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Natural history of autoimmune thyroiditis

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Abstract

One hundred and sixty-three asymptomatic people with thyroid antibodies or raised serum thyrotrophin (TSH) concentrations, or both, and 209 age-matched and sex-matched controls without either marker of thyroid disorder were followed up for four years to determine the natural history of autoimmune thyroiditis. Mildly raised TSH concentrations alone and the presence of thyroid antibodies alone did not significantly increase the risk of developing overt hypothyroidism during the four years compared with the controls. Overt hypothyroidism developed at the rate of 5% a year in women who initially had both raised TSH concentrations and thyroid antibodies.

Prophylactic treatment with thyroxine may be justified in women found to have both markers of impending thyroid failure. The cost effectiveness of screening the adult population remains to be evaluated.

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Introduction

Overt hypothyroidism is a common condition that develops insidiously and is often not recognised until it has been present for a considerable time. The clinical features are not specific, and the diagnosis is often made only when there is a full range of the symptoms and signs that are associated with myxoedema. In overt primary hypothyroidism serum thyrotrophin (TSH) concentrations are invariably raised, thyroxine concentrations are depressed, and thyroid antibodies are usually present, reflecting the underlying autoimmune process that is believed to be the usual cause. Raised TSH concentrations and thyroid antibodies are present before the clinical features become apparent and may be used to identify people at risk of progression to overt hypothyroidism.

The prevalence of these markers of thyroid dysfunction has been reported,[1-3] but little is known of the incidence of overt hypothyroidism in people who possess one or other or both markers. Necropsy studies of people dying from various causes have shown that lymphocytic infiltration of the thyroid (which correlates well with the presence of thyroid antibodies) is present in many such people who have lived a normal span and never had clinical evidence of thyroid disease during life.[4-6] Nevertheless, possibly an appreciable proportion of people with evidence of autoimmune thyroiditis will develop overt hypothyroidism and the earliest marker may be a raised serum TSH concentration. The present study was undertaken to determine the course of autoimmune thyroiditis and the incidence of overt hypothyroidism in the community.

Methods

The original survey was conducted in the community of Whickham near Newcastle upon Tyne.[1] All people identified in the original survey as having either thyroid antibodies or raised TSH concentrations, or both, in the absence of overt or treated thyroid disease, together with age-matched and sex-matched controls without either marker of thyroid disorder, were selected for follow-up. Participants were reassessed at two-year intervals over four years.

The reassessment consisted of a symptomatic inquiry and examination particularly for evidence of thyroid disease and vascular disease. A standard questionnaire for chest pain on effort and possible myocardial infarction[7] was repeated, and blood pressure recorded using a random zero sphygmomanometer[8] with the patient recumbent after 12-lead electrocardiography. A fasting blood sample was taken for the following measurements: serum concentrations of TSH,[9] thyroxine (Thyopac-4, Amersham), and triiodothyronine[10]; triiodothyronine Sephadex uptake (Thyopac-3, Amersham) used in conjunction with the thyroxine concentration to derive a free thyroxine index,[11] thyroglobulin antibodies,[12] and thyroid cytoplasmic (microsomal) antibodies by immunofluorescence[13] and microsomal haemagglutination techniques[14]; antibodies to gastric parietal cells, smooth muscle, mitochondria, and antinuclear factor measured by an immunofluorescence technique; and serum concentrations of cholesterol (Technicon method file N24a), triglyceride,[15] and glucose (oxidase method, Autoanalyser).

Serum from each subject was divided, half being used immediately for the above investigations and the remainder stored at −20°C until the end of the four-year study. Basal samples and those obtained at two-year and four-year follow-up were then retested in the same assay.

Thyroglobulin antibodies were scored as present at a titre of 1/20 or more and microsomal antibodies at a titre of 1/100 or more; serum TSH concentrations were defined as raised when greater than 6 mU/l in the original survey.

A postal questionnaire was sent after four years to all the other participants in the original Whickham survey, who had not been selected for special follow-up as above. This questionnaire asked if the person had developed any thyroid, heart, or blood pressure troubles since seen in the original survey. Affirmative replies were checked against family practitioner and hospital records. Practitioner records were also checked for those who failed to reply. Certified causes of death were ascertained for all people who had died during the follow-up. Data from completed questionnaires were transferred to punch cards, which were then processed using the Statistical Package for the Social Sciences.[16]

Results

Two hundred and fifty-two people with thyroid antibodies or raised TSH concentrations, or both, and 297 age-matched and sex-matched controls without either marker of thyroid disorder were selected for the follow-up study. Patients with one or both markers who had received antithyroid treatment were not included in the study. The proportion of women to men was roughly 3:1, reflecting the predominance of autoimmune thyroiditis in the former. The mean (±SD) age at selection for all subjects studied was 49 ± 15 years.

Three-quarters of those selected were seen for reassessment after two years and two-thirds after four years. At four years the proportions of subjects who had died (5·6%), moved out of the area (8·2%), or refused to participate (18·4%) were similar in the subjects with markers and controls (table I). The age and sex distributions of the 372 people remaining in the study at the end of the four years were similar in the controls and people with markers. The marker group was subdivided into: (*a*) those with antibodies and normal initial TSH concentrations; (*b*) those with raised initial TSH concentrations but no antibodies; and (*c*) those with both antibodies and raised initial TSH concentrations (table II).

TABLE I—*Numbers of people selected for study and outcome of follow-up after two and four years*

	Controls			People with markers			
	Men (n = 81)	Women (n = 216)	Total(%) (n = 297)	Men (n = 61)	Women (n = 191)	Total(%) (n = 252)	Total(%) (n = 549)
Two-year follow-up							
Seen	61	176	237 (80)	45	143	188 (75)	425 (77)
Not seen:							
Died	8	4	12 (4)	3	8	11 (4)	23 (4)
Moved	5	3	8 (3)	8	9	17 (7)	25 (5)
Refused	7	33	40 (13)	5	31	36 (14)	76 (14)
Four-year follow-up							
Seen	51	158	209 (70)	39	124	163 (65)	372 (68)
Not seen:							
Died	2	3	5 (2)	1	2	3 (1)	8 (1)
Moved	6	6	12 (4)	1	7	8 (3)	20 (4)
Refused	2	9	11 (4)	4	10	14 (6)	25 (5)

TABLE II—*Numbers of people who completed four years of follow-up*

	Men	Women
Controls	51	158
People with markers:	39	124
Antibodies alone	20	67
Raised TSH alone	9	27
Antibodies and raised TSH	10	30
	90	282

The postal questionnaire was sent to 2163 people without raised TSH concentrations or thyroid antibodies seen in the original survey, and to 76 people who had declined to participate in the special follow-up study. Replies were received from 1748 (78%), and information on the remaining 491 (22%) was sought from practitioners' records; 142 (6%) had died and 205 (9%) had moved from the area.

Causes of death for all subjects followed up in any way were ascertained from death certificates and were cardiovascular disease (2·7%), cerebrovascular disease (1·6%), and miscellaneous, including malignant disease (2·2%). The proportions of deaths due to these

causes were not significantly different between the controls and the people with markers or those sent the questionnaire.

CHANGE IN THYROID FUNCTION

Antibodies

Sera were available from all but four of the 372 people seen throughout the four-year follow-up. Thirty men and 97 women were initially positive for thyroid (predominantly microsomal) antibodies. Nine subjects were initially weakly positive for antibodies (five thyroglobulin and four microsomal); this was not confirmed on retesting the stored sera, and the results remained negative at two-year and four-year follow-up. These nine may be regarded as originally giving false-positive results.

Three women were strongly positive for microsomal antibodies (one of whom was also strongly positive for thyroglobulin antibodies), and this was confirmed on retesting the original sera, but antibodies were absent at two-year and four-year follow-up. Antibodies thus disappeared from three out of 88 women over four years.

Sixty men (51 controls and nine subjects with raised initial TSH concentrations) and 185 women (158 controls and 27 subjects with raised initial TSH concentrations) had no antibodies initially. Ten women who were thought to have no antibodies when first tested but were positive for microsomal antibodies after two and four years were found to have been positive for antibodies when the original sera were retested; they may be regarded as originally giving false-negative results. Antibodies developed in 16 women (13 controls and three subjects with raised initial TSH concentrations) who had no antibodies originally, confirmed on retesting. Antibodies thus appeared in 16 out of 175 women over four years. The antibody state of the men did not change throughout the study.

TSH

Sera for assay of TSH concentrations were available from 353 of the 372 people seen throughout the follow-up. Samples were obtained from 190 controls (139 women and 51 men) and 163 subjects with markers (124 women and 39 men). TSH concentrations in all the groups studied were significantly lower at the two-year follow-up than basally and at four-year follow-up. This interassay variation was eliminated when all the avilable sera from each subject were retested in the same assay at the end of the follow-up, although the reassay values tended to be lower than the original values (table III).

Mean TSH concentrations in the controls did not vary significantly over the four years when retested, and only 5% of the women and none of the men developed a concentration above 6 mU/l. Mean concentrations in the 67 women and 20 men who initially had only antibodies as a marker were significantly higher than those in the controls throughout the study but remained in the normal range, and only 10 (12%) of these subjects developed a concentration above 6 mU/l over the four years. Mean concentrations in the 27 women and nine men who initially had raised concentrations but no antibodies tended to regress to the mean over four years, although this decline was not significant when the samples were reassayed. The concentrations in this group ranged from 6 to 10 mU/l initially and rose above this subsequently in only one subject. Mean concentrations in the 30 women and 10 men who initially had antibodies and raised concentrations were significantly higher than those in the people who initially had only one marker. Concentrations remained raised in this group throughout the study (excluding those who developed overt hypothyroidism, whose concentration fell in response to treatment—see below). The range of initial concentrations in this group was 6-24 mU/l; the concentration fell in only one subject, in whom it had initially been about 6 mU/l.

TABLE III—*Mean TSH concentrations (mU/l) basally and at two-year and four-year follow-up, comparing values obtained originally and when samples were reassayed at end of study**

	No of subjects	Original values			Values on reassay		
		Basal	2-year	4-year	Basal	2-year	4-year
		Men					
Controls	49	2·0	1·5	2·6	1·6	1·5	1·2
People with markers:							
Antibodies alone	17	2·8	3·0	4·5	3·2	2·8	2·8
Raised TSH alone	9	8·1	2·7	5·3	4·0	2·9	3·4
Antibodies and raised TSH	7	8·4	5·9	11·1	5·8	5·9	9·2
		Women					
Controls	129	2·5	2·1	3·6	1·9	1·8	1·8
People with markers:							
Antibodies alone	53	2·7	2·4	4·4	2·4	2·4	2·8
Raised TSH alone	27	7·4	2·7	5·0	3·4	3·1	3·2
Antibodies and raised TSH	21	11·0	8·5	12·8	7·0	8·0	8·6

*Subjects who became overtly hypothyroid and were treated during the study and those for whom samples were missing are excluded.

TABLE IV—*Mean free thyroxine index basally and at two-year and four-year follow-up**

	Men				Women			
	No of subjects	Free thyroxine index			No of subjects	Free thyroxine index		
		Basal	2-year	4-year		Basal	2-year	4-year
Controls	51	94	112	97	127	101	112	103
People with markers:								
Antibodies alone	20	97	104	96	53	100	103	96
Raised TSH alone	9	100	114	88	20	89	110	96
Antibodies and raised TSH	10	79	90	82	20	84	76	71

*Subjects who became overtly hypothyroid and were treated during the study and those for whom samples were missing are excluded.

Circulating thyroid hormone concentrations

Mean free thyroxine index was lowest at all stages in the people with both markers (table IV). Mean values were higher in all subjects at two-year follow-up than originally or at the four-year follow-up, except in women with both markers, in whom the index fell steadily. The fall in the index in this group was significant, whereas fluctuations in the controls and other marker groups may be explained by normal interassay variation.

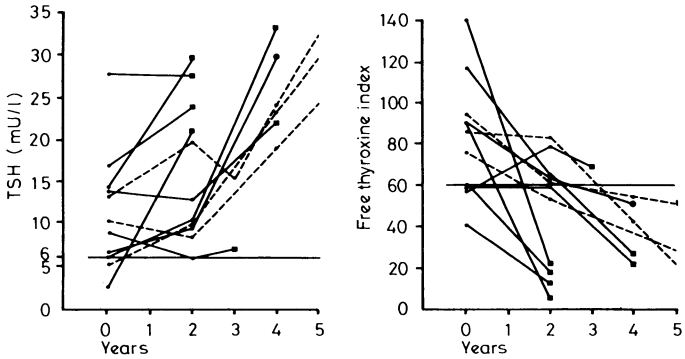
Mean triiodothyronine concentrations were not significantly different between controls and any marker group either initially or at two- and four-year follow-up.

Thyrotoxicosis

Thyrotoxicosis developed in two women, both controls, who developed clinical as well as biochemical features of hyperthyroidism. Five other women, who did not have clinical evidence of hyperthyroidism, showed borderline increases in serum thyroxine concentrations and free thyroxine index, which were not confirmed on retesting.

DEVELOPMENT OF OVERT HYPOTHYROIDISM

Seven women and one man became overtly hypothyroid during the study, four in the first and four in the second two years. All eight had thyroid antibodies and seven raised TSH concentrations when first seen. All developed symptoms and signs consistent with clinical hypothyroidism. Their TSH concentrations rose and thyroxine concentrations fell before treatment with thyroxine (figure), which led to clinical improvement and return of these two concentrations to the normal range. Three other women, who had antibodies and raised



TSH concentrations and free thyroxine index in seven women (———■) and one man (———●) who developed overt hypothyroidism during the study and three women (- - - -) who subsequently developed clinical as well as biochemical evidence of hypothyroidism.

TSH concentrations initially (6, 10, and 14 mU/l respectively), also showed a progressive rise in TSH concentrations and fall in thyroxine concentrations to below the normal range but were not recognised as clinically hypothyroid at the four-year follow-up. It was predicted that they would soon become overtly hypothyroid, and this occurred in all three within the following year. These three subjects although biochemically hypothyroid were not included in the subsequent analysis of the incidence of overt hypothyroidism.

One woman of the 67 who initially had antibodies but normal TSH concentrations became overtly hypothyroid during the four years. None of the controls and none of the subjects who initially had raised TSH concentrations but no antibodies became overtly hypothyroid.

Six of the 30 women and one of the 10 men who initially had both raised TSH concentrations and thyroid antibodies became overtly hypothyroid during four years.

None of the subjects sent the questionnaire after four years had developed overt thyroid disease; thus, on the assumption that those identified in the group with markers represent all the cases of overt hypothyroidism occurring in the original sample of the population (1285 men, 1494 women) the annual incidence of overt hypothyroidism is between 1 and 2/1000 women and about 1/5000 men.

ELECTROCARDIOGRAPHIC CHANGES

An association between minor electrocardiographic changes and raised TSH concentrations but not the presence of antibodies was found in women in the original survey. This association was present in women selected for follow-up but disappeared over the four years. Fifteen women initially had raised TSH concentrations and minor electrocardiographic changes, but both of these returned to normal in six (four of whom were treated with thyroxine); the TSH concentration fell spontaneously to normal in six others, whose electrocardiographic abnormalities persisted (four of whom had evidence of ischaemic heart disease); and the concentrations remained raised in three, whose electrocardiograms returned to normal.

LIPID CONCENTRATIONS

Mean fasting cholesterol and triglyceride concentrations were not significantly different between controls and the marker group at all stages of follow-up. Mean (±SD) basal cholesterol concentrations in the women with both markers of thyroid disease were higher than those in the controls (6·9±1·20 *v* 6·3±1·14 mmol/l; 267±46 *v* 244±44 mg/100 ml), and this difference persisted but did not increase during the follow-up (6·7±1·24 *v* 6·1±1·19 mmol/l (259±48 *v* 236±46 mg/100 ml) after four years). Mean cholesterol concentrations in the women with only one marker were not significantly different from those in the controls at any stage. Among the eight people who developed overt hypothyroidism four originally had cholesterol concentrations below and four above the mean in the controls.

Discussion

By itself a raised TSH concentration did not appear to have any predictive value for the development of overt hypothyroidism over four years. Possibly this was because most of the concentrations were only slightly increased—that is, between 6 and 10 mU/l. The mean and range of TSH concentrations were considerably higher in subjects in whom TSH concentrations were raised and antibodies present: 5% of these women developed overt hypothyroidism a year. In a highly selected group of subjects with autoimmune thyroiditis whose initial TSH concentrations were above 19 mU/l Gordin and Lamberg[17] showed that overt hypothyroidism developed at a rate of roughly 10% per annum over three years. Thus the higher the TSH concentration the greater the likelihood of developing overt hypothyroidism. We were unable to show any relation between the degree of increase of TSH concentrations and increasing titre of antibodies.

Interassay variation is considerable in all radioimmunoassays and was a major handicap in our evaluation of borderline values, most of which fell at two years but were higher at four years. Repeat assays of all the stored samples after four years eliminated interassay variation but did not exclude the effect of deterioration of the earlier samples because of longer storage. All samples were taken between 9 and 11 am so that diurnal variation was unlikely to account for the observed variation, and people were seen close to the anniversary of their original visit, so that seasonal variation was not a factor. Nevertheless, the mild fluctuations in TSH values might have been spontaneous, while the mean free thyroxine index was higher at two years than basally or at four years. In practical terms, in the absence of any evidence of underlying autoimmune thyroiditis mildly raised TSH concentrations are of doubtful clinical importance and should be rechecked.

Antibodies were initially scored as present at very low titres—that is, 1/20 for thyroglobulin, 1/10 for cytoplasmic immunofluorescence, and 1/100 for microsomal haemagglutination. Although microsomal haemagglutination occurred in over 80% of subjects in whom results of immunofluorescence testing were positive,[14] perhaps not surprisingly up to 5% of tests yielded false-positive or false-negative results. Thyroglobulin titres of 1/40 and microsomal titres of 1/200 or more disappeared genuinely from only three subjects. It was to be expected that antibodies would appear spontaneously in some women in the middle age range, and our annual incidence of 2% is consistent with the known rapid rise in the prevalence of antibodies in women aged over 45. Mean microsomal antibody titres tended to increase (by one dilution—that is, from 1/400 to 1/800) over the four years in those in whom these antibodies were present at the beginning of the study.

The meaning of minor electrocardiographic changes remains

open to question. Minor ST and T-wave changes have some prognostic importance for ischaemic heart disease[18 19] but are evanescent. In the original survey[20] minor electrocardiographic changes showed a weak association with raised TSH concentrations, but this disappeared during follow-up. The proportion of deaths due to cardiovascular disease was not significantly different between controls and the marker groups. Thus there was no evidence of any association between ischaemic heart disease and symptomless autoimmune thyroiditis,[21] but the numbers were small.

Mean fasting cholesterol and triglyceride concentrations were not significantly different between controls and subjects with only one marker. Although mean cholesterol concentrations were slightly higher in women with both markers, they were within the normal range, did not change during follow-up, and had no prognostic value in identifying those who developed overt hypothyroidism. There was thus no evidence to support the hypothesis that raised cholesterol concentrations indicate premyxoedema.[22 23]

PREVENTION OF OVERT HYPOTHYROIDISM

In our survey three women with unequivocal biochemical hypothyroidism were not detected clinically. Should people with antibodies and raised TSH concentrations be treated with thyroxine to prevent the development of overt hypothyroidism? The people in this study were not patients but randomly selected from a cross-section of the community. Before advocating widespread screening of adult women for raised TSH concentration and antibodies it is important to decide whether subjects having these should be treated. Arguments in favour of treatment are as follows: (*a*) overt hypothyroidism develops insidiously and may impair mental and physical function; (*b*) the incidence of overt hypothyroidism in women with both markers is 5% per annum. Moreover, this is cumulative, so that after four years 20% are affected and after 10 years half might have overt hypothyroidism; (*c*) treatment is simple, cheap, and effective; and (*d*) women may not realise they were functioning below normal until they realise how much better they feel with treatment.

Arguments against treatment of asymptomatic individuals with both markers include: (*a*) many women live their normal span without ever developing clinical evidence of thyroid disorder; (*b*) treatment may prevent one in 20 developing overt hypothyroidism in one year, but 19 will be treated unnecessarily; (*c*) thyroxine may be dangerous particularly in exacerbating ischaemic heart disease; (*d*) some of the cases of overt hypothyroidism will be recognised anyway; and (*e*) some people with overt hypothyroidism fail to take their thyroxine regularly, and hence probably those women who are asymptomatic and feel no benefit from treatment may default.

If the data from Whickham are applicable to the population of Great Britain with roughly 20 million adult women, 5% (that is, one million) would have both raised TSH concentrations and thyroid antibodies. Of them, 5% per annum (that is, 50 000) might develop or be prevented from developing overt hypothyroidism. The logistics of setting up a screening programme for all adult women would be considerable. Higher returns for the investment would be obtained from screening, say, only women over the age of 45. The cost effectiveness of such a programme would depend on the balance between its costs and the cost of the morbidity of untreated hypothyroidism, which is much more difficult to determine.

Until now we have not advocated treatment for *asymptomatic* people found to have thyroid antibodies or raised TSH concentrations on the grounds that the natural course was not known and that the benefits of treatment might not outweigh the disadvantages. Now our view has been modified by the findings of the present study. It seems reasonable to recommend thyroxine treatment for women presenting to their doctor who are found to have both raised TSH concentrations and antibodies (but neither alone) provided there is no hazard—for example, exacerbating ischaemic heart disease. Nevertheless, we are not advocating a widespread screening programme for autoimmune thyroditis in the whole population: this must await a precise economic evaluation. On the other hand, it may be worth while screening high-risk groups such as postmenopausal women attending a clinic for any reason or in hospital wards (particularly geriatric) and women attending diabetic clinics or thyroid clinics who have had destructive treatment of the thyroid by surgery or radioiodine.

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