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ORIGINAL ARTICLE

Natural history of subclinical hyperthyroidism in elderly patients with TSH between 0·1 and 0·4 mIU/l: a prospective study

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Summary

Context One important aspect in the decision to treat or not elderly patients with subclinical hyperthyroidism (SCH) is the risk of progression to overt hyperthyroidism (OH).

Objective To define the natural history of endogenous SCH in elderly patients with TSH between 0·1 and 0·4 mIU/l.

Design Prospective study. One hundred and two women aged ≥60 years with persistently low TSH ranging from 0·1 to 0·4 mIU/l and normal free T4 and T3 were studied. Patients using L-T4 or antithyroid drugs, previously treated for hyperthyroidism, with pituitary disease, using corticosteroids, amiodarone, dopaminergic agonists, with atrial fibrillation or heart disease were excluded. Seven patients had Graves' disease, 91 had nodular disease and 4 presented no defined cause. The time of follow-up ranged from 12 to 70 months (median 41 months).

Results Three patients progressed to OH (elevated T4 and/or T3) and four other patients to persistently low TSH (<0·1 mIU/l) in the presence of increase in serum T3 when compared with baseline. These patients were treated. Twenty-four women presented sustained normalization of TSH and none progressed to hypothyroidism. SCH with TSH in the 0·1–0·4 mIU/l range persisted in 71 patients, 4 of them (5·6%) being treated because of the development of atrial fibrillation or heart disease during follow-up. The only independent predictor of progression of SCH was an initial TSH value <0·2 mIU/l.

Conclusions In elderly patients with endogenous SCH and TSH between 0·1 and 0·4 mIU/l progression to clinical hyperthyroidism is uncommon (approximately 1% per year), spontaneous TSH normalization may occur, and persistence of SCH for many years is the most likely.

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Introduction

One important aspect in the decision to treat or not elderly patients with subclinical hyperthyroidism [SCH (persistently low TSH, excluding nonthyroid causes, in the presence of normal T4 and T3 levels)] is the risk of progression to overt hyperthyroidism (OH). Elderly subjects with SCH and TSH <0·1 mIU/l present a marked risk of progressing to OH[1–5] and there is consensus regarding the need for treating these patients.[6–11]

Considering that SCH is more common in the elderly patients,[12,13] that these patients require different management and that TSH >0·1 mIU/l is more frequent than TSH <0·1 mIU/l,[5,14–18] studies evaluating the risk of progression to OH in elderly patients with endogenous SCH and TSH between 0·1 and 0·4 mIU/l are of interest for clinical practice. In this specific situation, older studies have shown that progression to OH occurs in exceptional cases,[4,14,15] whereas in a recent series, progression to clinical thyrotoxicosis was common among patients aged ≥65 years with TSH in the 0·1 to 0·5 mIU/l range.[5] The need for treatment in these cases, in the absence of atrial fibrillation or heart disease, remains controversial.[6,7,10,11,19,20]

In order to contribute to this definition, a prospective study regarding the natural history of endogenous SCH in elderly patients with TSH between 0·1 and 0·4 mIU/l was conducted.

Materials and methods

Subjects and study design

Prospective study. All women aged ≥60 years seen on an outpatient basis by the author (P.W. Rosario) between March 2003 and March 2008 were screened for thyroid dysfunction (measurement of TSH), regardless of the reason for their visit. Values ranging from 0·1 to 0·4 mIU/l were the initial criterion for selection. Patients using L-T4 or antithyroid drugs; previously treated for hyperthyroidism; with pituitary disease; and using corticosteroids, amiodarone, dopaminergic agonists, tiratricol (weight loss formulations) were excluded. In the remaining patients, TSH (new measurement), free T4 and T3 were measured after 12 weeks. Persistently low TSH ranging from 0·1 to 0·4 mIU/l and normal free T4 and T3 were necessary for the diagnosis of SCH.

Graves' disease was diagnosed when diffuse uptake was detected by scintigraphy associated with ophthalmopathy and/or positive

TSH-receptor antibody (TRAb). Uni- or multinodular disease was defined by scintigraphy and thyroid nodule(s) were confirmed by ultrasonography. The cause of SCH was not established if diffuse uptake was detected by scintigraphy but no ophthalmopathy or TRAb were present.

Patients with known atrial fibrillation or heart disease or who were diagnosed with these conditions after a clinical suspicion were treated for SCH and excluded.

Patients who were not treated initially were submitted to clinical and laboratory (TSH, free T4 and T3) evaluation at intervals of 3–6 months.

The study was approved by the Ethics Committee of our Institution.

The following outcome variables were analysed: rate of spontaneous and sustained normalization of TSH (>0·4 mIU/l on two or more consecutive assessments performed at intervals ≥3 months); need for treatment due to the development of atrial fibrillation or heart disease; persistence; and progression of SCH [in the latter case, progression to OH (elevated T4 and/or T3) or persistently TSH <0·1 mIU/l (on two or more consecutive assessments performed at intervals ≥8 weeks) in the presence of any increase in serum T3 compared to baseline]. Data obtained until the last assessment were considered in the case of patients who were lost ($n = 3$) or died ($n = 5$) during follow-up.

Assays

TSH was measured with a chemiluminescent assay (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA, USA), with reference values of 0·4–4 mIU/l, *functional sensitivity* of 0·02 mIU/l, and *intra- and interassay* coefficients of variation <7% for values ranging from 0·1 to 40 mIU/l. Free T4 and total T3 were also measured with a chemiluminescent assay (Immulite 2000, Diagnostic Products Corporation), with reference values of 9–23 pmol/l and 1·2–2·7 nmol/l, respectively. TRAb were determined by a radioimmunoassay (radioreceptor), with >10% inhibition being considered to be positive.

Imaging

Ultrasound was performed with a multifrequency (10 MHz) linear transducer. Scintigraphy was carried out 24 h after the administration of 100–300 μCi ^{131}I.

Statistical analysis

The χ^2-test or Fisher's exact test were used for ratio comparisons. Multivariate Cox regression models were used to assess the independent effect of different variables on the risk to progression of SCH. The level of significance was set at $P < 0{\cdot}05$.

Results

A total of 117 patients had TSH between 0·1 and 0·4 mIU/l in the absence of any apparent cause (use of L-T4, history of hyperthyroidism, pituitary disease, or use of others medications). However, repetition of the test after 3 months showed spontaneous normalization in 15 (13%), 12 of them without nodular thyroid disease or Graves' disease. The remaining 102 patients comprised the group followed up in this study.

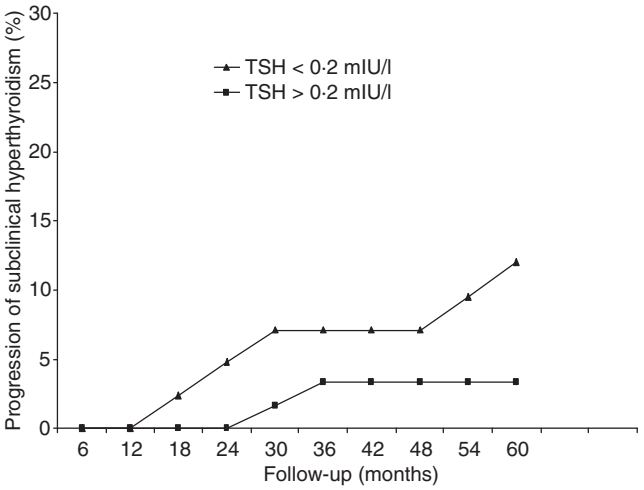

Fig. 1 Patients who presented progression of SCH during follow-up according to initial TSH values.

The age of the patients at diagnosis ranged from 60 to 78 years (median 68 years). Ninety-one patients had nodular disease and 11 presented diffuse uptake detected by scintigraphy [2 with ophthalmopathy and TRAb, 5 with TRAb only (Graves' disease) and no ophthalmopathy or TRAb was present in 4 (cause of SCH not established)]. TSH levels ranged from 0·1 to 0·38 mIU/l (median 0·23 mIU/l), free T4 from 15·3 to 22 pmol/l (median 18 pmol/l), and total T3 from 1·8 to 2·6 nmol/l (median 2·2 nmol/l). The time of follow-up ranged from 12 to 70 months (median 41 months).

Three (2·9%) patients progressed to OH (elevated T4 and/or T3) and 4 (3·9%) other patients to persistently low TSH (<0·1 mIU/l) in the presence of increase in serum T3 when compared with baseline. These patients were treated. Twenty-four (23·5%) women presented sustained normalization of TSH. None of the patients progressed to hypothyroidism. SCH with TSH in the 0·1 to 0·4 mIU/l range persisted in 71 patients (69·5%), 4 (5·6%) of them being treated due to the development of atrial fibrillation ($n = 3$) or heart disease ($n = 1$) during follow-up. Thus, 11 (10·8%) patients required treatment. Among patients with nodular disease ($n = 91$), 3 (3·3%) progressed to OH, 3 (3·3%) others to persistently low TSH (<0·1 mIU/l), 20 (22%) presented normalization of TSH, and 65 (71·4%) persisted with TSH in the 0·1 to 0·4 mIU/l range. Ten (11%) patients with nodular disease required treatment.

The only independent predictor of progression of SCH was an initial TSH value <0·2 mIU/L [5/42 (12%) *vs.* 2/60 (3·3%) with TSH ≥0·2 mIU/l ($P < 0{\cdot}05$)]. The percentage of patients who presented progression of SCH during follow-up according to initial TSH values is shown in Fig. 1.

Discussion

According to the objective of this study, this discussion will be limited to the natural history of endogenous SCH in elderly patients with TSH ≥0·1 mIU/l.

Previous studies had evaluated the progression to clinical hyperthyroidism and predictive factors of this outcome in patients with autonomous thyroid nodules and normal thyroid hormone levels, but TSH levels were not determined.[21,22] Thus, it is unknown how many patients had normal, reduced or undetectable TSH and, consequently, what were the progression rates to thyrotoxicosis according to initial TSH levels.

Current knowledge about the natural history of endogenous SCH with TSH ≥0·1 mIU/l is based on observational studies that were not optimized for this purpose.[4,14,15] These studies showed that the rate of progression to clinically manifest hyperthyroidism was very low in the situation discussed. In the study of Parle *et al.*[4] none of the 50 elderly patients with TSH between 0·05 and 0·5 mIU/l followed up for 1 year progressed to clinical hyperthyroidism. The same group found that only 3/70 subjects aged >60 years with TSH <0·5 mIU/l progressed to clinical thyrotoxicosis after 10 years of follow-up.[15] Sawin *et al.* reported that only 1/168 patients with initial TSH between 0·1 and 0·4 mIU/l progressed to long-term clinically manifest hyperthyroidism.[14] No second measurement of TSH at an interval of 2 or 3 months was performed in these studies. Furthermore, nonthyroid causes of low TSH were not excluded in detail and the presence of thyroid disease was not demonstrated. Reduced (detectable) TSH alone does not necessarily indicate SCH in the absence of confirmation by a new measurement, adequate exclusion of nonthyroid causes and/or confirmation of thyroid disease. Thus, it is possible that a smaller number of patients in fact presented SCH in those studies,[4,14,15] and the rates reported may therefore not reflect the true natural history of endogenous SCH in elderly with TSH ≥0·1 mIU/l.

In contrast to previous studies,[4,14,15] a recent study in which the TSH measurement was repeated, nonthyroid causes of low TSH were excluded, and 53/56 patients had confirmed thyroid disease (the diagnosis of SCH was unequivocal), reported a rate of progression to OH of 32% within only 4 years in patients with TSH between 0·1 and 0·5 mIU/l, but the study was retrospective.[5]

In the present study, low TSH was confirmed after 3 months, nonthyroid causes were excluded before the definition of SCH, and thyroid disease was demonstrated in 96% of the patients with this diagnosis. Subsequent mean follow-up of 41 months showed that only 3/102 patients progressed to OH (elevated T4 and/or T3); whereas 4 other patients progressed to persistently low TSH (<0·1 mIU/l) in the presence of increase in serum T3 when compared with baseline (but still normal). In contrast to the previous investigations, our study was prospective, was performed with this objective, i.e. evaluation of the natural history of endogenous SCH, and was more judicious in establishing the diagnosis of SCH.

In a previous study from our group, we reported a rate of progression to OH of 27% within only 2 years in patients with endogenous SCH and TSH <0·1 mIU/l,[23] a value much higher than that observed in the present investigation. The distinction between TSH <0·1 mIU/l *vs.* 0·1 to 0·45 mIU/l seems adequate,[6] at least when investigating the natural history of endogenous SCH. The progression to OH is clearly more frequent in the first group.

In view of the limitations mentioned earlier (no second measurement of TSH was obtained at an interval of 2 or 3 months, nonthyroid causes of low TSH were not excluded in detail, lack of demonstration of the presence of thyroid disease), the surprising rate of spontaneous TSH normalization already in the first year (76%) reported by Parle *et al.*[4] for elderly patients with TSH between 0·05 and 0·5 mIU/l and by Meyerovitch *et al.*[24] for subjects with TSH <0·35 mIU/l after 5 years (51%) might be overestimated. In the series of Díez and Iglesias, this rate was only 10·5% for patients with TSH between 0·1 and 0·5 mIU/l after 4 years of follow-up.[5] We found a TSH normalization rate of 23·5% after 3·5 years of follow-up.

We conclude that in elderly patients with endogenous SCH and TSH between 0·1 and 0·4 mIU/l progression to OH is uncommon (approximately 1% per year), spontaneous TSH normalization may occur, and persistence of SCH for many years is the most likely. In the last group (persistently low TSH between 0·1 and 0·4 mIU/l), the rate of development of atrial fibrillation or heart disease was approximately 1·6% per year. Taken together with recent data demonstrating the lack of an association between SCH and higher overall or cardiovascular mortality in the elderly,[25] these results favour the clinical-laboratory follow-up of these patients instead of the ready institution of treatment, and indicate the need for further studies on the natural history and true repercussions of SCH in elderly patients with TSH between 0·1 and 0·4 mIU/l and even for randomized trials evaluating the benefit of intervention with antithyroid drugs or radioiodine before progression of the disease.

Competing interests/financial disclosure

The author has nothing to disclose.

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