Thyroid Disease in the Elderly. Part 2. Predictability of Subclinical Hypothyroidism

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Background. The purpose of this study was to determine how well hypothyroidism could be predicted from clinical signs and symptoms in elderly patients with no known history of thyroid disease.

Methods. This retrospective study was conducted in a primary care geriatrics clinic. Two hundred eighty-three patients (205 women, 78 men), who were between the ages of 60 and 97 years of age and had no history of thyroid disease, were included in the study. Medical records of patients were reviewed for data obtained at their first visit to the clinic: serum thyroid-stimulating hormone (TSH), free thyroxine (T_4), height, weight, demographic variables, clinical signs and symptoms of hypothyroidism, previous history of thyroid disease and treatment with thyroid medications, and current medications.

Results. Of the 283 patients with no previous history of thyroid disease, 15.4% of men and 14.6% of women had subclinical hypothyroidism (TSH levels of 5.0 to 14.9 μU/mL, and normal free T_4 levels [0.7 to 2.0 ng/dL]). Overt hypothyroidism (TSH $\geq$ 15.0 μU/mL, low free T_4 < 0.7 ng/dL) was discovered and subsequently treated in one male and two female patients. There were no significant differences ($P > .05$) in the frequencies of any of the clinical signs and symptoms of hypothyroidism between euthyroid and hypothyroid patients. There was no significant relationship between TSH levels and the total number of hypothyroid symptoms experienced by all patients ($r = -.004$, $P = .99$). Logistic regression analyses determined that clinical signs and symptoms were poor predictors of subclinical hypothyroidism in these elderly patients.

Conclusions. Thyroid status could not be predicted from clinical signs and symptoms in this sample of elderly community-dwelling patients. This finding substantiates the difficulty of diagnosing subclinical hypothyroidism in the elderly based solely on clinical features.

Key words. Hypothyroidism; thyrotropin (thyroid-stimulating hormone); geriatric assessment; logistic (regression) models. (*J Fam Pract 1994; 38:583-588*)

It is generally agreed that hypothyroidism is common in the elderly, although it can have an atypical presentation in this patient population.[1,2] Classic signs and symptoms of overt, clinical hypothyroidism are often unrecognized until late in the disease and are nonspecific, resembling symptoms of nonthyroidal diseases and the aging process itself. Patients with subclinical or compensated hypothyroidism have normal thyroid hormone concentrations and may not show clinical features of hypothyroidism, except for elevated levels of thyroid-stimulating hormone (TSH). Studies tracking the natural progression of subclinical hypothyroidism have revealed that about one third of patients with subclinical hypothyroidism developed overt hypothyroidism.[3,4]

Given the vague, nonspecific symptoms associated with thyroid failure in the elderly, it has been suggested that TSH tests be part of routine thyroid function screening in the geriatric population.[1,2,5] The benefit of routine TSH screening is still questioned because of lack of evidence that treatment of asymptomatic people im-

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proves outcomes. Recently, Zazove et al[6] considered thyroid function screening to be a high-effort intervention given the cost of screening all elderly. Thus, they did not support routine thyroid screening as a preventive health care recommendation, even for elderly women.

One possible solution to this issue would be to make more effective use of all the clinical information available. While no single clinical sign is a reliable indicator of thyroid failure, it is possible that an index combining several signs, each slightly associated with hypothyroidism, would be a valuable predictive tool with little or no associated cost. White and Walmsley,[7] for example, found that 78% of patients with five or more symptoms of hypothyroidism were diagnosed as hypothyroid by laboratory function tests. A similar approach could prove useful in an elderly population.

The purpose of this study was to determine the predictability of subclinical hypothyroidism based on clinical signs and symptoms in elderly patients with no known history of thyroid disease.

Methods

Patients

Patients with no previously diagnosed thyroid disease (N = 283) were selected from the patient population of a primary care geriatrics clinic of the Department of Family Medicine, Oklahoma City, Oklahoma. This clinic was located at the O'Donoghue Rehabilitation Institute. The patients were community-dwelling elders who were self-referred to the clinic. None of the patients were referred to the clinic from the inpatient rehabilitation service. The age distribution of the patient sample was: 3.2%, 60 to 64 years old; 41.3%, 65 to 74; 41%, 75 to 84; and 14.5%, 85 years and older.

This retrospective study reviewed the medical records of the patients for demographic variables, height and weight, TSH levels, free T_4 levels, clinical signs and symptoms of hypothyroidism, and medications obtained at the first visit to the clinic. A detailed medical history questionnaire, which provided data on previous history of thyroid disease and medications, was completed by each patient at home and brought to the first clinic appointment. Each patient underwent a comprehensive physical examination and routine laboratory tests as part of the initial visit. Current signs and symptoms of hypothyroidism were obtained both from the review of systems completed by the patient before the visit and from the physical examination. Presence or absence of 26 possible clinical signs and symptoms were recorded (Table 1).[8] All patients were examined by board-certified family physicians who also had Certificates of Added Qualification in Geriatrics.

Table 1. 26 Signs and Symptoms Classically Attributed to Hypothyroidism

Weakness	Lethargy*
Anorexia	Constipation
Weight gain*	Hair loss
Dry skin*	Hair coarseness*
Coarse skin	Cold skin*
Skin pallor*	Decreased sweating
Sensation of cold	Peripheral edema
Lip pallor	Facial edema
Eyelid edema*	Hoarseness or aphonia
Thick tongue	Palpitation*
Slow speech	Dyspnea*
Memory impairment*	Deafness
Nervousness	Precordial pain

List adapted from Ingbar[8]
**Denotes clinical signs that were entered into the model for prediction of thyroid status by forward selection multiple regression analysis.*

Thyroid Screening

TSH determination is part of the routine blood screening performed on new patients at this geriatrics clinic. Patients who had elevated TSH levels detected from the initial screening had free T_4 tests during the first follow-up visit. Thus, free T_4 data were not available for patients with normal TSH levels. Blood samples were obtained by venipuncture with patients in a non-fasting state. Serum TSH levels were assayed by highly sensitive immunoassay kits (Nichols Institute, San Juan Capistrano, Calif) based on competitive binding of monoclonal antibodies with high affinity and specificity for TSH. The sensitivity of the TSH immunoassay was 0.04 μU/mL (0.04 mU/L). Serum free T_4 levels were determined by a competitive immunoassay procedure (Ciba-Corning Automated Chemiluminescence System, Ciba-Corning Diagnostics Corporation, Medfield, Mass). Interassay variations ranged from 4.1% to 11.7% for TSH and from 5.7% to 11.4% for free T_4. Patients were categorized as having subclinical hypothyroidism if their TSH levels were within the range of 5.0 to 14.9 μU/mL (5.0 to 14.9 mU/L) and free T_4 levels were normal (0.7 to 2.0 ng/dL [9–25.7 pmol/L]). The criteria for overt hypothyroidism were TSH levels $\geq$15 μU/mL ($\geq$15 mU/L) and low free T_4 levels ($<$0.7 ng/dL [$<$9 pmol/L]).

Data Analyses

The relationships of thyroid variables (ie, thyroid status, history of thyroid disease, current thyroid replacement) with categorical variables (eg, hypothyroid symptoms) were analyzed by chi-square. Descriptive statistics were computed on continuous variables using SAS means

Table 2. Physical Characteristics of Study Patients (N = 283)

Characteristic	Men (n = 78)		Women (n = 205)	
	Mean	SD	Mean	SD
Age (y)	76.9	7.0	76.8	7.4
Weight (kg)	75.1	13.8	64.4	15.0
Height (cm)	174.5	8.4	157.9	7.1

SD denotes standard deviation.

procedure. Multiple regression of thyroid status on prognostic variables was used to screen for variables that would be important predictors of hypothyroidism. The variables identified were then used in a logistic regression analysis of a randomly chosen half of those patients who were euthyroid or previously undiagnosed subclinical hypothyroid. The predictive power of the logistic models was evaluated by varying the criterion used to classify patients as "euthyroid" vs "hypothyroid," and plotting the resulting sensitivity and specificity function as a receiver operating characteristic (ROC) curve. All statistical analyses were performed using SAS(Statistical Package for the Social Sciences, Cary, NC, SAS Institute, 1985). The level of significance was set at .05.

Results

Patient Characteristics

The medical records of 283 patients, who had no previous history of thyroid disease and were between the ages of 60 and 97 years, were reviewed. Table 2 shows the physical characteristics of the male and female patients who did not have a history of thyroid disease.

Patients were categorized according to thyroid status (euthyroid, subclinical hypothyroid, overt hypothyroid) at the time of the first visit to the clinic. In the 78 male and 205 female patients, 12(15.4%) men and 30(14.6%) women were classified as subclinical hypothyroid; of these, 2 men and 10 women subsequently were prescribed thyroid replacement therapy. Only 1(1.3%) male patient and 2(1.0%) female patients met the criteria for overt hypothyroidism and were given thyroid replacement. There was no difference in the prevalence of hypothyroidism for men and women ($\chi^2 = 0.08, P = .96$). Given that prediction of subclinical hypothyroidism was our primary goal, the small number of overt hypothyroid patients was omitted from the remaining statistical analyses.

Symptom Frequency

There were no significant differences in the frequencies of hypothyroid symptoms between euthyroid and subclinical hypothyroid patients (Table 3). Lethargy (48.3% euthyroid, 54.8% subclinical hypothyroid) and memory impairment (60.4% euthyroid, 45.2% subclinical hypothyroid) were common symptoms in the elderly patients, irrespective of thyroid status. Subclinical hypothyroid patients showed slightly higher frequencies of dry skin (40.5%) and dyspnea (42.9%) as compared with euthyroid patients (dry skin 36.5%, dyspnea 37.4%). Coarse hair, skin pallor, and cold skin each were noted in the subclinical hypothyroid patient group but were not present in any euthyroid patients. Eight symptoms listed in Table 1 (coarse skin, slow speech, decreased sweating, thick tongue, facial edema, hair loss, lip pallor, anorexia) were not present in any of the patients in this sample.

Table 3. Frequency of Clinical Signs and Symptoms of Hypothyroidism in Patients with No History of Thyroid Disease

Symptom or Sign*	Euthyroid (n = 230) No. (%)	Subclinical Hypothyroid† (n = 42) No. (%)
Lethargy	111 (48.3)	23 (54.8)
Coarse hair	0 (0)	1 (2.4)
Skin pallor	0 (0)	1 (2.4)
Dry skin	84 (36.5)	17 (40.5)
Cold skin	0 (0)	1 (2.4)
Eyelid edema	1 (0.4)	1 (2.4)
Memory impairment	139 (60.4)	19 (45.2)
Dyspnea	86 (37.4)	18 (42.9)
Weight gain	4 (1.7)	1 (2.4)
Palpitation	64 (27.8)	8 (19.1)

**Clinical signs and symptoms from Table 1 entered into the model for prediction of thyroid status by forward selection multiple regression analysis.*
†Thyroid-stimulating hormone, 5.0–14.9 μU/mL; normal free T^4, 0.7–2.0 ng/dL.
NOTE: Chi-square analysis found no significant relationships (P > .05) between thyroid status and prevalence of each symptom.

Figure 1 shows the relationship between TSH levels and the total number of hypothyroid symptoms experienced by the patients. It is evident that there was no significant relationship between these two variables ($r = -.0004, P = .99$). We also classified symptoms according to number (high, >4; intermediate, 3 to 4; and low, 1 to 2) since the presence of more than four symptoms was previously reported to be predictive of hypothyroidism.[7] As shown in Table 4, the three categories of symptoms were incapable of discriminating between hypothyroid and euthyroid patients ($P = .16$). Overall, elevated TSH levels were found in only 17.3% of the patients in the high symptom category.

Predictability of Thyroid Status

Multivariate analyses were performed to determine whether it was possible to predict the thyroid status of patients not previously identified as having any thyroid problems based on their current symptoms. The analysis

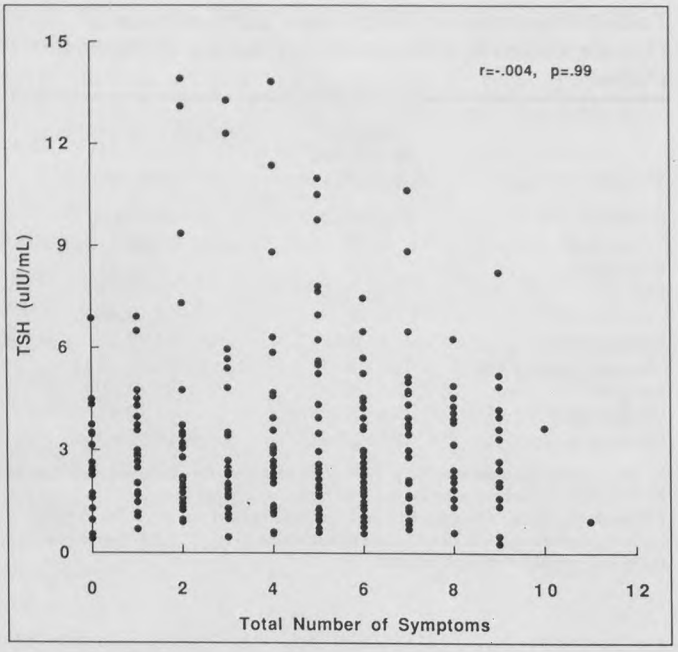

Figure 1. Relationship between thyroid-stimulating hormone (TSH) levels and total number of hypothyroid symptoms experienced by the patient sample (N = 283).

used a "cross-validation" strategy, in which a model is fit to one subset of the data and evaluated on another subset.

To find the most useful patient characteristics to include in the model, multiple regression was used with all the patients in the data set who were either euthyroid (TSH < 5.0 μU/mL [<5.0 mU/L]) or subclinical hypothyroid (TSH 5.0 to 14.9 μU/mL [5.0 to 14.9 mU/L]) to identify clinical variables that were related to thyroid status. All clinical symptoms in Table 1 were used in the analysis, with the exception of the eight that were not present in any patients (coarse skin, slow speech, decreased sweating, thick tongue, facial edema, hair loss, lip pallor, and anorexia). Patient age and 10 of the symptoms were included in the multiple regression model by the forward selection procedure (Table 1).

Table 4. Comparison of Number of Symptoms and Elevated Thyroid-Stimulating Hormone (TSH) Levels in the Diagnosis of Subclinical Hypothyroidism in Elderly Patients

No. of Hypothyroid Symptoms (Classification)	No. of Patients	No. of Patients with a Diagnosis of Subclinical Hypothyroidism Based on TSH Levels*† n (%)
>4 (High)	139	24 (17.3)
3 to 4 (Intermediate)	60	11 (18.3)
1 to 2 (Low)	81	7 (8.6)

*$\chi^2 = 3.7$, P = .16 *for thyroid status vs classification for number of symptoms.*
†*Thyroid-stimulating hormone, 5.0–1.49 μU/mL; normal free T_4, 0.7–2.0 ng/dL.*

Only five of these patient characteristics were statistically significant predictors of thyroid status (age, cold skin, coarse hair, skin pallor, and memory impairment.)

Some of the symptoms occurred only rarely, which violates the assumption of standard regression analysis that predictors are normally distributed. Therefore, a forward selection logistic regression procedure was applied to the same data with the same set of predictor symptoms. Using a relaxed entry criterion ($P = .20$), a model with 5 symptoms was found. These were the same variables that were statistically significant in the multiple regression procedure. For comparison purposes, a logistic regression model was fit using the 11 variables identified by the forward selection multiple regression model.

To test the generalizability of these models, cross-validation procedures were performed. The patients were randomly divided into two sets, with the constraint that each set have the same proportion of subclinical hypothyroid patients. Two logistic regression models were fit to the first set, one with 11 variables that is likely to overfit, the other with 5 predictors. Neither model was statistically significant at the .05 level.

These models (with 11 and 5 predictors) were then applied to the patients in the second sample. Varying the criterion for calling a case "subclinical hypothyroid" allows an ROC curve to be drawn. Figures 2 and 3 show the ROC curves for the 11-variable and 5-variable models. With the 11-variable model, the ROC curve for the training model shows moderate performance in separating subclinical hypothyroid patients from euthyroid patients, but when the model is applied to the cross-validation set, the curve is close to the ascending diagonal, which represents chance performance. For the 5-variable model (Figure 3), the ROC curves for both the training sample and the cross-validation sample are very close to the diagonal. Therefore, although the logistic regression models seem at first to do well in predicting which patients in a given set are starting to have thyroid dysfunction, the cross-validation analysis shows the models have essentially no predictive power when applied to cases that were not used in building the models.

Discussion

The nonspecificity and insensitivity of the clinical manifestations of hypothyroidism in the elderly were confirmed by the findings of this study. The "classic" clinical signs and symptoms of hypothyroidism are no more frequent in patients with elevated TSH than in the euthyroid elderly. The lack of a relationship between clinical symptoms and thyroid status was further evidenced by the inability of a high frequency of symptoms (>4) to

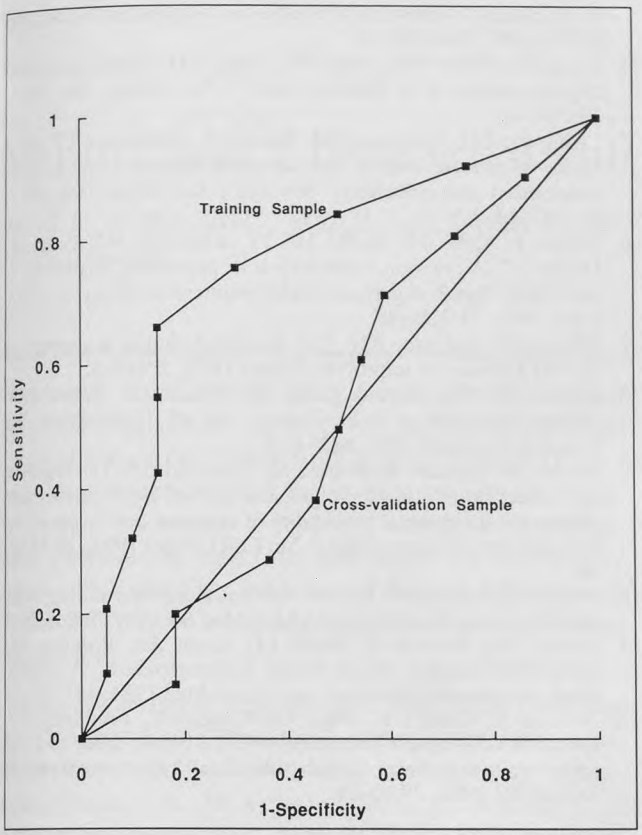

Figure 2. Receiver operating characteristic (ROC) curves for training sample (n = 135) and cross-validation sample (n = 137) in the 11-variable logistic regression model.

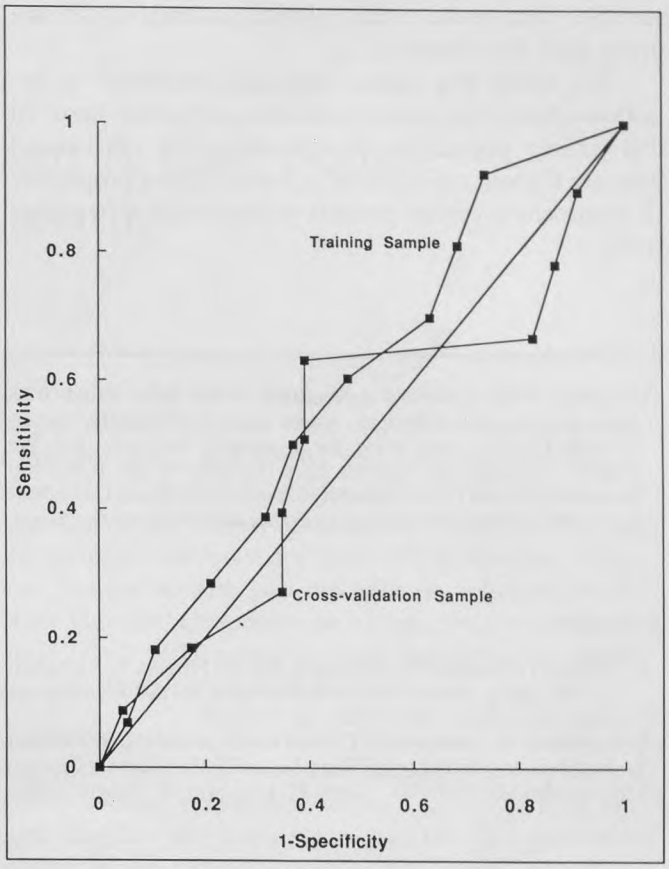

Figure 3. Receiver operating characteristic (ROC) curves for training sample (n = 135) and cross-validation sample (n = 137) in the 5-variable logistic regression model.

identify a higher proportion of subclinical hypothyroid patients diagnosed by elevated TSH levels. White and Walmsley[7] have previously reported that 78% of the patients with five or more hypothyroid symptoms were diagnosed as hypothyroid from laboratory thyroid function tests. However, the patient population in that study was not limited to the elderly.

Although clinical signs individually are inadequate predictors of hypothyroidism, they may be useful when considered together. Logistic regression, which has been shown effective in producing models that predict, for example, the presence of coronary artery disease,[9] did not predict subclinical hypothyroidism in this study. The logistic regression model poorly identified subclinical hypothyroid patients when applied to a cross-validation sample. Thus, physicians cannot rely solely on clinical signs to indicate when an elderly patient's thyroid is in the process of failing. Our findings support previous observations by physicians[1,2] concerning the difficulty of clinical diagnosis of thyroid problems in the geriatric population. In the absence of predictability from clinical symptoms, TSH screening is the only way to identify patients developing hypothyroidism in a timely manner.

Management of subclinical hypothyroidism includes two options: (1) to observe the patient for progression to overt hypothyroidism; or (2) to prescribe thyroid replacement therapy. Drinka and Nolten[10] noted that prophylactic thyroid treatment can benefit the patient by preventing the clinical manifestations of overt hypothyroidism and by improving nonspecific symptoms of mild hypothyroidism, such as myocardial contractility abnormalities, fatigue, and cold intolerance. There are few randomized control studies that have examined the therapeutic value of thyroid replacement therapy in patients with subclinical hypothyroidism. In a double-blind placebo-controlled trial, Cooper and coworkers[11] found that symptoms commonly associated with subclinical hypothyroidism improved in 47% of the patients treated with thyroxine, compared with 18.8% of the patients in the placebo group. Nystrom and associates[12] estimated that one in four women with subclinical hypothyroidism would benefit from thyroid replacement based on improvements in psychometric tests in a double-blind crossover study. Unfortunately, there were no pretreatment

variables that could predict which patients would improve with the treatment.

We found that classic signs and symptoms of hypothyroidism were poor predictors of thyroid status in this patient population. It remains to be determined whether thyroid replacement is beneficial as a prophylactic treatment in certain patients with subclinical hypothyroidism.

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