Older Subjects with Hyperthyroidism Present with a Paucity of Symptoms and Signs: A Large Cross-Sectional Study

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Context: The absence of classical symptoms and signs of hyperthyroidism often results in delayed diagnosis and treatment.

Objectives: The objective of the study was to determine the prevalence of symptoms and signs of hyperthyroidism according to patients' age and gender as well as severity and type of hyperthyroidism.

Design, Participants and Setting: This was a cross-sectional study of 3049 consecutive patients with hyperthyroidism presenting to a single secondary/tertiary care clinic.

Main Outcome Measures: Calculation of adjusted odds ratios for presence/absence of symptoms/signs of hyperthyroidism simultaneously analyzing the influence of patients' age/gender, disease etiology/severity, symptom duration, and smoking.

Results: The majority of patients older than 61 yr had two or more symptoms. The lowest proportion of subjects reporting five or more symptoms was found in those older than 61 yr. Increasing age was associated with reduced adjusted odds ratio for the presence of most classical symptoms except for weight loss and shortness of breath, independent of disease severity. Those with more severe hyperthyroidism and smokers had increased odds ratios for most symptoms. Older age, higher serum free T_4 concentrations at diagnosis, male gender, and toxic nodular hyperthyroidism were independently associated with risk of atrial fibrillation. Signs of ophthalmopathy were associated with increasing age, smoking, longer symptom duration, and female gender.

Conclusions: Classical symptoms and signs of hyperthyroidism are significantly less prevalent in older patients and more prevalent in smokers and subjects with higher free T_4 concentrations. We propose a lower threshold for performing thyroid function tests in patients older than 60 yr, especially in those presenting with atrial fibrillation, weight loss, or shortness of breath. **(*J Clin Endocrinol Metab* 95: 2715–2726, 2010)**

Hyperthyroidism affects 3% of women and 0.3% of males (1) and is associated with significant morbidity and mortality, mainly from cardiovascular and cerebrovascular disease (2, 3). In iodine-replete areas, the underlying diagnosis is Graves' disease in 60–80% and toxic nodular hyperthyroidism in most others (4, 5). Patients commonly complain of fatigue, anxiety, tremor, weight loss, palpitation, and heat sensitivity. Clinical signs include tachycardia, the presence of goiter, and a tremor. Signs of ophthalmopathy may be present in those with Graves' disease (4, 5). Atrial fibrillation (AF) is rare before age 50 yr but is present in up to 20% of older patients (3, 4).

The clinical presentation of patients varies widely (4). If patients present with subtle or atypical features, there

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Abbreviations: AF, Atrial fibrillation; AOR, adjusted odds ratio; fT4, free T_4; NOSPECS, no signs or symptoms; only signs, no symptoms; signs only; proptosis; eye muscle involvement; corneal involvement; sight visual acuity reduction.

may be a delay in diagnosis and therapy, potentially resulting in a worse outcome (6). Although hyperthyroidism is more common in older patients, the diagnosis may be difficult in the elderly, who may have few symptoms or signs resulting in masked hyperthyroidism (7, 8). In addition, the nonspecific signs detected in elderly people are often attributed to other illnesses or aging (6, 8).

Few studies have systematically addressed the influence of age on clinical features of hyperthyroidism in large patient cohorts and most current evidence is anecdotal (6, 9–12). The largest report (from 1988), demonstrated a reduction in frequency of many classical symptoms in 880 patients older than 50 yr, except for weight loss and AF (8). That study investigated Graves' disease patients only and was further limited by not considering factors such as disease severity, symptom duration, and smoking history. Clarity regarding the effects of age on clinical manifestations of hyperthyroidism is important in view of the ageing population (7) and because of the significant increase in vascular mortality experienced by elderly people (3, 13). The identification of symptom patterns indicative of hyperthyroidism in older patients may also guide clinicians to test thyroid function in certain patient groups.

A number of small series indicated that the biochemical severity and duration of Graves' disease significantly affect the clinical presentation (14). There is also good evidence for a causal link between smoking and the development and severity of Graves' ophthalmopathy (15, 16). We have shown that higher presenting free T_4 (fT4) concentrations and smoking independently predict the presence of thyroid eye disease in patients with Graves' disease (17).

Materials and Methods

We collected data on 3049 patients with overt hyperthyroidism presenting consecutively to the Multidisciplinary Thyroid Clinic, a secondary/tertiary referral center, at the UHB Foundation National Health Service Trust (Birmingham, UK), between January 1984 and September 2008. This study was performed with the approval of the University Hospital Birmingham Research and Development Directorate. Subjects were referred in accord with current U.K. guidance, stipulating that any patient with abnormal thyroid function tests indicating hyperthyroidism can expect to be referred to a specialist at diagnosis (18). All patients were evaluated by a senior clinician at presentation and the clinic proforma detailing presence or absence of symptoms was completed in all cases. This structured questionnaire was used for all patients throughout the study years. Symptoms of thyroid ophthalmopathy were determined in patients with Graves' disease. All patients underwent a physical examination recording pulse rate/rhythm and presence of tremor, palpable goiter, and/or thyroid eye disease.

Hyperthyroidism was confirmed biochemically through measurement of serum fT4 and/or free T_3 and serum TSH concentrations. Thyroid function tests and thyroid antibody status were determined as described previously (17, 19) at the time of evaluation of symptoms and signs. The severity of ophthalmopathy was classified according to the no signs or symptoms; only signs, no symptoms; signs only; proptosis; eye muscle involvement; corneal involvement; sight visual acuity reduction (NOSPECS) score as previously described (17): 1) absent (NOSPECS 0); 2) mild (NOSPECS 1: lid lag/retraction); 3) moderate (NOSPECS 2–3: periorbital edema/proptosis); or 4) severe (NOSPECS 4–6: eye muscle involvement/corneal involvement/sight loss). We elected to categorize the severity of eye disease according to these criteria because this study was performed throughout a time period of 24 yr and NOSPECS scores were documented in all patients. The presence of AF on clinical examination was confirmed electrocardiographically.

Patients were divided into quartiles according to age at presentation: 766 (16–32 yr), 772 (33–44 yr), 779 (45–60 yr), and 732 (≥61 yr)] and were categorized by simple clinical and immunological criteria into three diagnostic groups as described previously (20): Graves' disease, toxic nodular hyperthyroidism, and hyperthyroidism of indeterminate etiology. Graves' disease was defined as biochemical hyperthyroidism and two of the following: a palpable diffuse goiter, a significant titer (>1:100) of thyroid peroxidase, and/or thyroglobulin antibodies and/or the presence of thyroid eye disease. Toxic nodular hyperthyroidism was defined as hyperthyroidism and a palpable nodular goiter. Patients not fulfilling these criteria were categorized indeterminate, representing a mixed group with Graves' disease, toxic nodular hyperthyroidism, or both, the size of this indeterminate group reflecting our policy of not performing routine radionuclide imaging or thyroid receptor antibody measurements in patients with hyperthyroidism, consistent with the majority of U.K. practice (21). Follow-up indicated that the group of patients with indeterminate etiology also contained 28 patients with transient hyperthyroidism due to subacute thyroiditis and the analysis was repeated after exclusion of these patients (Supplemental Tables 1–4, published as supplemental data on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

The following factors were defined at diagnosis: patients' gender, age at diagnosis, and symptom duration (in months). Patients were classified as current smoker or nonsmoker (*i.e.* nonsmokers and ex-smokers). A list of current medications was also documented including treatment with β-blockers or amiodarone.

Statistical analysis

Statistical analyses were performed using SigmaStat software (version 3.2; SPSS Science Software U.K. Ltd., Birmingham, UK) and Minitab (version 15; Coventry, UK). χ^2 tests were used for association between categorical variables. The Kruskall-Wallis test was used to determine differences between continuous variables (Table 1 and Supplemental Table 1). Binary logistic regression analyses were performed to determine the influence of patients' age, gender, disease severity (as defined by the presenting serum fT4 concentration), symptom duration, disease etiology, and smoking history on the presence of symptoms. Age was analyzed as a continuous variable (Tables 2 and 4 and Supplemental Tables 2, 4, 6 and 8) and as a categorical variable (Tables 3 and 5 and Supplemental Tables 3, 5, 7 and 9). Binary and ordinal logistic regression analyses were performed to determine the influence of clinical and biochemical factors on clinical signs. χ^2 tests were used to compare the number of symptoms reported by patients in each age category (Fig. 1, A and B). Analyses were performed considering all patients (Tables 1–5), excluding pa-

TABLE 1. Demographic, clinical, and laboratory details of 3049 patients presenting with hyperthyroidism

	All patients, n (%) (n = 3049)	Patients aged 16–32 yr (n = 766)	Patients aged 33–44 yr (n = 772)	Patients aged 45–60 yr (n = 779)	Patients aged ≥61 yr (n = 732)	*P* value
Gender						
Male	650 (21.3%)	141 (18.4%)	148 (19.2%)	166 (21.3%)	195 (26.6%)	<0.001
Female	2398 (78.6%)	625 (81.6%)	624 (80.8%)	613 (78.7%)	537 (73.4%)	
Smoking history						
Current smoker	852 (27.9%)	218 (28.5%)	265 (34.3%)	239 (30.9%)	130 (17.8%)	<0.001
Nonsmoker	2197 (72.1%)	548 (71.5%)	507 (70.2%)	540 (69.1%)	5 (82.2%)	
Underlying etiology of hyperthyroidism						
Graves' disease	1189 (39.0%)	418 (54.6%)	381 (49.4%)	294 (37.7%)	96 (13.1%)	
Toxic nodular hyperthyroidism	369 (12.1%)	16 (2.1%)	39 (5.1%)	108 (13.9%)	206 (28.1%)	<0.001
Indeterminate etiology	1491 (48.9%)	332 (43.3%)	352 (45.6%)	377 (48.4%)	430 (58.7%)	
fT4 at diagnosis (pmol/liter)						
Mean (±SEM)	48.65 ± 0.45	56.56 ± 0.99	51.67 ± 0.92	45.47 ± 0.77	40.61 ± 0.76	<0.001
Range	22.1–150	22.1–150	22.1–150	22.1–150	22.1–150	
Duration of symptoms (months)						
Mean (±SEM)	8.23 ± 0.17	7.90 ± 0.32	8.15 ± 0.34	8.28 ± 0.31	8.64 ± 0.37	NS
Range	1–72	1–48	1–72	1–36	1–48	
Drug treatment						
Patients taking β-blockers	711 (23.3%)	173 (22.5%)	168 (21.8%)	210 (27.0%)	160 (21.9%)	0.05
Patients taking amiodarone	60 (2.0%)	5 (0.7%)	7 (0.9%)	11 (1.4%)	37 (5.1%)	<0.001

Patients were divided in quartiles according to age. χ^2 tests and Kruskall-Wallis tests were performed to compare prevalences in the different age categories. NS, Not significant.

tients with subacute thyroiditis (Supplemental Tables 1–5) and excluding those treated with beta-blockers/amiodarone (Supplemental Tables 6–9). We also determined whether the use of β-blockers exerts independent effects simultaneously analyzing the influence of patients' age, gender, disease etiology, severity, and duration as well as smoking history on symptoms of hyperthyroidism.

Results

Clinical and laboratory characteristics of patient population (Table 1)

The patient population comprised 2398 adult females and 650 adult males aged between 16 and 88 yr at diagnosis (mean 46.65 ± 0.32 yr). There was a lower female to male ratio in those 61 yr old or older compared with younger age groups. The proportion of active smokers was lowest in older patients. Toxic nodular hyperthyroidism was more common in the oldest age group compared with younger subjects and younger patients presented with more severe hyperthyroidism. The mean symptom duration before presentation was similar across age groups. The number of patients receiving treatment with β-blockers was highest in those aged 45–60 yr but was similar when comparing the youngest and oldest patients. The highest proportion of patients taking amiodarone therapy was found in the oldest age group.

Reported symptoms of hyperthyroidism

Weight loss was the most commonly reported symptom of hyperthyroidism (present in 60.7%) but 7.2% of patients reported weight gain. Heat intolerance, tremor, and palpitation were present in about 50% of subjects, and anxiety was reported by 41% of patients. Eye symptoms were reported by 11.4% of Graves' disease patients (Table 2).

Influence of demographic, clinical, and laboratory characteristics on prevalence of symptoms (Table 2)

Increasing age (continuous variable) was independently associated with reduced adjusted odds ratios (AORs) for the majority of symptoms, except for weight loss and shortness of breath, which were more common in older patients. Symptoms of thyroid ophthalmopathy were more common in older than younger patients with Graves' disease. Patients with more severe hyperthyroidism had significantly increased odds ratios for reporting most classical symptoms. Subjects with a longer symptom duration were less likely to report weight loss, but the prevalence of other symptoms was unaffected by a longer history of disease.

Females were more likely to report weight gain, palpitation, and neck enlargement than males, although symptom patterns were similar across genders for other symptoms. The underlying disease etiology had few associations with the prevalence of classical symptoms,

TABLE 2. Frequency of reported symptoms of hyperthyroidism

	Total (n = 3049)	AOR age overall annual increment	AOR disease severity (per 1 pmol/liter increment in serum fT4 conc)	AOR duration of symptoms (per 1 month increment)	AOR female gender	AOR toxic nodular disease	AOR smoking
Reported symptom							
Weight gain	219 (7.2%)	**0.97 (0.96–0.99) *P* < 0.001**	**0.98 (0.97–0.99) *P* < 0.001**	**1.03 (1.01–1.05) *P* = 0.002**	1.51 (0.94–2.41) *P* = NS	**2.47 (1.45–4.22) *P* = 0.001**	0.86 (0.59–1.25) *P* = NS
Weight loss	1850 (60.7%)	**1.02 (1.01–1.02) *P* < 0.001**	**1.01 (1.01–1.02) *P* < 0.001**	**0.97 (0.96–0.98) *P* < 0.001**	**0.68 (0.54–0.86) *P* < 0.001**	**0.51 (0.37–0.70) *P* < 0.001**	**1.42 (1.16–1.75) *P* = 0.001**
Heat intolerance	1674 (54.9%)	**0.99 (0.98–0.99) *P* < 0.001**	1.00 (1.00–1.00) *P* = NS	0.99 (0.98–1.00) *P* = NS	0.94 (0.77–1.16) *P* = NS	0.86 (0.63–1.15) *P* = NS	1.08 (0.89–1.30) *P* = NS
Tremor	1644 (53.9%)	**0.99 (0.99–1.00) *P* = 0.04**	**1.01 (1.00–1.01) *P* < 0.001**	0.99 (0.98–1.00) *P* = NS	0.93 (0.75–1.15) *P* = NS	**0.66 (0.49–0.90) *P* = 0.008**	**1.51 (1.11–1.64) *P* = 0.002**
Palpitation	1548 (50.8%)	**0.99 (0.99–1.00) *P* = 0.002**	**1.00 (1.00–1.01) *P* = 0.01**	0.99 (0.98–1.00) *P* = NS	**1.39 (1.13–1.70) *P* = 0.002**	0.75 (0.56–1.01) *P* = NS	**1.36 (1.12–1.64) *P* = 0.002**
Anxiety	1249 (41.0%)	**0.99 (0.98–0.99) *P* < 0.001**	1.00 (1.00–1.00) *P* = NS	1.00 (0.99–1.00) *P* = NS	1.11 (0.90–1.36) *P* = NS	**0.70 (0.51–0.96) *P* = 0.03**	**1.20 (1.00–1.45) *P* = 0.05**
Increased frequency of bowel movement	679 (22.3%)	0.99 (0.99–1.00) *P* = NS	**1.01 (1.00–1.01) *P* = 0.003**	1.00 (0.99–1.01) *P* = NS	0.98 (0.77–1.28) *P* = NS	0.70 (0.49–1.02) *P* = NS	1.10 (0.89–1.36) *P* = NS
Neck enlargement	664 (21.8%)	**0.97 (0.97–0.98) *P* < 0.001**	**1.01 (1.00–1.01) *P* = 0.001**	1.00 (0.99–1.01) *P* = NS	**1.75 (1.34–2.29) *P* < 0.001**		0.95 (0.76–1.18) *P* = NS
Shortness of breath	320 (10.5%)	**1.02 (1.01–1.03) *P* < 0.001**	**1.01 (1.00–1.01) *P* = 0.001**	0.99 (0.97–1.01) *P* = NS	1.28 (0.91–1.80) *P* = NS	0.73 (0.45–1.18) *P* = NS	0.96 (0.71–1.30) *P* = NS
Eye symptoms (GD subjects only, n = 1189)	136 (11.4%)	**1.02 (1.01–1.04) *P* = 0.001**	1.00 (0.99–1.01) *P* = NS	**1.03 (1.01–1.06) *P* = 0.005**	0.93 (0.56–1.55) *P* = NS		1.24 (0.83–1.86) *P* = NS

Logistic regression analysis was undertaken simultaneously analyzing patients' age (continuous variable) and gender, disease severity (defined as the presenting serum fT4 concentration), duration of symptoms, underlying etiology of hyperthyroidism, and smoking history. The AOR, 95% confidence intervals, and *P* values for each of the variables examined are displayed. Significant findings are indicated in *bold*. GD, Graves' disease; conc, concentration; NS, not significant.

TABLE 3. Prevalence of reported symptoms according to age in patients presenting with hyperthyroidism

	16–32 yr (n = 766)	AOR	33–44 yr (n = 772)	AOR (95% CI), *P* value	45–60 yr (n = 779)	AOR (95% CI), *P* value	≥61 yr (n = 732)	AOR (95% CI), *P* value
Reported symptom								
Weight gain	58 (7.6%)	1.00	64 (8.3%)	0.85 (0.55–1.30) *P* = NS	49 (6.3%)	**0.50 (0.31–0.80)** ***P* = 0.004**	48 (6.6%)	**0.38 (0.22–0.64)** ***P* < 0.001**
Weight loss	440 (57.4%)	1.00	462 (59.8%)	1.26 (0.98–1.62) *P* = NS	509 (65.3%)	**1.82 (1.40–2.37)** ***P* < 0.001**	439 (60.0%)	**1.73 (1.30–2.30)** ***P* < 0.001**
Heat intolerance	432 (56.4%)	1.00	459 (59.5%)	1.15 (0.90–1.45) *P* = NS	483 (62.0%)	**1.29 (1.01–1.65)** ***P* = 0.04**	300 (41.0%)	**0.56 (0.43–0.73)** ***P* < 0.001**
Tremor	420 (54.8%)	1.00	463 (60.0%)	**1.34 (1.05–1.71)** ***P* = 0.02**	470 (60.3%)	**1.46 (1.14–1.88)** ***P* = 0.003**	291 (39.8%)	**0.74 (0.56–0.96)** ***P* = 0.02**
Palpitation	381 (49.7%)	1.00	453 (58.7%)	**1.60 (1.27–2.03)** ***P* < 0.001**	433 (55.6%)	**1.43 (1.12–1.81)** ***P* = 0.004**	281 (38.4%)	**0.75 (0.58–0.98)** ***P* = 0.03**
Anxiety	308 (40.2%)	1.00	354 (45.9%)	1.22 (0.97–1.54) *P* = NS	385 (49.4%)	**1.34 (1.06–1.70)** ***P* = 0.02**	202 (27.6%)	**0.55 (0.42–0.72)** ***P* < 0.001**
Neck enlargement	251 (32.8%)	1.00	197 (25.5%)	**0.67 (0.52–0.86)** ***P* = 0.002**	122 (15.7%)	**0.37 (0.28–0.49)** ***P* < 0.001**	94 (12.8%)	**0.33 (0.21–0.45)** ***P* < 0.001**
Increased frequency of bowel movement	173 (22.6%)	1.00	208 (26.9%) ***P* = 0.03**	**1.33 (1.03–1.73)**	198 (25.4%)	1.27 (0.97–1.66) *P* = NS	100 (13.7%)	**0.71 (0.51–0.98)** ***P* = 0.03**
Shortness of breath	56 (7.3%)	1.00	73 (9.5%)	1.49 (0.99–2.23) *P* = NS	95 (12.2%)	**1.91 (1.27–2.87)** ***P* = 0.002**	96 (13.1%)	**2.50 (1.62–3.87)** ***P* < 0.001**
Eye symptoms in patients with GD subjects only (n = 1189)	36/418 (8.6%)	1.00	44/381 (11.6%)	**1.85 (1.08–3.15)** ***P* = 0.03**	45/294 (15.3%)	**2.68 (1.55–4.61)** ***P* < 0.001**	11/96 (11.5%)	1.89 (0.85–4.18) *P* = NS

Logistic regression analysis was performed simultaneously analyzing patients' age (categorical variable) and gender, smoking history, severity of hyperthyroidism (defined by the presenting serum fT4 concentration), duration of symptoms, and underlying etiology of hyperthyroidism. AORs and 95% confidence intervals are displayed. Significant findings are indicated in *bold*. CI, Confidence interval; NS, not significant; GD, Graves' disease.

TABLE 4. Clinical signs of hyperthyroidism detected in patients presenting with hyperthyroidism

	Total (n = 3049)	AOR age overall annual increment	AOR disease severity (per 1 pmol/liter increment in serum fT4 conc)	AOR duration of symptoms (per 1 month increment)	AOR female gender	AOR toxic nodular disease	AOR smoking
Clinical sign at presentation							
Atrial fibrillation	125 (4.1%)	**1.08 (1.06–1.10) *P* < 0.001**	**1.01 (1.00–1.02) *P* = 0.03**	1.00 (0.97–1.03) *P* = NS	**0.59 (0.36–0.96) *P* = 0.03**	**3.12 (1.26–7.79) *P* = 0.02**	0.57 (0.29–1.12) *P* = NS
Tremor	1275 (41.8%)	1.00 (0.99–1.00) *P* = NS	**1.01 (1.01–1.01) *P* < 0.001**	**0.99 (0.98–1.00) *P* = 0.05**	0.87 (0.71–1.07) *P* = NS	0.76 (0.56–1.03) *P* = NS	**1.24 (1.03–1.49) *P* = 0.02**
Palpable goiter	2115 (69.4%)	**0.96 (0.96–0.97) *P* < 0.001**	**1.01 (1.01–1.02) *P* < 0.001**	**1.01 (1.00–1.03) *P* = 0.05**	**2.05 (1.63–2.58) *P* < 0.001**		**1.30 (1.04–1.63) *P* = 0.02**
Thyroid eye disease (TED) in patients with GD (n = 1189)							
No evidence of TED (NOSPECS 0)	445 (37.4%)						
Mild TED (NOSPECS 1)	237 (19.9%)	**1.02 (1.01–1.03) *P* = 0.001**	1.00 (1.00–1.01) *P* = NS	1.02 (1.00–1.03) **P = 0.05**	**1.47 (1.04–2.07) *P* = 0.04**		**1.46 (1.12–1.92) *P* = 0.006**
Moderate TED (NOSPECS 2–3)	484 (40.7%)						
Severe TED (NOSPECS ≥4)	23 (1.9%)						

Logistic regression analysis was undertaken simultaneously analyzing patients' age (continuous variable) and gender, disease severity (defined as the presenting serum fT4 concentration), duration of symptoms, underlying etiology of hyperthyroidism and smoking history. The adjusted odds ratios (AOR), 95% confidence intervals and *P* values for each of the variables examined are displayed. Significant findings are indicated in *bold*. GD, Graves' disease; conc, concentration; NS, not significant.

TABLE 5. Clinical signs of hyperthyroidism at presentation according to age

	16–32 yr (n = 766)	AOR	33–44 yr (n = 772)	AOR (95% CI) *P* value	45–60 yr (n = 779)	AOR (95% CI) *P* value	≥61 yr (n = 732)	AOR (95% CI) *P* value
Clinical sign at presentation								
Atrial fibrillation	1 (0.1%)	1.00	6 (0.8%)	6.17 (0.74–51.61) *P* = NS	23 (3.0%)	**11.70 (1.51–90.49) *P* = 0.02**	95 (13.0%)	**64.77 (8.78–477.6) *P* < 0.001**
Tremor	365 (47.7%)	1.00	309 (40.0%)	**0.74 (0.58–0.93) *P* = 0.01**	321 (41.2%)	0.81 (0.64–1.03) *P* = NS	280 (38.3%)	0.82 (0.63–1.08) *P* = NS
Palpable goiter	645 (84.2%)	1.00	625 (80.9%)	0.87 (0.63–1.21) *P* = NS	505 (64.8%)	**0.35 (0.26–0.47) *P* < 0.001**	340 (46.4%)	**0.19 (0.14–0.25) *P* < 0.001**
Thyroid eye disease (TED) in patients with GD (n = 1189)								
No evidence of TED (NOSPECS 0)	179/418 (42.8%)		151/381 (39.6%)		91/294 (31.0%)		24/96 (25.0%)	
Mild TED (NOSPECS 1)	84/418 (20.1%)	1.00	72/381 (18.9%)	1.26 (0.91–1.74) *P* = NS	58/294 (19.7%)	**1.80 (1.26–2.56) *P* = 0.001**	23/96 (24.0%)	**1.78 (1.06–2.99) *P* = 0.03**
Moderate TED (NOSPECS 2–3)	149/418 (35.7%)		152/381 (39.9%)		139/294 (47.3%)		44/96 (45.8%)	
Severe TED (NOSPECS ≥4)	6/418 (1.4%)		6/381 (1.6%)		5/294 (2.0%)		5/96 (5.2%)	

Logistic regression analysis was performed simultaneously analyzing patients' age and gender, smoking history, severity of hyperthyroidism, duration of symptoms and underlying etiology of hyperthyroidism. Adjusted odds ratios and 95% confidence intervals are displayed. Significant findings are indicated in *bold*. CI, Confidence interval; NS, not significant; GD, Graves' disease.

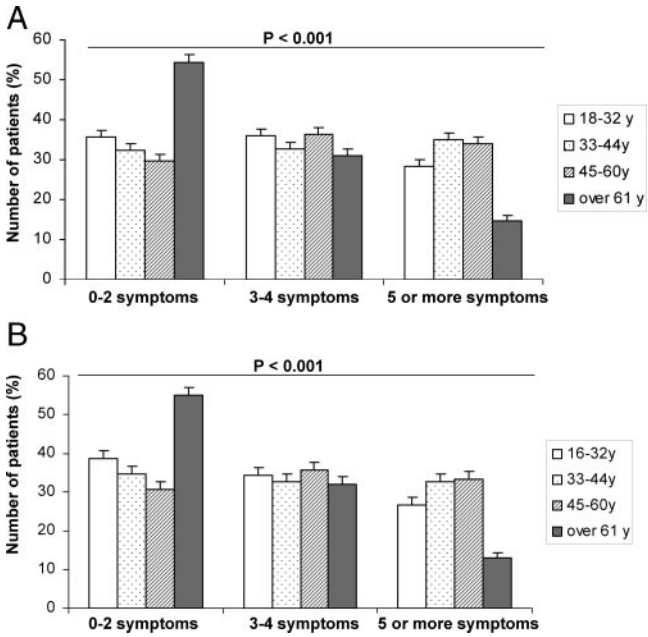

FIG. 1. A, Number of symptoms of hyperthyroidism reported by patients in the respective age groups, indicating that the majority of patients aged older than 61 yr reported a maximum of two symptoms. The lowest proportion of patients reporting five or more symptoms was found in patients older than 61 yr. B, Number of symptoms of hyperthyroidism reported by patients after exclusion of those taking β-blockers or amiodarone.

whereas smoking was associated with increased AOR for weight loss, tremor, palpitation, and anxiety when compared with nonsmokers. In those with Graves' disease, smoking was also more likely to be associated with eye symptoms.

Because treatment with β-blockers or amiodarone may affect symptoms of hyperthyroidism (4), we repeated the same regression analyses excluding patients receiving treatment with β-blockers (n = 711) or amiodarone (n = 60) at presentation (Supplemental Table 6). The influence of age, disease severity, and smoking on symptoms of hyperthyroidism was similar after the exclusion of these patients. In multivariate analyses, those receiving β-blockers were more likely to report weight loss [AOR 1.31 (1.05–1.63), $P = 0.02$] and palpitation [AOR 1.50 (1.23–1.83), $P < 0.001$] compared with those not on β-blockers. The reporting of other symptoms was not affected by the use of these drugs. Symptom patterns were similar after exclusion of patients with subacute thyroiditis (Supplemental Table 2).

Frequency of symptoms according to age (Table 3)

The logistic regression was repeated analyzing age as a categorical variable. Patients aged 61 yr or older had reduced AOR for the presence of most classical symptoms except for weight loss and shortness of breath. In those aged 45–60 yr, most symptoms were more common when compared with the youngest patients except for weight gain and neck enlargement. Similar patterns were evident when excluding those with thyroiditis (Supplemental Table 3) and excluding patients receiving β-blockers or amiodarone (Supplemental Table 6).

Next we evaluated the number of reported symptoms in different age groups. The highest proportion of patients with few symptoms (*i.e.* 0/1/2 symptoms) was found in those aged 61 yr or older (54.4%, $P < 0.001$) compared with those aged 16–32 yr (35.6%), 33–44 yr (32.4%), and 45–60 yr (29.8%) (Fig. 1A). The frequencies of patients with a complete absence of symptoms were 11.6, 9.2, 8.1, and 12.0% in the respective age categories. The lowest number of patients reporting five or more symptoms was found in the oldest patients (14.8%, $P < 0.001$), whereas these proportions were similar in younger patients [28.3% (16–32 yr), 34.9% (33–44 yr) and 33.9% (45–60 yr), P = NS]. After exclusion of those receiving β-blockers or amiodarone, similar patterns of symptom frequencies were evident (Fig. 1B).

Influence of demographic, clinical, and laboratory parameters on clinical signs of hyperthyroidism

In the whole group, patients presented with a mean pulse rate of 84.4 beats/min (bpm), and this was unchanged when excluding those undergoing treatment with β-blockers or amiodarone (mean 84.4 bpm). Patients in the oldest age categories had lower pulse rates compared with younger patients. AF was present in 4.1% of patients, and its presence was independently associated with increasing age, more severe biochemical disease, and an underlying diagnosis of toxic nodular hyperthyroidism. Women were less likely to have AF; neither smoking nor a longer duration of symptoms significantly affected the presence of this arrhythmia (Table 4). Similar findings were evident after exclusion of patients with subacute thyroiditis (Supplemental Table 4). After excluding patients receiving amiodarone or β-blockers, increasing age and disease severity were significantly associated with the finding of AF, but female gender and an underlying toxic nodular hyperthyroidism did not affect the likelihood of AF (Supplemental Table 8).

The presence of tremor was noted in 41.8% of patients, and this was associated with more severe hyperthyroidism, a shorter symptom duration, and smoking (Table 4). The association between symptom duration and tremor was no longer present when patients receiving amiodarone or β-blockers were excluded (Supplemental Table 8). The majority of patients (69.8%) presented with a palpable goiter and this was associated with younger age, more severe disease, longer symptom duration, female gender, and smoking (Table 4). These associations were also

present in those not on β-blockers or amiodarone, except for symptom duration and smoking (Supplemental Table 8).

Thyroid eye disease was absent or mild in the majority of patients with Graves' disease, severe ophthalmopathy being present in only 1.9%. The finding of moderate/severe ophthalmopathy was more likely in older patients, current smokers, females, and those with longer disease duration (Table 4). After the exclusion of patients receiving amiodarone or β-blockers, older age, and female gender were independently associated with more severe eye disease (Supplemental Table 8).

Effects of age on clinical signs of hyperthyroidism

Analyzing age as a categorical variable, those aged 45–60 yr and 61 yr or older had increased AOR for AF compared with those aged 16–32 yr. Tremor was least common in those aged 33–44 yr but was not different when comparing older with younger age groups. The presence of a palpable goiter was less common in older patients. Moderate or severe ophthalmopathy was more commonly present in patients aged 45–60 yr and 61 yr or older compared with younger patients (Table 5). After excluding those with thyroiditis (Supplemental Table 4) and when considering only patients who were not treated with β-blockers or amiodarone (Supplemental Table 9), similar results were evident.

Discussion

This is the first large study of hyperthyroid subjects to simultaneously investigate the influence of age and a number of other clinical and biochemical parameters on presenting symptoms and signs of hyperthyroidism. Our results indicate that more than 50% of patients aged 61 yr or older present with very few symptoms of hyperthyroidism, whereas this proportion is significantly lower (around 30%) in younger patients. The prevalence of most symptoms was lower in older patients, except for weight loss and shortness of breath, independent of disease severity. More severe hyperthyroidism and current smoking were associated with increased AOR for most symptoms, whereas patients' gender, the underlying disease etiology and disease duration only affected the prevalence of a minority of symptoms. The risk of presenting with AF was increased in older patients, those with higher serum fT4 concentrations, males, and subjects with toxic nodular hyperthyroidism. Signs of thyroid ophthalmopathy were more likely in older patients, those with longer disease duration, current smokers, and females.

The strengths of this study are the large number of patients studied, the consistent and detailed evaluation of patients' symptom reporting through use of a standardized clinic proforma, and the completeness of patient follow-up. We acknowledge the following limitations to our study. First, our data are derived from an iodine-replete U.K. population and caution should be exercised extrapolating the data to different regions with different iodine intake. Second, the presence/absence of goiter was determined by physical examination only and ultrasonography or thyroid scintigraphy were not routinely performed in keeping with common U.K. practice (21). Third, the underlying disease etiology was not determined in nearly 50% of patients (indeterminate etiology). This group comprised patients with Graves' disease and toxic nodular hyperthyroidism, although most of these patients would be expected to have Graves' disease because of the higher prevalence of this condition in the United Kingdom (1, 22). Notably, recent evidence has indicated that clear-cut discrimination between Graves' disease and toxic nodular hyperthyroidism is still not possible in nearly 50% of cases, even after scintigraphy and iodine uptake measurements (23). Furthermore, because treatment modalities are similar for both forms of hyperthyroidism, routine radionuclide scanning is not recommended (24). In addition, measurement of TSH receptor antibodies, which may aid in the distinction between Graves' disease and toxic nodular hyperthyroidism, was not routinely available. Fourth, the increased reporting of shortness of breath by older patients could be in part due to underlying cardiovascular and respiratory disease, and data were not corrected for the presence of these comorbidities. And fifth, a number of subjects may have been referred to our center after the finding of abnormal thyroid function tests during the work-up of presentation with AF or goiter, thereby potentially introducing a degree of selection bias.

Our data confirm previous findings of an increased prevalence of toxic nodular hyperthyroidism in older patients (25, 26). Previous studies indicated that advancing age is associated with less severe Graves' hyperthyroidism (17, 27). Many patients in our series had an underlying diagnosis of Graves' disease, and we confirmed that older patients presented with significantly lower serum fT4 concentrations. The mechanisms driving the presence of less severe Graves' hyperthyroidism in older age groups remain incompletely understood. Some have suggested that changes in thyroid hormone economy, including reduced production of thyroid hormones with advancing age, may be responsible (7).

Previous smaller studies (6, 9–12) indicated a lower prevalence of many classical symptoms of hyperthyroidism in older patients. Nordyke *et al.* (8) reported little difference in the prevalence of most symptoms of hyperthyroidism until the fifth decade after which there was a decrease in frequency. The only findings that increased

after age 50 yr were weight loss and atrial fibrillation. Our study confirms an increase in prevalence of weight loss in older patients and also identifies shortness of breath as a symptom commonly reported in the elderly. We did not take into account coexisting cardiovascular or respiratory diseases, which is likely to have been more prevalent in the older age group and may have influenced symptoms of shortness of breath. However, these findings were still evident when excluding patients receiving β-blockers or amiodarone. Importantly, our findings indicate associations between advancing age and symptoms of hyperthyroidism independent of disease severity and disease etiology, factors not considered in the smaller study by Nordyke *et al.* (8). Subjects undergoing treatment with β-blockers were more likely to report palpitation and weight loss. It is likely that subjects with palpitation were preferentially treated with β-blockers, although the increased reporting of weight loss with the use of these drugs remains unexplained.

We confirmed a very high prevalence of asymptomatic hyperthyroidism in patients aged 61 yr or older with more than half reporting two or more symptoms. Interestingly, the proportion of patients who were entirely asymptomatic was similar in the oldest and youngest age category (11.6 and 12%). The question remains why patients without symptoms of hyperthyroidism had thyroid function tests performed; it is plausible that biochemical hyperthyroidism was diagnosed while the patients were undergoing tests for unrelated complaints, which would themselves be more prevalent in the elderly. The mechanisms accounting for asymptomatic hyperthyroidism in the elderly remain elusive, although an age-related decline in tissue responsiveness resulting in a variant form of thyroid hormone resistance syndrome may play a role (7). A further question that arises is whether therapeutic intervention is required in asymptomatic hyperthyroidism. With mounting evidence regarding the significant morbidity and mortality associated with mild or subclinical hyperthyroidism in elderly subjects (28, 29), it appears advisable to normalize thyroid hormone concentrations, even in asymptomatic patients (7).

A number of small studies investigated the effects of higher concentrations of circulating thyroid hormones on clinical manifestations of hyperthyroidism (14, 30, 31). One report indicated that there was no relationship between the Hyperthyroid Symptom Scale in 25 patients with Graves' disease (31), whereas a further study demonstrated a positive correlation between the clinical symptom score and serum fT4 in 39 Graves' disease subjects (30). Our results indicate significant relationships between presenting serum fT4 and a number of symptoms of hyperthyroidism, independent of disease etiology and patients' age.

The presence of AF has been reported in 2–20% of patients with hyperthyroidism (3), and patients with underlying heart disease are particularly at risk (32). Moreover, in patients older than 60 yr, a low serum TSH concentration is associated with a 3-fold increased risk of development of AF (33). In contrast, AF was prevalent in only 2% of 13,000 Japanese subjects with hyperthyroidism with a stepwise increase in prevalence with age to around 15% in patients older than 70 yr (34). Our study indicates an overall prevalence of AF in 4.1% of hyperthyroid subjects, with the highest rates found in those aged older than 61 yr (13%), confirming these previous reports. Furthermore, we demonstrated that age is independently associated with an increased likelihood of atrial fibrillation. Data from the cohort of 40,628 hyperthyroid patients in the Danish National Registry have indicated that 8.3% of patients developed AF, although the parameters associated with the highest risk rates were male gender, ischemic or valvular heart disease, or congestive heart failure (32). In keeping with these findings and our previous reports (35), our data demonstrate independently increased AOR for AF in males and those with higher serum fT4 concentrations. It has been reported that the risk of arrhythmias is higher in those with toxic nodular hyperthyroidism when compared with Graves' disease patients (36). Our data indicate that an underlying diagnosis of toxic nodular hyperthyroidism is indeed independently associated with an increased likelihood of presenting with AF.

Smoking has been proposed as an etiological factor in the development of Graves' disease (37) and toxic nodular hyperthyroidism (38), although few studies have addressed the relationship between smoking and classical features of hyperthyroidism. We now show that hyperthyroid patients who smoke are more likely to present with weight loss, tremor, palpitation, and anxiety. In keeping with studies suggesting a goitrogenic role of cigarette smoking (39, 40), we found an increased likelihood of a palpable goiter in current smokers.

A recent systematic review has confirmed strong evidence for a causal link between cigarette smoking and development and progression of thyroid ophthalmopathy (16). Our findings confirm an increased likelihood of signs of thyroid ophthalmopathy in current smokers and furthermore that advancing age is independently associated with symptoms and signs of thyroid eye disease. A previous report indicated that the severity of Graves' ophthalmopathy is associated with age and with male gender (41). Our finding of more severe ophthalmopathy in females is in contrast with this previous study.

It has been proposed that routine screening for thyroid dysfunction should be considered to identify cases of asymptomatic hyperthyroidism. Most current expert guidance (42) advises against routine population-based screening in healthy adults, although an aggressive case finding in women older than 60 yr and other high-risk groups may be useful (42). In a study of 726 patients with recent-onset atrial fibrillation who underwent thyroid function testing, less than 1% of patients had overt thyroid dysfunction, and it was proposed that routine screening with TSH measurement should be applied to those patients at higher risk of having undiagnosed thyroid disease (43). Our data now provide strong evidence that clinicians should have a low threshold for performing thyroid function tests in patients aged older than 60 yr, especially those presenting with AF as well as weight loss and shortness of breath.

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