 months after achieving a euthyroid state (36 (3)% vs 38 (4)%), p = 0.29, fig 1).

**DISCUSSION**
Although an increased workload caused by the induction of a hyperdynamic circulation during hyperthyroidism can trigger the onset of heart failure in patients with pre-existing heart disease, it may also directly induce CHF. Nevertheless, there are limited data on the incidence of CHF in patients with hyperthyroidism. This study showed that 6% of patients with hyperthyroidism developed CHF and the annual incidence is 5.6 per 100 000 general population. Consistent with previous
of overexpression of β-adrenergic receptors than female animals, possibly because of upregulation of a hyperthyroid-related gene by androgens. This increased cardiac sensitivity to β-adrenergic stimulation in males may account for their higher incidence of left ventricular systolic dysfunction related to hyperthyroidism.

The availability of effective treatment for primary hyperthyroidism has led to the widespread belief that it is a benign disorder and that all the associated adverse effects are reversible with no long-term sequelae. Although prior case studies have shown that left ventricular function improves in the majority of patients after treatment of hyperthyroidism, persistent dilated cardiomyopathy was observed in a significant proportion of patients. This is the first systematic study to show that persistent and potentially fatal dilated cardiomyopathy developed in approximately 1% (6/519 patients, including one patient who died of refractory heart failure) of patients with primary hyperthyroidism. Up to one-third of patients with left ventricular systolic dysfunction at presentation had persistent dilated cardiomyopathy during long-term follow-up. Long-term follow-up is thus vital to detect the persistence of cardiomyopathy in those patients with hyperthyroidism who have left ventricular systolic dysfunction at initial presentation.

Study limitation

In this study, echocardiography was performed only in patients with signs and symptoms of CHF. The incidence of subclinical left ventricular systolic dysfunction in those patients without CHF thus remains unknown.

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Competing interests: None.

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A 54-year-old man was admitted to our cardiovascular department because of angina on effort (Canadian class II). Angina was characterised by marked variability of the threshold and occasional episodes of rest angina. He was hypertensive, was an ex-smoker and had diabetes. In 1998, he had an inferolateral myocardial infarction and was administered medical treatment including aspirin and β-blockers. He remained asymptomatic on medical treatment up to 6 months prior to admission, when he had recurrence of angina on effort in spite of medical treatment including aspirin, β-blockers, sartan and statin. During current hospital stay, an echocardiogram revealed mild impairment of left ventricular function (ejection fraction 45%), inferolateral akinesia and moderate mitral regurgitation. A dobutamine stress test showed viable myocardium in the akinetic region. The patient underwent coronary angiography, which revealed proximal occlusion of the left circumflex artery of small size, proximal occlusion of the right coronary artery (RCA) and normal left anterior descending artery (LAD). Mild opacification of distal RCA was noted through collateral circulation originating from the septal branches of LAD (panel A). Reopening of the RCA was then attempted using a bilateral femoral approach with cannulation of the RCA by a guiding catheter and of the left coronary artery by a diagnostic catheter. A Pilot 200 guidewire (Guidant Corp, Santa Clara, California, USA) and an over the wire balloon 1.5/20 mm (Maverick 2, Boston Scientific Scimed, Maple Grove, Minnesota, USA) were initially used. Immediately prior to wire advancement across the occlusion, re-injection of the contrast medium into the RCA showed a striking improvement of collateral circulation from Rentrop class 1 to Rentrop class 3, and full opacification of posterior descending, posterolateral branch and distal part of the RCA near to the occlusion point (panel B). Notably, no intracoronary nitrates were administered due to low arterial pressure (90/60 mm Hg) since the start of the procedure. This sudden change of collateral function helped operators in wire advancement through the occlusion and entry in the distal true lumen. After multiple balloon dilatation and deployment of three drug-eluting stents (Taxus, Boston Scientific, Natick, Massachusetts, USA), the RCA was reconstructed and angiographic result was optimal (panel C). Dynamic collateral coronary circulation in man has been previously demonstrated using non-invasive techniques, and well explains the variability of anginal threshold on effort. This is the first angiographic documentation that collateral circulation in man can be extremely dynamic.

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