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The Effect of 131-I Treatment of Graves' Disease May Be Potentiated by the Coadministration of Lithium

Martin NM, Patel M, Nijher GM, Misra S, Murphy E, Meeran K. Adjuvant lithium improves the efficacy of radioactive iodine treatment in Graves' and toxic nodular disease. Clin Endocrinol 2012;77:621-7.

SUMMARY

BACKGROUND

Lithium shares with iodide a strong inhibiting effect on thyroid hormone secretion. It differs from iodide by not interfering with the transport of iodide by the sodium/iodide symporter (NIS) into the follicles. As a consequence, it increases the time that single doses of iodide and its isotopes are retained within the thyroid. This is the basis for postulating an increased efficiency of ^{131}I treatment (RAI) if given together with lithium as compared with ^{131}I alone. Lithium does not affect the peripheral metabolism of thyroid hormones. Indeed, the majority of studies performed so far indicate a higher efficiency of RAI plus lithium than of RAI alone. The present study confirms these findings in by far the largest group of patients hitherto reported.

METHODS AND RESULTS

A total of 204 patients were studied: 103 received RAI alone and 101 received lithium in addition to RAI. Approximately 80% of these patients were suffering from Graves' disease, and the remainder presented with multinodular toxic goiter. An average dose of 500 MBq (13.5 mCi) was given. A standard dose of 800 mg of lithium per day was started 3 days before RAI and given for a total of 10 days. Antithyroid drug treatment was not resumed after treatment with RAI. Thyroxine treatment (100 μg of T_4 per day) was started whenever serum FT_4 fell below 14.5 pmol/L. Serum thyroid hormone concentrations were monitored frequently while serum lithium concentrations were not evaluated.

During the 12-month follow-up, serum FT_4 and FT_3 were clearly lower at all times in the lithium-treated group. FT_4 and FT_3 were decreased by approximately 12% to 17% with respect to the RAI-alone group. With lithium added to RAI, the proportion of patients cured after 1 year of treatment was slightly higher (93% vs. 84%). The time to remission was also shortened by lithium treatment, which seemed to be as effective in patients with multinodular goiter as in those with Graves' disease, but the group of multinodular goiters

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was too small for any definite statement. The group of patients with endocrine ophthalmopathy was also small and, moreover, these patients were often receiving steroid treatment, making any conclusions in this respect impossible.

CONCLUSIONS

This article confirms that combined treatment with RAI and lithium induces euthyroidism or hypothyroidism more rapidly and in a greater percentage of patients than in those receiving a standard dose of ^{131}I (approximately 500 MBq) only. An additional advantage results from the inhibiting effect of lithium on thyroid hormone secretion, since this strategy obliterates the well-known transient increase of FT_4 and FT_3 following the administration of radioactive iodine. The treatment was as effective in multinodular goiter as in Graves' disease.

ANALYSIS AND COMMENTARY

One question not addressed in this study is that of the potential adverse effects of lithium. Indeed, in patients with cardiac and renal disorders, lithium needs to be given with great caution, and its blood level should be monitored during the treatment. This was not done in the present article, but the dose of 800 mg per day is in the low range. Even this dose had a clear-cut inhibitory effect on thyroid hormone secretion. Indeed, the peaking of circulating hormones after ^{131}I irradiation may have been avoided. Throughout the study, serum thyroid hormone levels were slightly lower in the lithium-treated patients, despite the fact that lithium was given over only 10 days. There is little doubt that the addition of lithium increases the efficiency of ^{131}I treatment.

This is certainly a great advantage in areas where legal limitations do not allow giving high doses of ^{131}I. For instance, in Switzerland and Germany, the maximum outpatient dose allowed is 200 MBq (5.4 mCi). In these areas, the combined treatment is most advantageous. However, in countries such as Britain and the United States, where legislation is more liberal, one has to leave it to individual doctors and their patients to decide whether it is preferable to simply increase the dose of ^{131}I without adding lithium.

It is astonishing that in this study the success rate of treatment of multinodular goiters with the same dose of ^{131}I and lithium was similar to that in Graves' disease. In a country like Switzerland, where large goiters were formerly a frequent clinical finding, the dose of irradiation per gram of goiter tissue varies greatly, with higher doses being recommended for larger goiters. Today, the observation of multinodular goiters of large size has become exceptional.

— Albert G. Burger, MD

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Treatment of Hyperthyroidism with Larger Doses of Radioactive Iodine Produces a Higher Success Rate

Sztal-Mazer S, Nakatani VY, Bortolini LG, Boguszewski CL, Graf H, de Carvalho GA. Evidence for higher success rates and successful treatment earlier in Graves' disease with higher radioactive iodine doses. Thyroid 2012;22:991-5. doi: 10.1089/thy.2011.0362. Epub September 6, 2012.

SUMMARY

Background

The ideal dose of radioactive iodine-131 (RAI) to cure hyperthyroidism has not been determined, despite more than 60 years of experience with this treatment. Too often patients receive either a dose that causes hypothyroidism within a few months or a dose that produces an insufficient effect, resulting in prolongation of hyperthyroidism. The lack of ability to provide a dose that achieves the euthyroid state has led to acceptance of hypothyroidism as the preferred outcome. The ATA guideline on treatment of hyperthyroidism with RAI states: "Sufficient radiation should be administered in a single dose (typically 10–15 mCi) to render the patient with Graves' disease hypothyroid" (1).

In the current report, the authors compared various doses of ^{131}I with regard to the time required for correcting the hyperthyroidism and the success rate of the various doses used.

Methods

Records were reviewed of all patients with Graves' disease treated with RAI from January 1994 to July 2009 at the Federal University of Parana, Curitiba, Brazil. Successful treatment was defined as hypothyroidism or euthyroidism and being off all antithyroid drugs after a single dose of RAI. Success rates were defined as the number of patients who achieved the successful result after the RAI dose. Antithyroid drugs were not given after the RAI treatment. The doses were divided into groups I (<15 mCi), II (16 to 20 mCi), and III (>21 mCi).

Results

A total of 258 patients were treated with RAI and followed adequately; 85.6% were women, and the mean age was 38.6 years. Mean RAI uptake was 53%. RAI was given after previous treatment with antithyroid drugs in 81% of patients either because of treatment failure (70%) or disease recurrence (11%), or as first-line treatment in 16%, or because of failed surgery in about 2%. The dose was empiric in 85%, calculated in 12%, or based on unknown factors in 2%. The mean (±SD) dose was 21.4± 6.5mCi, with a range between 6 and 29.9 mCi. There were 61 patients in group I, 95 in group II, and 97 in group III. The percentage of patients in each of the three groups in whom hypothyroidism or euthyroidism developed after the RAI dose was 73.7% in group I, 84.9% in group II, and 89.0% in group III (P = 0.045). The average time to successful treatment was 8.1, 4.6, and 2.9 months, respectively.

Conclusions

This study provides evidence that success after RAI therapy for Graves' disease correlates with the dose administered and that successful treatment is achieved earlier with higher doses.

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ANALYSIS AND COMMENTARY

This study is a strong argument for more is better, but does not consider any downside to the large dose of ^{131}I. The ATA is much more conservative: doses of 10 to 15 mCi are the arbitrary doses; or calculated doses are 0.15 mCi/g of estimated thyroid weight corrected for the 24-hour thyroid uptake (1). In my experience, calculated doses are often <10 mCi. In the current study, there was no estimate of thyroid size as a basis for the dose. A study of ^{131}I therapy of hyperthyroidism in Berlin in 1995 pointed out that the success rate of a fixed dose of 15 mCi overall was 71% and was inversely related to thyroid size (2); the calculated radiation dose to the thyroid for a success rate of 85%, similar to group II, was 250 Gy (25,000 rad), a dose seldom achieved by radiation therapy of nonthyroid cancers. Are there consequences of this high-dose therapy other than hypothyroidism?

Franklyn et al. reported a slight increase in small bowel cancer and thyroid cancer in 7500 patients treated with RAI for hyperthyroidism (3). A Finnish study of 2793 patients found slightly increased mortality from cancer of the stomach, kidney and breast compared with a control group (4). However, a recent review of carcinogenicity after RAI for benign thyroid disease concluded that "the absolute risk of developing cancer after ^{131}I therapy for benign thyroid diseases seems low or negligible" (5). Nevertheless, radiation-induced neoplasia is proportional to radiation dose; in this respect, less is better.

The authors treated mainly a lower socioeconomic group in a public hospital outpatient department. They ignored the need for lifelong therapy with levothyroxine as a side effect, as does the current ATA recommendation stated above. I suspect that people in a lower socioeconomic group are more likely to run out of medicine and suffer the consequences of hypothyroidism than a middle-class patient with more access to care.

— Jerome M. Hershman, MD

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Is There Sufficient Evidence That Thyroid Dysfunction and Autoimmunity Are Risk Factors for Gestational Diabetes?

Karakosta P, Alegakis D, Georgiou V, Roumeliotaki T, Fthenou E, Vassilaki M, Boumpas D, Castanas E, Kogevinas M, Chatzi L. Thyroid dysfunction and autoantibodies in early pregnancy are associated with increased risk of gestational diabetes and adverse birth outcomes. J Clin Endocrinol Metab. September 26, 2012 [Epub ahead of print].

SUMMARY

Background

Maternal thyroid dysfunction, especially in early pregnancy, may lead to pregnancy complications and adverse birth outcomes. The objective of the authors was to assess the prevalence of thyroid dysfunction and autoimmunity in pregnant women and to examine their relationship with adverse pregnancy and neonatal outcomes in a large-scale, population-based cohort of an iodine-sufficient area of the Mediterranean: Crete, Greece.

Methods

The study used data from the prospective mother–child cohort "Rhea" study in Crete, Greece. During a 12-month period, a total of 1170 women with singleton pregnancies participated in this analysis; maternal serum for the determination of TSH, FT_4, FT_3, TPOAb and TgAb was obtained at a mean (±SD) gestational age of 14.1±3.6 weeks. Multivariable log-Poisson regression models were used to adjust for confounders. Outcomes included gestational diabetes (GDM), gestational hypertension/preeclampsia, cesarean section, preterm delivery, low birth weight, and small-for-gestational-age neonates. The reference intervals of serum TSH levels were 0.05 to 2.53 mU/ml for the first trimester and 0.18 to 2.73 mU/ml for the second trimester.

Results

Mothers with serum TSH concentrations within the reference range were considered to have normal (n = 1062, 90.8%), high (n= 79, 6.8%), or low (n= 29, 2.5%) TSH status. High TPOAb titers were found in 153 (13%) and high TgAb in 83 (7%). Women were screened for GDM at 24 to 28 weeks and were classified as having GDM if two or more of the four plasma glucose values obtained during the 100-g, 3-hour oral glucose-tolerance test were abnormal. The combination of high TSH and thyroid autoimmunity in early pregnancy was associated with (1) a fourfold increased risk for gestational diabetes (relative risk [RR], 4.3; 95% CI, 2.1 to 8.9], affecting 6 of 32 women, only one of whom had a TSH level >4 mU/ml and (2) a threefold increased risk for low-birth-weight neonates, affecting 5 of 32 women (RR, 3.1; 95% CI, 1.2 to 8.0) after adjustment for several confounders. Euthyroid women positive for thyroid antibodies had a significant increase in spontaneous preterm delivery (22 of 148; RR, 1.7; 95% CI, 1.1 to 2.8). The obstetrical outcome was similar regardless of whether or not women were using thyroid medications.

Conclusions

High TSH levels and thyroid autoimmunity in early pregnancy may detrimentally affect pregnancy and birth outcomes.

ANALYSIS AND COMMENTARY

There is agreement in the literature that severe untreated or poorly controlled thyroid dysfunction in pregnancy is the cause of serious obstetrical and neonatal complications (1). However, there is no consistency in the overall obstetrical and neonatal outcomes of women with subclinical hypothyroidism or euthyroid chronic thyroiditis. It is accepted

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that women diagnosed with subclinical hyperthyroidism early in pregnancy do not have an increased incidence of complications, considering that in many of these situations a low serum TSH is a physiological finding early in pregnancy (2). Several publications in the past decade, including a meta-analysis (3), have reported a high incidence of miscarriages and prematurity in series of women suffering from subclinical hypothyroidism or euthyroid autoimmune disease, with some exceptions (4). In the vast majority of published articles, thyroid tests, including measurement of antibodies (mostly TPOAb), were done only in early pregnancy, without follow-up during the course of gestation, nor an indication of the prepregnancy thyroid status. Furthermore, the vast majority of the publications failed to mention whether hypothyroidism was properly corrected before delivery. The study by Karakosta et al. suffers from the same shortcomings: thyroid tests were performed only early in pregnancy (mean gestational age, 14.1 weeks); therefore, the authors were unable to assess miscarriage rate. They reported a significant incidence of GDM, but only in women with mild subclinical hypothyroidism (TSH <4 mU/ml) with positive antibodies, but not in euthyroid women with positive antibodies or those with high TSH and negative antibodies. The authors considered potential confounders, but hyperglycemia was not included. The incidence of other complications, such as prematurity, is limited to euthyroid women with positive antibodies and low-birth-weight neonates and to women with elevated serum TSH values, with or without antibodies. The authors did not comment or speculate about the disparity in outcomes in the different thyroid groups.

It is my personal opinion that in spite of the fourfold increased risk for GDM reported by the authors, larger studies with additional data obtained at different stages of gestation should be performed before accepting these findings. Interestingly, in their conclusions the authors did not mention their novel finding of thyroid dysfunction and autoimmunity as a risk factor for GDM.

— Jorge H. Mestman, MD

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Is There a Cost-Effective Way of Predicting Postthyroidectomy Hypocalcemia?

Lazard DS, Godiris-Petit G, Wagner I, Sarfati E, Chabolle F. Early detection of hypocalcemia after total/completion thyroidectomy: routinely usable algorithm based on serum calcium level. World J Surg. August 2, 2012 [Epub ahead of print]. doi: 10.1007/s00268-012-1727-5.

SUMMARY

Background

Transient and permanent hypocalcemia and hypoparathyroidism may occur in up to 30% of patients after total or completion thyroidectomy. Hypocalcemia is the most common complication of thyroid surgery. This was a prospective study of preoperative and postoperative calcium and phosphorus levels after total or completion thyroidectomy, with the creation of an algorithm to detect patients at risk of hypocalcemia.

Methods and Results

This was a retrospective analysis at a single academic center of a prospectively created database. This observational study examined 136 patients who underwent total thyroidectomy or completion thyroidectomy. Serum calcium and phosphorus were measured preoperatively and postoperatively at 6, 12, 20, and 48 hours after skin closure. Hypocalcemia was defined as a postoperative calcium level of ≤7.6 mg/dl (1.9 mmol/L) or symptoms of hypocalcemia any time after surgery; 24% of patients had hypocalcemia by this definition. Calcium was not administered before 20 hours after surgery, and calcium levels were compared. The lowest level of calcium occurred at 12 and 20 hours after surgery. At 20 hours, the difference had the best area under the receiver operating characteristic (ROC) curves (0.87), and a difference of –1.2 mg/dl (–0.3 mmol/L) or less was a significantly more frequent indicator of hypocalcemia (P = 0.0001). Serum phosphorus was not helpful in predicting hypocalcemia.

Conclusions

The comparison of four postoperative times for collection of calcium levels showed that 12 and 20 hours postoperative levels display similar rates of hypocalcemia, but the 6-hour value was too early and was less reliable. A decrease of ≥1.2 mg/dl (0.3 mmol/L) between the preoperative calcium level and the value at 20 hours after surgery was the best predictor of hypocalcemia (100% sensitivity and 88.4% specificity). None of the patients at with a calcium level >7.6 mg/dl at 20 hours after surgery, even with a drop at hour 20 of 1.2 mg/dl as compared with preoperative levels, had hypocalcemia at 48 hours. This combination of preoperative and hour-20 postoperative calcium levels predicted 79% of the patients in whom hypocalcemia eventually developed. The authors recommend that this algorithm be used cautiously until a larger validation study is performed.

ANALYSIS AND COMMENTARY

Hypocalcemia is the most common complication after total thyroidectomy. As thyroid surgeries at some institutions are becoming an outpatient procedure, it is important to identify predictors of significant hypocalcemia that may occur after the patient has returned home. Predictors for safe early discharge have been based on calcium (1), ionized calcium (2), and parathyroid hormone levels (3,4). Parathyroid hormone levels appear to be a reliable marker (4) of hypoparathyroidism requiring treatment, but quick turnaround times for parathyroid assays in the postoperative period are relatively expensive and may not be universally available. This group focused on postoperative calcium levels, since the results of the test are quickly available and the test is inexpensive. Although the decrease in parathyroid levels occurs as soon as 1 hour after damage to the

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glands (4), the calcium decline is delayed, as shown by this study until 12 to 20 hours after surgery. This study suggests that the change in calcium level is too delayed to be used for safe same-day discharge or even discharge the morning after surgery. Since most of my patients are being discharged sooner than 20 hours after surgery, this study suggests that postoperative calcium levels before 20 hours may not be predictive of which patients will have hypocalcemia and which require calcium and calcitriol supplementation at discharge. I will encourage our service to obtain immunoreactive (iPTH) levels during the late evening prior to discharge the next morning to help predict which patients should receive calcium and calcitriol supplementation after discharge (3).

— Stephanie L. Lee, MD, PhD

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Thyroid Nodule Size Larger Than 4 cm Does Not Increase the Risk of False Negative FNA Cytology or the Risk of Malignancy

Burch HB, Shrestha M, Crothers BA. The impact of thyroid nodule size on the risk of malignancy and accuracy of fine-needle aspiration: a ten-year study from a single institution. Thyroid September 10, 2012 [Epub ahead of print].

SUMMARY

Background

In current practice, thyroid nodules are evaluated by ultrasound and FNA. In addition to the cytologic diagnosis, the size of the nodule is often used as a basis for referral of the patient for thyroidectomy. In this study, the authors evaluated whether nodule size >4 cm affected the accuracy of thyroid FNA or the incidence of malignancy.

Methods

During a 10 year period (2001–2011), 3013 patients had FNA of thyroid nodules at the Walter Reed Army Medical Center. Only patients who had subsequent thyroid surgery were included in the analysis. Nodule size was assessed by ultrasound measurement of the largest diameter and categorized as 0.5 to 0.9 cm (group A), 1.0 to 3.9 cm (group B), and ≥4 cm (group C). FNA cytology was categorized by the Bethesda System for Reporting Thyroid Cytopathology: benign, atypia (follicular lesion of undetermined significance), follicular neoplasm, suspicious for malignancy, or malignant. All categories except for benign were considered positive for calculation of the sensitivity and specificity of the FNA.

Results

Included in the analysis were 540 patients with 695 nodules. The average age was 49 years, and 71% were female. The FNA results were benign in 417 nodules (60%), atypia in 22 (3.2%), follicular neoplasm in 122 (17.6%), suspicious for malignancy in 77 (11.1%), and malignant in 57 (8.2%). There were 35 nodules in group A, 533 nodules in group B, and 127 nodules in group C. The malignancy rate based on surgical pathology was 18.6% (129 of 695 nodules) and did not differ among the size categories. The malignancy rate was 23% in both men and women. The yield of malignancy for a benign FNA was 7%, atypia 3.2%, follicular neoplasm 23%, suspicious for malignancy 34%, and malignant 79%.

False negative rates did not differ significantly based on size. The accuracy and specificity of FNA increased as the size of the nodule increased. The accuracy of FNA cytology was 60%, 68%, and 80% in groups A, B, and C, respectively. The specificity was 59%, 65%, and 83%. However, negative predictive values were not significantly different among the three groups.

Conclusions

The results show that thyroid nodule size ≥4 cm does not increase the risk of false negative FNA results or the overall risk of malignancy.

ANALYSIS AND COMMENTARY

In the days before FNA of nodules, a nodule >4 cm in a man was considered grounds for surgical removal because of a high suspicion of malignancy based on the factors of sex and size. The current study showed no difference in the incidence of malignancy based on sex. More recent work has shown that larger nodules are not more likely to be malignant than smaller nodules, but calcified nodules in men are more likely to be malignant (1). Other clinical factors, such as suspicious features on ultrasound, nodule growth, local compressive symptoms, very large nodule size, and patient concern may be the basis for surgery in large nodules that are cytologically benign.

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In some studies, a false negative (benign) cytology rate of 11% to 20% was found in nodules ≥4 cm, leading to concern that all nodules >4 cm should be removed (2-4). However, others have found a false negative result of only 4% in nodules of this size, somewhat lower than the 7% found in this study (5, 6).

The 2009 ATA guidelines recommend that nodules <1 cm not be biopsied unless they have features that are suspicious for malignancy. On this basis, there is concern about the basis for including group A in this study, even though there were only 35 nodules in this group. Nevertheless, I am reassured by their main conclusion stating that large nodules do not predispose to FNA cytology that is falsely negative.

— Jerome M. Hershman, MD

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A Protein That Prolongs the Action of cAMP-Dependent Protein Kinases Is Overexpressed in Papillary Thyroid Cancer

Cantara S, D'Angeli F, Toti P, Lignitto L, Castagna MG, Capuano S, Prabhakar BS, Feliciello A, Pacini F. Expression of the Ring ligase praja2 in thyroid cancer. J Clin Endocrinol Metab. September 4, 2012 [Epub ahead of print]. doi: 10.1210/jc.2012-2360.

SUMMARY

Background

Praja2 is a ubiquitin ligase that can anchor cAMP-dependent protein kinases (PKAs) under basal conditions. When cAMP levels in a cell rise, however, the PKA catalytic subunits become free and phosphorylate praja2, activating it, promoting the ubiquitination and degradation of the regulatory subunits of PKA to which it is bound, thus prolonging the activity of free catalytic subunits (1). The current paper provides data showing that praja2 mRNA and protein levels are overexpressed in papillary but not anaplastic thyroid cancer.

Methods

Samples from 36 papillary thyroid cancers (PTCs), 6 anaplastic cancers and 14 benign nodules were obtained from patients who had been evaluated and treated according to ATA guidelines; 14 samples were also obtained from normal regions of the thyroids of some of these patients. Praja2 mRNA levels were assessed by (semi)quantitative RT-PCR on all 70 samples (expressed on the basis of two reference mRNAs). Praja2 protein was prepared from 8 PTCs, 4 benign nodules, and 2 anaplastic cancers as well as samples from 5 normal regions. Total praja2 levels were measured on Western blots using polyclonal antibodies, as described Lignitto et al. (1). Praja2 subcellular distribution was assessed by immunohistochemistry on samples using a monoclonal antibody from Sigma. Possible cross-reactivity of antibodies with the homologous protein praja1 was not discussed.

Results

The mean level of praja2 mRNA in the 36 PTCs was significantly greater ($P<0.001$) than the mean levels in the 6 anaplastic cancers, 14 benign nodules, or 14 "normal" samples, although the values found in 6 of the normal samples overlapped with the values seen in almost all of the PTC samples. The mean messenger RNA (mRNA) level in RET/PTC1 tumors ($n = 6$) was about 20% higher than in BRAF V600E tumors ($n = 26$), and about 5 times higher than in RET/PTC3 tumors ($n = 4$). mRNA from normal areas of the thyroids of 7 patients with PTCs was available for comparison with mRNA from the cancerous areas, and in each case the levels were higher in the cancer samples ($P<0.02$). On Western blots, the mean level of praja2 was significantly higher in 8 PTC samples than in any of the 2 anaplastic cancers, 4 benign nodules or 5 normal samples (when combined, $P<0.001$). Immunohistochemistry showed strong cytoplasmic staining in classical PTC, less in follicular variant and insular PTC, and hardly any in anaplastic cancer. No information was given concerning the level or subcellular distribution of immunoreactivity in normal thyroid tissue.

Conclusions

The mRNA and protein levels of praja2 are elevated in differentiated PTCs, and they correlate with PTC mutational status, whereas they are not elevated in anaplastic thyroid cancer.

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ANALYSIS AND COMMENTARY

The transcription factor CREB is a major substrate for free PKA catalytic subunits. When the free catalytic subunits phosphorylate CREB, it binds to the promoters of genes with CREB binding sites and increases their expression. Praja2 is such a gene. The substantial overexpression of praja2 presumably would provoke a cell to counter with some physiological homeostatic responses, however. In future studies, it will be important to determine the status of other factors known to affect PKA activity, such as other anchoring proteins, phosphodiesterases and heat-stable protein inhibitors, as well as the status of other proteins that praja2 binds and ubiquitinates, such as ELK and MAGE-D1. In other tissues, the level of praja2 expression changes in response to various stimuli, including neural differentiation, contact inhibition, hypothermia, experimental colitis, and estrogen replacement. Thus, it is quite possible that the overexpression of praja2 seen in PTC reflects a homeostatic response to changes that occur as papillary cancer develops. Nonetheless, it is still possible that praja2 does play a role in the development of PTCs, whereas this would not seem to be the case in the development of anaplastic cancer or benign adenomas. Such a role would presumably be more prominent in RET/PTC1 and BRAFV600E papillary tumors than in RET/PTC3 tumors, although the numbers of some variants studied were small.

Even if the level of praja2 should turn out to display so much physiological variability that it cannot be used for the diagnosis of PTC, its ability to regulate PKA activity may well prove important clinically for understanding anomalies in the regulation of normal thyroid function.

— Stephen W. Spaulding, MD

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A Benign Gene Expression Classifier Result on an Indeterminate Thyroid FNA May Reduce the Need for Thyroidectomy

Duick DS, Klopper JP, Diggans JC, Friedman L, Kennedy GC, Lanman RB, McIver B. The impact of benign gene expression classifier test results on the endocrinologist-patient decision to operate on patients with thyroid nodules with indeterminate fine-needle aspiration cytopathology. Thyroid 2012;22:996-1001. Epub August 8, 2012; doi: 10.1089/thy.2012.0180.

SUMMARY

Background

Nodules classified as "indeterminate" by cytology make up about 15% to 30% of biopsy results. This classification is much more common that that of overt malignancy, which is found in only 5% of biopsied nodules. The Bethesda classification system divides the indeterminate classification into follicular lesion of undetermined significance (FLUS), follicular neoplasm, and suspicious for malignancy, with the possibility of the nodule being malignant being about 10%, 25%, and 65%, respectively, in the three categories.

The Afirma gene expression classifier (AGEC) is claimed to have a 95% negative predictive value when it is applied to indeterminate nodules in the two less-likely-to-be-malignant categories. The evaluation of this classifier, including its pitfalls, was reported in the August issue of Clinical Thyroidology (1). The purpose of the current study was to determine how the AGEC influenced the joint decision of the endocrinologist and patient to operate on an indeterminate nodule when AGEC reading of the nodule was benign. There was the tacit assumption that all patients with nodules classified cytologically as indeterminate would have been referred for surgery.

Methods

This retrospective multicenter study included patients of 51 endocrinologists at 21 practice sites who obtained the AGEC on cytologic specimens of thyroid nodules >1 cm whose FNAs were read as indeterminate. When the AGEC was classified as negative for malignancy, the investigators determined whether patients were referred for surgery. In addition, the basis for surgery was determined.

Results

The study analyzed data on 368 patients (395 nodules) with a median size of 2.4 cm. Surgery was performed on only 28 patients (7.6%) of those whose FNA was cytologically indeterminate but whose AGEC was benign; the predicted number based on other data compiled by Veracyte investigators would have been 74% (2). The primary reasons that surgery was recommended to the 28 patients with benign results on AGEC were that the nodule was large in 13 patients, symptomatic in 7, rapidly growing in 3, symptomatic in 7, a second suspicious nodule in 3, suspicious on ultrasonography in 2, suspicious on cytology in 2, and not otherwise specified in 12. (Apparently, patients could have more than one reason.) Hemithyroidectomy was the surgery for 68% of the patients; the rest had a total thyroidectomy.

Conclusions

A benign Afirma gene expression classifier result led to a marked reduction in performing thyroidectomy in patients with cytologically indeterminate nodules.

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ANALYSIS AND COMMENTARY

This study has a number of significant shortcomings. It did not subdivide the nodules in the indeterminate category. The number whose cytology was either FLUS or follicular neoplasm was not stated. Apparently, only 2 were suspicious; another Afirma study has not recommended the use of the gene classifier for nodules that are suspicious for malignancy for two reasons; first, almost two-thirds of these nodules turn out to be cancers, and second, the classifier mistakenly classified 6% of a small group of suspicious nodules as benign when they were really malignant (3).

It would be interesting to know the number of patients whose cytology was in the indeterminate category and whose AGEC was classified as suspicious, but this was not stated; only those classified by AGEC as benign were the subject of the study.

The study does not state the number of malignant nodules found in the 28 patients who actually had thyroidectomy. The justification that the study focused only on how many patients were spared thyroidectomy is not a sufficient reason for this omission.

At the recent ATA meeting in Quebec, McIver and colleagues from the Mayo Clinic presented their additional experience with the AGEC. They reported that only 23% of indeterminate nodules were classified by AGEC as benign. Of the 27 AGEC "suspicious" nodules that went to surgery, only 4 (15%) were malignant (4).

— Jerome M. Hershman, MD

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Will Stem Cell Autotransplants Be Clinically Effective for Treating Some Causes of Hypothyroidism?

Antonica F, Kasprzyk DF, Opitz R, Iacovino M, Liao X-H, Dumitrescu AM, Refetoff S, Peremans K, Manto M, Kyba M, Costagliola S. Generation of functional thyroid from embryonic stem cells. Nature. October 10, 2012 [Epub ahead of print]. doi:10.1038/nature11525.

SUMMARY

Background

Embryonic stem-cell research has a translational goal of replacing the function of defective or destroyed organs. Dozens of genes are specifically enriched in the cell bud that forms in the floor of the embryonic pharynx and develops into the thyroid gland (1). A number of research groups have tested various combinations of intrinsic and extrinsic factors on stem-cell preparations in attempts to find which are necessary and sufficient for thyroidogenesis. This exciting report from an international collaboration between several labs now provides a specific combination of factors and exposure times that promotes functional thyroid tissue in hypothyroid mice, and seems to hold promise for the development of human thyroid autotransplants in the future.

Methods

Mouse embryonic stem cells were engineered to overexpress two transcription factors: PAX8 and NKX2-1 (also called TTF-1) only when doxycycline was added to the culture medium. The cells were cultured in hanging drops for 4 days to differentiate into embryoid bodies, which were grown in Matrigel; doxycycline was then added. After various times, mRNA from treated embryoid bodies was tested for Foxe1, (another transcription factor needed for thyroid development), TSH receptor, sodium/iodide symporter (NIS), and thyroglobulin mRNA; the histology of embryoid bodies was also examined.

Results

All of the mRNAs mentioned above were detected, and of particular interest, prominent autocrine production of endogenous Nkx2-1 and Pax8 was also seen, but the cells did not form follicular structures. However, if the doxycycline treatment was limited to days 4 to 6, and then TSH was added, the cells formed three-dimensional structures resembling follicles by 21 days. These cells expressed NIS and e-cadherin on the basolateral side of the follicles, and they also iodinated thyroglobulin. These follicle-like organoids were then grafted under the kidney capsule of hypothyroid mice. Within a month, the grafts had formed a network of small vessels, and the mean serum level of thyroxine in the mice rose, TSH fell, and the body temperature of the mice normalized.

Conclusions

Transient overexpression of the transcription factors NKX2-1 and PAX8 in cultured mouse embryonic stem cells, followed by TSH stimulation for several weeks, caused differentiation into thyroid follicular cells that formed functional thyroid tissue in hypothyroid mice.

ANALYSIS AND COMMENTARY

Obtaining human-induced stem cells is not yet a routine procedure, and there is no guarantee that the specific method described for mouse embryonic stem cells will work, but eventually a way to reprogram pluripotent stem cells obtained from a patient's skin will probably be found. True, clinical trials are not just around the corner, but someday thyroid autotransplants will become available. It seems time to start mulling over clinical questions. For example, congenital thyroid dysgenesis is a common problem, but few causative mutations have been identified.

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Would pluripotent stem cells from these patients remain defective in differentiating into thyroid tissue, or would epigenetic programming be reset so that thyrocyte precursors would survive and develop normally? If a patient who had a total thyroidectomy for cancer were to be given a thyroid autograft, would the new thyroid develop the same cancer? Would patients previously treated for Hashimoto's or Graves' disease who received thyroid autografts have recurrent disease? These will be fascinating questions to answer in the coming era of genetic engineering of stem cells so that they produce specific organs, as pioneered by this year's two winners of the Nobel Prize in Physiology or Medicine, John B. Gurdon and Shinya Yamanaka.

— Stephen W. Spaulding, MD

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