CLINICAL THYROIDOLOGY

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EDITOR'S COMMENTS

This is the third 2009 issue of *Clinical Thyroidology*. As you may know, each issue will be sent to you as a separate list of articles that can be downloaded separately or as the entire document.

You will notice that the articles contain figures with the ATA logo and a citation with the volume and issue numbers. We encourage you to continue using figures from *Clinical Thyroidology* in your lectures, which we hope will be useful to you and your students.

WHAT'S NEW The last page which lists new reviews has been expanded to REVIEWS & HOT ARTICLES. The last page now contains references to important reviews and very recent articles that look especially important to the editors.

Articles designated as an EDITOR'S CHOICE are especially important studies that we recommend you read in their entirety.

We welcome your feedback and suggestions on these changes.

Beginning with the first review article for *Clinical Thyroidology* by Dr. Elaine Ron, authors can cite our CONCISE REVIEWS by using the electronic citation at the end of each review.

We wish to thank Drs. David Cooper, Irwin Klein, and David Steward for their contributions to this issue of *Clinical Thyroidology*. Each provided expert opinions on articles in this issue.

Ernest L. Mazzaferri, MD, MACP
Jennifer A. Sipos, MD

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Amiodarone-induced thyrotoxicosis is associated with a nearly threefold increased risk for major adverse cardiovascular events that must be identified and treated

SUMMARY

BACKGROUND Amiodarone-induced thyrotoxicosis (AIT) is a common clinical condition that is notoriously difficult to manage; however, the risk for subsequent adverse cardiovascular events in patients with AIT is largely unknown. The aim of this study was to assess the clinical characteristics of major adverse cardiovascular events, including ventricular tachycardia and death, in patients with AIT as compared with euthyroid patients.

METHODS This is a retrospective study of patients treated at the Cardiac Medical Unit, Grantham Hospital, Hong Kong, from January 2000 through December 2005. The study subjects were stable cardiac patients treated with amiodarone for at least 3 months. Excluded from the study were patients with end-stage heart failure or incessant ventricular tachyarrhythmias not controlled by medical therapy, or uncorrected severe valvular abnormality, complex congenital heart disease, or cancer. The study patients were retrospectively evaluated for major adverse cardiovascular events, defined as cardiac death, myocardial infarction, stroke, and heart failure, or ventricular arrhythmias that required hospitalization, as compared with the baseline clinical characteristics, laboratory parameters, and outcomes in euthyroid patients.

RESULTS The study subjects were 354 patients (mean age ±SD, 61.8±14.1 yr), the majority of whom (64.7%) were male. The overall duration of follow-up was 48.6±26.7 months. Among the various groups of patients, there were neither significant differences in the prevalence of underlying heart disease and baseline left ventricular ejection fraction nor significant differences in the indications, duration, cumulative dose, or average daily dose of amiodarone (P>0.05) (Figure 1). However, patients with AIT were younger (56.7± 14.6 vs. 62.3±13.7 years; P = 0.01) as compared with euthyroid patients, while those with amiodarone-induced hypothyroidism were more likely to be female (47.9% vs. 33%; P = 0.03) and to have hyperlipidemia (28.8% vs. 12.9%; P = 0.03) as compared with those who remained euthyroid (Figure 1). After 28.2±23.3 months of amiodarone therapy, AIT developed in 57 patients (16.1%), 224 (63.3%) remained euthyroid, and after a mean duration of 27.2±23.3 months, amiodarone-induced hypothyroidism developed in 73 (20.6%) (Figure 2). Among the 57 patients with AIT, 5 had suspected type I or II AIT (1 with a history of Graves' disease and 4 with diffuse goiter with increased ultrasound Doppler flow) and 13 had suspected type II AIT (5 with negative thyroglobulin antibodies and 8 with diffuse Doppler flow by ultrasound); in 35 patients, the diagnosis of AIT type I or II was uncertain.

Ischemic heart disease was the most common underlying cardiac abnormality, and atrial fibrillation was the most common indication (75%) for amiodarone therapy, followed by ventricular tachycardia (19%) (Figure 4). The left ventricular ejection fraction was less than 45% in one third of the patients (mean, 51.2±16.8),. As

compared with euthyroid patients, those with AIT had a higher rate of major adverse cardiovascular events (31.6% vs. 10.7%; P<0.01), which was mainly caused by a higher rate of ventricular arrhythmias that required hospital admission (7.0% vs. 1.3%, P = 0.03) (Figure 3). Cox regression multivariate analysis revealed two independent predictors of major adverse cardiovascular events: AIT (hazard ratio, 2.68; confidence interval, 1.53 to 4.68; P<0.01) and left ventricular ejection fraction less than 45% (hazard ratio, 2.52; confidence interval 1.43 to 4.42; P<0.01) Amiodarone was discontinued in most patients (89%), and three were given prednisolone. Antithyroid drug therapy was prescribed
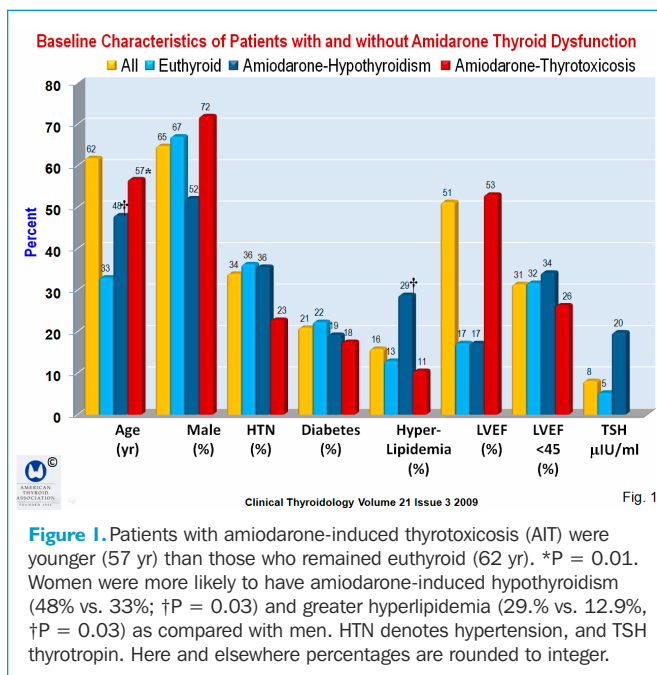
Figure 1. Patients with amiodarone-induced thyrotoxicosis (AIT) were younger (57 yr) than those who remained euthyroid (62 yr). *P = 0.01. Women were more likely to have amiodarone-induced hypothyroidism (48% vs. 33%; †P = 0.03) and greater hyperlipidemia (29.% vs. 12.9%, †P = 0.03) as compared with men. HTN denotes hypertension, and TSH thyrotropin. Here and elsewhere percentages are rounded to integer.
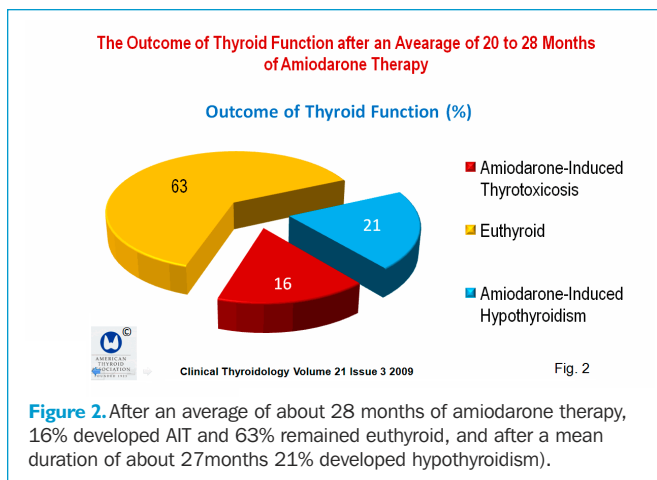
Figure 2. After an average of about 28 months of amiodarone therapy, 16% developed AIT and 63% remained euthyroid, and after a mean duration of about 27months 21% developed hypothyroidism).
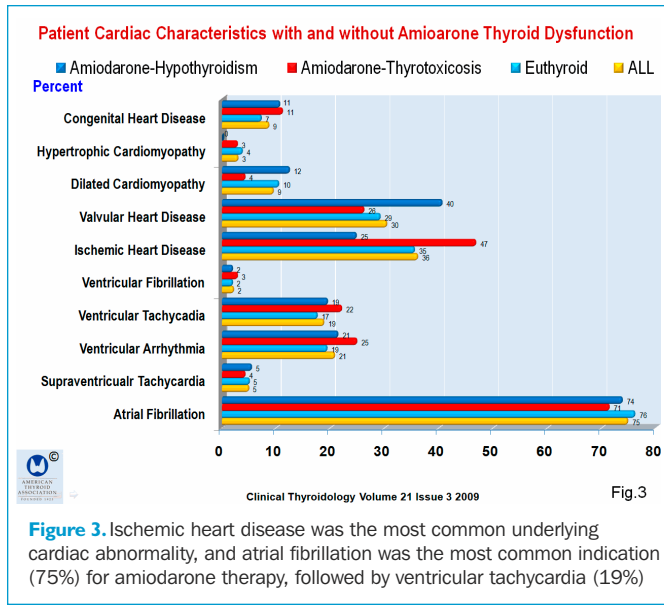
Figure 3. Ischemic heart disease was the most common underlying cardiac abnormality, and atrial fibrillation was the most common indication (75%) for amiodarone therapy, followed by ventricular tachycardia (19%)

Figure 4. The characteristics and duration of follow-up and the incidence of AIT in patients with and without major adverse cardiovascular events (MACE). CV denotes cardiovascular. *P<0.01, comparing with euthyroid patients. †P = 0.03 comparing patients with AIT with euthyroid patients

for 47 patients (83%) and radioiodine therapy was prescribed for 5 (9%) but none required thyroidectomy.

CONCLUSION Amiodarone-induced thyrotoxicosis is associated

with a nearly threefold increased risk for major adverse cardiovascular events including relevant ventricular arrhythmia that required hospitalization and treatment. Cardiovascular mortality was 12%. in the AIT I and II groups, compared with 5% in the euthyroid groups.

COMMENTARY

It has long been recognized that amiodarone, a potent class III anti-arrhythmic agent, can exert profound effects on thyroid function (1, 2). While there are clear structural similarities between the amiodarone molecule and levothyroxine, multiple lines of investigation have demonstrated that these changes in thyroid hormone levels in serum are a result of the high iodine content (33% by weight) of the amiodarone molecule. The widespread use of amiodarone for the treatment of both ventricular and atrial arrhythmias has led to the often observed development of both hypothyroidism and hyperthyroidism in patients with significant coexistent cardiac disease. While the incidence of these findings varies throughout the world, presumably as a result of the differing iodine content in the diet, the development of hypothyroidism is more frequent than that of amiodarone induced thyrotoxicosis (AIT) (2). In contrast, the treatment of AIT is much more challenging as these patients are characteristically resistant to anti-thyroid therapy with thiourea drugs, have insufficient iodine uptake into the thyroid gland to make radioiodine therapy feasible, and respond in an unpredictable way to anti-inflammatory therapy with corticosteroids (3). In the accompanying article we have our clinical impression confirmed with the finding that AIT carries a nearly threefold increased risk for major adverse cardiovascular events. These events, including ventricular tachycardia, cardiovascular hospitalization and cardiovascular death, are almost certainly the result of the underlying cardiac pathophysiology which is worsened by the thyrotoxic state. Yiu and colleagues report a 16% prevalence of AIT over approximately 28 months of amiodarone treatment. This is much greater than would be expected in a North American patient population. The characterization of the type of AIT (type I or II) (4) was uncertain in the majority of cases and although this finding was the basis for amiodarone discontinuation, it is hard to find support for this recommendation in the management of this condition. While the authors do not comment, it would be

our recommendation that such patients be treated with beta-adrenergic blockade and that in patients with heart failure, carvedilol be the agent of choice. In our experience the onset of AIT may be heralded by a decrease in Coumadin requirements due to the increase in vitamin K metabolism in patients with atrial fibrillation or alternatively to the increase in defibrillator shocks of patients with ventricular tachycardia who have intracardiac devices. This latter observation is further confirmed by the findings of Yiu et al. While this remains a challenging clinical problem, the recent FDA advisory panel approval of dronedarone, a class III anti-arrhythmic amiodarone analog that has neither iodine nor associated effects on thyroid function (5, Klein unpublished observation), may become the anti-arrhythmic treatment of choice from a thyroidologists perspective.

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Low stress level is not causally related to biochemically less severe Graves' disease in older patients

SUMMARY

BACKGROUND The pathogenesis of Graves' disease is multifactorial, with genetic and environmental factors playing key roles in the clinical manifestations of the disease, including a relationship between stressful events in the year preceding the diagnosis of Graves' hyperthyroidism. Although environmental stimuli may provoke Graves' hyperthyroidism in genetically susceptible individuals, the relationship between exposure to environmental stressors and the severity of thyrotoxicosis has not been well studied. Conversely, advanced age is associated with less severe Graves' hyperthyroidism, but the mechanism behind this observable fact is incompletely understood. The hypothesis of this study is that advancing age is associated with less exposure to stress, resulting in lower production of thyrotropin-binding inhibitory immunoglobulin (TBII), thus leading to less severe Graves' hyperthyroidism.

METHODS This is a cross-sectional observational study in which patients with an untreated initial episode of Graves' hyperthyroidism were recruited from nine participating centers in the Netherlands from July 2002 through September 2005. The inclusion criteria were a serum thyrotropin (TSH) level of <0.4 μIU/ml and a serum free thyroxine (FT_4) level of >23 pmol/L, with or without a serum triiodothyronine (T_3) level of >2.7 nmol/L, and with diffuse ^{99m}Tc-pertechnetate uptake on thyroid scintigraphy. Patients with a relapse of hyperthyroidism, verbal communication problems, or abuse of alcohol or drugs were excluded from the study. A variety of clinical features were recorded, including the hyperthyroidism symptoms score (HSS) and the presence of pretibial myxedema and Graves' ophthalmopathy. The HSS questionnaire quantitatively measures the clinical severity of hyperthyroidism using 10 items on 0- to 4-point subscale. Study participants completed two stress and one mood questionnaire at the time of diagnosis before treatment was initiated. Stress exposure was quantitated by three questionnaires: the Dutch questionnaire on stressful life events experienced in the past 12 months from a checklist of 60 possible events, which classifies the total amount of pleasantness and the total amount of unpleasantness, with a maximum score of 240 for each; the Dutch Everyday Problem Checklist, a validated version of the Daily Hassles Scale, which consists of 114 items concerning daily hassles experienced in the past 2 months; and the Positive and Negative Affect Schedule (PANAS) that measures a person's current mood, in terms of a positive and negative affect consisting of 22 mood states. Also measured were serum T_3, T_4, free T_4 index (FT_4I) and free T_3 index (FT_3I), serum thyrotropin (TSH), and TBII. To analyze the influence of age on the severity of Graves' hyperthyroidism, patients were subdivided into four age groups: ≥29 years (n = 53), 30 to 39 years (n = 56), 40 to 49 years (n = 78), and ≥50 years (n = 76).

RESULTS The study subjects comprised 263 patients, 69 men (26%) and 194 women (74%), with a median age of 43 years (25th

and 75th interquartile range, 32 to 51). The relationship between age and the biochemical severity of Graves' hyperthyroidism at the time of diagnosis is shown in Figure 1. Advanced age was associated with less severe biochemical hyperthyroidism (FT_3I and
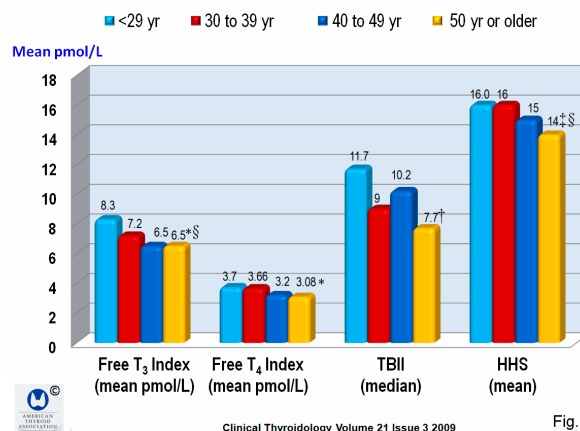
Figure 1. Values for serum FT_3I and FT_4I are pmol/L divided by 100. Advanced age was associated with less severe biochemical hyperthyroidism. *$P<0.01$ for FT_3I and FT_4I. †$P = 0.05$ for TBII. $P = 0.07$ for thyroperoxidase as compared with younger patients (data not shown). The clinical HSSs were significantly associated with less severe Graves' hyperthyroidism, ‡$P = 0.04$, with serum FT_3I ($r = 0.028$, §$P<0.01$). This figure is derived from data in Table 2 of Vox et al.

Figure 2. Age as determined for the amount of stress in 263 newly diagnosed patients with Graves' hyperthyroidism. Higher HSS scores were associated with higher frequencies and total scores for daily hassles, except for the intensity per hassle and the recently experienced stressful life event questionnaires. †$P = 0.02$. *$P <0.01$. The only other clinical characteristic associated with stress scores was goiter size, which positively correlated with both pleasantness and unpleasantness scores for recently experienced life event ($P<0.01$ and $P = 0.01$, respectively; data not shown). This figure is derived from data in Table 4 of Vox et al.

Multivariate Regression Analysis for the Effect of Stress Scores and Age on Clinical Severity HSS Gaves' Hyperthyroidism

Coefficient values shown on chart:
- Total Score Pleasantness: 0.026
- Number of Pleasant Life Events: 0.467
- Number of Unpleasant Life Events: 0.270
- Number of Life Events: -0.396
- Daily Hassles (Total): 0.110
- Positive Affect Score: -0.106
- Negative Affect (Score): 0.233
- Age: -0.040

X-axis: Coefficient (-0.4 to 0.5)

Clinical Thyroidology Volume 21 Issue 3 2009   Fig. 3

Figure 3. Multivariate analysis showed that the clinical severity of Graves' hyperthyroidism was not related to age or the amount of stress exposure but was independently related to the tendency to report negative feelings (P<0.01).

FT_4I; P<0.01), and clinically less severe Graves' hyperthyroidism according to the HSS (P = 0.04). Trend analysis between different age groups showed that serum TBII and to a lesser extent, thyroperoxidase, were decreased with advancing age (P

= 0.05 and P = 0.07, respectively). The HSS was significantly associated with serum FT_3I (r = 0.028, P<0.01) and to a lesser extent FT_4I (r = 0.017, P<0.01). Neither serum FT_4I, FT_3I, nor TBII was associated with PANAS scores; however, the total amount of pleasantness was directly associated with the FT_3I (P<0.01). Higher HSSs were associated with higher frequencies and total scores for daily hassles, except for the intensity per hassle and the recently experienced stressful life event questionnaires (Figure 2). The only other clinical characteristic associated with stress scores was goiter size, which positively correlated with both pleasantness and unpleasantness scores for recently experienced life events (P<0.01 and P = 0.01, respectively). Figure 2 shows the associations between age and various stress scores. Advanced age was associated with PNAS positive affect scores (P = 0.75) and with the frequencies of and total scores for daily hassles (P for trend, <0.01 for both), and with lower frequencies and scores for the recently experienced life events questionnaire (P<0.01). Multivariate analysis showed that the clinical severity of Graves' hyperthyroidism was not related to age or the amount of stress exposure but was independently related to the tendency to report negative feelings (P<0.01) (Figure 3).

CONCLUSION Although advancing age is associated with less exposure to stress and less severe clinical and biochemical tests of Graves' hyperthyroidism, these variables have no direct relationship to the severity of Graves' disease in older patients.

COMMENTARY

The relationship between the effects of age and clinical presentation of hyperthyroidism has intrigued clinicians and researchers for many years. While a number of studies, including the study by Vos et al. (1), have shown an age-related decrease in the degree of thyroid dysfunction in patients with Graves' disease, not all studies have shown this relationship (2, 3). The reasons usually given for the inverse relationship between age and thyroid dysfunction are decreased levels of TSAb in older patients, or a decreased responsiveness of thyrocytes to stimulation, or both. Furthermore, a decrease in serum T_3 that is well described in the "healthy" elderly is also likely operative in some older hyperthyroid patients as well (reviewed in 4), presumably due to occult comorbidity.

It has long been known that "older" people manifest fewer of the typical hyperthyroid symptoms than do their "younger" counterparts (5), but the reasons are uncertain. This is likely not related exclusively to the less deranged thyroid function in older individuals, given the statistically significant, but not terribly robust inverse relationship between thyroid function and symptoms noted by Vos et al. (1). Inspection of Figure 1 in their paper shows that Free T_3 and Free T_4 only accounted for a small part of the variability in the hyperthyroidism symptom score. It would have been interesting had the authors indicated in Figure 3 of their paper which patients were older and which were younger. Notably, others have shown major decreases in thyroid hormone action and responsiveness at the cellular level in aging animals and humans (6), which remain largely unexplained.

A relationship between stress and the onset of hyperthyroidism has been postulated beginning with the earliest case reports of Graves' disease. This connection has been documented in recent retrospective cohort studies (e.g., 7), and also in epidemiologic reports suggesting that stressful life events, such as war, can trigger the onset of Graves' disease in susceptible individuals (e.g., 8). How stress affects the immune system is uncertain, but may relate to altered circulating levels of glucocorticoids and/or catecholamines that influence the balance of cellular and humoral immunity (9).

In the paper by Vos et al. (1), the authors hypothesized that the milder biochemical abnormalities in hyperthyroid older persons might be due to less "stress" in their lives. Indeed, the authors did find that older persons lead less stressful lives. However, the degree of stress, as assessed by multiple validated instruments, was not related to the degree of thyroid dysfunction. Interestingly, however, one aspect of life stress, the negative affect score, was directly related in a statistically significant way to the hyperthyroid symptom score. Thus, patients whose mood tended to affect them in the most negative way tended to be more symptomatic when they became hyperthyroid.

The paper by Vos et al. (1) confirms the majority of studies showing that older hyperthyroid persons have fewer severe symptoms and less marked biochemical derangements than do younger patients. It is my feeling that this inverse relationship, while correct, only tells part of the story. The reasons underlying the decreased sensitivity of the elderly to the effect of thyroid hormone is a fundamental question in biology, and I hope that studies like this one will serve as an impetus to basic researchers to address this question in future studies.

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Annual 80th Meeting

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Patients with papillary thyroid cancer who have central neck compartment (level VI) lymph-node metastases have a 70 to 100% chance of concurrent ipsilateral lateral compartment involvement

SUMMARY

BACKGROUND The rates of papillary thyroid cancer lymph-node metastases in both low- and high-risk patients range from 25% to 60%, depending on the extent of surgery. While mortality rates for papillary thyroid cancer are generally favorable, especially in younger patients, the locoregional recurrence rates are high and remain as a significant cause of morbidity and major concern of anxiety for patients. The locoregional spread of tumor cells is thought to flow through the lymphatic system in a sequential fashion beginning from the thyroid gland to the central neck compartment and subsequently to ipsilateral lateral compartments and to contralateral and mediastinal compartments. Residual lymph-node metastases that remain after initial therapy are the most common cause of subsequent recurrence. As a consequence, recent focus has been on the systematic dissection of the central lymph-node compartment, although ipsilateral lateral lymph node metastases often occur with similar frequency. This is a retrospective comparative analysis of central and lateral neck lymph-node metastases.

METHODS This is a retrospective study of 88 consecutive patients, all of whom had total thyroidectomy and central and lateral ipsilateral lymph-node dissections for previously untreated papillary thyroid cancer. In addition, 32 of the 88 patients (36%) had contralateral neck dissections. Mediastinal lymph-node metastases resected in 5 patients were not considered in this study. The 88 thyroid glands underwent a standardized examination in which the entire thyroid gland was divided vertically to separate the right and left lobes, and then sectioned horizontally from the superior to the inferior pole. Conventional staining (hematoxylin and eosin) and thyroglobulin immunohistochemical examination were performed on every surgical specimen. Two subgroups were analyzed, patients who had central and lateral ipsilateral dissections, and those who had bilateral lateral neck dissections.

RESULTS When stratified into two groups, one with only ipsilateral lateral lymph-node dissection and the other with bilateral lateral lymph-node dissection, all of whom had central compartment dissection, the two study groups were largely similar in terms of gender, age and tumor histopathology, including tumor size, multifocality, extrathyroidal growth and distant metastases (Figure 1), and the number of positive lymph-node metastases per neck compartment (Figure 2). The two groups were thus combined in one subsequent analysis.

For comparative analysis, the ipsilateral lateral and central lymph-node metastases were stratified into four groups: 0, 1-5, 6- 10, and more than 10 positive lymph-node metastases. The number of lymph nodes excised was significantly related to the number of metastases in the compartment (Figure 3). There was a significant association between the central lymph node categories and the number of lymph nodes removed from the central compartment,

but not with the number of lymph nodes removed from the lateral neck. Ten of 22 patients (45%) who did not have central compartment lymph-node metastases had metastases in the ipsilateral side with the largest primary tumor, but no malignant lymph nodes were found in the contralateral lateral compartment (Figure 3). With each increasing category of central lymph-node metastases, there were significantly greater rates of lymph-node metastases (Figure 4). Among patients with only lateral lymph-node metastases, the successive increase in lateral lymph-node
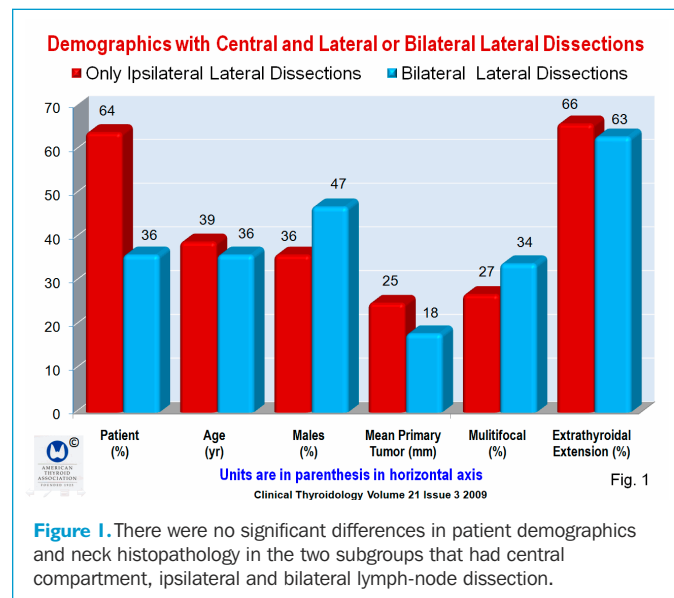
Figure 1. There were no significant differences in patient demographics and neck histopathology in the two subgroups that had central compartment, ipsilateral and bilateral lymph-node dissection.
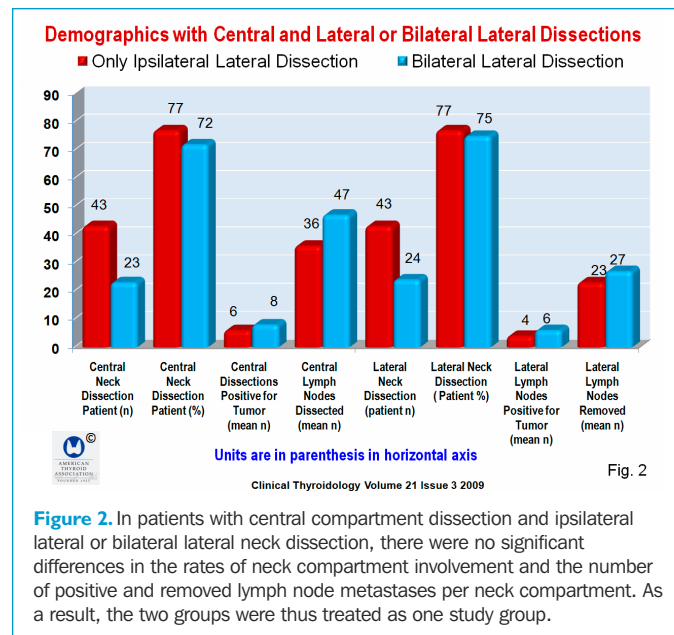
Figure 2. In patients with central compartment dissection and ipsilateral lateral or bilateral lateral neck dissection, there were no significant differences in the rates of neck compartment involvement and the number of positive and removed lymph node metastases per neck compartment. As a result, the two groups were thus treated as one study group.

Figure 3. The number of lymph nodes excised was significantly related to the number of metastases in the neck compartment.*P<0.001, comparing the number of lymph node metastases by categories †P = 0.003, ‡P= 0.009 comparing lateral lymph node metastases with the data from all four central lymph-node categories.

Figure 4. Among patients with only lateral lymph-node metastases, the successive increase in lateral lymph-node metastases was still present but was not influenced by the number of lateral lymph nodes removed. *P = 0.002, †P = 0.03, comparing lateral and contralateral lymph-node metastases with four central lymph-node categories.

metastases was still present but was not influenced by the number of lateral lymph nodes removed (Figure 4).

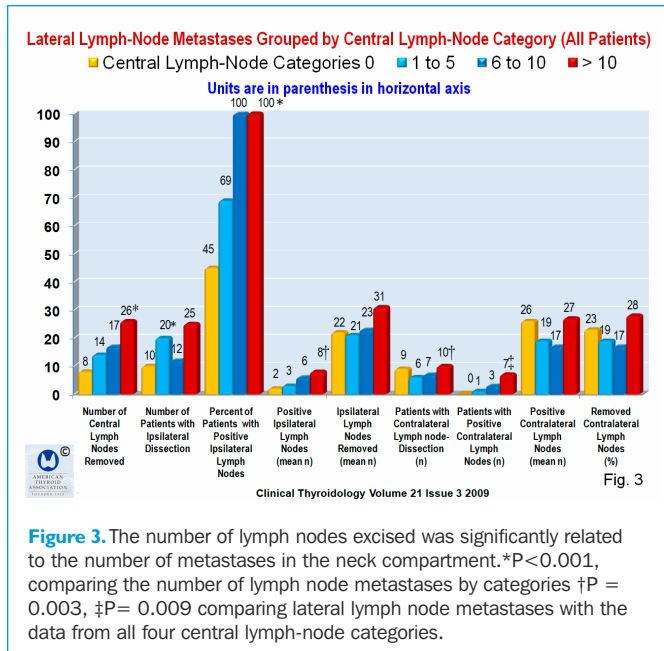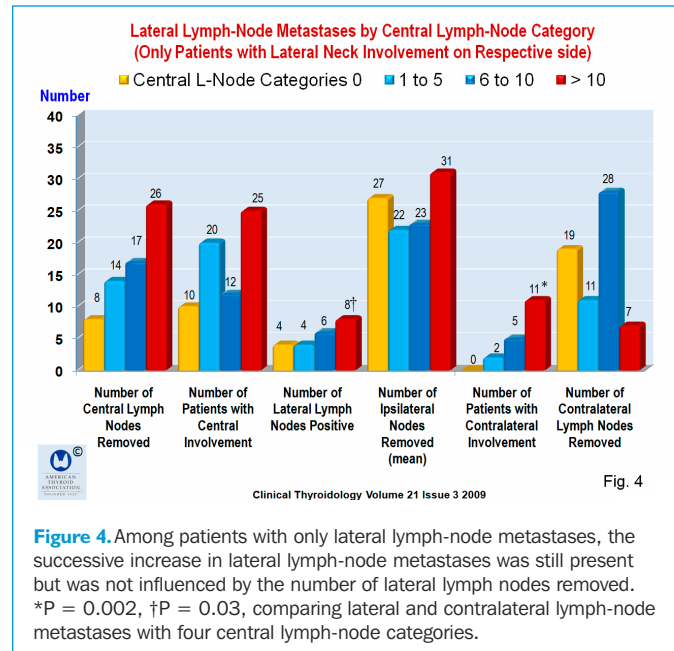Figure 4. Among patients with only lateral lymph-node metastases, the successive increase in lateral lymph-node metastases was still present but was not influenced by the number of lateral lymph nodes removed. *P = 0.002, †P = 0.03, comparing lateral and

contralateral lymph-node metastases with four central lymph-node categories.

CONCLUSION Patients with papillary thyroid cancer who have central neck compartment (level VI) lymph-node metastases have at least a 70% chance of ipsilateral lateral compartment involvement that should be considered for prophylactic dissection

COMMENTARY

The study by Machens et al (1) retrospectively evaluates 88 patients who had undergone lateral neck dissection (ipsilateral or bilateral) and central neck dissection as initial therapy for papillary thyroid carcinoma at the time of thyroidectomy. The group studied represents a subset (35%) of 251 patients initially treated surgically for papillary cancer at their institution. The indications for lateral neck dissection in this group were not explicitly stated in the manuscript. The stated aim of the study was to quantitatively explore any relationship between the number of metastatic central neck nodes with the presence and number of metastatic lateral neck nodes.

The results of this study clearly show an increased likelihood of lateral lymph node metastasis with increasing numbers of positive central neck nodes (table II). This is consistent with a recent paper by Kwyak et al. (2). Others have found this to also be true for more advanced T stages (3). The more difficult question is whether prophylactic lateral neck dissection should be performed based upon these risk factors in the absence of clinical or imaging evidence of lateral nodal metastasis. In areas such as Japan and Korea where postoperative radioiodine is used infrequently, this approach is advocated (4).

The authors suggest in their discussion that bilateral lateral neck dissection should be considered for patients with > 5 metastatic central neck nodes due to the high rate of positive

ipsilateral (100%) and contralateral (60-71%) nodal metastasis in the lateral neck. Further, the authors advocate consideration of ipsilateral lateral neck dissection for patients with between 1 and 5 metastatic central nodes based upon a high incidence of ipsilateral nodal metastasis (69%) in this study. The implication is that lateral neck dissection should be considered for completion of initial surgical management even if it requires a return to the operating room following prior thyroidectomy and central neck dissection based upon the final histopathological staging of the central compartment.

There is widespread agreement that all patients suspected of having papillary thyroid carcinoma should undergo neck imaging for detection of nodal metastasis using ultrasound and/or computed tomography (5). Ideally, this is performed prior to thyroidectomy based upon a cytological diagnosis or suspicion of malignancy such that appropriate therapeutic lateral neck dissection can be incorporated into initial surgical therapy (6). Unfortunately, our best imaging modalities are often unable to detect subclinical or microscopic nodal metastasis (7).

The presence of nodal metastasis has been shown to increase recurrence and mortality in well differentiated thyroid carcinoma (8). Comprehensive compartment oriented neck dissection results is lower rates of recurrence than node plucking or "berry picking" (9). The assumption behind prophylactic

neck dissection is those microscopic and macroscopic nodal metastases both have negative impacts on patient outcomes but a recent study by Bardet et al. (10) suggests that only macroscopic nodal disease impacts recurrence. Cranshaw et al. (11) reviewed the evidence and concluded that the presence of micrometastasis is of questionable significance, especially in regions where postoperative radioiodine use is common. In the United States, prophylactic lateral neck dissection is not routinely recommended (5).

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Elevated TSH levels normalize or remain unchanged in the majority of children with subclinical hypothyroidism

Wasniewska M, Salerno M, Cassio A, Corrias A, Aversa T, Zirilli G, Capalbo D, Bal M, Mussa A, de Luca F. Prospective evaluation of the natural course of idiopathic subclinical hypothyroidism in childhood and adolescence. Eur J Endocrinol 2009;160:417-21.
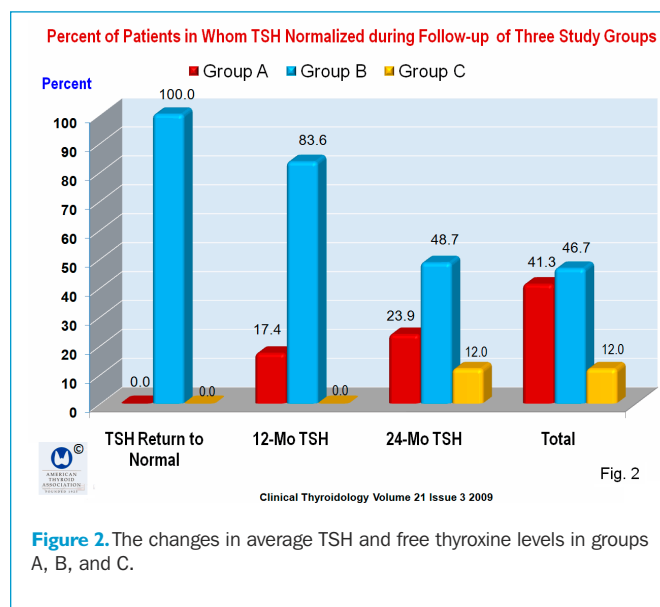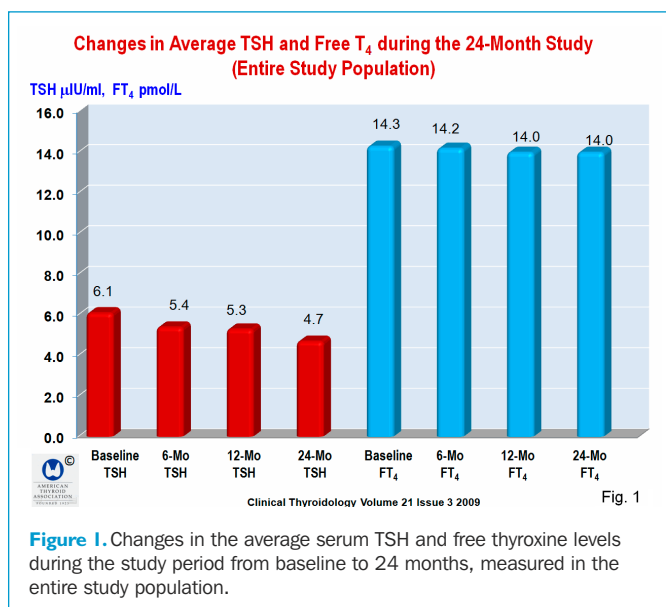
SUMMARY

BACKGROUND Subclinical hypothyroidism (SCH) is not very common during childhood and adolescence. Although data concerning the natural evolution of this disorder in children and adolescents is very sparse, some studies find that juvenile SCH may be a benign remitting process with a very low risk for progression to overt hypothyroidism. The aim of this study was to prospectively evaluate the course of SCH in children and adolescents with no underlying diseases and no risk factors that might interfere with the progression of SCH.
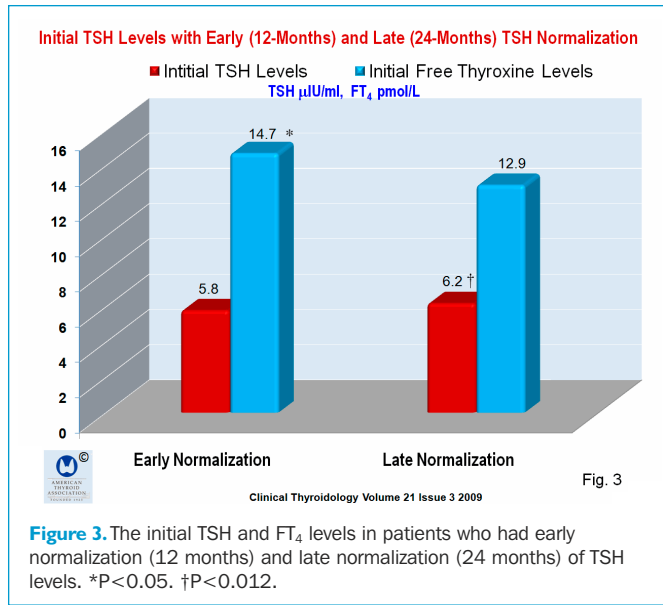
METHODS This is a 2-year multicenter study that prospectively evaluated the spontaneous changes in thyrotropin (TSH) and free thyroxine (FT_4) in a pediatric population comprising patients with idiopathic SCH without other nonthyroidal diseases and with no thyroid disorders or medications affecting the thyroid gland. The study subjects were children referred by community physicians because of an incidental finding of an elevated serum TSH concentration that was discovered during an annual checkup that included TSH measurement. SCH was defined as an elevated serum TSH level of 5 to 10 μIU/ml with a normal serum FT_4 concentration of 10.3 to 24.4 pmol/L, both of which were measured twice over a 1- to 2-month interval as a requirement for admission into the study. In addition, patients were screened for thyroid immune disorders with anti–thyroid peroxidase antibodies (TPOAb) and by thyroid ultrasonography performed by the same operator at entry and at the end of the 24-month study. None of the children were taking drugs known to interfere with thyroid function or had prior head or neck radiation or a prior false positive screen for congenital hypothyroidism. The study was performed in non-iodine-deficient areas. All the children with idiopathic SCH were studied as outpatients, and after the initial evaluation, they were prospectively evaluated in the hospital at 6, 12, and 24 months. During follow-up, patients were treated with levothyroxine if they exhibited a further increase in serum TSH levels greater than 10 μIU/ml. Thyroid-function tests were determined in a fasting state and were performed in the same laboratory for each subject.

RESULTS The study subjects comprised 92 patients younger than 15 years with a mean (±SD) age of 8.1±3.0 years (range, 5.0 to 14.9). In all, 67 patients (72.8%) were prepubertal and 25 (27.2%) were pubertal. During the first 6 months of follow-up, serum TSH concentrations declined significantly (Figure 1). The mean decrement in serum TSH from baseline to the end of the study was 1.0±2.1 μIU/ml. There was no relationship between gender, age, pubertal status, and serum FT_4, which did not change during follow-up and remained in the normal range throughout the study period (Figure 1). At the end of the study, only two patients had thyroid ultrasonography revealing changes compatible with Hashimoto's thyroiditis, and the others had normal thyroid glands. Except for the two children with abnormal ultrasonography, all the patients had undetectable serum TPOAb levels.

During the study, mean serum TSH levels decreased progressively while serum FT_4 levels remained unchanged. The serum TSH returned to normal (< 5 μIU/ml) in 38 of 92 patients (41%, group A), which occurred between 6 and 12 months in 16 and between 12 and 24 months in 22 patients (Figure 2). The decrease in TSH values was similar during the earlier and later periods of decline, when the TSH declined to <2 μIU/ml in only 2 patients (5.3%) while the majority of TSH levels (68.4%) normalized to between 3 and 4.3 μIU/ml. Serum TSH did not normalize during the entire observation period in the remaining 54 patients (58.7%,

Figure 1. Changes in the average serum TSH and free thyroxine levels during the study period from baseline to 24 months, measured in the entire study population.

Figure 2. The changes in average TSH and free thyroxine levels in groups A, B, and C.

Back to Contents

Figure 3. The initial TSH and FT_4 levels in patients who had early normalization (12 months) and late normalization (24 months) of TSH levels. *P<0.05. †P<0.012.

Figure 4. The percent of pubertal and prepubertal children in whom serum TSH normalized during follow-up. *P<0.05.

group B). During this time, the TSH remained between 5 and 10 μIU/ml in all but 11 patients (12%, group C) who had a further increase in serum TSH levels to between 10.5 and 15.0 μIU/ml, despite the normal FT_4 levels. In 2 of the 11 patients in group C, the TSH increase was accompanied by detectable TPOAb and ultrasonographic features of Hashimoto's thyroiditis at the end of follow-up. Initial serum TSH levels were higher among patients in whom TSH normalized late (24 months), as compared with those in whom it normalized early (12 months) (6.2±1.7 vs. 5.8±1.3 μIU/ml, P<0.0125), respectively, and the initial FT_4 levels were lower (12.9±3.3 vs. 14.7±3.3 pmol/L, P<0.05) in the two groups, respectively (Figure 3). However, even in patients in whom the TSH was slow to normalize, there was a significant decrease in serum TSH levels from baseline to 12 months (6.2±1.7 to
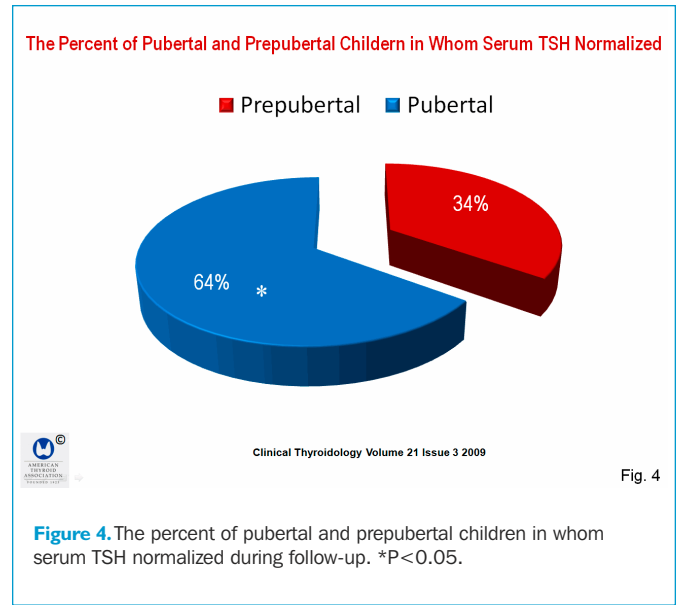
5.0 ±1.6 μIU/ml, P<0.05), respectively; however, there was no significant decrease in serum TSH from baseline to 12 months in the patients whose TSH did not normalize during the entire period of observation (Figure 4). The serum TSH normalized in a significantly greater number of pubertal than prepubertal patients (64.0 vs. 34.3%, P<0.01), but there were no differences between boys and girls (40.0 vs 42.8%, P>0.05).

CONCLUSION The spontaneous course of TSH levels in a pediatric population with idiopathic SCH is characterized by a progressive decrease in TSH over time in the majority of patients. This decrease was not associated with any changes in either FT_4 levels or the clinical status of the patient.

COMMENTARY

This is the first prospective study to investigate the natural evolution of SCH over time in a series of children and adolescents.

There are few studies of idiopathic SCH in pubertal and prepubertal children. Those that have been published report outcomes in patients with myriad causes of childhood SCH. For example, a study of 18 children and adolescents (age range, 5 to 19 years) with juvenile autoimmune thyroiditis with elevated serum TSH levels reported that after a mean follow-up of 5.8 years, 11 never received treatment (1). The mean duration during which the patients did not receive therapy was 47.3 months. At the end of the observation period, seven patients were euthyroid, approximately half continued to have an elevated serum TSH levels with normal serum T_4 concentrations, and only one became overtly hypothyroid. The authors suggested that juvenile SCH may be a benign process that undergoes spontaneous remission in a substantial number of patients, and that it may be possible to follow selected younger patients with a minimally elevated serum TSH concentrations rather than treating them empirically with levothyroxine. However, this is quite different from the study by

Wasniewska et al., which prospectively studied only patients with no evidence of thyroid disease, including Hashimoto's thyroiditis, at the time of enrollment and autoimmune thyroiditis developed in only 2 patients after 24 months of observation. Another study of newborns with high TSH levels at birth and with normal FT_4 and normal or only slightly elevated TSH, which is considered to be false positive congenital hypothyroidism, concluded that newborns classified as false positive for congenital hypothyroidism have a very high risk of SCH in infancy and early childhood (2), an observations confirmed by other studies (2).

The study by Wasniewska et al. is unique. The patients were carefully screened for other causes of SCH, including false negative congenital hypothyroidism. The patients underwent a follow-up of 2 years without therapy except for two patients in whom hypothyroidism developed. None of the patients in this study had any clinical signs or symptoms of hypothyroidism during their entire follow-up. Moreover, none of the patients showed any symptoms of hypothyroidism during follow-up, and there were no significant changes in both height and body-mass index throughout the observation period, although group C children were

overweight and remained so from the time of entry to the close of the study. By the end of the study, the percent of individuals who were overweight was slightly higher in group C but this was not statistically significant. The authors of this study concluded that the natural course of TSH elevations in a pediatric population with SCH is characterized by a progressive decrease over time and that the majority of patients have a normalization of, or stable mild increase in serum TSH with normal serum FT_4 concentrations. The data in this study are robust, which along with other studies (3-5) provide much proof for the authors' conclusion that TSH determination has no reason to be part of the routine checkup in children, except for specific protocols.

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Disease-free and cancer-specific survival is similar in familial and sporadic papillary thyroid cancer in Japanese patients

Ito Y, Kakudo K, Hirokawa M, Fukushima M, Yabuta T, Tomoda C, Inoue H, Kihara M, Higashiyama T, Uruno T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Miyauchi A. Biological behavior and prognosis of familial papillary thyroid carcinoma. Surgery 2009;145:100-5.

SUMMARY

BACKGROUND The risk for familial nonmedullary thyroid cancer (FNMTC) is elevated among individuals with first-degree relatives who have the same type of tumors. However, there is debate concerning the biologic characteristics of FNMTC. This is a study of the prevalence and biologic behavior of this familial disorder.

METHODS From 1987 through 2004, 6015 patients had initial surgical treatment of papillary thyroid carcinoma at Kuma Hospital in Japan. Among this group, 273 (4.5%) were classified as having familial nonmedullary thyroid cancer on the basis of two or more first-degree relatives with papillary cancer, including the index patient, none of whom had other familial thyroid cancer syndromes or prior exposure to radiation. The extent of thyroidectomy was based on preoperative neck ultrasound findings. Cervical lymph-node central compartment dissection was performed systematically (prophylactically) in 5706 (95%) patients with tumors larger than 1 cm without preoperatively identified lymph-node metastases, and was done therapeutically in patients with known cervical lymph-node metastases. Thereafter, patients had a once-yearly follow-up with ultrasonography and either chest roentgenography or computed tomography.

RESULTS In all, 273 of 255 patients (93.4%) were members of families with 2 affected individuals, including the patient under study, and 18 (6.6%) had 3 or more affected family members. Total or near-total thyroidectomy was performed in 177 of 273 (69%) with familial tumor and 2894 of 5742 (50%) patients with sporadic tumors, and lobectomy or less was performed in 72 of 273 (26%) with familial tumors and 2308 of 5742 (40%) with sporadic tumors (Figure 1). Among the patients with familial tumors, lymph-node compartment dissection was bilateral in 27 (10%), unilateral in 174 (64%) and limited to the central neck compartment in 62 (22%) or was not performed in 10 (3%) patients. Among the 5742 patients with sporadic disease, lymph-node compartment dissection was bilateral in 537 (9%), unilateral in 3800 (66%) and confined to the central neck compartment in 1106 (19%) and was not performed in 299 (6%) patients (Figure 1). Only 127 patients (2%) had postoperative ^{131}I remnant ablation. Tumor recurrence was based on the results of imaging studies. The positive predictive value of identifying tumor multicentricity on preoperative ultrasound was 80%, the negative predictive value 78%, the sensitivity 60%, and the specificity 90% (Figure 2). Multicentric tumors were detected by preoperative ultrasonography in 104 of 273 patients (38%) with familial tumors and in 1618 of 5742 (28%) with sporadic tumors (P<0.006, comparing sporadic tumor with familial tumor) (Figure 3). Multicentric tumors were confirmed by the surgical pathology in 127 of 273 patients (46%) with familial tumors and 2201 of 5742 (38%) with sporadic tumors (P = 0.008)

In all, tumor recurred in 463 of 5931 patients (7.8%) who underwent locally curative surgery, 21 (0.4%) with familial tumor and 442 (7.5%) with sporadic tumor (P = 0.004). Of patients that had less than near-total thyroidectomy, tumor growth appeared in remnant thyroid tissue in 4 of 85 (5%) with familial tumor, and 33 of 2844 (1%) with sporadic tumor (P<0.004). Recurrences among the 6051 patients were found in other organs in 342
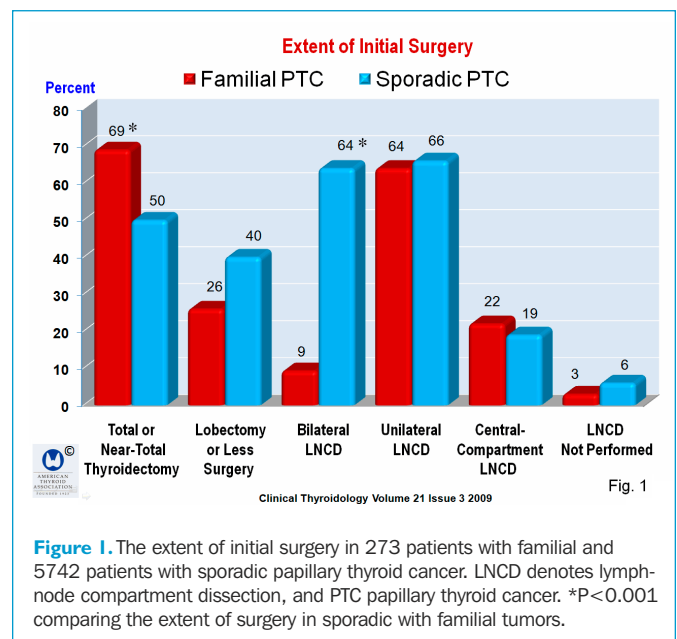
Figure 1. The extent of initial surgery in 273 patients with familial and 5742 patients with sporadic papillary thyroid cancer. LNCD denotes lymph-node compartment dissection, and PTC papillary thyroid cancer. *P<0.001 comparing the extent of surgery in sporadic with familial tumors.

Figure 2. The preoperative diagnostic accuracy of neck ultrasound examination is summarized. The main findings are a sensitivity of 60% and a positive predictive value of 80%.

Back to Contents

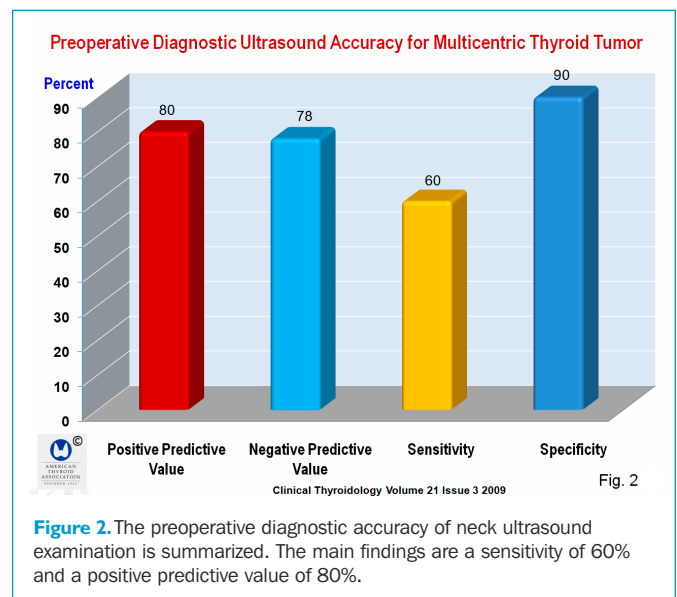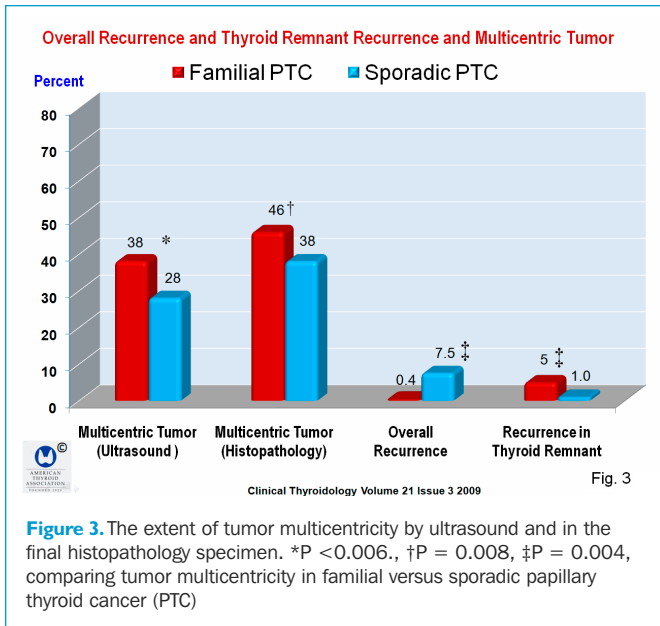**Figure 3.** The extent of tumor multicentricity by ultrasound and in the final histopathology specimen. *P <0.006., †P = 0.008, ‡P = 0.004, comparing tumor multicentricity in familial versus sporadic papillary thyroid cancer (PTC)

patients (5.7%), but there were no significant differences among patients with sporadic or familial tumors. There was no significant difference in disease-free survival and cancer-specific mortality rates among patients with familial or sporadic tumor.

Multivariate analysis found that the following variables influenced disease-free survival: tumor larger than 4 cm (P<0.001), tumor stage pT_4 (tumor of any size extending beyond the thyroid (P<0.0001), age 55 or older (P<0.001), male sex (P = 0.003), and stage N1b (bilateral, midline, or contralateral cervical or mediastinal lymph-node metastases, P<0.0001). In addition to distant metastases, multivariate analysis of disease–free survival found the same independent variables as found in the multivariate analysis of disease-free survival. Tumor multicentricity was not recognized as an independent variable in either multivariate analysis.

CONCLUSION Disease-free survival and cancer-specific mortality rates are similar in Japanese patients with sporadic and familial papillary thyroid cancer.

COMMENTARY

About 5% of papillary thyroid cancers are inherited as a familial tumor without other associated pathology, which is usually referred to as familial nonmedullary thyroid cancer (1). Although the causative gene(s) is yet to be identified, one family in Tasmania was found to have a mutation in chromosome 2q21 (2). A more recent study found that the polymorphic mature microRNAs from the passenger strand of pre-miR-146a contribute to familial thyroid cancer (3). How this will translate into clinically identifying patients with familial nonmedullary thyroid cancer awaits further study. Nonetheless, FNMTC is recognized as a distinct clinical entity in which almost all of the tumors are papillary thyroid cancers (4). Still, sporadic papillary cancer is so prevalent that up to 69% of two-hit families actually have sporadic, not familial, tumor (5). An estimated 1 of 338 persons with thyroid cancer (~3%) carries the genetic trait for familial papillary thyroid cancer, and its presence is most certain in families with 3 to 5 affected members, in which case there is a 96% likelihood it is an affected kindred (5).

It has been suggested that familial papillary thyroid cancer seems to have a less favorable prognosis as compared with sporadic tumors (1). Some studies find that familial papillary cancer is characterized by an earlier age at onset and a more aggressive phenotype than sporadic tumors (6). A study of 258 cases found that although sex, age, and tumor histology were similar to that with sporadic papillary cancer, familial tumors were more likely to have intrathyroidal dissemination (41% vs. 29%) and higher recurrence rates (16% vs. 10%) as compared with

sporadic tumors, without displaying significant differences in size, local invasion, or macroscopic metastasis (7). A meta-analysis found that individuals with familial papillary cancers have an increased risk of multifocal disease, local invasion, and lymph-node metastases and that these aggressive features appear to contribute to the higher recurrence rate and decreased disease-free survival rates in familial papillary thyroid cancer as compared with sporadic thyroid cancer (1).

The study by Ito et al. finds a somewhat different outcome than that reported by many others. Since this is a genetic disorder, familial papillary thyroid cancer in Japanese patients may be genetically predisposed to a less aggressive course. It also is important to note that that the majority of sporadic cases in the Ito study had only 2 family members with familial tumors, and the presence of this disease is much more certain when there are 3 to 5 affected kindred. Also, it is difficult to know the outcome of patients with familial tumors as compared with sporadic cases, as many patients in this series had less than total thyroidectomy without radioiodine ablation. Furthermore, neck ultrasonography had a sensitivity of less than 60%. Still, more patients with familial tumors in the Ito study had significantly greater rate of multifocal tumor as compared with patients who had sporadic disease, although this was not an independent variable in multivariate analysis. This is a complex problem that spans genetics, clinical diagnosis, and therapy, any of which can alter prognosis, thus altering the apparent behavior of a tumor.

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Differentiated thyroid cancer is more aggressive in prepubertal children, but the short-term outcomes are similar in prepubertal and pubertal children

SUMMARY

BACKGROUND Differentiated thyroid cancer is uncommon in children and adolescents. As a result, very young patients tend to be grouped with adolescents and young adults in clinical thyroid cancer studies. Thus, few studies address the differences in presentation and outcome between prepubertal children and adolescents. The aim of this study was to compare the clinical characteristics, course, and outcome of these tumors in prepubertal children and adolescents.

METHODS This is a retrospective study of 10 prepubertal and 17 pubertal patients with differentiated thyroid cancer that was initially diagnosed and treated from 1990 through 2008 at Schneider Children's Medical Center of Israel. All were treated with total thyroidectomy and postoperative ^{131}I for remnant ablation or treatment of metastases. Postoperative ^{131}I therapy was given empirically using doses suitable for adults of 30 to 100 mCi for remnant ablation, 150 mCi for neck or mediastinal lymph-node metastases, and 175 to 200 mCi for distant metastases—modified for children using the following formula: pediatric dose = adult dose × body weight (kg)/70—followed by thyroid-hormone thyrotropin (TSH) suppression to <0.05 μIU/ml. Patients with locoregional or distant metastases were retreated with [131]I. In addition, patients had repeated measurements of body-mass index (BMI). Follow-up at 3 to 6 month intervals consisted of clinical examinations, serum thyroglobulin (Tg) and anti-Tg antibody (TgAb) determinations, neck ultrasonography, chest radiography, and 2 to 5 mCi diagnostic whole-body ^{131}I scans and TSH-stimulated serum Tg measurements every 6 to 12 months within the first 2 years after initial therapy. Patients were considered to be free of tumor if the following were present: 2 consecutive negative diagnostic whole-body ^{131}I scans, undetectable or low serum (<2 μg/L) Tg levels during TSH suppression and stimulation (thyroid hormone withdrawal), and negative neck ultrasonography. Repeated evaluations were performed every 2 years for 4 years and every 5 years thereafter. Recurrent or persistent disease was identified by physical examination or neck ultrasonography and increasing serum Tg levels, with or without positive diagnostic whole-body scans.

RESULTS The study subjects comprised 27 patients less than 17 years of age, of whom 10 (37%) were prepubertal (Tanner stage 1) and 17 (63%) were pubertal (Tanner stage 4 to 5); 30% and 17.5% were males and 70% and 83% were females in the two age groups, respectively. The mean age ($\pm$SD) at diagnosis was 9.5 ± 2.2 years (range, 6.1 to 11.5) in the prepubertal group and 14.7 ± 1.7 (range, 12.5 to 17) in the pubertal group. The rate of familial thyroid cancer was higher in the prepubertal group (50%) as compared with the pubertal group (17.5%). Only the pubertal group had one patient with differentiated thyroid cancer associated with familial adenomatous polyposis and another with Cowden syndrome, and a third with exposure to external irradiation. At the time of initial diagnosis, more prepubertal than pubertal patients were symptomatic (60% vs. 41%), and a thyroid lump with enlarged cervical lymph nodes was found more often in prepubertal than pubertal patients (70.5% vs. 29.5%, P = 0.009).

Figure 1. Patient age and initial tumor characteristics (numbers rounded to integer). *P<0.01, †P = 0.009, comparing prepubertal and pubertal children. This figure and Figure 2 are adapted from data in Table 1 by Lazar et al.
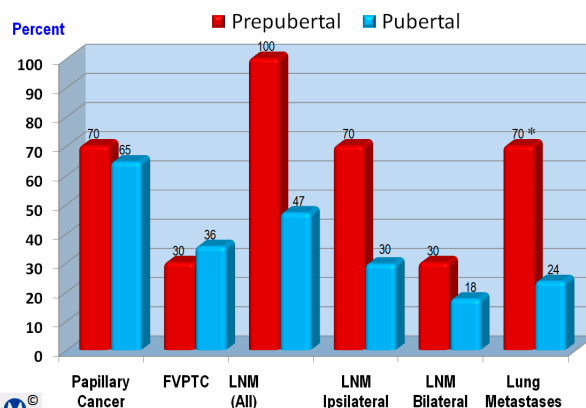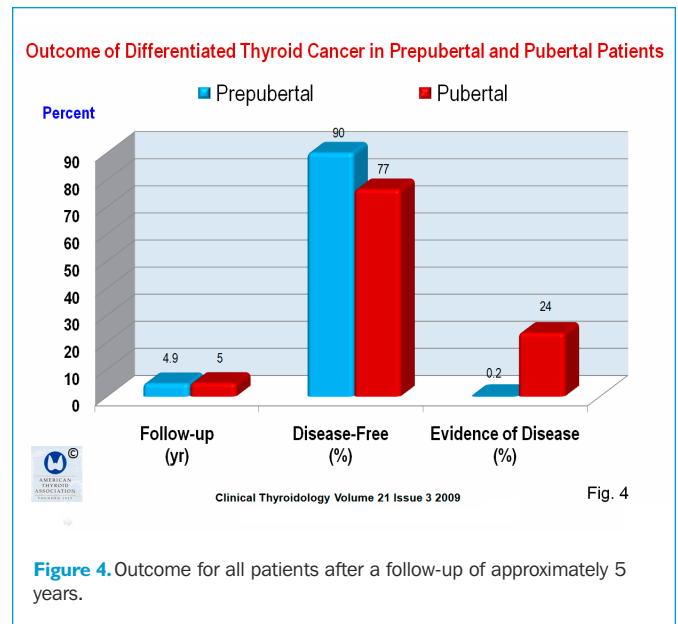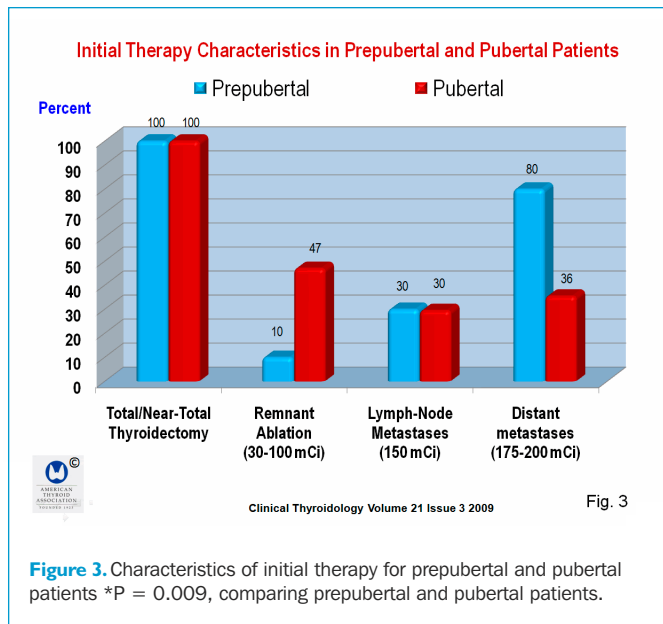

Figure 2. Initial patient and tumor characteristics. *P = 0.009, comparing prepubertal and pubertal children. PTCFC denotes Follicular variant papillary thyroid cancer, LNM denotes Lymph-node metastases, and All denotes ipsilateral and bilateral lymph-node metastases.

Back to Contents

Figure 3. Characteristics of initial therapy for prepubertal and pubertal patients *P = 0.009, comparing prepubertal and pubertal patients.

Figure 4. Outcome for all patients after a follow-up of approximately 5 years.

In the prepubertal and pubertal patients, the rates of papillary thyroid cancer (70% vs. 64.5%), follicular variant papillary thyroid cancer (30% vs. 35.5%), average tumor size (1.87±0.77 vs. 1.99±0.94 cm), and the rates of tumor multifocality (100 vs. 82.5%) were not significantly different. However, the prepubertal group had more tumors with extrathyroidal extension (80% vs. 35.5%, P = 0.012), more lymph-node metastases (100% vs. 47%, P = 0.009) and more lung metastases (70% vs. 23.5%, P = 0.009) as compared with the pubertal group (Figures 1 and 2).

All patients had total or near-total thyroidectomy with excision of suspicious lymph nodes. Neck lymph-node dissection was performed in 15 patients (56%) with clinically positive lymph-node metastases. There was no substantial difference in the initial surgery or in the surgical complications in the two groups (transient hypocalcemia in two patients and vocal-cord dysfunction in two patients with very extensive disease at the time of presentation). Prepubertal and pubertal patients were all treated with the adjusted adult equivalents of ^{131}I as follows: 30 to 100 mCi for remnant ablation (10% vs. 47%, P = 0.025), 150 mCi for lymph-node metastases (30% vs. 29.5%, P = not significant), and 175 to 200 mCi for lung metastases (60% vs. 23.5%, P = 0.29), in prepubertal and pubertal patients, respectively. The actual amount of ^{131}I administered ranged from 10 to 180 mCi on the basis of an adult-equivalent dose. The prepubertal

children, who had more invasive disease, were given an average of 140.9±41.6 mCi of ^{131}I as compared with adolescents who were treated with an average of 80±51.9 mCi (P = 0.004). Transient short-term adverse effects of ^{131}I were more common in the prepubertal children; however, mild myelosuppression was documented only in pubertal patients.

After a median follow-up of 5 years, the course and outcome were comparable in the two groups. One year after the initial ^{131}I therapy, 18 patients—7 prepubertal and 11 pubertal (67%)—had a complete remission of tumor, 4 patients (15%) had a partial response with residual locoregional tumor but achieved full remission after a second treatment with ^{131}I, and 4 pubertal patients (40% of the pubertal group) had persistent disease lasting longer than 4.5 to 5 years, 3 of whom developed iodine–non-avid tumors with elevated serum Tg levels in the range of 10 to 90 μg/L; 1 patient had locoregional disease in the thyroid bed and 3 had lung metastases. Five patients, 1 prepubertal and 4 pubertal, had a recurrence ranging from 2 to 10 years (median, 3.5) after therapy. The 20-year survival rate was 100% in both groups. During follow-up, the patients had normal growth and their BMI was within the reference range.

CONCLUSION Although differentiated thyroid cancer is more aggressive in prepubertal children, the clinical course and outcomes are similar in prepubertal and pubertal children.

COMMENTARY

Differentiated thyroid cancer in children and adolescents is uncommon, comprising only 1% of all cancers in prepubertal children and 7% in adolescents aged 15 to 19 years (1). However, 20% of thyroid nodules in children are malignant (2), as compared with only about 5% in adults (3). Moreover, children typically have more extensive disease than adults at the time of diagnosis, with approximately 40 to 90%, of children having lymph-node metastases (4) and about and 20 to 25% having distant metastases (5,6), whereas the rates of lymph-node metastases in both low- and high-risk papillary thyroid cancers in adults range from 25 to 60%, (7,8) and only about 2% of adults have distant metastases at the time of diagnosis. In addition, tumors are multifocal more often in children than in adults. Yet despite more advanced disease, survival rates for children and young adults with papillary thyroid cancer are generally much more favorable than those in adults. Nevertheless, some children die from progressive disease decades after their initial therapy, some of whom were prepubertal at the time of initial diagnosis (9). The natural history of papillary thyroid cancer is such that many adults reach normal life expectancy after total thyroidectomy and radioiodine therapy (10); however, there are no studies comparing life expectancy of children with papillary thyroid cancer treated with surgery and radioiodine with that of the general population.

Most studies of papillary thyroid cancer in children include adolescents and young adults, making it difficult to know the differences in tumor presentation, diagnosis, treatment, and outcome in patients who are prepuberal at the time of diagnosis, as compared with older children. The study by Lazar et al. is one of only a few showing that papillary thyroid cancer in prepubertal children has higher rates of extrathyroidal extension, lymph-node metastases and lung metastases at the time of diagnosis as compared with older children. This group of children received aggressive therapy. After 5 years of follow-up, 90% of the prepubertal children and 77% of the pubertal children were free of disease. Still, 24% of the pubertal patients had evidence of persistent disease.

A larger study by Handkiewicz-Junak et al. (11) of 235 children younger than 18 years of age with differentiated thyroid cancer, more than half of whom were younger than 15 years (10% <10 and 41% <15) found after a median follow-up of 6.8 years that total thyroidectomy and adjuvant radioiodine therapy independently decreased the risk for locoregional recurrence in childhood and adolescence. In all, 86% of the children remained free of recurrence and 14% had locoregional recurrence, including tumor in the thyroid bed, and none died of thyroid cancer. Multivariate analysis found that the significant risk factors for thyroid-bed recurrence were less than total thyroidectomy (relative risk, 9.5; P = 0.04) and lack of postsurgical radioiodine therapy (relative risk, 11, P = 0.03); and the significant factors for lymph-node recurrence were incomplete lymph-node surgery (relative risk, 1.9; P = 0.02) and lack of postsurgical radioiodine therapy (relative risk, 3.3; P = 0.02). An age of 18 years or less and sex did not correlate with locoregional recurrence. This robust study thus supports total thyroidectomy and postoperative radioiodine therapy for children.

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