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ETIOLOGY IS THE MAJOR FACTOR INFLUENCING THE PROGRESSION OF SUBCLINICAL HYPERTHYROIDISM

Schouten BJ, Brownlie BE, Frampton CM, Turner JG. **Subclinical thyrotoxicosis in an outpatient population—predictors of outcome**. Clin Endocrinol (Oxf) 2011;74:257-61.

SUMMARY

BACKGROUND

Subclinical hyperthyroidism (SCH) is readily detected with sensitive serum thyrotropin (TSH) assays. The rate of progression to overt hyperthyroidism is still uncertain and has not been related clearly to various etiologic factors. The authors performed a retrospective study of their patients at Christchurch Hospital in New Zealand to determine the rate of progression to overt hyperthyroidism and the risk factors for its development.

METHODS

During a 6-year period, 96 patients were identified with autonomous SCH. Patients on drugs known to influence thyroid function or other disorders that might lower TSH were excluded. Measurements included serum TSH, total thyroxine (T_4), free T_4 index based on thyroxine-binding globulin, total triiodothyronine, and antithyroid antibodies. The lower limit of serum TSH was 0.25 mU/L. Ninety-four patients had pertechnetate thyroid scintiscans. Follow-up ranged from 3 to 9.4 years (mean, 3.8).

RESULTS

Based on the scintiscan and clinical evaluation, 12 patients had subclinical Graves' disease, 70 had multinodular goiter and 14 had an autonomous nodule. Mean serum TSH was 0.03 mU/L in those with subclinical Graves, 0.08 in those with multinodular goiter, and 0.07 in those with an autonomous nodule. Progression to overt hyperthyroidism occurred in 8% of the total group at 1 year, 16% at 2 years, 21% at 3 years, and 26% at 5 years. During a 5-year follow-up, the progression to overt hyperthyroidism was 9% for the group with subclinical Graves' disease, 21% for those with multinodular goiter, and 61% for those with autonomous nodules. Statistical analysis was performed to assess the relative importance of age, sex, family history of thyrotoxicosis, symptoms at presentation (tremor, weight loss, or heat intolerance), thyroid nodule(s) on clinical examination, entry TSH level, antithyroid antibody status, and scintiscan category on subsequent development of overt disease. Only the underlying thyroid pathology determined by scintigraphy was an independent predictor of outcome (P = 0.003).

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CONCLUSIONS

Progression of SCH to overt hyperthyroidism occurred at a rate of 5 to 8% per year with disease etiology, as determined by thyroid scintigraphy, significantly influencing the risk of progression.

COMMENTARY

This is the largest series examining the influence of etiology on the progression of SCH to overt hyperthyroidism. It should be noted that of the 14 patients with autonomous nodules, it took only 2 years for overt hyperthyroidism to develop in the 8 in whom it occurred. Although it is difficult to generalize from such a small group, this was clearly a faster progression to overt disease than occurred with the multinodular group. However, among the 70 patients with multinodular goiter, 11 had thyroidectomy for obstructive symptoms. My experience in patients with multinodular goiter is that most with mild lowering of serum TSH do not progress for many years. I agree with the authors' recommendation that close follow-up is an important aspect of care.

Although the authors did not find that initial serum TSH influenced progression, the mean serum TSH was <0.1 mU/L in each group. Only the group with multinodular goiter had the upper TSH value of 0.15 mU/L. This is significant because the patients who are likely to progress and bear closer follow-up are those with serum TSH <0.1 mU/L, as shown in the recent large survey in Scotland (1), summarized in the January 2011 issue of Clinical Thyroidology.

— Jerome M. Hershman, MD

Reference

1. Vadiveloo T, Donnan PT, Cochrane L, Leese GP. The Thyroid Epidemiology, Audit, and Research Study (TEARS): the natural history of endogenous subclinical hyperthyroidism. J Clin Endocrinol Metab 2011;96:E1-E8.

PROGRESSION TO OVERT HYPERTHYROIDISM IS ONLY 1% PER YEAR WHEN TSH IS BETWEEN 0.1 AND 0.4 MIU/L

Rosario PW. **Natural history of subclinical hyperthyroidism in elderly patients with TSH between 0.1 and 0.4 mIU/l: a prospective study**. Clin Endocrinol (Oxf) 2010;72:685-8.

SUMMARY

BACKGROUND

Subclinical hyperthyroidism has a prevalence of about 0.5 to 1% in the elderly. The objective of this study was to determine the natural history of the condition when the thyrotropin (TSH) level is between 0.1 and 0.4 mIU/L.

METHODS

The author performed a prospective study of women over 60 years of age screened for thyroid dysfunction between the years 2003 and 2008. Patients with TSH between 0.1 and 0.4 mIU/L had repeat measurements of TSH, free thyroxine and triiodothyronine (T_3) after 12 weeks. Those with exogenous thyrotoxicosis or taking drugs that could influence thyroid function were excluded, as were those with atrial fibrillation or heart disease. Patients who met the TSH criterion on the repeat measurement with normal thyroid hormone levels also had a radioiodine scan and ultrasound scan to determine the cause of the subclinical hyperthyroidism. They were then followed at intervals of 3 to 6 months with repeated thyroid-function tests.

RESULTS

One hundred two women met the criteria for the study; their ages varied from 60 to 78 years. Nodular disease was found in 91 patients and Graves' disease in 11. Follow-up ranged from 12 to 70 months (median, 41). Twenty-four patients (23.5%) had persistent normalization of serum TSH. Three had overt hyperthyroidism (3%) and 4 had a decrease of serum TSH to <0.1 mIU/L with increasing but still normal serum T_3; these patients were treated. The remainder of the patients (70%) persisted with TSH in the 0.1 to 0.4 mIU/L range, but four had atrial fibrillation or heart disease during follow-up and were treated. The only predictor of development of overt hyperthyroidism was a serum TSH <0.2 mIU/L.

CONCLUSIONS

In older women with TSH between 0.1 and 0.4 mIU/L, progression to clinical hyperthyroidism occurs in approximately 1% per year. TSH may normalize in about one fourth, but most have persistence of subclinical hyperthyroidism, with serum TSH remaining in the same range.

COMMENTARY

This important prospective study shows that when serum TSH is between 0.1 and 0.4 mIU/L, progression to overt hyperthyroidism is only 1% per year. Those who have progression are likely to have serum TSH <0.2 mIU/L, thus getting close to the <0.1 mIU/L group, who have a much higher rate of progression to overt hyperthyroidism, 5 to 8% per year as reported in the Schouten et al. New Zealand study summarized in another article in this issue (1). Based on data recently reported from Scotland, the milder subclinical hyperthyroidism is 3.6-fold more common than the worrisome condition in which serum TSH is <0.1 mIU/L (2). It is pertinent that about 90% of the patients with this milder subclinical hyperthyroidism had nodular goiter, which is a less common cause of overt hyperthyroidism than Graves' disease in our older population. Occasionally, the nodular goiter may require intervention because of compressive symptoms, but the current study is reassuring in that only a very small proportion of those with "mild" subclinical hyperthyroidism progress to the overt condition. Sensitive serum TSH measurements now enable us to split hairs in prognosticating about our patients with suppressed serum TSH.

— Jerome M. Hershman, MD

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1. Schouten BJ, Brownlie BE, Frampton CM, Turner JG. Subclinical thyrotoxicosis in an outpatient population—predictors of outcome. Clin Endocrinol (Oxf) 2011;74:257-61.
2. Vadiveloo T, Donnan PT, Cochrane L, Leese GP. The Thyroid Epidemiology, Audit, and Research Study (TEARS): the natural history of endogenous subclinical hyperthyroidism. J Clin Endocrinol Metab 2011;96:E1-E8.

STIMULATED THYROGLOBULIN <0.2 NG/ML PREDICTS A NEGATIVE RADIOIODINE SCAN IN HIGH-RISK THYROID CANCER PATIENTS

de Meer SG, Vriens MR, Zelissen PM, Borel Rinkes IH, de Keizer B. **The role of routine diagnostic radioiodine whole-body scintigraphy in patients with high-risk differentiated thyroid cancer.** J Nucl Med 2011;52:56-9. Epub December 13, 2010.

SUMMARY

BACKGROUND

In patients with low-risk differentiated thyroid carcinoma, thyrotropin (TSH)-stimulated serum thyroglobulin is a more sensitive indicator of recurrence than whole-body radioiodine scans. However, this has not been shown for patients with more advanced stages of differentiated thyroid cancer. The purpose of this study was to determine whether routine diagnostic whole-body scans 6 to 12 months after initial treatment provide additional information to that provided by TSH-stimulated thyroglobulin measurements during the first year of follow-up of high-risk differentiated thyroid carcinoma.

METHODS

High-risk patients were those with tumors larger than 4 cm or tumors that were locally invasive or were associated with positive lymph nodes. Patients with distant metastasis were excluded. Stimulated thyroglobulin (Tg) was measured after recombinant human TSH (rhTSH) and compared with scans made using 100 MBq (2.7 mCi) diagnostic doses of radioactive iodine (^{131}I). The sensitivity of the Tg measurement was 0.2 ng/ml.

RESULTS

The study population was 112 patients; 81% had papillary carcinoma and 19% had follicular carcinoma. The median age was 48 years. The median tumor size was 30 mm; 43% were tumor–node–metastasis stage I. Stimulated Tg was >0.2 ng/ml in 65%; 8 patients of this group had positive scans. In 6 patients, there was recurrence only in the neck. One patient had a distant metastasis to the skull and another to the lung and brain.

Stimulated Tg was <0.2 ng/ml in 30% of patients. Only 1 of these patients had a positive scan in the neck. Additional studies did not reveal a source, and a diagnostic scan 1 year later was negative in this patient. Five percent of the patients had thyroglobulin antibodies that made the measurement of thyroglobulin unreliable.

CONCLUSIONS

Because the negative predictive value of stimulated thyroglobulin levels <0.2 ng/ml for disease recurrence in this study was 100%, the addition of a diagnostic whole-body scan offered no additional information.

COMMENTARY

Although the patients in this study were considered high risk, 43% were TNM stage I, presumably people under age 45, who have a more favorable prognosis. Only about one third of the 112 high-risk patients had stimulated Tg <0.2 ng/ml, so a generalization based on this relatively small group must be considered tentative. Nevertheless, the results show that stimulated Tg is a more sensitive indicator of recurrence than is the diagnostic scan, thus confirming the findings and practice in patients with low-risk thyroid cancer (1,2).

In my practice, I continue to perform diagnostic scans using 4 mCi of ^{131}I in most patients when I use rhTSH because the scan adds a relatively small additional cost to that of the rhTSH plus some inconvenience to the patient. But this must be balanced against the need to do a radioiodine scan when the stimulated Tg is positive, so why not do the scan as part of the initial procedure, especially in high-risk patients?

— Jerome M. Hershman, M.D.

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NECROSIS IN THE PRIMARY TUMOR AND LACK OF ^{131}I UPTAKE IN METASTASES PREDICT PROGRESSION OF METASTATIC THYROID CANCER

Deandreis D, Al Ghuzlan A, Leboulleux S, Lacroix L, Garsi JP, Talbot M, Lumbroso J, Baudin E, Caillou B, Bidart JM, Schlumberger M. **Do histological, immunohistochemical, and metabolic (radioiodine and fluorodeoxyglucose uptakes) patterns of metastatic thyroid cancer correlate with patient outcome?** Endocr Relat Cancer 2011;18:159-169.

SUMMARY

BACKGROUND AND METHODS

The prognosis for thyroid cancer patients with distant metastases is worse if they are over 45 or if the metastases do not take up radioactive iodine (^{131}I). This 5-year retrospective study surveyed a variety of possible prognostic features in 80 such patients who were followed for approximately 4 years (mean age at diagnosis, 55 years). All had had a total thyroidectomy and 54 had undergone lymph-node dissection. The distant metastases were diagnosed by ^{131}I whole-body scan, by computed tomography (CT) and/or by magnetic resonance imaging (MRI) during the initial evaluation of one fourth of the patients, but the metastases were found approximately 2.5 years later in three fourths of the patients, most in lung and/or bone. The primary tumor showed nonmedullary thyroid cancer with no undifferentiated components. All patients had a whole-body postablation scan with 100 mCi of ^{131}I, and those showing uptake in metastases were given 100 mCi every 6 to 12 months. In approximately 80%, a positron-emission tomography (PET)-CT scan with 18F-fluorodeoxyglucose (18 F-FDG) was performed within a year after the diagnosis of distant metastases, whereas the first PET-CT was done 2 to 10 years later in 20%. Patients with positive FDG scans were then followed annually with a PET scan, a CT scan, and/or an MRI.

RESULTS

Four patients had complete remissions after approximately 3 years of treatment with ^{131}I; all had distant metastases that took up ^{131}I but not FDG. On the other hand there was progression within 1 year in 16 patients: 15 had FDG-positive lesions (3 also had ^{131}I uptake), while 1 had FDG-negative but ^{131}I-positive lesions. At 2 years, there was 100% survival of those who had FDG-negative metastases, whereas only 60% of those with FDG-positive lesions had survived (70 to 80% survived if they had 1 to 10 lesions, but only 50% survived if they had more than 10 lesions). Of the 14 patients who died (median survival, 2 years), all had had FDG-positive metastases.

CONCLUSIONS

Based on multivariate analysis, only two factors were independently related to progressive disease: the presence of necrosis (both focal and diffuse, but not otherwise defined) and the absence of ^{131}I uptake. Age and necrosis were associated with FDG uptake, number of FDG-positive lesions and the maximum FDG uptake value in the most-avid lesion. Other factors previously associated with tumor aggressiveness—such as the histologic subtype of the primary lesion (papillary, follicular, poorly differentiated), extracapsular extension, vascular invasion, size, and the number of nodes affected, as well as immunohistochemical markers related to iodine and glucose metabolism, angiogenesis, and cell growth did not have independent prognostic value.

COMMENTARY

Necrosis is a factor taken into account when assessing the cytologic grade of thyroid cancers. The current study indicates that necrosis in the primary tumor is an independent factor of poor prognosis in patients who have distant metastases. However, spontaneous necrosis (defined as an area of degenerating cytoplasm and punctuate karyorectic nuclear debris without evidence of fibro-blastic stromal reaction, hemorrhage or identifiable needle track) is not invariably associated with a poor prognosis (1). In 14 patients (mean age, 50 years) who had encapsulated thyroid follicular-cell tumors that showed some necrosis, 1 died of disease at

6 years, 1 died of other causes at 11 years, 2 were alive with disease after 5 and 13 years, and the remaining 10 were alive with no evidence of disease with a mean follow-up of 10 years (1).

The authors found that the FDG positivity or negativity of distant metastases was not affected by whether the scan was done under TSH stimulation or under TSH suppression. However, the delay between when the distant metastases were found and when the initial FDG-PET-CT scan was performed raises concerns. (There can be discrepancies between repeat FDG scans, with a spontaneous shift from positive to negative (2), and some data indicate that higher TSH levels can increase FDG positivity).

Only 5% of the patients in this study had a complete remission following therapy with ^{131}I. This could reflect a selection bias because patients with aggressive disease may have been preferentially referred to this center to obtain access to their advanced research protocols and technology.

— Stephen W. Spaulding, MD

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THE MOST COMMON THYROID CANCER IS <1 CM IN A >45-YEAR–OLD, BUT NOT ALL SMALL CANCERS ARE INSIGNIFICANT

Hughes DT, Haymart MR, Miller BS, Gauger PG, Doherty GM. **The most commonly occurring papillary thyroid cancer in the United States is now a microcarcinoma in a patient older than 45 years.** Thyroid. January 26, 2011 [Epub ahead of print].

SUMMARY

BACKGROUND

Thyroid carcinoma has the fasting-growing incidence of all cancers in the National Cancer Institute's Surveillance, Epidemiology, and End results (SEER) database. The incidence of thyroid cancer has risen from 3.85 cases per 100,000 population in 1975 to 11.99 per 100,000 in 2007. The mortality has decreased slightly from 0.55 deaths per 100,000 in 1975 to 0.47 deaths per 100,000 in 2007, suggesting that there may be an increase in the proportion of lower-risk tumors being diagnosed.

METHODS

This was a retrospective evaluation of the papillary thyroid carcinoma (PTC) incidence rates from 1973 to 2006 reported in the SEER database, with an emphasis on new cases each year based on age and size.

RESULTS

Examination of the SEER database between 1974 and 2006 showed that the most common age to be diagnosed with PTC shifted from patients in their 30s to patient in the age range of 40 to 50 years. Until 1999, the majority of cases occurred in patients younger than 45 years, and after 1999, PTC became more common in patients older than 45 years. From 1988 to 2003, there was an increase in all sizes of PTC, with the largest increase in tumors <1 cm in patients older than 45 years.

CONCLUSIONS

This study demonstrates the changing demographics of patients in whom PTC developed between 1973 and 2006, based on a population database sponsored by the National Cancer Institute. When the patient was under the age of 45 years at diagnosis, the most common tumor size had decreased from 1.1 to 2 cm to <1 cm. Over the age of 45 years, the most common size of tumor has always been <1 cm in size. Because of the aging American population, the majority of patients diagnosed with PTC are now older than 45 years, while in the late 1980s the majority of PTC patients were in their late 20s and early 30s. The authors suggest that the disproportionate increase in PTC in patients older than 45 with <1 cm tumors may be related to increased early detection with imaging studies and treatment of incidentally discovered thyroid nodules.

COMMENTARY

There have been at least 4 studies demonstrating the increasing incidence of thyroid cancer, primarily PTC, in the American population using the SEER database (1). This database was designed to sample more than 28% of the population with representation of sex, race, and socioeconomic status that reflects a snapshot of America. Although there is no dispute that there has been a 2.5- to 3-fold increase in the diagnosis of thyroid cancer over the past 30 years, there continues to be controversy concerning whether this is simply increased detection of small, insignificant tumors, as initially described by Davies and Welch in 2006 (2). Studies such as those by Chen et al. (1), Morris and Myssiorek (3) and Hughes et al. (the article under discussion) demonstrate that the increase in thyroid cancers is occurring in all sizes of tumor. Morris et al. demonstrate that there is a doubling in incidence of large (4 to 6 cm) tumors. This current study is important because it shows, for the first time, the shift in the age of diagnosis of PTC to people older than 45 years. Although the largest proportion of tumors is small (<1 to 2 cm), they are not all insignificant. Morris et al. emphasize that extrathyroidal extension and cervical metastases in small tumors have doubled

in incidence in the past three decades. Based on the American Joint Committee on Cancer (AJCC) staging, a <2-cm thyroid cancer in a >45-year-old with paratracheal (level VI) nodes or extrathyroidal extension would be stage III; those with lateral nodes (level 2, 3, 4, or 5) would be stage IVA. This has serious implications because of the need for the evaluation and treatment of the higher-stage tumors, even if they are <1 cm at the time of diagnosis in an older person.

— Stephanie L. Lee, MD, PhD

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BRAF MUTATION GUIDES THERAPY OF NODULES WHEN CYTOPATHOLOGY IS INDETERMINATE

Kim SK, Hwang TS, Yoo YB, Han HS, Kim DL, Song KH, Lim SD, Kim WS, Paik NS. **Surgical results of thyroid nodules according to a management guideline based on the BRAFV600E mutation status.** J Clin Endocrinol Metab. January 14, 2011 [Epub ahead of print]. doi:10.1210/jc.2010-1082

SUMMARY

BACKGROUND AND METHODS

In Korea, more than 90% of well-differentiated thyroid cancer is papillary, and the BRAFV600E mutation is found in more than 80%, higher percentages than what are found in many Western countries. Over the 2-year period beginning in March 2007, the cytopathology in 865 fine-needle aspiration biopsies (FNAB) of thyroid nodules was prospectively analyzed at Konkuk University in Seoul using the 2008 National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Guidelines. The cover slips were then removed from the slides and "atypical cells of interest" were scraped and DNA was extracted and analyzed for the BRAFV600E mutation using polymerase chain reaction (PCR) with a biotinylated primer, purification with streptavidin–agarose and pyrosequencing.

RESULTS

In the 504 FNABs that were read as being "benign," no BRAFV600E mutants were found. The mutation was found in 32% of the 141 samples read as "atypical cells of undetermined significance" (ACUS), in 85% of the 54 samples read as "suspicious for malignancy," in 92% of the 140 samples read as "malignant," and in 10% of the 10 samples read as "suspicious for follicular neoplasm." BRAF status could not be assessed on 16 FNABs with insufficient material for cytopathologic assessment.

Surgery was advised in all cases in which FNAB cytology was read as suspicious for malignancy or malignant. Papillary thyroid carcinoma was found in all who actually underwent surgery, whether or not the BRAFV600E mutation was present.

In the cases read as "ACUS," surgery was recommended for all 45 cases in which BRAFV600E mutation appeared. Surgery was actually performed on 30: 29 proved to be papillary thyroid carcinoma, while 1 turned out to have nodular hyperplasia, a false positive. Surgery was also performed on 12 patients whose FNAB was read as "ACUS" but did not have the BRAFV600E mutation, because ultrasonography showed they were over 50% solid and over 2 cm in diameter, or were of any size but had suspicious features such as microcalcifications, irregular margins, hypoechogenicity, or abnormal neck lymphadenopathy. Eight turned out to be nodular hyperplasia, 1 was a follicular adenoma, 2 were papillary carcinomas and 1 was a follicular carcinoma. Thus, of 30 ACUS nodules with the BRAFV600E mutation, 29 had papillary carcinoma. In the 12 cases of ACUS that did not have a mutation in BRAF but had worrisome clinical features, 3 were malignant.

In all 10 cases read as "suspicious for follicular neoplasm," surgery was recommended. Of the 9 who did not have the BRAFV600E mutation, 3 had follicular carcinoma, 3 had nodular hyperplasia, 1 had a follicular adenoma, and 2 refused surgery.

CONCLUSIONS

Demonstrating that the BRAFV600E mutation is present in material from an FNAB that has been read as "ACUS" appears to be helpful in deciding whether to send a patient for surgery, even in the absence of troublesome clinical features.

COMMENTARY

The distribution of thyroid cancers in Korea is different from what is found in many Western countries, but if this method of analyzing FNABs for the BRAFV600E mutation can be adopted without too much difficulty and the results confirmed in places where a higher percentage of samples are read as "atypical cells of undetermined significance," it could simplify the preoperative evaluation and obviate the need to evaluate frozen sections intraoperatively in such cases. Methodologic problems, including "oversensitivity" can arise when analyzing DNA sequences in FNAB material. A report from another group in Seoul (1) looked for the BRAFV600E mutation in FNAB material left over after cytology slides were made. A multiplex PCR with a long primer interrupted by a series of 5-deoxyinosine residues was used on the FNAB material, while direct DNA sequencing was performed on DNA scraped from paraffin sections of surgical samples from 279 patients. The DNA analysis on leftover FNAB material detected 5 false positive BRAFV600E mutations, as compared with the direct DNA sequence data obtained from the paraffin material. Both papers confirm the finding of others (including the paper of Proietti, that was reviewed in the February 2011 issue of Clinical Thyroidology), namely that the BRAFV600E mutation is uncommon in predominantly follicular lesions (2).

— Stephen W. Spaulding, MD

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THYROID NODULE MACROCALCIFICATION DOES NOT MEAN THE NODULE IS BENIGN

Lu Z, Mu Y, Zhu H, Luo Y, Kong Q, Dou J, Lu J. **Clinical value of using ultrasound to assess calcification patterns in thyroid nodules.** World J Surg 2011;35:122-7.

SUMMARY

BACKGROUND

The most recent ATA guidelines for the evaluation of thyroid nodules and cancer emphasize the use of thyroid ultrasound to guide the clinician to which nodule requires biopsy to exclude malignancy. Microcalcifications are frequently cited as being highly specific for thyroid malignancy, especially for papillary thyroid carcinoma. However, the risk for malignancy of macrocalcifications is not widely known. The purpose of this study was to determine the clinical usefulness of calcification patterns of thyroid nodules detected on sonography in predicting malignancy.

METHODS

Ultrasonography was used to examine 2122 nodules in 1498 Chinese patients within 1 month before thyroidectomy. Calcification patterns including macrocalcifications, microcalcifications, rim calcifications, and isolated calcifications were correlated with histologic diagnosis.

RESULTS

A total of 12.2% of thyroid nodules with a mean (±SD) diameter of 2.3±1.5 cm were found to be malignant. Papillary thyroid carcinoma was found in 85.3% of all malignancies. Calcification of any pattern was found in 49.6% (128 of 258) of malignant and 15.7% (292 of 1864) of benign nodules. Microcalcifications were found in 33.7% (87 of 258) of malignant nodules and 6.4% (120 of 1864) of benign nodules; 95% of the thyroid malignancies associated with microcalcifications were papillary carcinomas, but 94% of the macrocalcifications were also associated with papillary carcinomas. The sensitivities of calcifications (all forms) and microcalcifications for predicting malignancy were 49.6% and 33.7%, respectively, with corresponding specificities of 84.3% and 93.6%.

CONCLUSIONS

Calcifications in this study were found by ultrasonography in 15.7% of benign and 49.6% of malignant nodules. Although microcalcification is specific (93.6%) for malignancy in this study, the presence of other patterns of calcification (macrocalcifications, rim calcifications, undefined calcification) was found in malignant nodules. It was previously considered that macrocalcifications were usually benign and did not need evaluation or surgery. This and several other reports suggest that all calcifications raise concern for thyroid malignancy. Macrocalcifications in this study were found in 37% of benign nodules and 27% of malignant nodules. Peripheral or eggshell calcification was thought to suggest slow growth or lack of growth of a nodule, but several studies have demonstrated that disruption or thickening of the calcification was suggestive of malignancy.

COMMENTARY

Calcifications can be found in both benign and malignant nodules. The most common thyroid cancer is papillary thyroid carcinoma and the most specific sonographic characteristic of this tumor is microcalcifications. But this article illustrates the expanding literature that macrocalcifications are also associated with malignancy, primarily papillary thyroid carcinoma (1-5). Macrocalcifications should not exclude a nodule from further investigation. This was acknowledged by the latest ATA guidelines, with the recommendation that all nodular calcification should be assessed for malignancy.

In my practice, I continue to perform thyroid ultrasonography to help determine the target of biopsy but do not consider that macrocalcifications indicate that a nodule is benign and does not require biopsy.

— Stephanie L. Lee, MD, PhD

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OVER HALF OF WOMEN WITH POSTPARTUM THYROIDITIS REMAIN HYPOTHYROID ONE YEAR LATER

Stagnaro-Green A, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Negro R. **High rate of persistent hypothyroidism in a large-scale prospective study of postpartum thyroiditis in Southern Italy.** J Clin Endocrinol Metab. December 29, 2010 [Epub ahead of print]. DOI: 10.1210/jc.2010-1980

SUMMARY

BACKGROUND

Postpartum thyroiditis (PPT) is a relatively common thyroid autoimmune disorder affecting women in the first 12 months following delivery, both full-term births and miscarriages. In a review of 21 publications (8000 women) from different countries the prevalence was 8.1% (range, 1.6 to 19) (1). The variability in the reported cases depends on patient selection, geographic and ethnic differences, diagnostic criteria, frequency and timing of blood samples, and perhaps iodine consumption in the population studied. PPT is defined as a syndrome of thyroid dysfunction occurring in women during the first year after parturition. In the present reviews, patient selection was limited to euthyroid thyroid peroxidase antibody (TPOAb)-positive women in the first trimester of pregnancy. Women with known chronic thyroiditis are at risk of developing the syndrome, particularly those with high TPOAb titers in the first trimester of pregnancy; in some studies, women expressing human leukocyte antigen haplotype DR 3, 4, or 5 are at higher risk (2). However, PPT has been reported in a small percentage of women without evidence of autoimmune thyroid disease (3). Patients with Graves' disease whose disease is in remission before conception are at higher risk of recurrence of hyperthyroidism in the year following delivery (4). There are controversies concerning whether the onset of Graves' hyperthyroidism is more common in the year following delivery. In its classical description, a sequence of three phases has been described, a bout of hyperthyroidism occurring within the first 2 to 4 months after delivery, followed by a hypothyroid phase lasting between 3 and 8 months, with a recovery phase of 6 to 12 months. In most published series, the vast majority of women returned to euthyroidism, and only 5 to 20% of them remain hypothyroid permanently (5). Not every patient goes through the three phases; one third suffered only the initial hyperthyroid phase, another third only the hypothyroid phase, and the rest go through the hyperthyroid, hypothyroid, and euthyroid phases. It is also reported that permanent hypothyroidism will develop in 30 to 50% of women within 5 years after the original episode. Stagnaro-Green et al., studied a population in Southern Italy with mild iodine deficiency, comprising 4562 women with a singleton pregnancy who were screened in the first 11 weeks of pregnancy. The aim "was to conduct a large prospective study of the incidence and clinical course of PPT." This group of women is part of a large-scale prospective trial evaluating the efficacy of screening for thyroid disease early in gestation and studying the impact of treatment on maternal and neonatal outcomes (6).

METHODS

A total of 4562 women who were within the first 11 weeks of pregnancy and had no known thyroid disease were recruited. All of them had serum thyrotropin (TSH), free thyroxine, and thyroid peroxidase antibody (TPOAb) levels measured at study entry. The authors excluded from the initial group 113 women with thyroid dysfunction and 45 women were lost to follow-up. All 4384 remaining women were euthyroid (serum TSH, <2.5 mIU/L) and most of them remained euthyroid through pregnancy. Serum TSH and TPOAb measurements were repeated 6 and 12 months postpartum, or at any time in the presence of symptoms or signs of thyroid dysfunction. Postpartum hyperthyroidism was defined as a serum TSH <0.27 mIU/L and postpartum hypothyroidism as a serum TSH of >4.2 mIU/L. The probability of PPT was modeled using logistic regression, with age, smoking history, previous pregnancies, week of first obstetrical visits, TPOAb positivity on study entry, and risk group (low or high) as potential predictors. Test results at 6 and 12 months postpartum were compared between progressions using analysis of variance with Scheffé tests for paired comparisons.

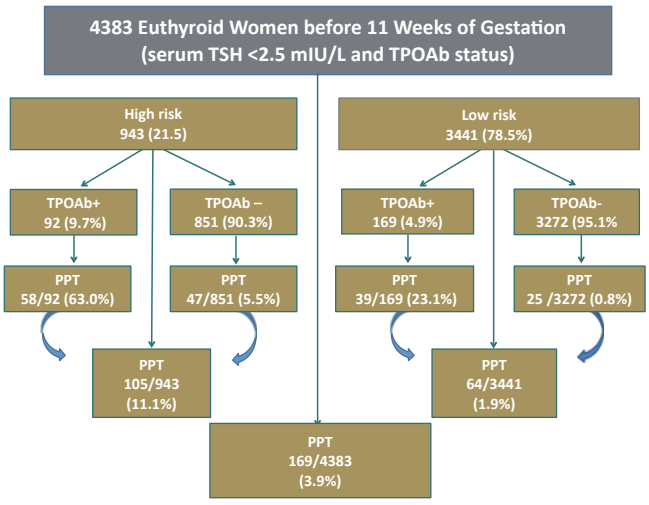
RESULTS

A total of 4383 women participated in the study; PPT developed in 169 (3.9%). Women were divided at the time of study entry, into two groups according to their risk for thyroid disease, based on a personal questionnaire and physical examination; there were 943 women in the high-risk group (21.5%) and 3441 (78.5%) in the low-risk group.

Of the 4384 women recruited, 261 were TPOAb-positive (5.9%), of whom 92 (35.2%) belonged to the high-risk group. The incidence of PPT was 58 of 92 (63.0%). Of the 261 women who were TPOAb–positive, 169 (64.8%) were part of the low-risk group. The incidence of PPT was 39 of 169 (23.1%). The total incidence of PPT in the TPOAb-positive group was 97 of 261 (37.2%).

Of the 4123 TPOAb-negative women, 851 were in the high-risk group and 47 of them had PPT (5.5%). Of the 3272 women in the low-risk group who were TPOAb–negative, 25 (0.8%) had PPT. The total incidence of PPT in TPOAb-negative women was 72 of 4123 (1.7%). The figure summarizes these data.

Incidence of PPT by risk group and thyroid antibody status in first trimester.



Logistic-regression analysis found that PPT was more likely to develop if the women were in the high-risk group versus the low-risk group (odds ratio [OR], 6.69; 95% confidence interval [CI], 4.63 to 9.68) and if they were TPOAb-positive (OR, 34.1; 95% CI, 3.5 to 49.6); all the other factors included in the logistic-regression analysis were not significantly associated with PPT.

The authors described six distinct clinical progressions of PPT in the 169 women: hypothyroidism at 6 months followed by euthyroidism at 12 months (27.2%), euthyroidism followed by hypothyroidism (22.5%), hypothyroidism followed by persistent hypothyroidism (18.3%), hyperthyroidism followed by hypothyroidism (13.6%), hyperthyroidism followed by euthyroidism (16.0%) and euthyroidism followed by hyperthyroidism (2.4%). A total of 54.4% had hypothyroidism at 12 months.

Overall, 82% of the 169 women in whom PPT developed had a hypothyroid phase, and 32% had a hyperthyroid phase. Thyroid antibody titers were not significantly different among patients who had the hyperthyroid phase as compared with the hypothyroid phase.

There was no difference in antibody titer at study entry between hypothyroid and euthyroid women at 12 months postpartum.

The median serum TSH at 6 months was significantly different (6.7 vs. 5.2 mIU/L; P<0.001) between women with persistent hypothyroidism and those who were euthyroid.

CONCLUSIONS

Of the 261 TPOAb-positive women, 97 (37.2%) had PPT, versus 72 (1.7%) of the 4123 TPOAb-negative women. Of the 169 women in whom PPT developed, 92 (54%) remained hypothyroid at the end of the first postpartum year. Of the 261 TPOAb-positive women, 52 (20%) were hypothyroid 1 year after delivery, versus 40 (1%) of 4123 TPOAb-negative women (P<0.001).

COMMENTARY

This study is the largest prospective cohort to evaluate the incidence, clinical presentation, and course of PPT. The author's findings differed from previous published reports: (1) The incidence of PPT was 3.9%. If 133 women with thyroid dysfunction at study entry (originally excluded) were included, the incidence of PPT would have increased to 6.7%. (2) Women classified as high risk for thyroid disease had a sixfold increase in the incidence of PPT. (3) The vast majority (82%) went through a hypothyroid phase. (4) Euthyroid TPOAb-positive women in the first trimester of pregnancy have a greater than 37% chance of PPT developing. (5) Fifty-four percent of the women in whom PPT developed remained hypothyroid at the conclusion of the first postpartum year.

This study supports the high incidence of a hypothyroid phase in the course of PPT. The most unexpected finding, as stated by the authors is the high incidence of permanent hypothyroidism, over 50% of their patients. The literature mentioned a 5 to 20% incidence of permanent hypothyroidism at 12 months postpartum and a 20 to 60% incidence of permanent hypothyroidism after 5 to 10 years. The authors speculated that the low incidence of PPT in their study represents an underestimation due to limited sampling only at 6 and 12 months postpartum.

The clinical diagnosis of PTT is a challenge for the physician; symptoms of hypothyroidism or hyperthyroidism are mild and nonspecific, and many patients remain undiagnosed. Some symptoms, such as fatigue and irritability may be attributed to the postpartum situation itself. Fatigue is a common symptom. Whether postpartum depression can be attributed to PPT is controversial, since it has been reported in euthyroid women who are TPOAb-positive. In clinical practice, some women may have severe symptoms of thyroid dysfunction and benefit from therapy. In the present study, there are no indications of the clinical severity of symptoms or the incidence of goiter. An important observation is the sixfold increase in the incidence of PPT in women classified as high risk, supporting the clinical value of a careful medical history and physical examination. Although not mentioned by the authors, the presence of an enlarged thyroid gland in the postpartum period should alert the physician to perform proper thyroid tests. The high incidence of permanent hypothyroidism at the end of the first year postpartum is a novel finding, and it suggests the importance of following women closely after the first year postpartum, particularly those who are planning future pregnancies. I hope the authors will continue to follow these patients to assess how many of them with mild subclinical hypothyroidism may return spontaneously to the euthyroid state.

The incidence of PPT in this study was lower than in other reports. It could be attributable to several reasons, as indicated by the authors, including the selection of patients: All their patients were euthyroid in the first trimester of pregnancy, and the thyroid tests were done routinely at 6 and 12 months postpartum. In other studies thyroid tests were performed every 3 months for 12 months, and this could have yielded a higher incidence of women with PPT. Graves' hyperthyroidism may present or recur in the postpartum period or 6 to 8 months after delivery. The authors reported that 2.4% of their patients were hyperthyroid at 12 months but euthyroid at 6 months, possibly representing the new onset of Graves' hyperthyroidism. Finally, the authors confirm previous studies reporting a typical course of PPT in women with negative antibodies, although only 1% of them were hypothyroid at 12 months, as compared with 20% of those with positive antibodies in the first trimester.

— Jorge Mestman, MD

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HEREDITARY ACTIVATING MUTATIONS OF THE TSH RECEPTOR LEAD TO HYPERTHYROIDISM

Hébrant A, van Staveren WC, Maenhaut C, Dumont JE, Leclère J. **Genetic hyperthyroidism: hyperthyroidism due to activating TSHR mutations.** Eur J Endocrinol 2011;164:1-9.

SUMMARY

BACKGROUND

Hereditary activating mutations of the TSH receptor can lead to hyperthyroidism. In 1982, the first description of a familial form of hyperthyroidism (familial nonautoimmune hyperthyroidism, in short: familial form) was published. The first author of the original article is now the senior author of the article under discussion. In 1995, sporadic forms of hyperthyroidism due to activating mutations of the thyrotropin (TSH) receptor were described. Many other cases of both forms have been added since then. They are characterized by diffuse hyperactivity of the whole thyroid. To this list can be added autonomous adenomas, well known to the clinician and often referred to as warm and/or toxic nodules and rare cases of hot thyroid carcinomas. In many of these adenomas, activating mutations have been discovered. Occasionally, these tumors do not bear a TSH-receptor mutation but have a constitutive activation of Gs proteins leading by this pathway to an activation of the cAMP pathway. This mechanism is also responsible for hyperthyroidism in the McCune–Albright syndrome. This is, however, a multiorgan disease, the mutations also being expressed in other cell types.

Finally, mutations of the TSH receptor have been reported that are not constitutively activating but have a higher affinity for luteinizing hormone and human chorionic gonadotropin. Hyperthyroidism develops in women during pregnancy.

RESULTS

The authors concentrate mainly on the familial and sporadic form of nonautoimmune hyperthyroidism. By 1997, five families comprising 49 patients with an activating germline mutation of the TSH receptor had been identified. The present review comprises the medical history of 152 patients with the familial form coming from 27 families and 15 sporadic cases. The familial forms have an autosomal dominant inheritance with no sexual predominance. In recent years, the clinical identity of both forms is becoming better known, since the number of cases described has been increasing at an accelerated speed. The supplementary tables are particularly interesting to study. Familial hyperthyroidism is rarely present at birth. The clinical picture develops occasionally in infancy but most frequently during adolescence and up to 30 years of age. An initial presentation of a familial form has even been described at the age of 48. When investigated, there was diffuse increased uptake of the thyroid and the volume of the thyroid was not always increased; in 26 of 97 cases, thyroid volume was even normal. In some rare cases, thyroid nodularity was seen. The clinical manifestations of hyperthyroidism are variable, even within different members of the same family bearing the same mutation.

In contrast to the familial form, sporadic cases occur without exception at birth or during the first year of life. They are clinically more severe than the familial forms, yet the severity is not uniform but widely variable. One explanation concerns the activity of the mutated TSH receptors. The mechanisms are, however, likely to be more complex.

In familial forms, exophthalmos was never described. Interestingly, the sporadic forms show some signs of eye changes that could be confused with exophthalmos. Prominence of the eyes, exophthalmia, and staring eyes are likely to be slightly different forms of description of the same sign: a protrusion of the eyes in the small orbits of neonates. It is nevertheless interesting that for unknown reasons, hyperthyroidism in neonates seems to increase the volume of the orbital tissues.

At present, most cases described have been in Europe and only two in the United States. The authors believe that this may be due to the more definitive treatment in the United States. When conservatively treated,

recurrences can be expected in nearly all cases. Absence of autoimmune parameters may have been the major trigger for more detailed investigation of these cases.

The identified mutations are described in detail in the tables and shown in one figure. The localization of most of these mutations is in the transmembrane part of the receptor protein, even though two mutations are described in the extracellular component. It is interesting to see that the localization of some mutations of the sporadic form coincides with the familial form. The missing information is the number of cases that have shown in vitro that the mutation plays the dominant role in activation of the thyroid cell.

By definition, autoimmunity is absent; by light microscopy, diffuse hyperplasia without any infiltration is seen. Circulating antibodies are absent in the familial form even though in the sporadic form antithyroid peroxidase and antithyroglobulin antibodies have occasionally been detected. In one case TSH-receptor–inhibiting antibodies were borderline positive.

In the 14 of 15 cases of the sporadic form, there was either prematurity, low birth rates, small goiter at birth, occasional craniosynostosis, and in approximately 60% mental retardation. Survival of these children means that the disease will be inherited by their offspring.

The underlying biologic defects of the familial and sporadic forms and of the autonomous adenomas are supposed to be indistinguishable: it consists in an activation of the cAMP cascade that is responsible for cell growth. Yet there are important quantitative differences since for diffuse goiter, one needs only one or two replications for increasing the functional mass and developing a small goiter while for adenoma one single cell needs to replicate many times in order to create a little tumor.

COMMENTARY

In 1982, the first publication regarding the syndrome of familial nonautoimmune hyperthyroidism encountered a lot of skepticism. At that time, it was still difficult to measure thyroid-stimulating antibodies and in many patients with Graves' disease the antibodies could not be detected. Today, the two forms of genetic hyperthyroidism are well accepted, but despite the marked increase in reported cases, these forms of hyperthyroidism remain rare. The autonomous adenomas are a separate entity having in common the underlying biologic mechanisms: stimulation of the cAMP cascade by presumably constitutively active TSH receptors. Recent studies indicate, however, that the relation between the clinical presentation and the in vitro activity of the constitutively active TSH receptor is poor (1,2). It has been suggested that additional concomitant mutations and/or environmental factors (e.g., iodine supply) may have to be taken into consideration.

In the Caucasian population, toxic adenomas with activating mutations are found in 40 to 50% of patients, and it is likely that this percentage is lower in the Asian population. Other mechanisms of constitutive activation in adenomas need to be discovered.

The clinical findings that the familial forms appear not at birth but between adolescence and 30 years is puzzling. The authors suggest that this can be explained by a slow replication of the mutated cells leading slowly to an increased number of autonomous cells. The clinician would therefore expect a progressive and slow decrease of serum TSH, but this clinical information is known for warm nodules evolving to toxic ones but not for the diffuse forms of hereditary forms of hyperthyroidism.

Chronic stimulation of thyroid cells favors the appearance of papillary cancers. At present, the number of cases is too small to lend support to this hypothesis. With increased numbers of cases, these forms of hyperthyroidism may yield important new information.

For the clinician, the sporadic forms are easy to differentiate from neonatal Graves' disease. Clinical history and positive tests for TSH-receptor antibodies as well as the self-limited duration of neonatal Graves' disease allow the differential diagnosis. For the familial form with later onset, the family history is always crucial. Yet in Graves' disease we can also find parents with a history of hyperthyroidism. Even today, we still encounter patients with hyperthyroidism who have diffuse goiter and no TSH-receptor antibodies, and thyroid histology, if available, does not always show evidence of autoimmune disease. Are these cases that we missed? What could be the clinical consequences? Patients certainly are eager to know about any familial risk, and they are entitled to this information. Fortunately, in the familial forms the severe neonatal forms are most uncommon. The sporadic forms survive now, and future generations may be at risk . In these very rare cases, it seems to me that genetic counseling is desirable.

— Albert Burger, MD

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Call for Nominations for the 2011 Awards
American Thyroid Association

▪ Distinguished Service Award ▪ Sidney H. Ingbar Distinguished Lectureship ▪
▪ Van Meter Lecture ▪ Paul Starr Lecture •
• Lewis E. Braverman Lecture • John B. Stanbury Thyroid Pathophysiology Medal ▪

The Van Meter Award Lecture established in 1930, recognizes outstanding contributions to research on the thyroid gland or related subjects. The award is given each year to an investigator who is not older than the age of 45 in the year of the award. The Van Meter award winner is kept secret until the time of the award lecture during the annual meeting. An honorarium and expenses are awarded to the Van Meter recipient. This award receives support from Mary Ann Liebert, Inc., Publishers.

Nominee: Date of Birth

Sidney H. Ingbar Distinguished Lectureship Award, endowed by contributions to honor the memory of Sidney H. Ingbar, recognizes outstanding academic achievements in thyroidology, in keeping with the innovation and vision that epitomized Dr. Ingbar's brilliant investigative career. The Ingbar award is conferred upon an established investigator who has made major contributions to thyroid-related research over many years. An honorarium will be presented to the recipient.

Nominee:

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Nominee:

The Distinguished Service Award (DSA) honors a member who has made important and continuing contributions to the American Thyroid Association (ATA). The DSA award certificate is presented at the ATA Annual Banquet.

Nominee:

The John B. Stanbury Thyroid Pathophysiology Medal recognizes outstanding research contributions, either conceptual or technical, to the understanding of thyroid physiology or the pathophysiology of thyroid disease, as evidenced by having a major impact on research or clinical practice related to thyroid diseases. A medal, funded by Dr. John Stanbury, is conferred at the Annual Banquet.

Nominee:

The Lewis E. Braverman Lectureship Award recognizes an individual who has demonstrated excellence and passion for mentoring fellows, students and junior faculty; has a long history of productive thyroid research; and is devoted to the ATA. The award is endowed by contributions to honor Dr. Lewis E. Braverman. An honorarium will be presented to the recipient.

Nominee:

Nominated by: (print or type) *Signature:* *Date:*

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1. Completed and signed Nomination Form (above).
2. CV and brief nomination letter, emphasizing major accomplishments.
3. List of 2 to 4 most significant publications with PDF or URL to provide access to these papers.

Call for Nominations for 2011
American Thyroid Association
Board of Directors

In accordance with the Bylaws of the American Thyroid Association, the Nominating Committee is soliciting nominations from the membership for candidates for the offices of President and Directors (2) to serve on the ATA Board of Directors. Candidates will be selected by the Nominating Committee and submitted to the ATA Board in June 2011.

A ballot will be sent to the membership electronically in late August 2011. Newly elected Board members will be announced at the Annual Business Meeting on Thursday, October 27, 2011.

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Nominee: _____

ATA Board Director

Two **Directors** will each serve a four-year term (2011-2015). See job description in Policies and Procedures under "Members Only" at www.thyroid.org. *Election of directors will be competitive.*

Nominee: _____

Nominee: _____

Nominated by (please print or type): _____

Signature: Date:

All nominations must be submitted to the Executive Director, Bobbi Smith, by letter, fax, or e-mail bsmith@thyroid.org by April 30, 2011.

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