Clinical THYROIDOLOGY

MAY 2013
VOLUME 25 • ISSUE 5

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Clinical Thyroidology

Clinical THYROIDOLOGY

VOLUME 25 • ISSUE 5 MAY 2013

Clin Thyroidol 2013;25:100–102.

Clinical Care of Women with Hypothyroidism during their Reproductive Years Requires Awareness of the Consequences by Patients and Clinicians

Jorge H. Mestman

Vadiveloo, T, Mires GT, Donnan PT, Leese GP. Thyroid testing in pregnant women with thyroid dysfunction in Tayside, Scotland: the thyroid epidemiology, audit and research study (TEARS). Clin Endocrinol (Oxf) 2013;78:466-71.

SUMMARY

Background

Early in normal pregnancy, thyroxine demands increase by 30% to 50%, and these demands are easily achieved in women not affected by thyroid pathology. The objective of these authors was to study a representative group of women of the U.K. population on thyroxine-replacement therapy to assess the pattern of serum TSH determination before and during pregnancy and the proportion of women who have their dose of thyroxine adjusted according to the recommendation of recently published guidelines.

Methods

Population

Health care data on pregnant women in Tayside, Scotland. Five principle databases were used to identify pregnant women on thyroxine therapy in the study population. These databases covered primary, secondary, and private health care. All pregnant women who were 18 years or older and who delivered between January 1, 1993, and March 31, 2011 in Tayside were identified. Patients were included in the study if they had at least three thyroxine prescriptions prior to pregnancy, at least one of which was within 6 months prior to pregnancy. The main outcome study was the number of TSH assays performed during pregnancy and the changes in dosage of thyroxine pre-

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scribed during pregnancy; the main analysis was performed using TSH trimester-specific ranges (0.4 to 2.5 mU/L in the first trimester and 0.4 to 3.0 mU/L in the second and third trimesters). Gestation was confirmed with either first- or early-second-trimester ultrasound scan.

The mean (±SD) age of these women was 32.1±5.2 years. The percentage of pregnant women who were prescribed thyroxine increased from 0.4% (95% CI, 0.3 to 0.7) in 1994 to 2.3% (95% CI, 2 to 3) in 2010

Results

The authors identified 950 pregnant women who had thyroxine prescribed prior to pregnancy. Overall, 96.9% of these women had at least one TSH assay performed during or just prior to pregnancy, 81.2% of them in the first trimester. In the first trimester, of 423 (55%) women who had elevated TSH, only 18 (4.3%) had at least one low FT_4 or T_4 level. Low or suppressed serum TSH was detected in about 15% of women in the last 2 months before conception or in the first trimester. In women with an elevated serum TSH in the first trimester, thyroxine dosage was increased in only 39.2%. There was a significant decrease in the median serum TSH during pregnancy—2.5 mU/L at 6 weeks, 2.6 mU/L at 12 weeks and 1.4 mU/L at 24 weeks, representative of active adjustment of the levothyroxine dose.

Conclusions

Many patients on long-term thyroxine therapy had a TSH above the reference range during pregnancy and especially, 55% of them, during the first trimester of pregnancy. Serum TSH concentration declined during pregnancy, reflecting active management. However, the decline in TSH occurs too late in pregnancy. It should be adjusted earlier.

ANALYSIS AND COMMENTARY

It is well established that in the first trimester of human pregnancy there is an increased demand for thyroid hormones, by about 30% to 50%. This increased demand is due to several factors, among them the half-life prolongation and increase in serum TBG level, an increase in renal iodine excretion, and the thyroid-stimulating effect of human chorionic gonadotropin. As a result of these changes, there is a slight FT_4 increase, albeit within the normal reference range, and a lowering of serum TSH, with a significant number of normal pregnancies with serum TSH values below 0.3 mIU/L and even with suppressed values. This increase in thyroid production provides transplacental passage of maternal thyroid hormones to the fetus, since the fetal hypothalamic–pituitary–thyroid axis is fully functioning only by 14 to 18 weeks of gestation. In women with normal thyroid-gland function, this increase in thyroid demand is easily compensated; however, women on thyroid-replacement therapy because of hypothyroidism (previous ablation or intrinsic thyroid disease) or those euthyroid women with chronic autoimmune thyroiditis, are at risk for hypothyroidism early in pregnancy, since the diseased or absent thyroid gland is unable to compensate for this increase in thyroxine demand. Even mild hypothyroidism in early pregnancy has been reported to affect maternal, obstetrical, and neonatal outcome, and motor and intellectual performance in their children, although not all the studies have consistent outcomes (1, 2). The most common maternal complications in women with hypothyroidism and even in euthyroid women with chronic thyroiditis are spontaneous miscarriages and preterm labor. Therefore, it is imperative to educate women of childbearing age who have thyroid disease and those on thyroid-replacement therapy about the importance if achieving an appropriate serum TSH level before contemplating pregnancy and to have the results of thyroid-function tests assessed shortly after conception. One study addressed the issue of thyroxine adjustment early after conception, with

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the recommendation to increase the thyroxine dose by about 25% of the prepregnancy dose (taking two extra doses of L-T_4) at the time of pregnancy diagnosis until thyroid-test results are available (3). In another study, the authors suggested keeping serum TSH around 1 mIU/L at the time of pregnancy planning, which will secure a serum TSH of <2.5 mIU/L in early pregnancy in almost 82.8% of the studied women (4). This concept could be applied to women on thyroxine-replacement therapy who are contemplating pregnancy, but not to those with euthyroid chronic thyroiditis. It is assumed that detecting and correcting hypothyroidism early in pregnancy would prevent pregnancy complications (5). As this and other studies have shown (6), over 40% of women on thyroxine-replacement therapy have a serum TSH above the trimester-specific reference range at the first obstetrical visit. Since the first obstetrical visit in the majority of women is after 8 weeks of gestation, prevention of hypothyroidism early in pregnancy should be a medical priority. Medical identification of these women is a public health necessity, similar to the identification of women in the prediabetic stage before conception. A proper medical and family history, along with detection of thyroid autoimmunity on physical examination (presence of goiter, vitiligo) and a determination of serum TSH and TPOAb will diagnose women with euthyroid thyroiditis who are at risk for hypothyroidism after conception. Since more than 50% of pregnancies in this country are unplanned, it will require a strong effort from our medical and obstetrical societies to provide patients and health care professionals proper medical education in order to avoid hypothyroidism early in pregnancy in women at risk.

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Clin Thyroidol 2013;25:103–104.

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The Placenta Is Capable of Compensating for Smoking-Induced Thiocyanate Inhibition of Its Iodide Symporter

Albert G. Burger

Andersen SL, Nøhr SB, Wu CS, Olsen J, Pedersen KM, Laurberg P. Thyroglobulin in smoking mothers and their newborns at delivery suggests autoregulation of placental iodide transport overcoming thiocyanate inhibition. Eur J Endocrinol. February 26, 2013 [Epub ahead of print].

SUMMARY

Background

Blood levels of thiocyanate are known to be increased in smokers. It has been reported that in a population exposed to moderate iodine deficiency hypothyroidism is more severe in smokers than in nonsmokers (1). Thiocyanate inhibits the sodium iodide symporter (NIS), which is the main thyroidal iodide transporter. NIS is also present in tissues other than the thyroid, such as the placenta and the lactating mammary gland. In the case of partial inhibition of NIS by thiocyanate, thyroid activity gradually increases in order to overcome the inhibition. This compensatory mechanism is reflected by increased serum thyroglobulin levels. The purpose of the article under discussion was to determine whether compensating mechanisms capable of overcoming NIS inhibition by thiocyanate also exist in the placental–fetal unit.

Methods

The study was performed before the introduction of mandatory iodine supplementation in Denmark (year 2000). A total of 140 healthy pregnant women were studied. All women were clinically judged to be free of any thyroid problems. Maternal-blood and cord-blood samples were obtained at delivery for the measurement of thyroglobulin. On day 5, breast milk and a fetal urine sample were obtained for the measurement of iodine. The history of smoking reported by the study subjects was verified by measuring a serum metabolite of nicotine. The correlation was excellent.

Results

Forty-seven of the 140 mothers were given an iodine supplement of 150 mg per day during the pregnancy. The number of smokers was similar in the group receiving iodine and those not receiving iodine, and urinary iodide concentrations were similar in smoking and nonsmoking mothers. In contrast, urinary iodine in breast-fed newborns from smoking mothers was significantly decreased. Moreover, breast milk iodine in smokers was only half of that in the controls.

As expected, there was a marked difference in serum thyroglobulin depending on iodine supplementation (maternal serum, 14 and 29 mg/L in the group on supplemental iodine and those not on supplemental iodine, respectively; cord serum, 13 vs. 60 mg/L). In addition, smoking increased maternal serum thyroglobulin independently of iodine supplementation by a factor of 1.56 and increased cord blood by a factor of 1.43. Not surprisingly, the effect was more striking in mothers without iodine supplementation. Since thiocyanate inhibits NIS, it was interesting to compare cord-blood to maternal-blood thyroglobulin levels in smokers and nonsmokers, with and without iodine supplementation. Unexpectedly, the ratio was not affected by smoking or by iodine supplementation.

Conclusions

In an area of moderate iodine deficiency, smoking, with its consequence of increased serum thiocyanate levels is associated with increased maternal-

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and cord-blood thyroglobulin levels. In mothers on moderate iodine supplementation, the thyroglobulin levels are lower than in mothers not receiving iodine supplementation, but the difference between smokers and nonsmokers is still present. However, the ratio of serum thyroglobulin in a given mother and her child was not altered by smoking or by iodine supplementation.

ANALYSIS AND COMMENTARY

It is well known that thiocyanate inhibits NIS and that thyroidal autoregulation of its activity is able to compensate for this interference. In contrast, although the maternal breast also expresses NIS, there appears to be no autoregulation in this tissue, since the iodine content of maternal milk is decreased by increased thiocyanate serum levels. The placental iodide transport is closer to that of the thyroid: indeed, it is assumed that it is regulated, at least to some extent, by human chorionic gonadotropin (HCG) stimulation. In addition to NIS, the placenta possesses other transporters of iodide that are not blocked by thiocyanate. Yet there is still a lot of uncertainty in this field. In the present article, the authors show that despite smoking and moderate iodine deficiency the ratio between the maternal and fetal thyroglobulin levels is not altered. This finding is taken to indicate that the placenta can also adjust to the partial inhibition of NIS by thiocyanate.

In clinical medicine it is often difficult to prove a concept. The authors believe that placental autoregulation is evidenced by the absence of a change in thyroglobulin ratio between mother and child when there is exposure to thiocyanate. Yet other explanations cannot be excluded; for instance, under the influence of thiocyanate, maternal iodide concentrations could increase, compensating for the decreased iodide uptake by the placenta.

Since smoking during pregnancy is widely discouraged, it is likely that the prevalence of smoking by child-bearing women has greatly decreased. There are many reasons for this recommendation, such as the fact that other aspects of endocrine function are perturbed by smoking (2). In this respect it is interesting to note the finding by these authors that infants breast-fed by smoking mothers have a markedly decreased urinary iodine excretion, requiring a compensatory increase in thyroid function.

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Clin Thyroidol 2013;25:105–106.

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The BRAF V600E Mutation Increases Mortality in Papillary Thyroid Cancer

Jerome M. Hershman

Xing M, Alzaharani AS, Carson KA, Viola D, Elisei R, Bendlova B, Yip L, Mian C, Vioanello F, Tuttle RM, et al. Association between BRAF V600E mutation and mortality in patients with papillary thyroid cancer. JAMA 2013;309:1493-1501

SUMMARY

Background

Papillary thyroid cancer (PTC) has a very low 5-year mortality, usually in the range of 3 to 5%. The BRAF V600E oncogenic mutation results in a valine to glutamic acid change in codon 600 of the BRAF protein, resulting in constitutive activation of the mitogen-activated protein kinase signaling pathway. This mutation occurs in about 45% of PTC and is more common in conventional PTC than in the follicular variant. The BRAF V600E mutation is associated with more aggressive tumors based on conventional staging and with higher recurrence of PTC as compared with PTC without the mutation (1). The purpose of the present multicenter study was to define the association between the BRAF V600E mutation and PTC-related mortality.

Methods

The retrospective study was conducted at 13 medical centers in 7 countries and included data on 1849 patients. The United States and Italy contributed about two thirds of the patients. Genomic DNA was isolated from the primary tumor and used to analyze the sequence of exon 15 of the BRAF gene for the V600E mutation. This was done after surgical and medical therapy to ensure that mutation status did not influence decisions about therapy. PTC-specific death was defined as death occurring from incurable advanced cancer that compromised vital organs.

Statistical analysis included Kaplan–Meier survival curves and Cox proportional-hazards regression analyses to compare survival in patients based on mutation status. Interactions of mutation status with various clinicopathological factors was calculated. There was no adjustment for multiple comparisons in doing subgroup analyses.

Results

The overall median follow-up time was 33 months after the initial treatment. The prevalence of the mutation was 45.7%. There were 56 PTC-related deaths among the 1849 patients, representing an overall mortality of 3.0%. Eighty percent of those who died had the BR AF mutation, and 5.3% of those with the BRAF mutation died, as compared with only 1.1% of those without the mutation (P<0.001). Rates of deaths per 1000 patient-years in mutation-positive versus mutation-negative patients were 12.9 (95% CI, 9.6 to 17.2) versus 2.5 (95% CI, 1.4 to 4.5).

The age-adjusted hazard ratio (HR) for those with the mutation was 2.66 (95% CI, 1.30 to 5.43). However, when aggressive tumor features of lymph-node metastases, extrathyroidal invasion, and distant metastases were included in the model, the association of the mutation with mortality was no longer statistically significant.

There was a significant positive interaction between the mutation and lymph-node metastases, distant metastases, stage IV disease, or patient age at diagnosis. The increased mortality with age was very evident in those with the mutation as compared without it. However, the association of the mutation

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with mortality was not statistically significant in patients with disease stages I, II, or III. In patients with distant metastases, the presence of the BRAF mutation increased mortality from 1.4% (without mutation) to 51.5% (with mutation).

Conclusions

This retrospective multicenter study shows that the presence of the BRAF V600E mutation was significantly associated with increased cancer-related mortality in patients with PTC.

ANALYSIS AND COMMENTARY

This important study with contributions from many countries provides convincing data to show that the BRAF V600E mutation causes PTC to be so aggressive that it results in mortality. The results also provide confidence in the staging system that uses conventional clinicopathological criteria to predict outcome. This does not detract from the conclusion that having the BRAF mutation makes PTC more aggressive. With time for the disease to develop, those with the mutation are more likely to progress to a worse outcome, previously recognized as recurrence and now shown to result in increased mortality.

Why does this occur? Tumors with the BRAF mutation are more likely to be dedifferentiated and to have lost the expression of the sodium–iodide symporter (NIS) so they do not concentrate radioiodine (1,2). The paper by Ho et al (reviewed in the April 2013 issue of Clinical Thyroidology, p. 76) shows that therapy that can induce reexpression of NIS usually fails in patients with this mutation (3). In addition, the BRAF mutation up-regulates various tumor-promoting molecules (1).

Should BRAF mutation status be included in assessing the risk of recurrence and mortality of thyroid cancer? The present study argues in favor of including this mutation as a predictor of mortality in high-risk patients based on conventional staging, but not in low-risk patients. In regard to recurrence, BRAF mutation status had an additional effect in predicting recurrence when added to conventional staging systems, including TNM, Ames, and Macis (4). The current study relating the BRAF V600E mutation to mortality as well as data showing that these tumors are more likely to recur provide a basis for using more aggressive treatment and surveillance in patients with this mutation.

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Clin Thyroidol 2013;25:107–108.

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Obesity Is Associated with Thyroid Cancer Risk in Women

Elizabeth N. Pearce

Han JM, Kim TY, Jeon MJ, Yim JH, Kim WG, Song DE, Hong SJ, Bae SJ, Kim HK, Shin MH, Shong YK, Kim WB. Obesity is a risk factor for thyroid cancer in a large, ultrasonographically screened population. Eur J Endocrinol. March 19, 2013 [Epub ahead of print].

SUMMARY

Background

Obesity is known to be a risk factor for many cancers; it has been estimated that approximately 6% of new U.S. cancers may be attributable to obesity (1). Previous observational studies have suggested a moderate association between increased body-mass index (BMI) and differentiated thyroid cancer risk in women (2,3) or in both sexes (4-6).

Methods

This cross-sectional study examined associations between obesity and thyroid cancer. The study population included 15,068 individuals selected from the 24,935 patients who underwent routine checkups at a single medical center in Seoul, Korea, in 2007 and 2008. Individuals with incomplete data were excluded, as were those with serum TSH <0.4 mIU/L or >10 mIU/L or a history of thyroid dysfunction, thyroid nodule, thyroid surgery, or thyroid cancer. Patients with a history of thyroid cancer in first-degree relatives were also excluded. Fasting glucose, triglyceride, insulin, and TSH measurements and height, weight, and waist circumference were ascertained in all subjects. Bioelectrical impedance was used to measure total body-fat mass, and the fat ratio was defined as the fat mass divided by the body weight. Thyroid ultrasonography was performed in all patients as part of the routine health screening, and 7472 (50%) of subjects had at least one thyroid nodule. FNA biopsies were performed on all of the 1427 patients with nodules >1 cm or with any suspicious ultrasonographic features. Of these, 269 subjects had suspicious cytopathologic findings. Following surgery, 251 patients had histologically proven papillary or follicular thyroid carcinoma, with a median tumor size of 0.6 cm; 76% of tumors were <1 cm, and 98.5% were papillary carcinomas. An additional seven patients with suspicious FNA findings who were observed without surgery, and nine who were lost to follow-up, were considered to have thyroid cancer for the purpose of analysis. Logistic-regression analyses were used to examine associations between obesity-related risk factors and thyroid cancer risk. All analyses were stratified by sex.

Results

Among women, the 140 patients with thyroid cancer were more likely to be obese (BMI, ≥25) than women without cancer (30% vs. 22%, P = 0.004) and had a higher mean waist circumference, fat ratio, and blood pressure. These differences were not observed in men. In logistic-regression models adjusted for age, smoking status, and serum TSH level, BMI was a significant predictor of thyroid cancer in women (odds ratio [OR], 1.63; 95% CI 1.24 to 2.10) but not in men (OR, 1.16; 95% CI, 0.85 to 1.57).

Conclusions

This is the first study to examine associations between obesity and thyroid cancer risk in a population systematically screened with ultrasound. Obesity, but not serum TSH or serum insulin, was associated with differentiated thyroid cancer risk in women. No associations with thyroid cancer risk were observed in men.

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ANALYSIS AND COMMENTARY

These data confirm previous studies demonstrating associations between obesity and thyroid cancer risk. Study strengths include the large sample size and the uniform diagnostic strategy for thyroid cancer. It is not possible to assess causality on the basis of a cross-sectional study, and the study is also limited by the use of a selected population and by assessment of a relatively small number of covariates. Importantly, most cancers in this study were papillary microcarcinomas <1 cm, and it is unclear whether results apply to cancers with greater clinical significance.

The reasons for the association between obesity and thyroid cancer risk remain poorly understood. Although no association between serum TSH and thyroid cancer was observed in this study, high serum TSH has been associated with increased thyroid cancer risk in other studies (7) and is thought to promote tumor growth. Hyperinsulinemia is thought to be mechanistically important for the development of some other types of cancer, but no association between fasting insulin levels and thyroid cancer risk was noted in this study. Adipokines and markers of inflammation and oxidative stress were not examined in this study, but are also potential mediators of the effects of obesity on oncogenesis and tumor growth.

Obesity and thyroid cancer rates are both increasing rapidly. It remains to be seen whether there is truly a causal relationship between the two. Prospective studies are needed to better define risks and to elucidate mechanisms for this relationship.

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Clin Thyroidol 2013;25:109–110.

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Does the Risk of Malignancy Increase When a Thyroid Nodule Is Larger Than 2 cm?

Jerome M. Hershman

Kamran SC, Marqusee E, Kim MI, Frates MC, Ritner J, Peters H, Benson CB, Doubilet PM, Cibas ES, Barletta J, Cho N, Gawande A, Ruan D, Moore FD Jr, Pou K, Larsen PR, Alexander EK. Thyroid nodule size and prediction of cancer. J Clin Endocrinol Metab 2013;98:564-70. Epub December 28, 2012; doi: 10.1210/jc.2012-2968.

SUMMARY

Background

In the evaluation of thyroid nodules for malignancy, the size of the nodule has been a cause for concern, mainly because the size—if it is a carcinoma—directly influences the staging. In addition, larger nodules in other organs, such as the adrenal gland, are more likely to be malignant. However, the data on size as a determinant of carcinoma in a thyroid nodule are conflicting (1-3). The current study assesses the impact of nodule size on the risk of cancer by analyzing a large clinical database.

Methods

The records of 4955 consecutive patients referred to Brigham and Women's hospital for evaluation of thyroid nodules during 1995–2009 were reviewed. Nodule size was measured in three dimensions by ultrasonography in all patients. The nodules were biopsied by fine-needle aspiration (FNA), and a cytopathologic diagnosis was made using the Bethesda classification. When patients underwent surgery, the final diagnosis was based on the surgical pathology.

Results

A total of 9339 nodules ≥1 cm were identified, and 7348 (78%) were evaluated by FNA. Those excluded usually had a high cystic component. The mean nodule size was 2.6 cm. The nodules were subdivided into the following groups by size: 1 to 1.9, 2 to 2.9, 3 to 3.9, and ≥4 cm and the percent of nodules in each group was 49%, 27%, 14%, and 11%, respectively. Nodule size had no influence on the distribution of cytology aspirates in each Bethesda category: the percentage of benign aspirates was 72% of nodules 1.0 to 1.9 cm; 67% of nodules 2.0 to 2.9 cm, 65% of nodules 3.0 to 3.9 cm, and 64% of nodules ≥4 cm. The nodules in 5% of each size group were classified as malignant. Six percent of the nodules 1 to 1.9 cm were considered suspicious, as were 8 to 9% of nodules in the larger size groups.

Based on surgical pathology, 927 of 7348 nodules (13%) were cancers. Papillary cancers made up 86% and follicular or Hürthle-cell carcinomas 8% of the cancers, the remainder being other cell types. The prevalence of cancer in relation to nodule size was 10.5% of those 1.0 to 1.9 cm, 13.5% of those 2.0 to 2.9 cm, 16.3% of those 3.0 to 3.9 cm, and 15.0% of those ≥4.0 cm. When the nodules 1.0 to 1.9 cm were compared with those ≥2.0 cm, the difference was statistically significant ($P<0.01$), but there were no differences in prevalence between the larger three groups. Increasing nodule size was associated with a lower proportion of papillary and a higher proportion of follicular or Hürthle-cell cancers as well as the rarer types (anaplastic, medullary, and lymphoma).

Conclusions

Increasing thyroid nodule size impacts cancer risk in a nonlinear manner with a threshold of 2.0 cm.

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ANALYSIS AND COMMENTARY

This large body of data has been analyzed very carefully and provides more concern for malignancy when the nodule is larger than 2 cm. In addition, the data suggest that larger solid nodules are more likely to be follicular carcinoma as compared with the smaller nodules. However, the literature concerning the size of nodules and the risk of malignancy is controversial. McHenry et al. evaluated 1023 patients with nodules; 673 underwent surgery (3). The mean (±SD) size of the benign nodules was larger, 4.4±2.4 cm as compared with 3.3±2.2 cm for malignant nodules ($P<0.05$). In an estimate of probability of malignancy based on size, their analysis showed that the likelihood of malignancy significantly decreased nonlinearly with increasing nodule size. The recent paper by Shrestha et al. (reviewed in the November 2012 issue of Clinical Thyroidology) found malignancy in 19.3% of 533 nodules 1.0 to 3.9 cm and 14.3% of 127 nodules ≥4 cm (4).

Another reason for concern in evaluating FNA results in large nodules is the possibility of a false negative result due to sampling error. The current study of Kamran et al found that the false negative rate was 1.3% in larger nodules and only slightly less in smaller nodules. Shrestha et al. also reported that false negative rates did not differ significantly based on nodule size (4).

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Clin Thyroidol 2013;25:111–112.

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Diagnostic 131-I SPECT/CT Scans Detect Unsuspected Metastases after Thyroidectomy for DTC

Jerome M. Hershman

Avram AM, Fig LM, Frey KA, Gross MD, Wong KK. Preablation 131-I scans with SPECT/CT in postoperative thyroid cancer patients: what is the impact on staging? J Clin Endocrinol Metab. February 21, 2013 [Epub ahead of print].

SUMMARY

Background

After surgery for differentiated thyroid cancer (DTC), routine postoperative radioiodine scans have largely been abandoned, for several reasons. First, the use of relatively large doses of radioiodine may "stun" residual thyroid tissue and prevent the uptake of a subsequent therapeutic dose. Second, in young patients with tumors <2 cm and no evidence of metastatic disease, routine thyroid ablation is no longer recommended. Third, in patients who are selected for radioiodine ablation, the posttherapy scan is believed to provide more information because it results from a much larger dose than that used for diagnostic scans. However, advances in scanning technology have resulted in better quality of diagnostic scans. In the present study, the authors prospectively performed postoperative scans in patients with DTC using single-photon-emission computed tomography (SPECT) combined with inline computed tomography (CT) that provides coregistration of tomographic functional data.

Methods

All patients with DTC at the University of Michigan between April 2007 and April 2011 who were referred for postoperative ^{131}I therapy underwent preablation ^{131}I planar and SPECT/CT imaging after preparation with a low-iodine diet for 2 weeks under conditions of thyroid hormone withdrawal. Images were acquired 24 hours after the administration of 1 mCi ^{131}I. Data were analyzed according to TNM staging and age <45 or ≥45 years. The diagnostic scans were evaluated by two experienced nuclear medicine specialists; one was unaware of the clinical data.

Results

Data were acquired on 320 patients; 43% were <45 years of age, and 68% were women. Ninety percent had papillary cancer. Regional nodal metastases were present in 47% of resected specimens.

The two observers agreed on interpretation of the scans in 84% of the cases. In 138 patients younger than age 45, the SPECT/CT detected distant metastases in 5 (4%), restaging them to stage 2, and nodal metastases in 61 (44%), of whom 24 were not considered to have nodal metastases at surgery. In 182 patients ≥45, the SPECT/CT detected distant metastases in 18 (28%) and nodal metastases in 51 (28%). Incorporation of these findings led to upstaging of the disease in 25% of the older patients.

In 67 patients with tumors of 1 to 2 cm, nodal metastases were found by SPECT/CT in 35 (52%) and distant metastases in 3 (4.5%). In 49 patients with tumors <1 cm, nodal metastases were found in 11 (22%) and distant metastases in 2 (4%).

In 303 patients, the diagnostic scan results were compared with the posttherapy scans. The results were concordant in 92%. In 6%, additional foci were found on the posttherapy scans, but in only 1.4% were new metastatic lesions found.

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Conclusions

Diagnostic preablation SPECT/CT scans detected regional metastases in 35% of patients and distant metastases in 8% of patients. This information changed staging in 4% of younger and 25% of older patients.

ANALYSIS AND COMMENTARY

This study could dramatically alter the use of diagnostic ^{131}I scans after thyroidectomy in postoperative patients with DTC . However, there is one major caveat. The group of patients studied were highly selected because they were referred to a nuclear medicine unit for ^{131}I ablation therapy, even though 43% were younger patients and less than half had nodal disease. The patients had more aggressive tumors than the usual group of patients with DTC. Pathology showed that 30% had vascular invasion, 63% had capsular invasion, and 26% had positive surgical margins.

The SPEC/CT showed an impressive number of patients with residual nodal disease. The finding of distant metastases on the scans in over one fourth of older patients is very surprising. There was no information provided with regard to how many of these new findings occurred in the patients with more aggressive pathologic results. In addition, there was no information concerning correlation with serum thyroglobulin in this group with distant metastases. Although the scans were read to include the classification of uptake in the thyroid bed, there was no comment on the frequency of this finding.

In patients selected for ^{131}I ablation, the positive findings on diagnostic SPECT/CT could influence the amount of the dose for ablation. Others have claimed utility for diagnostic ^{131}I scans before ablation (1). One study reported that SPECT/CT performed after radioablation was much more sensitive than planar imaging and detected nodal involvement in one fourth of patients with papillary thyroid carcinoma (2).

If the improved sensitivity for finding residual disease by SPECT/CT is confirmed in an unselected group of patients with DTC, then the wheel will have come full circle by a return to routine ^{131}I diagnostic scans in virtually all patients, a practice largely abandoned over a decade ago because of data showing that stimulated thyroglobulin and neck ultrasound are more sensitive diagnostic tools than ^{131}I scans. In the meantime, this study influences me to consider SPECT/CT for the patient who is classified as low risk and who is not selected for ^{131}I ablation because a negative result would give the patient a very good prognosis. Of course, cost considerations would influence the decision to use SPECT/CT in such a patient.

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Clin Thyroidol 2013;25:113–115.

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Surgeon-Performed Laryngeal Ultrasound Can Be Used to Screen for Vocal-Cord Palsy before Thyroid Surgery

Cord Sturgeon

Cheng SP, Lee JJ, Liu TP, Lee KS, Liu CL. Preoperative ultrasonography assessment of vocal cord movement during thyroid and parathyroid surgery. World J Surg 2012;36:2509-15.

SUMMARY

Background

Iatrogenic recurrent laryngeal-nerve (RLN) injury is a rare but well recognized and dreaded complication of thyroid or parathyroid surgery. The presence or absence of dysphonia is not a reliable predictor of vocal-cord function in the preoperative setting. Routine preoperative and postoperative laryngoscopy has been advocated by some experts, but remains controversial. Because laryngoscopy can be an invasive and uncomfortable procedure, a noninvasive method of screening patients for impaired vocal-cord mobility is desirable. A sonographic method to evaluate vocal-cord mobility would be an ideal inexpensive, painless, and noninvasive screening method. There is a paucity of data on the utility of transcutaneous ultrasound examination of the larynx as a screening tool to identify laryngeal dysfunction. This study was designed to evaluate the utility of ultrasound as a screening tool for the detection of impaired vocal-cord movement before thyroid or parathyroid surgery.

Methods

This was a single institution prospective study. In the first 6 months (first phase), patients scheduled for thyroid or parathyroid surgery underwent both routine preoperative laryngoscopy by experienced independent otolaryngologists and laryngeal ultrasonography. In the second 6 months of the study (second phase), all patients scheduled for thyroid or parathyroid surgery underwent laryngeal ultrasound first, and only some of these patients were then selectively evaluated by laryngoscopy. Patients with either abnormal vocal-cord movement on laryngeal ultrasound, with dysphonia despite apparently normal laryngeal ultrasound, or whose vocal-cord movement could not be assessed sonographically underwent laryngoscopy. Laryngeal ultrasound was performed by endocrine surgeons and not radiologists. Normal vocal-cord movement was defined as "symmetrically abductive and adductive motion of the true vocal cords during quiet respiration." The results of the laryngeal ultrasound were compared with the findings from laryngoscopy.

Results

In the first phase, 114 patients were evaluated preoperatively. Vocal-cord movement could be assessed sonographically in 82% (n = 93). In 2 of 93, patients the vocal-cord movement was determined to be abnormal on the ultrasound exam, and laryngoscopy revealed a unilateral vocal-cord palsy in both patients. In the second phase, vocal-cord motion was successfully evaluated in 349 of 415 patients (84%). Four patients with abnormal vocal-cord movement were identified sonographically, and each underwent laryngoscopy, which revealed unilateral vocal-cord palsy. For 66 of 415 patients (16%), vocal-cord movement could not be evaluated sonographically. Only 45 of these patients went on to laryngoscopy, and one vocal-cord palsy was identified.

Conclusions

The preoperative recognition of vocal-cord palsy can alert the surgeon to the possibility of an invasive

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malignancy and might also alter intraoperative management of the central neck. The routine use of preoperative laryngoscopy remains controversial. The selective use of preoperative laryngoscopy might be more cost-effective than routine laryngoscopy. In this study, it was possible for surgeons to sonographically evaluate vocal-cord movement in 84% of preoperative patients. The authors state that physicians who perform cervical ultrasound can easily and quickly learn to perform laryngeal ultrasound and that it can be performed in the office in 1 minute. The authors estimated that nearly two thirds of preoperative laryngoscopies could be avoided by the use of preoperative screening laryngeal ultrasound.

ANALYSIS AND COMMENTARY

The preoperative identification of vocal-cord dysfunction may impact surgical decision-making and alter the operative approach for benign and malignant disease. Unfortunately, vocal-cord dysfunction is not reliably ruled out by the absence of dysphonia. This has led some experts to recommend laryngoscopy for all patients who are about to undergo thyroid surgery, regardless of preoperative or postoperative voice quality. This recommendation has been met with some opposition because fiberoptic laryngoscopy is an invasive and costly procedure that is not performed by all surgeons, and it has a fairly low likelihood of identifying vocal-cord dysfunction in the nondysphonic population.

In this study, the success rate for documenting vocal-cord movement was 84%, and only 1.8% of preoperative patients in phase 1 (1.3% overall) were found to have a vocal-cord palsy. The authors postulated that laryngeal ultrasound would be cost-effective and easily adopted by endocrine surgeons. They estimated that approximately two thirds of preoperative laryngoscopies could be avoided by the use of screening laryngeal ultrasound.

Laryngeal ultrasound has been proposed as an alternative to fiberoptic laryngoscopy by these authors and others because it is inexpensive, rapid, noninvasive, and painless and generates an image that can be stored in the medical record. Laryngeal ultrasound to evaluate vocal-cord movement is not widely used, however. The greatest enthusiasm for this technique was historically in the pediatric population, in whom laryngoscopy is not tolerated without anesthesia (1, 2). The widespread adoption of this technique in the adult population has not occurred largely because of concerns regarding false negative results or the inability to sonographically image the vocal folds.

Several studies have had favorable findings, contributing to enthusiasm for laryngeal ultrasound in the adult population. Dedecjus et al. evaluated vocal-cord movement in 50 thyroidectomy patients during the preoperative and postoperative periods with both ultrasound and laryngoscopy. They found that the sonographic findings correlated with the laryngoscopy and concluded that it was a minimally invasive and reproducible method for the identification of postoperative vocal-cord dysfunction (3). Ooi et al. evaluated color Doppler imaging of the vocal cords and determined that it was just as accurate as laryngoscopy in the identification of vocal-cord palsy or paresis (4). Wang et al. evaluated 705 patients with laryngeal ultrasound and found that vocal-cord motion could be assessed in 87% of patients. Interestingly, they found laryngeal ultrasound to be more successful and accurate in female patients. They concluded that laryngeal ultrasound would be an alternative for the evaluation of vocal-cord movement in over 90% of women and about 50% of men (5). Not all studies have shared enthusiasm for laryngeal ultrasound, however. Sidhu et al. evaluated 100 postoperative patients with laryngeal ultrasound in 1999 and found that sensitivity was 62%, specificity was 97%, positive predictive value was 73%, and negative predictive value was

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95%; they concluded that the false positive and false negative rates were too high to use ultrasound as an alternative to nasopharyngoscopy (6).

There is an increasing demand from patients that medicine be practiced through minimally invasive low-risk procedures. The economics of health care delivery demand that we identify lower-cost alternatives to meet or exceed the standard of care. The culture of safety surrounding health care providers, and surgeons in particular, requires us to document our outcomes and complications. The findings of Cheng et al. suggest that laryngeal ultrasound might be an expedient, noninvasive, inexpensive, reproducible, and accurate method to interrogate and document vocal-cord mobility in most patients. With the increased availability of compact high-resolution ultrasound machines in the offices of thyroid surgeons, the use of laryngeal ultrasound to evaluate vocal-cord motion is certain to gain momentum. When used correctly, laryngeal ultrasound could accurately screen patients and direct patients who have a higher pretest probability of vocal-cord dysfunction for laryngoscopy.

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Clin Thyroidol 2013;25:116–118.

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Two single nucleotide polymorphisms (SNPs) in thyroid hormone receptor-alpha may affect the risk of obesity and dyslipidemia

Stephen W. Spaulding

Fernández-Real JM, Corella D, Goumidi L, Mercader JM, Valdés S, Rojo Martínez G, Ortega F, Martinez-Larrad MT, Gómez-Zumaquero JM, Salas-Salvadó J, Martinez González MA, Covas MI, Botas P, Delgado E, Cottel D, Ferrieres J, Amouyel P, Ricart W, Ros E, Meirhaeghe A, Serrano-Rios M, Soriguer F, Estruch R. Thyroid hormone receptor alpha gene variants increase the risk of developing obesity and show gene-diet interactions. Int J Obes. February 12, 2013 [Epub ahead of print]. doi:10.1038/ijo.2013.11.

SUMMARY

Background

Thyroid and lipid pathways interact at many levels. The authors of the current paper observed a patient with obesity and hypothyroidism who, while being overreplaced with L-T_4, continued to have bradycardia despite having a high free T_4, an undetectable TSH, and a 40-lb weight loss, although the body-mass index (BMI) remained above 30. They sequenced her entire thyroid hormone receptor-α (THRα) locus, and found a relatively uncommon single nucleotide polymorphism (SNP). The authors then examined the frequency of this mutation in samples from a cohort of patients at high risk for cardiovascular disease. They also examined the frequency of a more common SNP in THRα in two normal cohorts to determine whether either of these SNPs was associated with obesity or serum lipid disorders.

Methods

The authors had access to blood samples collected between 2003 and 2007 from a cohort of 4734 Spaniards at high risk of cardiovascular disease who had at least three risk factors (history of hypertension or dyslipidemia, BMI <25 , current smoker or family history of premature cardiovascular disease) or two risk factors plus a diagnosis of type 2 diabetes. Blood samples were also available from a cohort of 3417 healthy Spaniards from four regions of Spain taken between 1996 and 1999, as well as additional samples obtained between 2003 and 2005 from 2139 of the same subjects. Finally, 2325 normal French samples taken between 1995 and 1997 were studied. The samples were analyzed for TSH, free T_4 and free T_3 levels. The two SNPs in THRα were a relatively common SNP at residue (rs) 1568400, which is in linkage disequilibrium with the less common allele at rs12939700 found in the index case. Student's t-test and analysis of variance were used to compare crude differences of means between genotypes, while more complicated analyses were used to assess SNP associations with risks for obesity and high triglycerides, and to assess the interaction between the THRα polymorphisms and fat intake.

Results

In the cohort at high risk for cardiovascular disease, analysis for the SNP at rs12939700 (C/A in the index case) showed that 93% had C/C, 6.8% had C/A and 0.2% had A/A. Those with A/A or A/C were likely to be heavier and to have a BMI > 30 (P = 0.03).

Analysis for the SNP at rs15684000 in the normal Spanish cohort showed that 50% had A/A, 42% had A/G, and 8% had G/G. Those with A/G or G/G had a higher total cholesterol, fasting triglyceride levels, BMI, and larger waist circumference. The higher BMI remained significant after adjusting for age, sex, triglycerides and geographic region. In the subgroup of the same normal subjects who gave samples 6 years later, the risk of having developed obesity over the

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6-year period was significantly increased in GG homozygotes (odds ratio, 2.93; 95% CI, 1.05 to 6.95) after adjusting for age, sex, education, and thyroid function. Analysis of the normal French cohort detected associations either with BMI or with log-transformed triglyceride levels, depending on whether a G allele was considered dominant or recessive. In the high-cardiovascular-risk group (many of whom were obese), there was no significant association between SNPs at rs1568400 and BMI, but there was a significant interaction term between BMI and fat intake (P<0.001). In patients whose saturated fat intake was in the highest tertile, those with G/A or G/G had a significantly higher BMI than those with A/A, after controlling for energy intake and physical activity.

Conclusions

Two THRα gene polymorphisms display a moderate association with obesity, high triglycerides, and/or development of obesity.

ANALYSIS AND COMMENTARY

Differences in the function of THRα and THRβ are clearly evident in mice and patients with mutations in the THR genes, and THRα has been implicated in adipocyte growth and adrenergic sensitivity. Studies in vitro and on cells in culture, however, have not shown as much gene specificity, possibly indicating the importance of specific intracellular modifications of the receptors (1). What is more, the cellular responses to THRα expression depend on how the transcripts are spliced. The authors called attention to the fact that the SNP at rs12939700 is located at the end of a sequence that determines whether THRα transcripts will be spliced to make THRα1 mRNA (the active isoform) or to make THRα2 mRNA (the antagonistic isoform). Furthermore, this group of researchers previously studied factors that regulate THRα splicing, so it would be interesting to learn whether the ratio of the two THRα isoforms in the patient's fat differs from normal and/or whether any of the patient's splicing factors have unusual SNPs or mutations. Obviously, the A/C heterozygosity found at rs12939700 in the index patient is not solely responsible for her clinical features, although it is interesting that patients in the high-cardiovascular-risk group who had A/A or A/C were more likely to be heavier and to have a BMI >30. Additional clinical details on the patient (e.g., cardiovascular responses to exercise, evidence of Hashimoto's thyroiditis, sex hormone–binding globulin levels, etc.) would be interesting to know. Mutations or unusual SNPs in other genes known to influence thyroid receptor action, such as heterodimerization partners, coactivators, corepressors of THRα, covalent modifiers or cytoplasmic transporters of THRα, as well as thyroid hormone transporters and deiodinases could also be implicated. It is also quite possible that this SNP is not responsible for the associations with obesity but is simply in linkage disequilibrium with another region that is the actual cause of the metabolic changes observed. Plainly, studies on the SNP at rs12939700 need to be repeated in larger samples.

It was not clear whether the index patient was ever genotyped for the SNP at rs15684000, which the authors showed had some associations with increased BMI and triglycerides in two normal cohorts, whereas in the cohort at high risk for cardiovascular disease, the SNP analysis indicated a significant interaction between high saturated fat intake and obesity.

Genomewide association studies have uncovered several dozen gene variants much more highly associated with risk for obesity in the general population than either of the THRα SNPs, including some also known to be associated with thyroid hormone action (e.g., TUB, BNDF) or with thyroid hormone metabolism (e.g., TEB4) (2). Nonetheless, either of the SNPs in THRα reported in the current paper could be involved in the development of obesity indirectly, say in individuals who also have variants in other genes involved in thyroid or lipid pathways.

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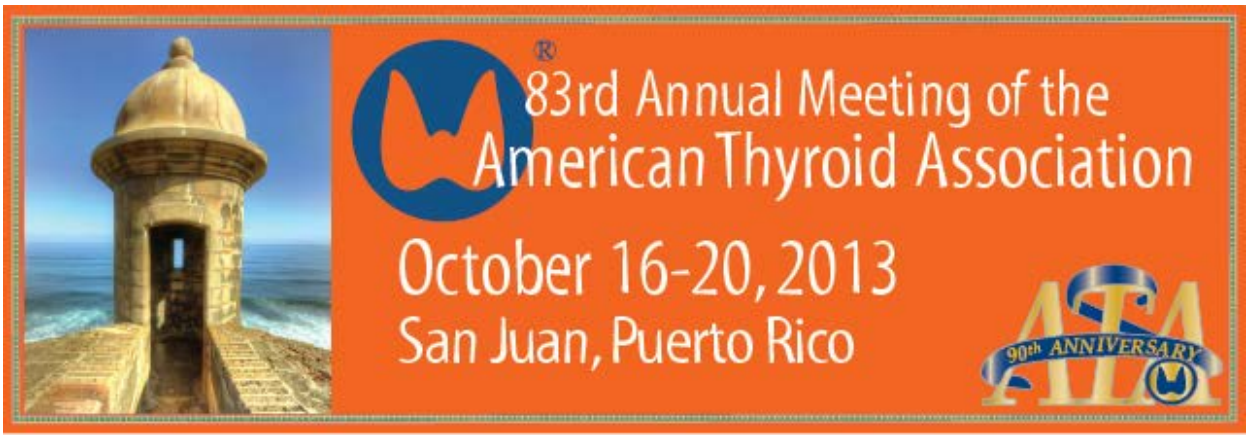

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