ORIGINAL RESEARCH

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Prevalence of atrial fibrillation in patients taking TSH suppression therapy for management of thyroid cancer

Abstract

Background: Suppression of thyroid stimulating hormone (TSH) below the normal range with administration of L-thyroxine has been shown to improve survival in patients treated for thyroid cancer (TC). Although most TC patients require long-term TSH suppression therapy, the effect of this treatment on cardiac rhythm remains unknown. A cross-sectional study was conducted to determine the prevalence of atrial fibrillation (AF) in TC patients on TSH suppressive therapy.

Methods: All TC patients seen between June 2009 and March 2010 through a multidisciplinary thyroid oncology clinic, Halifax, Nova Scotia, Canada, for whom TSH suppressive therapy had previously been recommended, were recruited into the study. Each patient underwent an electrocardiogram and filled out a questionnaire relevant to causes, signs/symptoms of AF and/or its complications. The prevalence of AF in this population then was compared against the published prevalence of AF in general populations.

Results: A total of 351 patients were seen in the thyroid clinic of which 136 patients met the inclusion criteria for the study. The mean age was 52 years, 85% were female, and mean follow-up duration prior to recruitment was 11 years. The mean TSH was 0.17 mIU/L (Normal: 0.35 – 5.5 mIU/L). There were 14 patients found to have AF (two patients had long-standing persistent AF and 12 patients had paroxysmal AF). The mean ages of patients with and without AF were 61.6 years and 51.4 years, respectively ($P = 0.01$). Prevalence of AF in the study group was 10.3%; the rate of AF in the TC patients aged 60 years and over (17.5%) was higher than the rate of AF in published data in people 60 years and over ($P < 0.001$). AF was diagnosed after the initiation of the TSH suppression therapy in all except one patient.

Conclusion: TSH suppression in thyroid cancer is associated with a high prevalence of AF, particularly in older individuals.

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Background

Low serum thyroid stimulating hormone (TSH) is a sensitive predictor of hyperthyroxinemia. In patients with thyroid cancer (TC), aggressive suppression of TSH to below the normal range has been shown to improve long-term survival [1]. Most TC patients are young [2] and, as part of their management, require long-term TSH suppression therapy; however, TSH suppression is not without risk. Previous studies have shown that low TSH is associated with increased bone loss [3] and higher risk of cardiac dysfunction [4]. Hyperthyroidism has a well-known association with AF [5] and, in an observational study a low TSH in individuals over the age of 60, was associated with a higher risk of AF [6]; however, the results of this study cannot be extrapolated to TC patients requiring TSH suppression. Iatrogenic hyperthyroidism is distinct from endogenous hyperthyroidism in that thyroid replacement therapy is usually given as levothyroxine (T4) whereas in endogenous thyroid disease frequently both T4 and triiodothyronine (T3) are elevated (7). Furthermore, most TC patients are young, whereas the risk of AF is higher in the older population. Thus, a cross-sectional study was conducted to assess the prevalence of AF in patients with TC who are undergoing TSH suppression therapy and compared that against the published prevalence rate of AF in the general population.

Materials and Methods

All surgically-treated TC patients in the province of Nova Scotia, Canada are followed through a single multidisciplinary thyroid oncology clinic. For the purpose of this study, all consecutive follow-up patients with a history of TC who were seen between June 2009 and March 2010 for their routine follow-up at the clinic for whom TSH suppressive therapy had been previously recommended were prospectively enrolled into the study. Patients for whom a non-suppressive dose of thyroxine was recommended, patients with medullary thyroid cancer, newly diagnosed thyroid cancer patients, pregnant females and patients with known pituitary abnormalities were excluded. The study was approved by the Research Ethics Board, Capital Health, Nova Scotia. A total of 351 patients were seen in the clinic of which 136 patients met the inclusion criteria and none of the patients approached for the study declined to participate. The recommended level of TSH suppression in all of these patients, although varied based on the staging of TC, was <0.35 mIU/L (Normal: $0.35 - 5.5$ mIU/L). Each patient underwent an electrocardiogram (ECG) and completed a questionnaire relevant to causes, signs/symptoms and complications of AF which included age, history of known AF, palpita-

tions, hypertension, stroke, coronary disease and valvular heart disease. Serum TSH values were recorded either at the time of visit (for patients who were assessed with unstimulated thyroglobulin) or within 12 weeks prior to the visit (in patients who had either received recombinant TSH or undergone thyroid hormone withdrawal). The prevalence of AF in this population then was compared against published prevalences of AF in the age-adjusted general population. The binomial distribution probability to compare the rate of AF in the cancer patients with the published general population rate [8] was used; a p value <0.05 was considered statistically significant. Baseline characteristics (Table-1) of the group identified above were described and compared using the chi-square test for significance of categorical data and the Student t - test for continuous data.

Results

A total of 136 patients had TSH suppression therapy recommended, all of whom consented to participate. There were 118 (85%) females and 18 (15%) males; the mean age was 52 years (range 18 – 86 years) and the mean duration of TSH suppression was 11 years (range 1 – 21 years). Fourteen (12 female and two male) patients had AF of which 2 (15%) had persistent AF while 12 (85%) had paroxysmal AF. The baseline characteristics of patients with and without AF are summarized in Table 1. The mean ages of patients with and without AF were 61.6 years and 51.4 years, respectively ($P = 0.26$). Although TSH suppressive therapy had been recommended in these patients, not all patients were adequately suppressed and the mean TSH values in patients with and without AF were not significantly different at 0.17 mIU/L and 0.19 mIU/L, respectively (range = $0.001 - 1.50$ mIU/L).

The recommended ranges of TSH suppression based on the American Thyroid Association Guidelines [9] are as follows: $0.1-0.01$ mIU/L in high risk TC; $0.1-0.5$ mIU/L in intermediate risk TC; and, $0.3-2.0$ mIU/L in low risk TC. Due to an overlap in TSH targets for intermediate and low risk patients, the lower limit of reference range for TSH in our institution being 0.35 mIU/L and lowest detectable limit of our TSH assay being 0.01 mIU/L, serum TSH values were categorized into four groups: less than 0.01 mIU/L; between 0.01 mIU/L and 0.1 mIU/L; between 0.1 mIU/L and 0.35 mIU/L; and, above 0.35 mIU/L (Figure 1). There were no significant differences in the overall distribution of serum TSH between AF and non-AF groups, with values in most patients within the range of $0.01-0.35$ mIU/L. Similarly, there were no significant differences in TSH values of AF versus non-AF patients across different age groups (Figure 2). Thirteen of the 14 patients

FIGURE 1. TSH values by atrial fibrillation status
TSH, thyroid stimulating hormone; AF, atrial fibrillation

FIGURE 2. Mean TSH values by age and atrial fibrillation status
TSH, thyroid stimulating hormone; AF, atrial fibrillation

with AF reported that their AF was diagnosed after the initiation of TSH suppression therapy whereas one patient had documented AF prior to the initiation of TSH suppression.

The overall prevalence of AF in this cohort was 10.3%. A third of all patients reported palpitations; however, the risk of palpitations was significantly higher in patients with AF, where 12 of 14 (85%) patients reported palpitations as compared with non-AF patients, among whom 36 of 122 (30%) reported palpitations ($P < 0.05$). Other risks for AF were similar in both

groups (Table 1). Although patients with AF were more likely to be on beta-blockers, calcium channel blockers and aspirin, these differences were not statistically significant, likely due to the small sample size.

The prevalence of AF in our study population was significantly higher than the reported prevalence in contemporary published population studies. In a large European population-based prospective cohort study, the overall prevalence of AF was 5.5%. When age (by decade) and sex adjusted, the pre-

dicted prevalence in our cohort would have been 2.02% [10]. In another large US cross-sectional study drawn from a health maintenance organization, the overall rate of diagnosed AF was 0.95%, and when adjusted for age (five year increments) and sex, the predicted prevalence in our cohort would have been 1.09% [8]. In our study, the risk of AF trended higher in the older age group, and women over the age of 60 years had a higher rate of AF than those younger than 60 years (18% vs. 8%; $P = 0.19$). Using the binomial distribution probability, the observed prevalence of AF in TC patients was significantly higher than either predicted value ($P < 0.0001$ for both comparisons). Among patients aged 60 years and over, the observed prevalence of AF was 17.5%; significantly higher than predicted sex- and age-adjusted risks of 5.4% ($P = 0.005$) [4, 9] to 3.3% ($P = 0.0003$).

Discussion

AF is the commonest arrhythmia seen in clinical practice and its prevalence increases with age. In the general population, the risk of AF rises with age and is nearly 4% for those above the age of 60 years [11]. The median age of AF patients is about 75 years and approximately 60% of AF patients over 75 years are female [8].

Multiple risk factors associated with onset of AF have been identified and include older age, male gender, hypertension, heart failure, valvular heart disease, cardiomyopathy, ventricular dysfunction and coronary artery disease [4, 10, 12-16]. The correct and timely management of AF is important because it is associated with increased mortality, deterioration in hemodynamic function, loss of atrioventricular (AV) synchrony, stroke and other embolic events [17].

AF is common in both overt and subclinical hyperthyroidism [18, 19]. In patients with overt hyperthyroidism, it has been reported that 8% of all patients, and 15% of patients between ages 70 to 79 years develop AF within 30 days of the diagnosis [18]. Similarly, subclinical hyperthyroidism is also associated with an increased risk of AF [6, 19]. While some studies have reported that subnormal TSH is associated with adverse effects on cardiac function [20], left ventricular hypertrophy [21] and diastolic dysfunction [22], others showed only minimal or no effect of TSH suppression on cardiac function [23]. A recent population-based study of patients on long-term thyroxine replacement reported that both elevated (>4 $\mu\text{U/L}$) and suppressed (<0.03 $\mu\text{U/L}$) TSH were associated with an increased risk of cardiovascular disease and dysrhythmias and for all endpoints the risk increased with age [4]. In a 10 year follow-up study of over two thousand individuals who were 60 years of age or older, Sawin et al. reported that low TSH was

associated with a three-fold higher risk of AF [6]. It is difficult to attribute this finding on the basis of other risk factors for AF in our cohort. Although there were more subjects with hypertension in the AF group (50% vs. 31%), this difference was not statistically significant. The incidence of other risk factors for AF was also similar in both groups.

Several studies have highlighted the role of TSH suppression therapy in long-term follow-up of TC. Although appropriate degree of TSH suppression is still unclear, one study showed that a constantly suppressed TSH (<0.05 mIU/L) was associated with longer relapse-free survival [24] whereas another study reported improved survival when TSH was suppressed to <0.1 mIU/L in advanced TC (stage III and IV) patients, <0.5 mIU/L in moderately advanced TC (stage II), whereas there was no additional benefit of TSH suppression in early (stage I) disease [1]. The American Thyroid Association, in their recent guidelines [9], have therefore recommended that, in the absence of specific contraindications, TSH should be maintained at <0.1 mIU/L indefinitely in patients with persistent disease, between 0.1-0.5 mIU/L for 5-10 years in patients who are clinically and biochemically free of the disease but who presented with high risk features, whereas in patients who are free of disease and have a low risk of recurrence TSH levels should be maintained between 0.35 – 2.0 mIU/L . TSH suppression therapy will, therefore, remain an essential goal of therapy and a better understanding of its risks and benefits will enable physicians to direct therapy appropriately.

In our study we were unable to find a correlation between the level of TSH suppression and occurrence of AF, possibly because this is a small retrospective study and needs validation with a larger prospective study. It is an important question to answer as it warrants more vigorous screening of subjects with TC on TSH suppression for AF because of the fact that presence of AF is associated with higher mortality and morbidity, and to consider whether anticoagulation should be administered.

Our study has several limitations. Although we identified a higher than expected prevalence of AF in a population of patients with prior TC in whom TSH was purposely suppressed below normal values with exogenous thyroid hormone, this small series was clearly limited by the absence of a direct comparison control group and by the sample size. Nonetheless, the development of AF after initiation of TSH suppression therapy, and the high rate seen in a relatively young cohort, are highly suggestive that the therapy played a role. A further limitation, as is often the case in studies of AF, was the potential for incomplete case-finding. AF is often intermittent, and may be asymptomatic. Thus, despite the use of questionnaires, chart

review and electrocardiography, the true incidence may have been underrepresented.

Conclusion

TSH suppression in thyroid cancer is associated with a high prevalence of AF, particularly among older individuals. Physicians treating thyroid cancer patients with TSH suppression should be mindful of possible incident atrial fibrillation.

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