PAPERS AND SHORT REPORTS

Diagnostic value of thyrotrophin releasing hormone tests in elderly patients with atrial fibrillation

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Abstract

A prospective study was carried out to compare clinical and biochemical thyroid states with responses of thyroid stimulating hormone (TSH) to thyrotrophin releasing hormone (TRH) in elderly patients with either atrial fibrillation (n=75; mean age (SD) 79·3 (6·0) years) or sinus rhythm (n=73; mean age 78·4 (5·6) years) admitted consecutively to the department of geriatric medicine. No patient in either group had symptoms or signs of hyperthyroidism. Overall, the TSH responses to TRH did not differ significantly between the two groups. Ten (13%) of the patients with atrial fibrillation (of whom four had raised thyroid hormone concentrations) and five (7%) of the patients with sinus rhythm showed no TSH response to TRH while 26% of each group (20 and 19 patients, respectively) showed a much reduced response. Only one of 13 patients with apparently isolated atrial fibrillation showed no TSH response to TRH, and none of these 13 patients was hyperthyroid. In particular, three patients (two with atrial fibrillation and one with sinus rhythm) who showed no TSH response to TRH at presentation exhibited a return of TSH response to TRH at follow up six weeks later.

In conclusion, reduced or absent TSH responses to TRH are common in sick elderly patients whether they have atrial fibrillation or sinus rhythm and whether they are euthyroid or hyperthyroid biochemically. An absence of response is therefore an uncertain marker of hyperthyroidism in these groups of patients, and diagnosis and ablative treatment should be based at least on the presence of raised circulating free triiodothyronine or free thyroxine concentrations, or both.

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Introduction

Atrial fibrillation is a common arrhythmia in elderly patients. In one study 11% of a fully ambulant group of patients over the age of 75 were shown to have atrial fibrillation.[1] Other studies have shown elderly patients in hospital to have a significant prevalence of atrial fibrillation varying from 4% to 14%.[2-4] In a younger population the most common predisposing factors are rheumatic, ischaemic, and hypertensive heart disease.[5] Earlier studies suggested that atrial fibrillation was often unaccompanied by other cardiac abnormalities, but ischaemic and myopathic processes were probably overlooked.[6] It is now appreciated that fibrosis of the sinoatrial node may result in disordered automaticity and predispose to atrial arrhythmias that may be paroxysmal. In elderly patients infections such as pneumonia or infections of the urinary tract are often associated with atrial fibrillation, and after the infection has been successfully treated sinus rhythm returns.[7] While in a younger population hyperthyroidism is associated with well recognised physical signs that only rarely include atrial fibrillation, in elderly hyperthyroid patients atrial fibrillation is often present[8] though the usual physical signs may be absent.[9]

It is now accepted practice to determine the thyroid state of patients presenting with atrial fibrillation. It has been suggested that routine laboratory measurements of thyroid hormones in such patients are inadequate and that a test with thyrotrophin releasing hormone should be performed as an absence of a response of thyroid stimulating hormone (TSH) to thyrotrophin releasing hormone (TRH) would facilitate diagnosis of minor degrees of overactivity.[10-12] This view has not been wholeheartedly accepted as the evidence to support it is limited.[13]

Minor degrees of thyrotoxicosis are difficult to confirm as tests for thyroid function can be unreliable. Concentrations of thyroid hormones in ill patients may be increased or decreased, and decreased concentrations can mask biochemical hyper-

thyroidism. Basal TSH concentrations are subject to diurnal variation and may also decline with age, as may the TSH response to TRH. Various pharmaceutical preparations may also influence conventional biochemical markers of thyroid function. The practical and financial implications of detailed assessment of thyroid state in all elderly patients with atrial fibrillation are considerable, and further clarification is needed. We therefore undertook a prospective study to compare clinical state, free thyroid hormone concentrations, and TSH responses to TRH in elderly patients presenting with sinus rhythm or atrial fibrillation to determine whether the yield of thyrotoxic atrial fibrillation was enhanced by carrying out a TRH test.[10]

Patients and methods

We investigated 75 patients who presented with atrial fibrillation (mean age (SD) 79·3 (6·6) years) and 73 who presented with sinus rhythm (mean age 78·4 (5·6) years). All patients were admitted as acute medical emergencies and underwent full clinical examination, including complete assessment of thyroid state. Blood samples were taken for measurement of free thyroid hormone concentrations and thyroid antibodies, and a standard TRH test (200 μg intravenously) was performed with blood sampling at 0 and 20 minutes for measurement of TSH. This test was performed at 1100, when daytime TSH concentrations are at their nadir.

After treatment of their presenting illness a total of 42 patients with atrial fibrillation and 49 patients with sinus rhythm were followed up at six weeks. The remaining patients were not available for follow up largely because they had died as a consequence of their illness. The follow up examination included full assessment of thyroid state, blood sampling for free thyroid hormone concentrations, and a repeat standard TRH test. Free triiodothyronine and free thyroxine concentrations were measured by analogue tracer method using Amerlex kits (Amersham International, Bucks). The interassay precision of the free thyroxine assay was 4·5% at 12·7 pmol/l (0·99 μg/100 ml) and 5·8% at 42 pmol/l (3·3 μg/100 ml), and that of the free triiodothyronine assay was 3·3% at 3·4 pmol/l (2·2 pg/100 ml) and 5·7% at 11 pmol/l (7·15 pg/100 ml). TSH concentrations were measured using an immunoradiometric assay for human TSH, which has been fully validated for clinical use and described previously.[14,15] The interassay precision of the TSH assay was less than 10% at 0·5 mU/l and 4% at 10 mU/l. The TSH antibodies used do not cross react with the gonadotrophins, and there is no negative interference in the assay for TSH caused by high gonadotrophin concentrations as standard curves can be superimposed in the presence or absence of a vast excess (100 000 units) of human chorionic gonadotrophin (S Woodhead, personal communication). With this assay the normal basal circulating TSH concentration at 1100 is less than 4 mU/l and the normal range of response to TRH (200 μg intravenously) 20 minutes after administration is 4·0-18·0 mU/l. Thyroglobulin and thyroid microsomal antibodies were measured using the tanned red cell technique. A significant titre was considered to be >1/160. Data were analysed by means of the Mann-Whitney test because of their skewed distribution.

Results

Table I shows the age and sex distributions for all patients. There were no significant differences in clinical or biochemical results between the two groups. Table II presents follow up data. The only significant difference to emerge was that free thyroxine concentrations in patients with atrial fibrillation were higher than those in patients with sinus rhythm ($p < 0.05$), a difference found in the whole sample and in women but not in men. When a multiplicity of such tests of significance are being performed little importance should be attached to such an isolated significant result.

Table III summarises the relevant clinical and biochemical data. No patients in either group showed any clinical evidence at any

TABLE I—*Mean (SD) data relating to thyroid state and response of TSH to TRH at presentation in all patients*

	Patients with atrial fibrillation			Patients with sinus rhythm		
	Men (n = 33)	Women (n = 42)	Total (n = 75)	Men (n = 28)	Women (n = 45)	Total (n = 73)
Age (years)	77·7 (7·9)	80·6 (5·2)	79·3 (6·6)	76·9 (5·0)	79·4 (5·8)	78·4 (5·6)
Free thyroxine (pmol/l)	15·2 (3·0)	16·3 (7·1)	15·8 (5·6)	14·5 (3·1)	16·0 (3·8)	15·4 (3·6)
Free triiodothyronine (pmol/l)	4·1 (1·5)	4·3 (2·4)	4·2 (2·0)	3·8 (1·4)	3·7 (1·1)	3·8 (1·2)
Basal TSH (mU/l)	1·8 (2·2)	2·8 (3·5)	2·3 (3·1)	1·2 (1·1)	1·4 (1·7)	1·3 (1·5)
Peak TSH at 20 mins (mU/l)	6·6 (5·6)	10·0 (10·9)	8·5 (9·1)	4·9 (3·3)	6·6 (5·2)	6·0 (4·6)
Change in TSH (mU/l)	4·8 (4·7)	7·3 (7·8)	6·2 (6·7)	3·8 (2·7)	5·2 (3·9)	4·7 (3·6)

Conversion: SI to traditional units—Thyroxine: 1 pmol/l = 78 pg/100 ml. Triiodothyronine: 1 pmol/l = 0·65 pg/100 ml.

TABLE II—*Mean (SD) data relating to thyroid state and response of TSH to TRH at six weeks' follow up*

	Patients with atrial fibrillation			Patients with sinus rhythm		
	Men (n = 23)	Women (n = 19)	Total (n = 42)	Men (n = 20)	Women (n = 29)	Total (n = 49)
Free thyroxine (pmol/l)	15·6 (3·4)	18·8 (6·4)*	17·0 (5·2)*	14·7 (2·0)	15·0 (3·5)	14·9 (3·0)
Free triiodothyronine (pmol/l)	4·9 (1·6)	5·4 (2·1)	5·1 (1·8)	5·1 (1·3)	4·6 (1·2)	4·8 (1·3)
Basal TSH (mU/l)	1·5 (1·2)	2·2 (2·4)	1·8 (1·8)	1·1 (1·3)	1·7 (2·4)	1·5 (2·0)
Peak TSH at 20 mins (mU/l)	5·9 (4·5)	10·4 (10·5)	7·9 (8·0)	4·9 (3·8)	7·4 (5·1)	6·4 (4·7)
Change in TSH (mU/l)	4·4 (3·5)	8·2 (8·2)	6·1 (6·3)	3·8 (2·8)	5·7 (3·6)	4·9 (3·4)

*Compared with data in group with sinus rhythm: $p < 0.05$.
Conversion: SI to traditional units—Thyroxine: 1 pmol/l = 78 pg/100 ml. Triiodothyronine: 1 pmol/l = 0·65 pg/100 ml.

TABLE III—*Summary of clinical and biochemical data on presentation in all patients*

	Patients with atrial fibrillation		Patients with sinus rhythm (n = 73)	
	Isolated atrial fibrillation (n = 13)	Other illness (n = 62)	Total (n = 75)	
Clinical hyperthyroidism:				
Raised free thyroxine or free triiodothyronine, or both (>26 and >9 pmol/l*)		4	4	
Absent TSH response to TRH (rise <1 mU/l at 20 mins)	1	9	10	5
Reduced TSH response to TRH (rise <2 mU/l at 20 mins)	2	18	20	19
Clinical hypothyroidism:				
Raised basal TSH (>6 mU/l)	1	9	10	3
Positive thyroglobulin antibody (titre >1/160)	1	4	5	
Positive microsomal antibody (titre >1/160)	2	7	9	4

* >2·01 mg/100 ml and >5·85 pg/100 ml.

TABLE IV—*Summary of clinical and biochemical data for patients with no TSH response to TRH*

Case No	Age (years)	Sex	Diagnosis	Goitre	Antibodies	At presentation: Rhythm*	Free triiodothyronine	Free thyroxine	Basal TSH	TSH at 20 mins	At follow up: Rhythm*	Free triiodothyronine	Free thyroxine	Basal TSH	TSH at 20 mins
						Hyperthyroid									
1	81	F	Pleurisy		+	AF	4·8	28·0	0·1	0·2	AF	8·5	31·3	<0·1	<0·1
2	72	F	Left ventricular failure: mitral valve disease	Small	+	AF	12·1	43·0	<0·1	<0·1	AF	8·8	33·8	<0·1	<0·1
3†	87	F	Left ventricular failure		-	AF	5·0	23·2	<0·1	<0·1	AF	8·6	28·3	<0·1	<0·1
4	72	F	Asthma	Small		AF	10·3	15·5	0·1	0·2					
						Euthyroid, followed up									
5	79	M	Isolated atrial fibrillation	Small	-	AF	6·4	18·0	0·1	0·2	SR	6·9	19·9	0·1	0·1
6	71	M	Pulmonary embolism		-	AF	3·4	16·0	0·2	1·2	AF	6·2	22·3	1·3	4·9
7	76	F	Chest infection	Moderate	-	AF	5·0	17·0	0·2	0·2	AF	5·3	16·5	0·3	1·0
8	84	F	Anterior myocardial infarction	Small	-	AF	5·8	21·9	1·6	1·6	SR	5·4	16·9	1·0	4·0
9	76	M	Chronic obstructive airway disease		-	SR	4·0	18·4	0·2	0·8	SR	3·5	16·0	0·3	0·5
10	83	F	Pneumonia		-	SR	5·0	22·8	<0·1	0·6	SR	6·3	17·7	1·2	5·0
11	87	M	Left hemiparesis		-	SR	3·0	14·0	0·3	0·3	SR	5·0	15·9	0·9	0·9
12	73	M	Syncope	Small	-	SR	5·2	13·8	0·1	0·2	SR	8·0	13·9	<0·1	0·4
						Euthyroid, not followed up									
13	72	F	Enteritis			AF	1·7	9·0	0·4	1·1					
14	80	F	Congestive heart failure	(1 cm nodule)	+	AF	3·0	16·3	0·1	0·3					
15	87	F	Osteoporosis		-	SR	4·4	12·7	0·1	0·1					

*AF = Atrial fibrillation, SR = sinus rhythm.

†Family history of autoimmune thyroid disease.

Conversion: SI to traditional units—Thyroxine: 1 pmol/l = 78 pg/100 ml. Triiodothyronine: 1 pmol/l = 0·65 pg/100 ml.

stage of either hyperthyroidism or hypothyroidism. Of the patients with atrial fibrillation, 13 presented with isolated fibrillation of recent onset and 62 with other illnesses (such as those documented in table IV) in which atrial fibrillation was either longstanding or of unknown duration. Of the patients with isolated atrial fibrillation, only one displayed no TSH response to administration of TRH (<1 mU/l rise at 20 minutes). One patient had a minimally raised basal TSH concentration (>5 mU/l) suggestive of primary hypothyroidism, and three patients had significant titres of thyroid antibodies. No patient in this group had raised free thyroxine or free triiodothyronine concentrations. Of the patients with atrial fibrillation who presented with other illnesses, four showed raised free triiodothyronine or free thyroxine concentrations, or both (all of whom showed no response to TRH), and nine patients in total showed no TSH response to administration of TRH. Basal TSH concentrations were marginally raised in a further nine patients, suggesting some degree of thyroid failure, and 11 patients had positive thyroid antibodies. Among patients presenting with sinus rhythm five showed no TSH response to TRH, and none had raised free triiodothyronine or free thyroxine concentrations, or both. Three patients had raised TSH concentrations, and four had positive thyroid antibodies.

Table IV presents data for the 15 patients with no TSH response to administration of TRH. Four patients (cases 1-4) were clearly hyperthyroid on the basis of their free hormone concentrations and absent TSH responses to TRH. More particularly, three patients (cases 6, 8, and 10) with persistently normal free hormone concentrations and no TSH responses on admission showed restoration of TSH responsiveness to TRH at follow up. Those patients who had small goitres associated with non-responsiveness to TRH (cases 5, 7, 8, 12, and 14) may have had "subclinical hyperthyroidism" due to a degree of thyroid autonomy. In two of these, however, sinus rhythm had returned spontaneously at follow up, and specific antithyroid treatment was not considered to be justified in any of the patients with small goitres on the basis of the available clinical and biochemical data.

Discussion

Frank hyperthyroidism was uncommon in this large group of elderly patients presenting consecutively with atrial fibrillation with or without other illnesses. In fact, mild biochemical primary hypothyroidism (raised basal TSH concentrations) was more common than biochemical hyperthyroidism (raised free triiodothyronine or free thyroxine concentrations, or both) both in the patients with atrial fibrillation (13% *v* 5%) and in the patients with sinus rhythm (4% *v* 0%). Four out of 75 patients (5%) showed definite biochemical evidence of hyperthyroidism (three at presentation and one at follow up). In another study 13% of patients showed evidence of hyperthyroidism.[11] Surprisingly, none of the 13 patients who presented with apparently isolated atrial fibrillation showed evidence of hyperthyroidism. In the one patient in this group who had no TSH response to TRH at presentation sinus rhythm returned at follow up and free thyroid hormone concentrations remained normal and unchanged. Altogether 10 of the 75 patients (13%) with atrial fibrillation and five of the 73 (7%) with sinus rhythm showed no TSH response to TRH. More importantly, three of these 15 patients (20%) showed a return of TSH responsiveness to TRH at follow up, including one patient who presented with apparently isolated atrial fibrillation. It appears, therefore, that the absence of a TSH response to TRH would have been an unreliable marker of hyperthyroidism in this group of patients. Definite abnormalities related to the thyroid were more common in the group with atrial fibrillation than in the group with sinus rhythm, including hyperthyroidism (5% *v* 0%), biochemical primary hypothyroidism (13% *v* 4%), and significant titres of thyroid microsomal or thyroglobulin antibodies, or both (19% *v* 6%).

In a younger population of normal subjects a rise in TSH concentrations after administration of TRH to above the upper limit of the normal range for TSH would be expected (the normal range in our laboratory using an immunoradiometric assay is 4·0-18·0 mU/l). In this elderly population 20 (26%) patients with atrial fibrillation and 19 (26%) patients with sinus rhythm showed a rise of less than 2 mU/l after administration of TRH with peak concentrations at 20 minutes remaining well within normal range. They would therefore be classed as showing a reduced TSH response to TRH in comparison with a younger population. Furthermore, such small TSH responses to TRH might be classed as absent using less sensitive and precise radioimmunoassays for human TSH. We do not have control data for a comparable healthy elderly population and therefore cannot ascribe such a reduction in TSH responsiveness to either the process of aging itself or the general state of health of our patients. It seems clear from these data, however, that reduced or absent TSH responses to TRH are quite common in the sick elderly population as measured by our immunoradiometric assay for TSH and as suggested also in other recent studies in which TSH was measured by radioimmunoassay.[16 17] This phenomenon is found whether these patients have sinus rhythm or atrial fibrillation and whether they are hyperthyroid or euthyroid according to free thyroid hormone concentrations. In most cases such reduced responsiveness cannot be firmly ascribed to hyperthyroidism. Indeed, we emphasise that some patients who show no TSH response to TRH on presentation may show restoration of TSH responsiveness at subsequent follow up.

In conclusion, reduced or absent TSH responses to TRH are common in sick, elderly patients, and treatment of hyperthyroidism in such patients should not be based solely on the finding of reduced or absent TSH responses. Assessment of the TSH response to TRH, however, can still be a useful tool when hyperthyroidism is suspected as the presence of a significant TSH response firmly excludes such a diagnosis. In the absence of clinical evidence of hyperthyroidism we would suggest that

treatment is limited to those patients who show raised free triiodothyronine or thyroxine concentrations, or both, on presentation or who show a rise in free hormone concentrations to above the normal range after treatment of their intercurrent illness. In more doubtful cases a significant TSH response to TRH will exclude hyperthyroidism. We disagree with the advice of Forfar and Toft[11 12] that in elderly patients with atrial fibrillation and normal thyroid hormone concentrations the absence of a TSH response to TRH is grounds for treatment (often destructive) of hyperthyroidism.

We are grateful to Professor M S J Pathy and Dr B D Sastry for allowing us to study their patients. We also thank Dr R G Newcombe for statistical advice.

References

1 Camm AJ, Evans KE, Ward DE, Martin A. The rhythm of the heart in active elderly subjects. *Am Heart J* 1980;**99**:598-603.
2 Wosika PH, Feldman E, Chesrow EJ, Myers GB. Unipolar precordial and limb lead electrocardiograms in the aged. *Geriatrics* 1950;**5**:131-41.
3 Martin A. The natural history of atrial fibrillation in the elderly. London: London University, 1974. (MD Thesis.)
4 Mihalick MJ, Fisch C. Electrocardiographic findings in the aged. *Am Heart J* 1974;**87**:117-28.
5 Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiological features of chronic atrial fibrillation. The Framingham study. *N Engl J Med* 1982;**17**: 1018-22.
6 Selzer A. Atrial fibrillation revisited. *N Engl J Med* 1982;**306**:1044-5.
7 Burch GE, Depasquale NP. Geriatric cardiology. *Am Heart J* 1969;**78**:700-8.
8 Sandler G, Wilson GM. The nature and prognosis of heart disease in thyrotoxicosis. *Q J Med* 1959;**28**:347-69.
9 Ronnou-Jessen V, Kirkegaard C. Hyperthyroidism—a disease of old age? *Br Med J* 1973;i:41.
10 Forfar JC, Toft AD. Thyrotoxic atrial fibrillation: an underdiagnosed condition. *Br Med J* 1982;**285**:909-10.
11 Forfar JC, Miller HC, Toft AD. Occult thyrotoxicosis: a correctable cause of "idiopathic" atrial fibrillation. *Am J Cardiol* 1979;**44**:9-12.
12 Forfar JC, Feer CM, Miller HC, Toft AD. Atrial fibrillation and isolated suppression of the pituitary-thyroid axis: response to specific antithyroid therapy. *Int J Cardiol* 1981;**1**:43-8.
13 Daly JG, Greenwood RM, Himsworth RL. Thyrotoxic atrial fibrillation. *Br Med J* 1982;**285**:1574.
14 John R, Jones MK. An automated immunoradiometric assay for human thyrotrophin. *Clin Chem* 1984;**30**:1396-8.
15 John R, Woodhead JS. An automated immunoradiometric assay of thyrotrophin (TSH) in dired blood filter paper spots. *Clin Chim Acta* 1982;**125**:329-40.
16 Stahelin HB, Staub JJ, Hew-Winzeler AM, Seiler WO, Girard J. Die TRH-TSH-regulation bei Hochbetagten und bei Patienten mit seniler Demenz. *Schweiz Med Wochenschr* 1982;**112**:1784-6.
17 Kissel C, Jacques C, Saint-Martin M, Schlienger JL, Kuntzmann F. Limites de l'intérêt du test à la thyrolibérine chez la personne agée. *Presse Med* 1984;**13**: 681.

(*Accepted 5 July 1985*)

Mechanisms of malignant hypercalcaemia in carcinoma of the breast

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Abstract

To investigate the mechanisms of hypercalcaemia in carcinoma of the breast, 22 patients with hypercalcaemia due to metastatic carcinoma were studied and the findings compared with those obtained in normal subjects and patients with benign and malignant breast disease without hypercalcaemia. As expected, patients with metastases of bone showed biochemical evidence of increased bone resorption. Whereas all patients with hypercalcaemia had skeletal metastases, not all patients with skeletal metastases had hypercalcaemia despite considerable degrees of bone resorption. The presence of hypercalcaemia was associated with a significant increase in renal tubular reabsorption of calcium ($p < 0.001$) and decreased reabsorption of phosphate ($p < 0.001$) despite adequate rehydration of patients.

These studies suggest that increased renal tubular reabsorption of calcium, possibly mediated by a humoral factor with activity similar to that of parathyroid hormone, contributes appreciably to the hypercalcaemia of malignant breast disease.

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Introduction

Hypercalcaemia is a common complication of breast cancer, occurring in 10-25% of patients with disseminated disease.[1-3] The main mechanism of hypercalcaemia is increased bone resorption due either to a direct effect of the tumour on bone or to agents liberated by the tumour that activate osteoclasts.[3 4] The discrepancy between the degree of hypercalcaemia and the extent to which the skeleton is affected by metastases suggests that other mechanisms may be important.[5 6] Among the other organ systems that have a role in homoeostasis of calcium, the contribution of intestinal absorption of calcium to hypercalcaemia is likely to be minimal, as patients with hypercalcaemia have reduced intestinal absorption of calcium and low serum concentrations of 1α,25-dihydroxycholecalciferol.[7 8] Impaired renal function is likely to be important as dehydration increases renal tubular reabsorption of calcium and thus aggravates hypercalcaemia.[9] Moreover, impaired glomerular filtration, a result of both hypercalcaemia and volume depletion, decreases the ability to excrete a challenge of calcium derived from bone.

Patients and methods

We studied 22 patients with malignant hypercalcaemia due to carcinoma of the breast. Six were receiving treatment with tamoxifen (20 mg daily by mouth), and seven showed biochemical evidence of hepatic metastases. None were taking oestrogens. All showed radio-