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Why Do Patients with Subclinical Hypothyroidism Get Overtreated?

Stephen W. Spaulding

Taylor PN, Iqbal A, Minassian C, Sayers A, Draman MS, Greenwood R, Hamilton W, Okosieme O, Panicker V, Thomas SL, Dayan C. Falling threshold for treatment of borderline elevated thyrotropin levels—balancing benefits and risks: evidence from a large community-based study. JAMA Intern Med. October 7, 2013 [Epub ahead of print]/ doi:10.1001/jamainternmed.2013.11312.

SUMMARY

Background

There is growing concern about patients with subclinical hypothyroidism receiving too much L-T_4, a problem found both in specialty and in primary care settings. Too much circulating thyroid hormone can increase the risk of atrial fibrillation and bone fragility, especially in the elderly. For patients who have a normal free T_4 level and whose TSH is above the upper limit of normal yet below 10 mU/L, the American Thyroid Association recommends considering treatment if the patient has symptoms suggestive of hypothyroidism, a positive anti-TPO titer, or evidence of atherosclerotic cardiovascular disease, heart failure, or associated risk factors for these diseases (1). British guidelines indicate that if screening thyroid-function tests have been performed for nonspecific symptoms in a normal healthy adult and the TSH is between 4 and 10 mU/L but the FT_4 is normal, L-T_4 is not recommended as routine therapy. However, repeat thyroid-function testing should be done in 3 to 6 months, after excluding nonthyroidal illness and drug interference (2). If the second test results are similar to the first, and if the anti-TPO titer is normal, a repeat measurement of TSH every 3 years is all that is required (2). In the United Kingdom, primary care physicians take care of most patients receiving L-T_4 for hypothyroidism. A computerized thyroid disease register assists physicians in keeping track of all the patients with hypothyroidism receiving L-T_4 and to ensure that physicians obtain thyroid-function tests on these patients every 12 months. The current study assessed how instituting these practice targets influenced L-T_4 prescribing behavior and whether this policy may have had unintended consequences.

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Methods

About 52,000 patients given an initial L-T_4 prescription within 90 days of a TSH determination were identified in the General Practice Research Database between 2001 and 2009, after excluding patients known to be taking thyroid-altering medications, those receiving L-T_4 for pregnancy, and those with a known history of hyperthyroidism, pituitary disease or thyroid surgery. Pretreatment TSH levels, L-T_4 prescriptions, and subsequent TSH levels were analyzed every 6 months for up to 5 years (if more than one determination had been obtained within a 6-month period, the most recent value was used). An "interpretable" free T_4 determination was available in about 35,000 cases at the time of the initial prescription of L-T_4, while in 21,000 cases a free T_4 level was available at the end of a patient's study. Unfortunately, no "interpretable" anti-TPO data were available. Other symptoms, clinical findings, diagnoses, clinic appointments, tests, and procedures were reviewed for the 3 months prior to initiating treatment with L-T_4, and, along with age and sex, were factored into the analyses. No information concerning mortality was provided. Logistic-regression analysis was used to assess the odds of a patient being given an L-T_4 prescription for a TSH of 10 mU/L or less. The odds of suppressed TSH developing at 5 years were also assessed by univariable logistic regression.

Results

The median TSH for which a new patient received L-T_4 fell steadily over the study period, from 8.7 mU/L in 2001 to 7.9 mU/L in 2009. After adjusting for multiple variables, the odds ratio for as of a patient receiving L-T_4 for a TSH of 10 mU/L or less was 1.30 (95% CI, 1.19 to 1.42; P<0.001) in 2009 as compared with 2001. In 2001, 42% of patients had a TSH above 10 mU/L, whereas in 2009, only 36% had a TSH above 10 mU/L (P<0.001). Of the patients whose initial TSH was between 4 and 10 mU/L, about 20,000 had an interpretable free T_4 before L-T_4 treatment was started. Strikingly, 83% of them had a normal free T_4. True, those who were given L-T_4 despite a normal free T_4 were more likely to be older and to have had pretreatment cardiovascular risk factors, but the majority (11,000) did not have a history of hypertension, diabetes, or elevated lipids and had no symptoms consistent with hypothyroidism. After 6 to 12 months of treatment, 2.7% of patients had a suppressed TSH (<0.1 mU/L), whereas after 54 to 60 months of treatment, the fraction with a frankly suppressed TSH had more than doubled (5.8%). Furthermore, the fraction of patients with a TSH between 0.1 mU/L and 0.5 mU/L rose from 6.3% after 6 to 12 months to 10.2% after 54 to 60 months of treatment. Patients who noted fatigue or depression before the initial prescription of L-T_4 were significantly more likely to have a suppressed TSH at 5 years, as were women whose initial TSH was either under 4 mU/L or over 10 mU/L. Although those with cardiac risk factors were less likely to have a suppressed TSH level, more than 10% of those with cardiac risk factors did have a low TSH level. The risk of being given a new prescription for a TSH between 4 and 10 mU/L was greatest in those 80 to 100 years old.

Conclusions

In the United Kingdom, the fraction of patients with marginal degrees of hypothyroidism treated with L-T_4 increased progressively between 2001 and 2009, apparently associated with the institution of new targets for general practitioners. The risk for a patient with a suppressed TSH or a TSH below the lower limit of normal was substantially greater after 5 years' treatment than after only 6 to 12 month's treatment.

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Stephen W. Spaulding

ANALYSIS AND COMMENTARY

The risks associated with having an elevated T_4/free T_4 appear to exceed the risks of having a TSH between 4 and 10 mU/L. Older patients are at particular risk for overtreatment, since their upper limit of normal for the level of TSH is slightly higher than that in younger patients (3). A review of records on 3900 community-dwelling apparently euthyroid Caucasian Australian men over 70 years of age found that those whose free T_4 was normal but in the highest quartile were 20% more likely to have died (odds ratio, 1.19; 95% CI,1.02 to 1.39) over 6 years of follow-up (4). In contrast, there was no altered risk of mortality associated with any quartile of TSH within the normal range (4).

What leads to overtreatment of patients with hypothyroidism? Patients who reported tiredness and depression at the initiation of treatment in this study were significantly more likely to have a suppressed TSH at the end of the study, perhaps because they requested extra L-T_4 to make them feel less lethargic or less depressed. (This may reflect U.K. guidelines on the use of thyroid-function tests, which states "The primary target of thyroxine replacement is to make the patient feel well and to achieve a serum TSH that is in the reference range. … The corresponding free T_4 will be within or slightly above its reference range" (2). In other cases, a fall in a patient's TSH level, a patient's failure to get a scheduled repeat TSH test, or some change in the patient's medications, co-morbid conditions, or diet that have reduced a patient's L-T_4 requirement may have escaped the physician's notice. Rarely, a patient with hypothyroidism can turn to hyperthyroidism because of a change in the activity of thyroid-stimulating antibodies versus the activity of thyroid-blocking antibodies (5). Similarly, a new hot nodule can turn hypothyroidism to hyperthyroidism. There is also evidence that the amount of L-T_4 a patient requires correlates with lean body mass, which tends to decrease with age.

Interestingly, almost 10% of the patients were no longer taking L-T_4 at the end of the study period. In one third of the patients with a TSH between 4 and 10 mU/L, only that single determination had been obtained before L-T_4 was given. Thus some of the patients may actually have had thyroid-function abnormalities, reflecting nonthyroidal illness. Furthermore, it is not unusual for a slightly elevated TSH level in an elderly patient to spontaneously normalize (6). On the other hand, some patients may have stopped taking L-T_4 and begun taking another form of thyroid hormone obtained online, such as a desiccated thyroid preparation.

Patients who may have had a TSH between 4 and 10 mU/L, but who did not receive a prescription for L-T_4 were not included in this study. The absence of anti-TPO data also weakens the interpretation of the data. Furthermore, several different TSH assays were being used during the study, and simply combining the results is not ideal, since some third-generation TSH assays can have a steeper TSH dose–response slope than others (3). More problematic, different free T_4 assays were being used: the consistency and reliability of different T_4 analog methods can be quite uneven, and results may not correlate well those obtained by dialysis (7). Nonetheless, until a large well-controlled, prospective, randomized trial of L-T_4 treatment of patients with subclinical hypothyroidism that includes a wide range of ages and TSH levels is performed, the practitioner needs to be wary of overtreatment with L-T_4.

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Overtreatment of Congenital Hypothyroidism in the First Two Years of Life May Result in a Worse Cognitive Outcome Later in Childhood than Undertreatment

Rosalind S. Brown*

Bongers-Schokking JJ, Resing WCM, de Rijke YB, de Ridder MA, de Muinck Keizer-Schrama SM. Cognitive development in congenital hypothyroidism: is overtreatment a greater threat than undertreatment? J Clin Endocrinol Metab 2013;98:4499-506. Epub August 26, 2013.

SUMMARY

Background

Despite significant gains in the cognitive outcome of babies with congenital hypothyroidism detected by newborn screening and treated early in life, controversy continues as to what constitutes optimal therapy. There is general agreement that babies whose treatment is initiated at <2 weeks of age do better than those whose therapy is started later, particularly when the congenital hypothyroidism is severe. Similarly, it is widely accepted that a starting l-thyroxine dose of 10 to 15 µg/kg/day results in a superior cognitive outcome than a dose of 6 to 8 µg/kg/day, as was recommended in the early days of newborn screening. However, most attention has focused on the adverse effects of the hypothyroidism and how rapidly the serum free T_4 and TSH concentrations should be normalized, with less concern for the potential influence of temporary iatrogenic hyperthyroxinemia. In this prospective study, the authors report the results of neuropsychological testing at 11 years of age in relation to overtreatment and undertreatment in the first 2 years of life in 55 of an original Dutch cohort of 61 children with congenital hypothyroidism.

Methods

Of 61 children with congenital hypothyroidism who were studied at 1.8 years of age, 46 were restudied at 6 years and 55 reassessed at 11 years. Results were compared with age-matched normal controls. Onset of l-thyroxine treatment was defined as early or late depending on whether it was commenced at <13 or >13 days of age. The initial l-thyroxine dose was considered to be high if it was >9.5 µg/kg/day and low if it was <9.5 µg/kg/day. Groups were also formed in relation to time to normalization of TSH (<10 mU/L): fast, <1 month; moderate, 1–2 months; and slow, >2 months. Periods of undertreatment or overtreatment, assessed on the basis of individual steady-state free T_4 and TSH concentrations, were defined as none, short (<3 months) and long (>3 months). The short version of the Revised Amsterdam Child Intelligence Test (RAKIT) was used to assess six separate domains, and scores were corrected for socioeconomic status and ethnicity.

Results

Neither short nor long free T_4 overtreatment had a discernible effect at 1.8 years, but both were associated with a significant decline in cognitive development at 11 years of age. When compared with those with no overtreatment, the deficits were 11.2 and 16 points, respectively. In contrast, both moderate and fast TSH normalization were associated with a higher mental development index at 1.8 years, but at 6 and 11 years this difference was no longer seen. There was no significant effect of either TSH or free T_4 undertreatment or TSH overtreatment at any age.

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Overtreatment of Congenital Hypothyroidism in the First Two Years of Life May Result in a Worse Cognitive Outcome Later in Childhood than Undertreatment

Rosalind S. Brown

Conclusions

Overtreatment in the first 2 years of life as reflected by the free T_4 concentration is more detrimental to later cognitive outcome than undertreatment. The rapidity of normalization of serum thyroid hormone and TSH levels, though associated with a short-term benefit, is not associated with a sustained improvement in neuropsychological performance later in childhood.

ANALYSIS AND COMMENTARY

This provocative study should cause us to pause and reconsider what constitutes optimal therapy for babies with congenital hypothyroidism, particularly those with severe disease who are the most at risk of neuropsychological sequelae. In particular, it challenges the overriding concern about the negative impact of prolonged hypothyroidism and the focus on correcting thyroid hormone levels ever more rapidly (1) by pointing out the potential negative impact of even short-term overtreatment. In clinical practice, it would not be feasible to compute a steady-state concentration of free T_4 or TSH for every patient, and it would have been of interest to have been provided with the absolute values of these variables. Nonetheless, the authors quite rightly point out that based on their findings, it would be reasonable to aim for free T_4 and TSH levels within the normal range in order to minimize the risk of overtreatment, rather than In the upper and lower half of normal, respectively, as currently recommended (2). It goes without saying that frequent monitoring of thyroid hormone levels is essential to achieve these goals, a point that has been emphasized by others recently (3).

It is of interest that overtreatment as assessed by steady-state serum free T_4 concentration, but not TSH, was associated with an adverse outcome at 11 years. The reason for this is not clear but could be a consequence of pituitary resistance, a relatively frequent finding in babies with congenital hypothyroidism in the first year of life (4). For the clinician, the take-home point is that the primary goal of therapy should be maintenance of a normal free T_4 concentration.

A final important and sobering lesson is the limited sensitivity and prognostic value of cognitive testing in the first year or two of life and the need for long-term follow-up in all such studies. In this, like other studies in the field (5,6), quite different conclusions would have been drawn had only results of cognitive testing at 1.8 years of age been available. With this in mind, I await with interest data concerning the long-term neuropsychological outcome of babies treated with a higher initial l-thyroxine dose (12 to 17 µg/kg/day) as advocated by some (1). Only when these data are available will it be possible to decide more rationally what truly constitutes optimal therapy in babies with congenital hypothyroidism.

*Boston Children's Hospital, Harvard Medical School

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Should the Approach to Management of Graves' Hyperthyroidism in Women of Child-Bearing Age Be Revised?

Jorge H. Mestman

Andersen L, Wu CS, Laurberg P. Birth defects after early pregnancy use of antithyroid drugs: a Danish nationwide study. J Clin Endocrinol Metab 2013;98:4373-81. Epub October 22, 2013.

SUMMARY

Background

Maternal and fetal complications occur in poorly controlled Graves' hyperthyroidism. Pregnancy outcome is successful in the majority of cases when antithyroid drugs have been used for over five decades and when the woman is carefully monitored. However, in the past few years, several reports have confirmed the results of early studies of congenital malformations when antithyroid drugs are used in the first trimester of pregnancy.

The authors' objective was to determine to what degree the use of methimazole/carbimazole (MMI/CMZ) and propylthiouracil (PTU) in early pregnancy is associated with an increased prevalence of birth defects.

Methods

This Danish Nationwide Register–based cohort study included 817,093 children born from 1996 to 2008. Exposure groups were assigned according to maternal antithyroid drug use in early pregnancy: PTU (564); MMI/CMZ (1097); MMI/CMZ and PTU (shifted in early pregnancy [159]); no antithyroid drug (antithyroid drug use, but not during pregnancy [3543]); and nonexposed (never used antithyroid drugs [811,730]). Multivariate logistic regression was used to estimate adjusted odds ratios (OR) with 95% confidence intervals (CI) for diagnosis of a birth defect before 2 years of age in exposed versus nonexposed children.

Results

The prevalence of birth defects was high in children exposed to antithyroid drugs in early pregnancy (PTU, 8.0%; MMI/CMZ, 9.1%; MMI/CMZ and PTU, 10.1%; no antithyroid drugs, 5.4%; nonexposed, 5.7%; P<0.001). Both maternal use of MMI/CMZ (adjusted OR, 1.66) and PTU (adjusted OR, 1.41) and maternal shift between MMI/CMZ and PTU in early pregnancy (adjusted OR, 1.82) were associated with an increased OR of birth defects. MMI/CMZ and PTU were associated with urinary system malformation and PTU with malformations in the face and neck region. Congenital malformations in children from mothers exposed to MMI/CMZ early in pregnancy (choanal atresia, esophageal atresia, omphalocele, omphalomesenteric duct anomalies, and aplasia cutis) were common (OR, 21.8 [95% CI, 13.4 to 35.4]).

Conclusions

Both MMI/CMZ and PTU were associated with birth defects, but the spectrum of malformations differed. The authors concluded that more studies are needed to corroborate results with regard to early pregnancy shifts from MMI/CMZ to PTU.

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Should the Approach to Management of Graves' Hyperthyroidism in Women of Child-Bearing Age Be Revised?

Jorge H. Mestman

ANALYSIS AND COMMENTARY

Diagnosis and management of hyperthyroidism in pregnancy is a challenge for the medical team. The most common cause of hyperthyroidism early in pregnancy is gestational thyrotoxicosis (1), a self-limited disorder that requires no specific antithyroid therapy and does not affect the outcome of pregnancy. Graves' hyperthyroidism affects about 0.5% of pregnant women, with different clinical presentations: (a) first diagnosed in pregnancy, (b) women on antithyroid drug therapy from before conception and either euthyroid or hyperthyroid at the time of conception, (c) recurrence of hyperthyroidism soon after conception in women in remission from previous antithyroid drug therapy, and (d) postablation therapy. Obstetrical and maternal complications are significant in women whose disease is poorly managed (2). Furthermore, the dosage of antithyroid drugs needs to be monitored frequently throughout gestation to avoid fetal thyroid dysfunction. The natural course of hyperthyroidism during gestation is characterized by an aggravation of symptoms in the first trimester, with amelioration in the second half of pregnancy, and, interestingly, antithyroid drug therapy may be discontinued in the last 6 to 8 weeks of pregnancy in about 30% of patients without recurrence of hyperthyroidism. Rebound of hyperthyroid symptoms is common in the first 3 months postpartum. Both MMI/CMZ and PTU have been used in pregnancy; PTU was the preferred drug for many years, supported by an early report of a congenital complication, aplasia cutis, in infants of two mothers treated with methimazole (3). Clementi et al. (4) described the syndrome of methimazole embryopathy, which includes choanal atresia, esophageal atresia, omphalocele, omphalomesenteric-duct anomalies, and aplasia cutis. Barbero et al. (5) described characteristic facial features in children whose mothers were treated with MMI in the first trimester. These complications are rare in the general population; however, in the past few years, several articles with large numbers of women exposed to antithyroid drugs consistently showed an association of specific malformations not only to MMI but also to PTU (6-8). Reports of liver failure in children and some adults undergoing PTU therapy prompted the ATA and the Food and Drug Administration to recommend the use of MMI in the management of thyrotoxicosis, with three exceptions: patients allergic to MMI, patients in their first trimester of pregnancy, and patients in hyperthyroid crisis (9). The recommendation suggested by the ATA and Endocrine Society is to prescribe PTU in the first trimester of pregnancy and MMI afterward, or to shift from MMI to PTU as soon as pregnancy is confirmed. In the present Danish Nationwide Register–based cohort study, 817,093 children born from 1996 to 2008 were included. Four groups were analyzed: (a) those with PTU exposure in the first trimester, (b) those with MMI exposure, and (c) those who took MMI and then switched to PTU at some time during the first trimester. These groups were compared with children of mothers with hyperthyroidism who were not exposed to antithyroid drugs during pregnancy and control infants. In addition to confirming a significant increase in congenital malformations in infants exposed to MMI and PTU in the first trimester, they made the interesting observation of congenital malformations in 16 (2 with choanal atresia) of 149 children whose mothers shifted from MMI to PTU at a median time of 44 days (range, 3 to 70) after conception.

In view of these findings, physicians should discuss with their patients with hyperthyroidism who are of child-bearing age several important aspects of future pregnancies: (a) the first, obvious, one is to avoid pregnancy until a proper diagnosis and therapeutic plan is in place (oral contraceptives are the most effective method when taken properly), (b) the potential risk of congenital malformations resulting from antithyroid drug exposure in the first trimester,

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(c) the potential risk of fetal dysfunction due to inappropriate antithyroid drug dosage in the second half of pregnancy, and the limited technical tools available to detect fetal thyroid dysfunction, (d) the risk of fetal hyperthyroidism in mothers with high titers of TSH receptor antibodies (although the incidence is low), (e) the possibility of a marked and persistent increase in TRAb titers after ^{131}I thyroid ablation (10), and (f) the importance of maintaining euthyroidism throughout pregnancy, regardless of the therapy chosen, with frequent contacts with the medical and obstetrical team. For women undergoing antithyroid drug therapy and accepting the potential risk of congenital malformations, it would be prudent to select PTU before conception and consider switching to MMI after the first trimester.

In summary, there is clear evidence from most studies published in the past few years, that both MMI/CMZ and PTU given in the first trimester of pregnancy present an unacceptable risk for congenital malformations. Thyroid ablation before pregnancy is an attractive therapeutic choice; surgery should be strongly considered in women with a relatively high serum TRAb titer. Recently, an allergic reaction to PTU at 7 weeks of gestation developed in one of my patients with recurrent hyperthyroidism who was in her second pregnancy; MMI was started a few days after the 10th week of gestation. The infant was born with a mild congenital defect in both ears. Therefore, the possibility of an allergic reaction to PTU should also be considered and discussed with the patient.

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Patients with Differentiated Carcinoma Are at increased Risk for Cardiovascular and All-Cause Mortality

Elizabeth N. Pearce

Klein Hesselink EN, Klein Hesselink MS, de Bock GH, Gansevoort RT, Bakker SJ, Vredeveld EJ, van der Horst-Schrivers AN, van der Horst IC, Kamphuisen PW, Plukker JT, Links TP, Lefrandt JD. Long-term cardiovascular mortality in patients with differentiated thyroid carcinoma: an observational study. J Clin Oncol 2013;31:4046-53. Epub October 7, 2013.

SUMMARY

Background

Because of the high survival rate of patients with differentiated thyroid cancer, potential long-term effects of cancer treatment are of concern. Although increased cardiovascular risk has been reported in patients with subclinical hyperthyroidism, to date TSH-suppressive thyroid hormone therapy has not been associated with increased mortality in thyroid cancer survivors (1-4).

Methods

This is a retrospective study using thyroid cancer cases from one cohort and general population controls from a second cohort. Cases were patients, 26 to 77 years of age, treated with thyroidectomy and radioactive iodine ablation for differentiated thyroid cancer at Groningen University Medical Center in the Netherlands between 1980 and 2010. Of 606 potentially eligible cases with differentiated thyroid cancer, 82 were excluded because of missing data and 110 were lost to follow-up. Three sex- and age-matched controls were randomly selected for each case from the general population subsample of the Prevention of Renal and Vascular End Stage Disease (PREVEND) study cohort, a prospective study conducted in the same region of the Netherlands. A total of 1572 controls were selected, and 1277 completed follow-up. Until 2007, thyroid hormone doses for all cancer cases were targeted to a goal TSH less than the reference range. Starting in 2007, the TSH target in low-risk patients was <0.1 mIU/L for the first 2 years, followed by a goal level of 1.0 mIU/L. Starting in 2007, the goal TSH for high-risk cancer cases was <0.01 mIU/L.

Causes of death were classified as due to cardiovascular disease, progression/recurrence of thyroid cancer, or other/unknown. The primary outcome was cardiovascular mortality. Secondary outcomes were all-cause mortality and associations between TSH-suppressive thyroid hormone therapy and outcomes. Causes of mortality for the cancer cases were determined from medical records and contact with physicians, whereas mortality for the controls was ascertained using Statistics Netherlands. Baseline was defined as the date of thyroid cancer diagnosis for the cases and the date of PREVEND entry for the controls. Cardiovascular risk factors were ascertained at baseline, including age, sex, body-mass index, use of diabetes medications, smoking status, use of antihypertensive medications, use of antihyperlipidemic medications, and history of cardiovascular disease (defined as a previous stroke, myocardial infarction, peripheral-artery disease, or revascularization procedure). Patients with thyroid cancer were classified as low-risk (TNM staging Tx-T2Nx-N0Mx-M0), intermediate risk (T_3 or N1), or high risk (T_4 or M1). Cumulative radioactive iodine doses and use of adjuvant external neck radiotherapy were ascertained for all patients with thyroid cancer.

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Patients with Differentiated Carcinoma Are at increased Risk for Cardiovascular and All-Cause Mortality

Elizabeth N. Pearce

Cox proportional-hazards regression, Kaplan–Meier survival analyses, and log-rank tests were used for analyses. Both crude and multivariate analyses were performed. For analyses of associations between TSH suppression and event-free survival, the geometric mean TSH values for each year of follow-up, excluding values resulting from periods of thyroid hormone withdrawal or use of recombinant human TSH, were used as predictors, and mean annual TSH was categorized as <0.02, 0.02 to 0.2, and >0.2 mIU/L.

Results

At baseline, treated diabetes (4.2% vs. 2.5%) and hypertension (17.7% vs. 11.5%) were more common among the cancer cases than among controls, and the patients with cancer were less likely to be current smokers (22.9% vs. 29.7%). The 414 patients were followed for a median of 8.5 years, during which time 22 died of cardiovascular disease, 39 of thyroid cancer, and 39 of other causes. The 1277 controls were followed for a median of 10.5 years, during which time 24 died of cardiovascular disease and 61 of other causes. Cardiovascular (P = 0.012) and all-cause (P<0.001) mortality were higher in the cases than in the controls. The hazard ratio for cardiovascular mortality in the cases compared with controls, adjusted for age, sex, and cardiovascular risk factors, was 3.35 (95% CI, 1.66 to 6.74) and the adjusted hazard ratio for all-cause mortality was 4.40 (95% CI, 3.15 to 6.14). For every 10-fold decrease in serum TSH, the hazard ratio for cardiovascular mortality, adjusted for age, sex, cardiovascular risk factors, thyroid cancer risk classification, cumulative radioactive iodine dose, tumor histology, and use of external-beam neck radiotherapy was 3.08 (95% CI. 1.32 to 7.21). After adjustment, mean TSH was not significantly associated with all-cause mortality.

Conclusions

Differentiated thyroid cancer was associated with an increased risk for cardiovascular and all-cause mortality, even after adjustment for age, sex, and cardiovascular risk factors. Lower serum TSH levels in the patients with thyroid cancer were associated with increased cardiovascular mortality risk.

ANALYSIS AND COMMENTARY

This is the first study to demonstrate increased cardiovascular mortality risk in patients with differentiated thyroid cancer. The cardiovascular risk was inversely associated with levels of serum TSH. Although not explored in this study, potential mechanisms for this association are increased incidence of atrial fibrillation, impaired diastolic function, and increased left ventricular mass in patients receiving TSH-suppressive thyroid hormone doses.

Strengths of the study include the relatively large sample size, long duration of follow-up, and adjustment for important risk factors. Limitations include the use of retrospective data (leading to limited information about some covariates, such as the use of antidiabetic medications as a proxy for the presence of diabetes), the use of two different cohorts with different mortality surveillance mechanisms, and substantial losses (19% to 21%) to follow-up. Future prospective cohort studies are needed to better understand predictors of cardiovascular risk among thyroid cancer survivors.

These data support the restriction of more stringent TSH suppression to patients with higher-risk thyroid cancers. The 2009 American Thyroid Association (ATA) thyroid cancer guidelines advocate initial TSH suppression to <0.1 mIU/L in high- and intermediate-risk patients, and to 0.1 to 0.5 mIU/L in low-risk patients (5). For long-term treatment, the guidelines recommend that TSH should be maintained at <0.1

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mIU/L indefinitely in patients with persistent disease. In those who presented with high-risk disease, but who become clinically and biochemically disease-free, TSH should be maintained at 0.1 to 0.5 mIU/L for 5 to 10 years. For low-risk patients who appear to be free of disease, the serum TSH may be allowed to rise to 0.3 to 2.0 mIU/L. Revised ATA thyroid cancer guidelines are currently in development and may provide additional guidance regarding risk stratification in the use of TSH suppression.

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The Risk of Papillary Thyroid Cancer Is Increased Among First- to Third-Degree Relatives

Angela M. Leung*

Oakley GM, Curtin K, Pimentel R, Buchmann L, Hunt J. Establishing a familial basis for papillary thyroid carcinoma using the Utah population database. JAMA Otolaryngol Head Neck Surg. October 3, 2013 [Epub ahead of print].

SUMMARY

Background

The incidence of thyroid cancer—the most common endocrine cancer, mainly composed of papillary thyroid cancer (PTC; ~80%)—has increased worldwide over the past several decades. Known risk factors for thyroid cancer include a history of head and neck radiation, iodine deficiency or excess, and other thyroid disease. Although most cases of PTC are sporadic, a small proportion may be genetically linked. The objective of this study was to assess the familial risks of PTC using a large population database.

Methods

This retrospective case–control study assessed familial patterns of PTC using the Utah Population Database from 1966 through 2011. The database contained 6.5 million patient records linked to the state's cancer records obtained from the Surveillance, Epidemiology, and End Results (SEER) database. Cases of PTC identified by International Classification of Diseases (ICD) codes were matched with controls by sex, year of birth, and place of birth in a ratio of 5:1, and assessed for the incidence of PTC diagnosed among first- through fifth-degree relatives.

Results

There were 4460 patients (78% women; mean [±SD] age at diagnosis, 44±15.9 years) with PTC during the study period. The odds ratios of PTC were increased among relatives of the index cases: 5.35 (95% CI, 4.4 to 6.5) in first-degree relatives, 2.24 (95% CI, 1.8 to 2.8) in second-degree relatives, and 1.76 (95% CI, 1.5 to 2.1) in third-degree relatives. The risks of PTC were not increased among fourth- to fifth-degree relatives or in the spouses of the probands.

Conclusions

In this large U.S.-based population research database, there was a fivefold increased risk of PTÇ among first-degree relatives of index cases; smaller but still significant risks were also observed among second- and third-degree relatives.

ANALYSIS AND COMMENTARY

The genetic susceptibility of a small proportion of nonmedullary thyroid cancer (NMTC) cases, excluding syndromic causes, is well known. Several studies have shown that familial NMTC, which accounts for 3% to 10% of all NMTC cases (1), is associated with increased risks of up to approximately eightfold among first-degree relatives. The major limitation among these previous studies was their inclusion of multiple subtypes of thyroid cancer. In the current study assessing only PTC, similarly increased risks, up to fivefold, were observed among first- to third-degree relatives.

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The Risk of Papillary Thyroid Cancer Is Increased Among First- to Third-Degree Relatives

Angela M. Leung

The strengths of this study include its large size, long duration of follow-up, and confirmation of thyroid cancer diagnoses using a comprehensive population research database and statewide cancer registry records. Although these data suggest a hereditable basis for a minority of PTC cases, these data were assessed using the population of one state, in which the incidence of thyroid cancer is relatively low, although the incidence in Utah was comparable and even slightly higher than national SEER data from 2006 to 2010 (2). In addition, the controls were matched using the general population, rather than individuals with known thyroid nodules, who would have represented a more comparable group with a similar risk of malignancy. Finally, although the findings suggest a familial basis for a proportion of PTC, further research is needed to elucidate whether these risks are truly based on genetic predisposition, perhaps through use of molecular markers and multi-institutional collaborations linking familial data, rather than a clustering of sporadic PTC cases.

*David Geffen School of Medicine, University of California at Los Angeles

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Next-Generation Sequencing Has Identified New Oncogenic Mutations in Thyroid Nodules

Jerome M. Hershman

Nikiforova MN, Wald AI, Roy S, Durso MB, Nikiforov YE. Targeted next-generation sequencing panel (ThyroSeq) for detection of mutations in thyroid cancer. J Clin Endocrinol Metab 2013;98:E1852-60. Epub August 26, 2013.

SUMMARY

Background

Detection of oncogenic mutations is becoming very important for the diagnosis of thyroid cancer in nodules. Ideally the oncogenes are found in thyroid fine-needle aspiration (FNA) biopsy material, especially when the cytologic diagnosis is in the indeterminate category, because the oncogenes will confirm the diagnosis of cancer. The current report shows the application of a new method called "next-generation sequencing" (NGS), with the aim of detecting most point mutations and small insertions or deletions known to occur in thyroid cancer.

Methods

NGS provides simultaneous analysis of large regions of the genome with a high sensitivity for detection of mutations and quantitative assessment of mutant alleles. Using this method, the authors studied 228 thyroid neoplastic and nonneoplastic specimens, including 57 papillary thyroid carcinomas (PTCs) (27 classical PTCs and 30 follicular variant of papillary carcinomas [FVPTCs]), 36 follicular carcinomas (18 conventional and 18 oncocytic), 10 poorly differentiated carcinomas, 27 anaplastic carcinomas, 15 medullary carcinomas, 83 histologically benign hyperplastic nodules, and 51 FNA samples from nodules that were subsequently resected .

Results

BRAF, TP53, or NRAS mutations were detected with a sensitivity that corresponds to 6% of cells with heterozygous mutation. Altogether, 115 mutations were detected in 228 thyroid specimens tested, including 110 mutations in 145 cancer samples and 5 mutations in 83 benign nodules. Most cancers contained a single mutation, but several contained multiple mutations.

In 19 classical PTCs, BRAF mutation was found in 16, PIK3CA in 3, TP53 in 2, and NRAS in 1. In FVPTC, RAS mutations were the most common. In follicular cancers, mutations included RAS, TSHR, TP53, and PTEN. A total of 74% of anaplastic thyroid cancers were found to have mutations, including TP53, BRAF, RAS, PI3KCA, PTEN, and CTNNB1, and 73% of 15 sporadic medullary thyroid cancers contained either RET or RAS mutations. Most mutations in the tumor samples were heterozygous with allele frequencies that corresponded to 40% to 96% of cells with a heterozygous mutation.

Only 5 of 83 benign hyperplastic nodules contained mutations, of which 2 were TSHR. DNA sufficient for the sequencing method was found in 50 of 51 FNA samples.

Conclusions

NGS allows simultaneous testing for multiple mutations with high accuracy and sensitivity and requires only a small amount of DNA. Point mutations were detected in 30% to 83% of specific types of thyroid cancer and in only 6% of benign thyroid nodules.

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Next-Generation Sequencing Has Identified New Oncogenic Mutations in Thyroid Nodules

Jerome M. Hershman

ANALYSIS AND COMMENTARY

This new method for genotyping thyroid tissue, including FNA samples, expands the repertoire of oncogenic mutations that have been used up to this time (1). It has led to the discovery of uncommon mutations, such as PTEN, TP53, PI3KCA, and TSHR. Activating mutations of the TSH receptor (TSHR) were reported previously in hot nodules (2). With the addition of these mutations to those of BRAF, RAS, and the PAX8/PPARg and RET/PTC rearrangements (now called "gene fusions"), 80% of thyroid cancers are now believed to have detectable mutations. When these mutations are added to the commercial panel of oncogenes, it is likely that a very high proportion of thyroid cancers will be detectable by NGS.

It is pertinent that the authors of this paper in the Nikiforov laboratory continue to be the leaders in this field. This was especially evident at the recent meeting of the American Thyroid Association.

Because of cost considerations, the main use of NGS may be restricted to indeterminate biopsies that now constitute the two categories of follicular lesion of undetermined significance and follicular neoplasm, according to the Bethesda classification of FNA cytology. However, reduction of cost by competition and by further improvements in sequencing may eventually permit extensive use of NGS on virtually all FNA biopsies.

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Telomerase Reverse Transcriptase (TERT) Mutations Are Common in Advanced Thyroid Cancer

Jerome M. Hershman

Landa I, Ganly I, Chan TA, Mitsutake N, Matsuse M, Ibrahimpasic T, Ghossein RA, Fagin JA. Frequent somatic TERT promoter mutations in thyroid cancer: higher prevalence in advanced forms of the disease. J Clin Endocrinol Metab 2013;98:E1562-6. Epub July 5, 2013; doi: 10.1210/jc.2013-2383.

SUMMARY

Background

Thyroid cancers contain oncogenic mutations that are considered "driver mutations" because they play a key role in the disordered proliferation and metastasis of the cancer. TERT encodes the reverse transcriptase component of telomerase, which adds telomere repeats to chromosome ends, thereby enabling cell replication. This paper shows that specific mutations in TERT are frequently found in thyroid cancers and may occur concurrently with mutations in the MAP kinase pathway.

Methods

The study included 183 thyroid tumors and 42 human thyroid cancer cell lines. DNA from the samples was tested by PCR for two mutations in the proximal promoter of TERT, C228T and C250T, as well as for mutations in BRAF and RAS.

Results

TERT mutations were found in 22% of papillary thyroid cancers (PTCs), 51% of advanced thyroid cancers, 23% of widely invasive Hürthle-cell cancers, and 86% of the thyroid cancer cell lines. There was a more frequent co-occurrence of TERT mutations with advanced thyroid tumors harboring BRAF and RAS mutations as compared with those that did not have these mutations. Only one of the two TERT mutations was found in a given tumor.

Conclusions

TERT mutations are highly prevalent in advanced thyroid cancers, especially those with BRAF or RAS mutations.

ANALYSIS AND COMMENTARY

TERT mutations have been found in some melanomas and glioblastomas. Acquisition of the TERT mutation could extend the life span of the tumor cell and thus provide time for other mutations to develop. Concurrently with this paper, the laboratory of M. Xing published a report on TERT mutations in thyroid cancer with similar findings with regard to prevalence (1). The Xing laboratory found that the C228T was much more common than the C250T mutation. During a presentation at the recent meeting of the ATA, Xing reported that tumors with both BRAF and TERT mutations had a much higher recurrence rate as compared with tumors that had only one of these mutations (2). It is likely that the two TERT mutations will become part of a panel of mutations that are detected in thyroid nodule FNAs by next-generation sequencing, as noted in the previous article in this issue.

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Can We Predict the Presence of Central Neck Nodal Metastasis in Patients with Papillary Thyroid Cancer?

Cord Sturgeon

Thompson AM, Turner RM, Hayen A, Aniss A, Jalaty S, Learoyd DL, Sidhu S, Delbridge L, Yeh MW, Clifton-Bligh R, Sywak M. A pre-operative nomogram for the prediction of ipsilateral central compartment lymph node metastases in papillary thyroid cancer. Thyroid. October 1, 2013 [Epub ahead of print].

SUMMARY

Background

Papillary thyroid cancer (PTC) has a high rate of central nodal metastasis at the time of diagnosis. Surgical series report an incidence of central nodal metastases of 20% to 80%. A therapeutic central neck dissection is appropriate when there is clinical suspicion or pathologic confirmation of central neck nodal metastasis. Because central nodal metastases may be difficult or impossible to detect by sonographic, radiologic, or clinical means, a method to predict the status of the central compartment using preoperative clinical characteristics may be valuable.

Methods

Retrospective analysis of a database made up of prospectively collected data from a single institution was performed. A total of 1589 subjects who underwent an index operation for PTC between 1968 and 2012 were identified. Of these, 914 patients were identified who underwent a total thyroidectomy and removal of central neck nodes (either selectively or prophylactically). In 84% of cases the nodes were ipsilateral only. Clinical factors and tumor features were evaluated for their ability to predict the nodal status of the central compartment through a linear regression model. Internal and external validation of the data set was performed.

Results

The rate of central nodal metastases was 43%. The mean maximum tumor diameter was 17.4 mm. Age, sex, tumor size, and multifocality were associated with central nodal status. Young and old age were associated with nodal metastasis (U-shaped curve). Men were 2.3 times more likely to have nodal metastases than women. Tumor size had a linear positive relationship to central nodal metastases; the rate was 60% for cancers greater than 5 cm.

Conclusions

Because prophylactic central neck dissection may increase the risk of surgical complications in exchange for marginal benefits in recurrence, and because radiologic studies and physical exam do not detect the presence of central neck nodal metastases well, there is benefit in preoperative risk stratification to guide decisions on how to manage the central compartment. Data from this study were used to create a nomogram that predicts the presence of central nodal metastases. A smart phone application was developed for the distribution of this nomogram.

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Can We Predict the Presence of Central Neck Nodal Metastasis in Patients with Papillary Thyroid Cancer?

Cord Sturgeon

ANALYSIS AND COMMENTARY

There is considerable controversy regarding the role of prophylactic central neck dissection in PTC. Some experts believe that prophylactic nodal dissection will reduce the central compartment recurrence rate and therefore they perform it routinely. Many reports have attempted to weigh the risks of prophylactic central neck dissection (specifically an increased risk of recurrent laryngeal-nerve injury and hypoparathyroidism) with the benefits of the reduction of central compartment metastases. Reoperative central neck dissection is believed to be more risky than a central neck dissection performed during the index operation for thyroid cancer. For all of these reasons, the limitation of central neck dissection to cases in which the probability of nodal metastases is highest is a meritorious goal. The criticisms of this study are that the authors did not discriminate between macroscopic and microscopic nodal metastases, which are believed to portend different clinical risks. In addition, the preoperative sonographic detection of multifocality may not be possible in many cases. The sonographic evaluation of the thyroid focuses on the dominant or most suspicious lesions in the thyroid and may fail to describe smaller, less clinically relevant lesions. If the application of this nomogram could reduce the probability of missing clinically significant nodal metastases and limit the number of patients who have to face the added risks of central neck dissection (including revisional central neck dissection), then it will prove to be useful in clinical practice. A number of other nomograms exist to aid the thyroid surgeon, including those that predict postoperative hypocalcemia (1), predict the need for performing FNA of a thyroid nodule (2), predict malignancy in thyroid nodules (3), and predict the probability of death from thyroid cancer (4). All nomograms should be used as a supplement to clinical knowledge and not as a substitute for clinical judgment or common sense.

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THYROID CANCER TUMOR BOARD

Discordant Cytopathological Diagnosis of Well-Differentiated Thyroid Cancer Affects Patient Treatment

Wendy Sacks

CASE SUMMARY

A teenage girl had been diagnosed with Hashimoto's thyroiditis and a thyroid nodule about 2 years ago. She has a family history of autoimmune thyroid disease, and a grandmother also had a goiter. Her thyroid function was normal on presentation. A neck ultrasound revealed a 3-cm nodule Fine-needle aspiration under ultrasound guidance was performed and cytology was consistent with follicular lesion of undetermined significance (FLUS). She sought several opinions for management of this nodule, and ultimately a decision was made to monitor it. Nine months later, a repeat ultrasound demonstrated growth of the nodule that then measured 4 cm in maximum dimension (Figure 1). A repeat biopsy with molecular testing revealed follicular neoplasm, benign Afirma gene expression classifier and negative MiRInform molecular panel. Because of the increase in nodule size and indeterminate cytology, a hemithyroidectomy was performed. Surgical pathology demonstrated a 4.5-cm minimally invasive follicular thyroid carcinoma (FTC) with a focus of vascular invasion. The margins were free of tumor. Also noted were foci of cellular architectural atypia, including insular and/or solid patterns.

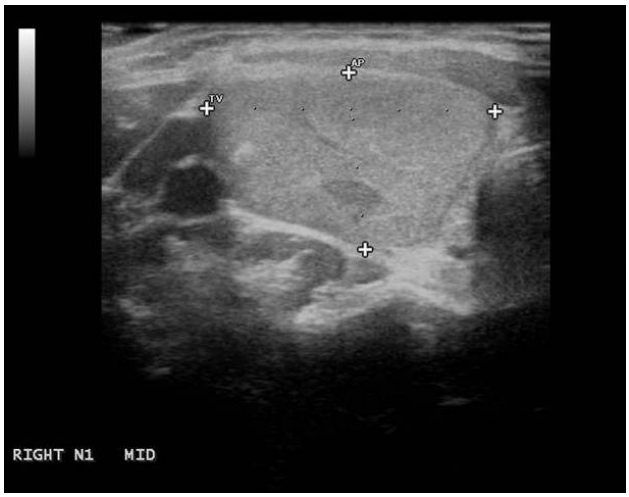

Figure 1. Transverse view of right thyroid nodule that measures 1.8 by 1.9 by 4 cm. The nodule is well circumscribed and has a heterogeneous echotexture, without evidence of suspicious ultrasound features such as microcalcifications or internal vascularity.

A young patient with minimally invasive FTC typically has an excellent prognosis, but the focus of vascular invasion and insular components suggest a more aggressive tumor. The family requested a second review of the pathology, which was sent to an international expert. The second reviewer agreed with the assessment, reporting "We are dealing with a carcinoma of follicular cells which exhibits both capsular and vascular invasion. The latter is rather impressive in the sense of involving a large vessel located well outside the capsule of the tumor and attached to the wall of the vessel. There is also evidence of capsular invasion in adjacent areas." He continues, "the other important point relates to a focal insular pattern of growth, focal mitotic activity, and necrosis. I believe that these features are those of a poorly differentiated carcinoma focally developed within a better-differentiated lesion. My diagnosis therefore is follicular carcinoma with capsular and vascular invasion and poorly differentiated foci. This tumor is likely to follow an aggressive clinical course."

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THYROID CANCER TUMOR BOARD: Discordant Cytopathological Diagnosis of Well-Differentiated Thyroid Cancer Affects Patient Treatment

Wendy Sacks

The patient underwent a completion thyroidectomy; there was no thyroid cancer in the contralateral lobe. Her family sought multiple opinions as to whether she should have postoperative treatment with radioactive iodine (RAI). Recommendations ranged from treating with 100 mCi to treating with 50 mCi to no RAI treatment (hormone suppression alone). After much discussion about the risks and benefits of ^{131}I, the family opted for the 100-mCi dose. Just before the treatment, the patient sought another opinion; during slide review, the pathological diagnosis changed to encapsulated FVPTC [follicular variant papillary thyroid carcinoma] without capsular involvement.

ANALYSIS AND DISCUSSION

The discrepancy between opinions in the interpretation and diagnosis of surgical pathology for thyroid cancer among intrainstitutional reviewers and interinstitutional reviewers has been well documented in the literature, with rates of discordance of up to 83%. Notably, this can have a significant impact on the treatment of the patient (1, 2). In one retrospective review of 66 thyroid cancer cases by pathologists at the Institute of Pathology at Leeds, there was an 18% discrepancy in the diagnosis of 66 thyroid cases diagnosed between January 2001 and March 2003 (1). The changed diagnoses altered treatment in 5 of 12 patients and altered prognosis in all 12.

An area of particular difficulty is the diagnosis of follicular thyroid adenoma (FA), follicular thyroid carcinoma (FTC) and the follicular variant of PTC (FV-PTC) (1, 3). FTCs are divided into two major categories based on the degree of invasiveness: minimally invasive FTC and widely invasive FTC. The differential diagnosis of minimally invasive FTC includes FV-PTC, the most common subset of papillary carcinoma, found in up to 56% of patients, depending on the geographic area (4, 5). FV-PTC is almost exclusively arranged in follicles lined by cells with characteristic papillary carcinoma nuclei. Furthermore, there are two categories of FV-PTC, encapsulated and invasive. Nuclear features encountered in follicular nodules often show some, but not all, of the nuclear features of PTC, making a clear-cut diagnosis of minimally invasive FTC or FV-PTC difficult. (3). A Mayo Clinic study in which 10 expert pathologists reviewed 87 cases initially diagnosed as FV-PTC (n = 84), FA (n = 2), and FTC (n = 1) demonstrated observer variability. There was 39% concordance from 10 expert pathologists after review of the same slides; concordance improved to 66.7% for cases with metastatic disease (6).

In addition to a similar invasive pattern (or lack thereof), encapsulated FV-PTC and minimally invasive FTC have other similarities. They rarely metastasize to lymph nodes (only 5% of cases), and the molecular profile is similar (Table 1). Encapsu-

Table 1. Histologic, Clinical and Molecular Profile of Encapsulated FV-PTC and Invasive FV-PTC.

Characteristic	Encapsulated FV-PTC	Nonencapsulated/Invasive FV-PTC
Invasiveness	Absent	Present
Lymph-node metastases	Rare	Common
Molecular testing	RAS, PAX8PPARγ	BRAF, RAS, RET/PTC
Overall genotype and phenotype most similar to:	FA/FTC	PTC

lated FV is close to the follicular carcinoma group of tumors, with a high prevalence of RAS mutation and very low BRAF mutation rate. Of 47 cases (28 encapsulated FV and 19 infiltrative FV) retrospectively reviewed at Memorial Sloan-Kettering from 1980 to 2002, a total of 11 of the 28 encapsulated FV had a mutation (10 RAS and 1 PAX8PPARγ) and 9 of 19 of the infiltrative FV group harbored a mutation (5 BRAF, 2 RAS, 2 RET/PTC) (7, 8). While molecular genotyping can better classify these tumors into clinically relevant entities, morphologic examination and interpretation remains the final determinant of categorization in a majority of cases.

Liu et al. at Memorial Sloan-Kettering reviewed prognoses for FV-PTC in a series of 78 patients between 1980 and 1995 (9). Sixty-one patients had encapsulated FV and 17 had nonencapsulated FV. Patients with the encapsulated FV-PTC had the following characteristics: 98% negative margins, 5% lymph-node involvement, 5% extrathyroidal extension, 16% lymphovascular invasion, 14% capsular invasion, and no distant metastases. Over a median follow-up of 11 years, none of the 42 patients with noninvasive, encapsulated FV-PTC had recurrences or metastases or died of disease. These authors suggest that noninvasive, encapsulated FV-PTC should denote a benign clinical behavior and propose that patients with this variant may be treated with lobectomy (9).

While unanimity among diagnostic consultants is ideal, patients should know that a difference of opinion is quite common among experts. It does not mean that a mistake has been made, but undertreatment and overtreatment can occur, depending on the diagnosis.

Conclusions

The young patient described above had a growing mass with an indeterminate preoperative diagnosis and negative molecular panel. Postoperative surgical pathologic review by the local institution and an outside expert reviewer first suggested a potentially aggressive 4.5-cm follicular thyroid carcinoma with vascular and capsular invasion. A third review at a different institution revealed encapsulated, noninvasive FV–PTC, a diagnosis which has a benign clinical course. Many reports in the literature identify interobserver variability in pathologic interpretation particularly for follicular carcinomas and follicular variants of papillary thyroid cancer. Changes in clinical management occur in a significant percentage of cases depending on the pathology. Perhaps Next-Gen Sequencing (see Hershman review) will enable further diagnostic certainty preoperatively to assist in guiding management for these cases. Rather than the 100-mCi dose of ^{131}I recommended for FTC, our patient received 30 mCi of ^{131}I at the outside institution for FV-PTC. The posttreatment scan showed iodine uptake in the thyroid bed only, consistent with residual thyroid tissue.

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Clinical THYROIDOLOGY
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CASE REPORT

A Hydatidiform Mole Can Cause Severe Gestational Hyperthyroidism

Shalini Bhat and Jelena Maletkovic*

OBJECTIVE: To report a new case of molar pregnancy associated with severe thyrotoxicosis.

Background

Gestational trophoblastic disease (GTD) is a rare complication of pregnancy that may be associated with thyrotoxicosis. The incidence of hydatidiform mole in the United States and other developed countries is about 1 in 1500 live births (1). Complete moles have the highest incidence of thyrotoxicosis, predominantly affect younger women, and present with vaginal bleeding most of the time. Hyperthyroidism in hyperemesis gravidarum occurs with greater frequency than in normal pregnancy. We describe a case of hyperthyroidism secondary to molar pregnancy highlighting the rare but important evaluation of hyperthyroidism in women of child-bearing age.

Case Report

A 20-year-old woman, gravida 2, para 1, presented to the emergency room with a history of nausea, weight loss of about 20 lb in 6 weeks, and intermittent vaginal bleeding. On examination, she had tachycardia (108 BPM), a blood pressure of 146/86 mm Hg, and a regular respiration rate of 18 breaths per minute. There was no exophthalmos, and her extraocular movements were normal. The thyroid gland was palpable and of normal size. Cardiovascular examination revealed sinus tachycardia without murmurs, rub, or gallops. Breath sounds were equal bilaterally, without rhonchi or wheezes. There was no peripheral edema. The size of the uterus was compatible with a 12-week gestation.

Ultrasonography of her enlarged uterus revealed that the uterine cavity was significantly distended and filled with an echogenic soft-tissue mass that had small cystic components, most compatible with complete molar pregnancy. Her thyroid-function tests were found to be markedly elevated (Table 1). Her thyrotropin (TSH) was <0.07 mIU/ml (normal range, 0.3 to 4.2), free thyroxine (FT_4) 5.59 ng/dl (normal range, 0.8 to 2.0), triiodothyronine (T_3) 465 ng/dl (normal range, 40 to 180), and human chorionic gonadotropin (hCG) close to 2 million mIU/ml. Laboratory data on admission revealed microcytic hypochromic anemia

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Table 1. Thyroid-Function Tests

	Day 1	Day 2 (Immediately after Dilatation and Curettage)	Day 2	Day 3 (1 Day after Dilatation and Curettage)
TSH (0.3–4.2 mIU/ml)	<0. 07	<0.10	<0.10	<0.07
FT_4 (0.8–2.0 ng/dl)	5.59	4.17	3.57	3.03
T_3 (40–180 ng/dl)	465	344	257	226
hCG	1,978,770	836,500		580,378

and elevated transaminase and alkaline phosphatase. The remainder of her electrolytes, complete blood count, and platelets were normal. Her electrocardiogram showed sinus tachycardia.

The patient underwent dilatation and curettage for evacuation of the mole. During the postoperative period respiratory failure secondary to noncardiogenic pulmonary edema developed. She required intubation and had a prolonged hospitalization but then stabilized and was discharged in good condition. Histopathology of all aborted specimens verified the diagnosis of partial mole, including a dystrophic fetus. The hCG values decreased to below detection after 12 weeks, and she was euthyroid at follow up with free T_4 of 1.1 ng/dl and TSH of 1.42 mU/l.

DISCUSSION AND CONCLUSIONS

GTD with thyrotoxicosis is a rare clinical scenario, but thyroid hyperstimulation by hCG can have severe clinical consequences. Complete hydatidiform mole most commonly presents with vaginal bleeding, occurring at 6 to 16 weeks of gestation in 80% to 90% of cases (1). The clinical signs and symptoms, such as hyperemesis, have occurred less frequently in more recent years because of earlier diagnosis resulting from widespread use of ultrasonography and accurate tests for hCG. In the past, approximately 55% to 60% of women with trophoblastic disease had clinically evident hyperthyroidism that could be severe at the time of diagnosis. However, in a review of 196 patients from the United Kingdom treated for gestational trophoblastic disease between 2005 and 2010, biochemical hyperthyroidism was present in 7% and clinical hyperthyroidism in only 2% (2). Hydatidiform moles are commonly associated with hCG levels markedly elevated above those of normal pregnancy, as can be seen in our patient, who had an hCG level close to 2 million mIU/ml. Approximately 50% of patients with molar pregnancy have preevacuation hCG levels >100,000 mIU/ml (3).

Tisne et al. reported the first case of clinical hyperthyroidism in a patient with hydatidiform mole in 1955 (4). The glycoprotein hormone hCG is a specific tumor marker for trophoblastic diseases. The analogy in the structure between hCG and TSH can cause cross-reactivity with their receptors. It has been shown that the homology in the hCG and TSH molecules, as well as in their receptors, is likely to be responsible for the cross-reactivity of hCG with the TSH receptor (5). Glinoer has estimated that "for every 10,000 mU/mL increase in serum hCG, FT_4 increases by 0.1 ng/dL and TSH decreases by 0.1 mIU/mL" (6). Molecular variants of hCG found in molar pregnancies have increased thyrotropic potency (7). When gestational trophoblastic disease causes a significant rise in hCG levels, it may induce hyperthyroidism that requires treatment. As expected, thyrotoxicosis resolves with treatment of GTD and normalization of hCG levels. The development of hyperthyroidism is largely influenced by the level of hCG and usually resolves with treatment of GTD. The consideration of this cause of hyperthyroidism in pregnancy should be diagnosed early and managed efficaciously before imminent dilatation and curettage is required for definitive management of the hydatidiform mole.

*Endocrinology Division, UCLA School of Medicine, Los Angeles, CA

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Letter: Desiccated Thyroid Extract Causes Nonphysiologic T_3 Peaks

To the Editor:

Hoang and associates once again raise the old question of a possible place for animal sources of desiccated thyroid extract (DTE) in the treatment of hypothyroidism (1). They stimulate new discussion but do not seem to break new ground. Of the 70 patients in their 16-week crossover study comparing DTE with l-thyroxine (L-T_4), 49% preferred DTE and reported a subjective improvement in quality of life, although there were no statistically significant differences between the groups on psychometric testing. Those preferring DTE also had a 3- to 4-lb weight loss, but started with higher mean body weights than those in the L-T_4 group (178.95 lb vs. 162.80 lb). Thyroid biochemical tests were within normal ranges in both groups. However, serum T_3 levels were statistically higher ($P<0.001$) in the subjects who preferred DTE when measured just before the once-daily dose of DTE (at the expected daily nadir). In the only 2 subjects given DTE who had T_3 measured both before and again 3 hours after DTE administration (near the expected T_3 peak levels) serum T_3 rose 23% and 36%. Such nonphysiologic changes in serum T_3 after DTE administration and resultant risks have long been known (2) and are the subject of concern (3). While Hoang et al. do briefly mention possible cardiovascular risks from these T_3 changes in the body of their report and in their supplementary data, they do not comment on such risks in their abstract, nor do they discuss potential adverse effects on bone turnover at all.

Exploring a role for DTE in the treatment of hypothyroidism with a well-designed, blinded, randomized clinical trial is laudable. However, when evaluating a therapy for a condition that affects millions of patients and for which an effective treatment already exists (4), this clinical trial should be powered and designed to detect adverse consequences. When the goal is physiologic replacement, care also needs to be exercised that normal physiology is restored. The study of Hoang and colleagues is provocative, but it does not achieve the minimum standard required to alter current clinical practice.

David S. Rosenthal, MD

Kenneth H. Hupart, MD

Division of Endocrinology, Diabetes and Metabolism
Nassau University Medical Center
East Meadow, NY

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American Thyroid Association (ATA)
Call for Proposals for Research Grants
Deadline: January 31, 2014

Electronic Submission: Proposals must be submitted electronically through the research grant application feature on the ATA website, www.thyroid.org beginning in early November 2013.

The American Thyroid Association (ATA) is pleased to announce the availability of funds to support new investigator initiated research projects in the area of thyroid function and disease. Topics may include, but are not limited to, Thyroid Autoimmunity, Iodine Uptake and Metabolism, Thyroid Cancer, Medullary Thyroid Cancer, Clinical Disorders of Thyroid Function, Thyroid Hormone Action and Metabolism, Thyroid Imaging, Thyroid Nodules and Goiter, Thyroid and Pregnancy, Thyroid Development and the Brain. Research awards are intended to assist new investigators, US or international, in obtaining preliminary data for submission of a more substantial application (e.g. to the National Institute of Health (NIH)). Research grants, up to $25,000 annually, will be awarded for up to two year terms. The second year funding is contingent on receipt and review of a satisfactory progress report from funded investigators in the fourth quarter of the first year of funding.

Guidelines for All Research Grant Proposals: As mentioned above, research awards are targeted for funding of new investigators to obtain preliminary data for submission of a more substantial application (e.g., to the NIH). Interested investigators should submit a brief description of the proposed research by January 31, 2014.

Eligibility of Applicant and Use of Funds Guidelines:
1. Individuals must be new investigators that are less than 6 years from completion of their post-doctoral fellowship and have never been a Principal Investigator (PI) on an NIH RO1 or equivalent grant (recipients of NIH R29, R21 and KO8 awards are eligible). Those who have a fellowship end date prior to 2008 are not eligible.
2. Faculty members (MD and PhD) are eligible; however, those investigators who have reached the rank of associate professor or higher are not eligible.
3. Postdoctoral fellows are eligible if their department provides written confirmation that at the time of the award the applicant will have a junior faculty position.
4. Students working towards an MD or a PhD are not eligible.
5. Investigators and individuals who have previously received ATA, ThyCa or THANC awards are not eligible.
6. Applications are limited to one per individual researcher.
7. The funds can be used for direct costs associated with the proposal, including technician's salary, supplies or equipment but not for PI's salary.
8. Applicants of ATA grants must be ATA members (submit application online if not already a member at www.thyroid.org).

Proposal Requirements:
1. Demographic information: Name /affiliation of applicant, complete work/home contact information – submitted into online system (do not include in grant proposal).
2. Grant Proposal (A short proposal that should be no longer than 900 words (including selected references) and no more than three double-spaced pages in 12 point type with 1" margins. These space requirements are absolute and nonconformance will preclude review. Do not include letterhead, name, address, institution, etc. This short proposal should include:
   - Title of proposed study
   - Background to the project
   - Hypothesis and/or outline of proposed studies
   - Outline of methodology
   - Anticipated results and implications
   - A short statement of how the grant will aid the applicant
   - Selected References (e.g. Uchino S, et al. World J Surg 2002;26:897-902)
3. CV (NIH-style CV – up to 4 pages) - including evidence that the applicant is a new investigator with date of completion of postdoctoral training and current grant support (if any). In the case of postdoctoral fellows, written confirmation that the applicant will have a junior faculty position at the time of the award, must be provided from the department chair. **Note: Without a suitable CV, applications will not be considered.**
4. Cover letter

Grant Review: The ATA Research Committee will rank proposals according to their scientific merit. Authors of selected proposals will be notified by March 30, 2014 and invited to submit a complete grant application.

An Invitation to Join the ATA

We invite you to join the American Thyroid Association (ATA). The leading worldwide organization dedicated to the advancement, understanding, prevention, diagnosis, and treatment of thyroid disorders and thyroid cancer, the ATA is an international individual membership organization with over 1600 members from 43 countries around the world. Celebrating its 90th anniversary, the ATA delivers its mission through several key endeavors: the publication of highly regarded monthly journals, ***THYROID***, *Clinical Thyroidology*, and *Clinical Thyroidology for Patients*; annual scientific meetings; biennial clinical and research symposia; research grant programs for young investigators; support of online professional, public, and patient educational programs through www.thyroid.org; and the development of evidence-based guidelines for clinical management of thyroid disease.

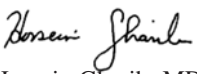
The annual meeting, held every fall, brings together over 1000 physicians and investigators from around the world to share the newest clinical and basic science research into thyroid disease. The meeting features posters, platform presentations, symposia, "meet the professor" workshops, discussion groups, and distinguished lectures. Awards are made to outstanding clinicians, academicians, young researchers, and dedicated Association members. Selected young investigators receive travel grants to attend the meeting. Every fifth year, the American Thyroid Association joins with the Latin American Thyroid Society, the European Thyroid Association, and the Asia Oceania Thyroid Association for an International Thyroid Congress.

Benefits of ATA membership include:

- **ATA Meetings:** The 84th Annual Meeting of the American Thyroid Association will be held October 29–November 2 in Coronado (San Diego), California, at the Hotel Del Coronado. The annual meeting engages you in collegial clinical and basic symposia, providing opportunities to interact with distinguished lecturers, gain insights on the latest research, and welcome our youngest members to the field.
- **ATA Guidelines:** Be a proud member of the leading thyroid organization developing clinical guidelines for the management of thyroid disease.
- **ATA Find a Thyroid Specialist:** ATA clinical members may choose to be listed in our online referral service (www.thyroid.org).
- **Access to Member Services:** Online access to member resources and the ATA membership directory, as well as leadership and governance resources including bylaws, announcements, and meeting minutes, are available 24/7.
- **ATA Publications:** *Thyroid* is one of the official journals of the ATA, published monthly, and includes peer-reviewed articles from physicians and scientists detailing the latest research in thyroid treatment and disease. *SIGNAL* is the ATA member newsletter which keeps you informed on upcoming meetings and public affairs issues, featuring highlights of the work of the Board and committees on your behalf. The online publications *Clinical Thyroidology* and *Clinical Thyroidology for Patients* offer summaries and reviews of the latest thyroid research. Coming soon in 2014, a new journal focused on *VideoEndocrinology* will be published online.
- **Patient Education Resources** explain thyroid disease in layman's language and support your clinical practice so that your patients are able to gain more understanding. *Clinical Thyroidology for Patients* is sent free to all "Friends of the ATA."
- **ATA Research**: The ATA offers 12 grants per year, six of which are funded by ThyCa: Thyroid Cancer Survivors, Inc. Two new grants in 2014 will be offered for developmental thyroidology and medullary thyroid cancer. Research by ATA members has led to important breakthroughs that have improved the lives of patients with thyroid diseases.

We look forward to welcoming you personally as a member at the next ATA meeting.

Sincerely,



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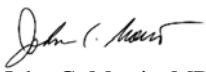

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American Thyroid Association
6066 Leesburg Pike
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Falls Church, VA 22041

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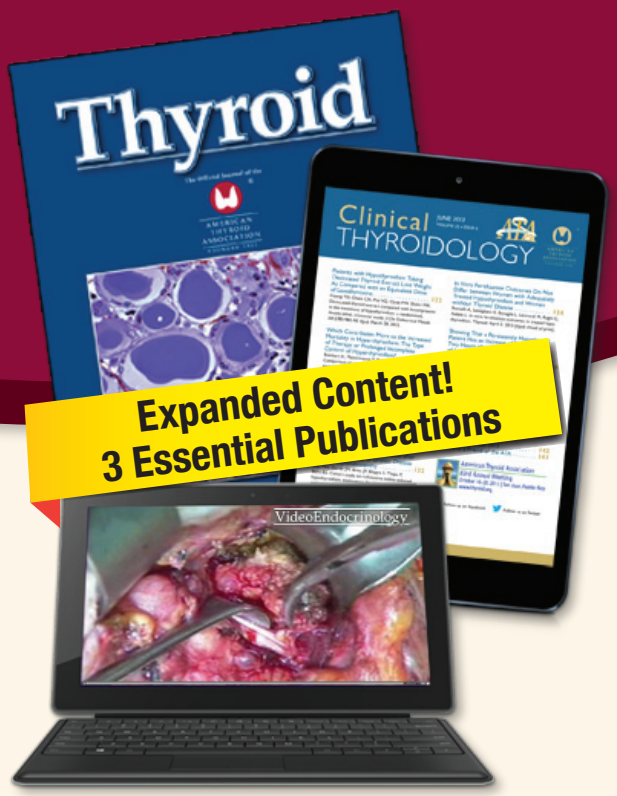

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The new design will provide quick and concise access to ATA's resources and education for members, the profession the public, and patients.

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Let your patients know that they can become Friends of the ATA by signing up to get the latest thyroid health information and to be among the first to know the latest cutting-edge thyroid research of importance to patients, their families and the public.

As a Friend of the ATA we will send you:

- *Clinical Thyroidology for Patients* -- This publication is a collection of summaries of recently published articles from the medical literature covering the broad spectrum of thyroid disorders.
- The Calendar of Events highlights educational forums and support groups that are organized by members of the Alliance for Thyroid Patient Education. The Alliance member groups consist of: the *American Thyroid Association,* the *Graves' Disease Foundation,* the *Light of Life Foundation* and *ThyCa: Thyroid Cancer Survivors' Association, Inc*.
- *Friends of the ATA e-news*, providing up-to-date information on thyroid issues, answers to thyroid questions from leading thyroid experts, and invitations to upcoming patient events.
- Updates on the latest patient resources through the ATA website and elsewhere on the World Wide Web.
- Special e-mail alerts about thyroid topics of special interest for patients and the public.

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The American Thyroid Association (ATA) is a nonprofit medical society composed of physicians and scientists who specialize in the research and treatment of thyroid diseases. Dedicated to improving the lives of the millions of Americans of all ages living with thyroid problems, we are strongly committed to serving as a resource for these patients and the public and to promoting the prevention, treatment, and cure of thyroid-related diseases.

With extensive online resources for thyroid patients, families, and the general public at *www.thyroid.org*, each year we reach thousands of people who have come to rely on us for health information they can trust.

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- Brochures on specific thyroid diseases;
- A database of ATA members called "Find a Thyroid Specialist";
- A toll-free telephone number with referrals to patient education materials and support groups; and
- Links to the ATA Alliance for Patient Education: organizations that provide support for understanding and coping with thyroid disease and its treatments.

Visit *www.thyroid.org* and become a *Friend of the ATA*.