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Editorial

Clinical Thyroidology Will Be Bundled with Thyroid and VideoEndocrinology

Clinical Thyroidology (*CT*) is changing. This outstanding summary publication from the American Thyroid Association has, since its inception, been offered to subscribers without a subscription fee. Because of its growing reputation and success, the ATA has made the decision to bundle *CT* with our field-leading scientific journal *Thyroid* and with a new video journal entitled *VideoEndocrinology*, the first video journal within our specialty. As a result of this decision, effective early next year, *CT* will no longer be provided without a subscription.

I am happy to say, however, that you will still be able to receive and read *CT* through one of several pathways:

1. If you are an ATA member, you will receive all three journals, including *CT*, as a benefit of your membership; this will occur without any increase in membership dues.

2. Your local medical library will include *CT* in its listings if it subscribes to *Thyroid*. Thus, if you have access to *Thyroid* through your library, you will automatically have access to *CT*. Actually, many of you very likely already have access to *Thyroid* through your library and read articles from it through them. You will also find *CT* there as soon as the package is offered.

3. If you are not a current member of ATA, you may join the ATA, and all three journals will be provided as a benefit of membership. To help you decide whether ATA membership is of interest to you, we will be offering a trial ATA membership for a small subscription fee and a 6-month duration. This will allow electronic access to our website, including the members-only portion of the site, where you can access *CT* along with *Thyroid* and *VideoEndocrinology* as well as a wealth of additional information, such as guidelines, press releases, white papers, industry-related announcements, committee news, patient education documents, and meeting planning items. We hope that all of you who are not already ATA members will take advantage of this offer, and through the trial membership find that full ATA membership will enhance your professional life and livelihood.

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4. You may personally subscribe to *Thyroid* and receive all three journals as part of the package. However, this will be more expensive than ATA membership, so I encourage you to take advantage of the trial ATA membership above and join the ATA instead.

We wish to thank you for your readership and support of *CT*. Our goal is to continue to provide the excellent content you have enjoyed while growing and further improving it, resulting in *CT* becoming a fully indexed journal. Thanks to the outstanding efforts of editor Jerry Hershman and his editorial board you can look forward to enjoying ever improving *CT* throughout your career.

John C. Morris
Secretary,
American Thyroid Association

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Are Biweekly Granulocyte Counts Effective in Forecasting the Onset of Agranulocytosis in Patients with Graves' Disease Who Are Receiving Antithyroid Drugs?

Stephen W. Spaulding

Nakamura H, Miyauchi A, Miyawaki N, Imagawa J. Analysis of 754 cases of antithyroid drug–induced agranulocytosis over 30 years in Japan. J Clin Endocrinol Metab. September 20, 2013 [Epub ahead of print]. doi: 10.1210/jc.2013-2569.

SUMMARY

Background

The rare complication of agranulocytosis remains at the back of the physician's mind when prescribing antithyroid drugs (ATDs) for Graves' disease. It appears that the mortality rate of this disorder has improved, in association with better therapy for sepsis and with increased awareness that a "trivial URI" can be an ominous sign in such patients. However, there is a persistent dichotomy of opinion about the value of performing routine granulocyte counts to monitor for the development of agranulocytosis. The American Thyroid Association's management guidelines for hyperthyroidism specifically state that routine monitoring of white-cell counts is not recommended, whereas in contrast, the Japanese package insert for MMI gives a strong warning to check blood counts every 2 weeks for the first 2 months of therapy.

Methods

Japanese Pharmaceutical Affairs Law states that physicians should report to the drug manufacturer any adverse drug reaction, including details on age, sex, dose at onset, time to onset, test results, treatment, and outcome. Over the 30-year period up to April 2011, a total of 754 patients with serious hematologic disorders associated with MMI or PTU use were reported to Chugai Pharmaceutical Co., the only Japanese manufacturer of MMI (1). (Chugai is also one of the two Japanese manufacturers of PTU.) The authors accepted a diagnosis of agranulocytosis if a granulocyte count under 500 per microliter had been documented in the report, whereas diagnoses of pancytopenia or aplastic anemia were accepted based on the reporting physician's diagnosis. Insurance reports submitted to the Japan Medical Data Center were used along with results from the 2010 Japanese census data to estimate the incidence of patients with newly diagnosed Graves' disease who were treated with MMI or PTU within a month of diagnosis; patients given a diagnosis of Graves' disease or a prescription for an ATD in the preceding 12 months were excluded, as were patients older than 64 because very few were insurance subscribers. Data obtained from Kuma Hospital between 2005 and 2012 were used to estimate the current sex and age distribution of new/untreated Graves' disease.

Results

Between 1981 and 2011, the Chugai Company received reports on major hematologic disorders in 754 patients: 670 had agranulocytosis and 84 had pancytopenia or aplastic anemia. MMI had been prescribed for 725 patients, and PTU for 28. Over the first two decades studied, the number of reports submitted each year tended to increase, while over the decade from 2001 to 2010, about 40 cases per year were reported. The authors estimated that about 33,500 patients 10 to 64 years of age were taking ATDs between April 2010 and March 2011, indicating that the annual incidence of major blood disorders was about 0.12% (40 of 33,500). The patients with

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Stephen W. Spaulding

these disorders were about 3 years older than the average patient with newly diagnosed Graves' disease seen at Kuma Hospital. The exact interval between the day ATD treatment started and the day the disorders appeared was available in 461 reports. In about 70%, the disorders had appeared within 60 days, and in about 85% the disorders had appeared within 90 days of the start of treatment. A granulocyte count above 1000 per microliter had been documented within 90 days of the onset of disorders in 221 patients. In about 20% of these cases, a granulocyte count above 1000 per microliter had been documented within a week of the onset of the disorder, and in 50% of cases it had been "normal" within 2 weeks of the onset of the disorder. In 20 case reports, multiple granulocyte counts had been documented over the 30 days before the onset of the disorder. When viewed in retrospect, over the 15 days before the disorder occurred, there seemed to be some decline in the granulocyte counts. In about half these cases, at least one count had been below 1500 per microliter.

Over the 30 years studied, 30 patient deaths were associated with ATD administration (30 of 754, or about 4%). On average, they were about 9 years older than patients with newly diagnosed Graves' disease seen at Kuma Hospital. All the patients who died had been taking MMI, although in one patient who had been switched to PTU because of urticaria, pancytopenia developed 26 days later. Apparently no white-cell/granulocyte data were available on any of the 30 cases of fatality within 90 days before agranulocytosis appeared. In 24 reports with sufficient data to establish a diagnosis, agranulocytosis was present in 17 cases and pancytopenia in 7. Nine patients were admitted on the day of or the day after symptoms began, while it took 3 days for 6 patients, 4 days for 1 patient, and 5 days for 2 patients to receive the diagnosis. Four patients did not visit a medical institution. Despite intensive care, 5 patients died within 3 days and 10 died within a week. The delay in diagnosis commonly reflected insufficient patient concern for symptoms, but in 5 cases, physicians had not obtained a granulocyte count, presumably because they did not know that the patient was taking an ATD.

Conclusions

The major blood disorders associated with ATDs generally have an abrupt onset and commonly occur within 3 months of initiating treatment; however, in about 15% of cases, the disorder appears after a longer period. It is critically important that each patient given an ATD also be given sufficient information about clinical signs that might suggest agranulocytosis. The urgency of discontinuing the drug and of obtaining a granulocyte count must be emphasized.

ANALYSIS AND COMMENTARY

Even when a granulocyte count was performed biweekly, it often provided no warning. Furthermore, fewer than 30% of the reports indicated that more than one granulocyte count had been performed within the 90 days before the disorder appeared, which suggests that biweekly counts often were not being performed (one cannot tell how many cases reflected patient noncompliance vs. physician noncompliance). This study excluded patients over 64 years of age, but even so, the patients who died were substantially older than the average age of the total group of afflicted patients. The data could be somewhat deficient if a physician forgot to report a case or missed the diagnosis in a case of sudden death. If, as it appears, no granulocyte counts had been performed within a week or two of the disorder in the 30 cases of fatality, it might be argued that had such a granulocyte count been done, it might have allowed the disorder to be discovered earlier, and thus some of the patients might have had a better outcome. Data that seem to bear on this issue were recently reported from Ito Hospital, where all patients with Graves' disease treated with ATDs do get routine biweekly complete blood counts (2). Nonetheless, of 39,149 patients given ATDs between 1983 and 2002, a major

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Stephen W. Spaulding

hematologic disorder developed in 55 (a frequency of 0.11%), and there was one fatality, in a 38-year-old woman (1 of 55, or about 2%). Assuming the Ito study patients were reported to Chugai Co., most cases would have been included in the current study, but despite the duplicated reports, the data indicate that the frequency of major blood disorders over the past 30 years apparently was under 0.15%. Similar comments apply to a study of children under the age of 15 years (1). The frequency of these disorders thus appears to be substantially less than the 0.3% to 0.6% previously reported for Japan (2,3).

It is not clear at what point a decline in the granulocyte count is sufficiently worrisome to discontinue ATD treatment. Of the 20 patients who had multiple granulocyte counts performed in the 30 days before agranulocytosis occurred, there were 9 in whom the count had dropped below 1500 per microliter. In patients with cancer, the risk for infection begins to increase at this level, although the effects of chemotherapeutic drugs on bronchoalveolar and gastrointestinal integrity may not permit these findings to be directly applied to ATD-related marrow disorders.

There is another side to the question: How many (if any) patients were saved from agranulocytosis because a decline in a biweekly granulocyte count prompted a physician to discontinue ATD therapy? Unfortunately, authors' databases could not provide information on this facet of the subject.

Clearly there are good reasons for obtaining a complete blood count—including a white-cell differential count—prior to beginning ATD therapy. For example, some patients normally have a lower granulocyte count, some patients with untreated Graves' disease have mild leukopenia (4), and patients with Graves' disease can have deficiencies in iron, folate or vitamin B12, and can have other autoimmune disorders, such as pernicious anemia.

The most important message is that physicians must carefully explain (and document) all the side effects of the antithyroid drugs, both to the patient as well as to a friend or relative of the patient, if possible. In addition, printed information detailing the side effects should be provided. Special emphasis should be given to possible symptoms of infection. The patient must understand that upon any suggestion of onset of a sore throat, URI, fever or other sign of infection, she must stop taking the ATD immediately and obtain a CBC, explaining to emergency medical personnel her previous use of an ATD.

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Thyrotoxic Periodic Paralysis Is Not Correlated With the Severity of Hyperthyroidism and Can Be Seen with All Forms of Hyperthyroidism

Albert G. Burger

Chang C-C, Cheng C-J, Sung C-C, Chiueh T-S, Lee C-H, Chau T, Lin S-H. A 10-year analysis of thyrotoxic periodic paralysis in 135 patients: focus on symptomatology and precipitants. Eur J Endocrinol 2013;169:529-36.

SUMMARY

Background

Thyrotoxic periodic paralysis (TPP) is characterized by acute and severe generalized weakness due to a shift of potassium into the intracellular space without loss of total body potassium content (1). The disease is best documented in patients of Asian origin who have hyperthyroidism, can occur with any kind of hyperthyroidism, and has to be differentiated from other causes of hypokalemic paralysis. Several factors have been reported to precipitate these crises, the best known being a carbohydrate load and strenuous exercise. This study from Taiwan is a prospective investigation extending from 2002 to 2012. It includes probably the largest group of patients observed over time in a single center.

Methods

Over a period of 10 years, 135 patients with TPP (130 men, 5 women) were studied in a prospective manner. The selection criteria were strict, excluding any other possible causes for an abrupt decrease in serum potassium. Thyroid function was evaluated not only by the classical biochemical and ultrasound criteria but also by clinical assessment using the Wayne Index. Special attention was given to possible precipitating factors (carbohydrate load, strenuous exercise, upper respiratory tract infection (URI), steroids, catecholamines, etc.). In 55 patients, it was possible to provoke an attack of hypokalemia with a glucose load (2 g per kilogram of body weight).

Results

The attacks occurred mainly in the morning and during summer and fall. Hyperthyroidism was confirmed by increased serum FT_4 and FT_3 levels and a serum TSH of <0.03 mU/L. Patients with Graves' disease accounted for 96% of the cases, but the attacks were also seen in patients with subacute thyroiditis and multinodular toxic goiter and even in patients using weight-reducing agents containing thyroid hormones. There was no correlation between TPP and the severity of hyperthyroidism. Only 24% of the patients were diagnosed with hyperthyroidism before the attack; the others were diagnosed at the moment of TPP. There were no familial cases. As expected, carbohydrate overload was present in 34% of the cases, being the best identifiable precipitating factor. Exercise as another precipitating cause accounted for only 7% of cases and URI for 8%. In 55 patients, the role of carbohydrate overload could be checked with intentional hyperglycemia which was induced not earlier than 24 hours after a spontaneous attack. Hypokalemia was seen in only 10 (18%) of 55 patients, but it was severe—the mean nadir of serum potassium was 2.5 mmol/L. To prevent further attacks, correction of hyperthyroidism was obviously crucial, and in the meantime the patient received beta-adrenergic blockers and oral potassium chloride supplements (8 to 16 mmol/day).

Conclusions

Thyrotoxic periodic paralysis is seen mainly in the Asian population. Even though it is associated with

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Thyrotoxic Periodic Paralysis Is Not Correlated With the Severity of Hyperthyroidism and Can Be Seen with All Forms of Hyperthyroidism

Albert G. Burger

hyperthyroidism, there is no correlation between the occurrence of the crisis and the severity of hyperthyroidism. Some patients even had no clinical symptoms of hyperthyroidism according to the Wayne Index. A carbohydrate overload can certainly precipitate thyrotoxic periodic paralysis but only in a minority of cases was induced hyperglycemia sufficient to cause an attack. The same is true for exercise-induced TPP. The treatment is symptomatic (potassium supplements and beta blockers), but more importantly hyperthyroidism must be treated rapidly.

ANALYSIS AND COMMENTARY

This report originates from Taiwan, yet it is now established that TPP is not limited to Asian populations with thyrotoxicosis (2). Latin American patients and even Caucasians and black patients with thyrotoxicosis have presented with attacks of TPP. The shift of serum potassium to the intracellular space is the hallmark of the disease. Rarely, the decrease in serum potassium is modest. Therefore, in the presence of unexplained muscle weakness in Graves' disease with TPP has to be considered. The pathophysiology is unclear. Recent progress indicates the presence of several mutations in at least one potassium channel gene, Kir2.x (3), and the term endocrine channelopathy is occasionally used to describe TPP. The well-known T_3-dependent Na+–K+–ATPase could also play an important role (4). it is interesting that among the many precipitating factors of TPP, increased insulin sensitivity has been reported (5). Insulin favors the shift of potassium into the intracellular space. Finally, TPP should not be confused with periodic hypokalemic paralysis in patients without increased thyroid hormone levels.

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Should Determination of Serum TPOAb and FT_4 Be Considered in the Evaluation of Thyroid Dysfunction in Pregnancy?

Jorge H. Mestman

Korevaar TI, Schalekamp-Timmermans S, de Rijke YB, Edward Visser W, Visser W, de Muinck Keizer-Schrama SM, Hofman A, Alec Ross H, Hooijkaas H, Tiemeier H, Bongers-Schokking JJ, Jaddoe VW, Visser TJ, Steegers EA, Medici M, Peeters RP. Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the Generation R Study. J Clin Endocrinol Metab. September 13, 2013 [Epub ahead of print].

SUMMARY

Background

Premature delivery is an important risk factor for child mortality and for psychiatric, metabolic, and cardiovascular disease later in life. In the majority of cases, the cause of prematurity cannot be identified. Currently, whether abnormal maternal thyroid function during pregnancy increases the risk for premature delivery remains controversial. The authors investigated the relation between maternal serum thyroid parameters and the risk of premature delivery in a large prospective, population-based study.

Methods

Serum TSH, FT_4, T_4, and TPO antibodies (TPOAb) were determined during early pregnancy in 5971 pregnant women from the Generation R Study, a population-based prospective study from fetal life onward in Rotterdam, The Netherlands. Data were available on maternal age, parity, smoking, socioeconomic status, ethnicity, maternal anthropometrics, and urinary iodine levels.

Results

Of all pregnant women, 5.0% had a premature delivery (<37 weeks of gestation), 4.4% had a spontaneous premature delivery, and 1.4% a very premature delivery (<34 weeks). High TSH levels and subclinical hypothyroidism were associated with premature delivery but not with spontaneous (in contrast with iatrogenic) premature delivery. Maternal hypothyroxinemia was associated with a 2.5-fold increased risk of premature delivery, a 3.4-fold increased risk of spontaneous premature delivery, and a 3.6-fold increased risk of very premature delivery. TPOAb positivity was associated with a 1.7-fold increased risk of premature delivery, a 2.1-fold increased risk of spontaneous premature delivery, and a 2.5-fold increased risk of very premature delivery. These effects remained similar after correction for TSH and FT_4 levels.

Conclusions

Hypothyroxinemia and TPOAb positivity are associated with an increased risk of premature delivery. The increased risk in TPOAb-positive women seems to be independent of thyroid function.

ANALYSIS AND COMMENTARY

Preterm delivery, defined as birth occurring at or before 37 weeks of gestation, is the leading cause of perinatal morbidity and mortality in the world and of serious diseases later in life (1). The Generation R Study (Rotterdam, The Netherlands) is a population-based prospective cohort study of subjects from fetal life until young adulthood (2). The study is designed

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to identify early environmental and genetic causes of normal and abnormal growth and development and health during fetal life, childhood, and adulthood. Past publications from the Generation R Study have described specific pregnancy and child neuropsychological outcomes. The present publication differs from previous studies in the literature by selecting patients according to the etiology of prematurity (spontaneous versus iatrogenic deliveries), excluding pregnancy comorbidities as cofactors in prematurity, and adjusting for other covariates, among them smoking, socioeconomic status, and ethnicity. The authors studied the independent effect on prematurity of thyroid dysfunction, autoimmunity (presence of TPOAb), and hypothyroxinemia. It is important that they measured iodine status, measuring urinary iodine concentration in a random subset of 1099 women at a mean gestational age of 12.9 weeks and finding that the population was iodine-sufficient. The prevalence of thyroid dysfunction in their population was similar to those reported in the literature, with a prevalence of TPOAb positivity of 5.6%. They also compared outcomes between TSH reference ranges according to their own population-based trimester-specific ranges and the reference range of <2.5 mU/L for the first trimester and <3.0 mU/L in the second and third trimesters of gestation as recommended by recent ATA and Endocrine Society Pregnancy Guidelines. Hypothyroxinemia was defined as a low serum FT_4 and normal serum TSH. Normal FT_4 levels are defined as levels within 2.5th to 97.5th percentiles.

The literature is not consistent with regard to pregnancy outcomes in women affected by thyroid dysfunction in the presence or absence of autoimmunity. Among the several reasons for this discrepancy is the variation in gestational age at the time of the study, the definition of maternal and obstetrical complications, ethnicity, maternal comorbidities (among them diabetes, chronic hypertension, and obesity), thyroid test reference ranges, and the presence of thyroid autoimmunity. Serum TSH, FT_4, and TPOAb were not evaluated in all publications. A recent meta-analysis showed that TPOAb-positive euthyroid women have an increased risk of a delivery before 37 weeks of gestation, although the mechanism by which TPOAbs may cause premature births is poorly understood (3). An extensive analysis of 13 studies concluded that there is a compelling argument in support of a relationship between preterm delivery and thyroid abnormalities (4). In the present study, although iatrogenic spontaneous deliveries were associated with clinical and subclinical hypothyroidism, mild thyroid dysfunction in the absence of autoimmunity and maternal comorbidities was not associated with spontaneous prematurity. This is, to my knowledge, an original observation. Hypothyroxinemia (normal TSH with low FT_4) as a risk for premature delivery has been investigated by only three groups (5-7), with negative results. Hypothyroxinemia is reported in studies from countries with iodine deficiency. The cause and physiologic mechanisms of "hypothyroxinemia" in countries with sufficient iodine supply is not clear. Even the authors of the present study stated that low levels of FT_4 due to iodine deficiency may be transient and/or have different consequences than other causes of hypothyroxinemia, but they did not elaborate on the other causes of hypothyroxinemia. The authors concluded that hypothyroxinemia by itself, in the absence of autoimmunity and comorbidities among women, is a significant risk for both iatrogenic and spontaneous premature and very premature delivery. This is indeed an intriguing finding. As stated by Negro et al. (8), the critical questions about the diagnosis of hypothyroxinemia in pregnancy are: 1) the definition of what constitutes an FT_4 level below the 2.5th percentile is unclear because regional and iodine status reference ranges have not been established; 2) perhaps equally problematic is that the accuracy of commonly used FT_4 measurements during pregnancy is questionable ; and 3) research to date evaluating the effect of isolated hypothyroxinemia on maternal

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and fetal outcomes has yielded conflicting data. In the discussion, the authors suggested that "screening for TPOAb positivity and hypothyroxinemia could be considered, especially among women with other risk factors for premature delivery." Although I agree with the first suggestion for TPOAb determination along with serum TSH in pregnancy, I am cautious about the interpretation of serum TF4 because of the lack of population-based trimester-specific reference ranges and the lack of accuracy of commonly used commercial FT_4 kits (9).

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Severe Maternal Hypothyroxinemia Is Associated with Probable Autism in Offspring

Elizabeth N. Pearce

Román GC, Ghassabian A, Bongers-Schokking JJ, Jaddoe VW, Hofman A, de Rijke YB, Verhulst FC, Tiemeier H. Association of gestational maternal hypothyroxinemia and increased autism risk. Ann Neurol. August 13, 2013 [Epub ahead of print].

SUMMARY

Background

Adequate thyroid hormone is required in pregnancy for normal neurodevelopment of the fetus. Previous studies have demonstrated that maternal hypothyroxinemia in early pregnancy is associated with adverse effects on child cognitive development (1). There are some histologic similarities between brain pathology in autism and animal models of maternal hypothyroxinemia (2). Hoshiko and colleagues have reported a possible association between neonatal hypothyroxinemia and autism (3). The aim of this study was to assess relationships between maternal thyroid function in early pregnancy and autism symptoms in offspring.

Methods

This was a prospective cohort study using data from the Generation R Study population-based birth cohort in the Netherlands. A total of 8,879 pregnant women were enrolled between 2002 and 2006. Free T_4 levels drawn prior to 18 weeks of gestation were available for 5100 of these women, of whom 4039 provided information about autism symptoms when their children were 6 years old. Parents reported autism symptoms using the Pervasive Developmental Problems (PDP) subscale of the Child Behavior Checklist for Toddlers and a short-form version of the Social Responsiveness Scale (SRS). Children with probable autism were defined as those with PDP scores greater than the 98th percentile and an SRS score in the top 5%. Maternal thyroid function was assessed at a mean of 13.4 weeks gestation: serum TSH, free T_4, and TPO antibodies were measured. Women were defined as having mild hypothyroxinemia if the free T_4 was below the 10th percentile with a normal TSH (0.03 to 2.5 mIU/L). Severe maternal hypothyroxinemia was defined as a free T_4 below the fifth percentile with a normal TSH. Logistic regression was used to assess the odds of having a child with probable autism in mothers with hypothyroxinemia versus mothers with normal free T_4 values. Multiple linear-regression models were also used to assess maternal thyroid function as a predictor of children's continuous PDP and SRS scores. Models were adjusted for the following covariates: child's sex, ethnicity, gestational age at delivery (assessed by prenatal ultrasound), birth weight, parental age, education, smoking, prenatal maternal psychopathology (assessed by the Brief Symptom Inventory, a validated self-report questionnaire), gestational age at maternal thyroid-function testing, and early pregnancy maternal folate and C-reactive protein levels. All models were subsequently also adjusted for child IQ (assessed by two subtests of the Snijders-Oomen Nonverbal Intelligence Test, Revised).

Results

Eighty children were defined as having probable autism. Severe maternal hypothyroxinemia was associated with an adjusted odds ratio of 3.89 (95% CI, 1.83 to 8.20) of having a child with probable autism. Mild maternal hypothyroxinemia was not associated with an increased risk for having a child with probable autism. Maternal TSH and TPO antibody positivity were not associated with an increased risk for probable autism. Results were similar in multivariate analyses treating PDP and SRS as con-

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tinuous outcomes. Effect estimates were smaller, but results remained significant after adjustment for child IQ. Results did not change when the data set was restricted to women whose thyroid function was assessed in the first trimester.

Conclusions

Severe maternal hypothyroxinemia in early pregnancy was consistently associated with autistic symptoms in children.

ANALYSIS AND COMMENTARY

The incidence and prevalence of autism spectrum disorders (ASD) has increased over the past several decades; currently, 1 in every 88 U.S. children is considered to be on the autism spectrum (4). The pathogenesis of ASD remains poorly understood, and there is great interest in identifying potentially modifiable risk factors. The strengths of this study include its prospective design, large population-based sample, and wide range of covariates assessed. The causes of maternal hypothyroxinemia in this study are unclear; thyroid autoimmunity was not associated with autism symptoms, and although urinary iodine concentrations are not reported in this paper, the Generation R cohort is known to be iodine-sufficient. Interventional studies are needed to determine whether screening for and treating isolated maternal hypothyroxinemia improves the developmental outcomes of children. In the absence of such interventional data, current ATA guidelines recommend against treatment for maternal hypothyroxinemia (5).

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Levothyroxine Treatment of Central Hypothyroidism Has a Beneficial Influence on Cardiovascular Risk Factors

Jerome M. Hershman

Klose M, Marina D, Hartoft-Nielsen ML, Klefter O, Gavan V, Hilsted L, Rasmussen AK, Feldt-Rasmussen U. Central hypothyroidism and its replacement have a significant influence on cardiovascular risk factors in adult hypopituitary patients. J Clin Endocrinol Metab. 2013;98:3802-10. Epub June 24, 2013; doi: 10.1210/jc.2013-1610.

SUMMARY

Background

Central hypothyroidism is a relatively rare disorder, occurring mainly in patients with pituitary tumors; it is often a consequence of the treatment of the tumor. The incidence of central hypothyroidism is estimated at 1:20,000 to 1:80,000 in the general population (1). Because of its rarity, the effect of central hypothyroidism on cardiovascular risk factors is difficult to assess. The current paper is a retrospective study of cardiovascular risk factors in growth hormone (GH)–deficient patients who also had central hypothyroidism in a single Danish hospital over a 20-year period.

Methods

The study included 209 patients with baseline thyroid function, uninterrupted GH therapy, and no Cushing's disease. Forty-six patients were TSH-sufficient (euthyroid) and 163 patients were characterized as TSH-deficient because they had an FT_4 <12 pmol/L (0.93 ng/dl). The TSH-deficient patients were divided into tertiles according to their FT_4 levels on levothyroxine therapy: the first tertile had the lowest FT_4 (<13.1 pmol/L), the second tertile an intermediate FT_4 (13.1 to 16.7 pmol/L), and the third tertile the highest FT_4 (>16.8 pmol/L) before commencing GH therapy. The 46 patients who were TSH-sufficient were compared with 54 patients in each tertile with regard to lipid parameters and body composition.

Results

At baseline, FT_4 was inversely associated was associated with a higher body-mass index (BMI) (r = –0.15; P = 0.03), waist circumference (r = –0.19; = 0.03), hip circumference (r = –0.20; P = 0.05), and directly associated with HDL (r = 0.28; P <0.001), independent of age, sex, and IGF-I. No significant correlations were observed between FT_4 and other body-composition or lipid markers.

Follow-up data were available for 192 patients at a median follow-up time of 4.1 years (range, 2.5 to 5.8) after initiation of GH therapy. At follow-up, 31 patients (16%) were categorized as TSH-sufficient and 161 (84%) as TSH-deficient. Twelve patients (21%) initially defined as TSH-sufficient were on levothyroxine treatment; 32 (64%) first-tertile, 28 (54%) second-tertile, and 17 (33%) third-tertile patients received an increased levothyroxine dose as compared with baseline, whereas 12 (27%) had a dose reduction and 2 had stopped levothyroxine treatment. An increase in FT_4 was associated with a decrease in BMI (r = –0.16; P = 0.03), lean body mass (r = –0.21; P<0.01), diastolic blood pressure (r = –0.17; P = 0.03), total cholesterol (r = –0.27; P<0.01), and LDL cholesterol (r = –0.26; P<0.01). These associations remained after adjustment for the change in IGF-I.

Conclusions

The data indicate the importance of optimal levothyroxine replacement to reduce cardiovascular risk in patients with central hypothyroidism.

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Jerome M. Hershman

ANALYSIS AND COMMENTARY

The rarity of central hypothyroidism makes it difficult to accumulate a significant number of patients to study its cardiovascular risk and nearly impossible to study its effects on cardiovascular events. Because these patients were part of a group also treated with GH and carefully followed with regard to various cardiovascular risk parameters, the data could be analyzed for the effects of levothyroxine therapy on these parameters. Since all of the patients were treated with GH, leading to an optimal level of IGF-I, the effects were considered to be unrelated to the GH therapy. However, the significant effects, mainly associations, were relatively modest. On the other hand, this is a somewhat heterogeneous group of patients. With regard to the lipid parameters, patients on lipid-lowering drugs were excluded from the analysis. Although the patients did not receive a dose of levothyroxine aimed at a specific target FT_4, a dose that achieves an FT_4 of >13 pmol/L (1.0 ng/dl) is generally considered euthyroid. In our clinic, we aim for the levothyroxine dose in patients with central hypothyroidism to achieve an FT_4 of >1.2 ng/dl.

A recent paper pointed out that there are patients with subclinical central hypothyroidism who can be diagnosed by echocardiography, even though their FT_4 is in the normal range (2) (reviewed in the June 2012 issue of Clinical Thyroidology). Treatment of these patients with levothyroxine improved the echocardiographic parameters. This finding is consistent with the results showing that the first tertile of patients with hypothyroidism in the current report had less desirable anthropomorphic and lipid measurements and that additional treatment with levothyroxine improved these parameters.

Because of the commercial importance of GH therapy, the beneficial effect of much cheaper therapy with levothyroxine in patients with hypothyroidism is often overlooked. This study shows the significant benefit of this simple therapy, which is widely accepted by these patients in contrast to the daily injection required for treatment with GH.

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Malignancy of a Thyroid Nodule Can Be Predicted by Ultrasonography if It Has Microcalcifications and Is Solid and Larger than 2 cm

Jerome M. Hershman

Smith-Bindman R, Lebda P, Feldstein VA, Sellami D, Goldstein RB, Brasic N, Jin C, Kornak J. Risk of thyroid cancer based on thyroid ultrasound imaging characteristics: results of a population-based study. JAMA Intern Med. August 26, 2013. [Epub ahead of print]. doi: 10.1001/jamainternmed.2013.9245.

SUMMARY

Background

Ultrasound imaging is a principal tool for selecting thyroid nodules for FNA biopsy in order to determine whether a nodule is benign or malignant. Choosing which nodules are worthy of biopsy based on ultrasound characteristics is especially important, and there is a vast literature on this topic. The purpose of this study was to identify the ultrasound imaging characteristics associated with malignant nodules in order to create a standardized system for predicting the risk of cancer in a thyroid nodule.

Methods

The authors conducted a retrospective case–control study of consecutive patients who underwent ultrasound thyroid imaging between January 2000 and March 30, 2005. Thyroid cancers were verified through the California Cancer Registry. Cancers diagnosed through March 30, 2007, were included to allow a minimum of 2 years of follow-up. Patients diagnosed as having thyroid cancer were matched 4 to 1 with controls without cancer matched for age sex and year of ultrasound examination. The study included 96 patients with cancer and 369 controls. In 43 patients with cancer, a single nodule was identified by ultrasound and considered malignant. In 50 patients with cancer, multiple nodules were identified; consequently, one investigator reviewed all records to determine which nodules were malignant, but in a small (unspecified) number of nodules, this could not be done. Each ultrasound was reviewed independently by two radiologists, with good consensus on the readings.

Single predictor modeling was used to assess the association between specific ultrasound characteristics and cancer status using generalized estimating equations. The ultrasound variables that were statistically significant in this model were combined in various ways for a final multiple predictor model.

Results

A total of 8806 patients had 11,618 thyroid ultrasound exams during the study period; 105 cancers were diagnosed 1 day to 6 years after the ultrasound imaging. The incidence of thyroid cancer was 0.9 per 100 ultrasound exams. Thyroid nodules were found in 97% of patients with cancer and in 56% of controls.

Microcalcifications were found in 38.2% of cancer nodules versus 5.4% of benign nodules; the corresponding odds ratio (OR) was 11.6 (95% CI, 6.5 to 20.0). The odds for cancer increased with nodule size. Although coarse calcifications, nodule echogenicity, central vascularity, margins, and shape (more tall than wide) were also significantly associated with cancer in the single predictor analysis, the odds ratios were smaller, ranging from 1.6 to 2.9.

In the multiple predictor model, only three characteristics were significantly associated with the risk of cancer: microcalcification, size greater than 2 cm, and solid composition. If any one of these three characteristics was present, the sensitivity was 0.88 (95% CI, 0.80 to 0.94). If all three were present, the likelihood ratio was 28 (95% CI, 23 to 34), but the sensitivity was 0.07.

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Malignancy of a Thyroid Nodule Can Be Predicted By Ultrasonography If It Has Microcalcifications And Is Solid and Larger than 2 cm

Jerome M. Hershman

Conclusions

Thyroid ultrasound imaging could be used to identify patients who have a low risk of cancer for whom biopsy could be deferred because they do not have any of the characteristics that predict malignancy.

ANALYSIS AND COMMENTARY

The authors claim that they have made a unique contribution by comparing the ultrasound characteristics of the cancer nodules with controls selected from a large number of patients without cancer. In both groups, there is purposely no data on FNA. The authors assert that other studies limited their analysis to patients who had biopsies based on the ultrasound examination, which led to ascertainment bias and overestimated the risk of cancer and the accuracy of ultrasound imaging. Unfortunately, this claim is difficult to accept. The authors show in tables of single predictor analysis that the usual ultrasound features of malignant nodules increase the odds ratio of malignancy: microcalcifications, solid, and larger than 2 cm. This last feature has been disputed (1). The multiple predictor model leads to discarding other features, such as coarse calcifications, more tall than wide, irregular borders, and increased intranodular vascularity, that have been found to be helpful as indicators of potential malignancy.

The authors cite the ATA guidelines as recommending FNA of nodules that are >0.5 cm, but this is erroneous (2). The revised guidelines recommend FNA of solid nodules >1 cm and nodules >0.5 cm only when they have suspicious sonographic features (2; Table 3).

Frates et al., in a consensus statement for the Society of Radiologists in Ultrasound in 2005 made reasonable recommendations with regard to which characteristics made nodules suspicious and worthy of FNA (3). Others have explored this area extensively with regard to diagnostic accuracy of various criteria for making a nodule suspicious for malignancy (4). There is agreement that cysts are not malignant, as found in this report. Perhaps the main contribution of the current article is that it will reopen the debate about whether it is worthwhile to perform FNA in nodules that are solid and 1 to 2 cm but without other criteria suggesting malignancy. In the commentary in the same issue of JAMA Internal Medicine as this article, Alexander and Cooper point out that hypoechoic, solid nodules larger than 1 to 1.5 cm with microcalcifications should be biopsied (5). Of course, these are likely to be papillary thyroid cancers. They also state that spongiform nodules as well as cysts need not be biopsied.

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Complete Cervical Sonography Is Essential for Operative Planning in Differentiated Thyroid Cancer

Cord Sturgeon

O'Connell K, Yen TW, Quiroz F, Evans DB, Wang TS. The utility of routine preoperative cervical ultrasonography in patients undergoing thyroidectomy for differentiated thyroid cancer. Surgery 2013;154:697-730. Epub September 5, 2013; doi: 10.1016/j.surg.2013.06.040.

SUMMARY

Background

Lymph-node metastases are found in 30% to 80% of cases of papillary thyroid cancer (PTC), are usually located in level VI (central compartment), and are a risk factor for disease recurrence. Cervical recurrence may be due to occult central neck metastases that were neither detected nor removed at the index operation. The ATA and the National Comprehensive Cancer Network (NCCN) both recommend preoperative cervical ultrasound for all patients with biopsy proven differentiated thyroid cancer (DTC) (1,2). This study was designed to assess the impact of preoperative cervical ultrasound on the surgical approach during an index operation for thyroid cancer. The authors hypothesized that preoperative ultrasound of the neck would identify clinically occult metastatic lymphadenopathy, which would alter the initial operative procedure in some patients with DTC.

Methods

This was a retrospective study of 70 patients with biopsy-proven DTC who underwent preoperative radiologist-performed ultrasound of the central and lateral nodal basins at a single high-volume institution in the midwestern United States. All patients underwent total thyroidectomy with appropriate lymph-node clearance. Data were collected on demographics, physical examination findings, preoperative sonographic findings, FNA results, extent of operation performed, number of lymph nodes retrieved, and final pathology.

Results

The authors found that 7% of their patients had results on physical examination that were consistent with palpable cervical adenopathy. In the remaining patients, with no palpable lymphadenopathy, 22% had sonographic evidence suspicious for lymphadenopathy. Within this subgroup of patients with sonographically suspicious nodes, 92% were confirmed to have nodal metastases on final pathology. The sensitivity of ultrasound for lateral neck metastases was 93%. A preoperative ultrasound changed the operative management in 23% of patients with biopsy-proven DTC.

Conclusions

The results of this study underscore the importance of the routine use of high-resolution preoperative cervical ultrasound in patients with DTC. The sonographic findings changed the operative management in 23% (16 of 70) of patients: 13 of the 16 patients had a more complete operation for pathologically confirmed, but clinically occult, lymph-node metastases, 2 avoided an unnecessary modified radical neck dissection, and 1 had false positive results on ultrasonography.

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Complete Cervical Sonography Is Essential for Operative Planning in Differentiated Thyroid Cancer

Cord Sturgeon

ANALYSIS AND COMMENTARY

Ultrasound is a key component of the preoperative workup and the postoperative surveillance for thyroid cancer. A preoperative cervical ultrasound including the thyroid and both central and lateral compartments is recommended by the ATA and NCCN guidelines (1,2). Both also recommend preoperative FNA biopsy of suspicious lymph nodes. In their longitudinal care algorithms, both the ATA and NCCN guidelines recommend periodic ultrasound (1,2). Physical examination is not sensitive for the presence of cervical-node metastases, and postoperatively, patients will be subjected to rigorous surveillance, including cervical ultrasound. Therefore, it behooves the surgeon to have knowledge of sonographically detectable metastases prior to the index operation for thyroid cancer so that a complete resection, including appropriate lymph-node clearance, can be performed. Theoretically, this should lead to better locoregional control of disease, and may decrease recurrence (3), and possibly the need for radioiodine therapy or reoperation.

In a prior study, a group from MD Anderson Cancer Center found that cervical ultrasound detected additional sites of metastatic disease not found on physical examination in 20% of patients undergoing an index operation for thyroid cancer, in 32% undergoing reoperation for persistent disease, and in 68% undergoing reoperation for recurrent disease (4). The operation performed was altered by the sonographic data in 39% of these patients. In a study from the University of Miami, surgeon-performed preoperative ultrasound identified nonpalpable metastatic lymph nodes in 24% of patients (5). In a study from the Mayo Clinic of over 700 patients with PTC, preoperative ultrasound detected nonpalpable nodal metastases in 32.9% (6). Preoperative ultrasound findings altered the operation in 40.5% of index cases and in 42.9% of reoperative cases.

In this contribution by O'Connell et al., 23% of the total group had findings from the preoperative ultrasound that changed the operative management. These findings are similar to those of other researchers who have studied the subject and underscore the importance of preoperative high-resolution sonographic imaging for patients with thyroid cancer. Taken together, these studies indicate that preoperative ultrasound has a high sensitivity for nodal disease and will detect nonpalpable nodal metastases in roughly 20% to 40% of patients with DTC and will alter the index operation in a similar percentage of patients. For these reasons, complete cervical sonography is an essential component of the preoperative workup and operative planning for patients with thyroid cancer.

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Cytopathologic Diagnosis of Thyroid Nodules Varies Considerably

Jerome M. Hershman

Cibas ES, Baloch ZW, Fellegara G, Livolsi VA, Raab SS, Rosai J, Diggans J, Friedman L, Kennedy GC, Kloos RT, Lanman RB, Mandel SJ, Sindy N, Steward DL, Zeiger MA, Haugen BR, Alexander EK. A prospective assessment defining the limitations of thyroid nodule pathologic evaluation. Ann Intern Med 2013;159:325-32. doi: 10.7326/0003-4819-159-5-201309030-00006.

SUMMARY

Background

The evaluation of a thyroid nodule depends on FNA and then cytopathology to classify it as benign, malignant, or if neither, to assign a probability of malignancy. The probability is based on the Bethesda system for reporting cytopathology (1). This paper examines the validity of the cytopathologic diagnosis by comparing the diagnostic classifications of "local cytopathologists" and "expert cytopathologist" on a large number of samples. In particular, concordance among the local versus expert cytopathologists and even the concordance of diagnoses by experts reviewing the blinded slides previously studied were evaluated. The results show that cytopathologic diagnosis of thyroid FNA specimens is variable and imprecise, even though it is the "gold standard" and is a cornerstone for the treatment of patients with thyroid nodules.

Methods

Patients were recruited from 14 academic centers and 35 community-based practices. FNA of nodules was performed under ultrasound. Histopathology reports and slides were obtained for 776 nodules from 653 patients, including 310 patients who had undergone thyroidectomy, but only 336 samples from 290 patients were actually used in the cytopathology study. The histopathology was reviewed by two study pathologists. Thyroid microcarcinomas that were found incidentally were excluded.

Because a high proportion of the local cytopathology reports did not use the Bethesda system, the reports were reclassified into this system by two of the three central cytopathology experts. The slide preparations varied by site; 74% were air-dried, and only 26% had alcohol-fixed or ThinPrep slides. Concordance between the local report and one expert was considered the final diagnosis. In discordant cases, the slides were sent to another expert; if the experts were concordant, that was considered the final diagnosis. If there was discordance between experts, a third expert reviewed the slides. Discordance among all three experts occurred in 26 cases, leaving 336 nodules that were the basis for the subsequent analysis. The degree of concordance was calculated using a k statistic.

Results

There was 91% concordance in the diagnosis of the 776 resected nodules with regard to their being benign or malignant in the comparison between the local and expert pathologists. Disagreement occurred most frequently with regard to follicular/Hürthle-cell carcinomas being called benign.

Using a compressed four-category cytopathology diagnosis (benign, indeterminate, malignant, inadequate), concordance between local and expert occurred in 74% of cases. When a six-category system was used that expanded indeterminate to AUS/FLUS, follicular neoplasm/suspicious for follicular

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neoplasm, or suspicious for malignancy, the concordance fell to 64%. The local pathologists tended to have more diagnoses in the indeterminate categories than the experts. The risk for cancer after a false benign diagnosis was similar for experts and local pathologists—about 10%.

When the same "blinded" cytopathology slides were read again by the same three experts more than 30 days after the previous reading, the proportion of identical diagnoses varied from 60% to 83%.

Conclusions

Substantial interobserver and intraobserver variability exists in the cytopathologic evaluation of thyroid nodules and this variability indicates the limitation of visual microscopic diagnosis.

ANALYSIS AND COMMENTARY

The authors of this study are leading authorities in cytopathology and the clinical management of thyroid cancer. Their striking observations in this carefully designed study confirm several other reports concerning the reproducibility, or lack of it, of thyroid cytopathology. Olson et al. recently reported that the cytopathology diagnosis according to the Bethesda system changed 32% of the time when the tertiary center reevaluated slides made by the referral institution (2). Davidov et al. reported that concordance between cytopathologists who evaluated 129 patients with indeterminate FNA biopsies was only 37% (48 of 129) using the Bethesda classification (3). A second opinion on 922 FNA slides found 122 disagreements (13%) in diagnosis, of which 44 were major with regard to a management decision (4).

In my personal reviews of cytopathology with our local experts, I see them struggle to be accurate, and I observe that there is a certain art to making the diagnosis that could lead to arbitrary decisions that might not have been made by others. Our department has had mandatory quality control. The outside experts often disagree on the diagnosis of "follicular neoplasm," with even more disagreement on the diagnosis of FLUS. The proportion of FNA that are diagnosed as FLUS/AUS varied between 3% and 27% among institutions, suggesting that the criteria for making this diagnosis are "soft" and that some cytopathologists avoid the diagnosis (5).

Unfortunately, the current study has some major limitations. First, the experts reviewed the local cytologic diagnosis and reclassified it into the Bethesda categories because 57% of the academic sites and 91% of the community sites did not use the Bethesda system. Formulating the classification pigeonhole from the written reports is one step removed from doing it on the slides themselves, especially in the somewhat murky indeterminate categories. Second, three fourths of the cytology slides on which the diagnosis was based were only air-dried, not alcohol-fixed. Alcohol-fixed slides are superior for evaluating nuclear details that are very important for diagnosis (6). Nevertheless, I believe that the message is valid: cytopathologic diagnosis is a somewhat uncertain science. The clinician must be wary and not forsake clinical judgment in the treatment of patients with thyroid nodules.

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Metformin Inhibits Thyrocyte Growth and Increases Complete Responses in Differentiated Thyroid Cancer in Patients with Diabetes

Artak Labadzhyan

Klubo-Gwiezdzinska J, Costello J Jr, Patel A, Bauer A, Jensen K, Mete M, Burman KD, Wartofsky L, Vasko V. Treatment with metformin is associated with higher remission rate in diabetic patients with thyroid cancer. J Clin Endocrinol Metab 2013;98:3269-79. Epub May 24, 2013.

SUMMARY

Background

Obesity and type 2 diabetes have both been linked to an increased risk for some types of cancer. Metformin has been shown to have antineoplastic effects in various cancers, and there are some encouraging data for its role in neoadjuvant and adjuvant therapy. In a prior study, these authors found that metformin decreased the growth of medullary thyroid cancer cells and down-regulated p70S6K and MAPK kinase/ERK signaling (1).

Methods

Medical records were evaluated retrospectively for the efficacy of thyroid cancer therapy in 240 patients who were followed for a mean (±SD) of 6.9±4.8 years. Inclusion criteria included a diagnosis of differentiated thyroid cancer (DTC), follow-up data after surgery and radioactive iodine (RAI) ablation, and a diagnosis of type 2 diabetes mellitus before the diagnosis of DTC. Patients were categorized into three groups: group 1 (n = 34) had been treated with metformin, group 2 (n = 21) had not received metformin therapy; and group 3 (n = 185) were control patients with DTC who had no history of diabetes or metformin use. The dose of metformin ranged from 500 mg to >2000 mg daily, with 21 of 34 patients receiving 1000 to 1500 mg/day. The mean duration of metformin treatment was 4.4±3 years. Complete response was defined as undetectable Tg levels (both suppressed and stimulated) and no evidence of disease on imaging studies. Progression-free survival (PFS) was assessed from the day of the last dose of RAI therapy until the last imaging study performed during the follow-up period. A multivariate logistic-regression model was used to compare treatment efficacy, and a Cox proportional-hazard models was used to assess significant factors affecting PFS.

The authors extended their previous studies with metformin to human follicular and papillary thyroid cancer cell lines, assessing proliferation, viability, and migration activity. Responses of cell signaling markers like phospho/total p70S6K, phospho pS6, phospho/total AKT, phospho/total ERK, phospho/total AMPK, poly polymerase (PARP), cyclin D1 to H2O2 stress were measured by Western blotting. Some human thyroid cancer samples were also immunostained for p-AMPK and phospho p70S6K.

RESULTS

The patients in the diabetes groups were similar in age, sex, mean glycated hemoglobin, mean body-mass index, insulin use, duration of insulin use, and use of other antidiabetes medications. The initial tumor size was significantly smaller in the patients with diabetes who received metformin; in contrast, the total amount of RAI given was higher in patients with diabetes who were not taking metformin and their mean TSH levels during follow-up was higher. The complete response (CR) rate was significantly lower in the patient with diabetes who were not taking metformin than in the controls or the patient with diabetes who were taking metformin; the duration of metformin treatment

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Metformin Inhibits Thyrocyte Growth and Increases Complete Responses in Differentiated Thyroid Cancer in Patients with Diabetes

Artak Labadzhyan

was not associated with complete response. Lack of treatment with metformin, presence of gross extrathyroidal extension, and distant metastases were significantly associated with lower CR rates (odds ratios, 0.03, 0.092, and 0.005, respectively). Age at diagnosis of cancer, lack of treatment with metformin, presence of lymph-node metastases, and presence of distant metastases were significantly associated with a risk for shorter progression-free survival (hazard ratios, 1.059, 9.218, 7.614, and 17.359, respectively).

Exposure to higher concentrations of metformin (5 mM) and to longer treatment times (3 days) made thyroid cancer cells grow somewhat more slowly, but metformin had no effect on cell migration. Metformin increased p-AMPK while inhibiting cyclin D and downstream targets of the mammalian target of rapamycin (mTOR) such as phospho p70S6K. Pretreating cells with 1 mM metformin increased their sensitivity to 0.1 to 0.5 mM H2O2, decreasing prosurvival signaling via pERK, while activating AMPK. Metformin did not affect the expression of sodium–iodide symporter. Immunostaining was positive for phospho p70S6K in cancer tissue from three of the six patients with diabetes who were not taking metformin, but it was negative in three samples from patients taking metformin.

CONCLUSIONS

In patients with diabetes who have differentiated thyroid cancer, metformin treatment is an independent factor for an increased likelihood for complete response, restoring it to the level of normal controls, and was also associated with longer progression-free survival. A possible molecular mechanism may involve metformin's action via the adenosine monophosphate-activated protein kinase (AMPK) pathway to inhibit cell growth, down-regulating cyclin D1 expression and downstream targets of mTOR.

ANALYSIS AND COMMENTARY

This study combines clinical and in vitro analyses to demonstrate a possible role for metformin in the treatment of DTC. The clinical data raise the possibility that metformin treatment affects tumor size. Although it could simply be due to chance, the 34 patients with diabetes who had been taking metformin had significantly smaller tumors, as compared to the 21 patients with diabetes who had not taken metformin or to the 128 controls (1.37 cm vs. 2.44 cm vs. 2.39 cm, respectively). It is somewhat worrisome that after RAI treatment, the mean TSH in the patients with diabetes who had not been taking metformin (0.65±0.79) remained at a significantly higher level than the mean TSH in patients with diabetes who were taking metformin (0.36±0.30) or in the controls (0.34±0.46). There is much controversy concerning the effects of metformin on TSH levels, and results may be influenced by multiple confounding factors, such as weight, smoking, and goiter.

A small prospective study has been performed on patients with insulin resistance as well as small nodules that were shown to be benign by FNAB: it found that 6 months of metformin resulted in a significant reduction in nodule size (2). Obviously, a prospective study with a larger size will be necessary to establish the association between metformin treatment and DTC response and survival, although this may be difficult to achieve. Nonetheless, this study suggests that metformin promotes pathways that lead to down-regulation of prosurvival signaling and to up-regulation of destructive signaling, which may make the cancer cells more amenable to the oxidative stress produced by cancer treatment. The results in the in vitro study underscore the importance that the AMPK-dependent pathways play. The modulation of AMPK by metformin may be the key step in determining the efficacy of metformin in the treatment of thyroid cancer.

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Metformin Inhibits Thyrocyte Growth and Increases Complete Responses in Differentiated Thyroid Cancer in Patients with Diabetes

Artak Labadzhyan

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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.

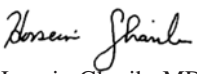
The annual meeting, held every fall, brings together over 1000 physicians and investigators from around the world to share the newest clinical and basic science research into thyroid disease. The meeting features posters, platform presentations, symposia, ''meet the professor'' workshops, discussion 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,



Hossein Gharib, MD
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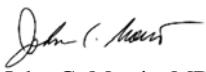

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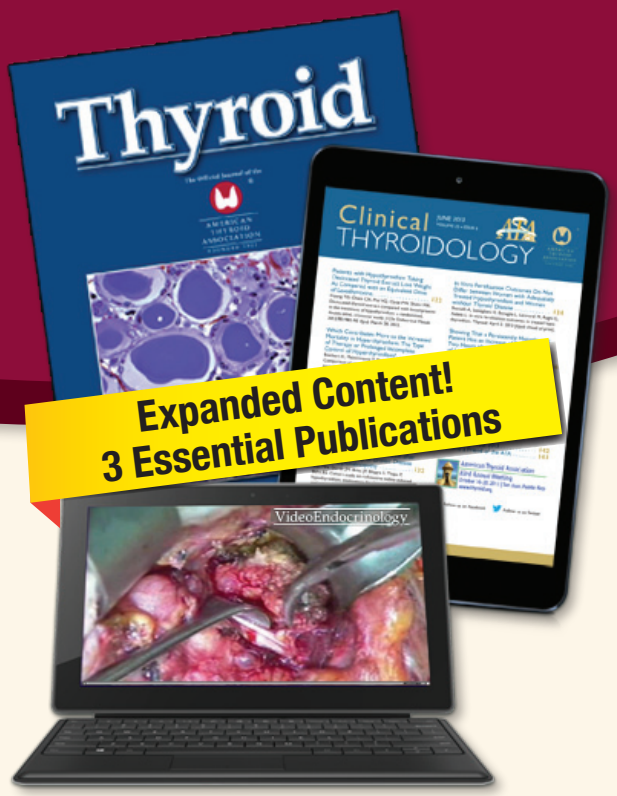

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- ***VideoEndocrinology*** provides cutting-edge videos of the latest surgical and diagnostic imaging techniques and technologies covering thyroid, parathyroid, and adrenal tumors and diseases, with minimally invasive, robotic, and open surgical procedures

The Official Journal of

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ATA WEBSITE WWW.THYROID.ORG REDESIGNED!

ATA website redesign has launched!
www.thyroid.org

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

Your feedback is welcome.

www.thyroid.org

Stay Informed About Thyroid Disease — Become a Friend of the ATA

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.

AMERICAN THYROID ASSOCIATION® FOUNDED 1923

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.

- Answers to frequently asked questions, or FAQs;
- 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*.